FACTORS AFFECTING DRUG DISTRIBUTION IN GRANULES

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BY

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ABSTRACT

The formulation and processing variables affecting the distribution of a low dose drug in granules prepared by the massing and screening method have been investigated. Five granule formulations were used to elucidate the effect of the "relative solubilities" on the drug distribution in granules. These were borax/lactose, sodium salicylate/ lactose, sulphadimidine/lactose, sodium salicylate/dibasic calcium orthophosphate (d.c.o.) and sulphadimidine/d.c.o. Water was used as the binder for the formulation containing lactose diluent and PVP binder for d.c.o.

Relative dissolution ratio R was derived. This was found to govern drug distribution in granules. The effect of dose variation for a soluble drug was shown to affect R which also explained why dosage uniformity in granules was more problematic in micro-dose than high dose drugs.

The effect of the massing action on dosage uniformity throughout the granule sizes has been elucidated. A higher R value in the granule formulation was found to cause some solute dissolution including the drug in the initially overwetted region. The binder distribution from this region now containing dissolved components enriched the drier area of the mix with the solutes. This action was found to be further enhanced by solute migration during drying. Thus the peak, drug concentration was obtained in the intermediate sized granules. For an appreciably high R value as in sodium salicylate/lactose formulation, a snow-balling action was envisaged to counter-act the massing action to a certain extent. This allowed a further low drug concentration in the fines. The d.c.o. diluent which showed a lesser degree of surface wetness was found to reduce this snow-balling action.

Massing a dry mix with a binder, of constant composition throughout the massing period, e.g. a solution simultaneously saturated with part of the drug and diluent, led to a directly related drug concentration with the granule size. Also massing sulphadimidine/d.c.o. dry mix with PVP binder caused a constant PVP binder composition during the massing as both components are poorly soluble. This led to an inverse relationship between the drug concentration and the granule size on account of the dilution effect of the directly related binder content with granule size. A formulation containing a drug with an R value lower than unity but a markedly higher diluent relative solubility, as in sulphadimidine/lactose granulation, produced the most uniform drug distribution in the granules. Although the lactose solubility is appreciable, its R value is still low due to its presence as a high dose, 98% w/w, diluent. A formulation was designed to make R value equal to 1. This was, as expected, found to lead to a uniform drug distribution irrespective of granule size or granule bed depth.

Other variables which were studied were drying temperature, binder concentration and binder type, intermediate granule screening during drying, excessive massing time, granule packing density during drying, granule bed thickness or height, particle size of both components and drying method. The action of initial larger drug particle sizes for a

moderately or poorly soluble drug was due to lack of ease of wetting for bonding to the initially overwetted mass and slower dissolution rate as in borax. The former action led to a lower concentration in the larger granules in the batch but the latter a higher concentration.

For a readily wettable drug e.g. sodium salicylate the rate of dissolution with particle size was found to be sufficiently rapid to cause a non-rate determining step. Intermediate screening of borax/lactose produced granules with a high borax concentration in the larger granules depending on the moisture content remaining as well as the sieve mesh used in the rescreening process. This was apportioned to abrasion and bonding of the wet fines to granules. The action of excessive (60 minute) massing time was found to produce the same effect as the increase in the binder volume. This was a further decrease in borax concentration in larger granules with a shift of the peak concentration in finergranules.

A comparative study of the drying method showed that the highest borax concentration was obtained in the larger granules dried by freeze drying, then vacuum drying, hot air oven and fluidised drying. The freeze dried granules further substantiates the distribution of the borax rich binder from the overwetted to the drier region of the wet mass during massing. It also showed that solute migration in a batch of granules dried on the tray caused a further depletion of borax from the larger to the intermediate granules. The effect in the granules dried by fluidisation was an abrasive action while that of the other drying methods was due to solute migration during drying.

All the factors affecting drug distribution during the drying in the hot air oven were found to be connected with the degree of solute migration. A denser packing of granules increased solute migration; a higher drying temperature decreased the migration; an increase in the height of granule bed increased the migration and led to a direct relationship between borax concentration and the mean granule size. An increase in the particle size of the diluent increased the effective volume of the binder in the pores available to increase the quantity of the dissolved drug and increase the solute migration of the drug. The larger pores in larger granules entrapped a higher quantity of the drug in the larger granules.

The concentration of drug in granules is therefore the net effect of the massing action and solute migration during drying.

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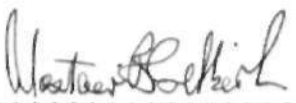
DECLARATION

All the experimental work described in this thesis was carried out by J. E. Ojile in the laboratories in Robert Gordon's Institute of Technology, Aberdeen in collaboration with Syntex Research Centre, Riccarton, Edinburgh and as acknowledged.

It has not been accepted in substance or concurrently submitted in candidature for any other degree.



Candidate



Director of Studies

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CHAPTER ONE

GENERAL INTRODUCTION
AND SCOPE OF INVESTIGATION

1 GENERAL INTRODUCTION AND SCOPE OF INVESTIGATION

The drug dosage form used most extensively in medication is the tablet. This may be partially attributed to their ease of administration. Tablets are administered without having to resort to the use of metering units. They are a stable dosage form as the actives are less reactive to degradative changes in the dry solid state. They are amenable to mass production.

An important prerequisite in tablet production is that tablets must contain the exact dose of drug within acceptable limits. The high activity or potency of many drugs currently in use, necessitates doses as low as 0.05 milligram as in some cardiac glycosides. The oral contraceptive tablet may contain less than 0.05 milligram of an oestrogenic drug in admixture with a progestogen, the dose of which may be a hundred times higher. There is therefore a need to ensure dosage uniformity in such low dose tablets. Any variation, no matter how quantitatively small, could create serious, if not fatal, consequences.

The drug dosage variations in tablets may arise in the following ways.

There may be variations in the weights of the compressed tablets. Even if the drug is uniformly distributed in the granules variations in tablet weight

will cause variations in drug content. Variations in tablet weight may arise as a result of non-uniform rate of flow of granules into the dies during compression or as a result of size segregation of granules.

In some cases there may be insignificant variations in tablet weight but the dose may vary appreciably throughout a batch of tablets. This may be a consequence of variations in the distribution of the drug in the granules prior to compression. This project is based on the latter aspect of dosage variation in tablets with emphasis on low doses of drugs. Factors which affect the distribution of a low dose drug in granules have been investigated. A study of the underlying mechanisms through which the variables affect the distribution of a drug in the granules has been elucidated. This provides a rationale for the design of granulations to minimise this type of variation by relating the nature of distribution in the granules to dosage uniformity in the subsequent tablets.

1.1 GRANULATION

Granulation involves the formation of a cluster of particles which become a permanent entity while retaining the original chemical properties of the constituent particles. The so formed cluster or agglomerate of particles is called a granule.

Granulation processes are applied in various industrial fields which include pharmaceutical, food, fertilizer, detergent, ceramic, water purification and powder mettalurgy.

In general terms, granules impart desirable flow properties, prevent segregation of components, reduce dust hazards and losses during handling. Granules are denser than the component particles and thus reduce space and cost of shipping and storage. Granules promote fluidization. They can be formed from component particles to desired definite sizes and shapes. In oil gasification plants, the wash-water stream is contaminated with soot. To meet the required sewage regulations the soot is removed by agglomeration or granulation with oil. The agglomerates are then easily removed to be burnt (Zuiderweg & Campagne, 1968).

In the pharmaceutical industry, granulation is an important preliminary step in the manufacture of tablets and capsules. The purpose of granulation is primarily to agglomerate the drug mix or ingredients together in order to form free-flowing granules and overcome dustiness during feeding into machines. Gioia (1980) summarised the advantages of good granule flowability in tabletting to include elimination of tabletting flaws such as capping. A smooth downward flow of granule minimises air pocket formation and the high permeability of granules eases the escape of air. The accurate volumetric fill of a uniform packing of granules at high speed not only allows high speed tabletting, tablet weight uniformity and reproducibility of tablet characteristics such as hardness, friability, disintegration and dissolution rates but also results in even compression pressure which lessens the wear and tear of the machine parts.

1.2.1 WET METHODS OF GRANULATION

The wet method of granulation involves wetting of the powdered mix with a liquid binder. Liquid binders include water, if the major component(s) is/are water soluble and aqueous or non-aqueous solution of substance such as gelatin, polyvinylpyrrolidone (pvp), etc. The wet method is the most common method of granulation in pharmacy.

The theories of granulation concern the mechanisms of agglomeration of particles, subsequent growth or enlargement of the agglomerates and the mechanisms of the binding forces which keep the particles together in a cluster or granule.

The wetting method of granulations may be summarised under pan granulation, granulation by massing and screening, fluidised granulation and spray dried granulation.

1.2.1.1 PAN GRANULATION

In pan granulation a liquid binder is sprayed from a nozzle onto particles tumbled in an inclined rotating drum usually fitted with baffles to prevent slipping of the particles at the wall. As a result of the rolling action of the drum, the granules are generally spherical and smooth (Ganderton & Hunter, 1971).

Until recently, the mechanisms proposed for agglomeration of particles to form granules were derived from earlier work done outwith pharmaceutical granulations. Most of the theories were based on work done with the pan granulation process only.

In a review by Barlow (1968) the mechanisms of granule formation and growth during granulation in a rotating pan were divided into three stages - nucleation, transition and ball growth.

Nucleation: During mixing with a spray of the binder, adhesion of particles occurs as a result of pendular bridge formation. This is a three phase loose agglomerate (Fig. 2). As tumbling continues the air gap is eliminated to form a compact nucleus (capillary stage) held together by capillary forces, (Newitt & Conway-Jones, 1958).

Transition: During this stage, two or more nuclei may adhere together. In addition, particles may adhere to the nuclei by a pendular linkage to form different sized granules. The granules are reshaped as a result of the drum rotation and inter-granular friction.

Ball Growth: Larger granules may break up. Some of the split granules from the larger granules may combine with small granules. Small granules may combine to form larger granules (Newitt & Conway-Jones, 1958). Kapur and Fuerstenau (1966) proposed that the large granules are only formed from smaller granules. Capes and Danckwerts (1965) and Capes (1967) proposed that the larger granules only break at a limiting size when the breaking stresses are greater than the bonds between the particles.

Sastry & Fuerstenau (1973) used a tracer method to identify the formation of agglomerates and their growth. Two identical forms of calcite differentiated only by fluorescent characteristics were mixed in a rotating drum.

The two calcites were nucleated separately before they were rotated together. The distribution of the forms of calcite revealed five mechanisms of growth (Figure 1). These were: nucleation of new particles from the wet feed; coalescence or clumping of the nuclei; breakage of agglomerates into fragments which distribute to surviving granules by layering; abrasion transfer in which a certain mass of material is transferred from one granule to another as a result of interaction in the pelletising charge; and snowballing or layering in which moist feed nuclei adhere to the surfaces to granules in a case where there is a continued addition of moist feed into the drum.

1.2.1.2 GRANULATION BY MASSING AND SCREENING

The dry mix is massed with a suitable liquid granulating agent (binder). The wet mass is then forced through a screen of desired aperture. The wet mass becomes more granular and is dried usually by fluidized gas or on trays in a hot oven. The dried granules may be passed through a sieve to break up large lumps which may have formed.

As a result of the complex interaction of moisture content, the contact time of the particles and the magnitude of the force exerted by the mixer during massing, a strict comparison between massing and screening and pan granulation is difficult (Hunter and Ganderton, 1971). These methods showed that the extent of granular growth as regards densification depended on both the cohesion of

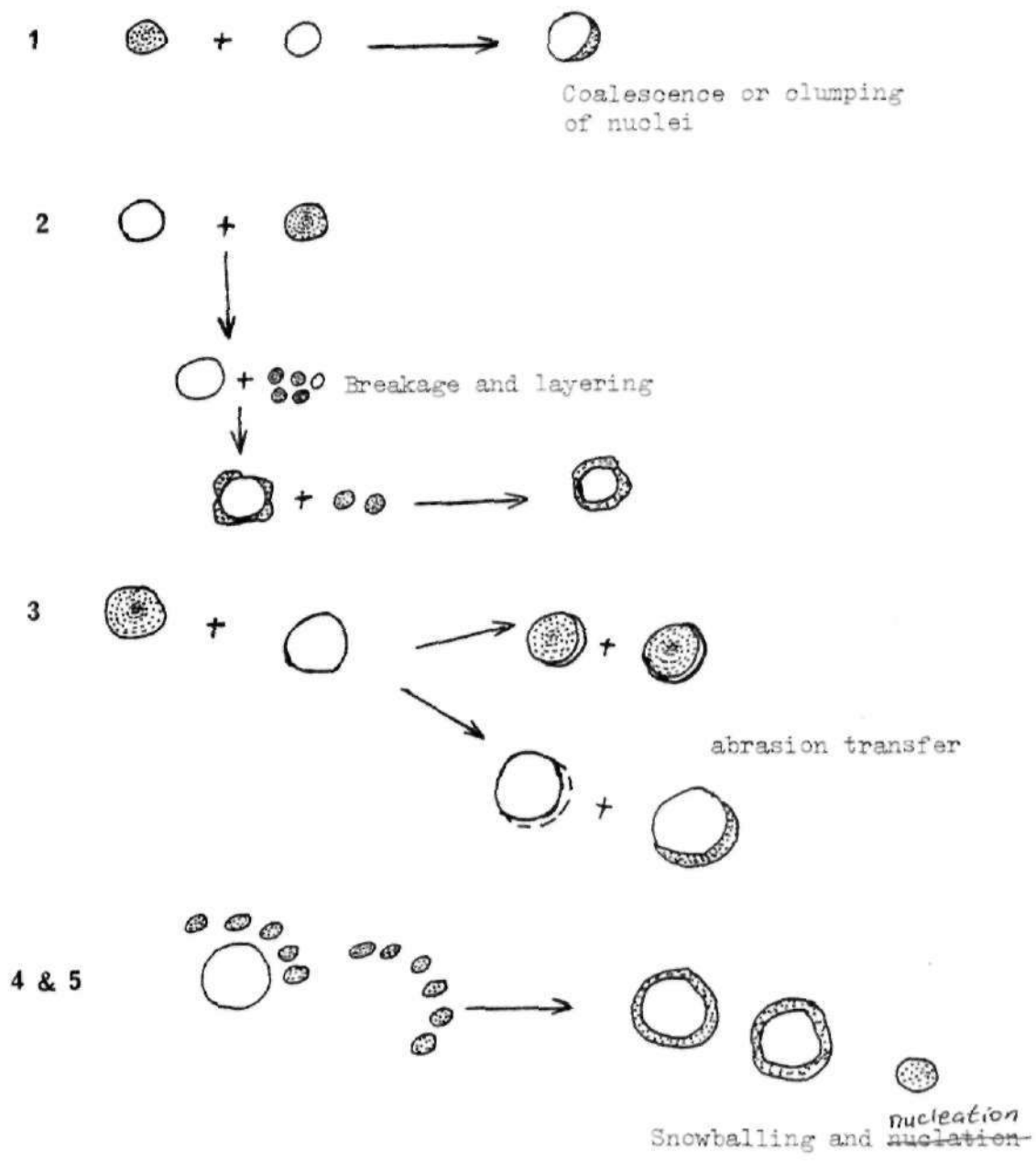


Figure 1: Proposed Method of Granule Ball Growth by Sastry & Fuerstenau (1973)

the powder and the type of mixer used.

Opakunle (1975) proposed a mechanism for granule formation and growth for a binary mixed powder massed in a Z-blade mixer and screened. This was related to the solubility of the binary components of the mix and their proportions. When water as a binder was added to the blend an initial incipient overwet powder contained a greater proportion of the more soluble component dissolved in the binder. The massing action broke the overwet clumps into smaller wet agglomerates which bonded drier particles to themselves. The rubbing action wetted the surfaces of the agglomerates again. More particles were bonded until all the powder was wetted uniformly depending on the massing time and moisture content.

The Carstensen et al (1976) and Zoglio et al (1976) mechanisms for granule formation and growth during massing were similar to Opakunle's (1975) proposal. The liquid binder overwetted the incident portions while the rest of the powder remained dry. The binder was then distributed during massing. Both large and small granules were formed. Provided an adequate amount of liquid was used, the granules equilibrated reaching a fairly uniform size. A prolonged massing or kneading destroyed the equilibrium structure of granules leading to compact granules.

1.2.1.3 GRANULATION BY SPHERONIZATION

This is a recent development which differs slightly from the granulation by massing and screening process

described. It is granulation of a plastic mass by extrusion. The dry mix is massed with excess of a binding agent to produce a pasty or plastic mass which is then forced through a screen and cut into segments to form cylindrical shaped granules. The diameter of the cylindrical granules is similar to the mesh size of the screen. The wet cylindrical segments are then fed into a marumerizer which utilises centrifugal forces and friction to form spherical granules. The granules are then dried. The granules, being compact with little or no pores, may create bioavailability problems if they are not very soluble in the gut.

Reynolds (1970) has described the spheronizing process in detail. The formation of the plastic mass may be regarded as an extreme form of excessive massing described by Zoglio et al (1976) in which the equilibrium granule structure is completely destroyed to form a compact, non-porous wet mass.

The intra-particle cohesion which was needed to form a cohesive and plastic mass was influenced by particle size, wetting and solution properties of the material and the surface tension and viscosity of the liquid binder.

Brociner (1968) using a granulator has thrown some light on the mechanisms of pelletisation. The peg granulator consists of a metal cylinder inside which is a rotating shaft carrying helically arranged pegs. A high speed film was used to show that the agglomerates were rotating about their own axes as well as being rotated round the drum by the beating pegs. The agglomerates

then became a series of chords which became spherical to successive deformations. There was a critical moisture content below which the granules became brittle but above which the increased plasticity of the agglomerates absorbed the energy of the beating pegs. The agglomerates then became larger.

1.2.1.4 GRANULATION BY FLUIDISATION

A bed of powdered particles is fluidised by a stream of hot gas through the bed. A liquid binder is sprayed into the fluidised chamber to make contact with the fluidised particles. Granules are formed by the agglomeration of the fluidised particles. As the required consistency of the granules is reached, the spraying of the binder is stopped.

Fluidised granulation is a one stage process, that is, the agglomeration by wetting and the subsequent drying operation are carried out in the same apparatus.

In fluidised granulation a possible mechanism of agglomeration was postulated by Scot, et al (1964). Two or more solid particles impinged with a droplet of the liquid binder. These particles were cemented together as the solvent evaporated. A further size enlargement occurred by impingement of other particles to the agglomerate or by impingement of agglomerate to agglomerate.

1.2.1.5 GRANULATION BY SPRAY DRYING

A solution or slurry of the powdered mix is forced at high pressure through a nozzle or atomiser to form a

spray into a chamber. A stream of hot gas is passed through the chamber to dry off the liquid leaving clusters of spherical particles from the droplets. Small spherical granules are so formed (Lyne 1972). The droplet size depended mainly on the speed from the atomizer which could be adjusted to give the required particle size of the granule formed. However Lyne (1972) suggested that the droplet size should not be too large in order to dry by the time it reached the wall of the chamber. The fine granule could be enlarged by subjecting it into the spray for 'attack' by other droplets which adhered and dry to form larger granules. The near spherical shape might shrink or puff during drying to lead to cratered surfaces.

1.2.1.6 GRANULATION BY CONTROLLED CRYSTALLISATION

Under selective crystallisation conditions large crystals are formed and, if necessary screened. Sodium chloride, acetylsalicylic acid and sulphadimidine crystals have been prepared in this way.

1.2.2 NON-WETTING METHODS OF GRANULATION

The non-wetting method of granulation involves the absence of wetting the powdered mix during the process.

1.2.2.1 DRY GRANULATION BY COMPACTION

This is brought about by compacting or slugging the fine particles under high pressure to form coarse tablets or slugs. The slugs are then passed through a comminuting mill to break them down into the required granule size by

using an appropriate sieve. Production of dust and segregation of particles, if the mix is made up of more than one component, are a common occurrence.

Peck (1958) reported that the compaction process involved three steps - packing, elastic and plastic deformation and "cold welding". The inter-atomic forces of the new surface of the particles brought together under high pressures result in bonding or "cold welding". In pharmaceutical tabletting, this method is rarely used except in drug materials which degenerate if subjected to the wet method. Some diluent or high dose drugs could be granulated in this way and dry mixed with drug or excipients, respectively, and compressed directly.

1.2.2.2 GRANULATION BY FUSION

This method is otherwise known as sintering or nodulizing (Orr, 1966) and requires the use of heat to melt a micro-component of the powdered mix. The temperature of the melting component is much below the melting point of the major component which is not affected by the heat. The fused component on cooling hardens to cement together the particles into granules. Goodhart, Draper & Ninger (1973) demonstrated how this could be applied in pharmacy by granulating an antacid formulation using a spray congealed fat-wax mixture as the fusing component. The fusing mass formed, was extruded to form granules.

1.3 BINDING MECHANISMS IN GRANULES

Having described the different methods of granulation

and the mechanisms of formation of agglomerates and their subsequent growth to form granules, it is equally important to appreciate the possible mechanisms of the binding forces which hold together the particles that make up the granule. Sastry & Fuerstenau (1973) pointed out that the forces which bind the particles together in a granule were of two kinds. These were applied (mechanical) and natural (physical) forces. The mechanical forces transport wetted particles or agglomerates into contact so that the natural forces may bring about their intactness.

The natural forces which bind the particles together may be summed up as follows (Peck, 1958, Rumpf, 1962, Orr (1966), Sherrington (1968), Barlow (1968), Pietsh (1969), Pilpel (1969), Frank (1971), Capes (1971/72), and Sastry & Fuerstenau (1973):-

1.3.1 BINDING FORCES BY FORMATION OF SOLID BRIDGES

The formation of solid bridges between particles in a granule may be brought about by:

1. sintering or partial melting at the point of contact (Goodhart, Draper & Ninger, 1973);
2. chemical reaction between the particles or binding substance; bridging can be effected when ferric oxide is reduced to ferrous oxide or when ammonia is reacted with superphosphate as in the fertiliser industry;
3. hardening of binders;
4. crystallisation of dissolved substances in the binder.

1.3.2 BINDING FORCES BY ADHESION AND COHESION IN IMMOBILISED BINDERS

1. Adhesives and viscous binders e.g. asphalt prevent the formation of a constant liquid pressure. Therefore capillary forces are absent. The binding force is a balance between the adhesional force at the points of contact between the binder and the solid particles and the cohesive force of the binder.
2. Adsorption layers are also not freely moveable. Water can form a meniscus only at a capillary radius of more than 30Å. Therefore an aqueous adsorption layer of less than 30Å apart can transmit molecular attraction forces between the particles.
   In compaction or briquetting the area of contact for adsorption is increased leading to high bonding forces.

1.3.3 BINDING FORCES BY ATTRACTION BETWEEN SOLID PARTICLES

In the absence of liquids, these forces are due to molecular attractive forces which might be van der Waals, electrostatic or magnetic. Van der Waals forces are the predominant forces binding particles together, acting over distances of up to 1000Å. Valence or chemical binding forces act at shorter distances, about 10Å.

The Heitler-London equation (Barlow, 1968) gives the value of tensile force F between 2 particles up to 1000Å apart:

$$F = \frac{8.3 \times 10^{-20} d}{a^2} \quad \text{kgf cm}^{-2}$$

where a = distance in cm between adjacent surfaces

d = particle diameter in cm

Rumpf (1962) calculated the van der Waals tensile strength between 1 micrometre particles 30 Å apart to be in the order of 1 kg force cm^{-2} which can be brought into contact by compaction or tabletting.

Electrostatic forces which are due to electron deficiencies or excesses on particles may be produced by interparticulate frictional forces and the frictional forces between particles and the container walls. Charges of opposite polarity result in attraction (Orr, 1966).

1.3.4 BINDING FORCES BY INTERLOCKING BETWEEN PARTICLES

Form-closed or interlocking binding is another possible binding mechanism in particles. Inter-particle bonding may occur, especially with fibrous, flat-shaped or bulky particles by a suitable motion or compression which mats or interlocks the particles together.

1.3.5 BINDING FORCES BY INTERFACIAL AND CAPILLARY PRESSURE AT FREELY MOVEABLE LIQUID SURFACES

The forces which bind particles together when wetted by non-adhesive liquid binders are either capillary forces or surface tension, the latter being the case when the liquid surrounds the particles. These forces give way to solid bridging by hardening or crystallisation after the solvent is dried off.

The liquid phase in the granule may be present in four states: pendular, funicular, capillary and droplet (figure 2).

1. Pendular State: The ratio of the liquid to void volume is low. The liquid is held in discrete lens-like rings at the points of contact between the particles and the air. The air forms a continuous phase. In between the particles are three phases - solid, liquid and air. The mutual attraction between the particles occurs by the surface tension of the liquid. The surface tension is directed along the liquid surface at the solid-liquid-gas contact while within the liquid-bridge a negative capillary pressure exists, if the solid is wetted, resulting in a mutual attraction of the opposite forces.
2. Funicular State: In the funicular state, there still exists the three phases but the liquid phase occupies most of the pores within the granule.
3. Capillary State: When all the space between the particles is filled with the liquid, the capillary state is reached. There are still concave cavities, menisci, between the particles but they occur at the surface only. Therefore a negative capillary pressure still exists to bind the particles together.
4. Droplet State: As the liquid completely envelopes the particles making a continuous convex liquid surface round the particles, the capillary forces give way to the surface tension of the liquid which holds the

particles captive (Orr, 1966). This is the case of slurries or solutions which are being atomised into droplets for spray drying.

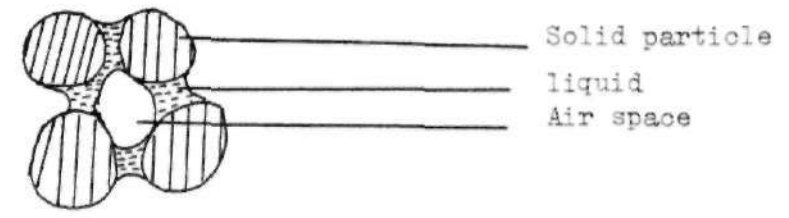
1.4 INFLUENCE OF VARIABLES IN PHARMACEUTICAL GRANULATION

The diversity in the number of processing variables encountered during granulation has led to much of the published work to be empirical in nature. Differences in the design and scale of equipment, in the physico-chemical nature of materials, in granulation methods, etc are reported to affect the granule properties. A granulation process which is a success in a product might prove a failure in another product as regards the physical and bioavailability properties of the granules.

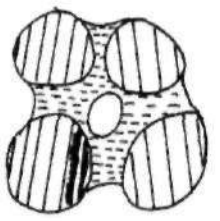
1.4.1 NATURE OF MATERIALS

1.4.1.1 PARTICLE SIZE OF MATERIALS

The particle size and size distribution of a material is reported to affect the agglomeration characteristics as well as the properties of the granules formed. Hunter and Ganderton (1972), using a Z-blade mixer showed that an increase in the particle size of lactose decreased the amount of binder necessary to adequately granulate the lactose. The strength and porosity of the granules formed were inversely related to the particle size of lactose granulated with equivalent amount of binder. They fractionated the lactose particles and found that monosized



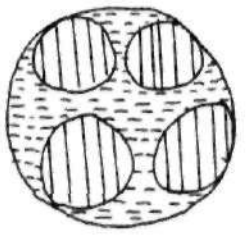
Pendular state
(liquid trapped)



Funicular state
(air trapped)



Capillary state
(air expelled)



Droplet state
(liquid surrounds particles)

Figure 21 A sketch to illustrate states of liquid phases binding particles.

particles further decreased the strength and increased the porosity of the granules. For a binary mixed powder, increase in the particle size of lactose which formed 75% of the mixture with boric acid was shown by Opakunle & Spring (1976) to increase the granule strength and decrease the porosity. It would therefore appear that the presence of another material has an effect on the packing behaviour and intactness of the granules.

Generally, a better mixing of powdered materials is achieved by narrowing the difference in the particle size of the components. However, Barlow (1968) reported that the presence of fines was necessary for allowing the formation of stronger granules. In fluidised granulation, Crooks & Schade (1978) showed that the particle size of the diluent was necessary to be large in order to decrease the cohesiveness of the powder mix which could more easily be fluidised. They further pointed out that an increase in the particle size of materials allowed less incorporation of the binder. Thus the granules formed could give desired disintegration and dissolution rates.

In the granulation of a ternary mixture consisting lactose, boric acid and different sizes of starch, Jaiyeoba & Spring (1979) found a decrease in the mean size of granules prepared from larger particle size of the starch.

This was reported to result from the high affinity of starch for water. The equilibrium moisture content of potato and maize starches was as high as 35.6% and 27.4% respectively at 100% R.H. Therefore a significant

proportion of binder was required to saturate the pores within the starch particles. This amount of binder would not then contribute to granule size formation as it is not available in the interparticulate spaces of the powder bed.

1.4.1.2 COHESIVENESS AND SOLUBILITIES OF MATERIALS

Newitt and Conway-Jones (1958) determined the amount of binder to granulate sand by correlating the tapped porosity of a bed of sand to the volume of binder required to saturate the pores. The volume of the binder was 90% of the void space. Sherrington (1968) reported that only 50% of the void space of the binder was required to produce maximum granule efficiency.

In the granulation of many fertilisers, some of the materials dissolve in the binder. The volume of the binder needed to saturate the inter-particulare pores is therefore decreased. Only 20-30% of the inter-particulare porosity of the binder volume is then required (Hignett & Slack, 1957).

Eaves and Jones (1973), comparing the packing properties of powdered glass (non-porous and non-cohesive), potassium chloride (non-porous but cohesive) and calcium phosphate (porous and cohesive) showed that the specific volume (volume/dry weight) for each material, for the same moisture content up to 50% w/w and a corresponding consolidation stress, was dependent on the nature of the bulk solids. The cohesive - van der Waals - forces in potassium chloride were enhanced with a low moisture content but decreased with a higher moisture

content. The glass powder gave a higher tensile strength with increased moisture content as a result of the cohesive forces of the moisture. The calcium phosphate accommodated more moisture without increasing in specific volume or in tensile strength as a result of the entry of the moisture into the intraparticulate pores. They concluded therefore that adequate densification and tensile strength of the granules formed would be obtained by massing non-porous and cohesive types of powder using a little binder and maximum amount of massing stress but a higher binder along with massing stress was required for glass and calcium phosphate types of powder. The latter case is in agreement with Hunter & Ganderton (1971).

As a result of the size and size distribution of particles, surface characteristics (e.g. roughness) and flow properties of a powder a mixture of two powders may not give intermediate properties in line with the proportions of the component powder. Varthalis & Pilpel (1976) found such anomalies in the properties of mixed lactose and oxytetracyline and of mixed lactose and paracetamol. They suggested that a measure of the apparent mean particle size could be used to determine the degree of mixedness of the mixture, previously determined by reference to a chemical analysis. They also pointed out that the packing arrangement of such a mixture might affect the strength, flow and porosity of the granules formed from the mix.

The influence of the properties of a binary mixture on granule properties were examined by Opakunle & Spring

(1976a). The binary mixtures in various proportions were lactose-sulphanilamide, lactose-boric acid, and lactose-citric acid. Granules of lactose-sulphanilamide were stronger and larger sized than granules made from separate components. The maximum size were from 90:10 mix and maximum strength from 50:50 mix. The lactose-citric acid mix required much less binder as a result of the greater solubility of citric acid. The more cohesive effect of sulphanilamide appeared to have outweighed the effect of the higher solubility of citric acid on granule strength and size. They concluded that while cohesiveness and wettability of a powder determined the granule strength, the extent of dissolution of the powder in the binder determined the mean granule size.

Jaiyeoba & Spring (1980) extended the work on granulation of binary mixtures to ternary components by inclusion of a poorly water-soluble third component which was kaolin, sulphanilamide or salicylic acid in 10% w/w concentration. They gave different aqueous contact angles of 0^{o}, 64^{o} and 103^{o} respectively, as a measure of the degree of wettability. The higher the angle the less was the measure of wettability. The values for lactose and boric acid powders were 30^{o} and 74^{o} respectively.

A typical formulation given was:

Lactose	81%
Boric Acid	9%
Heavy kaolin, sulphanilamide or salicylic acid to 1 kg weight	10%
Binding solution: 5% w/v aqueous pvp	150g

The strength and mean granule size of the granules were increased by the finer, more wettable but poorly soluble kaolin. The reasons proposed were a result of closer packing effect and increased interparticulate cohesion resulting in a higher amount of bridging contacts. The presence of sulphanilamide did not produce a pronounced difference in the mean granule size and strength as the degree of wettability lay between that of lactose and boric acid. The appreciably decreased mean granule size and strength in granules produced with inclusion of ascicular particles of salicylic acid (the sulphanilamide was also ascicular) was ascribed not to packing effect but to reduce access to wetting of the mix necessary for higher bridging contacts and binding of more particles.

1.4.2 VARIABLES IN EQUIPMENT AND METHOD OF GRANULATION

1.4.2.1 NON-FLUIDISED METHODS

Until recently, most of the scientific contributions to the schematic studies of granulations were derived from studies done outside the pharmaceutical industry. Newitt & Conway-Jones (1958) worked on fertilisers and Kapur & Fuerstenau (1964) worked on ores. The studies were mostly concerned with the theories of granulation with the pan tumbling method.

Ahmed and Pilpel (1967) granulated lactose in the pan by spraying solutions of acacia and PVP and obtained satisfactory spherical granules. However the more viscous nature of gelatin could not be sprayed satisfactorily.

Neff & Morris (1968) found an optimum moisture content which produced lactose granules of maximum porosity. The lactose granules were prepared by massing and screening in the dairy industry.

A comparative study of pharmaceutical granulation by different methods were documented by Fonna, Banker & Swarbrick (1966). The binder content which produced equivalent granules was found to depend on the granulation method. Ganderton & Hunter (1971) compared pan granulation and granulation by massing and screening using lactose and calcium phosphate as single component materials. The extreme ranges of binder volume necessary to make granules was 15 to 34% v/v for calcium phosphate.

The Z-blade mixer used for massing was found to produce more shear force than the rolling action of the pan method. Calcium phosphate granules prepared by the pan tumbling method required 174 to 191% v/v binder giving porosities of 68 and 56.8% respectively. Equivalent mass and screened granules were massed with 117 to 157% v/v binder giving a narrower range of porosities, 52 and 51% respectively. Above the upper limit of binder volume, the uncontrolled agglomeration was attributed to oversaturation of the intragranular pores with the binder. Excess binder was therefore available on the granular surface to bind more granules together. However, in fluidised granulation, rapid aggregation was reported to occur as a result of decreasing surface area of the granules. On a unit area basis, there was more atomised binder uptake which caused the rapid agglomeration (Crooks & Schade, 1978). With

lactose, the increase in densification of the granules with increased binder content was not appreciable although the pan granulation granules were denser than massed and screened granules (Ganderton & Hunter, 1971).

Ganderton & Hunter (1971) found pan granulated granules to be more spherical compared with the rough surface of the granules prepared by massing and screening. Later, the same authors (Hunter and Ganderton, 1973) examined the effect of type of mixers which made use of different modes of agitation. The mixers used were Planetary, Z-blade and Lodige-Morton mixers, the last of which consisted of high speed cutting ploughs rotating between dividing plates in a horizontal, cylindrical mixing chamber. The Lodige mixer had the greatest shear force, followed by the Z-blade mixer. The Z-blade mixer had no compacting component but as soon as a cohesive mass was formed, the twin opposing moving blades could effectively distribute the binder. The planetary mixer compacted some small portions of the mass against the wall of the mixer and therefore needed a longer massing time or more binder volume for effective distribution. Different mixers were found to produce calcium phosphate granules with varying porosities and strength. However variation of mixer type produced lactose granules whose properties were not significantly different.

The granulation of lactose was scaled up using three planetary mixers of same geometrical shape but dimensionally different. The mixing ability was compared by taking samples from specific regions of the mix at regular times and finding the moisture content of the samples. The

densification and massing time for reaching equilibrium granules were found to be proportional to the mixer capacity probably because the higher amount of material in the mixer produced an inertial opposition to the blade resulting in greater compacting forces.

Sinay & Tawahsi (1972) also worked on scaling up of mixing equipment and inferred that reproducible results could be attained by considering not only the geometric and dynamic similarities but also the ratio between size of sample and size of batch in both pilot and large scale equipment. Seidler (1977) compared the massing action of the planetary and Z-blade mixers which were used to mass a powdered mix before feeding into a Minimizer to produce spherical minigranules of a narrow size distribution. The minimizer consisted of a stationary vertical cylinder open at the top. At the bottom was a rotating assembly of scrapper arm, classifier plate and cutting blades. Like Hunter and Ganderton (1973) the Z-blade mixer was found to require less massing time and less binder for effective granulation compared to the Hobart planetary mixer. Compared with mass and screened granules, minigranules (Seidler, 1977) and spheronized granules (Jalal, et al, 1972) 1972 had a narrower band of size distribution and being more spherical were more flowable. The degree of sphericity of the spheronized granules depended on the rotation speed rather than the resident time (Woodruff & Nuessle, 1972). Malinowski & Smith (1975) found the spheronizer speed, moisture content and screen size to affect the properties of the granules. An increase in the spheronizer speed

was found to increase the flow rate, bulk density and decrease mean size of granules. The mean granule size was increased by increase in size of screen which also increased the flow rate. The latter properties were also obtained by increasing the binder content.

In the extrusion process, the strength of dried granules were directly related to the extrusion weight (Mitsui, Aoyama & Kaga, 1970).

1.4.2.2 FLUIDISED METHODS

Wurster (1959) introduced fluidised granulations for pharmaceutical application. Scott, et al (1964) designed a fluidised bed granulator which was also suitable for a continuous production of fluidised granules. They made a test run with 75 μm size of particles which agglomerated to 275 μm size of granules. The theory and design were extended by Rankell, Scott & others (1964) to investigate the process variables. The variables were the inlet air temperature, flow rate and nature of the binder. The same inlet air temperature as the bed temperature did not require latent heat of evaporation. Increase in the binder flow rate increased up to a limit the mean granule size. Water was less suitable to agglomerate the particles than simple syrup binder but better compressible granules were obtained with gelatin solution.

In the continuous batch processing, an increase in powder feed rate decreased granule size due to a lower concentration effect of the binder; largest granules were formed when the binder spraying nozzle was located in the

lowest position in the chamber resulting in a greater chance of contacts and a decrease in premature evaporation of the binder. They also found that colour uniformity of dyes was much better than oven dried granules.

Davies & Gloor (1971) worked on similar process variables in fluidisation and explained that the larger and less friable granules produced by the variables, e.g. increase in binder feed rate, a lower location of binder spray nozzle, decreased inlet air temperature, were all traceable to greater wetting of particles by the binder. Later they (Davies & Gloor, 1972) showed that the type and concentration of the binder affected the granule size, friability and porosity. The binder flow rate and viscosity were directly related to granule size, and indirectly related to granule friability. The lack of shear in fluidised granulation might decrease the incorporation of the atomised binder. Aulton, et al (1977) employed the incorporation of a surfactant which was observed to increase the wettability of the particles and also improved the dissolution rates of the granules.

1.4.2.3 SPRAY DRIED METHODS

Granulation by spray drying was described earlier (Section 1.2.1.5).

Gunsel and Lachman (1963) and Cornblum (1969) applied spray drying techniques to the granulation of pharmaceuticals. Asker and Becker (1966) produced spray dried granules of pharmaceutical organic compounds. Saka (1961) and Metcalfe (1956) produced spray dried granules which

encapsulated a flavouring volatile oil. An experimental spray drier was used by Fell & Newton (1970) to produce spray dried lactose which was a mixture of three polymorphs. Later, they (Fell & Newton, 1971) showed that the most significant variable which affected the physical properties of the spray dried lactose granules was the feed rate. Tablets compressed from spray dried lactose dried at lower inlet temperatures were found to be harder than those dried at higher inlet temperatures (Fell & Newton, 1971a) as a result of changes in the polymorphic form of lactose. Bank, et al (1971) found that an increase in the flow rate of the fluidising hot air caused a decrease in granule size. The sublimation of salicylic acid during spray drying was pointed out by Kawashima, et al (1972). They prepared spray dried granules from a slurry containing salicylic acid and sodium salicylate and found that some of the salicylic acid, not encapsulated, sublimed. Whether or not diffusion of vapour takes place during the transient spray drying time depended on the porosity of the peripheral layer (crust) of the granules and the contact angle of the binder. A binder with a higher contact angle would form a non-porous crust when saturated. Stresses set up by the vapour could cause a rupture making the granule surfaces cratered or shrived. A binder with a low contact angle would produce a thin film through which vapour could easily diffuse out. The resultant granules would have smooth and spherical surfaces.

1.4.3 INFLUENCE OF BINDERS

The type of binder, binder concentration and massing

time have all been shown to affect granulation.

1.4.3.1 TYPE OF BINDER

Ahmad & Pilpel (1967) compared three types of binders which were sprayed on tumbling lactose in the pan. Their results showed that gelatin, polyvinylpyrrolidone (PVP) and acacia binders produced satisfactory granules whose friability increased in the following order, acacia> PVP> gelatin. The viscosity of gelatin solution was said to resist the spraying of the solution for efficient mixing.

Acacia, compared to starch paste, was found to form stronger granules prepared by massing and screening (Chaudry & King, 1972). A mixture of binder might form granules of better properties than either pure binder. This was the case when Surowiecki, et al (1971) used an anhydrous mixture of rosin and glycerol as the binder.

In spray drying, Takenaka, et al (1971) used gum arabic, gelatin, polyvinyl alcohol (PVA), sodium carboxymethylcellulose (SCMC), methylcellulose and PVP separately as binders in aqueous slurry of synthetic aluminium silicate or magnesium carbonate. The fine granules produced were free flowing and could be compressed to form tablets of good physical properties. Kawashima, et al (1972) noticed some defects in spray dried granules from a slurry. Pits or holes were found on the surface of the granules. They compared the binding properties of different binders and found that the slurry of salicylic acid and sodium salicylate containing gelatin, PVA, SCMC, methylcellulose, tragacanth or sodium alginate when spray

dried showed granules with such pits which were absent with slurries containing gum arabic and PVP.

In fluidised granulation, Davies & Gloor (1972) showed that the physical properties of granules were greatly influenced by the type of a binder as well as its concentration whose increase resulted in increased adhesiveness and thus larger sized and less friable granules.

1.4.3.2 BINDER CONCENTRATION

The concentration of a binder is usually expressed as one of the following:

(a) Volume of binder as a percentage of the weight of dry mix, e.g. Selkirk (1974).

(b) Volume of binder as a percentage volume of the voids in a packed bed of the particles e.g. Capes & Dankwerts (1965).

(c) Volume of binder as a percentage of the volume of the Particles e.g. Newitt & Conway-Jones (1958), Ganderton & Hunter (1971).

The use of volume of binder as a percent of the dry weight of the mix is more or less based on a convention. A liquid binder was thought to be located mostly in the inter-particulate voids, hence the reason for expressing its volume as a fraction of the inter-particulate pores. Therefore this was thought to be more related to binder uptake, moreso when the particles contain intra-particulate pores. Calcium phosphate particles were reported to contain pores (Ganderton & Hunter, 1971 and Eaves & Jones,

1973). Expression of the binder volume as a fraction of the volume of the dry mix was said to be more related to the surface area of the particles which take up the binder.

However the solubility of the particles in the binder complicates the criterion. Sherrington (1968) indicated that the amount of liquid binder needed to saturate the inter-particulate voids was much less when part of the particles dissolved in the binder.

Increased binder content increased the density and strength of granules formed (Ganderton & Hunter, 1971 and Opakunle & Spring, 1976). Increase in the viscosity of a binder increased the strength of granules prepared by extrusion (Mitsui, et al, 1970). Chalmers & Elworthy (1976) showed that increase in the concentration of PVP increased the granule strength and size; and increase in the volume of the binding solution but keeping the amount of PVP constant also increased the granule size but not the strength. Stanley-Wood & Shubair (1979) described the mechanism of starch mucilage linkage with dicalcium phosphate dihydrate (DCP) particles as the concentration of starch in the mucilage varied. With the aid of photomicrographs, they showed that 15 and 20% w/w mucilage due to cohesion formed globules on which the DCP particles were bonded but at 2% the particles were coated with a film of the binder which bind the particles together.

1.4.3.3 MASSING TIME

Changes in consistency of a powder mix during massing were found to be synchronous with the changes in torques

on the paddle of the mixer. Methods were therefore devised to monitor the changes in the powder mix with a view to determining instrumentally the end point during massing (Travers, Rogerson & Jones, 1975). Further investigations on massing end point by instrumental measurement of torque on the paddle of a planetary mixer were undertaken by Lindberg et al (1974) and (1977). They equipped the paddle of the mixer with a bar and wire with strain gauges forming a bridge circuit. The torque on the paddle was monitored via the bridge circuit and the changes occurring during massing were recorded. Lindberg (1977) used the instrumented paddle to determine the end point of massing an antacid powder mix with lactose. The changes in consistency of the mass were simultaneous with the changes in torque which rapidly increased at the predetermined end point. Layers of material building up at the sides and bottom of the bowl as massing continued interfered with the torque values and resulted in values which were unrepresentative of the picture in the entire mass. Increase in torque was obtained with increase in binder viscosity, in binder volume and in the mean size of lactose. It was also shown that the amount of binder which overmassed 150 μm size of lactose was inadequate for massing, 35 μm size.

Leuenberger, Beir and Sucker (1979) also presented a typical power consumption curve during massing. They divided the curves into five phases. During the first phase there was no significant increase in power consumption; the particles were just moistened. At phase two, with

either a further addition of binder or increase in massing time, the power consumption increased rapidly as the particles started agglomerating. In phase three a plateau of consumption from prior determination indicated the end point phase. In phase four, a pasty mass formed increased the power consumption and phase five decreased rapidly the power consumption denoting the breakdown of the doughy mass to a semi-solid mass with a longer massing or a further addition of the binder.

A long massing time increased densification of granules (Ganderton & Hunter, 1971). An increase in massing time in some binary blends were shown to increase granule size up to a limit beyond which longer massing decreased the granule size (Opakunle & Spring, 1976b).

Carstensen & others (1976) and Zoglio, et al (1976) described the distribution kinetics of water during massing. The part of the mix which first comes in contact with the water is excessively wet. Large agglomerates are formed from this excessively wet area. The binder then distributes as massing continued leading to presence of both small and large granules. Subsequently a state of equilibrium is reached with a fairly equal range of granule size. Zoglio, et al (1976) also described the situation when massing is prolonged. The equilibrium granular structure is destroyed leading to compact granules which cause a prolonged drying time of the granules. The prolonged massing also allows more of the soluble components in the mix to dissolve in the binder.

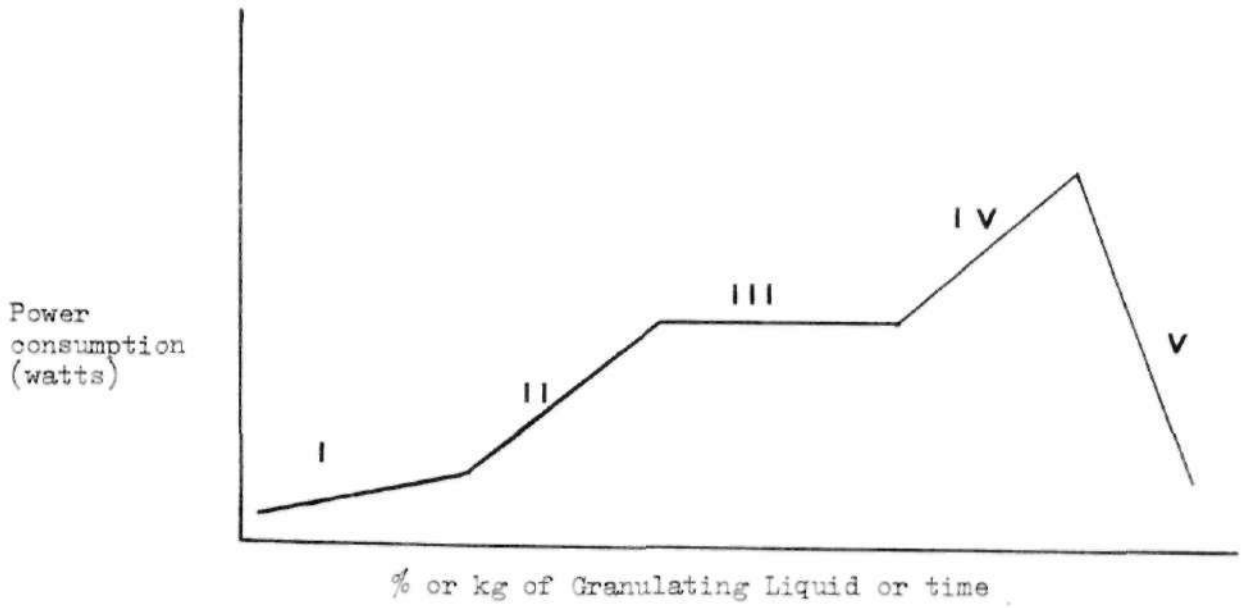


Figure 3: A sketch of power consumption curve during massing, according to Leuenberger, et al (1979).

The end point of massing as shown by Tiamraj & Baillie (1978) could be determined by measurement of the "unconfined, undrained shear strength" during the massing. The effect of massing a dry mix, of 0.4% w/w erythrosine in granular lactose, with 11% w/w starch from 10% w/w mucilage on the shear strength of the mass calculated from triaxial compression test was determined. The shear strength and the dissolution time for 50% erythrosine in the tablet were found to be inversely related to the massing time for up to 21 minutes. Therefore the desired release rate of a drug from the tablet could be determined by judicious use of the measure of the shear strength during massing.

Tiamraj (1979) introduced the use of a scanning electron microscope to study the microfabric nature of granules after various massing periods. An increase in the number of globular structures in the granules was directly related to the massing time. Possible explanations for this phenomenon were proposed. An earlier study showed the increase in contact angle of water on lactose as the concentration of starch/lactose mix increased. Therefore if the lactose "absorbed" free water in the starch mucilage, the concentration of starch/ lactose mix on crystal surfaces would increase the tendency for a higher angle of contact (non-wetting) and eventually to globule formation. It was shown that globules, although formed when starch was omitted in the lactose mix were markedly fewer in number.

1.5 DRYING OF PHARMACEUTICAL GRANULES

Ganderton (1968) had classified the drying to two methods which depended on the state of motion of the drying granules - static and methods involving movement of granules during drying.

1.5.1 STATIC BED DRYING AND DRYING MECHANISMS:

1.5.1.1 HOT AIR OVEN

The most common of these is tray drying in the oven. In this method, heated air in the oven is circulated over the trays by baffles or fans. The mechanism of drying involves the evaporation of moisture from the surface. The liquid is brought to the surface by capillary action.

Pharmaceutical granules, being usually porous, contain a complicated net work of interconnecting pores and channels with wide variations of cross-sections.

Across each pore is formed a meniscus which sets up capillary forces by the interfacial tension between the liquid and the solid. The capillary forces possess components in the direction perpendicular to the surface of the liquid. A driving force which results moves the liquid to the surface through the capillaries. The liquid evaporates from the surface.

The curvature of the meniscus depends on the cross-section of the pore, the smaller the cross-section of the pore, the greater the capillary force which could also result in flow of liquid out of the larger pores. Larger pores are then replaced by air.

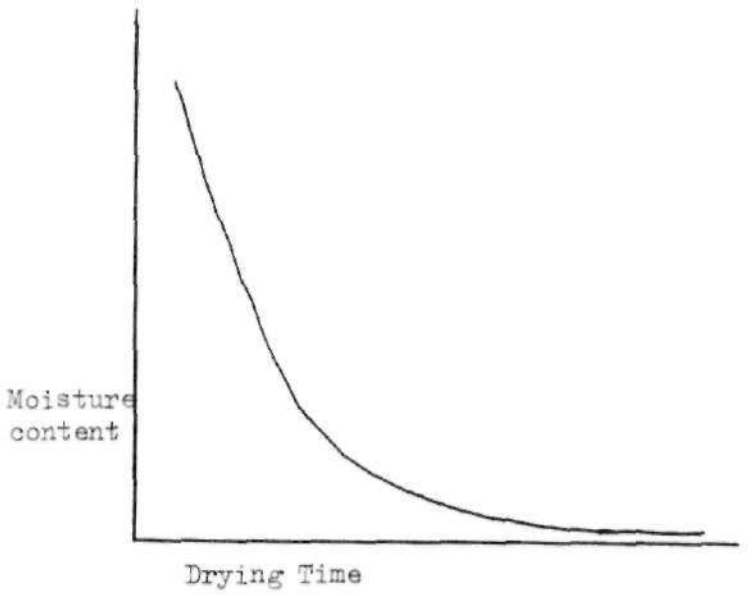
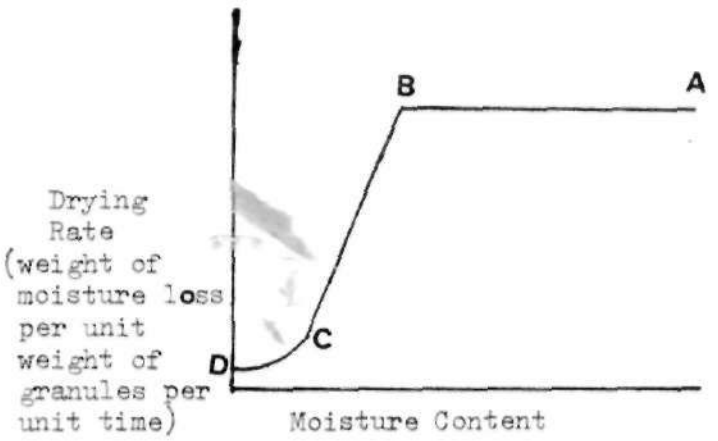


Figure 4: Drying curves of porous granules on tray.



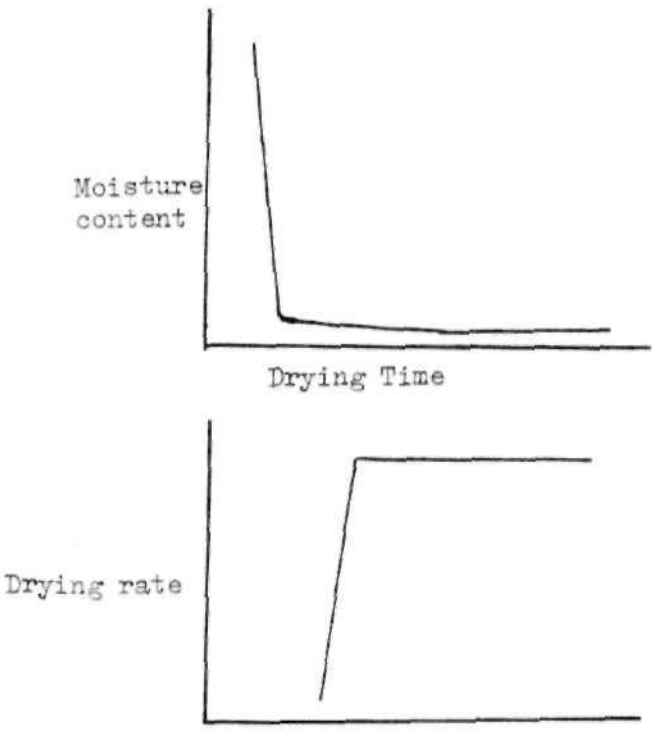


Figure 5: Drying curves of granules in a fluidised bed (after Scott, et al, 1963)

The drying rate is constant as long as the pores at the surface are laden with the liquid. The constant rate is denoted by AB in figure 4.

As the pores are progressively depleted with the liquid, the meniscus recedes into the bed. The rate of drying begins to fall as the rate of evaporation from the surface is not balanced by the capillary flow. The liquid is still in a continuous phase with air only dispersed in it. This stage of drying is the funicular state. The first falling rate denoted by BC is usually linear.

As drying proceeds more air replaces the pores evacuated by the liquid to form a continuous phase called the pendicular state. The interfacial tension in the capillaries breaks. The remaining liquid is isolated in corners and interstices of the pores. The rate of drying further decreases usually in a curved shape denoted by CD. The discrete patches or rings of the liquid during this stage is removed by evaporation brought about by conduction of heat through the solids in the bed.

For large sized pores as in a bed of wet sand, the effect of gravity which opposes the capillary flow to the top layer become more predominant. The constant rate period is shortened, as shown by AB in figure 6. If the container bottom is perforated or porous, the bottom surface is also a drying surface. The gravity and capillary forces acting downwards move the liquid to the bottom surface where evaporation also occurs. The constant rate is then as represented by ABB'.

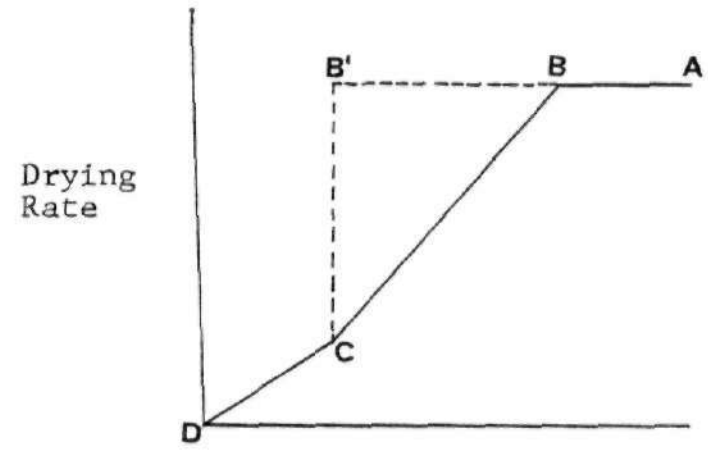


Figure 6 Drying Curve of Large-Pored Granules as in Sand

During drying of granules in a static bed, intra- and inter-granular migrations of solutes dissolved in the liquid occur. This is one of the causes of dosage non-uniformity in granules and hence tablets (see Section 1.6).

1.5.1.2 VACUUM OVEN

In vacuum tray drying, granules are dried in a heated vacuum oven. The liquid in vaporised form is continually removed by suction through a vacuum line. Otherwise accumulation of the unescapable vapour would prolong the drying even up to two days or more.

The recovery of expensive solvents is possible by collection of the vapour through the vacuum line and cooling although this sort of recovery is not unique to vacuum drying.

At a suitable temperature, generalised evaporation of the liquid even up to the boiling point can be achieved. The boiling point of liquids is greatly reduced under a vacuum. In a case like this, migration of components dissolved in the liquid is minimal. Travers (1975) obtained uniform salt distribution in layers of granules dried in the vacuum. He attributed the uniformity to flash drying into the intergranular voids.

1.5.1.3 FREEZE DRYING

Freeze drying is a form of vacuum drying in which the moisture is frozen at a very low temperature. The ice crystals are then sublimed.

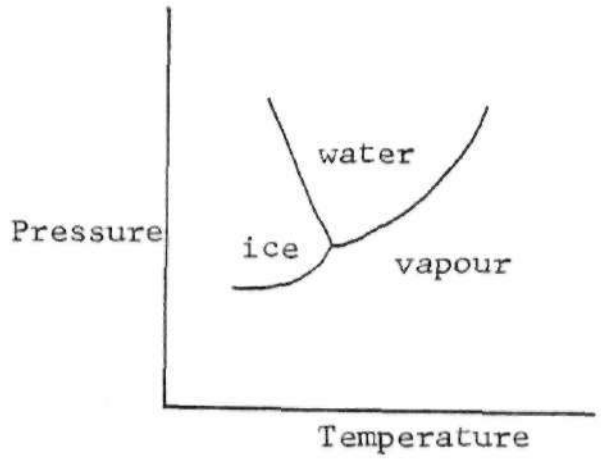


Figure 7 Phase diagram of water to illustrate the mechanisms in freeze drying

The drying principle in freeze drying is explained from the phase diagram of water above.

Under a vacuum and low temperature, the moisture in the granules are frozen to form ice. Keeping the pressure in vacuum, and increasing the low temperature of the granules, the ice sublimes into vapour. Therefore there is no migration of dissolved solutes in the binder by capillary forces.

1.5.1.4 INFRARED OVEN

Infrared radiation when absorbed appears as heat. Travers (1975) showed that much of the drying by this process occurred at the surface of the granule bed as a result of poor penetrating energy. Therefore this process maintained migration of binding solution to the surface by capillary forces.

1.5.1.5 MICROWAVE OVEN

Drying of granules by microwave (high frequency) radiation involves easy penetration into the granule bed causing evaporation of the solvent from within the entire granules and thus minimising solute migration. This was demonstrated by Travers (1975).

However drying by microwave radiation has not been widely used possibly due to some leakage of radiation from the oven which could cause some damages of sensitive body tissues such as the eye. In addition the high energy involved will probably result in the degradation of many drugs.

1.5.2 NON-STATIC BED DRYING

1.5.2.1 AGITATED DRYING

In agitated driers, e.g. as in tumble drying, the granules are constantly set in motion. This causes a disruption of capillary flow. While inter-granular migration of the binding solution is interrupted, intra-granular migration might still take place. In agitated drying, granules are dried more quickly as inner and wetter granule surfaces are continually exposed for evaporation.

1.5.2.2 FLUIDISED-BED DRYING

Kulling & Simon (1980) described the fundamental concepts, states of fluidisation, drying and humidity control in fluidised-bed technology as applied to pharmaceuticals. They also described the application of the technology to agglomeration of particles in one fluidised-bed unit — the fluidised-bed spray granulator. Coating or encapsulation of granules or even tablets and capsules could be employed using the fluidised-bed spray granulation as mentioned earlier (Section 1.2.1.4). The agglomeration and drying is a one-stage process.

Fluidised-bed drying of granules involves the passage of a heated gas blown at a high fluidising velocity through the bed of granules from the base. As the velocity of the forced gas is increased, the pressure drop across the bed also increases. At a certain velocity called the

incipient velocity the frictional drag on the particles equals the effective weight (actual weight minus buoyancy) of the granules. The fluidised gas pressure reaches the entrainment velocity when the granules are carried over or suspended by the fluidising gas.

Kulling & Simon (1980) described the states of fluidisation to include particulate fluidisation which is characterised by even concentration of granules per unit volume throughout the fluidised chamber. Particulate fluidisation is not common in practice in pharmaceutical granulations. The more common state is the aggregative fluidisation where the concentration of granules per unit volume fluctuates with time throughout the bed even with a constant fluidising gas velocity. Types of aggregative fluidisation include a boiling bed where some of the fluidised gas form bubbles whose size is approximately equal to the diameter of the granules. In a situation where the size of bubbles is larger than the granules but smaller than the cross-section of the fluidising chamber, a bubbling bed fluidisation results. The bubbles may form to occupy the entire cross-section of the chamber to form a slugging bed fluidisation. In this case the granules are separated in layers or slugs which continually build up from the bottom in succession and break. When the fluidised gas forms vertical channels through the bed, a channelling bed fluidisation occurs.

Most pharmaceutical granules in a bed are composed of granules with different sizes and densities. In such a system the fluidised granules may be classified to form

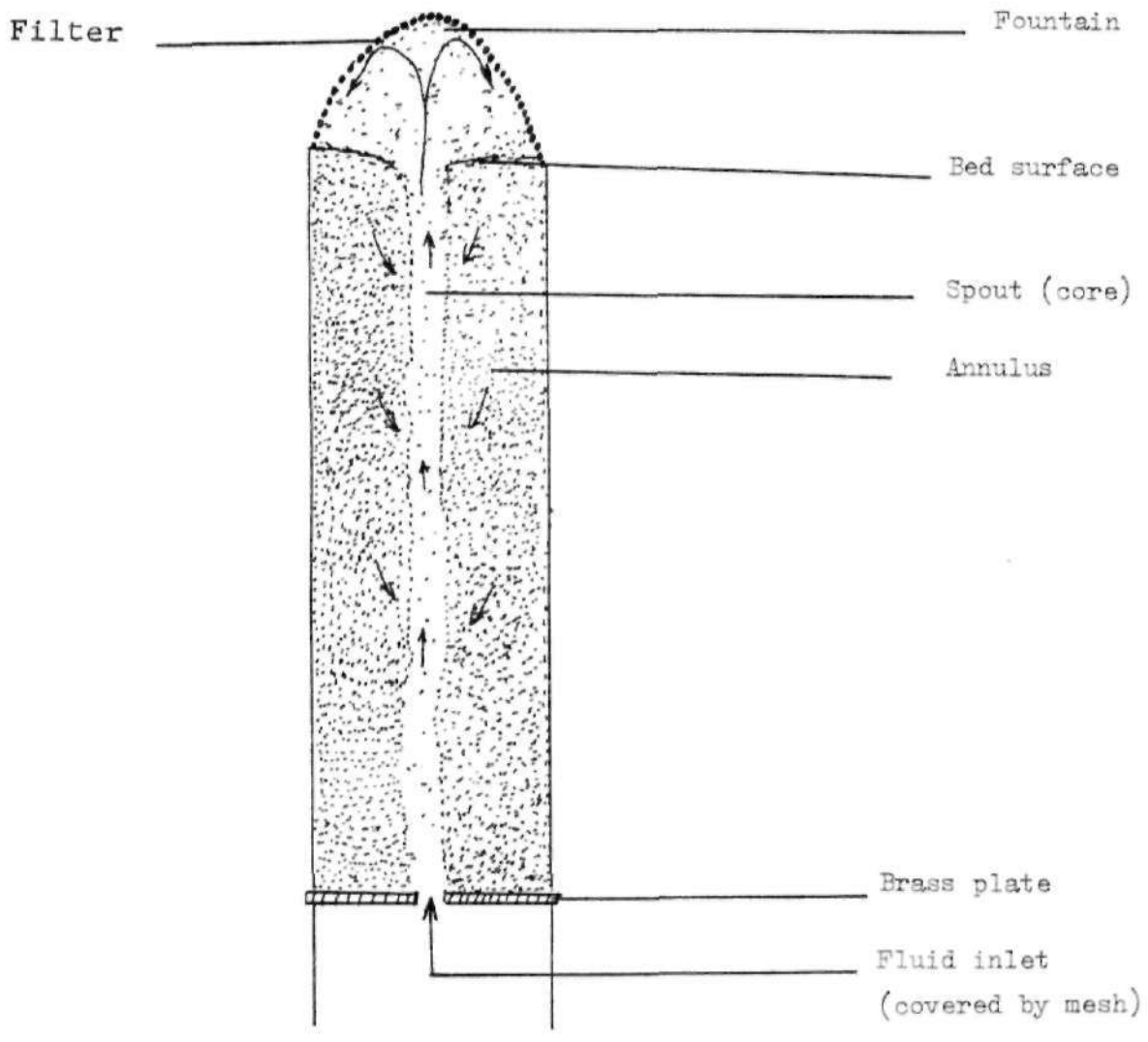


Figure 8: The spouted bed (after King & Harrison, 1980)

classifying bed where uniform concentration of the granules could only be present in a given horizontal cross-section.

A fluidising gas may be directed from an opening smaller than the horizontal cross-section of the bed to form a spouting bed (Kulling & Simon, 1980; Suciu & Patrascu, 1978; and King & Harrison, 1980). A spouting bed also forms when the hot gas is forced through the entire bed with a conical base (Suciu & Patrascu, 1978). At a high enough velocity the fluidising gas (or medium) passes through the core of the chamber carrying granules with it to form a fountain at the top (figure 8). The movement of granules at the sides of the vessel (annulus) is restricted because only a smaller portion of the fluidising gas passes through them. The annulus is building from the top from the fountain. By a downward flow due partly to gravitational forces, granules in the annulus are entering the core and spouted, and so on.

Some advantages of fluidised drying of granules include a possible automatic charging and discharging of granules, an extremely reduced drying time compared with drying in the hot air oven and the absence of caking of granules to containers or to themselves and thereby requiring no dry screening. A temperature profile during drying is possible by the use of a preprogrammed control of a temperature regulating device. Temperature probes of the inlet and outlet fluidising gas are available. An indication that the drying process is completed is shown by the decrease in the temperature differential between

the inlet and outlet fluidising gas. The temperature therefore could be maintained at an effective level only to be lowered after most of the surface moisture has been dried off. By a wet bulb effect the temperature of the drying granules is low even though the temperature of the fluidised gas is high. Therefore a judicious use of the temperature profile could permit the drying of thermolabile products.

In an ideal fluidised system, the granules are individually dispersed with no intergranular contacts. Therefore intergranular migration of solution is hindered. However intragranular migration of constituents, dissolved in the binder, to the granule periphery were reported by Travers (1975).

1.5.2.3 SPRAY DRYING

Spray drying involves the dispersion of a slurry or solution into droplets through spray nozzles or high speed discs directed counter-current or concurrent to a stream of hot gas. The droplets encasing the particles in the slurry or containing solutes in the solution are rapidly evaporated to form fine granules. As a result of the short time involved, intragranular migration to the periphery of granules might be minimal. Intergranular contacts during drying, if at all, is transient. Thus intergranular migration of soluble components is absent or negligible.

1.5.3 DRYING VARIABLES

Drying of limestone granules pan granulated with salt solution and dried at various temperatures ranging from 50 to 450°C showed that the tensile strength of the granules increased with the drying temperature until 300°C. Beyond 300°C, the strength decreased as a result of the force exerted by inner vapour pressure (Pietsch, 1969). A salt crust was formed as a result of capillary liquid flow during the early stages of drying (Capes, 1970/71). A simple equation was put up relating the strength of granules and the drying temperature (Capes 1971/72):

$$L = kD^n$$

L = granule strength

D = diameter of granule

k and n are constants related to the amount of salt present in the granules and distribution of the crystalline bonds respectively.

A higher temperature of drying increased the value of n; and k increased with salt concentration below the saturation point.

Shubin (1957) utilised radioactive tracer techniques to investigate the phase transition during the drying process. He passed a saturated solution of a radioactive salt through a bed of sand as shown in figure 9. Variation in the conditions of drying which affected the phase transition within and on the bed caused some deposition of the radioactive salt as the solution evaporated. The vertically moveable Geiger Counter

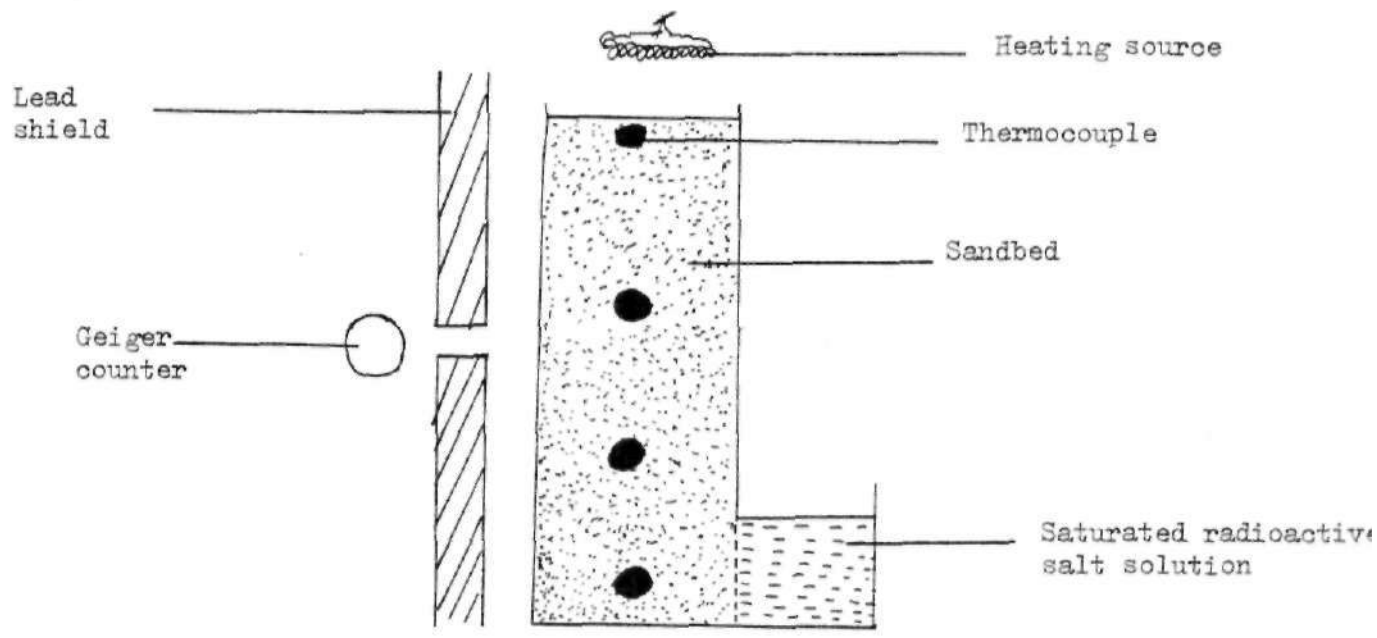


Figure 9: A set up of drying of a bed of sand by Shubin, 1957

recorded the concentration of the radioactive salt throughout the sand bed. He argued that the salt solution being saturated would not dissolve any deposited salt as capillary forces drive the solution towards the drying surface. However he did not indicate the possibility that the expected higher temperature towards the heat source at the top would subsequently cause unsaturation and thereby allowing the solution to dissolve some of the already deposited salt.

The effect of granule size on drying rate during the first falling rate was investigated (Opakunle, Bhutani & Bhatia, 1975). Unsaturation of the granule surface occurred at higher moisture content with large sized granules due to restricted capillary flow. The drying time was longer as the major part of drying was in the falling rate. For sulphathiazole granules which were more porous as a result of unbound moisture due to poor solubility, drying was quicker. Lactose granules, on the other hand, contained bound moisture resulting in less pores. Much of the drying was by diffusion with less capillary flow to the surface resulting in a longer drying time. The above authors and Peck, Max & Ahluwalia (1971) showed that if the drying rates and the critical points were known, the drying time from the initial to the desired moisture content could be calculated. Bhutani & Bhatia (1975) using different binders of varying concentrations and viscosities showed that drying rates were low with binders which reduced the porosity of the granules. They also described the phase transitions of liquid and mechanisms

during the drying process.

Scott, et al (1963a) compared fluidised drying to tray drying of pharmaceutical and showed the advantage of fluidised process to consist of a shorter drying time which was at least 7-8% of the tray drying time. Less floor space was required in fluidised drying; the high fluidised temperature did not reach the temperature of the granules as a result of wet bulb effect; and intergranular migration of solutes dissolved in solution was absent.

Granular motion and classification in fluidised drying and mode of diffusion of the moisture were investigated by Zoglio, Streng & Carstensen (1975). They indicated that small granules dried faster and became less dense while the large sized granules which were denser showed classification to the lower central zone of the drying chamber. The rate limiting step in fluidised bed, unlike rotary drying where it was water diffusion rate to the surface, was proposed to be external water vapour diffusion depending on the linear air velocities.

A slurry containing chlorpromazine hydrochloride, lubricant and colourant were spray dried to form free flowing fine granules with uniform colour and of narrow size distribution (Raff, Robinson & Svedres, 1961). Colour migration of dyes experienced during tray drying was absent.

1.6 DISTRIBUTION OF DRUGS IN GRANULES

Factors which influence uniform distribution of a drug in a dry mix before granulation depend on the particle size

and shape, particle size distribution, density, moisture content, static charges and cohesion. Others include the type and capacity of mixers and mixing time. A perfect mix of granules with glidants, lubricants or extra-granular disintegrants before compression could segregate during subsequent handling, for example, transferring the mix from the mixer to the hopper (Larson & Banker, 1976).

The choice of excipients for uniform mixing of a drug was shown by Johnson (1973) to affect the degree of mixedness. The mixture quality of the unmilled cyclopenthiazide was found to improve with wheat or maize starch in preference to lactose.

Content uniformity in tablets was highlighted as a very important factor of a satisfactory tablet (Burlinson, 1954). Moskalyk, et al (1961) urged for the need for more effective control in lighter tablets which usually contain potent drugs after observing that tablet weight became increasingly less uniform as the mean weight of the tablet decreased. Banker, Christian & Dekay (1958) pointed out the fact that variations in the amount of active ingredients in a set of tablets coupled with variations in the weight distribution of the tablets could lead to serious variations of drug content greater or smaller than desirable.

An attempt to tackle the problem of dosage variations in tablets from the drug distribution in granules prior to compression was initiated by Lachman & Sylwestrowicz (1964). They found a direct relationship between the concentration of a hydrophobic drug and granule size

but did not give full granulation details. This phenomenon was attributed to entrapment of the drug particles within the granules or adhesion of the drug particles to the bigger granules. The drug particles were said to be difficult to dislodge on account of the smaller relative surface area of the big granules. In preparing lynoestrenol tablets by using ethanolic solution for massing, Cox, et al (1968) proposed two possibilities for the variations. They were of the opinion that the handling before drying might result in segregation to the top to where the drug in solution migrated by capillary forces during drying.

Their second proposal was that the drug entrapped in the larger granules as such granules are expected to have wider pores.

Nicholson & Enever (1974) were led by this latter possibility to prepare primary granules of calcium sulphate which were sized to -22 + 44 mesh, -44 + 60, -60 +85, ∠85. The pure powder (3 μm size) was also used. The sized granules were massed and screened respectively. The -12 + 44 mesh granules from the respective batches were characterised. The porosities of the -12 + 44 mesh granules were found to increase with decrease in the primary granule size although this was not evident in the granules from the fines and the powder. The latter effect was said to be due to lack of penetration of all pores in the granules formed from the fines and the powder at the mercury intrusion pressure employed. Same sized granules but different porosities were sprayed with a solution of reserpine and instantaneously dried to

prevent capillary migration of the drug. On analysis they showed an increase in reserpine content with increase in porosity of respective granules.

Solute Migration :

One of the major factors affecting variation of drug content in granules prepared by wet granulation is migration of solutes including drug by capillary forces during the drying process. Chaudry & King (1972) found only 12% of sodium warfarin tablets compressed from granules prepared by wet granulation and tray dried, was within the official limits. Prior to drying, the drug was shown to be uniformly distributed in the granules. Therefore the non-uniformity after drying was apportioned to migration of solution to the drying surface by capillary forces. They used TLC techniques and observed the fluorescence, under ultraviolet light, of the drug in combination with certain additives. Calcium phosphate in the presence of alginic acid and not starch paste was found to inhibit migration of the drug as indicated by zero or negligible R_f values. They attributed the inhibition to affinity of the drug to the additive.

A comprehensive investigation of some factors affecting tablet mottling was carried out by March (1973). Armstrong, March & others (1973) showed that the reduced mottling of coloured tablets by the adsorption of some dyes by wheat but not by potato starch as claimed by Zografi & Mattocks (1963 and 1963a) was actually due to an elastic deformation. Granules deformed elastically during compression would prevent the exposure of the

reduced colour in granule interiors which would have been exposed by plastic deformation. However, the reduced mottling effect for potato and wheat starches was not appreciably divergent. Less mottling could be observed in coloured tablets produced with yellow (570 nm) or white tablets because the human eye is less sensitive to blue (400 nm) or red (700 nm) as colours less sensitive to the eye appear to reflect less light from them (Armstrong & March, 1974, and 1978). The underlying cause of mottling in coloured tablets is the migration of dye solution during drying from the interior to the periphery of granules. Minimisation of the migration was shown by Armstrong & March (1974a) to include such manufacturing variables as fluidised drying of the granules as opposed to tray drying where inter-granular migration is prominent. They pointed out that comminution during dry-screening could expose the colour deficient granule interiors. Smaller sized granules were shown to produce less mottling than larger granules as a result of a higher colour intensity in the larger surface area to volume ratio of the small granules and also the high colour variation in intensity for a longer distance (radius) through which migration occurs in larger granules. An increase in compaction pressure was also a manufacturing variable which was demonstrated to increase mottling as a higher degree of rupture of granules is eminent at higher pressures.

In their study of the effect of variables in formulation of coloured granules, Armstrong & March (1974b) showed that all the binders, viscous or not, used by them produced

mottled tablets to the same extent except acacia which, by virtue of its colour, produced less colour contrasts with the dyes. Granules produced from lactose and mannitol produced less mottling because of a less severe plastic deformation compared with the more brittle dibasic calcium phosphate granules. They showed that the use of dye lakes (binding of dyes to insoluble substrates, in this case aluminium hydroxide) instead of parent dyes could reduce mottling provided anionics and extremes of pH are absent to prevent leaching or elution from the substrates. Dibasic calcium orthophosphate has a high pH value and lactose was said to contain some traces of anionic impurities such as chloride.

Intragranular migration of PVP in binder solution massed with heavy magnesium carbonate was shown by Ridgway & Rubinstein (1971) to take place towards the granule periphery. They observed a synchronous decrease in PVP content from the periphery radially towards the centre with hardness and modules of elasticity.

In a subsequent report these authors (Rubinstein & Ridgway, 1974) showed that the PVP distribution was affected by drying temperature of the granules. At a higher drying temperature the PVP content was higher at the crust but constant towards the core as a result of "back diffusion" - diffusion of PVP from the more concentrated zones which was unnoticed during the predominant capillary transport. Also, using a poorly soluble diluent, heavy kaolin, Travers (1974) examined the intragranular migration of salt incorporated during massing as a solution. The granules were

dried by fluidisation and by vacuum tumbling. About 4% of the salt was lost in the fines of the fluidised dried granules as a result of fluidised abrasion at the initial stage of drying before the granules attained enough strength. Intragranular migration to the granule periphery were more pronounced in the fluidised than the vacuum dried granules. Flashing into the voids in vacuum drying was reported to have minimised migration (Travers, 1975). Migration in granules dried by hot air in the oven and by low frequency (infrared) and high frequency (microwave) radiations were studied (Travers, 1975). Convectional mass transfer in tray drying was slow, thus allowing a sustained solute migration to the drying surfaces. The low penetrating energy available in infrared radiation absorbed as heat also maintained migration. Microwave radiation being powerful penetrated easily and faster to cause evaporation of moisture directly from the voids, thus greatly minimising migration of solution. In vacuum drying heat was transferred by surface absorption of radiation whose intensity was proportional to the fourth power of absolute temperature. Therefore lower temperatures allowed migration. The lack of migration was related to flashing into the voids.

In the same report Travers (1975) also explored the effect of the drying methods on intergranular migration in beds with evaporation taking place from top and bottom of bed (the tray was perforated). Microwave drying produced a uniform intergranular salt content. There was a gradual increase of salt content to drying surfaces of granules dried in the oven. An even distribution, except for a

slight increase at the bottom layer of granules, was obtained in the vacuum drier. Infrared dried granules contained higher salt content at the middle layer with a higher depletion from the bottom.

In a subsequent report (Travers and Patel, 1979) using lactose as the diluent, the migration of salt initially dissolved in PVP solution was shown to be less than in equivalent granules in the previous reports because of a dilution effect of dissolved lactose as well as PVP which was also migrating along with the salt.

Massing time was shown to affect the distribution of drug in granules. Selkirk (1974) using 2% w/w borax in lactose massed with water as binder in a Z-blade mixer showed that massing time had a significant effect on borax distribution in the granules.

Three massing times 0.5, 2 and 10 minutes were considered. The massing time was directly related to the borax concentration in the big sized granules but inversely related to the content in the fines. Two minutes massing was shown to give the most fairly uniform distribution in the various sized granules. The high variations of borax content with 0.5 minute massing was explained to result from inadequate time for the binder to get evenly distributed. Ten minutes massing produced opposing variations in sized granules because of longer massing which allowed more dissolution of the components especially lactose which encapsulated the less soluble borax in the big sized granules. However, in another investigation, Selkirk (1976) this time using a planetary mixer showed that the

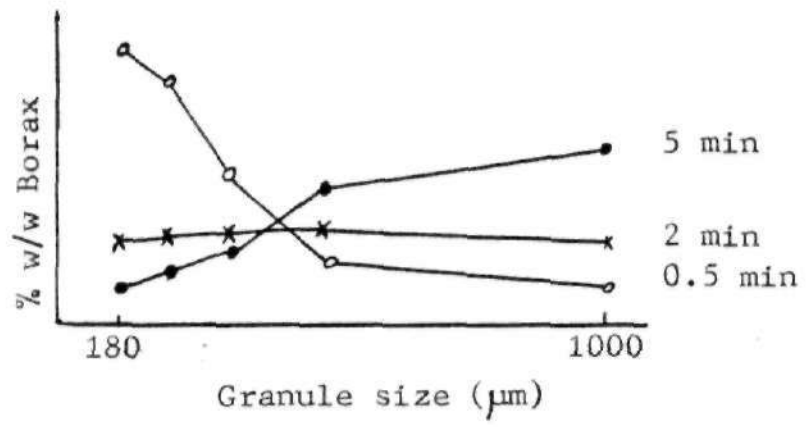


Figure 10 Effect of massing time on distribution in size of granules prepared by massing 2% w/w borax/ lactose dry mix with water (Selkirk, 1974)

same massing time variations did not significantly affect distribution of borax in the same formulation, indicating that uniform distribution was achieved even by only 0.5 minute of massing. The planetary mixer has less attritive forces necessary for dissolving the components in the more evenly distributed binder, thus leading to less migration of solutes and therefore less variations in distribution of borax.

In the same report, Selkirk (1976), showed that binder concentration had a significant role on borax distribution in the granules. 12% v/w water gave the least variation of borax content in the sized granules; 16% v/w gave the highest variations with 14% v/w binder giving intermediate values. In each case the highest borax concentration was in the intermediate sized granules. Granule size distribution was shown to be affected by the binder concentration which was directly related to the fraction of the big sized granules. The migration of the more soluble lactose to the granule periphery during drying was shown by the low borax (that is, higher lactose) content in the abraded fines.

The influence of the type and proportion of a binary mix, massing time (5, 15 and 60 minutes), binder concentration and initial particle size of lactose on distribution of the components throughout the granule sizes formed were investigated by Opakunle & Spring (1977). Lactose in proportion from 10 to 90% w/w were massed with boric acid (solubility 1:20), citric acid (solubility 3:5) and sulphanilamide (poorly soluble) respectively. It was shown that the

increase in massing time increased the lactose content in the fines with a more uniform lactose distribution in granules of up to 50% lactose than for granules massed with more than 50% w/w lactose. The effect of binder concentration was found to depend on the massing time as well as the proportion and type of components in the mix. Smaller lactose particles were shown to give a more uniform content than unfractionated or coarser lactose particles. Decrease in binder concentration gave higher variations of lactose content throughout the granule sizes. The larger sized granules in all blends were found to contain the expected content of lactose.

Very low concentration of a drug even though dissolved in the binder may preferentially remain in the crystal bridges holding the particles to form granules. This was a probable solution given by Whitaker & Spring (1977) who studied the distribution of sulphanilamide and the more soluble sulphacetamide sodium respectively in lactose using a concentration range of 0.02 to 2% w/w of the respective drugs as a dry mix before massing, or dissolved in the PVP binder solution either partly or wholly. The granules were dried in the oven and in fluidised bed respectively. They found no significantly marked difference ~~to~~ in these variables in the distribution of the drug in the sized granules except in the fines.

The fines from the lower dose of drug had higher content than the mean. They claimed that the concept of solute migration was insufficient to explain the results.

Dingwall & Ismail (1977) examined the distribution of four binders - PVP and gelatin as solution binders, and starch and methylcellulose as mucilagenous binders - onto glass spheres (0.8 and 0.4 cm diameter). More binder uptake in the smaller size of spheres was shown and the distribution of the mucilagenous binders was not uniform. The binder content on a unit area basis was about the same in the large and small glass spheres.

The influence of the particle size of the diluent and viscosity of the binder (PVP) on the migration of the water soluble drug, propoxyphene hydrochloride, were explored by Warren & Price (1977). The amount of drug migrating was shown to increase with a decrease in the particle size of the lactose. This was attributed to a decrease in the capillary size, with particle size decrease, which caused increased capillary forces for transportation of the solution to the drying surfaces. The decrease in particle size was thought to increase the exposed surface area of the particles, thus allowing more particulate contacts and decreasing the volume of pores. They showed that the decrease in particle size reached a limit below which capillary forces were unable to suck the binding solution which therefore dried by evaporation and vapour diffusion. Increase in viscosity of PVP solution (working viscosities were 1 to 1000 cps) was found to decrease migration and above 90 cps, no significant migration was observed. Drying temperature (40 - 80^{o}C) were found to give no significant effect on the drug migration.

Crooks & Schade (1978) investigated the distribution of 5% w/w phenylbutazone (poorly water-soluble) in lactose granules prepared by fluidisation using atomised 10% w/v aqueous PVP solution as binder. Despite the wide difference between the particle size of lactose and the drug, homogeneity of the drug was obtained after dry mixing by fluidisation, a technique earlier reported by Wurster (1959). The advantages of using larger sized lactose particles and micronised drug were the ease of fluidisation of the less cohesive larger particles and the necessity of increasing the surface area of a hydrophobic drug for bioavailability reasons. A smaller particle size of all the components would require more binder uptake by virtue of larger exposed surface area which would create some dissolution delays. Increase in binder flow rate increased the granule mean size as well as increasing uniformity of drug content in the granules. The uniformity was related to the big sized granules which through impacts caused a ball-milling action which broke the smaller drug rich agglomerates which were in turn picked up by the larger granules. The failure of granulation with 10% w/v PVP in absolute alcohol in place of water was due to lack of solubility of lactose in the alcohol necessary for formation of crystalline bridges.

Attainment of a pronounced uniform drug distribution in granules by employing molecular scale drug entrapment in polymer ~~lactices~~ latices was examined by Larson & Banker (1976). A colloidal polymer suspension (latex) of a linear anionic charged acrylic copolymer was mixed with the drug - metha-

pyrilene hydrochloride. The flocculated polymer laden with the drug was separated by a physical means, dried and size reduced to the required size of granules. The conventional massing and screening procedure was found to be very inferior to this new method as regards narrower granule size distribution band and high drug uniformity in the granules. However, a universal application of this method is not likely as many drugs are unable to be entrapped at the molecular level.

1.7 PROPERTIES OF GRANULES AFFECTING TABLET PROPERTIES

Granule properties, such as hardness, granule size distribution, intra- and inter-granular porosities, flow rate, surface characteristics e.g. sphericity, etc have been shown to affect the properties of tablets compressed from these granules.

Granule size and shape affect the filling of a tablet die for compression (Ridgway & Scotton, 1970). The mean contained weight was greater for regular than for irregular granules. A maximum die fill was obtained when the ratio of die diameter to granule diameter was about 20 regardless of granule shape. The size of granules was important in obtaining granules with maximum flow rates, into dies in fast moving tablet presses (Danish & Parrot, 1971). By using granules of sodium chloride and lactose a relationship between the flow rate and the diameter of the granules and the tablet die diameter was studied. The rate of flow was directly related to the diameter of the die and up to a limit inversely related to the granule size. Seidler (1977)

showed a much faster rate of flow with minigranules than those from massing and screening of a comparable size and size distribution.

A study of the pore structure of tablets compressed from both ungranulated powder and from massed and screened granules was undertaken by Selkirk & Ganderton (1970). The results showed a negligible pore size change over the compression pressures used for tablets made from the powder. The granules produced tablets with a wider pore size distribution at low compression pressures. A comparison of the pore structure of lactose tablets compressed from dry granulated granules and those from massing and screening was made (Selkirk & Ganderton, 1970a). Dry granulation affected the pore structure of tablets when the compression pressure of the slugs was high; when the granules formed from the slugs were large; and when the tabletting pressures were low. The tablet pore structure was destroyed with high compression pressures. Compression of mass and screened granules produced tablets with a larger pore structure which persisted even at higher compression pressures. Ganderton & Selkirk (1970) prepared sucrose and lactose tablets by massing and screening. The pore structure of the tablets were found to be dependent on the inter- and intra-granular porosities of the granules. Strong granules compressed under low pressures, granules of higher density and larger sized granules were shown to form tablets with a more open structure which were necessary for fast disintegration and dissolution rates.

Granules of lactose were prepared by massing and

screening and by massing and comminution (Selkirk, 1973). The former process produced irregular shaped granules compared with the smoother, more spherical, more closely packed and denser granules prepared by massing and comminution. The more open structure in granules by massing and screening was ascribed to the rubbing and screening action which tended to open up the wet mass. However, the tablet pore structure from both methods being the same showed that the packing of granules might not always affect the pore structure of tablets. A correlation between the dissolution constants and the porosity of granules was shown by Cruaud and others (1980) to exist for a high porosity value of the granules. The limiting process in this case is the penetration of water into the dislodged granules. This correlation holds as far as the value of the porosity is high.

Chaudry & King (1972) comparing the binding activity of starch paste and acacia on granules and tabletting the granules obtained harder tablets from the harder granules binded by acacia. The disintegrating time of the harder tablets were much longer.

The effect of type of starch as well as massing time and type of mixer during granulation on tablet dissolution rate was investigated by Tiamraj and Dingwall (1978).

They found that the state of equilibrium granular size as proposed by Carstensen and others (1976) and Zoglio, et al (1976) was found to be applicable to the dissolution rate of erythrosine from the tablet. The possible effect of variations in drug content from tablet

to tablet was eliminated by reference to total release of a water soluble dye used as a tracer. It was also found that for massing time from 15 to 30 minutes, the type of mixer - ZZ blade, planetary, lodige or ribbon blade - did not vary appreciably the dissolution rate of erythrosine from the tablet.

The concentration of a binder on granule surfaces was found by Seager, et al (1978) to be lower for granules prepared by precompression, moderate for wet massed granules and highest for spray coated granules. Consequently the friability and hardness of the tablets increased and decreased respectively, in the following manufacturing process: roller compaction, wet massing and then spray coating.

Walker, et al (1978) showed that the distribution of a drug throughout the cross-sections of a tablet might not always be homogenous even if the individual tablets contain the acceptable dose content.

The relationship between a low dose drug content in the various sizes of granules and the degree of dosage uniformity in the tablets is yet to receive attention in published work.

CHAPTER TWO

CHARACTERISATION OF MATERIALS AND METHODS

2. CHARACTERISATION OF MATERIALS AND METHODS

Introduction

The dissolution of an adequate amount of substance in solution as a binder, prior to massing, or of a considerable amount of some of the components of pharmaceutical mixed powders during massing, is an essential prerequisite for sustaining granule formation necessary for compression into good quality tablets. Therefore, the materials selected in this project as drugs and diluents are those with varying solubilities in the binder. The representative substances taken as drugs are organic chemicals in recognition of the fact that the majority of potent drugs currently in use are organic in nature. It is also well documented that the mean particle size of powders plays an important role in the physical characteristics of the resultant granules (Hunter and Ganderton, 1972; Opakunle and Spring, 1976; Jaiyeoba and Spring, 1979). In this regard, the same particle size of a particular drug or diluent used for this thesis was maintained constant except for those studies requiring particle size as the variable. Drugs or diluents of the same grade but not bearing the same batch numbers were subjected to particle size measurements to ensure that the mean particle size was the same.

All experimental procedures were kept constant while only one variable was introduced so that any difference in the results could be taken as a consequence of the particular variable concerned.

2.1 MATERIALS

The materials used were borax B.P. (Macarthys) and lactose B.P. (Serolac Brand, Whey Products Unigate Foods Ltd., Trowbridge, Wiltshire, U.K.). Borax was used to represent a moderately soluble drug which was easy to assay. Lactose is one of the common diluents in pharmaceutical use. Other materials of varying solubilities later introduced as drugs in the investigations were salicylic acid B.P. (Macarthys), sulphadimidine B.P. (Thornton & Ross Ltd., Linthwaite Laboratories, Huddersfield) and sodium salicylate B.P. (Macarthys). Diluents included on account of their poor solubilities as shown in the table (Table 1) were heavy magnesium carbonate B.P. (Thornton & Ross Ltd.), pure dibasic calcium orthophosphate (Koch-Light Laboratories Ltd., Colnbrock, Bucks, England) and Emcompress or dibasic calcium orthophosphate dihydrate (Kinsley & Keith Fine Chemicals Ltd., Croydon, England). Polyvinylpyrrolidone (PVP) with a molecular weight of approximately 44,000 (BDH Chemicals Ltd., Poole, England) was used as a binder for these two poorly soluble diluents. Normally a 15% w/v aqueous solution was used in the granulations although varying concentrations from 10% w/v to 25% w/v were used to investigate the effect of PVP concentrations in some of the granulations.

2.1.1 ESTIMATION OF SOLUBILITIES OF MATERIALS

The respective solubilities of the drugs and diluents used in this study were determined. 250 cm^3 of water was poured into a 600 cm^3 - beaker; for diluents other

than lactose, 450 cm^3 of water was used. An excess of the powdered material was added to the water and stirred adequately by a magnetic stirrer for two hours. The beaker with its contents was kept overnight in an oven maintained at 20°C. It was enclosed in a polythene bag to prevent excessive evaporation of the water. The saturated solution at the room temperature of 20°C ± 1 was obtained by filtration under vacuum with a filtration unit (size XX1104700; Millipore Corporation, Bedford, Mass., U.S.A.) fitted with a Nuflow membrane (size 47mm, Grade 0.45 micrometre, Code N47145; Oxoid Ltd., Southwark, London, U.K.).

The concentration of borax in the solution saturated with borax was determined by titrating a standardised hydrochloric acid (approximately 0.01M) with the borax solution diluted appropriately to a known volume with water (see section 2.5.4.1). For sodium salicylate, salicylic acid or sulphadimidine the respective saturated solutions were also diluted to known volumes whose concentrations were determined by ultraviolet spectroscopy (Section 2.5.4.2).

The concentrations of the diluents - lactose, heavy magnesium carbonate and dibasic calcium orthophosphate - in the respective saturated solutions were estimated by a modified gravimetric method. This was achieved by massing a known volume of the saturated solution with a powdered material which is not prone to form residual, equilibrium bound moisture. Opakunle and others (1975) have shown that soluble powders could form bound moisture

contents while poorly soluble ones do not. Massing of the saturated solution was found imperative when it was observed that evaporation of water in a solution co-saturated with borax and lactose formed a "skin-like" crust on the surface which retarded further evaporation of the moisture. The massed material formed granular particles with the solution to form a considerable increase in the exposed surface area available for complete evaporation of the moisture.

One kilogram of pure dibasic calcium orthophosphate powder, dried to constant weight in a vacuum at 70°C, was massed with 400.0 cm^3 (but 200.0 cm^3 for lactose) of the saturated solution for 3 minutes in a planetary mixer (Model AE200, Hobart Manufacturing Co. Ltd., London, U.K.) which was weighed empty with its paddle on a top loading balance (Sauter Toppan, Type SD6000/0.1g, August Sauter KG, Ebingen, W. Germany). The mixer with its paddle and its contents were dried for 24 hours in a hot air oven at 60°C, and for a further 24 hours at 70°C in a vacuum oven (Thermostat Vacuum oven; Townson & Mercer Ltd., Croydon, England) with the shelves removed to facilitate entry of the mixer.

The difference in the weight of the mixer, paddle and the dried pure dibasic calcium orthophosphate gave the weight of the material saturated in the given volume of the solution from which the solubility was calculated. The values of the solubilities were as presented in Table 1.

Material	Solubility	Density ($g.cm^{-3}$)
Borax crystals	1:20	1.73
Borax crystals dried in vacuum	1:15	
Borax saturated along with lactose	1:10	
Salicylic Acid	1:550	1.44
Sulphadimidine	1:1897 @ 20°C 1:680 @ 30°C	1.45
Sodium Salicylate	1:1	1.58
Lactose	1:6	1.53
Lactose saturated along with Borax	1:3	
Heavy Magnesium Carbonate	1:3330	2.26
Pure Dibasic Calcium Orthophosphate	Practically insoluble	2.92

Table 1 SOLUBILITY AND DENSITY OF MATERIALS

2.1.2 DENSITY MEASUREMENT OF MATERIALS

The volume occupied by a known weight of a material (powder or granules) was measured by Beckman air comparison pycnometer (Model 930, Beckman Instruments Ltd.) and the true density of the material was then calculated. The air comparison pycnometer operates on the principle of air displacement at 1-2 atmospheres of pressure. It is accurate to 0.01 cm^3. The respective densities of materials are as presented in Table 1.

2.1.3 PARTICLE SIZE MEASUREMENT

The weight of material occupying 1 cm^3 (numerically equal to density) was used to measure the mean particle size of material with a Fisher Subsieve Sizer (Model 95, Fisher Scientific Co., Pittsburgh, P.A., U.S.A.). The Fisher Subsieve Sizer measures particle size up to 50 micrometres. For bigger average mean sizes of powdered materials, larger than 50 micrometres, size analysis by sieving was undertaken.

2.1.4 PARTICLE SIZE REDUCTION AND PARTICLE SIZE ENLARGEMENT

Drugs and diluents not subjected to size reduction, enlargement or size fractionation by sieving throughout the investigations were salicylic acid, sodium salicylate, lactose and heavy magnesium carbonate. Their mean sizes were as marketed by the suppliers or manufacturers.

Drug or diluent		Mean particle size (μm)
Salicylic acid powder		8.3
Sodium salicylate powder		8.7
Sodium salicylate crystals (flakes)		28.8
Lactose "Unigate grade 170" size		13.5
Lactose granules "DMV" grade (De Melkindustrie Veghel, Holland)	45/50 mesh	350
	80 mesh	180
	150 mesh	105

Borax crystals were size reduced, Emcompress granules were fractionated and sulphadimidine powdered particles were enlarged as described below.

Borax Crystals:

The mean particle size of the crystalline borax was 37 micrometres. The crystals were dried in the thermostat vacuum oven at 70°. After reconnection of the vacuum line for some five hours the dried crystals were sieved. The following size subdivision was obtained.

Mesh number	Weight of crystals retained on mesh	
	Gram Weight	% Weight
60	19.5	3.5
85	94.3	17.0
pan	439.4	79.5
	553.2	100.0

The mean particle size of the crystals retained on the pan was 30 micrometres as measured by the Fisher Subsieve Sizer.

The fine crystals were milled with the vibratory ball mill (Griffin & George Ltd., U.K.) to the desired size by sampling intermittently and measuring the mean particle size of the sample.

The mean particle size of borax in micrometres used in the investigation were as follows: 250, 180, 37.0, 30.0, 10.0, 7.2 and 4.0. Apart from investigations where different particle sizes of borax were required as a variable, the 10 micrometre size was used throughout in borax/lactose granulations.

Dibasic Calcium Orthophosphate:

There were two particle sized granules of dibasic calcium orthophosphate, the pure dibasic calcium orthophosphate 2.4 micrometres size which was slightly acidic, and Emcompress, dibasic calcium orthophosphate dihydrate (-40 + 200 micrometres). The latter, coarse particles, were used in granulations where the particle size effect was considered. Emcompress is slightly alkaline.

The coarse Emcompress particles were sieved into size fractions with Fritsch Analysette Sieve Shaker as follows. 200 grams were sieved at settings of 8 amplitude, permanent vibration mode and shaken for 15 minutes in sieves arranged in mesh descending order of 315, 200, 160 micrometres and pan. Each size fraction was resieved once more. The size fractions were stored in polythene bags. Some of the size unfractionated Emcompress was also stored in a similar manner.

Sulphadimidine:

The mean particle size of sulphadimidine available was 8.6 micrometres. It was necessary to obtain particle sizes larger and smaller for use in investigations requiring the particle size of sulphadimidine as a variable. This was brought about by dissolving the sulphadimidine in a solution of sodium hydroxide to form sulphadimidine sodium. The solution was heated to a fixed temperature on a preset hot magnetic plate and stirred. Hydrochloric acid was added from a separating funnel. The sulphadimidine precipitate was obtained by filtration. The particle size of the sulphadimidine which precipitated from the reaction depended on the temperature of the sulphadimidine sodium solution. The higher the temperature the coarser was the particle size.

Sulphad.	+ Sod.Hydrox.	⟶	Water			
278.3g	40g		+			
34.7875g	250cm^3 0.5M		Sulphad.Sod.	⟶	Hydrochl.Acid	Sulphad.
			300.3g		36.5g	278.3g
			37.5375g		250cm^3 0.5M	34.7875g
						+
						Sod. Chlor.

104.4 grams of sulphadimidine was weighed and 750 cm^3 of 0.5M sodium hydroxide solution was added and stirred until all the sulphadimidine dissolved. The solution was filtered.

250 cm^3 of the solution was poured into each of three one-litre beakers and stirred on a magnetic hot plate. During stirring the temperature of the liquids in the beakers was maintained at 25°C, 50°C and 85°C respectively. 0.5M hydrochloric acid was added to each beaker at the rate of one drop per second.

It was observed that while the precipitates formed in the two hot beakers were fine, the precipitates in the beaker maintained at 25°C produced dispersing lumps. The precipitates of sulphadimidine were filtered off respectively, washed with four 200 millilitre-aliquots of distilled water one after the other and kept to dry in the hot air oven at 60°C over the weekend.

The mean particle size of the sulphadimidine were 4.4, 14.6 and 17.6 micrometres from solutions kept during the reaction at 25°C, 50°C and 85°C respectively.

2.1.5 ESTIMATION OF DISSOLUTION RATE OF BORAX AND SODIUM SALICYLATE PARTICLES

Preliminary studies for the dissolution rate of borax and sodium salicylate particles enclosed in a semi-permeable membrane tubing (Visking Tubing, Scientific Instrument Centre Ltd., London W.C. 1, England) immersed in water at room temperature by the up and down movements of a tablet disintegration apparatus (Manesty Machines Ltd., Liverpool, England) proved unsatisfactory. Some of the borax crystallized in the tubing during the process.

The alternative method adopted was to add a pre-determined amount of water to the particles in a 100 cm^3 conical flask stoppered and shaken by the minimum vibrations of a flask shaker (Griffin & George Ltd., Great Britain). Samples of the solution were withdrawn at regular intervals and filtered.

Since the solubility of borax is dependent on the concentration of lactose in the solution (Figure 11), it was found necessary to use appropriate amounts of borax in

admixture with lactose in order to dissolve both to saturation. Their solubilities in a co-saturated solution were found to be two times their respective single component solubilities. These were 1:3 and 1:10 for lactose and borax, respectively, in a cosaturated solution. Therefore 5.0 and 16.7 grams of borax and lactose particles respectively were weighed in the conical flask. 50 cm^3 volume of water was added and stoppered. The shaker was started. Every minute 5.0 cm^3 of the solution was siphoned through a Millipore filter unit fixed to the nozzle of the 10 cm^3 syringe. This volume was delivered into a volumetric flask.

The 5.0 cm^3 volume was replaced into a conical flask through the syringe with the filter unit attached in order to wash off any undissolved borax particles trapped during sampling. The results of the rate of dissolution are shown in Figure 18. For the estimation of the dissolution rate of sodium salicylate particles, the presence of lactose was not necessary since the amount dissolved was independent of admixture with lactose. The solubility of sodium salicylate is 1:1. Therefore all of it is capable of dissolving in a 2% w/w dry mix with lactose massed with 14% v/w water without being saturated.

5.0 grams of sodium salicylate was weighed in the conical flask and subjected to all the procedures as for borax described above.

2.2 PREPARATION OF GRANULES

The concentration by weight of drug material, except when investigating the drug concentration effect, was 2%.

The size of each batch was 500 g, and 750 g when using pure dibasic calcium orthophosphate diluent as a result of a higher true density.

2.2.1 BINDER AND BINDER VOLUME

After some preliminary trials, the necessary binder concentrations for borax/lactose granulations were observed to vary from 12% to 18% v/w of water with 18% presenting an overwet state. Granulation for lactose alone by massing and screening required in the range of 15.3 to 33.7% v/v (that is 23.4 to 51.6% v/w) of water with 51.6% v/w being overwet (Ganderton & Hunter, 1971). The difference appears to result from the mutual increase in solubility of borax and lactose in solution (Figure 11).

It is apparent that a more soluble material requires less binder as much of the material dissolves and increases the saturation of the voids between the particles. The working concentration of water as a binder for borax/lactose granulations selected was 14% v/w with a five minute massing time. In some of the experiments, the binder contained dissolved borax or lactose or both up to a saturated solution. A saturated solution was formed at room temperature by stirring excess of the material(s) in water for at least two hours and keeping overnight to ensure an equilibrium state. The solution was filtered using filter funnel under gravity to remove the excess (undissolved) material(s). The amount of solute(s) dissolved to form the binder was calculated to form part of the dry weight of the batch.

Figure 11 Effect of concentration of lactose in solution on the solubility of borax in the solution

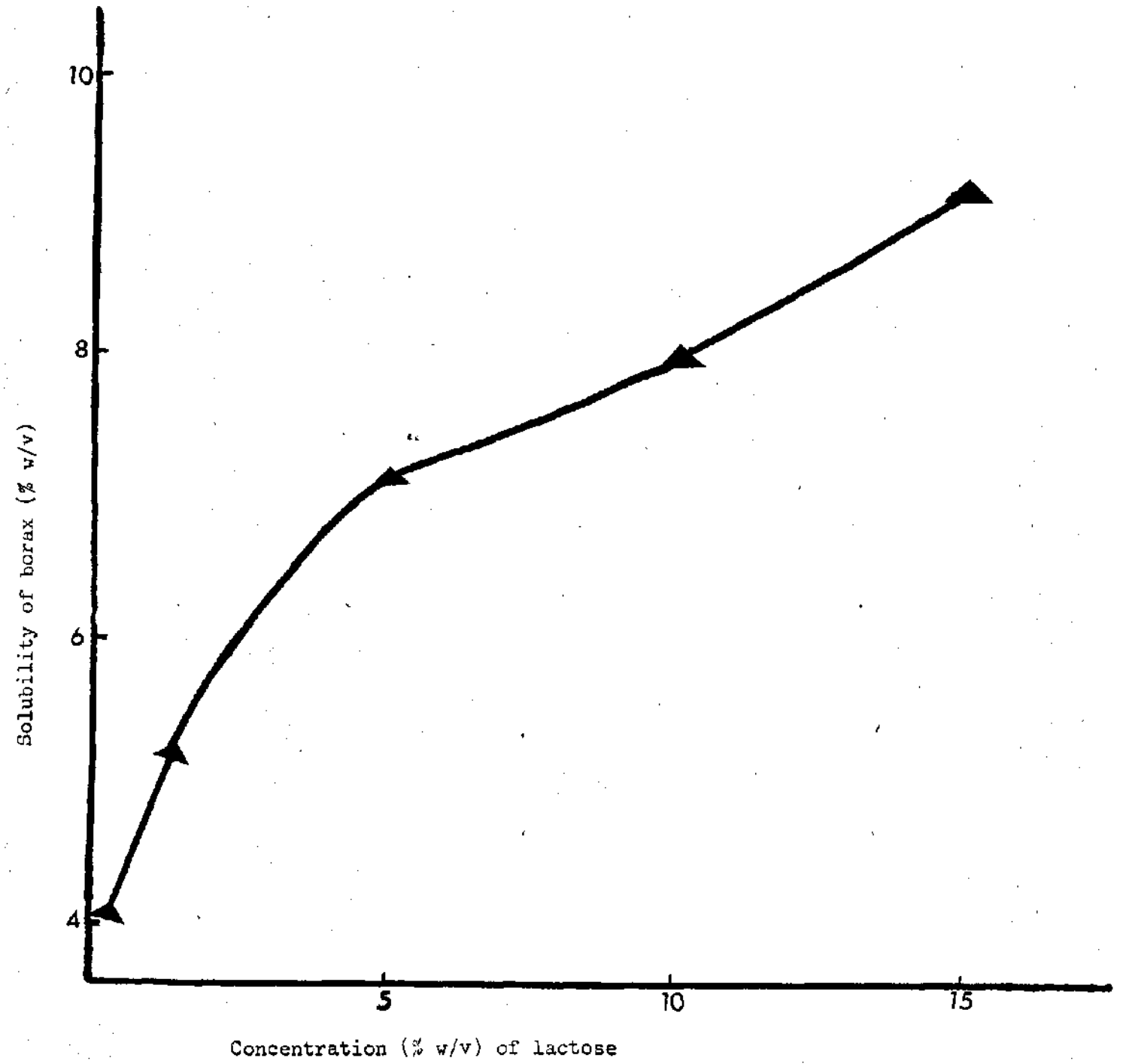
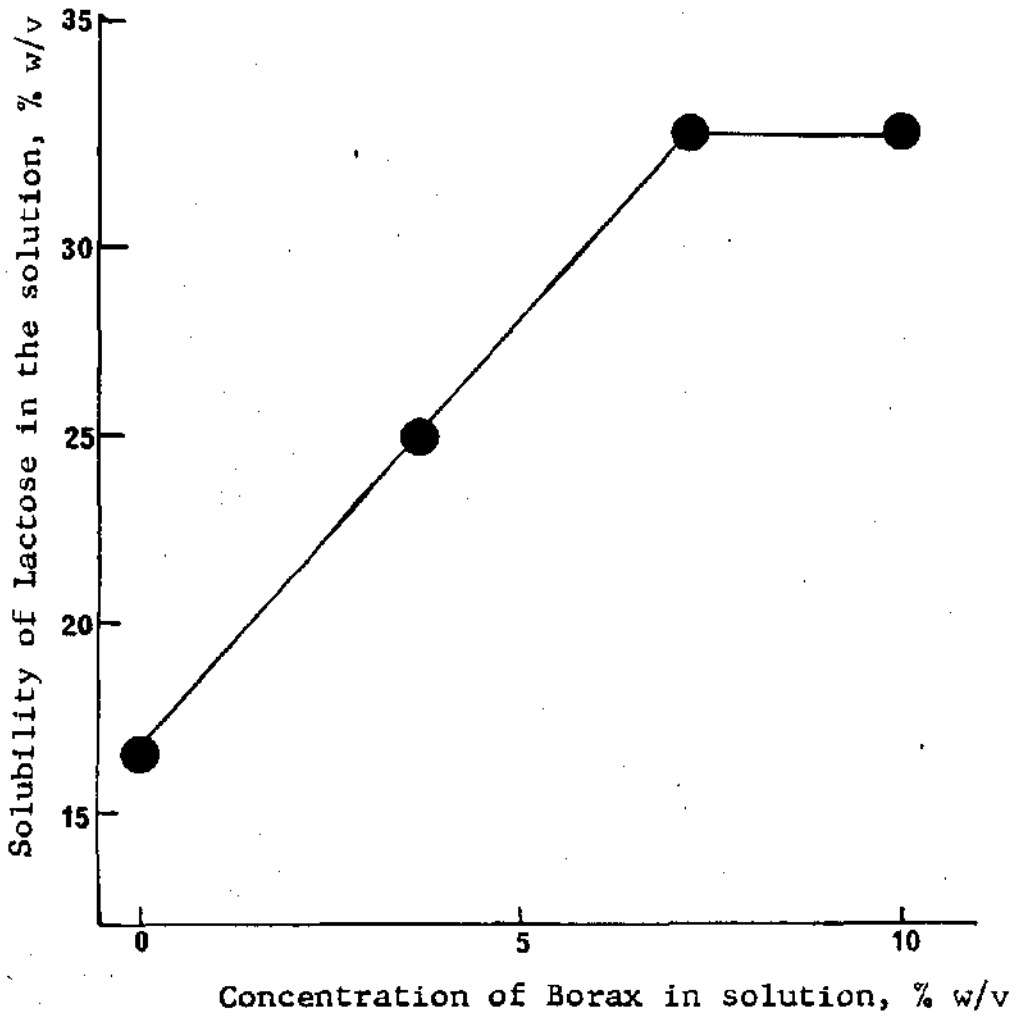


Figure 11(b) Effect of concentration of borax in solution on the solubility of lactose in the solution.



The volume of binder used for massing other powdered materials was that which, after 5 minutes massing, gave the same wet consistency of massed powders as that for 14% v/w for borax/lactose granulation (Table 2).

Drug/Diluent	Binder and Concentration	
Borax/Lactose	water	14% v/w
Salicylic Acid/Lactose	water	20% v/w
Sodium Salicylate/Lactose	water	14% v/w
Sodium Salicylate/h.m.c.	water	60% v/w
Sodium Salicylate/h.m.c.	15% w/v PVP	45% v/w
Sodium Salicylate/d.c.o.	15% w/v PVP	33% v/w
Sulphadimidine/Lactose	water	20% v/w
Sulphadimidine/h.m.c.	15% PVP	47% v/w
Sulphadimidine/d.c.o.	15% w/v	33% v/w

Table 2 WORKING CONCENTRATIONS OF BINDERS FOR POWER MIX OF MATERIALS

h.m.c. = heavy magnesium carbonate

d.c.o. = pure dibasic calcium orthophosphate

Preparation of PVP solution as a binder

The required weight of PVP was weighed in a beaker on the August Sauter loading balance. About half of the required volume of water was added and kept overnight as PVP is known to have a slow dissolution rate. This was transferred to a measuring flask and the volume was made up with water.

2.2.2 DRY MIXING AND MASSING TIME

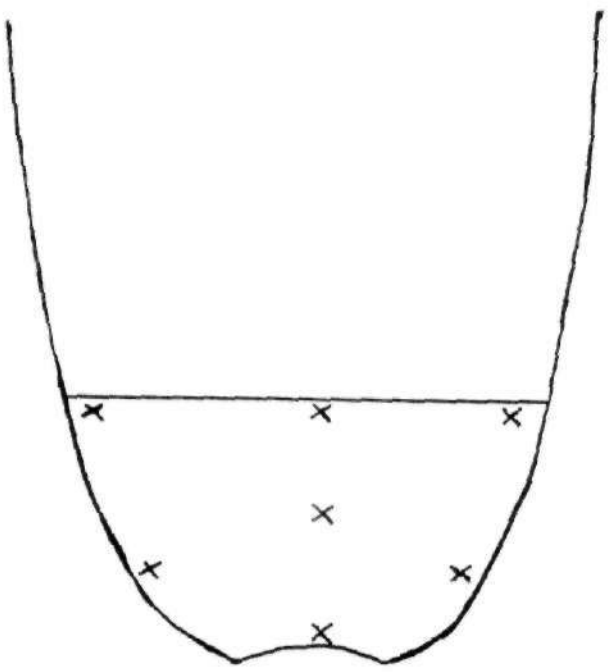
The mixer used for dry mixing and massing was a planetary mixer (Model AE200, The Hobart Manufacturing Co. Ltd., London). The frequency of the planetary motion of the paddle was 50 per minute. However, it is possible that this speed could be reduced slightly as massing proceeded as a result of increase in torques (Travers, Rogers & Jones, 1975). To achieve a thorough mix during dry mixing and massing, the mixer was stopped, after every 2 minutes, to scrape in the sides and bottom with the paddle of the mixer.

Choice of dry mixing time

The diluent was sieved through 500 micrometre mesh to exclude lumps and weighed in the bowl of the mixer tared on the top loading balance. The drug was weighed with Sartorius Digital Analytical balance (Type 2442, Sartorius-Werke GMBH Gottingen, W. Germany) and added to the diluent.

Dry mixing time of 2, 5 and 10 minutes each for the three batches was undertaken. About 2 g sample from each batch, after the dry mixing was taken from the positions marked X in the sketch (Figure 12 below).

Figure 12 Positioning of samples taken after dry mixing or massing from the mixer



The degree of mixing M was calculated by the method of Ashton and Valentine (1966).

$$M^2 = \frac{\log(\sigma_o^2/\sigma^2)}{\log(\sigma_o^2/\sigma_r^2)}$$

where σ_o^2 is the variance of an unmixed sample

σ_r^2 of randomly mixed sample

and σ^2 of sample under investigation

M is 1 for a completely random mix and zero for an unmixed material.

Mixing Time (minutes)	Degree of Mixing
2	0.81
5	0.96
10	0.89

Therefore 5 minutes mixing period was chosen. The five minutes mixing time was found adequate also for other combinations, e.g. sulphadimidine in pure dibasic calcium orthophosphate gave a 0.999 degree of mixing for seven samples taken similarly.

A massing time of 5 minutes was also chosen as the mass after the 5 minutes massing appeared homogenous.

2.2.3 CONCENTRATION OF DRUG IN AGGLOMERATES DURING MASSING

Estimation of the dry weight concentration of drug in the agglomerates during massing was undertaken. Agglomerates in this sense refer to the massed lumps formed by the incipient binder liquid with the dry mix which break down

during massing to form an equilibrium granular state.

About 30 grams of the dry mix accurately weighed were sampled randomly to determine the actual mean content of the drug in the dry mix. Lactose was used as the diluent (98% w/w) and borax, sodium salicylate or sulphadimidine as the drug. 14% v/w (but 20% v/w for the dry mix containing sulphadimidine) of the binder was added to the dry mix. Samples of the agglomerates, each about 30 grams, were hand-picked after massing time of 0, 0.5, 1, 2 and 5 minutes. Sampling by the hand-picking techniques was preferred to wet sieving. The agitation in the sieving could cause snow-balling of the drier particles to the agglomerates. In addition, the agitation causes some of the moderately wetted dry mix to form loose agglomerates which would be difficult to distinguish from the original agglomerates. The samples were dried for two days in the hot air oven at $60^{o}C$. After four hours of drying the clay-like mass of the samples taken at the start and after 0.5 minutes of massing were scrapped from the wall of the containers and broken down to ensure complete drying.

The analysis of the drug in the dried agglomerates and rest of mix was undertaken using the whole sample. This will eliminate sampling errors which might arise from migration of dissolved solutes during drying or segregation of granule sizes during subsequent handlings. The whole weight accurately weighed was dissolved in water (or 0.1M NaOH for sulphadimidine) and diluted to 500 cm^3 with water. For borax the standardised hydrochloric acid

was titrated with 15.0 cm^3 of the solution. For analysis of the other drugs, 15.0 cm^3 was pipetted and diluted appropriately for u/v spectrophotometric analysis (section 2.5.4.2).

2.3 GRANULATING PROCEDURES OF DRY MIX FOR NORMAL OR EXCESSIVE MASSING

A typical formula for borax/lactose granulation is presented as below:

Borax	Mean size 10 micrometres	2% w/w 10.0000 g
Lactose	Mean size 14 micrometres	98% w/w 490.0 g
Water		14% v/w 70.0 cm^3

The lactose was sieved to remove lumps through a sieve of 500 micrometre mesh. The sieved lactose was added to the bowl of the planetary mixer set and tared on the sauter top loading balance. The amount of borax accurately weighed was added to the lactose. The container in which borax was weighed was completely cleared by wiping into the mixer bowl with part of the weighed lactose.

Dry mixing in the planetary mixer was undertaken for 5 minutes. The sides and bottom of the mixer were scraped with the paddle of the mixer after two and four minutes of mixing. The whole volume of binder (water) was added randomly on top of the dry mix, taking care to avoid wetting the sides of the bowl during this addition. A five minute massing period exclusive of the time used for scraping the sides and bottom of the bowl (after two and four minutes) was employed for a normal massing. The wet mass was force screened with the Erweka reciprocating granulator fitted with a sieve of 1680 micrometre mesh

as described below (section 2.3.1). For excessive massing, the top of the mixer bowl was covered with a designed conical shaped polythene bag which did not interrupt the massing.

After thirty-five minutes of massing a pasty mass was formed which was stuck to and rotating with the paddle. The mass was scraped off the paddle after 35, 45 and 55 minutes of massing. The total massing time was 60 minutes. The plastic mass was forced by hand through 1680 micrometre mesh sieve. To avoid excessive "worming", the wet granules were shaken off the sieve as soon as they were formed through the sieve. This was also the procedure used for wet screening of the pasty mass formed by massing with 18% v/w water for five minutes. The granules were dried to a constant weight in the hot air oven at 48°C. They were sieved through 1200 micrometre mesh of sieve with difficulty because of the presence of significant amounts of oversize and caked granules.

2.3.1 WET FORCE SCREENING AND DRY SCREENING OF GRANULES

The wet mass after the 5 minutes massing was placed in a reciprocating granulator (Type FGs, Eweka Apparatebau-GMBH Heusenstamm Kr. Offenbach, W. Germany) connected to the mains via a variable voltage regulator (Variac 0-270V, Zenith Electrical Co. Ltd., London). The output was set between 80 to 100V and the granulator speed set at 1. This resulted in 50 reciprocations per minute. 1680 micrometre mesh screen fitted in the granulator was used for wet force screening but 1200 micrometre mesh was used for dry screening. The reciprocating speed was adjusted

by the Variac rheostat for dry screening to give a minimum speed possible so that as little as possible of granules are abraded or broken. This would give granule size analysis representative of the variable.

2.3.2 RESCREENING OF GRANULES DURING DRYING IN THE OVEN

In some of the investigations, it was desired to dry the granules in an oven for a specified time and then re-screen the granules through a specified mesh size after drying for the desired time.

Samples of granules were taken to fill plastic jars each 100 cm^3 volume and height 7.0 cm during the force wet screening, just before the rescreening and during the rescreening. These were dried to constant weight in the hot air oven, vacuum oven or freeze drier as specified.

The rescreened granules left on the tray were dried in the oven to constant weight. Weighing of the granules and tray and of the granules and plastic jars were done before drying, just before re-screening, after re-screening and after complete drying. This allowed the moisture content at the various stages to be calculated.

2.4 DRYING OF GRANULES

This was specified for each investigation. The thermostatic hot air oven set at $48^{o}C$ was used.

The drying tray used measured 49 cm x 32 cm. A smaller tray measuring 29 cm x 23 cm when used contained the weight of granules dimensionally equivalent to that of the larger tray. The smaller tray was employed in

vacuum drying, freeze drying and hot air oven drying, the latter, for automatic plotting of drying rates.

Thick-bed drying of granules was simulated by filling a plastic jar of 100 cm^3 volume and 7 cm height with random samples of granules immediately after wet force-screening.

2.4.1 MEASUREMENT OF DRYING RATES OF GRANULES IN THE HOT AIR OVEN

A knowledge of the drying rate of the granules is essential in predicting the drying time. The moisture content of rescreened granules during drying, as would be seen later, is an important factor which affects the distribution of a drug in granules.

The measurement of the drying rates of granules was carried out by adapting an Instron Universal Testing Instrument (Model TM-M, Instron Corporation, Canton, Massachusetts, U.S.A.). This method allowed the drying curve plot without disturbing the drying process as the oven was not tampered with during the drying. The change in weight of the granules with time as drying proceeded (drying curve) was automatically plotted on a moving chart whose speed was known.

The drying rate expressed as loss of moisture per unit time against time or per cent moisture content was plotted from the drying curves. The tangent to the curve at any desired moisture content or time was drawn to give the slope or the rate of drying (Figure 22).

Principle of Operation of the Instron Load Cell

The load cell operates on the principle of an automatic balancing potentiometer. A battery supplies a steady current along a slide wire. The voltage across the sliding wire depends on the position of the sliding contact. The voltage is then automatically related to the voltage from the rectified amplifier of the tray load containing the granules. The difference in voltage is amplified by causing a balancing motor to move the sliding contact in order to balance the potentiometer circuit. The position of the pen on the chart is a function of the tray load.

Calibration of the Instron

Gram weights equal to the desired dry weight of granules were put on the tray suspended to the Instron receptor passed through the top of the oven. Appropriate controls were adjusted to set the pen at zero end of the chart. Weights equal to the expected moisture to be dried off were added to the tray. The pen would move towards the end of the chart. It was adjusted to scale 10 (end) of the chart by using the appropriate controls.

When the tray containing the wet granules was suspended, the oven was closed and the fine balancing control of the Instron adjusted to put the pen at scale 10 (end) of the chart and the automatic drying curve plot was started. Drying was completed when the curve showed no change in weight with time.

2.4.2 A COMPARATIVE STUDY OF DRYING METHODS

A comparative study of the method of drying the granules on the distribution of borax in granules was undertaken.

The size of each of the drying trays used for drying in the hot air oven at 48°C, in the vacuum oven at 48°C and pressure of 6 kNM^{-2} and in the freeze drier (Model EF6, Edwards Freeze Driers, U.K.) was 29 cm x 23 cm compared with 49 cm x 32 cm area of tray used normally for drying in the hot air oven. 570.0 g wet weight of granules was the batch size of borax/lactose granules used on the larger tray. Therefore 242.5 g weight was the dimensional equivalent weight of the wet granules taken for drying on each of the smaller trays. The use of this equivalent weight of granules on the smaller trays was considered essential to keep the thickness of granules on the trays the same. The amount of dissolved solutes migrated during drying was shown in earlier investigations to depend also on the thickness of the bed of granules. It was established that the increase in the wet batch size from 570.0 g to 727.4 g required for the three smaller trays, did not affect the borax distribution in the various sizes of granules from 570.0 g of the wet weight dried in the larger tray. Therefore the batch of granules was prepared and dried in the smaller trays each in the hot air oven at 48°C, in the vacuum oven at 48°C and in the freeze drier. The small plastic jars filled with samples of the granules were each used to dry the granules in each type of drier. For fluidised drying, the normal size

of batch of granules was prepared and 242.5 g weight was dried in the smaller size of tray in the hot air oven at 48°C as before and the same weight dried in the laboratory fluidised bed drier (Model FBD/L72, Assoc. Co. Palmer Research Laboratories, P.R.L. Engineering Ltd., Mostyn Flintshire, U.K.) set at 50°C inlet temperature and dried for 2 hours. There was no loss on drying after keeping the granules on the larger tray in the hot air oven kept at 50°C for 2 hours, showing that drying in the fluidised state to constant weight was complete by the 2 hours drying time.

2.5 CHARACTERISATION OF GRANULES

2.5.1 GRANULE SIZE ANALYSIS

In a preliminary trial, the weight of samples of dry screened granules in a batch was varied between and including 100 and 300 g and shaken on test sieves (Endocotts Test Sieves Ltd., London, U.K.) for 30 minutes. The arrangement of the sieves in descending order of mesh sizes was 1680, 1000, 710, 500, 355, 250, 180 micrometres and pan. The percent granule size distribution did not show any appreciable variations. It was found necessary to sieve enough granules so that each sieve fraction would be adequate for subsequent drug analysis. To this end 280 g of granules were sieved for 30 minutes. The weight of granules retained by each sieve was the difference between the initial empty weight and final weight of a sieve after sieving.

2.5.2 SECTIONING OF THICK-BED LAYER OF GRANULES FOR ANALYSIS

Granules were dried in plastic jars of 7.0 cm height to represent thick-bed drying of granules. After the granules were dried to constant weight, the jar was marked into seven parts each 1 cm apart from the next. Each layer, starting from the top, was sectioned into a separate 100 ml beaker. The drug was dissolved to a known volume with water for borax and sodium salicylate but 0.1M NaOH for sulphadimidine, diluted appropriately and analysed.

2.5.3 MEASUREMENT OF INTRAGRANULAR POROSITY

The porosity of a granule is the fraction of the volume of the granule made up of pores. It is usually expressed as a percentage.

Some processing variables are known to have an effect on the density or porosity of the granule formed (Ganderton & Hunter, 1971). A compact granule is expected to have reduced pores which could affect the migration of components in solution including the drug. Gray (1968) related the packing arrangement of mono-sized spheres to porosity and co-ordination number. For a given sphere in the arrangement, the co-ordination number is the number of contacts made with other adjoining spheres. In

Packing Arrangement	Co-ordination Number	Porosity
cubic	6	47.6
ortho-rhombic	8	39.5
tetragonal	10	30.2
rhombohedral	12	26.0

pharmaceutical granulations, mono-sized spheres are uncommon. Also, as a result of the binding forces, contacts of particles with one another might be a mixture of a different pattern from the above statistical packing arrangement. The measurement of the porosity of the granules could give some insight to a theoretical calculation of a drug content in the granules.

Porosity ε, from the definition stated above, could be related to the volume of pores Vp and the bulk volume V' as:

$$\varepsilon = \frac{Vp}{V'}$$

Rearrangement gives:

$$\varepsilon = 1 - \frac{\rho'}{\rho}$$

where ρ is the actual density and ρ' the bulk density of the granule.

For same weight of granule,

$$\varepsilon = 1 - \frac{V}{V'}$$

where V is actual volume and V' the bulk volume.

The actual volume of the granule was measured by the Beckman air comparison pycnometer.

Measurement of Bulk Volume of a Granule by Mercury Intrusion Porosimetry

To measure the bulk volume of granules by liquid displacement method it is a prerequisite that the liquid should be non-wetting and unable to penetrate the intragranular pores. Washburn (1921) related the pore diameter d which could be penetrated by a non-wetting

liquid e.g. mercury with the applied pressure P, the surface tension T and the contact angle θ of the liquid as:

$$d = \frac{-4T \cos\theta}{P}$$

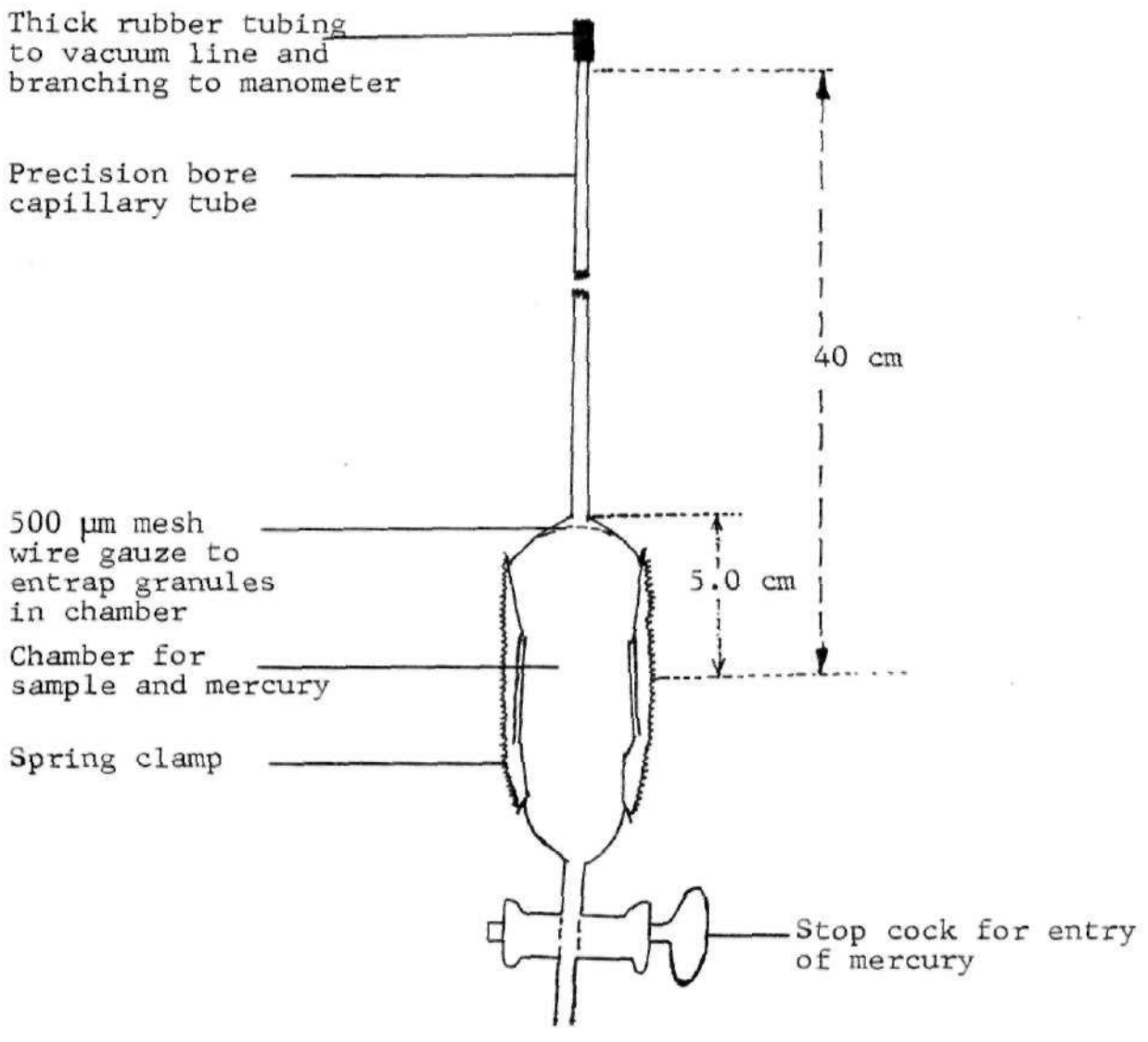
Therefore low applied pressure to the liquid surrounding the granule, a non-wetting liquid with high surface tension and high contact angle are required so that the intragranular pores are not penetrated by the liquid. Mercury is known to have a high surface tension (0.48 Nm^{-2}) and a high contact angle (140°). Hunter (1972) and Opakunle (1975) used small applied pressures. The latter considered 13.3 kNm^{-2} pressure and at the same time ensuring that the granules were not too much to allow proper enveloping of individual granules.

The mercury pycnometer constructed (Figure 13) was similar to that of Strickland, Busse and Higuchi (1956). 19/26 Quickfit ground glass joints were used. A precision bore capillary tube was fused to the upper sample chamber. The volume of the pycnometer chamber as measured using the weight and hence volume of mercury filling it was 13.93 cm^3. The capillary tube was connected to a mercury manometer and to a vacuum line. A cm-graph chart was attached throughout the 35 cm length of the capillary tube for measuring mercury level.

Operation of the Mercury Pycnometer

To calculate the volume capacity of the capillary tube and volume of the pycnometer chamber, mercury was sucked up, by operating the vacuum line and stop cock, to reach the 35 cm length of the capillary tube. The

Figure 13 Mercury pycnometer constructed



vacuum was disconnected and pressure gradually introduced to atmospheric pressure so that the mercury could be emptied under gravity. The height of mercury in the capillary was noted. Mercury was allowed to drip to a weighed 50 cm^3 beaker down to the zero mark of the capillary and reweighed. The rest of mercury occupying the chamber was added to the beaker and reweighed. Assuming that the density of mercury at room temperature was 13.6 gcm^{-3}, the volume capacity of the precision bore capillary tube and volume of the pycnometer chamber was calculated.

About 2 g weight of granules retained by 1000 micrometre mesh was accurately weighed and transferred to the weighed lower half of the chamber after measuring the actual volume with the Beckman air comparison pycnometer. Vacuum grease was lightly applied to the contact part of the lower chamber and fitted to the upper chamber. The spring clamps were fastened. Mercury was admitted into the chamber up to not more than 2 cm mark of the capillary tube. After equilibrium was reached, the height of mercury was measured to 0.1 cm accuracy. The manometer reading was taken. The atmospheric pressure from a standard barometer was read to 0.01 kNm^{-2}. The vacuum line was disconnected and pressure increased to atmospheric. Some mercury was admitted into a weighed 50 cm^3 beaker down to below the lower chamber - the vacuum grease applied to the inside edge of the lower chamber was wiped off - and weighed with the beaker to get the colume occupied by the mercury.

A typical calculation for the intragranular porosity is presented below. Atmospheric pressure read from a

standard barometer a = 102.66 kNm^{-2}. Medium height of the pycnometer chamber to zero mark of capillary tube b = 5.0 cm.

Volume of pycnometer bulb c = 13.93 cm^3

Volume capacity of pycnometer capillary tube d = 0.0428 $cm^3 cm^{-1}$

Weight of beaker + lower pycnometer chamber e = 159.3376 g

Weight of beaker + lower pycnometer chamber + granules f = 161.4933 g

Weight of sample of granules g = f - e = 2.1557 g

True volume of the sample of granules measured by Beckman air comparison pycnometer h = 1.245 cm^3

Manometer reading i = 101.72 kNm^{-2}

Residual atmospheric pressure on pycnometer j = a - i = 0.94 kNm^{-2}

Pressure by mercury in capillary k = 0 kNm^{-2}

Pressure exerted on granules by mercury l = b + k = 6.67 kNm^{-2}

Total applied pressure acting in pycnometer m = j + l = 7.61 kNm^{-2}

Weight of container + granules + lower pycnometer n = 323.7413 g

Volume of mercury encasing granules $O = \frac{(n - f)}{13.6} = 11.93\ cm^3$

Total volume of mercury and granules p = C + kd = 13.93 cm^3

Bulk volume of granules in pycnometer q = P - O = 2.00 cm^3

Intragranular porosity of granules $= (1 - \frac{h}{q}) \times 100\% = 37.5\%$

SD = 0.56

2.5.4 METHOD OF ANALYSIS OF DRUGS IN GRANULES

The drug/diluent combinations so far employed are

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borax/lactose, salicylic acid/lactose, sodium salicylate/ heavy magnesium carbonate, sulphadimidine/lactose, sulphadimidine/heavy magnesium carbonate and sulphadimidine/ pure dibasic calcium orthophosphate.

2.5.4.1 ANALYSIS OF BORAX IN GRANULES

The reaction between borax and hydrochloric acid is:

$$Na_2B_4O_710H_2O + 2HCl \longrightarrow 4H_3BO_3 + 2NaCl + 5H_2O$$

$\therefore$ $Na_2B_4O_710H_2O = 2HCl$

381.4 g $Na_2B_4O_710H_2O \equiv$ 200 ml $^{N}/_{1}$ HCl

$\equiv$ 20000 $^{N}/_{100}$ HCl

0.01907g$Na_2B_4O_710H_2O \equiv$ 10 ml $^{N}/_{100}$ HCl

Since granules were dried to constant weight, it is logical that borax dried to constant weight was used to standardise the HCl solution. 25% moisture loss was measured on drying borax to constant weight under vacuum at 70°C.

$\therefore$ 75% 0.01907g $Na_2B_4O_710H_2O \equiv$ 10 ml $^{N}/_{100}$ HCl

that is 0.0143g $Na_2B_4O10H_2O \equiv$ 10 ml $^{N}/_{100}$ HCl

Suppose 0.0143g of the borax was contained in 25 ml of solution, 1000 ml (1 litre) of solution would contain 0.527 g of the borax.

For calibration, about 0.6 g of the borax was weighed accurately and dissolved in distilled water to make 1 litre of solution. Hydrochloric acid (about $^{N}/_{100}$ strength) was titrated with 25.0 ml of the borax solution pipetted to a 50 ml beaker and stirred by magnetic bugs using Auto-burette (Type ABUIC) Titrator (Type TTTIC) unit (Radiometer Copenhagen, V.A. Howe & Co. Ltd., Pembridge

Road, London, England).

The end point was set at pH 4.5 as evident from a preliminary titration curve (Figure 14).

The titration was automatically stopped when the pH of 4.5 was reached. The volume of HCl titrated was read from the digital counter to 1/100th of a millilitre. For the same concentration and volume of borax solution, the volume of HCl automatically titrated was reproducible.

The calibration of the HCl solution was that weight of borax, dried to constant weight, equivalent to 1.0 ml of the HCl. 10 litres of the HCl solution was made in a bell-shaped glass jar stoppered and connected to the auto-burette titrator unit via a delivery tube.

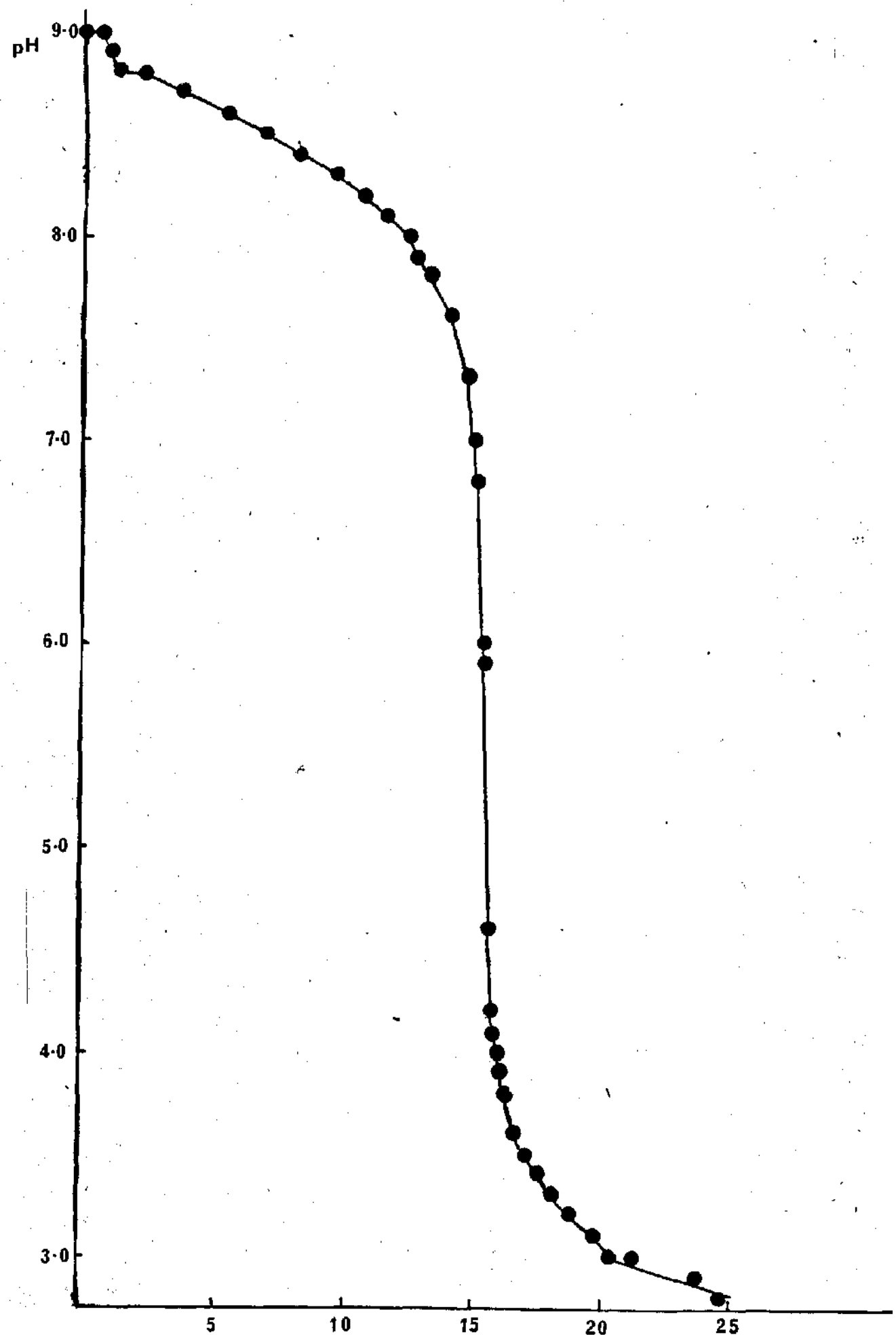
Influence of Presence of Lactose in Analytic Results

The working concentration of borax was 2% w/w overall in lactose except when the effect of the concentration of borax in the low dose range was investigated. For other drugs and diluents subsequently employed the concentration of each drug in a diluent was maintained at 2% as this project is principally concerned with the distribution of a low dose drug.

If the concentration of borax in a certain size of granules is exactly 2% then one gram weight would contain 0.02 g borax and 0.98 g lactose. Therefore, two solutions designated A and B were made such that 0.02 g borax was contained in 25 ml of A and of B but 0.98 g lactose was in the 25 ml of B as well. 25 ml volume was chosen as in the actual analysis, 25 ml of water was added to 1 gram weight of granules to dissolve. To ensure exactly the

Figure 14

Variation of pH of Borax Solution (0.02g dissolved in 25.0 cm^3 of water) with addition 0.01M HCl.



same drug concentration in A and B, the solutions were made from a stock solution of borax and then diluted appropriately after dissolving the required proportion of lactose in B. A standardized HCl was titrated using the autoburette titrator unit with 25.0 ml from A and B respectively and repeated thrice. The results were tabulated (Table 3). Since the results were within ± 0.1%, it would appear that the presence of lactose did not affect the titration with borax solution at the working concentrations considered.

Analysis of Borax in Borax/Lactose Granules

About 1 gram of granules was accurately weighed into a 50 ml beaker. 25 ml of de-ionized water was added. A magnetic bug was added and set to spin on a magnetic stirring plate until the solution was clear. The autoburette was set to be filled with HCl which also set the digital volume counter to zero. The beaker was fixed to the autoburette titration. The magnetic bug was set to stir the solution during titration. The titration was switched on to stop automatically when pH 4.5 was reached as end point. The volume of acid titrated was taken as shown by the digital counter. Ten determinations were made for each sieve fraction of granules except in the fines where only up to five were made as the fractional weight was small.

The analysis by layers of granules dried in plastic jars to show the extent of intergranular migration was made by weighing the whole granules in the layer and dissolving in

		1	2	3	4	mean	Standard Deviation	% Deviation From Expected
Vol of HCl	A	14.96	14.95	14.95	14.96			
	B	14.97	14.94	14.97	14.96			
% of Expected borax in solution	A	2.0002%	1.9988%	1.9988%	2.0002%	1.9995%	0.0008	-0.03%
	B	2.0015%	1.9975%	2.0015%	2.0002%	2.0002%	0.0019	+0.10%

Table 3 TITRATING HCl (1 ml = 0.001337 g borax, dried) AGAINST 25.0 ml OF SOLUTION CONTAINING BORAX

water so that 25 ml of the solution represented one gram weight of the granules. The 25 ml was set for titration as before.

2.5.4.2 ANALYSIS OF OTHER DRUGS

The granulations undertaken include sodium salicylate in lactose and heavy magnesium carbonate; salicylic acid in lactose; sulphadimidine in lactose, in heavy magnesium carbonate and in pure dibasic calcium orthophosphate. For heavy magnesium carbonate and pure dibasic calcium orthophosphate, PVP solution as binder was used. These two diluents are not soluble in water (Table 1) and so cannot form crystalline bridges on drying. The formation of crystalline bridges in granules by components dissolved in the binder are necessary for the maintenance of granules formed while wet. Each pure drug solution appropriately diluted was scanned with Pye Unicam SP800 uv/vis scanning spectrophotometer and compared with the same concentration of drug but also containing the required proportion of the diluent lactose or containing the required concentration of PVP and equivalent filtered solution of the insoluble diluent. At the chosen wavelength giving peak absorbance, the presence of the excipients in solution did not alter the absorbance of the drug (Table 4). The filtration procedure also did not alter the concentration of each of the drugs.

Having established the suitable wavelength giving the peak absorbance using the scanning spectrophotometer, calibration and subsequent analysis of the drugs were made with Pye Unicam SP500 Series 2 uv/vis. spectrophotometer.

Drug/Diluent	Wavelength with Peak Absorbance Chosen			
	Drug Alone		Drug with Excipient	
Salicylic Acid/Lactose	298nm	1.06	298nm	1.06
Sodium Salicylate/Lactose	297	1.44	298	1.44
Sodium Salicylate/Heavy Mag. Carb.	297	0.44	297	0.44
Sod. Sal./Heavy Mag. Carb. with PVP	297	0.52	297	0.515
Sulphadimidine/Lactose	257	0.82	257	0.825
Sulphadimidine/Heavy Mag. Carb.	259	0.81	259	0.81
Sulphad./Dibasic Calc. Orthophos. with PVP	259	0.41	259	0.42

Table 4 SHOWING INFLUENCE OF EXCIPIENTS ON ABSORBANCE OF DRUG IN THE ANALYSIS

A typical calibration curve subjected to regression analysis for sulphadimidine in presence of dibasic calcium orthophosphate diluent and PVP binder is presented (Table 5).

2.5.4.2.1 LACTOSE AS DILUENT

Since lactose is soluble in water (solubility 1:6) and forming as much as 98% w/w of unsieved granules, the need for using a binder other than water was not necessary. 1 g of granules of given size was weighed accurately in a 75 ml beaker. About 30 ml of double distilled water for sodium salicylate or salicylic acid but 30 ml of 0.02N NaOH solution for sulphadimidine granules were added and stirred by a magnetic bug on a magnetic plate until the solution was clear. This was further diluted to 200 ml with water. 20 ml of the further diluted solution of salicylic acid or sodium salicylate or 5 ml for sulphadimidine was diluted to 100 ml and the absorbance read at the appropriate wavelength. The analysis was repeated five times. Multiplying the absorbance for 1 g weight of granules by the calibration factor gave the concentration of drug in the granules.

2.5.4.2.2 HEAVY MAGNESIUM CARBONATE OR DIBASIC CALCIUM ORTHOPHOSPHATE AS DILUENT AND PVP SOLUTION AS BINDER

About one gram of granules was weighed accurately. 30 ml of distilled water for sodium salicylate or 30 ml of 0.02N NaOH for sulphadimidine were added and stirred as before for about 10 minutes and kept overnight to ensure

Conc. Sulphadimidine Solution (% w/v)	Conc. in Granules Taking 0.0005% Soln. ≡ 2% w/w in Granules (% w/w) [y axis]	Absorbance at 259 nm [x axis]
0.001096	4.0784	0.835
0.0005098	2.0392	0.421
0.0002549	1.0196	0.218
0.00020392	0.81568	0.176

Regression Analysis

Correlation coefficient	= 0.999992
Slope	= 4.95422
y-intercept	= -0.0554 (negligible)
Calibration: % w/w Sulph. in granules	= 4.95422 X absorbance for 1 g wt. of granules

Table 5 CALIBRATION FOR SULPHADIMIDINE IN GRANULES

complete dissolution of the PVP and the drug. The supernatant solution was first poured to the 250 ml funnel of the Millipore filtration unit fitted with the Nuflow membrane filter and connected to a vacuum pressure. About 30 ml water was added to the remaining suspension and shaken before pouring into the filtration unit. The beaker was rinsed with water and poured into the funnel. The residue was washed with water (about 20 ml). The filtrate was poured into a 200 ml flask through one of the two openings, at the 'neck' of the filtration chamber, which were initially stoppered during the filtration process. The chamber was rinsed twice with 40 ml of water each injected through one of the filtrate chamber openings with a 20 ml syringe. The 200 ml volume of flask was made up with water.

For sulphadimidine, 5 ml was pipetted and diluted to 100 ml and the absorbance read. For sodium salicylate, 20 ml was pipetted and diluted to 100 ml and the absorbance of the solution read at the calibrated wavelength. In all cases water was used as the blank after initially establishing that 0.02N NaOH appropriately diluted did not give any difference as a blank solution compared with water. During the analysis of drugs by layers where the weight of granules was obviously more than one gram, the dilution of solution was made by the number of gram weight of granules. The calibration factor was multiplied by this dilution. The dilutions were then followed as described before.

2.6 LIMITATION OF USE OF HEAVY MAGNESIUM CARBONATE AND SALICYLIC ACID

The use of heavy magnesium carbonate and salicylic acid was limited as explained below.

Heavy Magnesium Carbonate as a Diluent

The use of heavy magnesium carbonate (h.m.c.) as a poorly soluble diluent was limited. As a result of its alkalinity it was shown to allow some of the sulphadimidine intended to remain poorly soluble during the granulations, to dissolve during the processes.

The values of the solubilities of sulphadimidine in the different conditions of binder are presented in Table 6.

Salicylic Acid as a Poorly Soluble Drug

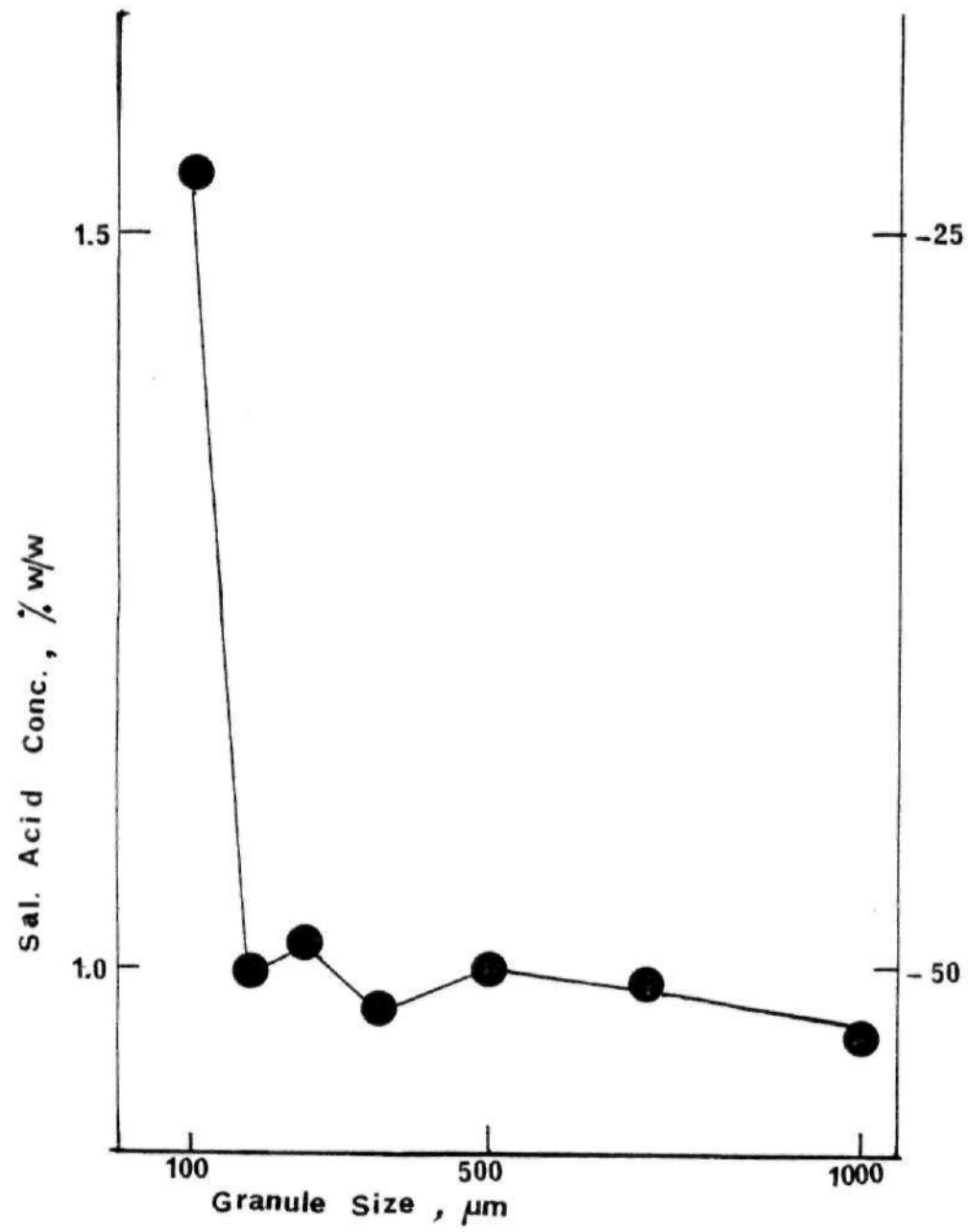
Salicylic acid was intended to represent a drug which is poorly soluble in the binder. Its use was however discontinued. This was because preliminary results showed that even as low as 30°C temperature of drying in the hot air oven, ascicular crystals were seen to be deposited on top of granules on the tray as well as in the corners and surfaces of the oven. This deposition of the crystals was attributed to sublimation of much of the salicylic acid from the granules during the drying process. The sublimates were deposited as ascicular crystals. Those crystals formed on top of granules on the tray formed part of the fines which consequently caused an appreciable high concentration in the fines (Figure 15).

Therefore sulphadimidine was chosen instead as the poorly soluble drug in the binder in all subsequent

pH of distilled water	5.7
pH of 15% w/v PVP aqueous solution	3.5
pH of Saturated solution of pure dibasic calcium orthophosphate in 15% w/v PVP	4.7
pH of saturated solution of heavy magnesium carbonate (h.m.c.)	
In water	9.1
in 15% PVP	8.5
Solubility of sulphadimidine (SDM) in 15% w/v PVP (pH = 3.5)	1:2180
Solubility of SDM in water (pH = 5.5)	1:1897
Solubility of SDM in 15% w/v PVP co-saturated with Emcompress (pH = 5.7)	1:1907
Solubility of SDM in 15% w/v PVP co-saturated with h.m.c. (pH = 8.5)	1:412
Solubility of SDM co-saturated with h.m.c. in water (pH = 9.1)	1:100

Table 6 SOLUBILITIES OF SULPHADIMIDINE IN BINDER UNDER DIFFERENT pH VALUES

Figure 15 Effect of sublimation of salicylic acid on the distribution of the salicylic acid in granule sizes of a batch prepared by massing 2% w/w salicylic acid/lactose with 20% v/w water and drying in the oven at 30°C



micro-dose granulations where the use of a poorly soluble drug was required.

3.1

DRUG DISTRIBUTION DURING MASSING OF DRUG/DILUENT POWDER MIX

2.7 REPRODUCIBILITY OF THE RESULTS

It has been pointed out and stressed that all the experimental procedures were kept constant while only one variable was introduced. However it was necessary to make four batches of granules by massing a 2% w/w dry mix of borax and lactose with water (14% v/w). Each batch was subjected to granule size analysis and the borax content in the various sieved sizes of granules throughout the batch was analysed. The results are presented on Table 7.

Granule Size (μm) mesh of sieve retaining granules	% Weight of Granules						Concentration, % w/w, of Borax in Granules					
	1	2	3	4	Mean	SD	1	2	3	4	Mean	SD
1000	30	32	31	30	31	0.96	1.9602	1.9838	1.9634	1.9701	1.9694	0.011
710	20	20	20	19	20	0.50	2.0272	2.0218	2.0226	2.0313	2.0257	0.004
500	17	17	16	16	17	0.58	2.0407	2.0352	2.0445	2.0496	2.0425	0.006
355	15	15	15	15	15	0	2.0319	2.0260	2.0331	2.0340	2.0313	0.004
250	10	9	10	11	10	0.82	2.0143	2.0033	2.0145	1.9910	2.0066	0.010
180	5	4	5	5	5	0.50	1.9452	1.9762	1.9601	1.9420	1.9684	0.020
< 180	3	3	3	4	3	0.50	1.7295	1.7384	1.7192	1.7111	1.7246	0.012

Table 7 REPRODUCIBILITY OF RESULTS SHOWING GRANULE SIZE DISTRIBUTION AND CONCENTRATION OF BORAX IN GRANULE SIZES OF 4 BATCHES OF GRANULES PREPARED UNDER THE SAME CONDITIONS

3.1 DRUG DISTRIBUTION DURING MASSING OF DRUG/DILUENT POWDER MIX

3.1.1 INTRODUCTION

In a wet granulation process, a binder solution is initially added to the drug/diluent mix. The site of addition of the binder results in an overwetted region (Carstensen, et al, 1976). The massing action subsequently distributes the binder to other areas of the mix until an equilibrium granular state has been achieved.

Variation in granule size has been reported to be a consequence of variation in binder uptake by the material being granulated (Dingwall and Ismail, 1977). The largest granules have been shown to be formed from the wettest region of the mix (Opakunle and Spring, 1976). Thus the initial overwetted region of the mass will give rise to the major portion of the largest granules.

Consider a powder mix containing a drug and a diluent both of which are, to a greater or lesser extent, water soluble. Let water be the binder used for the granulation of the powder mix. After the addition of the water to the mix, some dissolution of both the drug and diluent will take place in the overwetted region. Thus the binder which is then distributed to the rest of the mass is no longer pure water but is now a solution of the drug and diluent. The composition of this solution will be a function of the relative solubilities and dissolution rates of the drug and diluent.

Thus the binder then used to mass the overwetted

region, producing the bulk of the largest granules, will have a different composition from that which is used to mass the rest of the mix. Therefore any parameters which affect the composition of the solution formed in the overwetted region will also affect the concentration of the drug in the overwetted region, and thus in the largest granules, as well as in the rest of the mix. Such parameters will include, the relative solubilities of the drug and diluent and also their relative dissolution rates in the binder.

3.1.2 EFFECT OF RELATIVE SOLUBILITIES OF DRUG AND DILUENT

The relative solubility of a drug, S_{dr} or diluent S_{di}, in this context is defined as the percentage of the drug or diluent on a dry basis which is capable of dissolving in the binder.

$$S_{dr} = \frac{a}{a+b+c} \times 100\%$$

and $$S_{di} = \frac{b}{a+b+c} \times 100\%$$

where a and b are the respective weight in solution of the drug and diluent and c, the weight of the binder, e.g. PVP, dissolved in the solution.

The relative solubility of a drug is therefore the concentration of the drug with reference to the weight of other solids dissolved in the binder. The values of the relative solubilities of the drug/diluent granulations studied are shown on Table 8.

The overall drug concentration in the granules was 2% w/w. Therefore, when the relative solubility of e.g.

Drug	Diluent	Binder	Solubility			% Relative Solubility		
			Drug	Diluent	PVP	Drug	Diluent	PVP
Sodium Salicylate	h.m.c.	60% v/w water	1:1	1:3330	-	99.7	0.3	-
Sodium Salicylate	h.m.c.	45% v/w of 15% w/v PVP	1:1	1:3330	1:1	22.8	0.2	77.0
Sodium Salicylate	d.c.o.	33% v/w of 15% w/v PVP	1:1	insoluble	1:1	28.8	0	71.2
Sodium Salicylate	lactose	14% v/w water	1:1	1:6	-	46.1	53.9	-
Borax	lactose	14% v/w water	co-saturated 1:10	co-saturated 1:3	-	23.1	76.9	-
Sulphadimidine	lactose	20% v/w water	1:1897	1:6	-	0.3	99.7	-
Sulphadimidine	h.m.c.	47% v/w of 15% w/v PVP	1:412	1:3330	1:1	1.6%	0.2	98.2
Sulphadimidine	d.c.o.	33% v/w of 15% w/v PVP	1:1907	insoluble	1:1	0.4	0	99.6

h.m.c. = heavy magnesium carbonate

d.c.o. = pure dibasic calcium orthophosphate

Table 8 VALUE OF RELATIVE SOLUBILITIES OF DRUG/DILUENT MIX IN BINDER

sodium salicylate in the binder in a sodium salicylate/ lactose granulation is 46.1% (Table 8), it means that any distribution of binder from the overwetted region will lead to an appreciable decrease of sodium salicylate from that region and a corresponding concentration in the rest of the mix. In the case of sulphadimidine/lactose granulations with water, only 0.3% w/w of sulphadimidine and 99.7% w/w of lactose (Table 8) are capable of dissolving in the binder. Thus the binder distribution from the overwetted region will result in a higher concentration of sulphadimidine remaining in the overwetted region.

Figure 16 shows the effect of massing time on the concentration of drug in the overwetted region of agglomerates. The sulphadimidine concentration in the agglomerated overwetted region continues to increase during massing, showing that the lactose, as predicted, is undergoing a net transfer from the overwetted area.

In the granulation of 2% borax in lactose using water as the binder, the relative solubility of the borax is such that a decrease in borax concentration with massing time is observed. A concomitant enriching of the other areas of the mix by distribution and wetting of the borax-rich binder from the agglomerates is shown in Figure 17.

Figure 16 shows that sodium salicylate with 46.1% relative solubility leads to a higher rate of decrease from the agglomerates compared with borax with a lower relative solubility of 23.1%. However, its concentration in the agglomerates in equilibrated granules, that is, after five minutes massing, increased slightly to exceed that of

Figure 16 Effect of Massing Time on Drug Concentration in Agglomerates with 13.5 μm Lactose as the Diluent

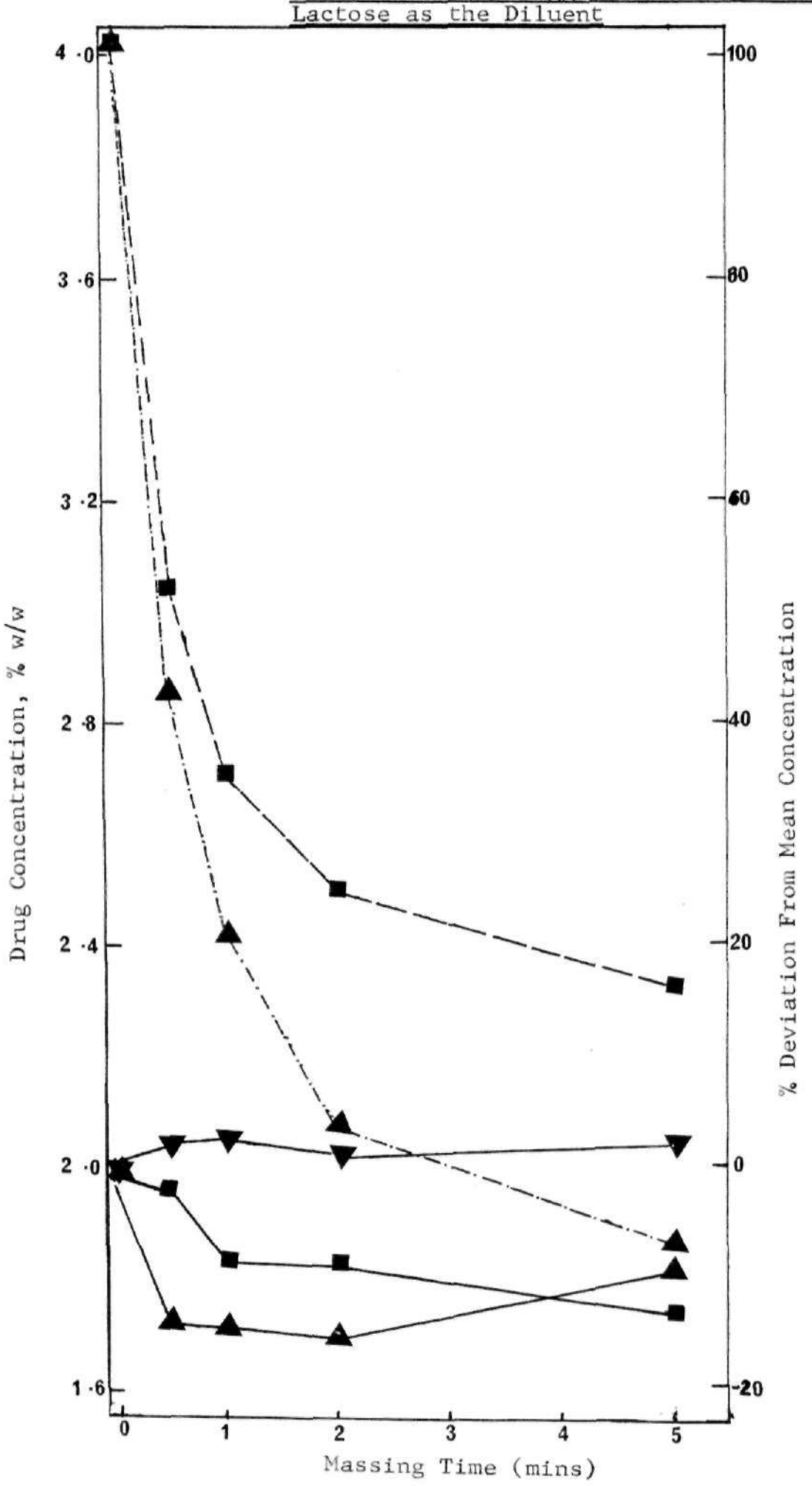
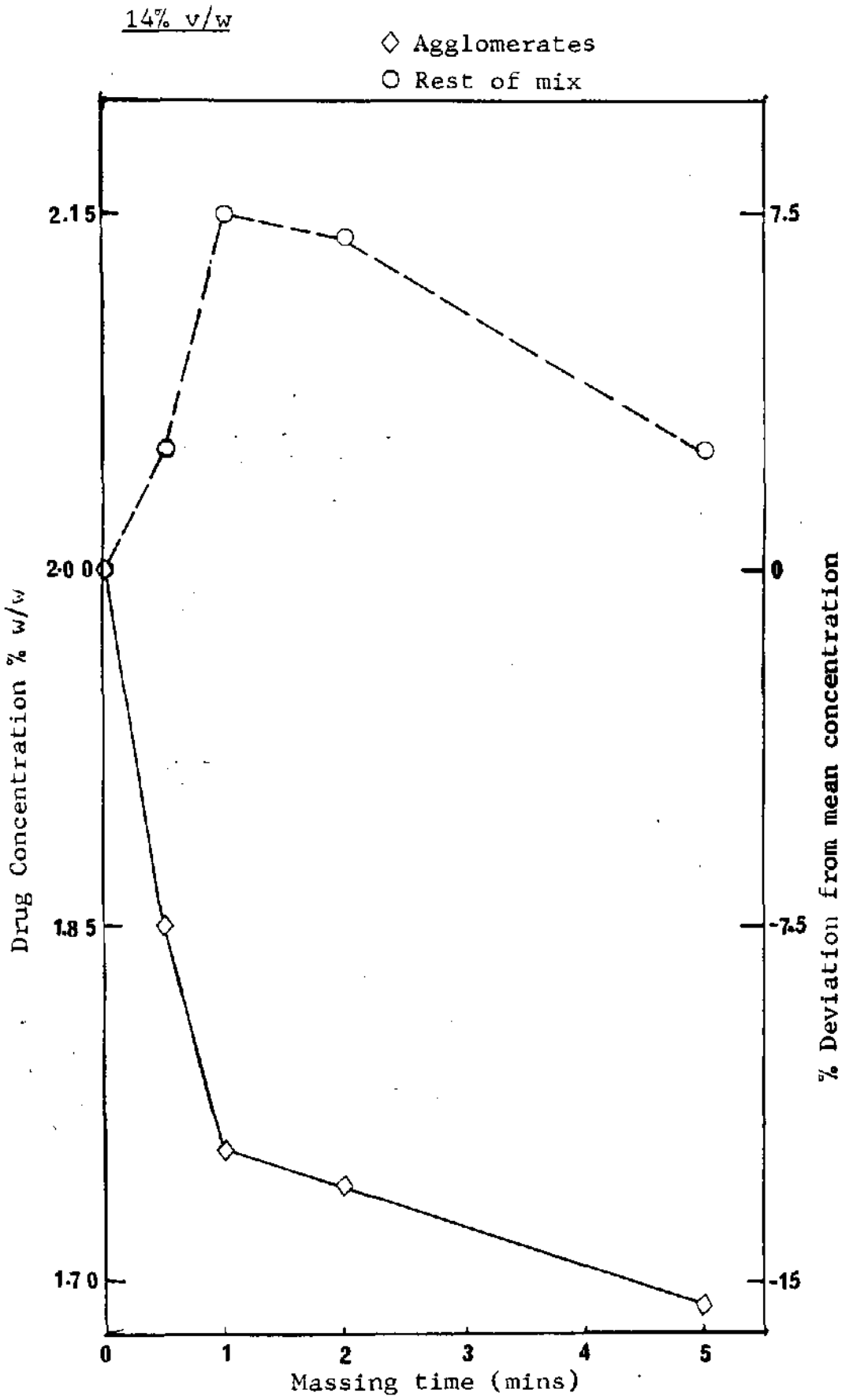


Figure 17 Effect of Massing Time on Borax Distribution in Agglomerates and Rest of Mix Using 2% w/w Borax/Lactose Dry Mix and Massing With Water, 14% v/w



borax. This is possibly caused by the higher rate of wetting and dissolution (Figure 18) of sodium salicylate particles from the drier part of the mix. This ease of wetting (Sastry and Fuerstenau, 1973) would allow a snow-balling action. Snow-balling with borax would not be sustained as ease of wetting is necessary for the binding action. In addition, some lactose particles may likewise undergo the snow-balling effect but this amount compared to its overall concentration (98% w/w) will not cause any appreciable differences.

3.1.3 EFFECT OF RELATIVE DISSOLUTION RATE ON THE CONCENTRATION OF DRUG IN AGGLOMERATES DURING MASSING.

A comparative effect of the particle size of the drugs used on their dissolution rate is presented in Figure 18. This shows that the rate of dissolution of the moderately soluble borax is proportional to its particle size. It is therefore expected that when different particle sizes of borax are respectively mixed with lactose and massed with water, the rate of dissolution of the borax will vary. Larger particles will dissolve more slowly in the binder. Consequently a lower concentration of borax will be dissolved within a given massing time with a corresponding lower loss of borax from the overwet region during binder distribution. Thus the concentration of borax remaining in the agglomerates will be higher.

Figure 19 shows the effect of the particle size of borax on its concentration in the agglomerates during massing. As predicted, the following borax particle sizes,

Figure 18 Effect of Particle Size of a Soluble Drug on its Rate of Dissolution in Water
(Borax was present in admixture with lactose)

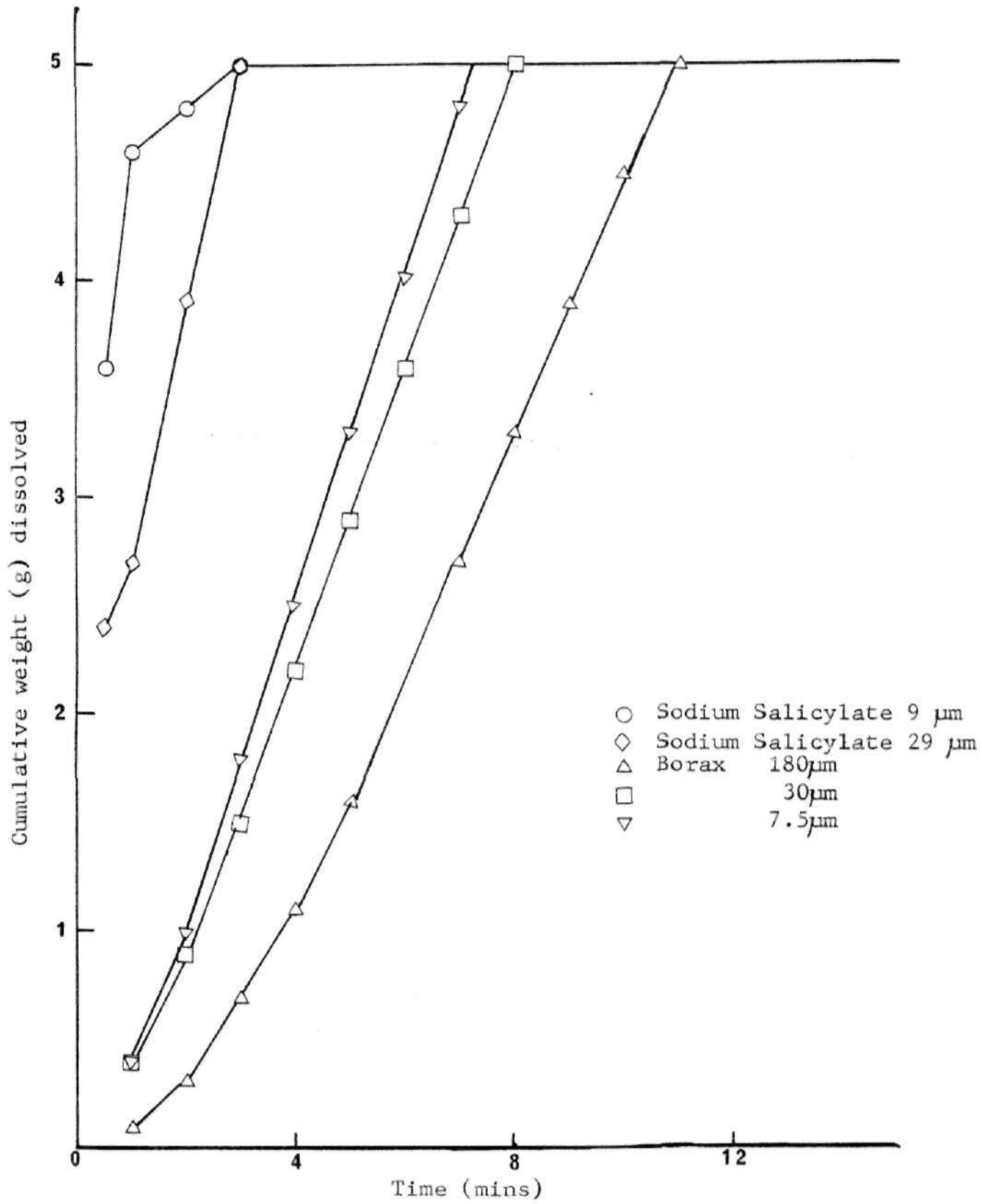
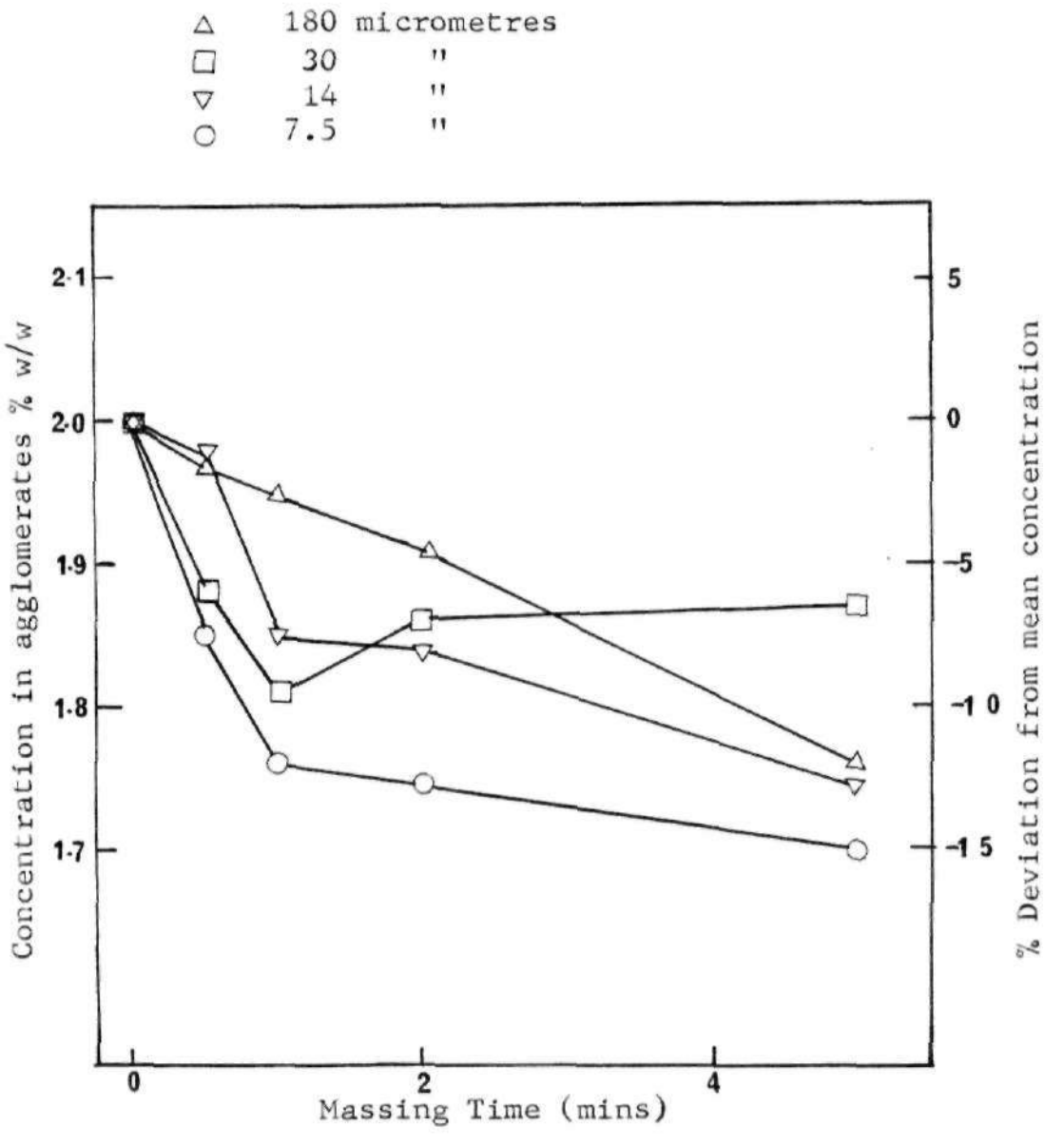


Figure 19 Effect of Borax Particle Size on its Concentration in Agglomerates During Massing



7.5, 14 and 180 micrometres, produced an inverse relationship with its concentration in the agglomerates for a given massing time. However, the rate of depletion of the 30 micrometre fraction of borax is much higher than expected. At present no explanation for this discrepancy is given.

Although the rate of dissolution of the more soluble sodium salicylate was initially proportional to its particle size, the rate was much higher than that of borax; and differences due to particle size effects quickly disappeared (Figure 18). It is therefore expected that the rate of dissolution of sodium salicylate in the binder during massing unlike borax will not be a rate determining step in relation to its particle size.

3.1.4 EFFECT OF PRESATURATION OF COMPONENT(S) AS BINDER

Occasionally in pharmaceutical practice the binder may be saturated with the drug before massing takes place. This is a measure taken to ensure a more uniform distribution of a low dose drug throughout the batch of granules. Since the solubility of borax increases in the presence of lactose (Figure 11), a saturated solution of borax and lactose is preferred to that of borax alone in the case of borax/lactose granulation.

The addition of such a binder will inhibit dissolution of solids from the overwetted region. Initially this region will have a high drug content (Figure 16). However, as the binder is distributed, the drug concentration in this region will rapidly fall as the ratio of binder to solids fall. It should, however, be noted that the concentration after massing is still higher than the 2% w/w of the dry

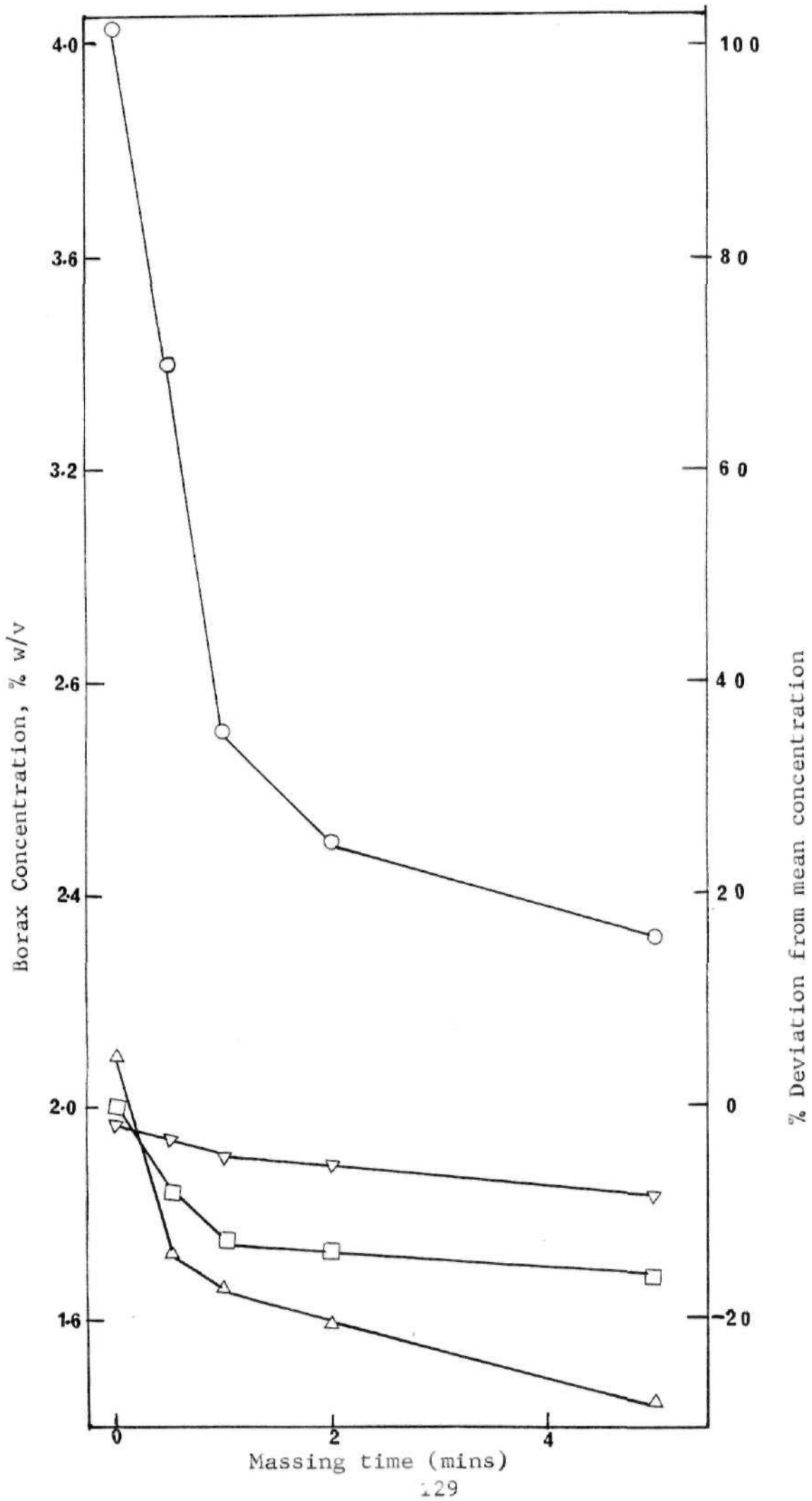
mix (Figures 16 and 20). This is because the largest granules are the wettest (Opakunle and Spring, 1976) and binder uptake is a function of granule size (Dingwall and Ismail, 1977). A similar situation will be found with sodium salicylate (Figure 16).

The above two publications (Opakunle and Spring, 1976; and Dingwall and Ismail, 1977) however, did not explain why bigger granules were formed as a result of a higher binder uptake. The explanations are traceable to the volume of pores and numbers of intragranular bridging contacts. Bigger granules have wider pores (Nicholson and Enever, 1974) as well as a higher number of contact points between the intragranular particles. This is because the exposed surface area to volume ratio is lower in the larger than in smaller granules. The binder will be located in these pores while some of it will be present at the contacts as bridges. The biggest granule will thus contain the highest relative volume of the binder and consequently become the wettest.

However, in a system where all the intragranular pores are oversaturated with the binder, the resulting "spilled" binder will form a film coating on the granules. In such a situation the higher exposed surface area to volume ratio of smaller granules becomes more predominant except, perhaps, over-aggregation of the granules takes place with an adequate massing action.

Figure 20 shows that saturation of the binder with borax alone also affected the borax concentration in the agglomerates during massing. As expected, the initial

Figure 20


4·0
3·6
3·2
2·6
2·4
2·0
1·6
Borax Concentration, % w/v
100
80
60
40
20
0
-20
% Deviation from mean concentration
0
2
4
Massing time (mins)

concentration of borax in the agglomerates was more than 2%. As a result of its increase in solubility in the presence of lactose, the effect of the binder is similar to that of an aqueous granulation, although the net loss of borax from the agglomerates will be more marked as a result of improved concentration of borax in the binder.

The initial concentration of borax on addition of saturated lactose as the binder to the dry mix will be less than 2% (Figure 20). This is a dilution effect of lactose in the overwetted region. Like saturated borax binder, the saturated lactose binder will act as an aqueous binder capable of dissolving borax and lactose from the overwetted region, although the loss of borax from the agglomerates during massing will be less marked as a result of an improved concentration of lactose in the binder.

As expected the granulation of the mix with pure water produced concentration - massing time results which are intermediate between those of massing with saturated lactose and then with saturated borax.

3.2

EFFECT OF SOLUTE MIGRATION DURING GRANULE DRYING ON DRUG DISTRIBUTION

3.2 EFFECT OF SOLUTE MIGRATION DURING GRANULE DRYING ON DRUG DISTRIBUTION

3.2.1 INTRODUCTION

Granules prepared by massing and screening must be dried. During this drying process, the migration of binder solution by capillary forces which transport the binder to the drying surface has been shown to take place (Chaudry and King, 1972). This migration can be both intra-granular (Rubinstein and Ridgway, 1974) and inter-granular (Travers, 1975).

The migration of solutes through a bed of granules in a plastic jar was used as a model (figure 21) to simulate the radial migration of solutes within the granule. This model was used to study both intra- and inter-granular migration. Ridgway and Rubinstein (1971) have studied the radial migration of PVP binder towards the granule periphery by direct sectioning of the granules. Abrasion techniques (Selkirk, 1976) were employed to show the migration of solutes towards the granule periphery where the solutes were deposited as a crust. Sectioning of a bed of granules into layers to show the extent of intergranular migration was adopted by Travers (1975) and Warren and Price (1977).

In this study, the abrasion techniques and also the sectioning into layers of the granule bed have been used to examine intragranular and intergranular migration of solutes during drying.

The migration of binder, and solutes which dissolved in it, during drying has been shown to have a major effect on borax distribution in 2% w/w borax/lactose granules

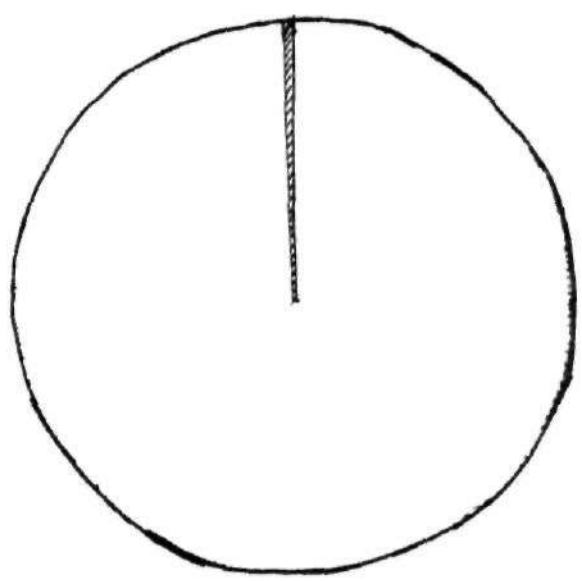


Figure 21: A sketch of a granule showing a shaded cross-section to represent the radial (intra-granular) migration of solutes from the granule core towards the granule periphery.

Inter-granular migration of solutes as shown by migration of solutes in a packed bed of granules in a plastic jar indicates an off-shoot model of radial migration.

(Selkirk, 1976). Factors such as particle size (Warren and Price, 1977), method of drying (Travers, 1975), binder viscosity (Chaudry and King, 1972) and drying temperature (Rubinstein and Ridgway, 1974) have been shown to affect the extent of solute migration.

3.2.2 EFFECT OF DRYING TEMPERATURE

Figure 22 shows the effect of temperature on drying rates of a bed of granules. An increase in the drying temperature increases the rate of drying. Thus drying at a higher temperature leads to a shorter drying time.

There was a short constant rate period for granules dried at 48°C. At higher temperatures, this constant rate period was absent. This is due to the higher rate of drying which exceeds the rate of binder migration to the surface. The gradual falling rate for 32°C drying temperature leading to a longer drying time was expected but it is not certain why there was no initial constant rate period.

A saturated borax solution was used as a binder for massing lactose powder. The resultant granules containing 0.6% w/w dose of borax were dried at 25 and 48°C respectively in the oven. The extent of migration was greater in granules dried at 25°C than at 48°C (figure 23). The concentration of borax in the top layer of granules dried at 25°C was 63% above the nominal dose compared with only 18% deviation in the top layer of granules dried at 48°C. The equivalent variations of borax concentration in the bottom layer below the nominal dose due to loss by migration of solutes towards the top layer were 35 and 25% for granules dried at 25° and 48°C respectively.

Figure 22 Effect of Temperature of Drying of Granules on Drying Rates

N.B. Although the points of the graphs were plotted with reference to the x- and y- axis scales, the Y-axis were inadvently wrong.

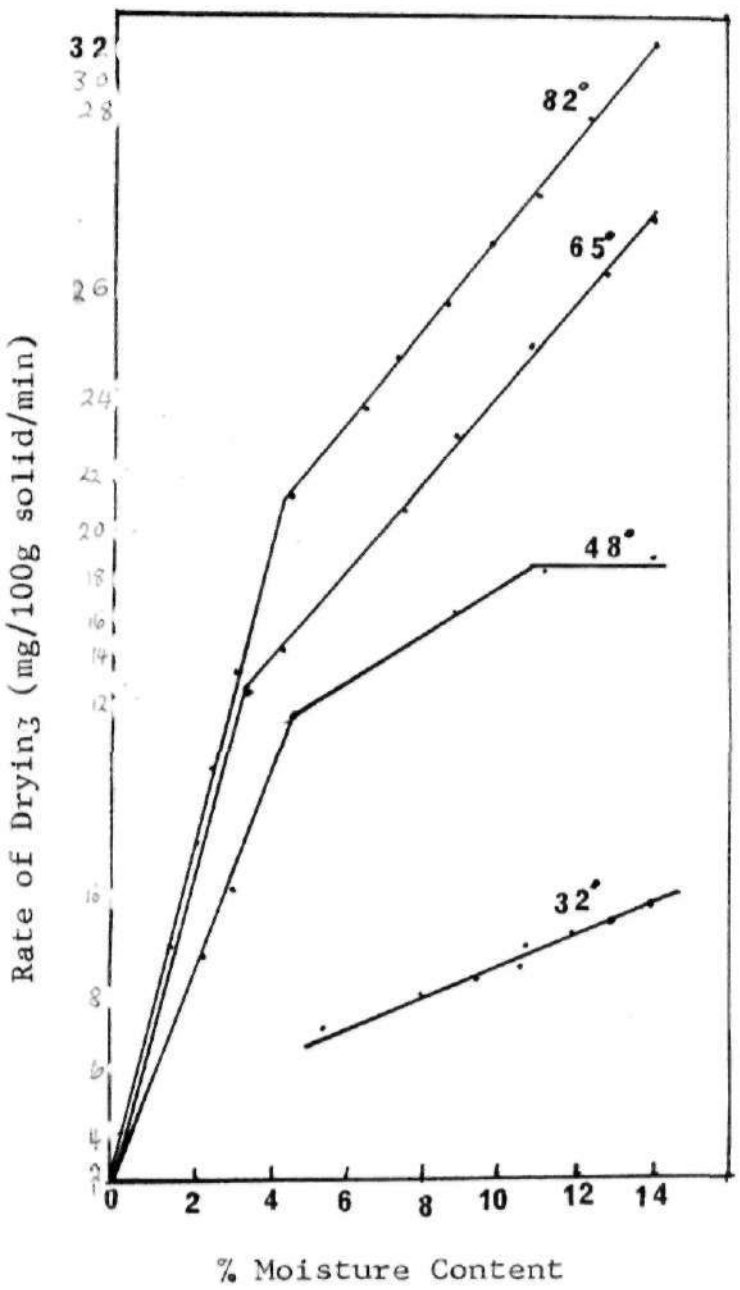
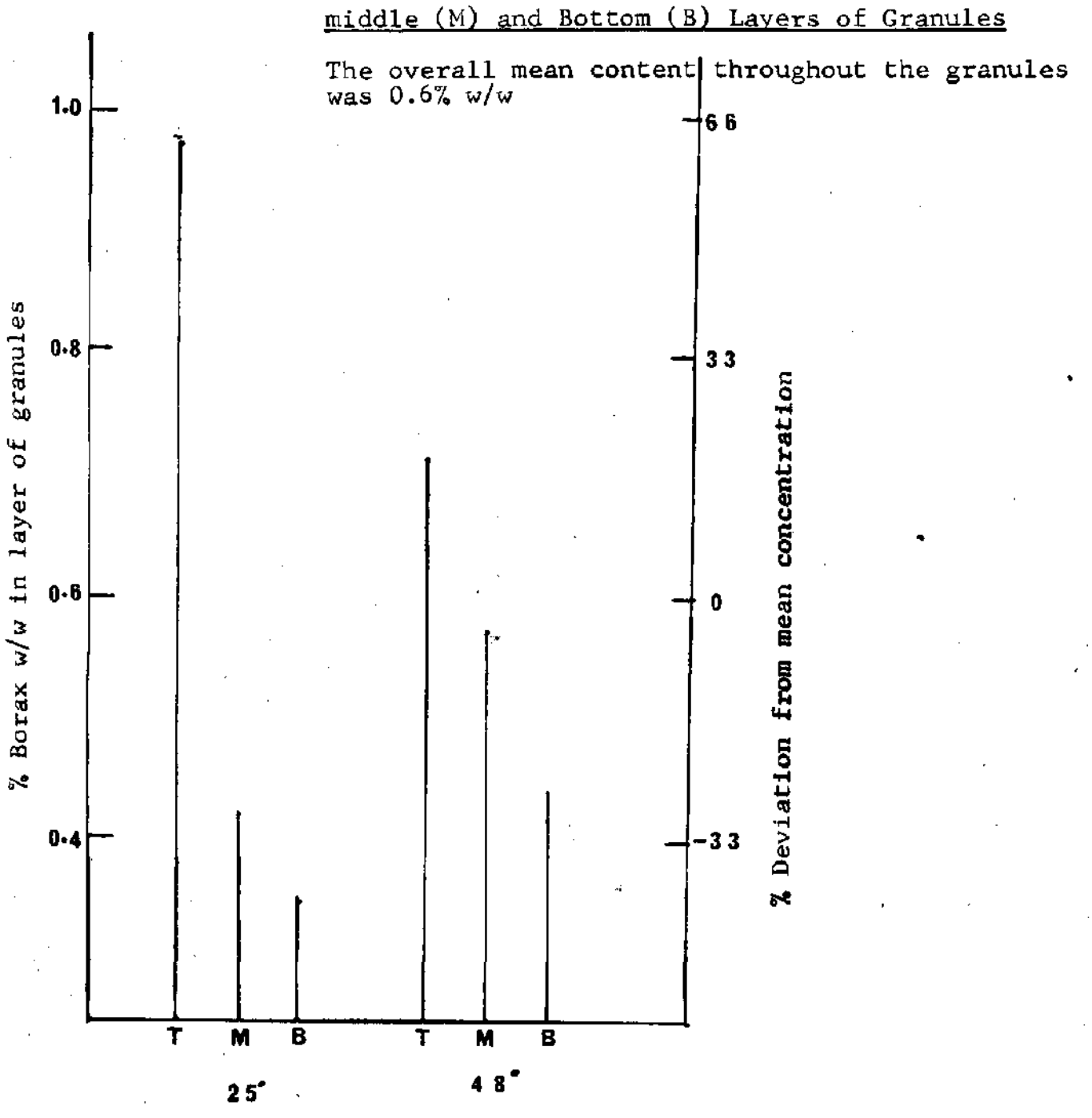


Figure 23 Effect of Temperature of Drying of Granules in Plastic Jar on Borax Distribution in Top (T), middle (M) and Bottom (B) Layers of Granules

The overall mean content throughout the granules was 0.6% w/w



Layer of Granules

There are two main factors which would contribute to a lower net migration of solutes in granules dried at the higher ($48^{o}C$) temperature. The first is related to a dilution effect of lactose, a higher quantity of which will dissolve in the binder during the higher temperature of drying. Since all the borax was present as a solution, only lactose was present as a powdered material some of which will dissolve in the borax solution. The solubility of lactose is enhanced at higher temperatures. Thus a higher quantity of lactose in solution would migrate along with the borax and thereby diluting the effective concentration of borax in the layers.

The second factor is related to a higher extent of in situ evaporation of moisture directly from within the granule bed dried at the higher temperature. While appreciating the fact that convective heat transfer is the predominant drying process the increase in drying time of a thick bed of granules will cause the container walls to equilibrate with the oven temperature. This will allow some measure of conductive heat transfer through the container walls, which would be higher with the higher drying temperature. Thus a portion of the moisture will evaporate from within the granules and the vapour diffuse through the pores in the granule bed. This will decrease the volume of binder, and therefore the amount of solutes, available for migration towards the bed surface.

On the other hand, a lower drying temperature leads to a lower drying rate (figure 22). This allows a sustained constant rate period when the rate of binder

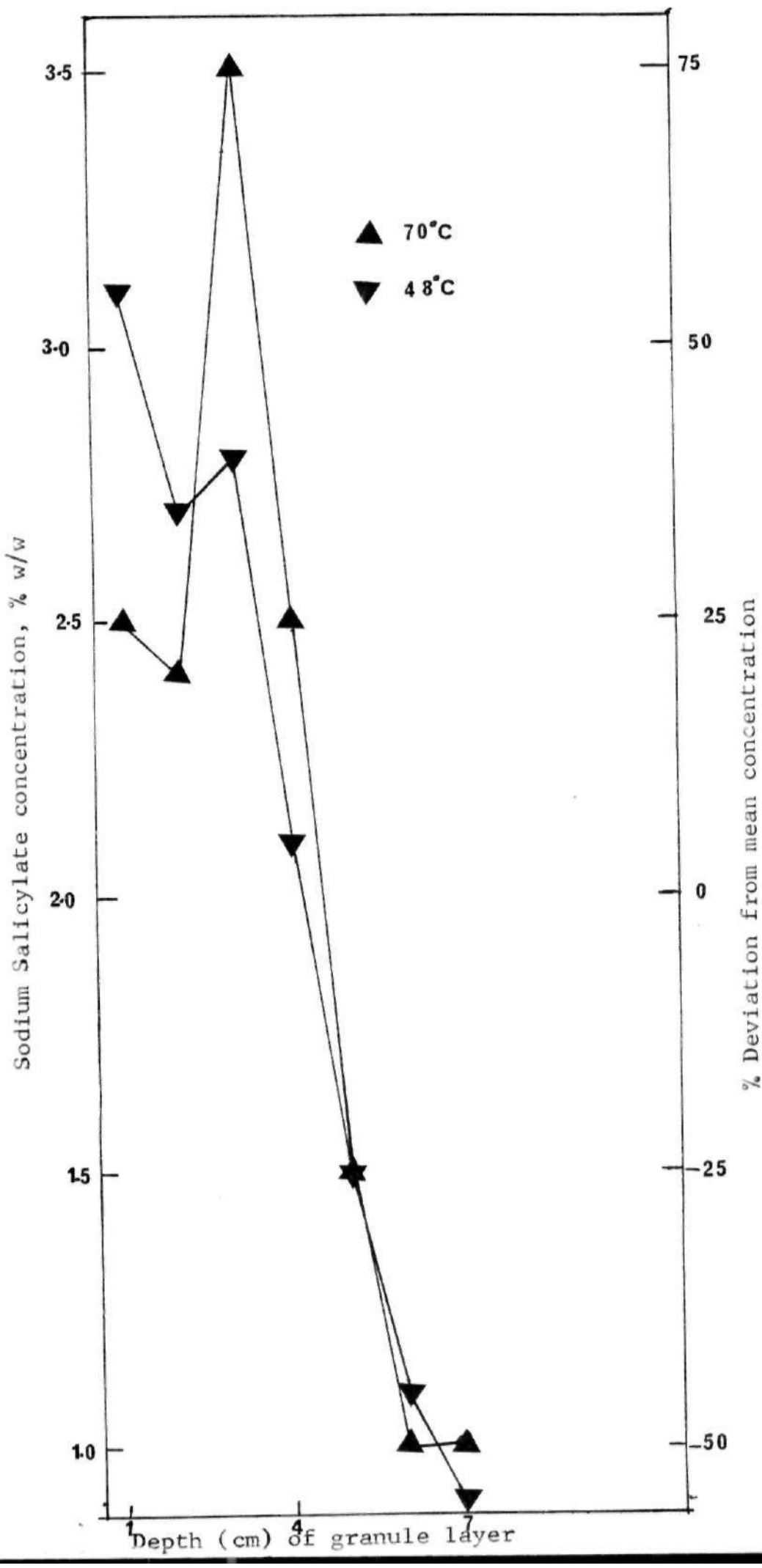
transport to the granule surface equilibrates with the rate of moisture evaporation from the surface. Thus a greater quantity of solutes, consisting of mainly borax, are deposited on the surface.

Figure 24 shows the effect of drying temperature on the distribution of sodium salicylate in a granulation containing 2% w/w sodium salicylate/lactose massed with 14% v/w water. The concentration of sodium salicylate on the top layer of granules dried at a lower temperature, 48°C, was higher than in granules dried at a higher, 70°C, temperature. This may be attributed to a higher temperature which allows a higher rate of evaporation from the bed surface than the rate of migration of the binder solution, and thus solutes, to the surface of the bed. There was therefore no constant rate period to maintain the deposition of the solutes at the surface. Thus the evaporative front receded into the granule bed and sustained at 3 centimetres from the bed surface until the pendular liquid state was reached.

Although there is comparatively much less heat transfer by conduction in a hot air oven where the heat transfer is predominantly convective, it is still expected that the layer of granules where the effect of heat conduction into the granule bed will mostly be felt is the bottom layer. The bottom layer of the granules has the largest area of contact with the container. Therefore the effect of heat conduction through the container wall will be more marked in the drug concentration in the bottom layer. The amount of heat conduction through the

Figure 24 Effect of Drying Temperature in the Oven on Distribution of Sodium Salicylate Throughout the Layers of a Thick Bed of Granules Prepared by Massing 2% w/w Sodium Salicylate 28.8 μm/Lactose 13.5 μm with 14% v/w Water

Figure 24


3·5
3·0
2·5
2·0
1·5
1·0
75
50
25
0
-25
-50
70°C
48°C
Sodium Salicylate concentration, % w/w
% Deviation from mean concentration
1
4
7
Depth (cm) of granule layer

container bottom to the bottom layer of granules will be higher with a higher drying temperature. Thus the amount of moisture evaporated directly from the bottom layer will be higher at 70°C. Consequently the volume of binder available for solute migration from this bottom layer is decreased more appreciably. The concentration of sodium salicylate in the bottom layer dried at 70°C will then be higher than at 48°C as obtained in Figure 24.

It has been illustrated in Figure 21 that the intergranular migration of a binder solution to the surface of a granule bed dried in the plastic jar was an "off-shoot" of intragranular migration from the granule interior to the periphery. The abrasion techniques applied to granule surfaces (Selkirk, 1976) give a measure of intragranular solute migration to the granule periphery to form a crust. This abrasion techniques showed that the amount of intragranular migration of solutes to the granule periphery decreased as the drying temperature increased up to 65°C (Table 9). Beyond 65°C, there was no marked difference in the concentration of borax in the abraded fines. Thus the abrasion results are similar to and confirm the plastic jar model (Table 9, Figures 23 and 24).

The variation in the concentration of borax is expressed as the percentage deviation between granules before abrasion and fines produced by these granules after abrasion. The higher heat transfer into the tray dried granules at higher temperatures allows in situ vaporisation of moisture. Thus the volume of binder available for capillary migration and thus transportation of the solutes

Drying Temperature ^{o}C	32°			48°			65°			82°		
	Weight		% drug content	Weight		% drug content	Weight		% drug content	Weight		% drug content
	gm	%		gm	%		gm	%		gm	%	
1000 µm granules before abrasion	106.0	100	1.9079	61.4	100	1.5701	65.7	100	1.9169	90	100	1.9445
1000 µm granules remaining	48.3	45.6	-	37.1	60.4	1.9413	25.5	38.8	1.8794	33.9	37.7	-
1000 µm granules abraded to 710 µm	41.2	38.9	1.9600	18.0	29.3	-	26.5	40.3	1.9513	40.1	44.6	1.9869
180 µm granules	11.3	10.7	-	-	-	-	2.9	4.4	-	9.1	10.1	-
>180 µm granules (fines)	11.1	10.5	1.4875	6.3	10.3	1.6488	6.1	9.3	1.6904	9.0	10.0	1.6389
Extrapolated content in 10% fines	-	10.0	1.4167	-	10.0	1.6008	-	-	1.8176	-	10.0	1.8210
% Deviation between unabraded granules and fines	-	-	26	-	-	19	-	-	5	-	-	6

Table 9 EFFECT OF TEMPERATURE OF DRYING OF GRANULES ON DRUG CONTENT IN FINES ABRADED FROM PERIPHERY OF COARSE GRANULES

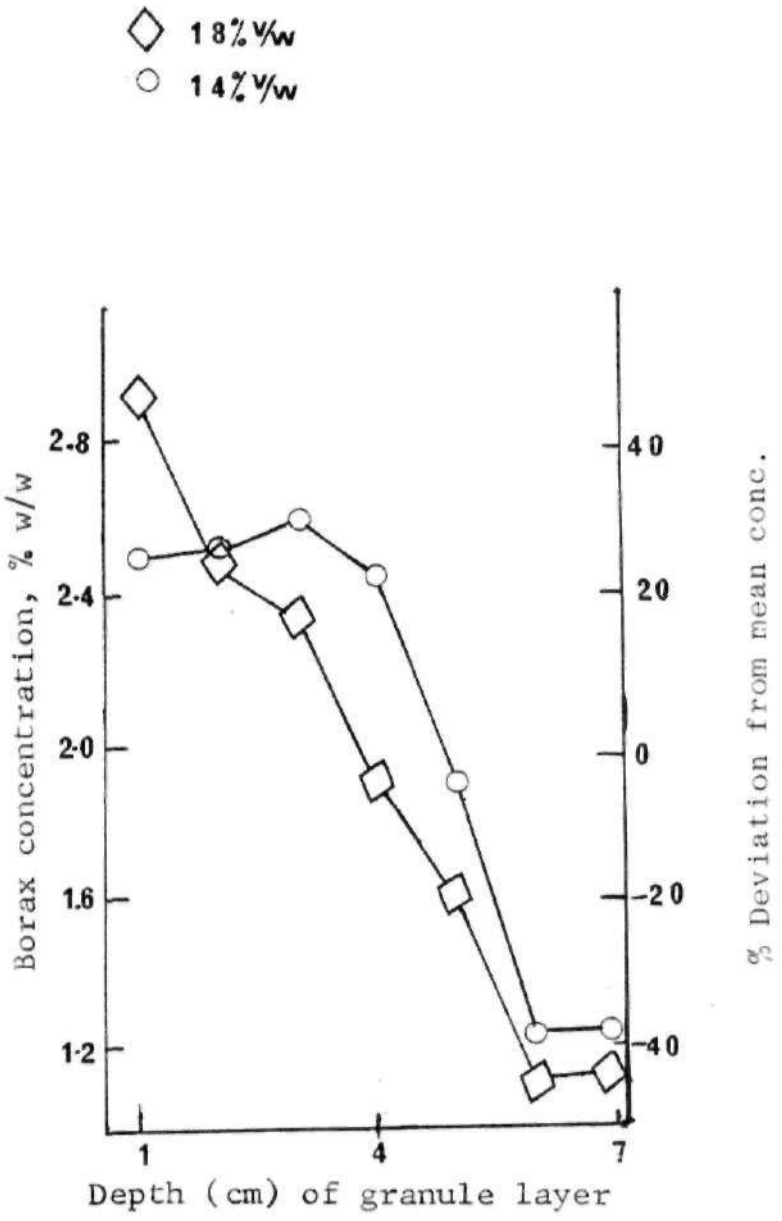
will be decreased. This therefore accounts for the decrease in solute migration to the granule periphery with an increase in the granule drying temperature.

3.2.3 EFFECT OF BINDER CONCENTRATION

Figure 25 shows the effect of binder volume on the distribution of borax in layers of a thick bed of granules. The highest borax concentration was in the top layer of granules massed with 18% w/w binder. The peak concentration in granules with 14% v/w binder was lower and was 3 centimetres deep from the upper surface of the bed. More solutes dissolve in the higher binder volume which is available to be drawn to the surface layer by capillary forces. A longer constant rate period and therefore a higher solute deposition took place as the moisture evaporated from the surface. As drying proceeds the volume of the binder reaching the surface reaches a critical moisture content below which capillary forces fail to draw the binder to the surface (Ridgway and Callow, 1967). The evaporative front continues to recede into the bed of granules. This leads to a progressive decrease of borax concentration down through the granule bed. The critical moisture content of 11% (figure 22 for 48^{o}C) is close to the initial lower binder volume of 14% v/w. Therefore this lower binder volume causes the evaporative front to recede, within a shorter time, from the surface leading to a peak borax concentration within the bed.

The concentration of borax at the bottom layer was similar to that of the layer preceding it. This is so

Figure 25 Effect of Binder Volume on Borax Distribution in Layers of Granules



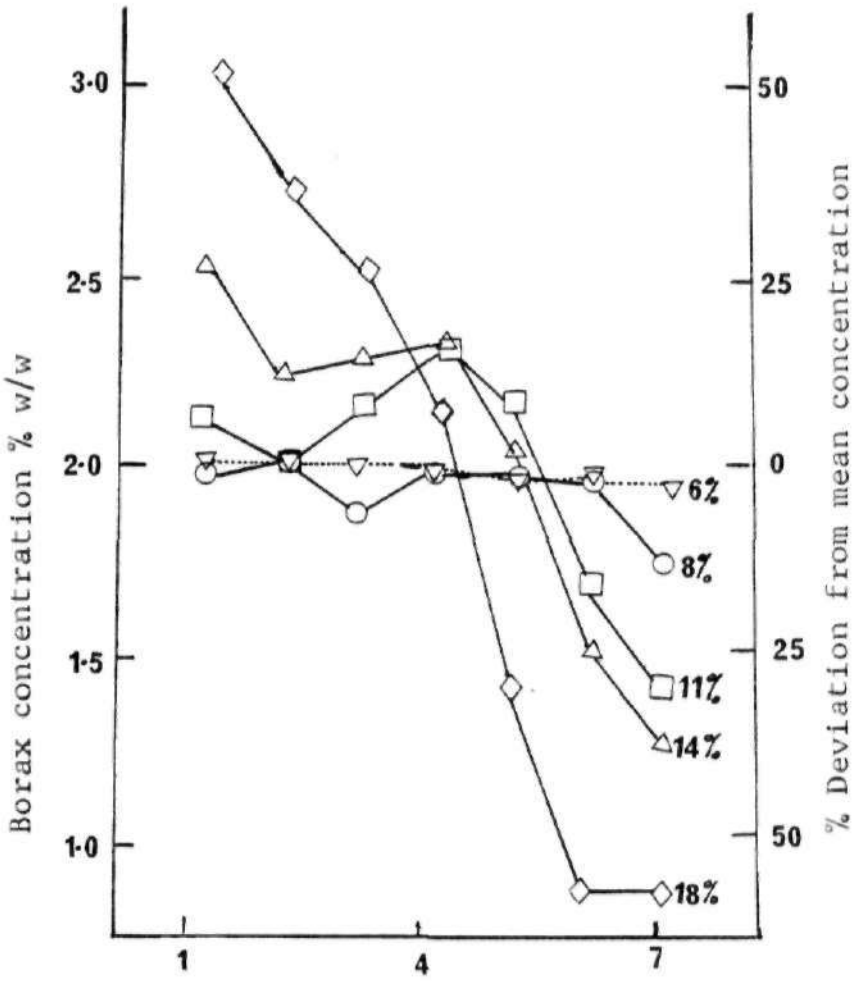
for each of the two binder volumes (figure 25). Back diffusion of solutes from a more concentrated layer to the less concentrated bottom layer after migration, a terminology used earlier by Rubinstein and Ridgway (1974), was proposed by Travers (1975) to explain this phenomenon. However, as has already been shown in Figure 24 some measure of heat transfer through the larger surface area of contact between the granules and the container bottom allowed some direct in situ evaporation of moisture, and thus vapour difusion, from the bottom layer. Therefore the amount of binder available for migration from this bottom layer is less. Consequently the concentration of the borax in the bottom layer would be expected to be similar to that in the preceeding layer as shown in Figure 25.

Rescreening of granules during drying

Granules were dried to a pre-chosen moisture content on a shallow (spread) bed of granules on a tray before rescreening the granules into a packed bed contained in a plastic jar and further drying was undertaken to study the effect of the initial moisture content on migration.

A steady change of borax concentration in the granule layers was obtained with a decrease in the initial moisture content (Figure 26). When the moisture content of the rescreened and packed bed of granules was at or just below the critical moisture content, that is at 11% or below (Figures 22 for 48°C and 26), there was an insufficient capillary action to maintain the flow of the binder to the surface layer. As a result the peak concentration of borax receded to the inner layers of the granule bed.

Figure 26 Effect of Time of Intermediate Screening and Moisture Content Remaining on Borax Distribution in Granule Layers



When the initial moisture content was in the region of the second falling rate, i.e. 6% v/w the moisture is in the pendular state. During this state capillary transport of the binder is absent. The binder will only be dried by in situ moisture evaporation thus leaving some deposits of the solutes at the points where the evaporation takes place. The heat transfer necessary for this in situ evaporation is expected to be mostly by conduction which is a very slow process. At 8% v/w there was a very little evidence of migration with even less migration occurring at an initial moisture content of 6%.

Concentration of PVP in binder

The drying rate curves for granules massed with 10% and 15% PVP were similar although the first falling rate was slightly higher with the 10% granulation, (Figure 27). An increase in the concentration of PVP solution increases the viscosity of the binder which will decrease migration (Warren and Price, 1977). Therefore the drying rate of the more dilute solution would be expected to be higher. However the lower drying rates of 20% w/v PVP solution rather than that of 25% w/v obtained appears to be a contradiction. The explanation may be related to a closer intra- and inter-granular packing with 25% as a result of the expected higher adhesive force in the more viscous binder as tabulated below.

PVP Binder Concentration % w/v	25	20	15	10
Packing density (g cm^{-3}) of granules	0.75	0.65	0.66	0.66

This will lead to a decrease in the capillary pore size. Such a decrease in the pore size has been shown by Warren

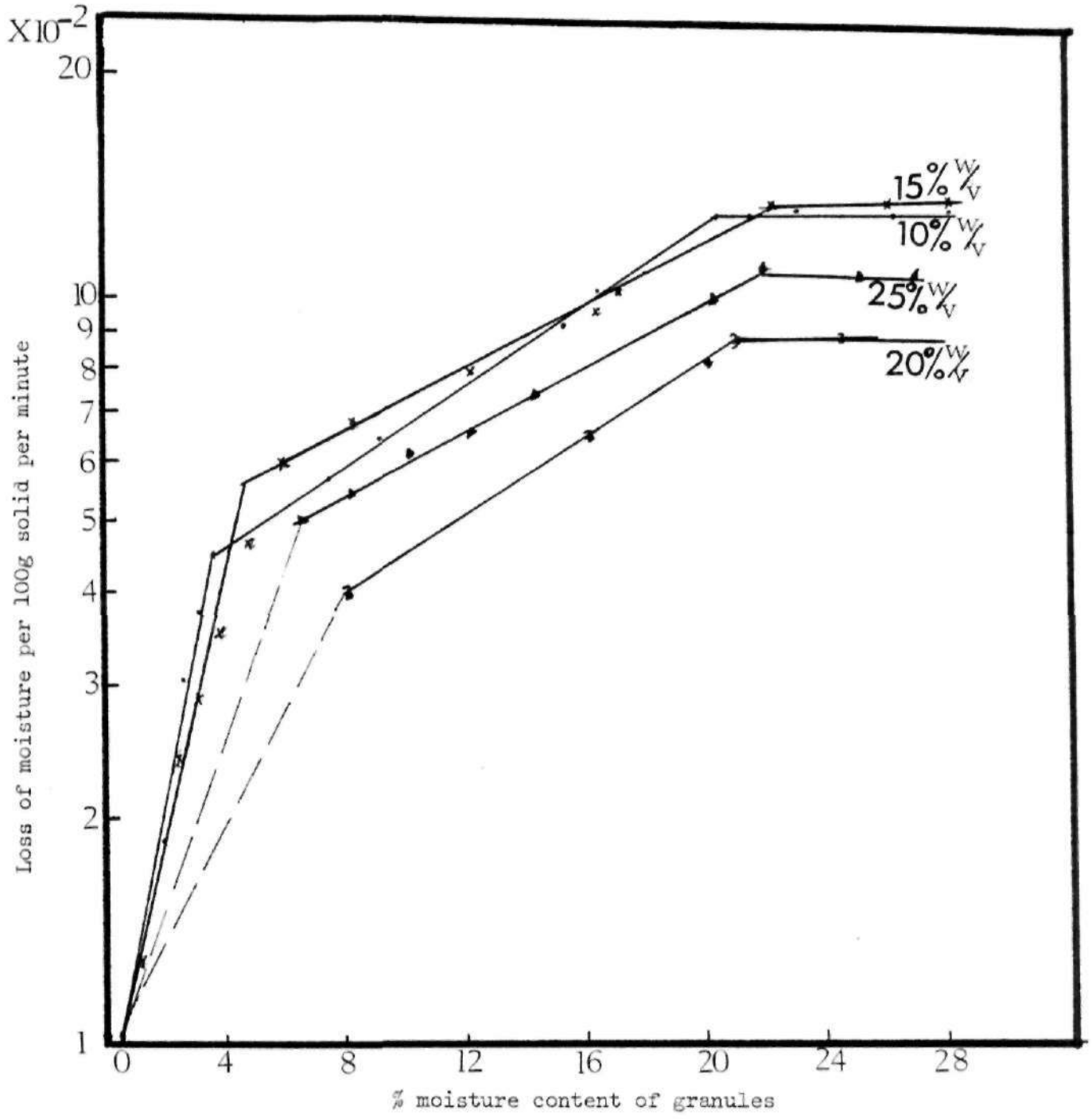


Figure 27 Effect of concentration of PVP solution as binder on drying rates of granules of 2% Sulphadimidine in pure dibasic calcium orthophosphate massed with 33% v/w of PVP solution.

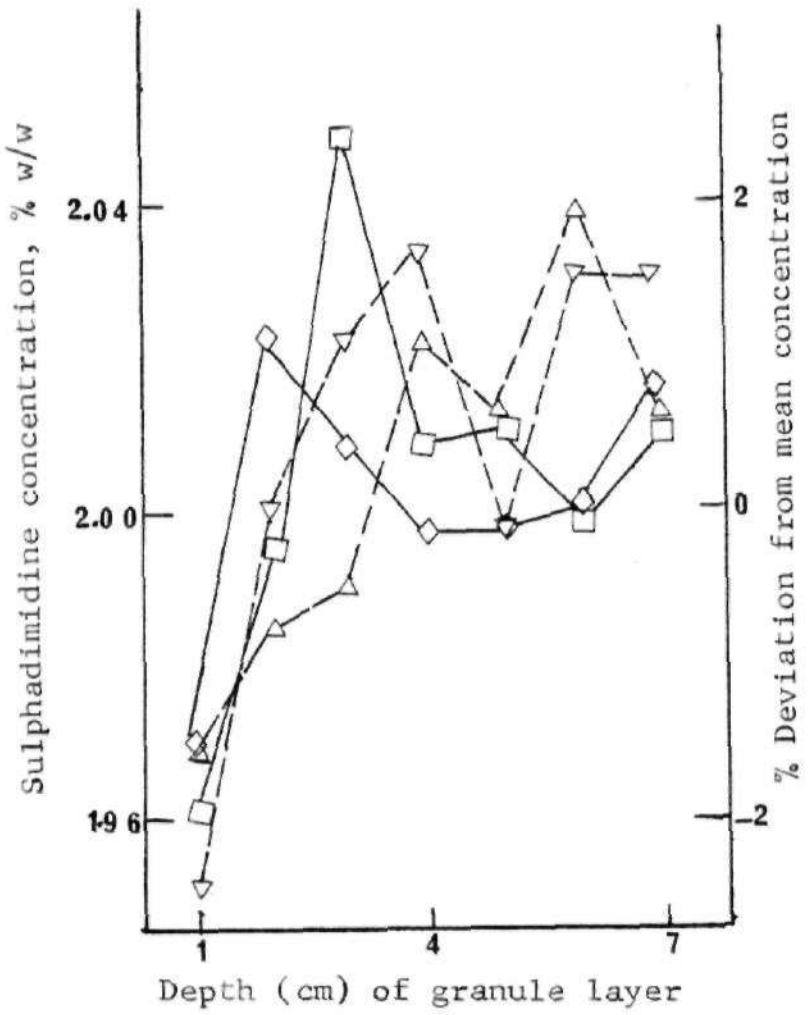
and Price (1977) to increase the capillary forces available to draw the binder to the surface.

The constant rate period ceases at 20% moisture content despite the relatively higher binder volume when compared with the higher drying rate in previous borax/lactose granules dried at the same temperature (Figures 22 and 27). The viscous nature of the PVP binder is expected to be one of the contributory factors causing the differences in the drying rates of the two granulations. Therefore as expected the PVP binder in sulphadimidine/dibasic calcium orthophosphate granules took comparatively longer drying times compared with the water binder in borax/lactose granules.

The effect of PVP concentration on solute migration and thus on the distribution of sulphadimidine in layers of granules did not produce a simple relationship (Figure 28). However a lower drug concentration was generally contained in the top layer. Although a comparatively higher volume, 33% v/w, of binder was used only the migration of PVP is expected as the dry mix components are poorly soluble. Any PVP migration towards the drying surface 'dilutes' the concentration of the drug (Travers and Patel, 1979). On the whole, the migration of binder was less marked as only some $\pm$ 2% deviation in the concentration of sulphadimidine was obtained in the layers. This is a pointer to show that the distribution of a drug is most uniform during drying when both the drug and diluent are poorly soluble in the binder which is viscous such as PVP. The solute migration is limited to PVP only. This is even minimised by the viscous effect of the PVP binder (Warren and Price, 1977).

Figure 28 Effect of Concentration of PVP Solution as Binder on the Distribution of Sulphadimidine in Granule Layers. The Diluent Used was Dibasic Calcium Orthophosphate

Note The effect of the particle size as shown is not significantly different.



△ 25% w/v PVP solution

▽ 20%

◇ 15%

□ 10%

3.2.4 EFFECT OF GRANULE PACKING DENSITY

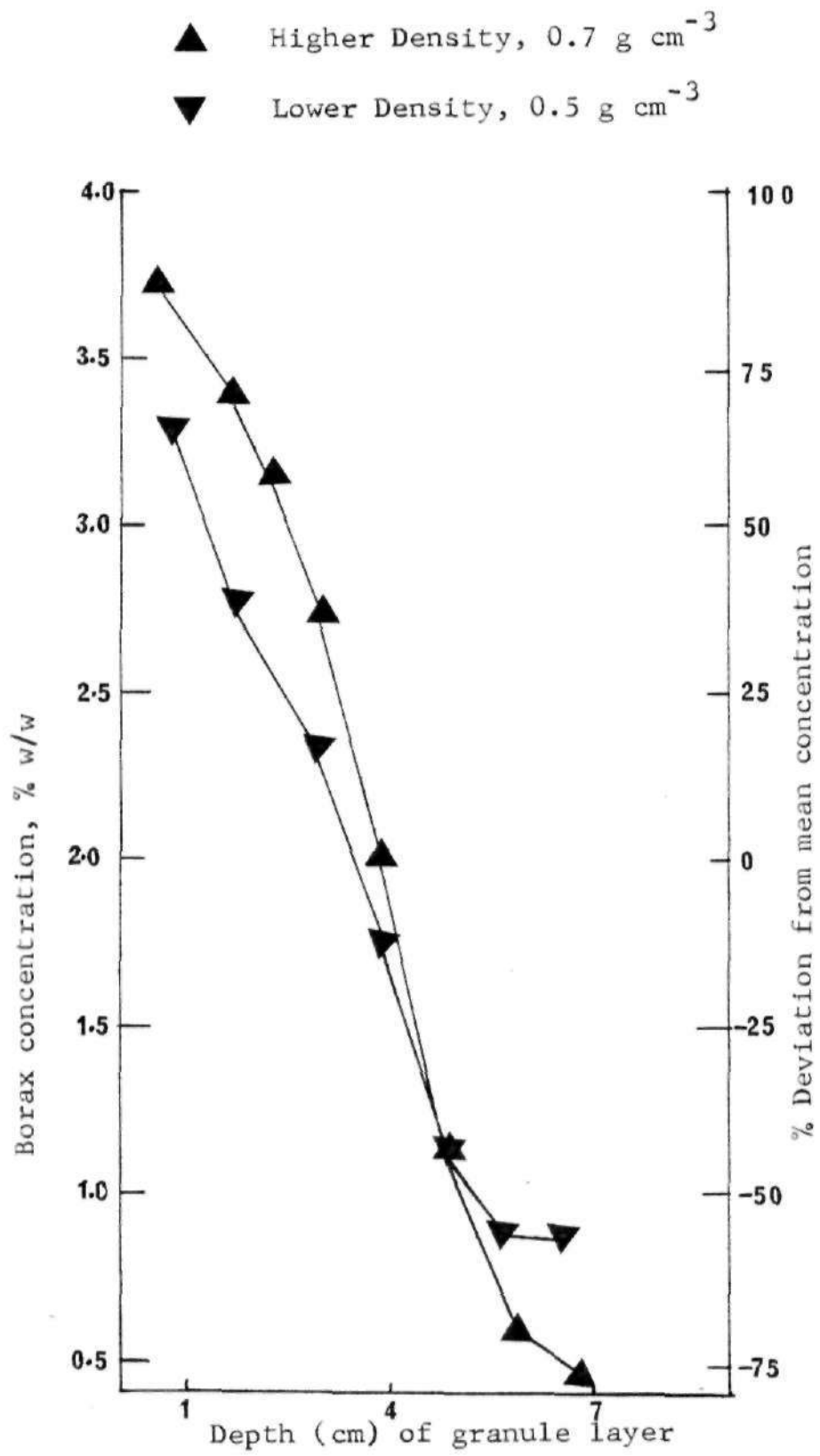
If a thick bed of granules is tapped down the packing density of the granules is increased. This allows a closer intergranular contact and thus leads to a reduction in the intergranular pore size in the bed. This smaller size of capillaries will support a greater height of liquid binder in the capillary and funicular states. Therefore a longer constant rate period and a higher binder volume will allow a higher amount of solutes to be deposited on the surface.

Figure 29 shows this more marked migration of solutes in the more densely packed granules. Warren and Price (1977) have shown that the use of a smaller particle size of lactose as the diluent decreased the capillary pore size of granules which increased the capillary forces necessary for transporting the binder to the drying surfaces. Thus any procedure which leads to a decrease in the pore size of granules during drying will increase the extent of solute migration.

3.2.5 EFFECT OF GRANULE BED THICKNESS ON GRANULE SIZE AND BORAX DISTRIBUTION

The drying time of a thick bed of granules is much longer than that of a shallow spread of granules of equal amount on a tray. In a shallow bed, the heat of the oven is easily transferred through the larger exposed areas of the granules. This will lead to a shorter constant rate period but a substantially greater quantity of moisture evaporation within that period. There will

Figure 29 Effect of Packing Density on the Distribution of 2% w/w Borax/Lactose Granule Layers



be some measure of direct evaporation of the major part of the moisture in the binder. As a result, only a smaller scale of inter-granular migration of solutes will take place.

Conversely the transfer of heat, other than the convective heat transfer on the bed surface, into a thick bed of granules involves a much slower process - a longer constant rate period but a lower rate of moisture evaporation. Thus evaporation takes place at the surface of the bed as long as the capillary and funicular states exist in which case capillary forces continue to transport the binder solution to the granule bed surface.

It would normally be expected that the migration of solutes to the surface will lead to a larger mean granule size of the granules in the top layer. However Table 10 shows that the proportion of large granules was the same in the top and bottom layers and only slightly lower in the middle layer. The migration and deposition of solutes in the top layer would lead to harder granules which are expected to be more resistant to dry screening abrasion. The deposits of the solutes would also bridge some smaller granules together. The bottom layer of granules by virtue of their larger surface area of proximity with the container allowed some direct evaporation of moisture resulting in crystallized solute bridges. Thus a high proportion of large granules would be obtained. In the case of the middle layer, it can be seen that the concentration of borax was higher than in the bottom layer. However it would be expected that any deposition of solutes would

Size of sieve (μm) retaining granules	% Cumulative weight of granules				
	Tray dried	Top layer of thick bed	Middle layer	Bottom layer	Whole layer of thick bed
1000	26	33	30	33	32
710	50	55	53	56	55
500	70	72	70	72	71
355	84	85	84	85	85
250	94	94	93	93	93
180	98	97	97	97	97
< 180	100	100	100	100	100

Table 10 EFFECT OF DRYING A THICK BED OF BORAX/LACTOSE GRANULES ON GRANULE SIZE DISTRIBUTION IN THE LAYERS AS COMPARED TO THAT OF TRAY DRIED GRANULES FROM THE SAME BATCH

take place mostly during the pendular state allowing the solute deposition in the pores rather than at the bridges. This would therefore contribute less to granule size effects.

The lower proportion of large granules dried on the tray is expected due to less solute dissolution during the comparatively shorter time of constant rate period before the binder equilibrates with the oven temperature. This is shown in Table 10 and Figure 30.

In Figure 31 as expected the concentration of borax in the 3 layers of granules is directly related to the height of the layer. This is shown as a vertical displacement of the respective borax concentration/granule size curves. The shapes of the respective curves are similar. There is a gradual decrease in borax concentration as the granule size decreases. This was also the case with the borax concentration in granule sizes of the whole batch of granules contained in the thick bed.

The same sample of granules dried on the tray gave rise to the peak borax concentration in the intermediate sized granules, a result consistent with that obtained by Selkirk (1976). The explanation for this is given later in Figure 46. However, the reason for the borax concentration being directly related to the size of thick bed dried granules is traceable to the action of solute migration in the bed during drying. This migration of solutes involves the transportation of binder through the granule pores from the bottom to the top layer of

Figure 30 Effect of Drying a Thick Bed of Borax/Lactose Granules on Granule Size Distribution Compared to that of Tray Dried Granules

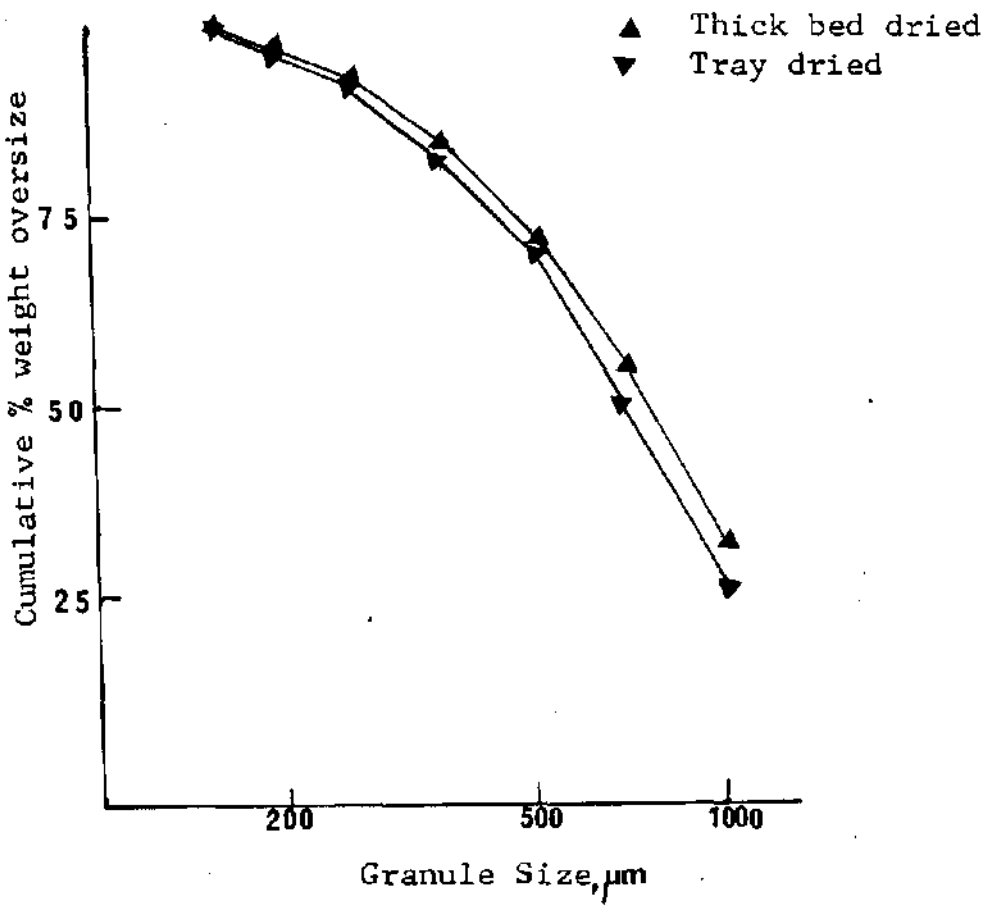
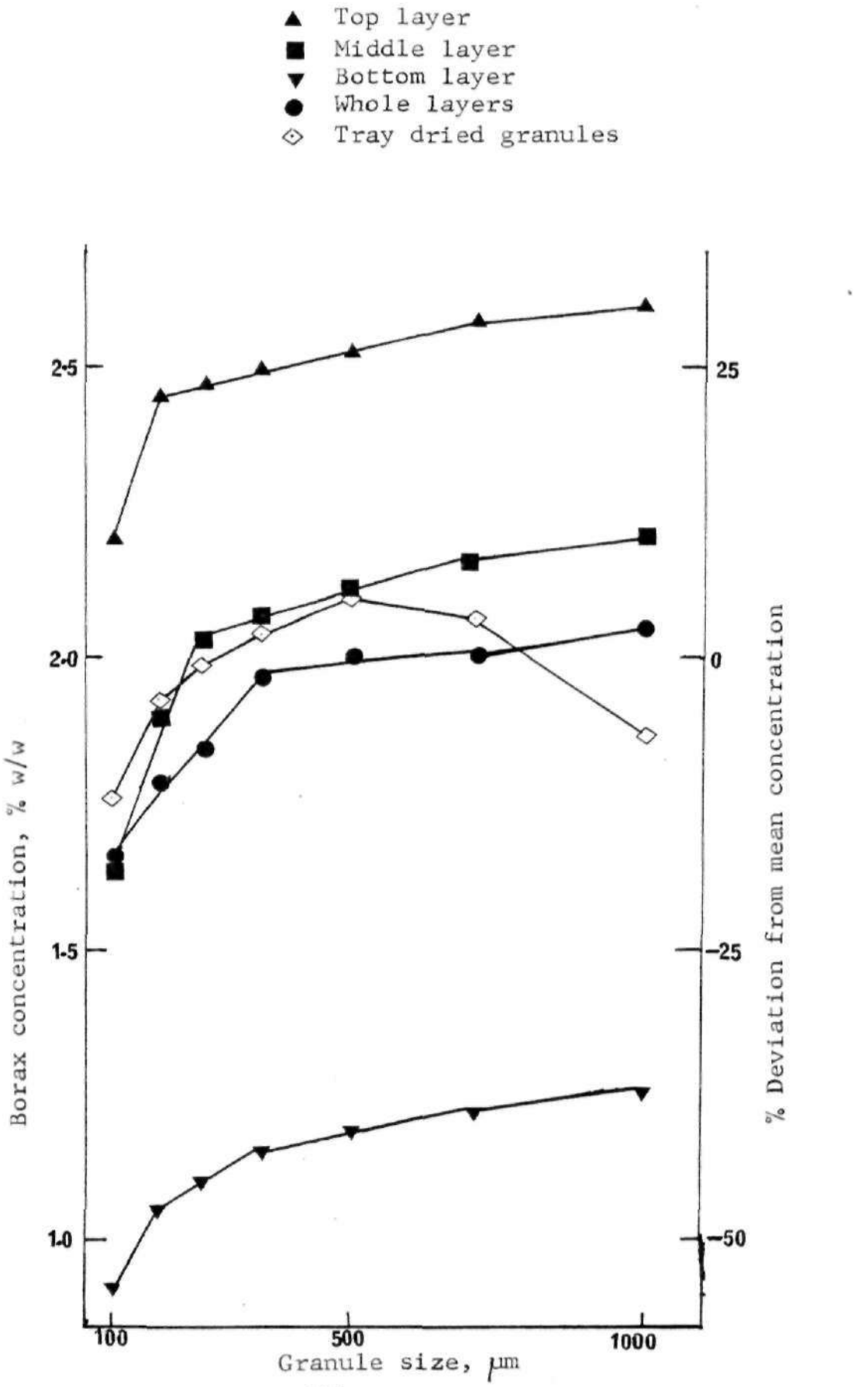


Figure 31 Effect of Drying a Thick Bed of Borax/Lactose Granules on Borax Distribution in Granules Sizes of the Top, Middle and Bottom Bed of Granules Compared to Overall Distribution and to Tray Dried Granules



granules as long as the capillary and funicular states exist. When the suction potential generated by the capillaries is insufficient to transport the binder to the surface the evaporation front recedes into the granule bed. This leads to a gradual recession of drying front from the top to the bottom layers. Therefore the concentration of borax would be a function of the height of the bed (Figure 31). As a result, the deposit of borax for any given height along a horizontal cross-section of granule layer is expected to be uniform. It would therefore be further expected that the concentration of borax in the granule sizes for the given horizontal cross-section would depend on the granule size. Larger granules have larger pores (Nicholson and Enever, 1974) which would retain a higher binder volume at the pendular liquid state where the evaporation of the moisture leaves the solutes in the pores. The concentration would thus be higher in larger granules as obtained.

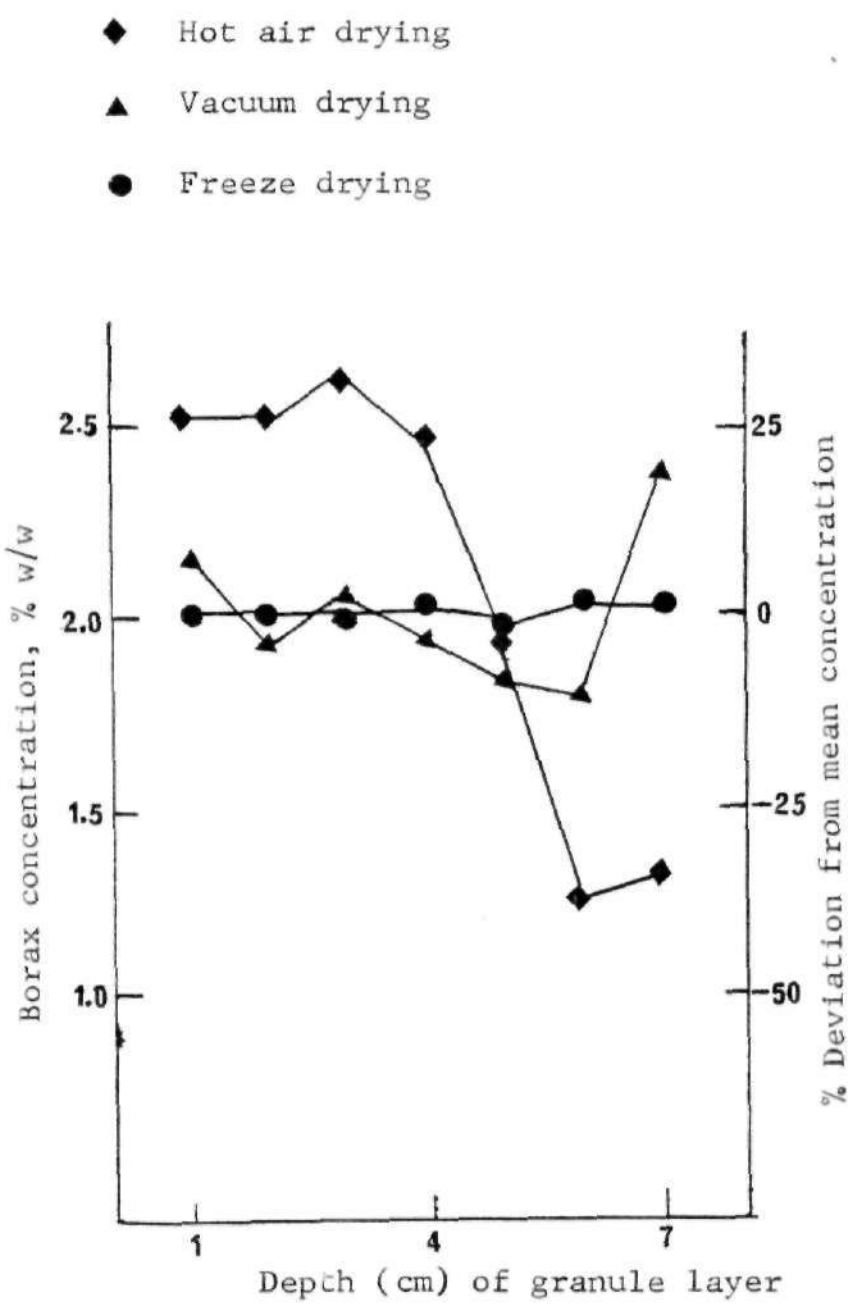
3.2.6 EFFECT OF DRYING METHOD

The effect of drying method on the extent of solute migration in a thick bed of granules is presented in Figure 32.

As expected there was no migration of solutes when the bed was subjected to freeze drying. This form of drying involves the formation of ice and its sublimation below freezing temperature and a vacuum range of pressure.

Some capillary solute migration took place in the vacuum dried granules leading to peak concentration of borax in the bottom layer and the granule bed surface

Figure 32 Effect of Drying Method of Borax/Lactose Granules on Distribution in Granule Layers



layer. This result is similar to that obtained by Travers (1975) using granules containing sodium chloride and kaolin. He proposed flash drying into the inter-granular voids to explain the characteristic curve.

Another explanation may be connected to the effect of heat transfer through the container bottom to the bottom layer of granules. Drying in a vacuum oven is a slow process as convection is almost absent due to lack of air motion. Drying will therefore take place by heat conduction into the granule bed through the walls and bottom of the container. As the sectioning of granules into layers involves a horizontal cross-section only the container influence at the bottom layer will be pronounced Therefore the evaporative front will continue to be more predominant at the bottom layer until enough heat is transferred into the entire bed where rapid vaporisation of moisture will occur.

Water is reported to boil at $35^{o}C$ in a vacuum at 0.06 bar or 6×10^{3} N m^{-2} (Carter, 1972). It is however expected that the binder is not pure water and this will raise the boiling point.

The distribution of borax in layers of granules dried in the hot air oven has been described already (Figure 25 for 14% v/w binder). Drying is achieved on the bed surface by convection. The capillary action continues to draw the binder to the surface where evaporation of the moisture takes place leaving a deposit of solutes. When the critical moisture content, below which the capillary action is unable to saturate the surface with the binder,

is reached, the evaporative front recedes gradually into the bed. A gradual decrease of borax concentration will be expected down the bed layers. The peak concentration at 3 centimetres depth is attributed to the inability of the capillary forces to sustain the faster evaporation at the surface leading to a more prolonged evaporative front at this depth.

The results in Figure 32 show that this solute migration is highest in granules dried in the hot air oven, followed by vacuum drying and absent in free dried granules. Intergranular migration in fluidised dried granules was not undertaken. It was difficult to have a stationery thick bed drying in the fluidised state as drying of granules in this system involves the suspension of granules in the form of aggregates in the fluidising gas.

3.2.7 EFFECT OF PARTICLE SIZE OF DRUG AND DILUENT

The particle size of powdered materials for granulation has been shown to affect the porosity of the granules (Hunter and Ganderton, 1972; Opakunle and Spring, 1976). This porosity of the granules has in turn been shown by Warren and Price (1977) to affect solute migration. It would therefore be expected that the effect of the particle size of the materials which affect the porosity of the granules formed will affect the migration of the solutes and thus the concentration of a low dose drug in the granules.

3.2.7.1 Drug Particle Size

The drug concentration used in this study was 2% w/w. At this concentration the particle size of the drug will not

markedly affect the capillarity of the granules formed and therefore will not appreciably affect solute migration. The only expected effect of the size of the low dose drug will be the rate of its dissolution in the binder during massing (Figure 19) and during the higher temperature of drying. However drying of a packed bed of granules in a plastic jar caused a considerably longer drying time. It would thus be expected that the dissolution rate would not be a rate determining step except perhaps on the top and bottom layers of the granule bed. Depending on the moisture content, the top layer may reach the pendular state within a short time. The bottom layer may also lose some of its moisture by in situ evaporation as a result of heat transfer through the container bottom as discussed before.

From Figures 33 to 37 it is shown that the particle size of a low dose drug as predicted above has a negligible effect on migration of solutes in a thick bed of granules. For example, a comparison between a predissolved sodium salicylate in the binder shows that the particles of sodium salicylate incorporated as a dry mix also dissolved completely during massing or at least by the drying time (Figure 33). Thus the results are not appreciably different.

3.2.7.2 Diluent Particle Size

An increase in the particle size of the diluent will reduce the volume of a binder (Hunter and Ganderton, 1972) necessary for intra-particulate bridging. This is due to the decrease in the net surface area of the larger particles

Figure 33 Effect of Sodium Salicylate Particle Size on its Distribution in Granule Layers

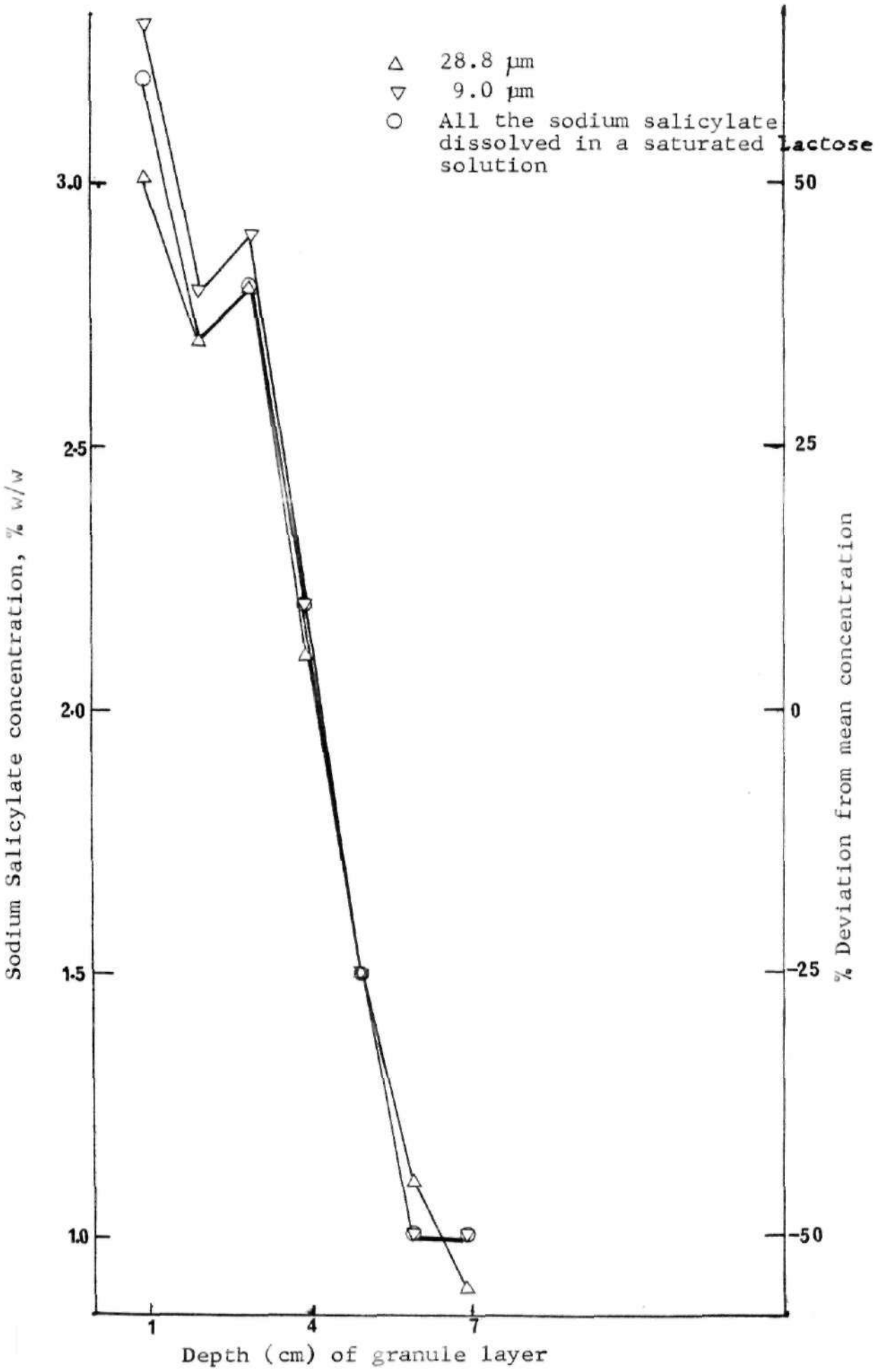


Figure 34 Effect of Borax Particle Size on its Distribution in Layers of Granules Prepared by Massing 2% w/w Borax/Lactose with Water, 14% v/w

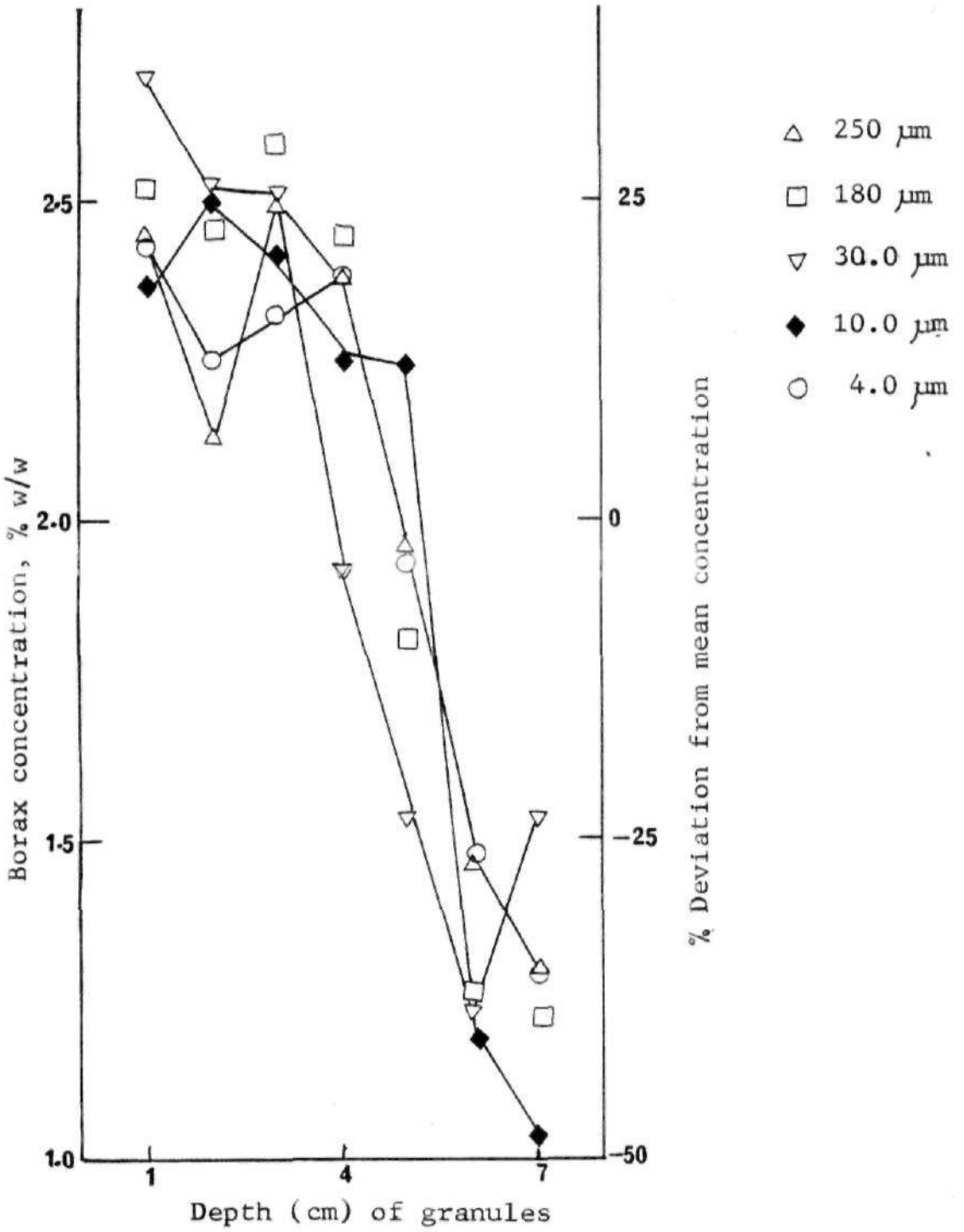


Figure 35 Effect of Sulphadimidine Particle Size on its Distribution in Layers of Granules Prepared by Massing 2% w/w Sulphadimidine/Lactose Dry Mix with Water, 20% v/w

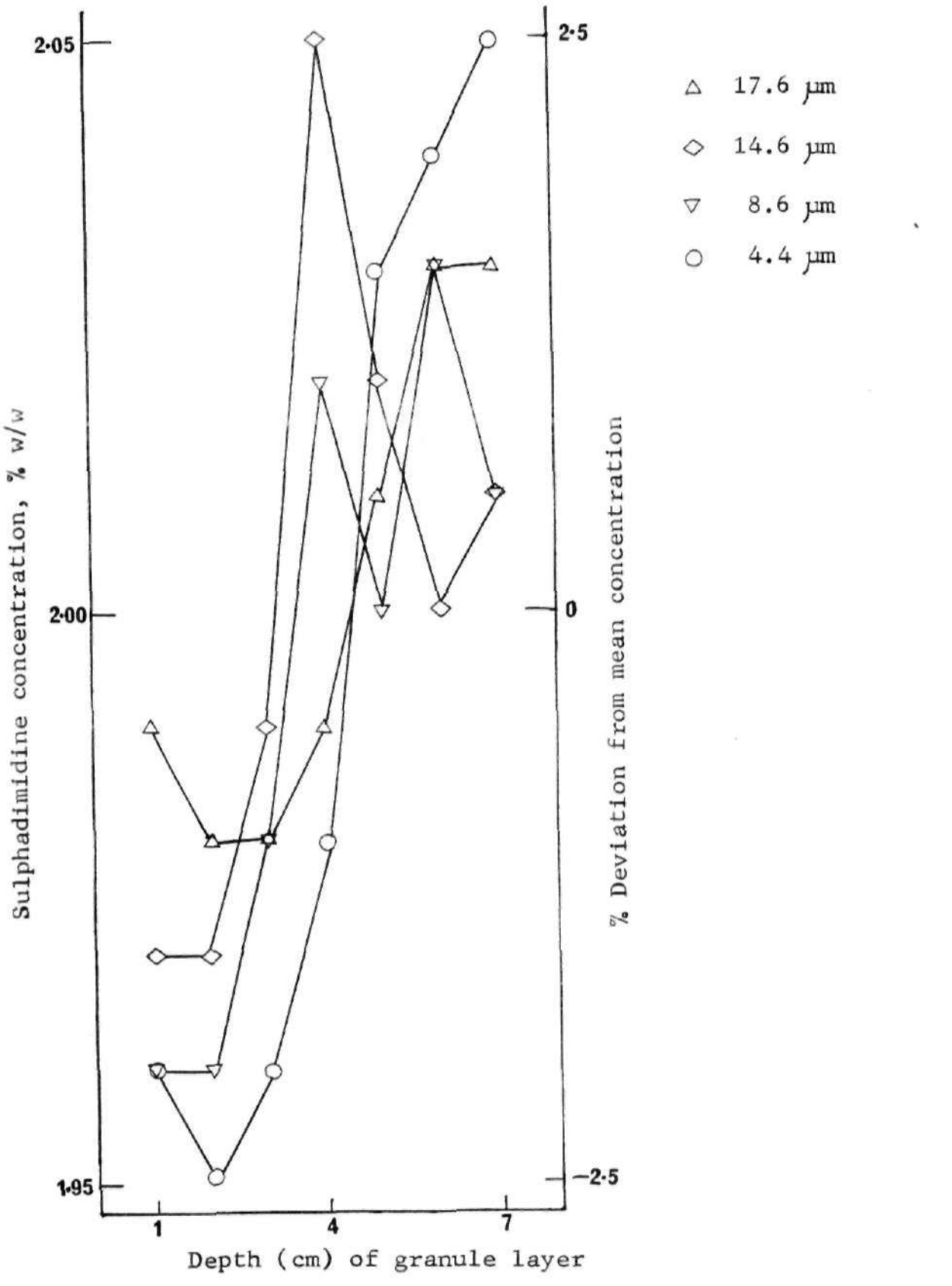


Figure 36

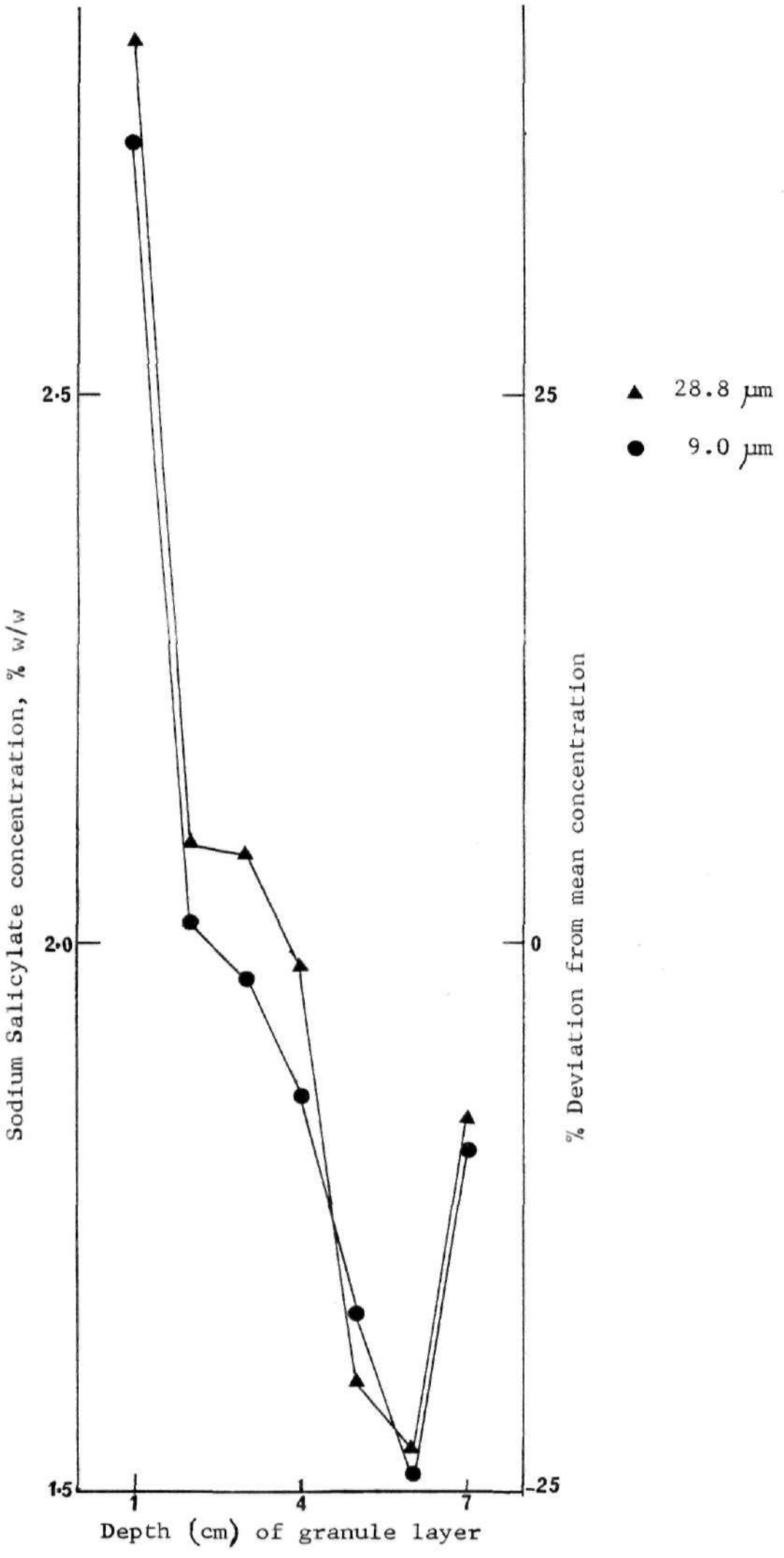
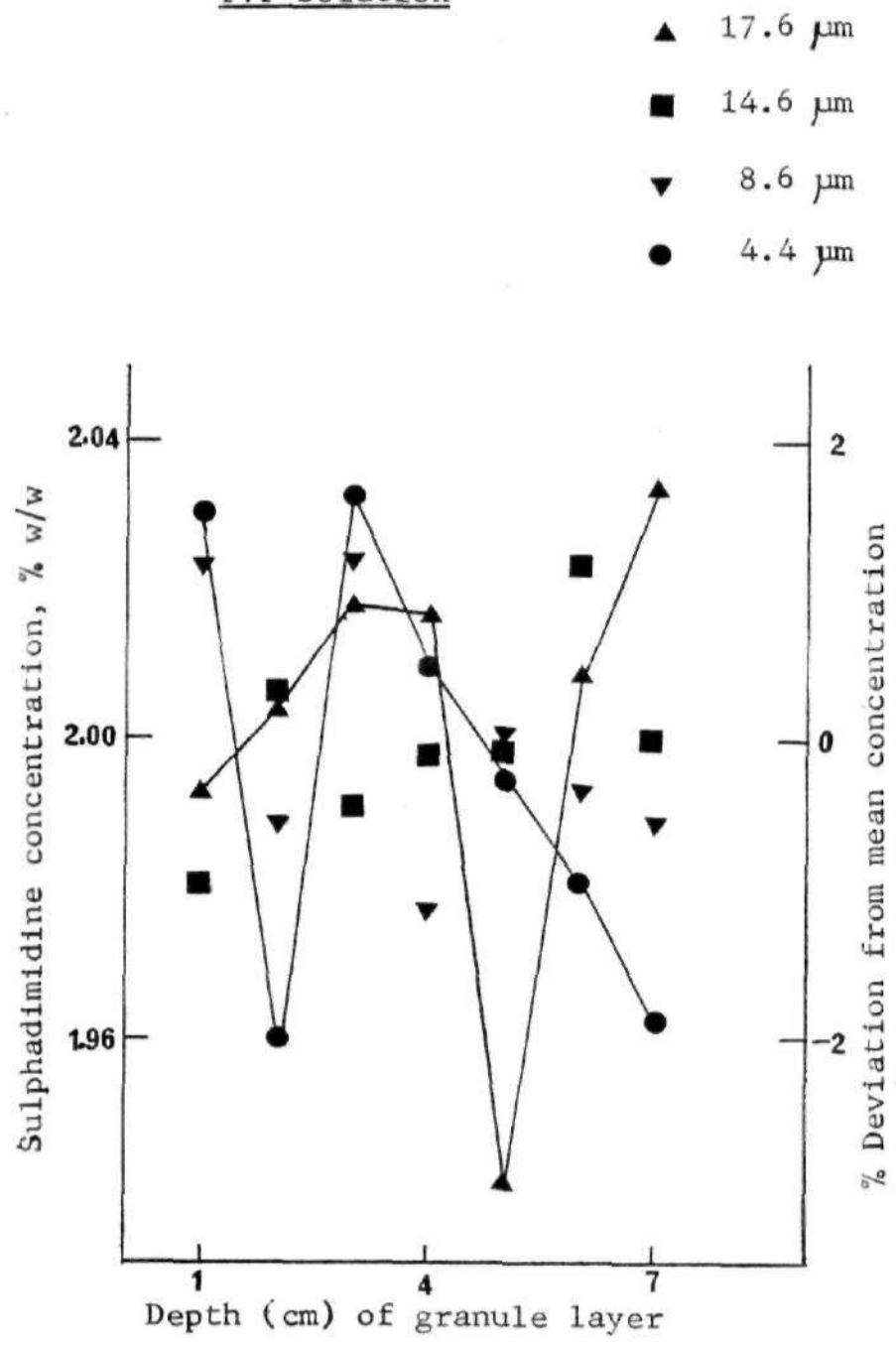

2·5
2·0
1·5
Sodium Salicylate concentration, % w/w
25
0
-25
% Deviation from mean concentration
▲ 28.8 µm
● 9.0 µm
1
4
7
Depth (cm) of granule layer

Figure 37 Effect of Sulphadimidine Particle Size on its Distribution in Layers of Granules Prepared by Massing 2% w/w Sulphadimidine/Dibasic Calcium Orthophosphate 2.4 μm with 33% v/w of 15% w/v PVP Solution



These results are not significant.

available for intra-granular contacts or solid-bridging. Therefore a higher volume of the binder will be available for solute migration. This higher effective binder volume will increase the saturation level of the intra-granular voids. Thus more binder will be available to cause a closer inter-granular packing effect leading to an increase in the packing density of the bed of granules for drying (Table 11). A closer packing of granules by tapping of the same batch of granules has previously been demonstrated to enhance solute migration (Figure 29). Consequently the effect of increase in the particle size of the diluent on solute migration is similar to the effect of increasing the binder volume for granulating smaller particles.

Figure 38 shows how an increase in PVP binder volume increased the migration of the PVP towards the drying surface. The particle size of the micro-component, sulphadimidine, did not make any substantial difference (only $\pm$ 2% deviation) in the migration. However, the particle size of a major component, Emcompress as the diluent, increased the migration of PVP leading to a higher ($\pm$ 6%) deviation (Figure 39). Although the packing density of the granules prepared from the unfractionated Emcompress was appreciably higher (Table 11), the migration of PVP was not consistent and did not bear any simple relationship with the initial particle size. However the same size of unfractionated Emcompress caused a substantial migration of sodium salicylate (Figure 40).

Figure 38 Effect of Sulphadimidine Particle Size and Binder Volume on Distribution of Sulphadimidine in Layers of Granules Prepared by Massing 2% w/w Sulphadimidine/Lactose Dry Mix with a Given Volume of Water

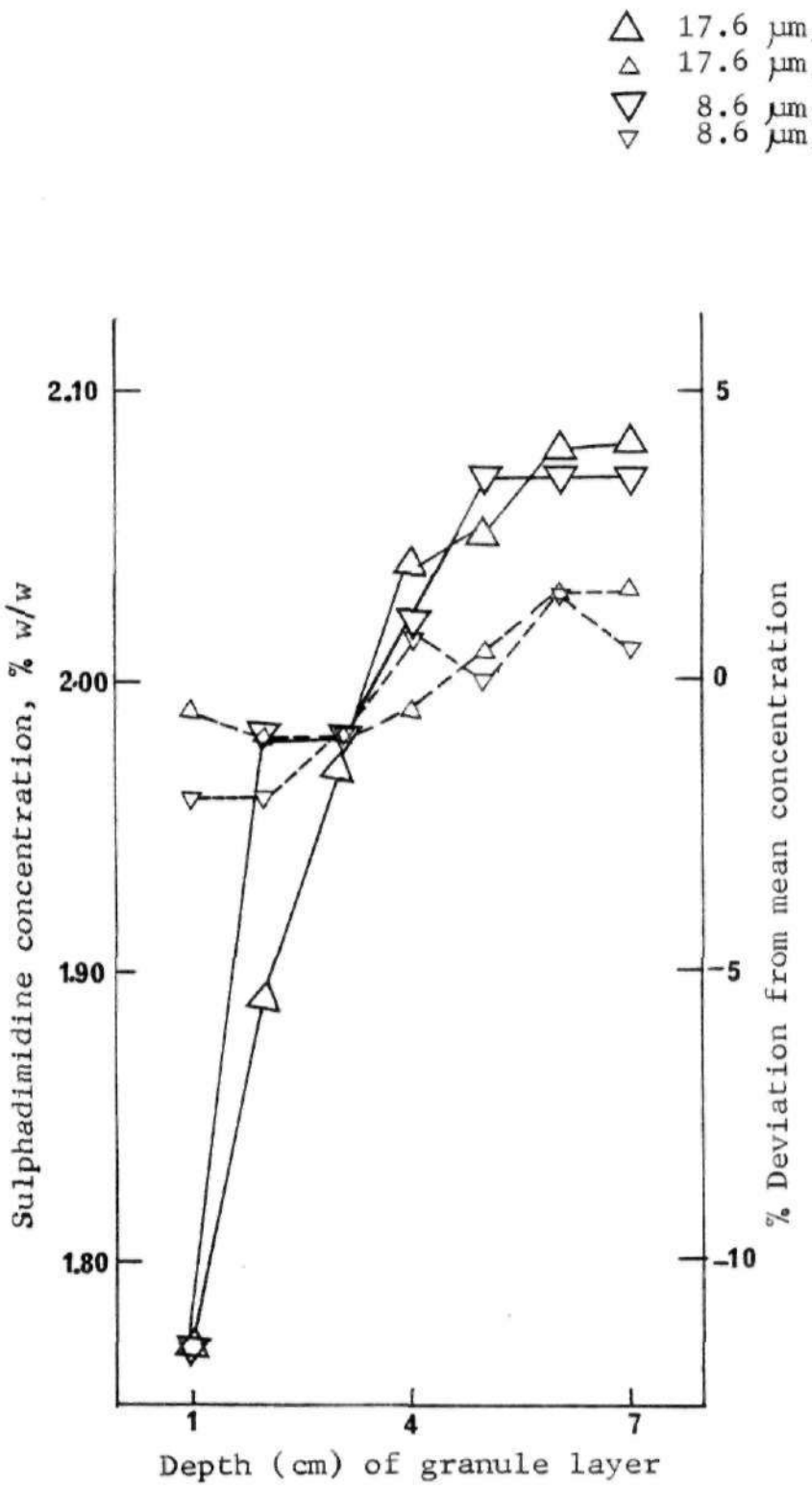
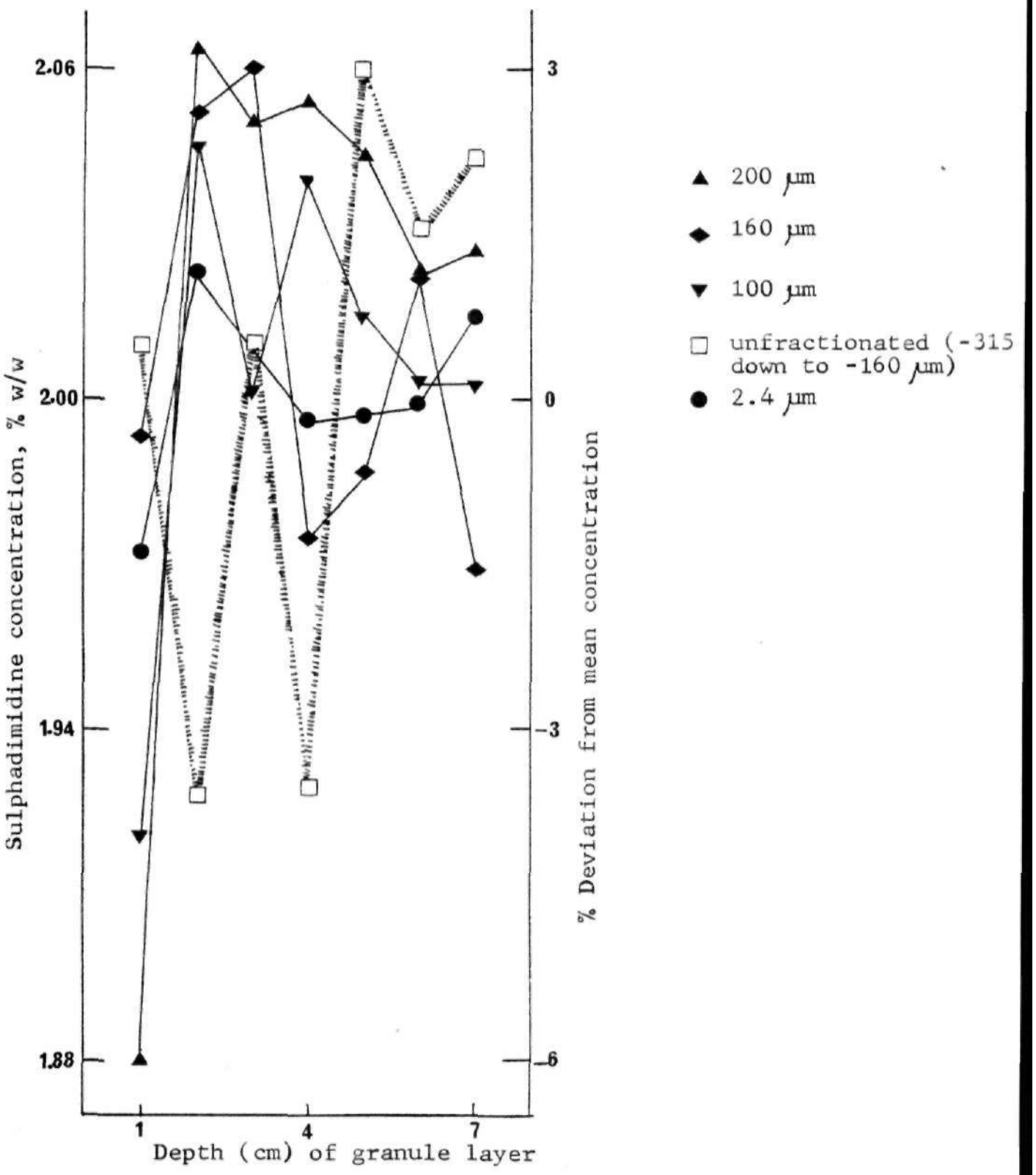


Figure 39 Effect of Dibasic Calcium Orthophosphate Particle Size and Size Distribution on the Distribution of Sulphadimidine with 33% v/w of 15% w/v PVP Binder



Particle Size of Lactose	µm	350		180	105	13.5
Packing density of borax/lactose granules,	gcm^{-3}	0.63		0.63	0.49	0.42
Packing density of SDM/lactose granules	gcm^{-3}	0.64		0.58	0.44	0.39
Particle size of d.c.o.	µm	Unfractionated	200	160	100	4.4
Packing density of sod. sal./d.c.o. granules	gcm^{-3}	0.74	0.49	0.51	0.55	0.68
Packing density of SDM/d.c.o. granules	gcm^{-3}	0.70	0.58	0.55	0.52	0.66

SDM = sulphadimidine

d.c.o. = pure dibasic calcium orthophosphate

Table 11: Effect of particle size of diluent on the packing density of granules which filled the plastic jar container. The density was calculated with reference to the dry weight of the granules.

Figure 40 Effect of Particle Size of Dibasic Calcium Orthophosphate on Distribution of Sodium Salicylate in Layers of Granules Prepared by Massing the Dry Mix with 33% v/w of 15% w/v PVP Solution

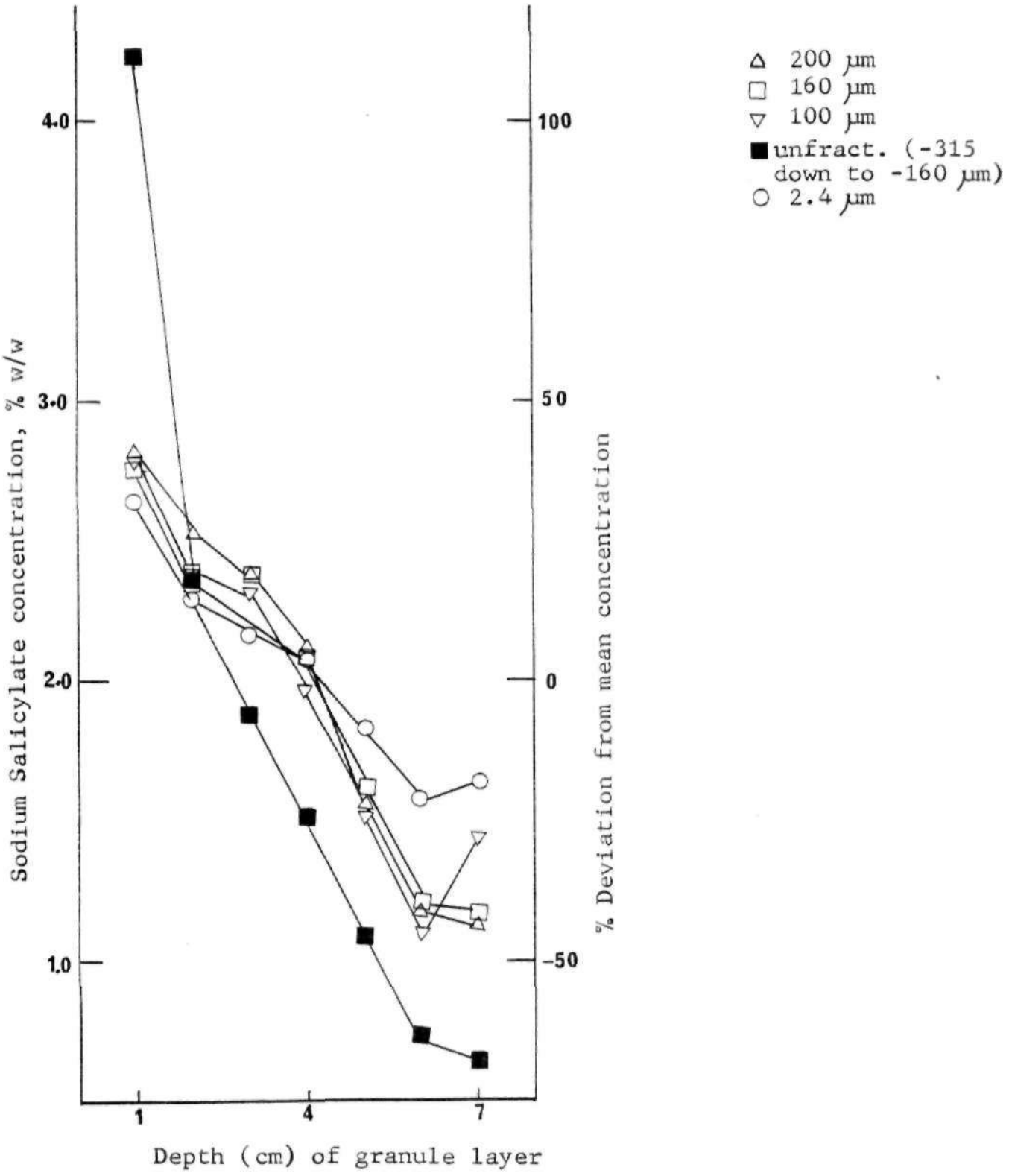


Figure 41 shows the effect of lactose particle size on borax distribution in the granule layers. There was no appreciable difference in the migration of solutes in granules prepared from the initial granular sizes, 105 to 350 micrometres, of lactose. However the migration of borax in granules prepared with the much finer 13.5 micrometres fraction of lactose was much lower. This shows that there must be an optimum initial size beyond which the high amount of solute migration would produce only negligible differences in the migration. The finer lactose used in the granulation produced ± 30% deviation compared with a much higher variation leading to -60% to +115% deviation in granules prepared from the initially larger sizes of lactose.

The extent of migration of lactose (Figure 42) seen as a decrease in sulphadimidine concentration at the upper layers was proportional to the particle size of the same particle size range used in Figure 41. This is attributed to the higher volume of binder available in the pores of granules containing the larger lactose particles. Thus more lactose would dissolve within the longer drying time and migrate to the top layer resulting in a lower concentration of the non-migrating sulphadimidine. Unlike Figure 41, the results here are only within ± 10%. This again shows that the migration of a diluent contributes less in affecting the concentration of the drug present in the granules as a low dose.

When the diluent particles are markedly porous as in the Emcompress particles the location of the binder in

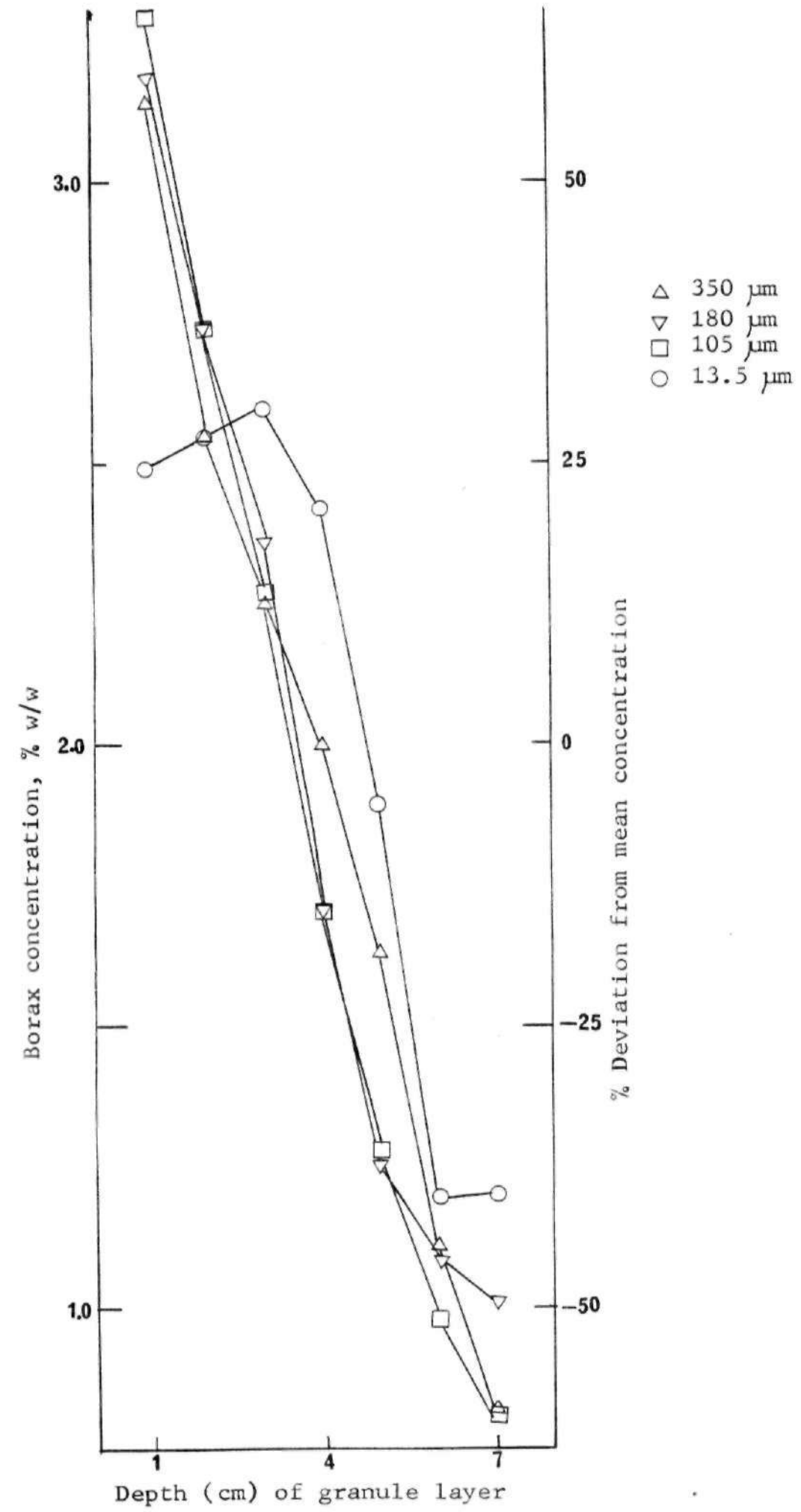
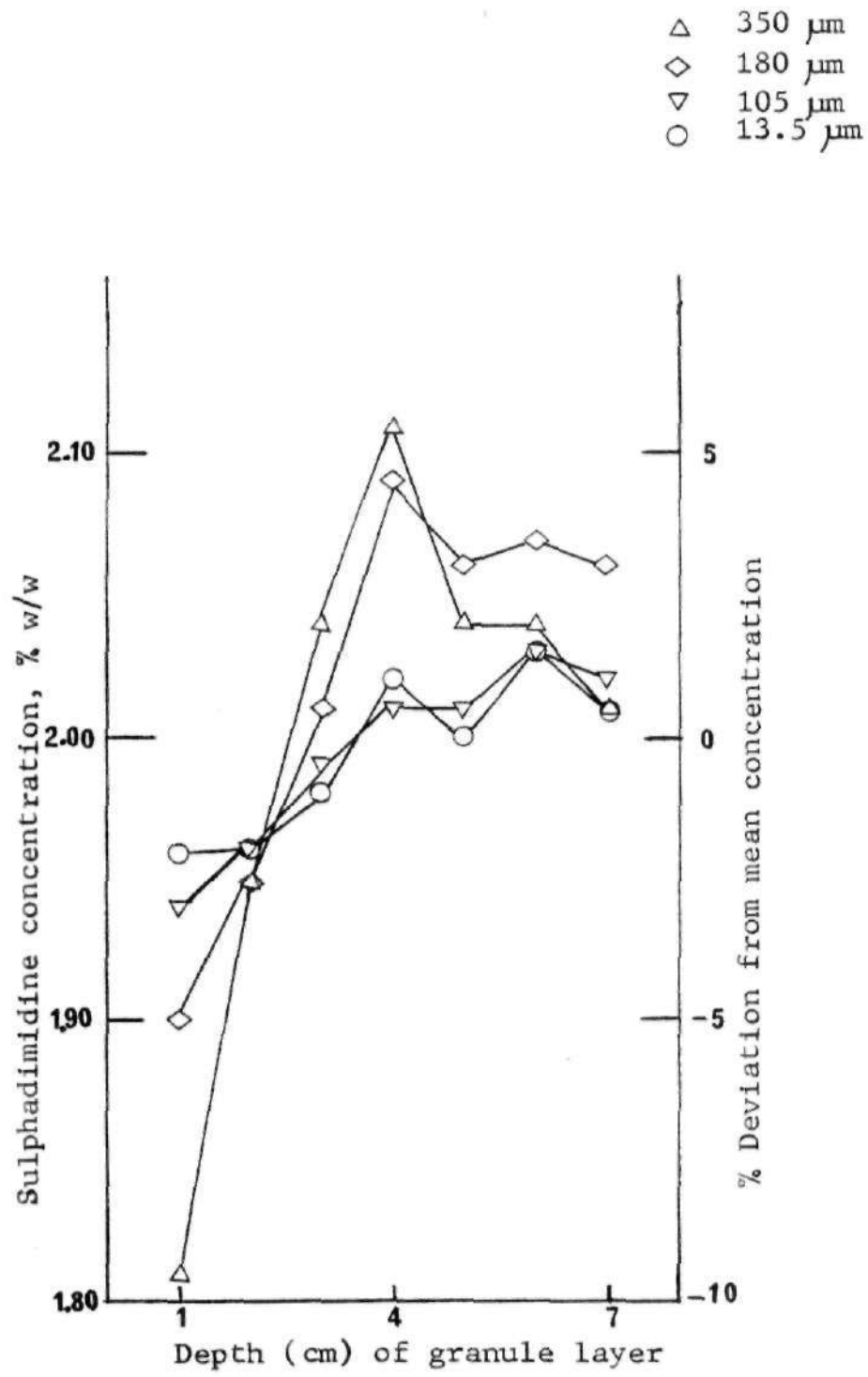

3.0
2.0
1.0
Borax concentration, % w/w
50
25
0
−25
−50
% Deviation from mean concentration
△ 350 µm
▽ 180 µm
□ 105 µm
○ 13.5 µm
1
4
7
Depth (cm) of granule layer

Figure 42 Effect of Lactose Particle Size on Sulphadimidine Distribution in Layers of Granules Prepared by Massing the Dry Mix with Water



these pores reduces the effective volume of binder for intra-particulate bridging. This accounts for the less marked differences in the packing density of granules massed with the Emcompress particles (Table 11).

3.2.8 EFFECT OF RELATIVE SOLUBILITY OF DRUG IN BINDER

The relative solubility of a drug is a major factor affecting distribution of the drug in layers of a thick bed of granules dried in the oven as shown by the results in the preceding investigations e.g. Table 12. Figure 43 (b) shows that there is a linear relationship between relative solubility and the extent of migration. Other parameters, e.g. diluent particle size, either inhibit or enhance the effect of the relative solubility.

In a system where the relative solubility of the drug is less than the drug concentration in the dry mix, solute migration will be seen as the migration of all soluble components, other than the poorly soluble drug, dissolved in the binder towards the surface of the granule bed. Therefore the lower layers would contain a higher concentration of the drug and vice versa. For example, the solutes which dissolved in the binder may include part of the diluent and PVP in PVP binder. Their migration towards the granule bed surface 'concentrates' the drug in the bottom layers and consequently 'dilutes' the drug concentration in the upper layers (Travers and Patel, 1979).

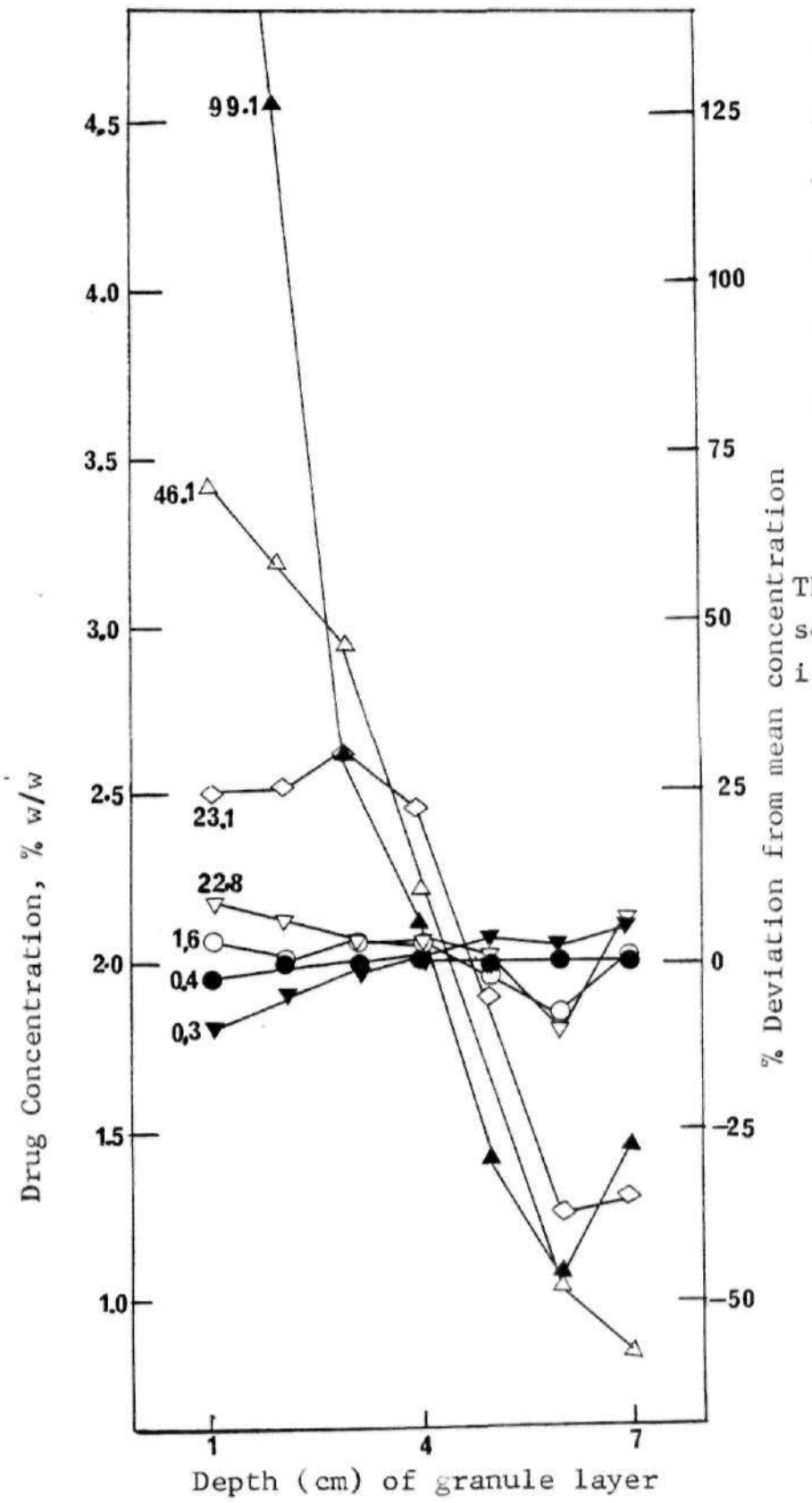
Such a system was exemplified by drying of sulphadimidine granules (Figure 35). Here only lactose

Drug /Diluent	Relative Solubility of drug from Table 8	Max range of Deviation from Drug mean content	Reference
Sodium salicylate/ lactose	46.1	±65%	Figure 33
Borax/lactose	23.1	±40%	Figure 34
Sulphadimidine/ lactose	0.3	±2.5%	Figure 35
Sodium salicylate/ d.c.o.	28.8	±40%	Figure 36
Sulphadimidine/d.c.o.	0.4	±2%	Figure 37

d.c.o. = pure dibasic calcium orthophosphate

Table 12 : Effect of relative solubility on solute migration in a thick bed of granules

Figure 45 (a) Effect of Relative Solubility of a Drug on the Distribution of the Drug in Layers of Granules



▲ Sodium Salicylate/h.m.c. (60% v/w water)

△ Sodium Salicylate/ lactose (20% v/w water)

◇ Borax/lactose (14% v/w water)

▽ Sodium Salicylate/h.m.c. (45% v/w of 15% w/v PVP)

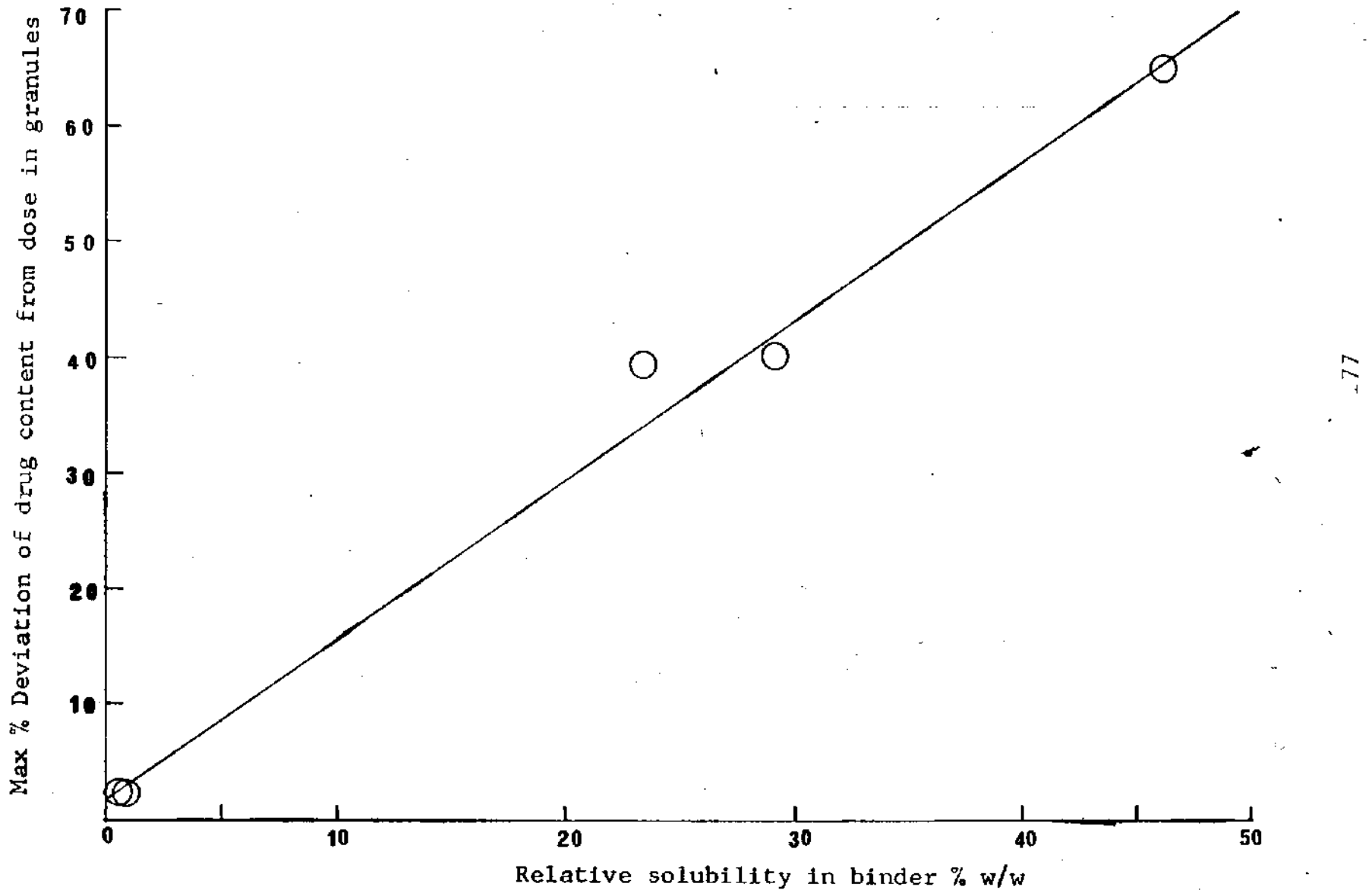
○ Sulphadimidine/h.m.c. (47% v/w of 15% w/v PVP)

● Sulphadimidine/d.c.o. (33% v/w of 15% w/v PVP)

▼ Sulphadimidine/lactose (20% v/w water)

The values of the relative solubility for each granulation is given on the graph

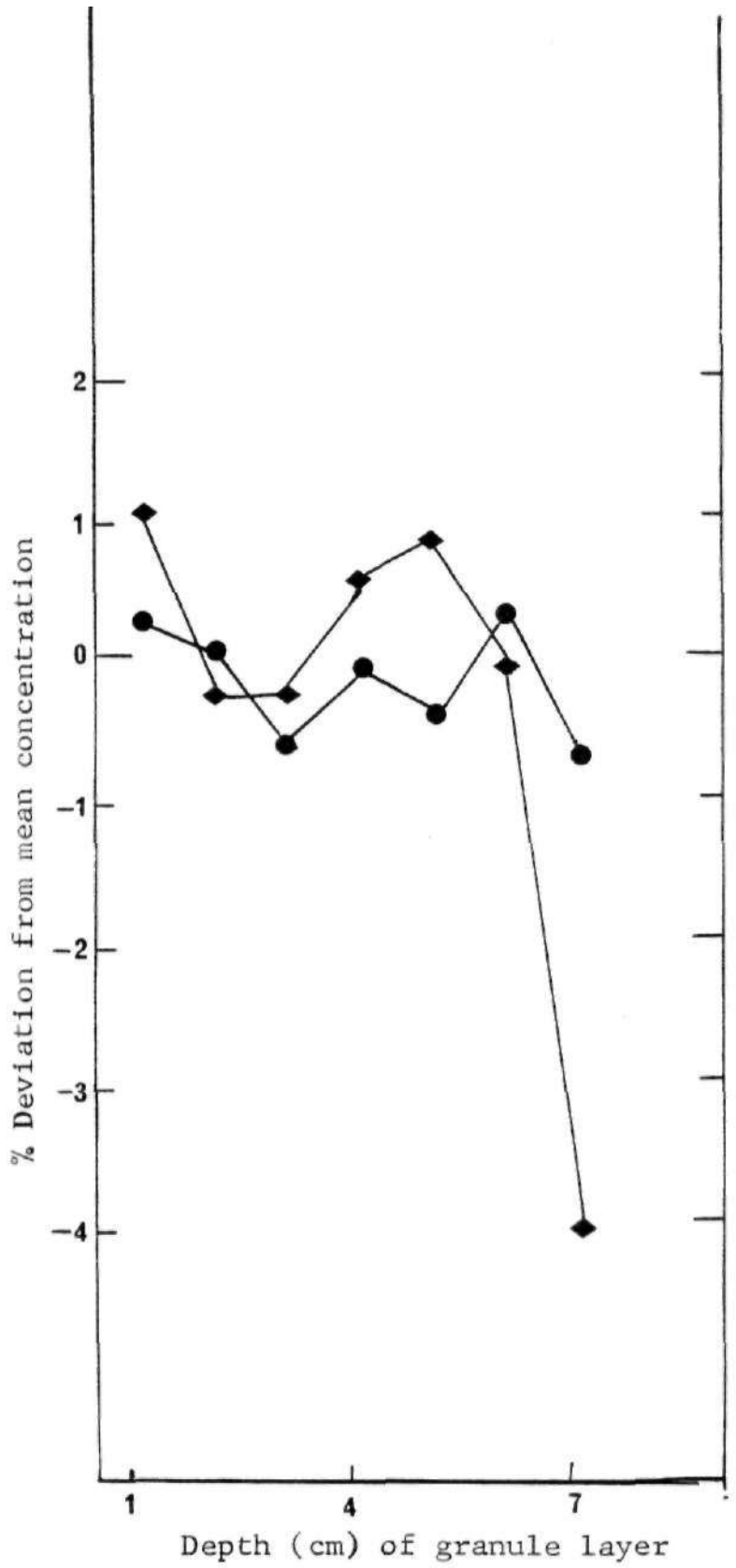
Figure 43 (b) Effect of Relative Solubility on Maximum Variation of Drug Distribution Throughout the Layers of a Batch of Granules



dissolved in the binder would migrate to the drying surface. Only the PVP present in the binder would migrate in drying of sulphadimidine/Emcompress granulation with PVP solution as the binder (Figure 37). In this case the overall effect on the drug concentration is minimal. The PVP dry weight concentration in this granulation is 4.95% w/w. If the migration of all the PVP in one layer to the next upper layer was possible, the effect on the concentration of sulphadimidine in the lower layer would rise from 2.00% to 2.10%. Conversely the concentration of PVP in the upper layer would dilute the sulphadimidine concentration to 1.90% w/w. Therefore the maximum deviation expected would be ± 5% compared to ± 2% obtained (Figure 37).

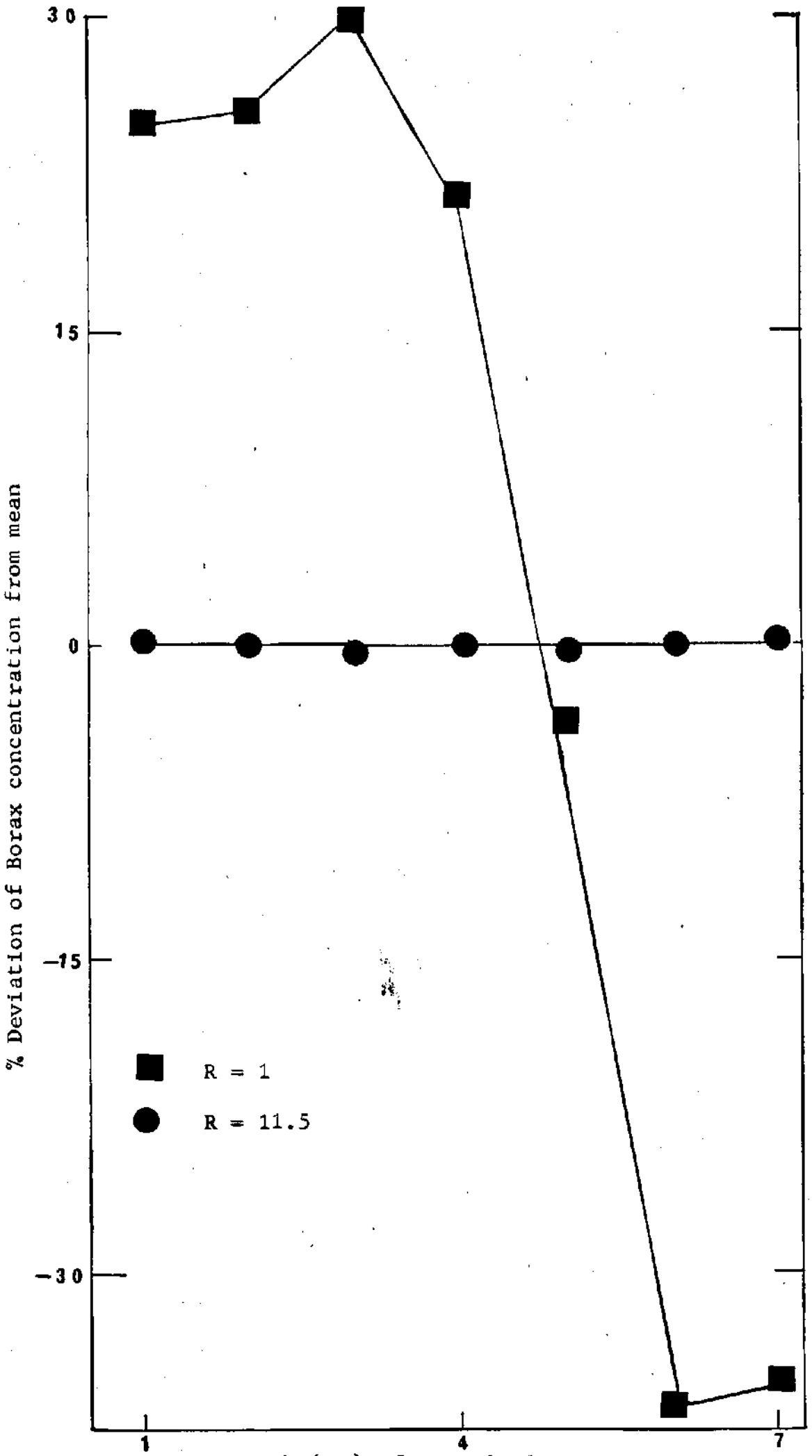
There are possibly three reasons for this low variation obtained. Firstly, the inhibition of binder migration by the viscous nature of the PVP binder has been shown by Warren and Price (1977). Secondly, it is also not likely that a granule loses all its binder content. Some of the binder being located at the intragranular contact points or bridges would preferrentially remain and would therefore not take part in solute migration (Whitaker and Spring, 1977). Thirdly, the binder remaining in the pores in the pendular moisture is unable to be affected by the capillary forces and would therefore not migrate from the pores. Thus, the evaporation of the moisture from the pores would leave deposits of the solutes, in this case PVP, in the pores.

From Table 12 and Figure 43 the relative solubility of the drug is directly related to the variation in the drug concentration in the layers of granules. However the granules prepared by massing with PVP binder, as in sodium salicylate/dibasic calcium orthophosphate (d.c.o.) and sulphadimidine/d.c.o., gave rise to a comparatively low deviation due to the minimisation of solute migration by the viscous nature of the PVP binder. Figure 43 also shows that the migration of solutes towards the drying surface as indicated by the drug concentration in the top layer of granules, is directly related to the relative solubility of the drug. It is also shown that the migration leads to a small deviation in the drug concentration in the layers as the relative solubility value gets close to the dry mix concentration. It follows therefore that when the dry mix concentration is equal to the dry weight concentration of components dissolved in the binder, there will be no net effect on solute migration. The binder should be such that no more of the drug or the diluent dissolves in it during massing and during drying. This proposal was tested by massing a co-saturated solution of borax and lactose formed at 25°C with borax/lactose dry mix of equal weight by dry weight concentration which was 30.1% w/w and drying the granules at 25°C. Figure 44 (a) shows only $\pm$ 0.8% deviation compared with a control granulation massed with pure water which gave $\pm$ 4% deviation. This comparatively low deviation of $\pm$ 4% obtained with the control granulation emphasises the fact that dosage uniformity is a problem with low dose drugs especially



◆ Co-saturated solution of borax and lactose
● Water as binder (used as a control)

Figure 44 (a) Effect of a Unity Value of Relative Dissolution Ratio on Drug Distribution Throughout the Layers of a Batch of Granules


30
15
0
−15
−30
% Deviation of Borax concentration from mean
R = 1
R = 11.5
1
4
7
Depth (cm) of granule layer

if they are soluble in the binder. Figure 44 (b) shows the effect of migration of solutes when the relative solubility is higher than the dry mix concentration of the components. It also shows the uniform distribution of borax throughout the layers of granules prepared by massing the dry mix with a binder solution containing equal dry weight concentration of the components.

3.3

FACTORS AFFECTING THE DISTRIBUTION OF A LOW DOSE DRUG THROUGHOUT A BATCH OF GRANULES

3.3.1 INTRODUCTION

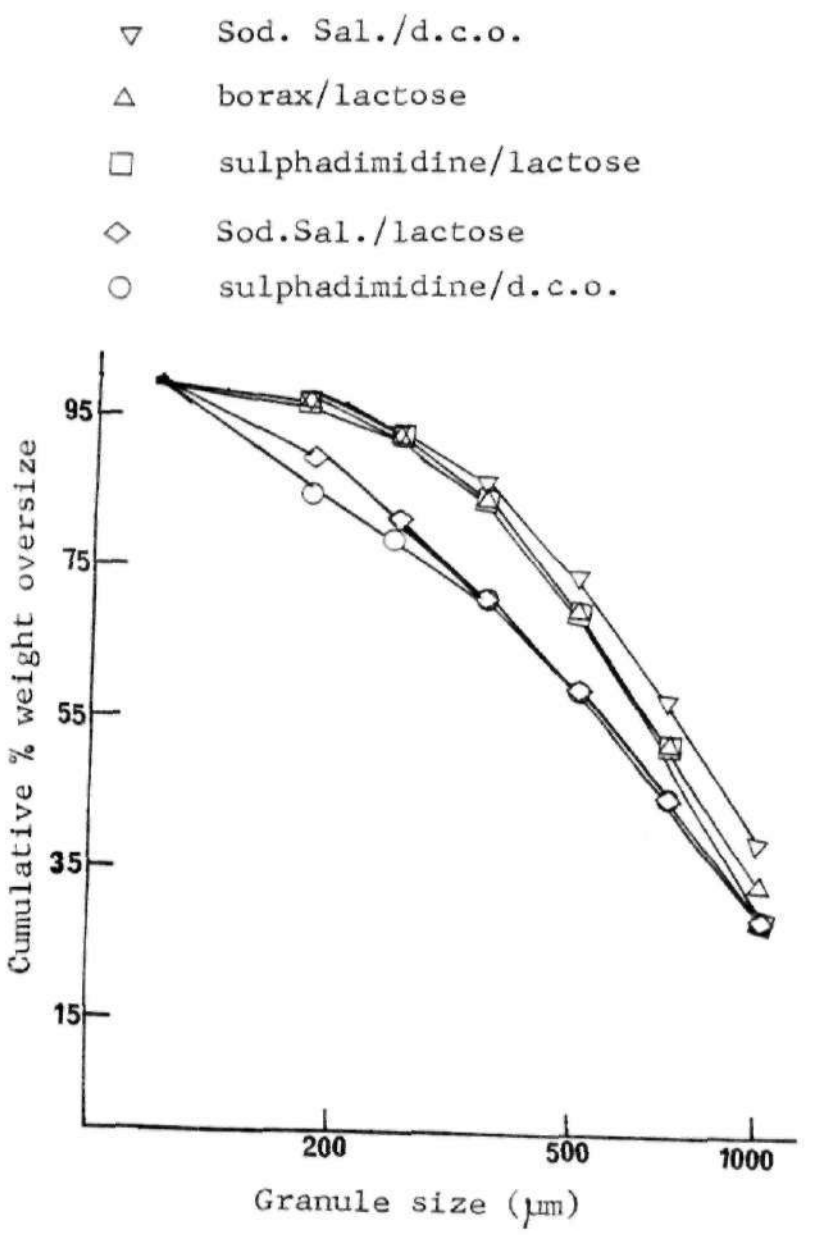
Some of the factors which affect the distribution of a drug in the overwetted region and the rest of the mix during massing have been identified (Figures 16-20). These include the relative solubilities of the drug and diluent, the rate of dissolution of the particles and the binder composition before massing. It is therefore logical to examine how these factors together with the formulation and processing variables affect granule size and drug distribution in the granule sizes throughout a batch of granules.

3.3.2 EFFECT OF RELATIVE SOLUBILITY OF DRUG IN BINDER

In Figure 45, sodium salicylate/dibasic calcium orthophosphate (d.c.o.) formulation produced the highest amount of large granules followed by borax/lactose formulation. The smallest amount of the large granules was obtained in the granulations of sodium salicylate/lactose, sulphadimidine/lactose and sulphadimidine/d.c.o.

The cohesive nature of d.c.o. and the fact that all the sodium salicylate was capable of dissolving in the PVP binder account for the higher proportion of large sized granules compared with the sulphadimidine/d.c.o. granules which have only the PVP sustaining the binding action. Although the sodium salicylate/lactose formulation contains a much more soluble drug than borax in the borax/lactose granulation, more fines were produced with the former. The less fines produced in the borax/lactose granulation is attributed to the mutual increase in the solubilities of borax and lactose (Figure 11). Thus many more solid

Figure 45 Effect of drug relative solubility in a formulation on granule size distribution



bridges formed from the crystallised solutes were available to bind particles together, therefore forming a larger mean size of granules.

The above results have shown that a major factor which determines the mean granule size is the amount of dissolved components which would form adequate intragranular crystalline bridges. Cohesiveness of a powdered material as in d.c.o. (Ganderton and Hunter, 1971; Eaves and Jones, 1973) also leads to a higher proportion of larger granules formed with an effective massing action.

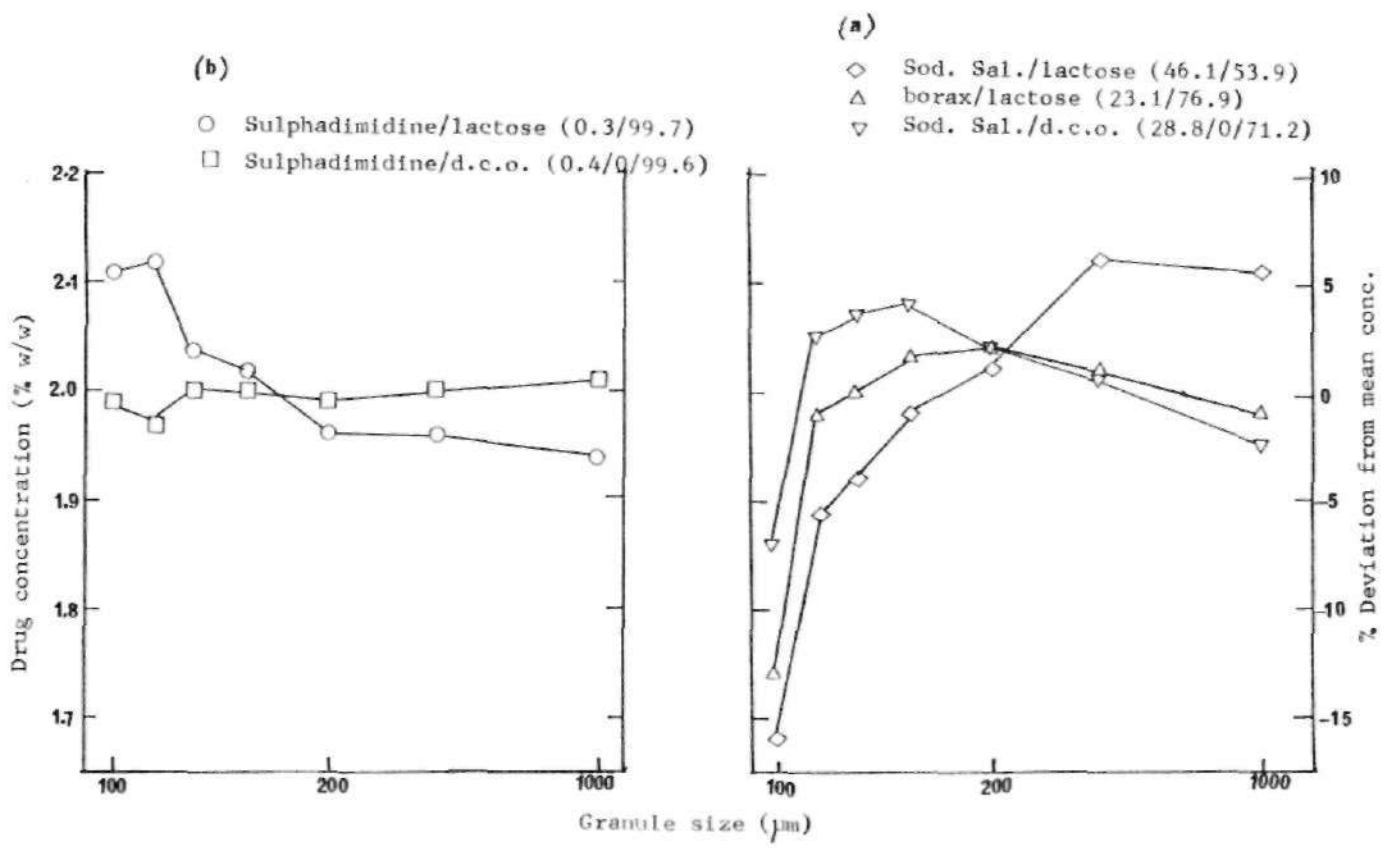
Effect of relative solubility on drug distribution in a granule batch

Figure 46 shows the effect of the relative solubility of a drug in the binder on its distribution in granule sizes.

All the three granulation formulations in Figure 46 (a) contain higher relative solubilities compared with the overall dry mix concentration of 2% w/w. The concentration of the drug in each of the three granule formulations increased with a decrease in granule size until a peak concentration was found in the intermediate sized granules. The concentration then decreased with a decrease in granule size, leading to the lowest drug concentration in the fines. This result is consistent with that obtained by Selkirk (1976) using the borax/lactose formulation.

It has already been shown in Figure 16 that the concentration of sodium salicylate in the equilibrated granules of sodium salicylate/lactose formed from the initially overwetted region was lower than 2% but higher than the concentration of borax in equivalent borax/

Figure 46 Effect of relative solubility of drug on the distribution of the drug throughout the granule sizes in the batch. The relative solubilities of drug/diluent/binder are given under the legends in brackets.



lactose granules. The largest granules in a batch are formed from the bulk of the initially overwetted region (Opakunle and Spring, 1976). As a result of solute depletion during massing from this overwetted area (Figure 17), the expected concentration in the biggest granules should be less than 2% provided the drug has a higher relative solubility than its dry mix concentration. The higher the relative solubility is, the higher the drug depletion will be and will thus lead to a lower concentration in the biggest granules with a consequent higher peak concentration in the intermediate granules. This is in agreement with the results in Figure 46 (a) for sodium salicylate/dibasic calcium orthophosphate (d.c.o.) and borax/lactose granule batches, the relative solubilities of the drugs being 28.8% and 23.1% w/w respectively. Sodium salicylate in the sodium salicylate/lactose formulation with the highest relative solubility of 46.1% w/w should therefore have the lowest concentration in the biggest granules. The contrary was obtained. The concentration was even higher than the dry mix concentration of 2% w/w. The explanation is shown in Figure 16 where the concentration of the sodium salicylate in the agglomerates depleted markedly during the initial massing but then increased appreciably in the equilibrated granules. This increase was attributed to a snow-balling effect of some of the sodium salicylate, in the drier areas of the mix, onto the wetter, bigger agglomerates. The snow-balling action during the wet process of granulation has been demonstrated by Sastry and Fuerstenau (1973). Thus the concentration in the

biggest granules was higher than 2% but the peak concentration was still contained in the intermediate granules due to a vestigial effect of some of the solute transfer resulting from the binder distribution during massing. It is also expected that some migration of solute during drying would take place. Therefore the concentration of the drug in the granules is the net effect of the massing action as well as the migration of solutes during drying. It has been shown in Figure 43 that a drug with a higher value of relative solubility in the binder caused a higher extent of its migration.

The concentration in the fines of a batch of granules containing a drug of a markedly high relative solubility as shown in Figure 46 (a) is the lowest as a consequence of a greater wetting action which causes a higher amount of incorporation of the readily soluble drug into the wetter agglomerates during massing. Thus the concentration of sodium salicylate in the fines of sodium salicylate/lactose granules is the lowest out of the three formulations. This should be followed by the concentration of sodium salicylate in sodium salicylate/d.c.o. granules; but a higher concentration was obtained. However, the distribution of sodium salicylate in the sodium salicylate/d.c.o. granules giving the characteristic peak concentration in the intermediate sized granules is more an effect of the distribution of a binder solution during massing due to a less marked snow-balling action. The snow-balling action of some of the sodium salicylate in the drier areas of the wet mix onto the wetter agglomerates during massing was less marked as

a result of the observed "drier feel" or a more absorptive action of the d.c.o. diluent during the massing. This relatively drier surface of the agglomerates would thus minimise the snow-balling action of the readily wettable sodium salicylate. The borax concentration in borax/ lactose granule fines is also much lower than 2% due to some measure of, but relatively lower snow-balling action by virtue of its lower relative solubility and thus a lower wetting rate.

Figure 46 (b) shows the distribution of the poorly soluble sulphadimidine in granules of sulphadimidine/d.c.o. with PVP binder and in granules of sulphadimidine/lactose with water binder.

The most uniform drug distribution in the sizes of granules was obtained in granules containing the lactose diluent. The relative solubility of sulphadimidine is 0.3% w/w and of lactose 99.7% w/w. This shows that the sulphadimidine is virtually insoluble and therefore absent in the binder. The relative solubility of lactose is very close to its dry mix concentration of 98% w/w. This gives a difference of only 1.7% of lactose capable of forming crystalline bridges and also depleting from the overwetted area of the wet mix to the other regions during the massing action (Figure 16). This then accounts for why there is only $\pm$ 2% deviation in drug concentration with granule size.

The relative solubility of sulphadimidine in sulphadimidine/d.c.o. formulation is 0.4% w/w which is almost the same as in the sulphadimidine/lactose granules discussed above. However the concentration of sulphadimidine in

granule sizes gives a different profile. With the exception of the fines, the concentration of sulphadimidine is inversely related to the granule size. The underlying influence is that none of the dry mix components dissolves in the PVP binder. Thus the initially overwetted mix with the PVP binder would distribute the binder of constant composition to form equilibrium granules. The binder content would be proportional to the granule size (Dingwall and Ismail, 1977). Consequently by a dilution effect (Travers and Patel, 1979) the concentration of sulphadimidine would be inversely related to the granule size as is shown. However the slight decrease of the concentration in the fines compared with that in the 180 micrometres of the granules is connected with some measure of dry screening action. This would cause the PVP-rich crust (Ridgway and Rubinstein, 1971) especially of the biggest granules to be abraded to form part of the fines, thus leading to the slight decrease. It will be seen later in this thesis (Figure 64) how the minimisation of this abrasive action by the use of a higher PVP concentration, e.g. 20% and 25% w/v, leads to stronger and thus unabradable granules. In this instance the sulphadimidine concentration is indirectly related to the granule size including the fines.

Thus the concentration of a low dose drug in granule sizes depends on the value of the relative solubility in the binder. When the value is much higher than its dry mix concentration, the distribution of the binder in which it dissolves shifts the peak concentration of the drug from the biggest to intermediate sized granules. The

migration of the drug in solution during drying is directly related to its relative solubility. A higher variation thus takes place in granules containing a drug of higher relative solubility (Figure 43). Therefore the distribution of the drug in a batch of granules is governed by the binder composition and distribution during massing and by solute migration during drying. Both of these processes produce a variation which is linearly related to the relative solubility (Figure 43 (b)).

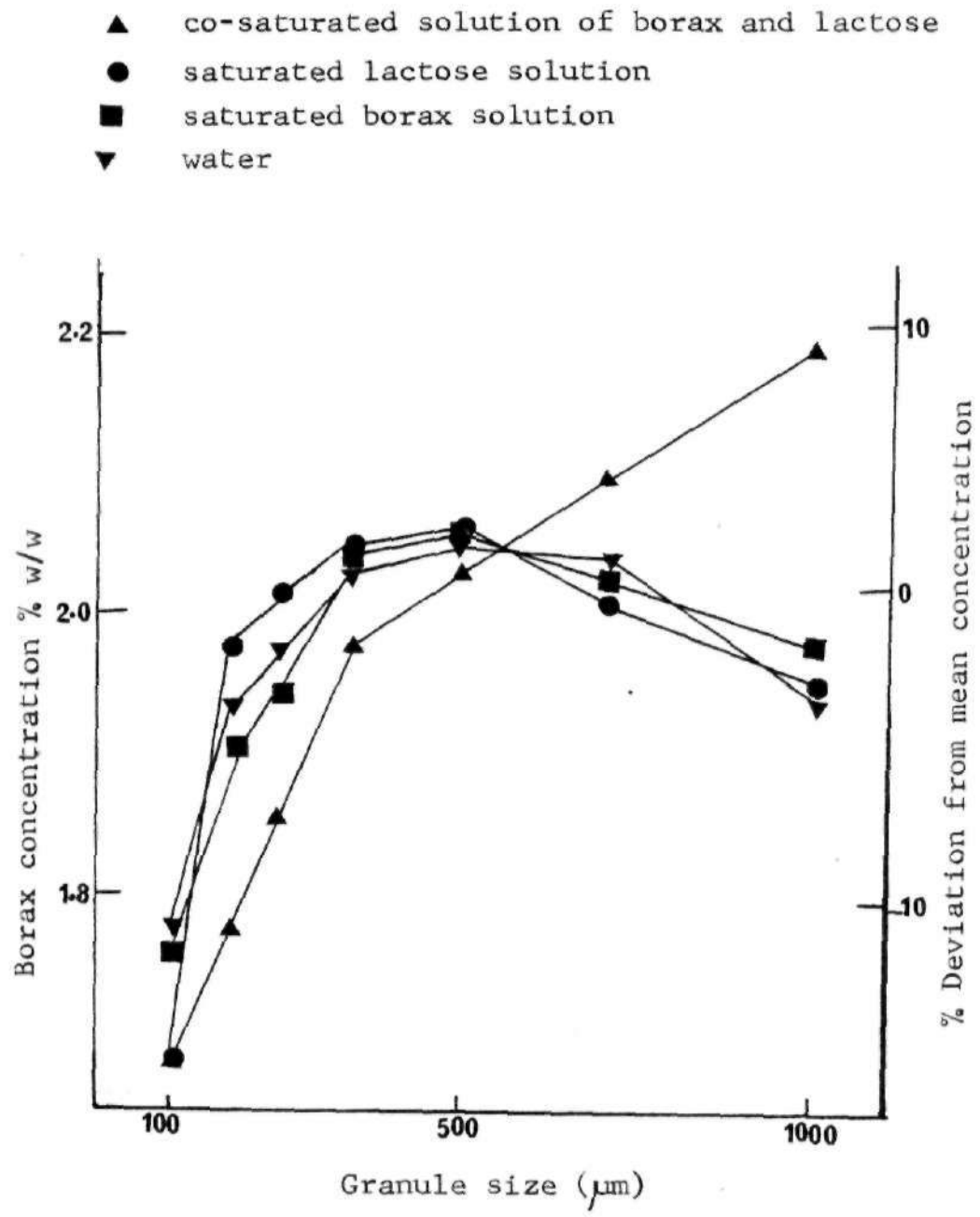
3.3.2 EFFECT OF PRE-DISSOLUTION OF PART OF DRY MIX IN BINDER

Figure 47 shows similar borax concentration-granule size curves for massing the borax/lactose mix with water or with a saturated solution of either borax or lactose. In all three cases, there is a peak concentration in the mid-sized granules.

An appreciably different curve from these three curves was obtained for granules prepared by massing a dry mix with a binder co-saturated with both lactose and borax.

The mutual increase in the solubilities of both components during the granulation of borax/lactose mix has been shown (Figure 11). Therefore a presaturation of borax alone in the binder prior to massing only behaved in a similar manner to unsaturated borax during massing. Similarly, a saturated lactose solution as the binder becomes unsaturated during massing due to the presence of borax in the mix.

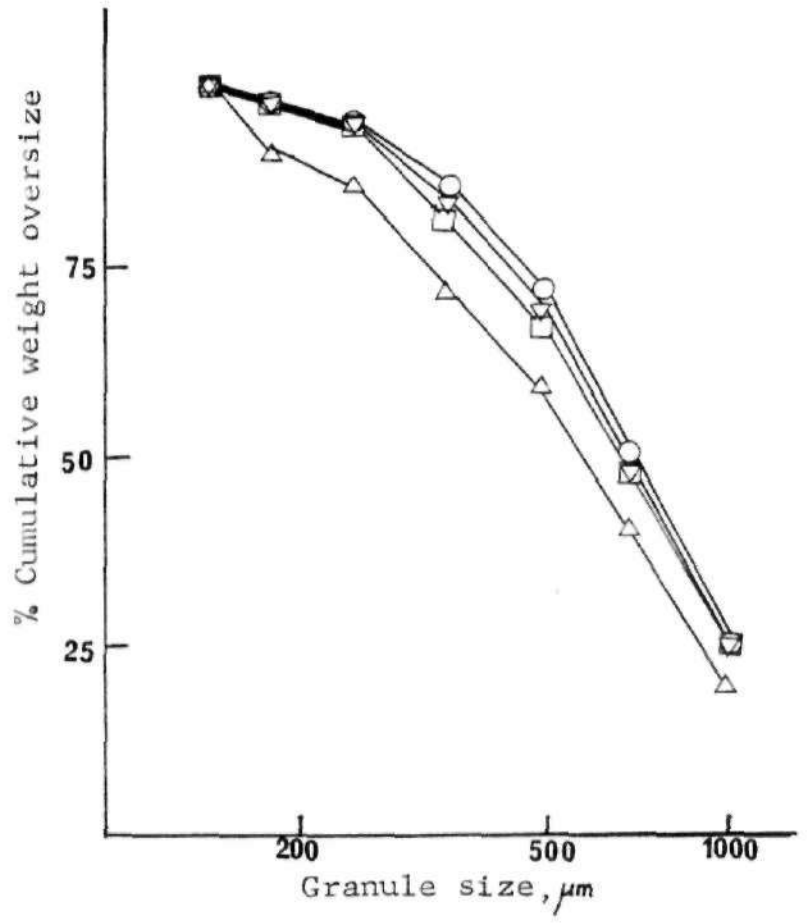
Figure 47 Effect of the initial binder composition on borax distribution throughout the granule sizes in the batch



The effect of binder distribution, depending on the binder composition, during massing has been shown (Figure 20). The reasons for a lower borax concentration using a presaturated borax and a slightly higher concentration using a presaturated lactose in the equilibrated agglomerates have been discussed. These therefore explain the differences in borax concentration in the biggest granules for presaturated lactose and borax granulations respectively (Figures 20 and 47). The use of water as the binder which gave intermediate results (Figure 20) produced a corresponding intermediate effect only in the intermediate sized granules possibly as a consequence of solute migration during drying. Evidence of this is given by the higher binder content in the large sized granules as shown by the higher fraction of the large sized granules prepared with water as the binder (Figure 48 and Table 14 under 2% w/w). A higher binder content is contained in bigger granules (Dingwall and Ismail, 1977). This higher binder content caused a higher migration of borax-rich binder solution from the larger granules. Thus a slightly lower concentration of borax was obtained in the biggest granules in the batch prepared by massing with water.

In the granulation using a presaturated solution of borax and lactose as the binder the borax concentration was directly related to granule size. This profile is quite different from the other three granulations. This is attributed to the absence of the dissolution, in the binder, of lactose and borax from the dry mix during massing.

Figure 48 Effect of initial binder composition on granule size distribution in the batch



△ co-saturated solution of borax and lactos
▽ water
□ saturated lactose
○ saturated borax

The binder contains 70% and 26% of the available borax and lactose respectively in the granulation. Thus the distribution of this borax-rich binder of constant composition and the directly related binder content with granule size shown earlier (Figure 20) are responsible for this borax/granule size profile.

Although solute migration will affect the distribution of borax in a pre-cosaturated binder, the volume of the binder available to take part in the migration is slightly reduced (e.g. Figure 33 for sodium salicylate/lactose) due to a less wetting effect as the solution becomes more concentrated. This non-wetting tendency was visible during massing. It was shown by less sticking of individual granules and the ease of formation of equilibrium granules. This non-wetting phenomenon has been highlighted by Tiamraj (1979) who related the action to the presence and increase in "globular structures" as more components dissolved in the binder during massing. The appreciable fraction of fines and the low fraction of large granules in a batch prepared by massing with the pre-cosaturated binder (Figure 48) further substanciates the less wetting action.

Figure 49 shows a similar direct relationship between sodium salicylate concentration and granule size when both drug and lactose diluent were maximally dissolved in the binder. As expected, a binder solution containing all the sodium salicylate alone produced a similar profile although the concentration in the large granules as expected is slightly higher.

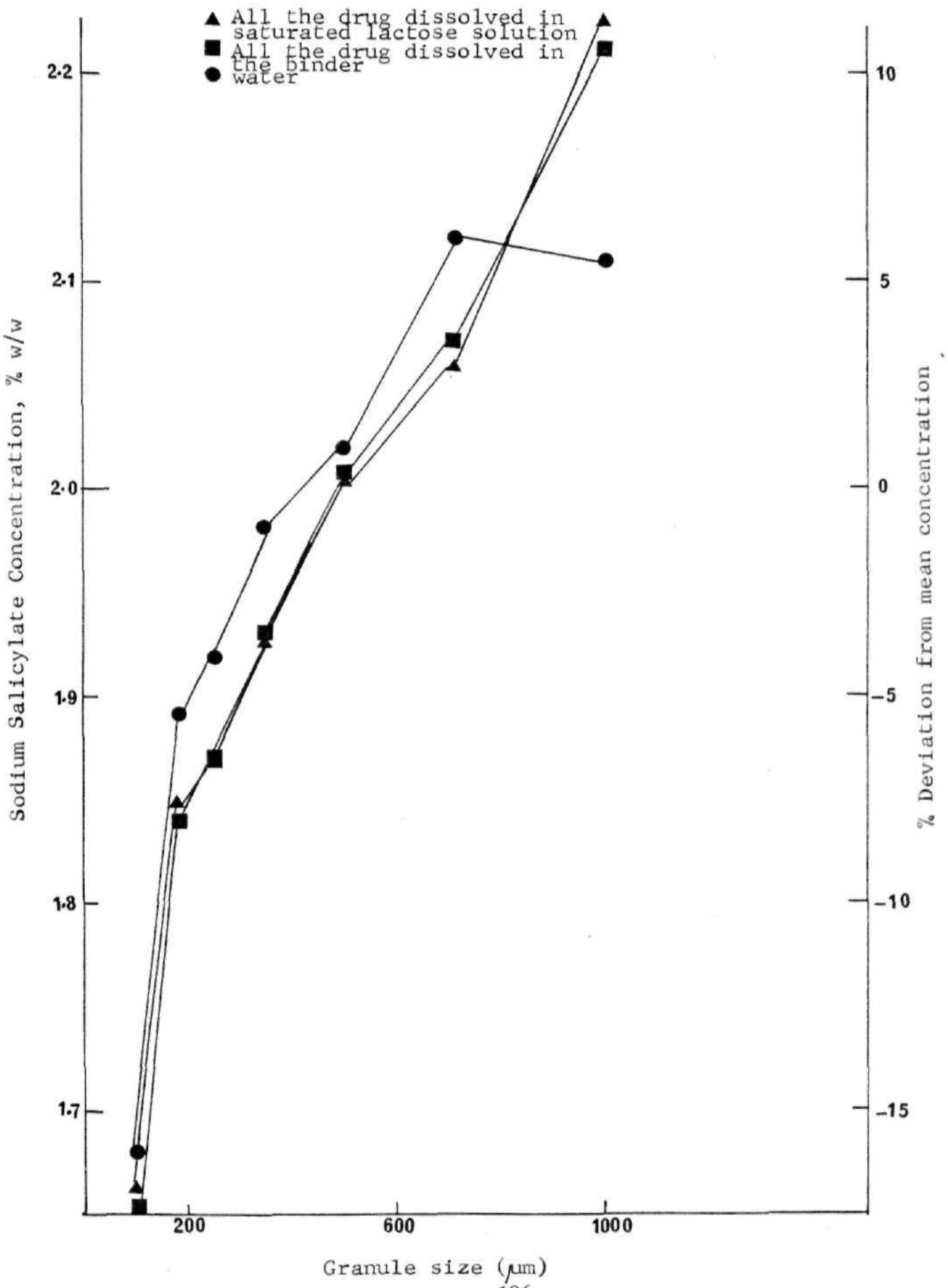
Table 13: Granule size Distribution.

Sieve mesh (μm) retaining granules	Binder Composition and Cumulative % Weight Oversize		
	Water	All drug dissolved	*All drug dissolved in a saturated lactose
1000	28	26	27
710	46	43	46
500	60	57	60
355	72	69	73
250	82	79	83
180	89	87	90
>180	100	100	100

*The 2.7% volume occupied by the solutes was saturated with part of lactose and added to the binder before massing

Figure 49 EFFECT OF INITIAL BINDER COMPOSITION ON DISTRIBUTION OF SODIUM SALICYLATE IN SODIUM SALICYLATE/LACTOSE GRANULES

Figure 49 Effect of initial binder composition on distribution of sodium salicylate in sodium salicylate/lactose granules



Granule Size Distribution

The granule size distribution for 2% w/w borax/lactose granulations with water or a saturated solution of either or both components is presented in Figure 48. The fraction of large granules is similar when water, saturated borax or saturated lactose respectively was used as the binder. However the proportion of fines was lowest with water as the binder. This is apportioned to the greater wetting ability of pure water than either solution. In the case of the pre-cosaturated binder, a markedly lower fraction of large granules and a much higher fraction of fines was found compared with the other batches. The contributory factors include the decreased effective volume of the solvent (water) when both components were saturated in it. For instance, the volume of water evaporated completely in a co-saturated solution massed with dibasic calcium orthophosphate as the substrate was 51.0 millilitres per 70.0 millilitres of the co-saturated solution. This means that for a 14% v/w binder the volume occupied by the dissolved components in the binder was 2.7% v/w. Secondly, it is due to the lack of wetting of the co-saturated solution. As mentioned earlier the poor wetting properties were visibly noticed during massing and have also been demonstrated by Tiamraj (1979).

The relative differences in the granule size distribution in sodium salicylate/lactose granules containing binder of different initial composition was similar to that described for borax/lactose granules (Table 14)

3.3.4 EFFECT OF DOSE OF DRUG IN GRANULES

Figures 50-52 show the effect of initial borax concentration on the relative concentration/granule size profiles. Figure 50 represents the situation when water is used as a binder, Figure 51 when saturated borax solution is used and Figure 52 when saturated lactose solution is used as the binder. The relative concentration of borax in all cases again reached a peak in the intermediate sized granules. As shown earlier (Figure 47) the peak concentrations were so contained in the intermediate sized granules as a consequence of the state of saturation of the binder in the dry mix. The behaviour of any of these three binder compositions is related to the increase in the solubilities of both components in each others presence. Thus the distribution of the binder having a different composition from the initial content led to the relative peak concentration in the intermediate granules.

Figure 53 shows the effect of the initial overall borax concentration on the relative concentration/granule size profiles. It represents the situation when both borax and lactose are simultaneously saturated to form the binder solution. The relative concentration-granule size curves as shown in Figure 53 now give a markedly different shape. All the borax was present as a solution along with saturated lactose for doses up to 1.5% w/w. For 2% dosage, 0.3% was present in the dry mix before massing. Generally, irrespective of the dose, there is a direct relationship between the relative borax concentration and the granule size. This is attributed to

Figure 50 Effect of dose of borax on its distribution in granules prepared by massing with water as binder

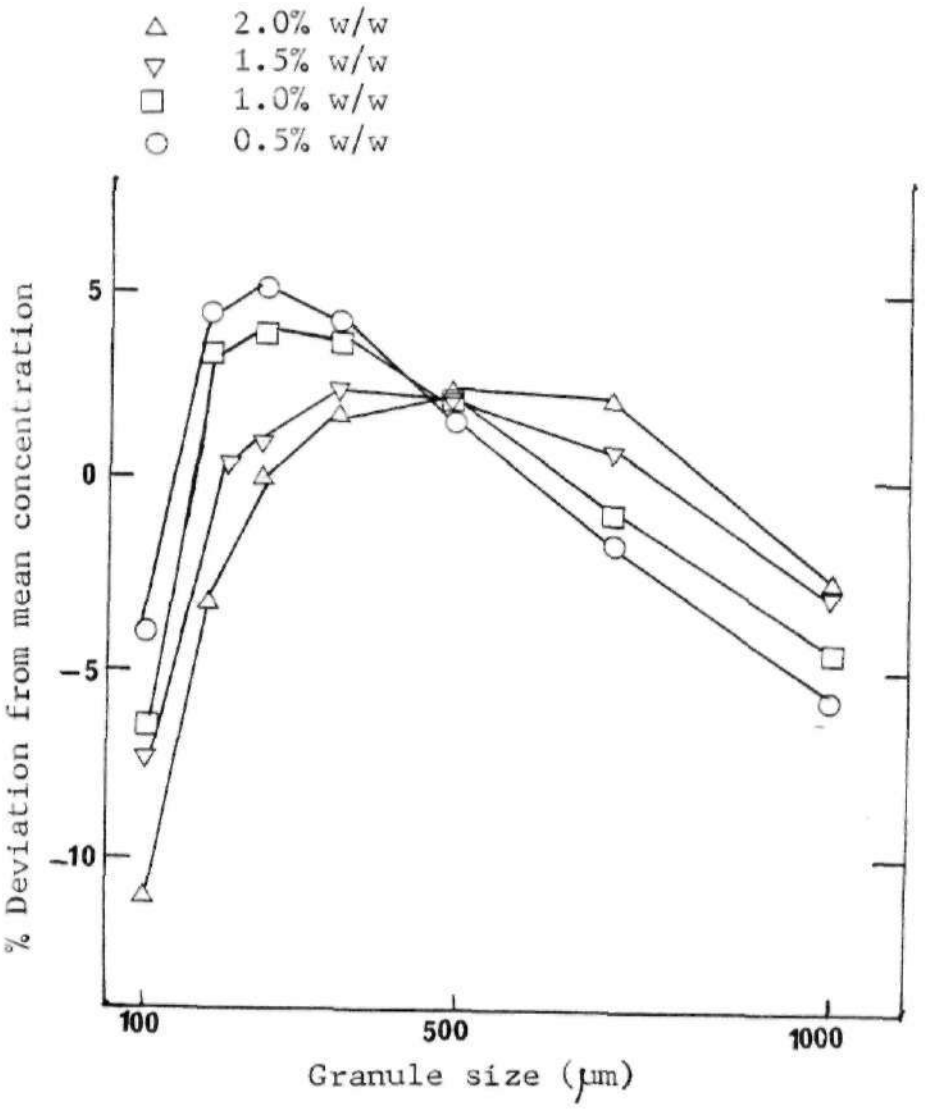


Figure 51 Effect of dose of borax on its distribution in granules prepared by massing with binder saturated with part of or all of borax in the formulation.

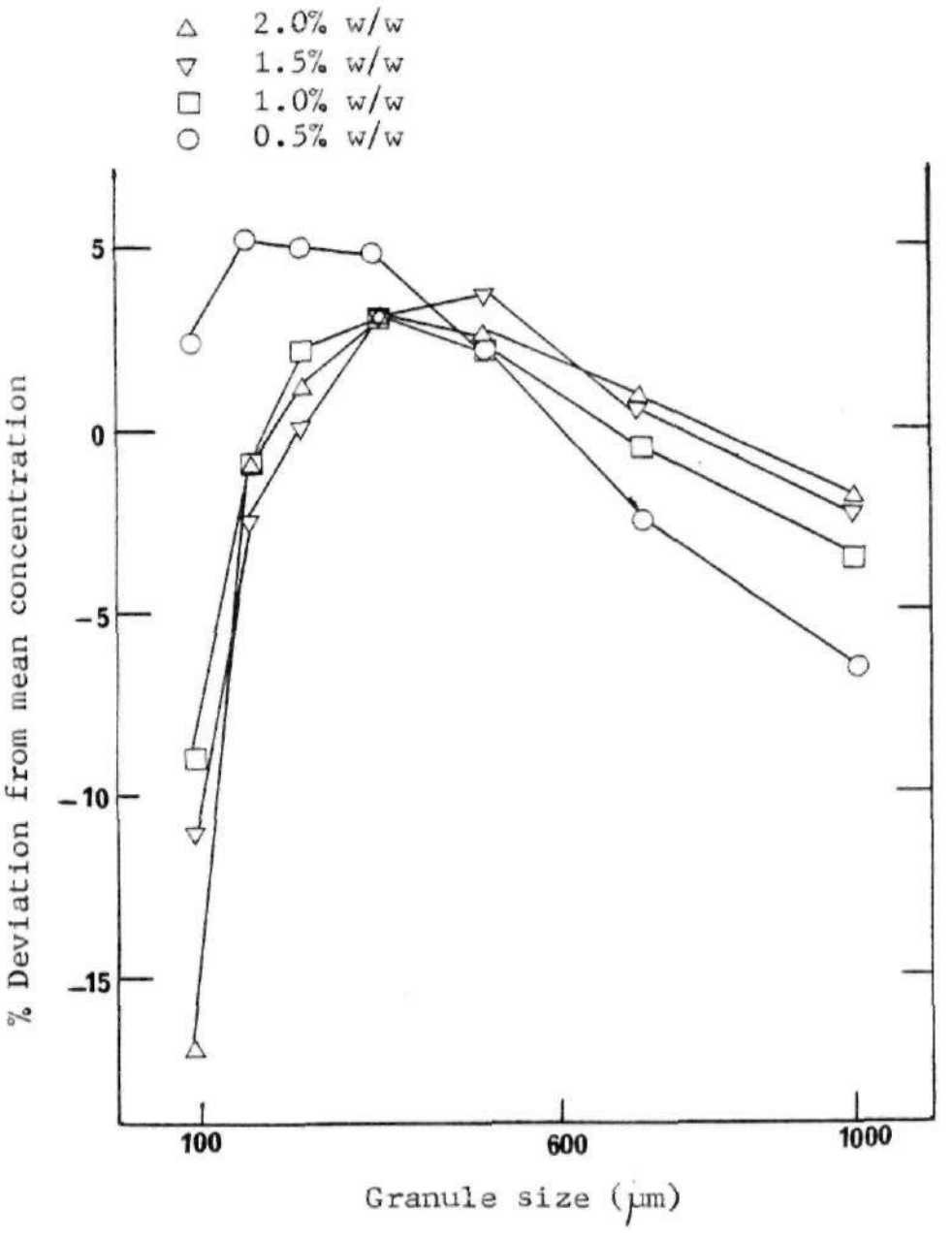


Figure 52 Effect of dose of borax on its distribution in granule size in a batch prepared by massing the dry mix with a binder saturated with part of the lactose diluent

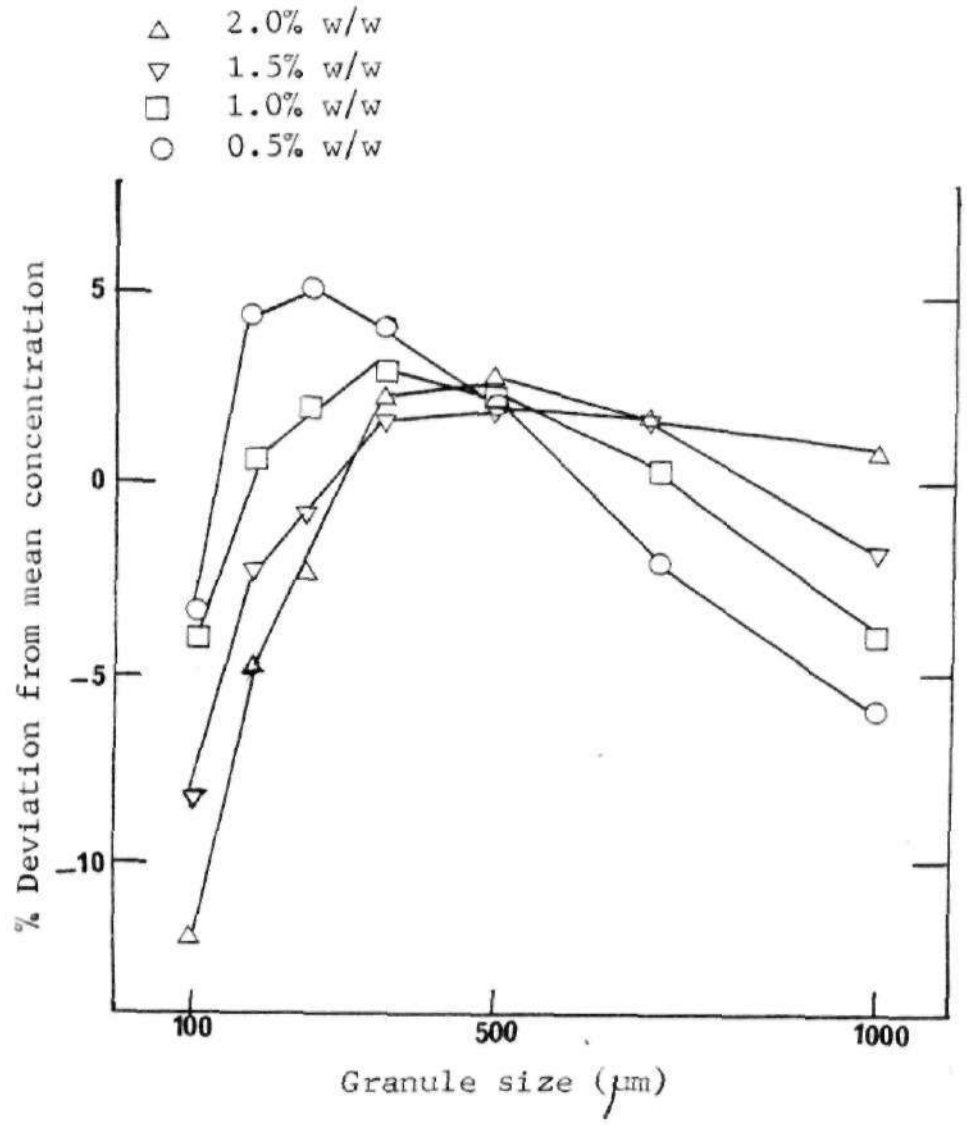
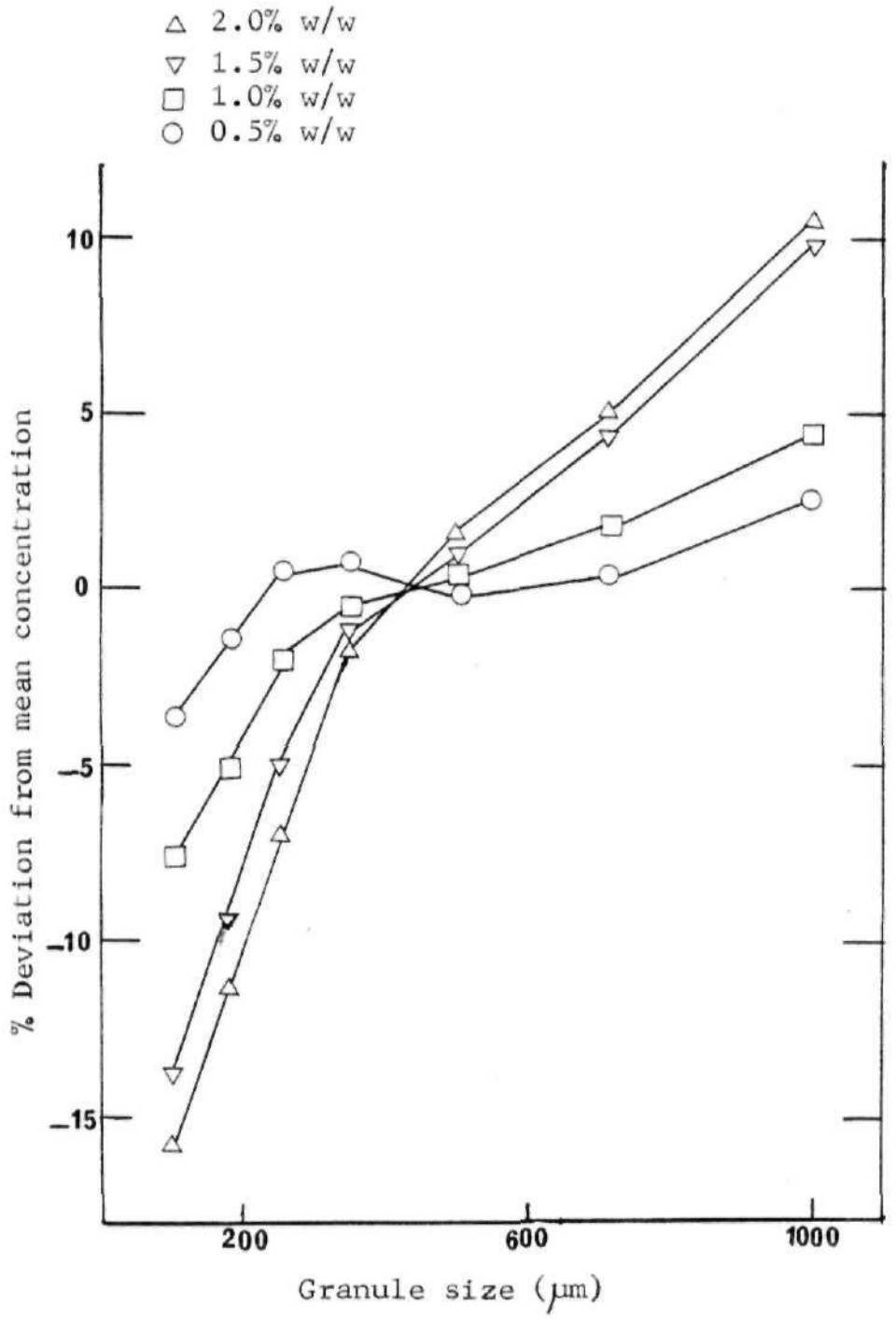


Figure 53 Effect of dose variation of borax on its equivalent distribution in granule sizes in a batch prepared by massing the dry mix with binder co-saturated with borax and lactose. For doses up to 1.5% w/w borax, all the borax was capable of dissolving in the binder.



the distribution of the borax-laden binder of constant composition during massing (Figures 20 and 47).

When the same drug/diluent granulations are being considered for elucidating the effect of dose in the granulation, the term relative dissolution ratio has been devised to estimate the effect of the drug concentration (or the dose) in the granules.

The relative dissolution ratio R is defined as:

$$R\% = \frac{S_{dr}}{D} \times 100\%$$

where S_{dr} is the relative solubility of the drug in the binder and

D is the dose of the drug in the granules.

The variation in the value of the relative dissolution ratio with variation in the dose of the drug in granules is presented below:

Borax Dose	Lactose Solubility in presence of borax	Borax relative solubility S_{dr} (% w/w)	Borax relative dissolution ratio R (% w/w)
0.5	1:4	12.5	25.0
1.0	1:3	17.5	17.5
1.5	1:3	23.1	15.4
2.0	1:3	23.1	11.5
30.1	1:3	30.1*	1.0

* value at 25°C, the other values are at 20°C

A higher value of R indicates a higher depletion of borax concentration during massing and thus leading to a lower concentration in the largest granules and a resultant

higher relative concentration in the intermediate sized granules and the fines (Figures 50, 51, 52 and 53). It therefore follows that a lower dose if reasonably soluble leads to a lower relative concentration in the largest granules and a higher relative concentration in the smaller granules and the fines.

When R is equal to 1, any dissolution of the drug in the binder if not initially saturated and the distribution of the binder including a saturated one during massing will not affect the concentration of the drug throughout the granules in the batch. The net concentration will still be constant.

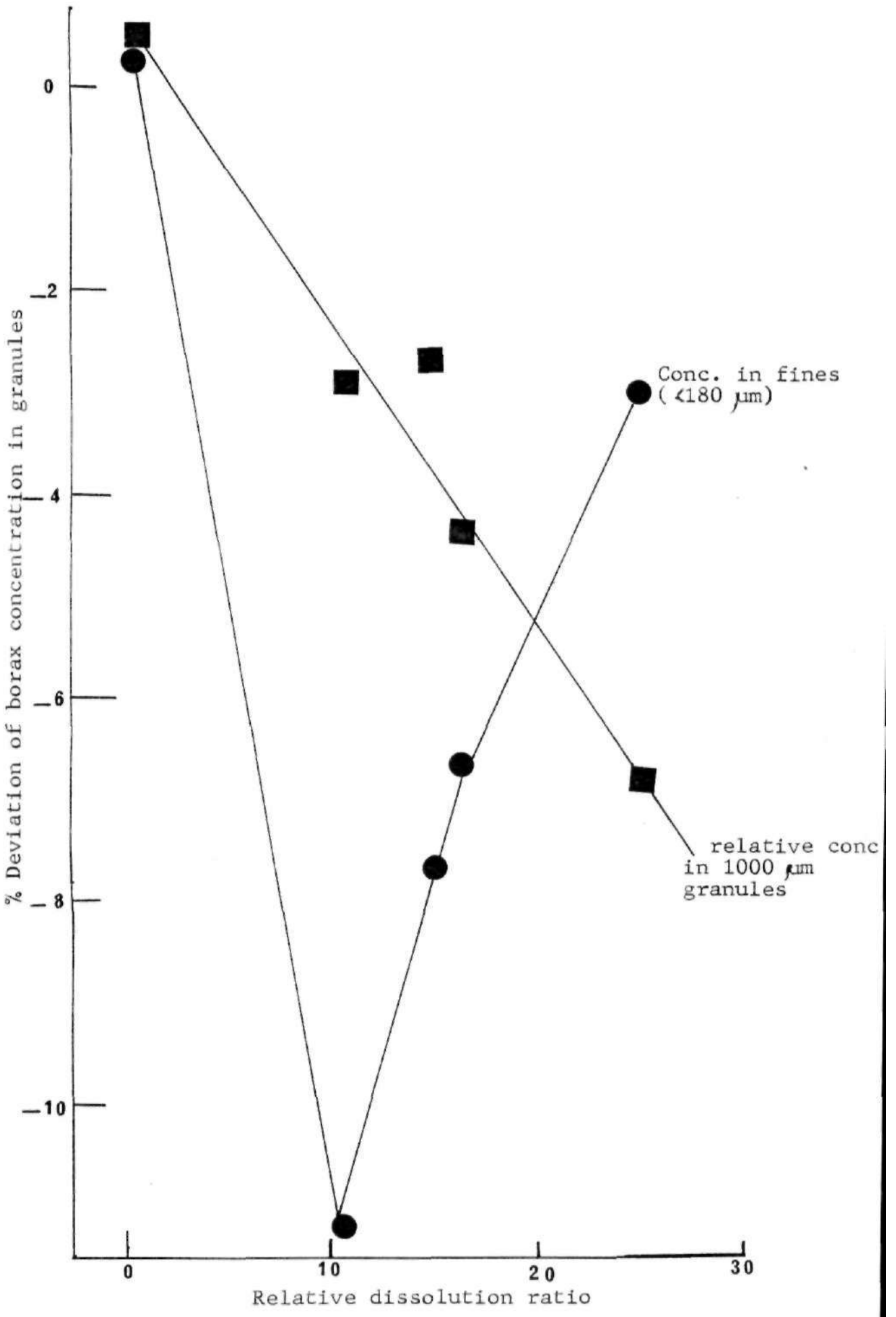
Figure 53 (b) shows an inverse linear relationship between the concentration in the largest granules and the relative dissolution ratio. The relative deviation in the fines decreases with R to a limit and then gives a steep increase to give near zero deviation when R equals 1.

Granule Size Distribution

The granule size distribution is presented in Table 14. The proportion of 1000micrometre (largest) granules is directly related to the dose of borax in the granules. This is a consequence of the mutual increase in the solubilities of borax and lactose (Figure 11). This enhanced increase in the solubilities of both components leads to a higher quantity of dissolved solutes which is one of the necessary prerequisites for forming granules of a higher mean size (Chalmers and Elworthy, 1976).

The increase in the dose of borax was also found to decrease the porosity of the granules (Table 15). This

Figure 53 (b) Effect of relative dissolution ratio on the relative concentration in the largest granules and in the fines.



Concentration of borax in granules	Content in water (14% v/w) as binder	Cumulative % weight of granules retained by given mesh of sieve in micrometres						
		1000	710	500	355	250	180	<180
0.5% w/w	water	18	45	66	80	92	95	100
	borax	18	45	66	79	92	96	100
	lactose	18	42	61	75	87	92	100
	borax + lactose	16	41	61	74	85	90	100
1.0% w/w	water	20	45	64	78	85	93	100
	borax	20	46	64	78	86	94	100
	lactose	20	44	64	77	89	94	100
	borax + lactose	18	42	61	74	85	90	100
1.5% w/w	water	21	45	66	80	92	96	100
	borax	20	47	68	83	94	97	100
	lactose	22	47	66	79	51	95	100
	borax + lactose	18	41	59	72	82	88	100
2.0% w/w	water	24	49	70	84	94	97	100
	borax	25	51	72	85	94	96	100
	lactose	24	49	67	81	93	95	100
	borax + lactose	20	44	62	75	88	91	100

Table 14 EFFECT OF CONCENTRATION OF BORAX AND CONTENT IN BINDER BEFORE MASSING ON GRANULE SIZE DISTRIBUTION

Concentration of Borax in granule	Porosity
0.5% w/w	43.9%
1.0% w/w	41.2%
1.5% w/w	40.0%
2.0% w/w	37.4%

Table 15 (a) EFFECT OF CONCENTRATION OF BORAX IN GRANULES MASSED WITH WATER AS BINDER ON THE POROSITY OF GRANULES

Binder Concentration	Massing Time	Porosity
18%	5	34.7%
14%	60	35.4%
14%	5	37.4%
14% co-saturated	5	39.1%

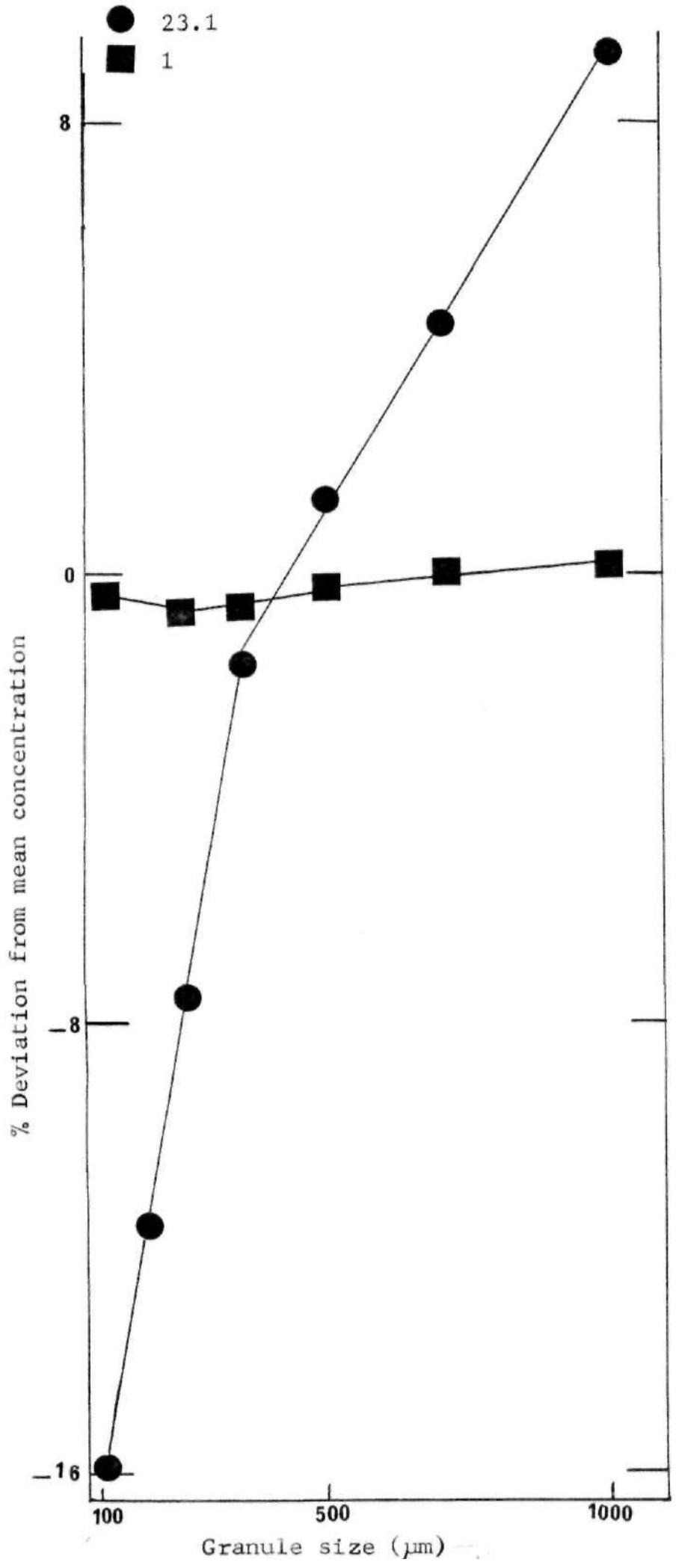
Table 15 (b) EFFECT OF BINDER CONCENTRATION AND EXCESSIVE MASSING TIME ON POROSITY OF BORAX/LACTOSE GRANULES

again is attributed to the improved solubilities of both components in the binder. The drying of granules at the pendular liquid phase involves the evaporation of water from the pores and thus leaves deposits of solutes in the pores. The quantity of the solutes would be higher with a higher concentration of solutes and would therefore lead to a decrease in the granule porosity.

EFFECT OF MASSING A DRY MIX HAVING EQUAL COMPOSITION WITH THAT SATURATED IN THE BINDER

The reasons for the peak concentration in the intermediate sized granules of a drug with an appreciable higher relative solubility than its dry mix concentration has been shown in Figures 17 and 46. It will then follow that when the dry weight concentration of the drug and diluent dissolved in the binder is equal to the concentration of the drug in the dry mix, i.e. when the relative dissolution rate is equal to 1, there will be no net transfer of components during massing. Thus by a judicious choice of the solubilities of the components in the binder the concentration of the drug in the various layers (Figure 44) and in the various sizes of granules in the batch could be kept constant. If the dry weight composition of this binder is constant during drying the concentration of the drug in the granule sizes will also remain constant. Therefore no net amount of solutes should dissolve in the binder during massing and also during the granule drying. This may be ensured by the concentration of the components in the binder being numerically equal to their respective

Figure 54 (a) Effect of relative dissolution ratio on drug distribution in granule sizes.



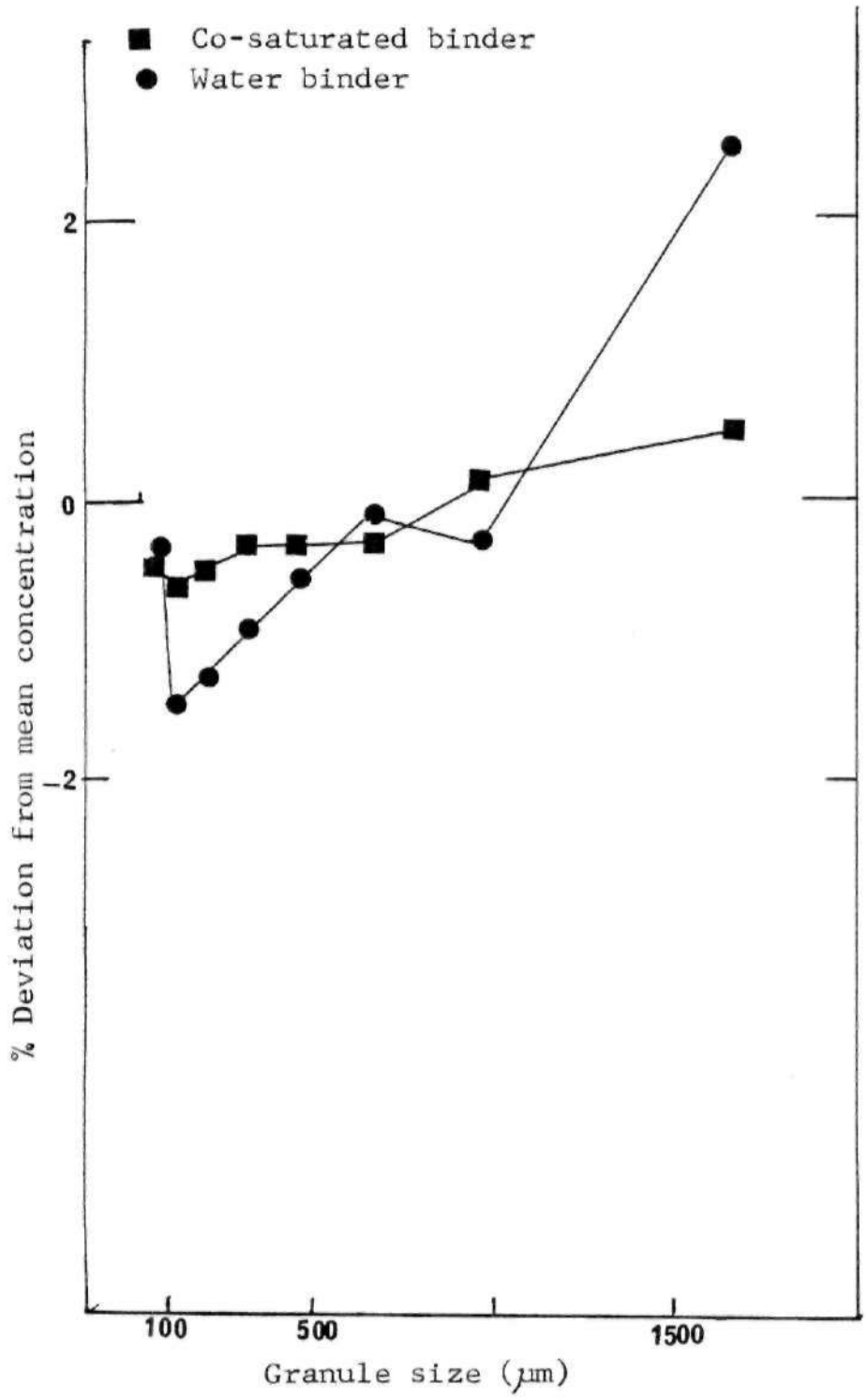


Figure 54 (b) Effect of dissolution of both components in binder giving a relative dissolution ratio of 1 compared with massing the same dry mix concentration with water.

relative solubilities and the drying temperature should be maintained the same as the massing temperature.

This model was verified by forming a co-saturated solution, of borax and lactose at 25°C, as the binder for massing a borax/lactose dry mix having the same dry weight concentration ratio as in the binder. This concentration by analysis was found to be 30.1% w/w. The granules were also dried at 25°C in order to keep the dissolved components in the binder constant.

Figure 54 (b) shows the effect of massing the 30.1% w/w borax/lactose dry mix with the binder containing the same 30.1% w/w borax/lactose as a co-saturated solution. This was compared with massing a dry mix of equal concentration with pure water as the binder.

The overall deviation in the concentration of borax in the granule sizes in the batch prepared with the use of the co-saturated binder produced only ± 0.5% compared with the control granulation with water which gave ± 3% (Figure 54 (b)). The fact that the control granulation produced only ± 3% deviation, although this is 6 times higher than the model, again emphasises that dosage uniformity is more problematic in micro-doses than higher doses especially for drug/diluent systems with relative dissolution ratios deviating from unity.

Figure 54 (a) shows this effect of the relative dissolution ratio on dosage uniformity in the granule sizes. When the relative dissolution ratio is numerically equal to 1 the distribution in the granule sizes is uniform compared with that in the granules prepared by massing with

a binder containing an appreciably higher ratio of drug concentration than it is in the dry mix, i.e. 23.1 : 0.6.

3.3.5 EFFECT OF DRYING METHOD

Granule Size Distribution

The vacuum and hot air dried granules produced similar granule size distributions as presented in Figure 56.

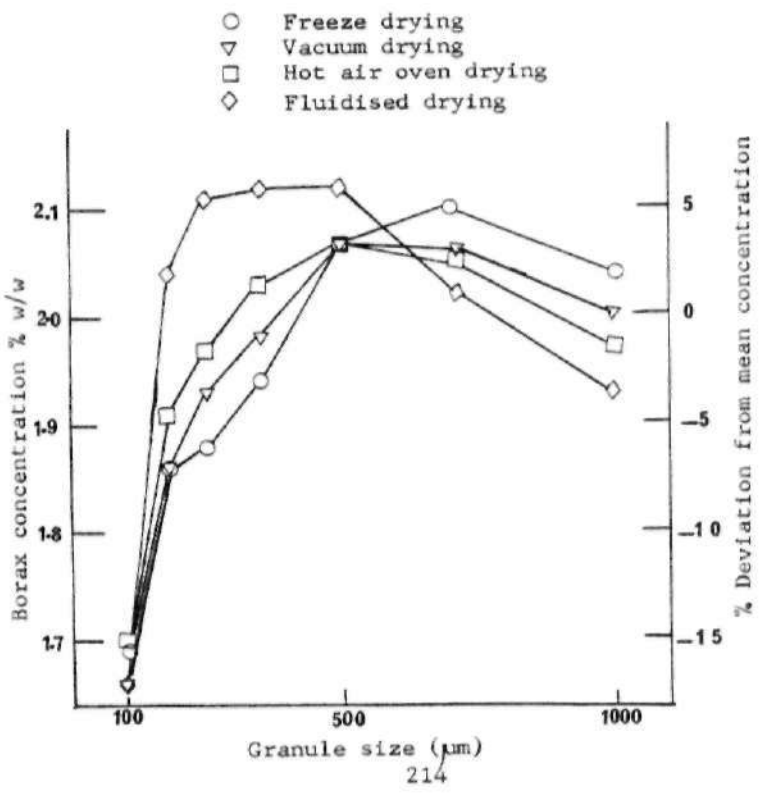
These granules were formed at room temperature but dried at 48°C. The increase in temperature during drying is expected to increase the weight of borax and lactose dissolving in the binder. The granules dried in the vacuum oven contained less fines than those dried in the hot air oven. This is attributed to the longer time of drying in the vacuum oven as a result of the slower conductive heat transfer necessary to dry the granules during the pendular phase. Thus a higher binder volume would be available at the drying temperature for a longer time in which case more solutes would dissolve and therefore reduce the number of fines.

The freeze dried granules as expected have the lowest fraction of large granules. Two reasons may be advanced for this. Firstly, freeze drying entails solidification of moisture before subliming. Water is known to increase in volume when it freezes. This expansion could disrupt the bridging at the intra-particulate contacts. Such a disruption will be more marked at the bridging contacts than in the pores which could accommodate the expansion to a certain extent. Secondly, freeze drying involves an appreciable reduction of the temperature of granules formed

Figure 56 Effect of drying method on distribution of borax in sizes of granules in a batch prepared by massing 2% borax/lactose dry mix with 14% v/w water

Effect of Drying Method on Granule Size Distribution

Sieve mesh (μm) retaining granules	% Cumulative weight retained on sieve			
	Hot air oven	Vacuum oven	Fluidisation	Freeze drying
1000	30	29	27	23
710	49	49	45	42
500	65	65	60	60
355	79	79	73	75
250	89	92	83	90
180	95	97	90	95
<180	100	100	100	100



at room temperature. Therefore no more of the components are expected to dissolve after massing. Thus less solutes are available to crystallise at the initial intra-granular liquid bridges after drying. The crystallisation of solutes at these liquid bridges is necessary to sustain the sizes of granules formed during the massing and wet-screening processes.

The highest fraction of fines was obtained in fluidised dried granules. Fluidised abrasion at the initial stage of drying before the granules attain enough strength (Travers, 1974) led to the production of fines with this drying method.

Drug Distribution

It has been shown earlier (Figure 32) that the migration of solutes during freeze drying is absent. The appreciably lower temperature of drying has been pointed out above to inhibit the dissolution of the solutes during the drying process. Therefore the concentration of the drug throughout the granules would be expected to reveal the borax concentration in the granules immediately after massing and wet force-screening. The peak concentration was obtained in 710 micrometres of granules and not in the largest (1000 micrometres) granules (Figure 56). Freeze drying therefore further substantiates the concept of the dissolution and depletion of some of the soluble components in the overwetted region during massing (Figures 17 and 56).

A comparison between granules dried by freeze drying and by the other methods also shows the extent of the effect of solute migration during drying on the concentration of

borax in sizes of granules. Thus the migration of the binder solution containing a drug such as borax with a high dissolution ratio causes an increase in the drug concentration in the intermediate sized granules at the expense of the larger granules as shown in Figure 56. A higher extent of solute migration in the granules dried in the hot air oven than those dried in the vacuum oven has been shown earlier (Figure 32). This higher migration is demonstrated in Figure 56 for the granules on the tray, dried in the hot air oven as a lower borax concentration in the larger sizes but a higher concentration in the intermediate sized granules.

It has been shown (Figure 17) that the concentration in the largest granules was higher than would be expected as some of the drug-laden, distributed binder agglomerated some particles to form part of the large sized granules. These granules have a higher borax concentration and were distinguished between the fingers by their loose formation at the wet stage. Fluidised abrasion during the early stages of drying (Travers, 1974) would "size reduce" these loosly formed granules which subsequently form part of the intermediate granules and the fines as obtained (Figure 56). As expected, these granules being formed by wetting of particles with the binder containing dissolved solutes contained a markedly higher concentration of borax. A higher percentage of the initially agglomerated granules formed directly from the overwetted region being more resistant to abrasion was less affected by this fluidised abrasion. Thus borax concentration as a result of solute

depletion during massing as expected, and obtained, is markedly lower. Consequently the lowest concentration was obtained in the larger sized granules but the highest concentration in the intermediate sized granules.

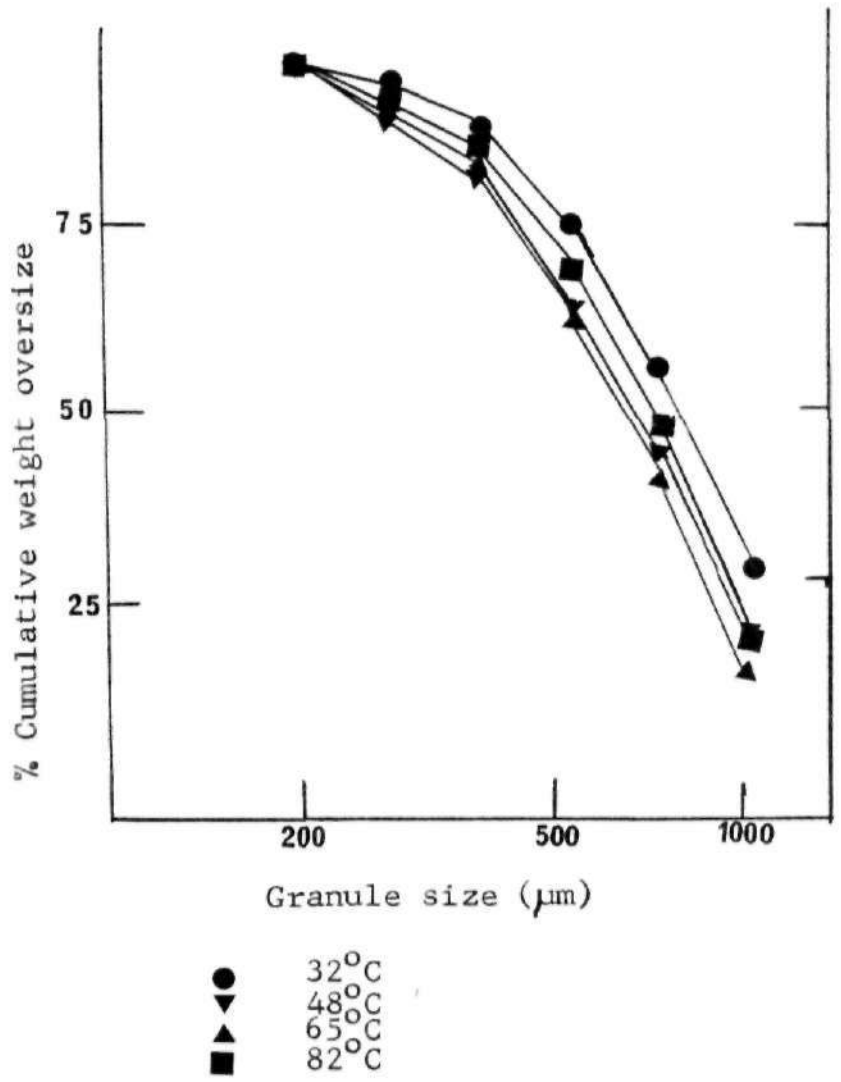
3.3.6 EFFECT OF DRYING TEMPERATURE

Granule Size Distribution

Figure 57 shows the effect of the drying temperature in a hot air oven on the granule size distribution of borax/lactose granules. A higher proportion of large granules was obtained by drying at a lower temperature. This may be attributed to the differences in the quantity of solutes that dissolved during the drying.

It is appreciated that the bulk of the granules size formation was formed during massing and force-screening. The granules at this stage are being held together by the capillary forces of the binder solution at the contact points. The binding action by crystallisation of solutes at these contacts, after moisture evaporation, replaces the liquid binding forces maintaining the granules at the wet stage. Thus any reduction or absence of the amount of solutes crystallising at the contacts will lead to weaker granules after drying. Any subsequent handling e.g. dry-screening will cause a more marked reduction of granule size. A higher drying temperature leads to a faster rate of drying (Figure 22). This faster rate of drying reduces the binder volume remaining for adequate solute dissolution before the binder equilibrates with the temperature of the oven.

Figure 57 Effect of drying temperature on size distribution of borax/lactose granules



On the other hand the slower rate of drying at a lower temperature allows a higher binder volume to remain and equilibrate with the oven temperature. This will therefore allow dissolution of more solutes necessary to crystallise and replace the binder liquid bridges. Also, the higher volume of binder taking part in inter - granular migration may bind some granules together to make larger ones. Thus the proportion of large granules will increase. The migration of solutes to the granule surface which leads to a higher fraction of large granules in the granule top layer has earlier been demonstrated in Table 10.

However for sodium salicylate/lactose granules dried at 70° and 48°C respectively, only a negligibly higher fraction of large granules was obtained at the higher drying temperature as shown below.

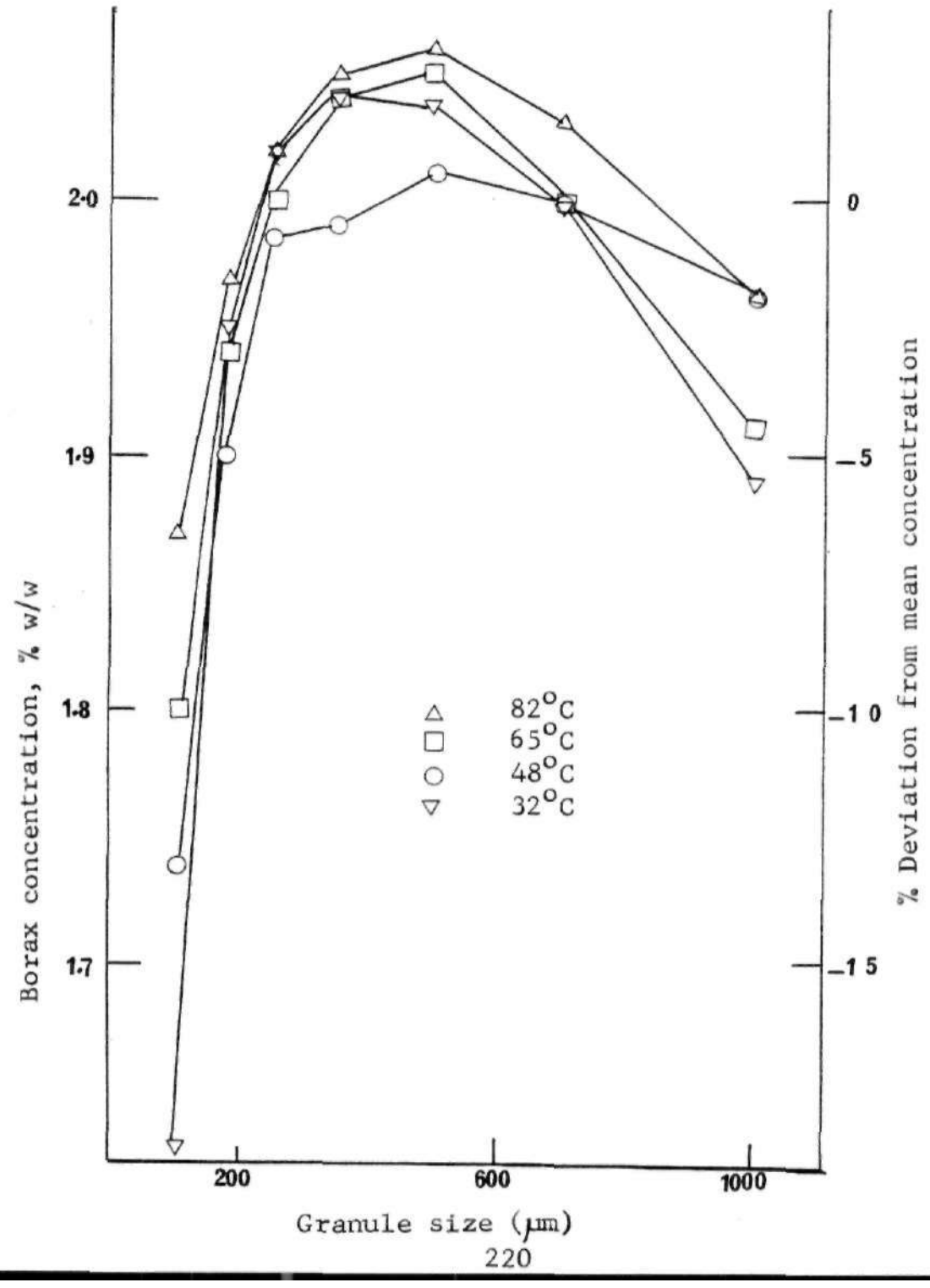
Granule size µm		1000	710	500	355	250	180	<180
Oversize cumulative weight % for a given temperature	70°C	29	48	61	73	83	90	100
	48°C	28	46	60	72	82	89	100

A possible explanation may be related to the appreciable high rate of dissolution of the sodium salicylate (Figure 18). Consequently no appreciable differences in granule size distribution were obtained.

Drug Concentration

The concentration of borax in the large granules (figure 58) did not show any clear relationship with the drying temperature but there is a noticeable pattern in concentration in the

Figure 58 Effect of drying temperature on borax distribution in granule sizes in a batch prepared by massing 2% w/w borax/lactose with water, 14% v/w

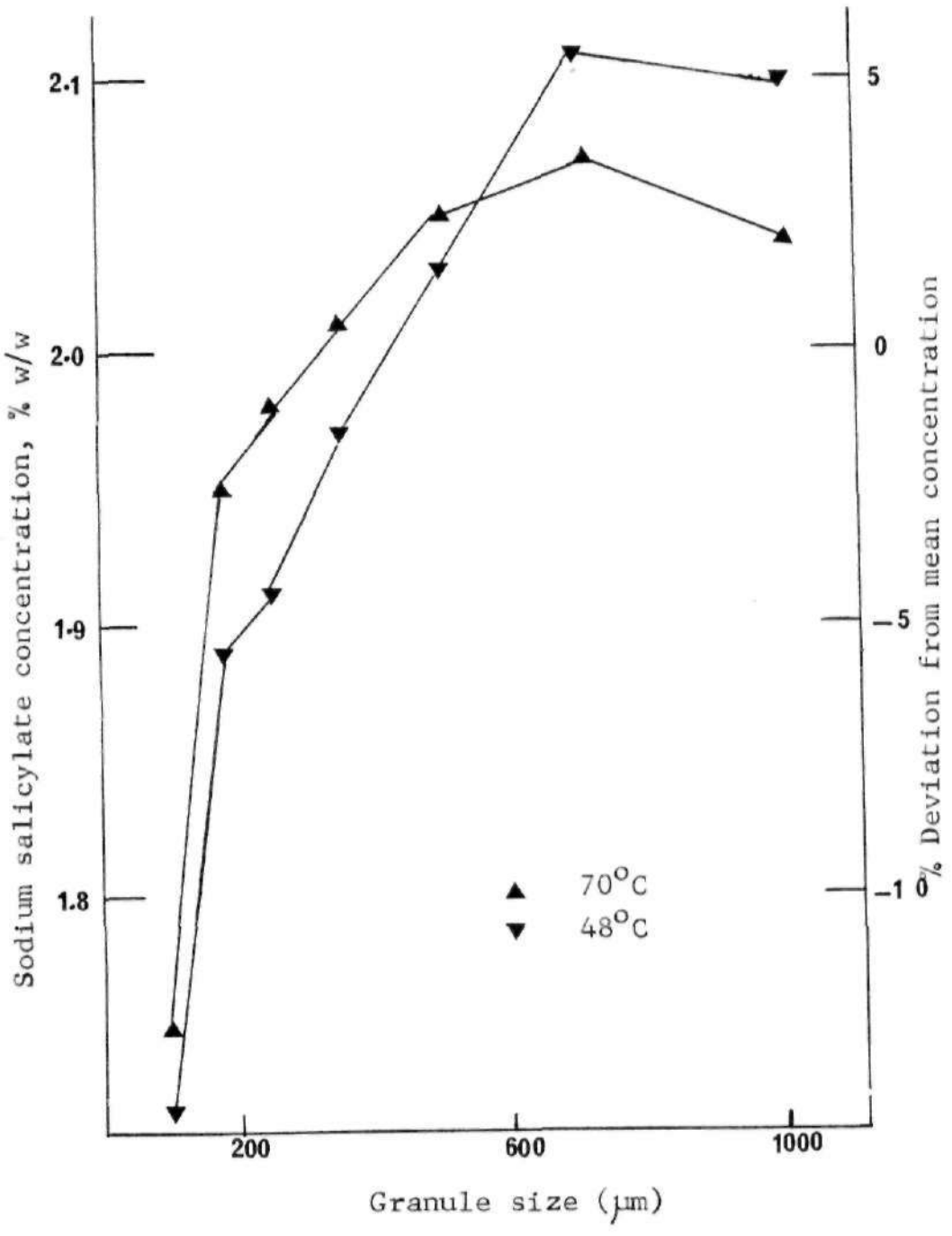


fines. A higher temperature of drying led to a higher concentration of borax in the fines.

It has been shown in Figure 24 and Table 9 that a higher temperature of drying decreases the migration of borax. It has also been discussed above that the higher drying temperature caused a lower fraction of large granules (Figure 57); and this is related to the decreased quantity of dissolved solutes as a result of the faster rate of moisture evaporation before the binder equilibrated with the oven temperature. The lack of adequate crystallised solutes resulting from the less dissolution of the solutes will lead to more fragile granules. Subsequent processes e.g. dry screening will break rather than abrade a higher proportion of these fragile granules. This is expected to increase the concentration of borax in the fines. Therefore the borax concentration in the fines will be related to the degree of breakage which will be higher for granules dried at a higher temperature. This conforms to the lower fraction of larger granules (Figure 57) and the increase in the concentration of borax in the fines with a higher drying temperature (Table 9).

Figure 59 also shows a higher concentration of sodium salicylate in the intermediate sized granules but a less marked higher concentration in the fines for granules dried at a higher temperature. Since sodium salicylate is very readily soluble, most of it should have dissolved by the time the equilibrium granules were formed during massing. Therefore during drying, an increase in the migration would be seen as a dilution of the concentration

Figure 59 Effect of drying temperature of sodium salicylate/ lactose granules on the distribution of the sodium salicylate in granule sizes in a batch



of sodium salicylate in the intermediate sized granules and the fines. This migration as shown before is more marked at a lower drying temperature.

3.3.7 EFFECT OF BINDER CONCENTRATION

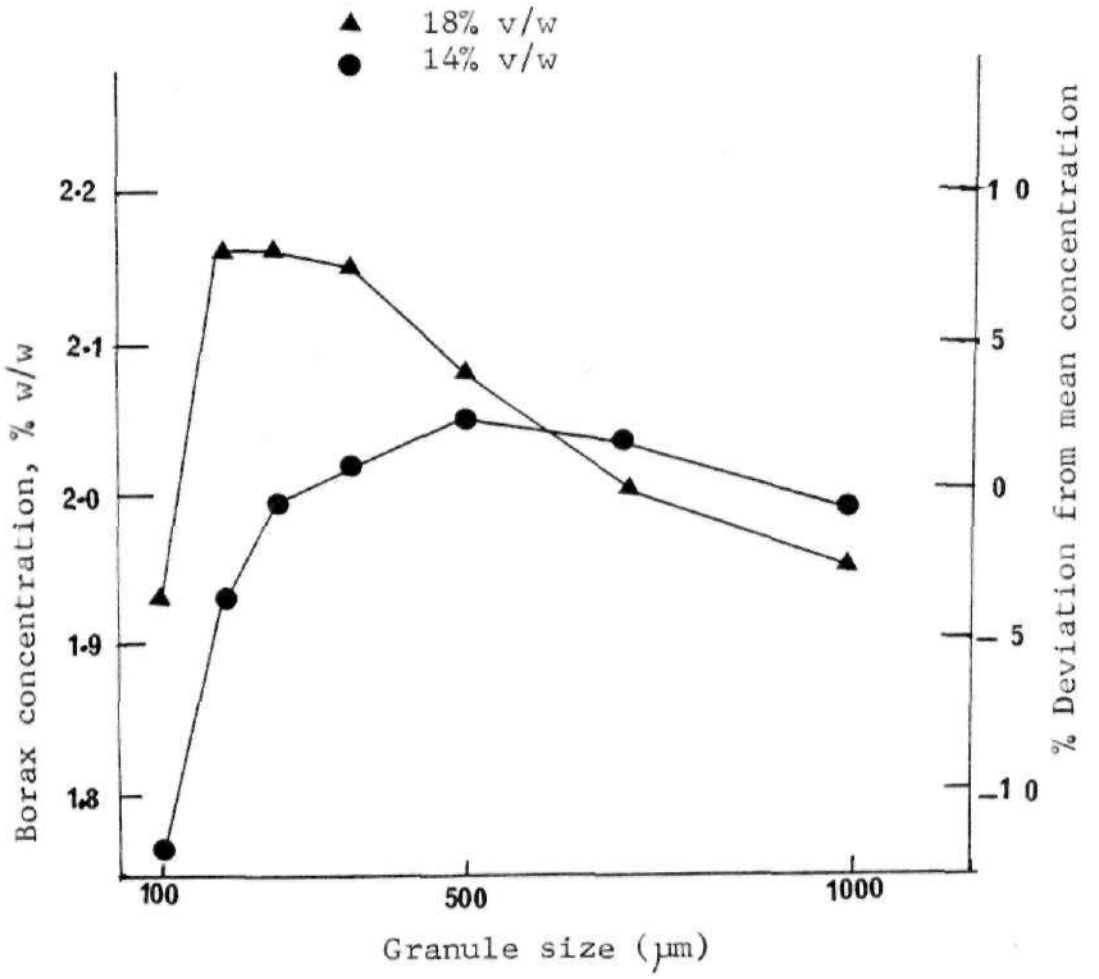
In Figure 60, the concentration of borax in the large granules is lower with 18% binder volume than with 14%. The peak concentration is higher and contained in even smaller granules with the higher volume of the binder.

The occurrence of the peak concentration in intermediate sized granules for the 14% v/w water granulation has already been discussed (Figure 46). In massing with the higher binder volume of 18% v/w water, the distribution of the binder from the overwetted region will be expected to form secondary agglomerates from which some redistribution of the binder to other drier areas will take place. The binder being redistributed from these secondary agglomerates will dissolve even more solutes. In such a granulation process the peak concentration will be shifted to granule sizes smaller than that contained with the lower binder volume.

The binder volume may be increased to such an extent that all the intra-granular pores are oversaturated. In such a case, rapid agglomeration of granules takes place to form a mass which produces "worm-like" extrudates during wet screening (Hunter, 1972). Such was the case with the 18% v/w binder used for massing the borax/lactose dry mix.

Under these conditions the granules will have the

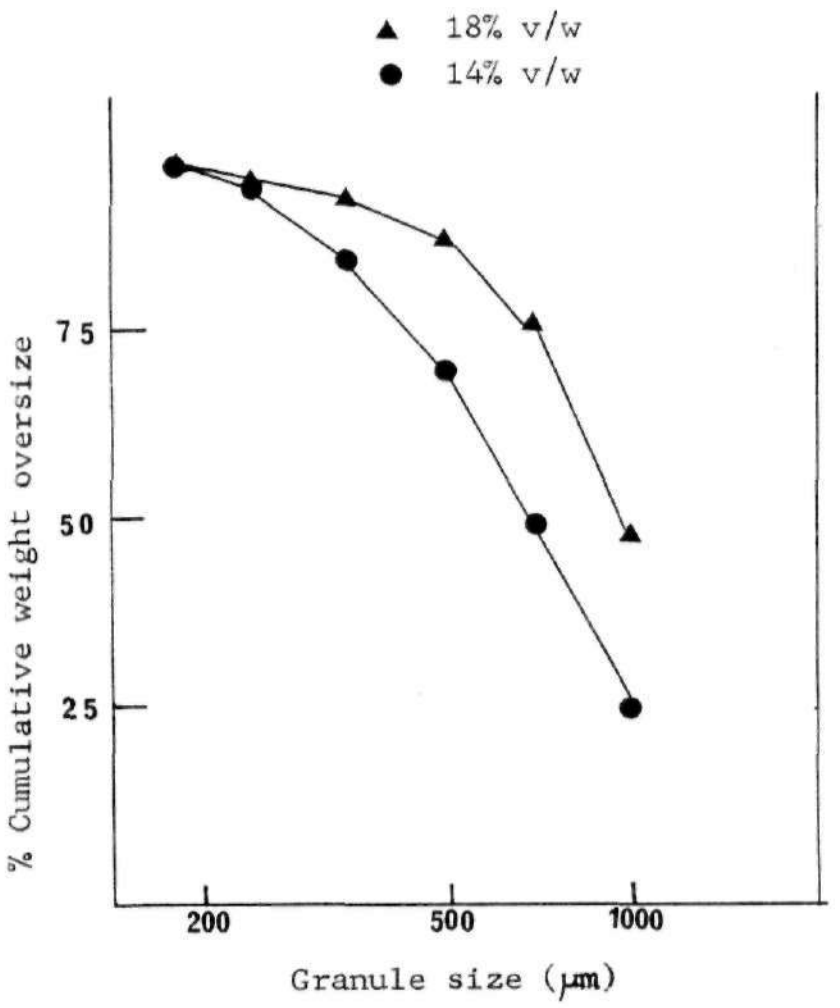
Figure 60 Effect of binder volume on borax distribution throughout the granule sizes in the batch



"spilled" binder, coating them. The quantity of the binder coating the granules will be inversely related to granule size (Dingwall and Ismail, 1977) as a result of the larger relative surface area available for coating on smaller granules. This binder now contains a reasonable quantity of dissolved components. Thus the peak concentration in granules of such a system will be contained in smaller granules. This too is in agreement with the results in Figure 60 for 18% v/w binder. However, the concentration in the fines is lower than in 180 micrometre granules. It is known that fines are mostly a consequence of the extent of granulation failure. It is expected that a much higher relative quantity of borax will be wetted to be incorporated in the granules than lactose. The relative solubility of lactose although higher produces a less significant effect on the overall concentration of borax. The fines are therefore expected to contain less borax than the overall dose of 2% w/w.

The granule size distribution in Figure 61 shows a marked effect on the amount of large sized granules. The higher binder volume produced a higher proportion of large granules. This is consistent with the results obtained by Hunter and Ganderton (1973), Chalmers and Elworthy (1976) and Selkirk (1976). A higher volume of binder increases the saturation level of intra-granular pores, thereby allowing a higher area of particle "linkages" necessary for forming larger granules. In addition, a higher weight of solutes will dissolve in the higher volume of the binder. Therefore the crystallisation of the solutes within the

Figure 61 Effect of binder volume on granule size distribution of borax/lactose granules in the batch



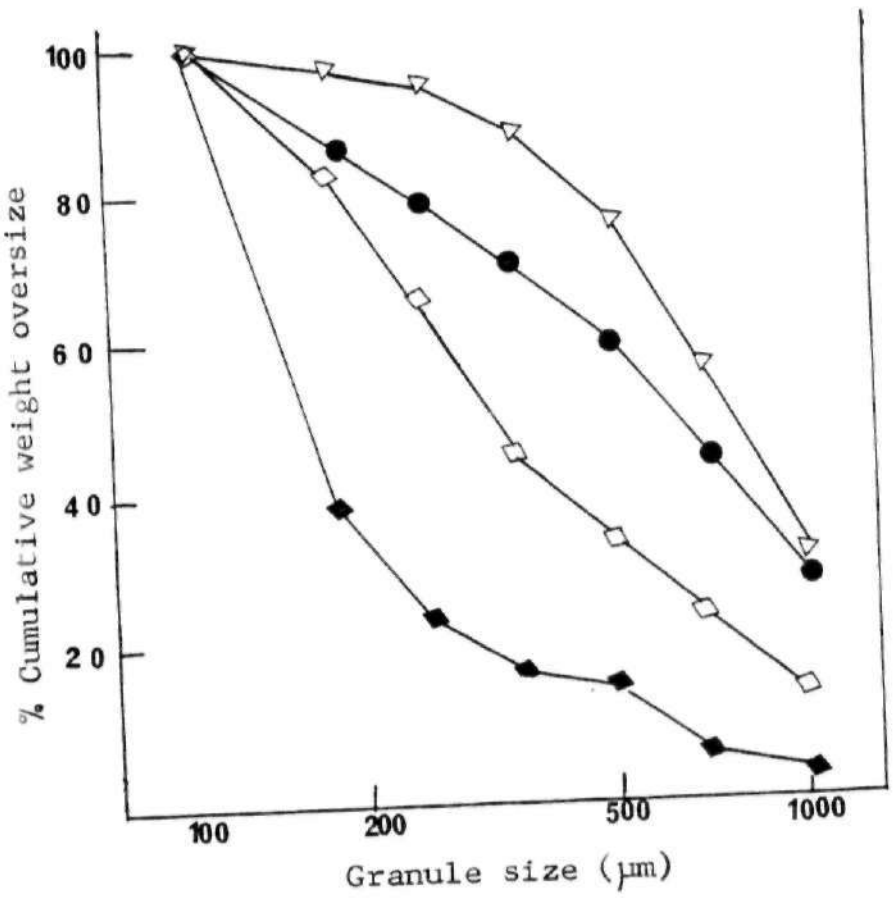
pores and at the liquid bridges keep intact the granules formed during the wet process. The dissolution of solutes in the binder is necessary for maintaining stronger granules, otherwise a more increase in the binder (solvent) volume leads to a higher fraction of large but weak granules (Chalmers and Elworthy, 1976), which may break into fines in subsequent handlings e.g. during dry screening.

Concentration of PVP binder

When water is used as the binder a reasonable quantity of the components should be able to dissolve in the binder during massing and/or drying. This is necessary for maintaining the aggregates of particles or granules formed during the massing and wet screening by capillary forces generated by the liquid binder in the pores. The evaporation of the binder solvent during drying leaves crystallised solutes as intra-granular solid bridges. Figure 62 shows the effect of an inadequate quantity of dissolved solutes (2% w/w sodium salicylate/heavy magnesium carbonate massed with 60% v/w water) in the granulation. Most of the granules formed during massing and wet screening "crumbled", when the water evaporated, as a result of an insufficient amount of crystallised solids necessary for sustaining the sizes of granules bound together by capillary forces in the wet stage. Consequently over 60% of the granules was made up of fines. For such a granulation predissolved solutes in the binder e.g. PVP is desirable.

Figure 62 shows the appreciable larger granule size distribution when 45% v/w of 15% w/v PVP was used in place of the 60% v/w water in the sodium salicylate/heavy magnesium carbonate granulation.

Figure 62 Effect of relative solubilities of drug/diluent granule formulation on granule size distribution throughout the batch



◆ Sodium salicylate/h.m.c. water 60% v/w
◇ Sodium salicylate/h.m.c. 15% w/v PVP 45% v/w
● Sulphadimidine/d.c.o. 15% w/v PVP 33% v/w
▽ Sulphadimidine/lactose water 20% v/w

The effect of the increase in the concentration of PVP in the binder on granule size and drug distribution was studied (Figures 63 and 64). The granule size distribution profiles (Figure 63) show an increase of the amount of large sized granules with an increase in the concentration of PVP solution used as the binder. Apart from the increase in the viscosity, as a result of the increase in the concentration of PVP solution, the increase in the dry weight is available to form more crystalline bridges and decrease porosity.

The distribution of sulphadimidine in sizes of granules is shown to be higher in the same large sized granules prepared from massing with a higher PVP concentration in the binder (Figure 64). The concentration in the large granules should increase with a lower concentration of PVP solution. As shown below the higher concentration of PVP in solution, indicates a higher dry weight of PVP.

Concentration of PVP in solution (% w/v)	Overall dry weight of PVP in granules (% w/w)
25	8.25
20	6.6
15	4.95
10	3.3

The higher concentration of binder should dilute the concentration of sulphadimidine but the reverse was the case as shown by the results (Figure 64). It is possible that the adhesive nature of the PVP binder (which is higher with a higher PVP concentration) coupled with the cohesive nature of sulphadimidine allowed some measure of

Figure 63 Effect of the concentration of PVP solution as a binder on sulphadimidine/dibasic calcium orthophosphate granule size distribution in the batch.

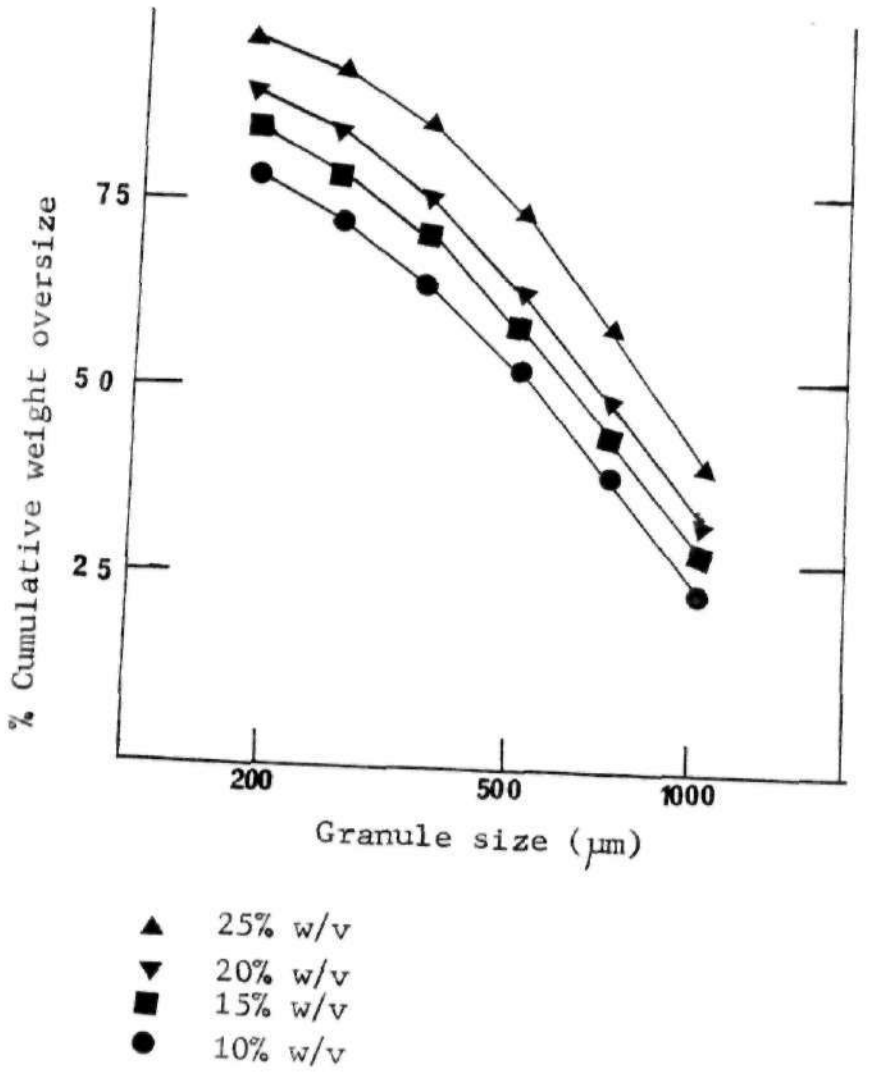
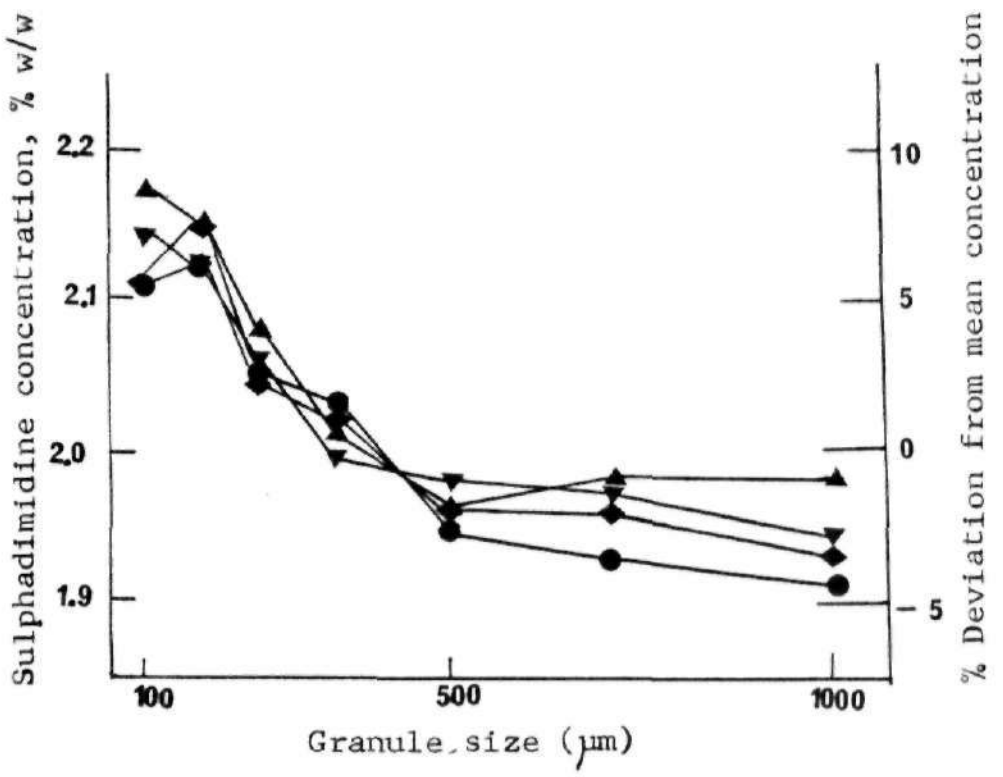


Figure 64 Effect of the concentration of PVP solution as a binder on sulphadimidine distribution throughout the sizes of sulphadimidine/dibasic calcium orthophosphate granules



▲ 25% w/v
▼ 20% w/v
◆ 15% w/v
● 10% w/v

snow-balling of the drug to the wetter granules during massing.

While the fines with 10 and 15% w/v of PVP solution had a slightly lower content than 180 μm granules, the fines with 20 and 25% w/v had the highest sulphadimidine concentration. It appears that dry screening abrasion was 'resisted' by granules massed with a higher concentration of PVP. The breaking load of tablets and hence of granules increases, up to a limit, with increase in the concentration of PVP solution (Chalmers & Elworthy, 1976). Therefore the weaker granules obtained from massing with the two weaker or more dilute solutions could be abraded causing PVP rich fines which would dilute the sulphadimidine concentration in the ungranulated fines. The result below gives an evidence for this proposal (Table 16).

The concentration in the fines from granules with 25% and 20% w/v PVP solution is equal to the theoretical concentration of the drug in a dry mix before massing. This also reveals that the fines were ungranulated dry mix, that is, not bound together by the PVP binder.

Rescreening of Granules During Drying

Although the rescreening of granules during drying was a measure taken to examine the effect of binder concentration, the rescreening action also abraded the surface of granules before these granules acquire sufficient strength after subsequent drying.

The result of the granule size distribution for granules which were additionally screened after 30 minutes of drying are shown in Table 17 and Figure 65. The

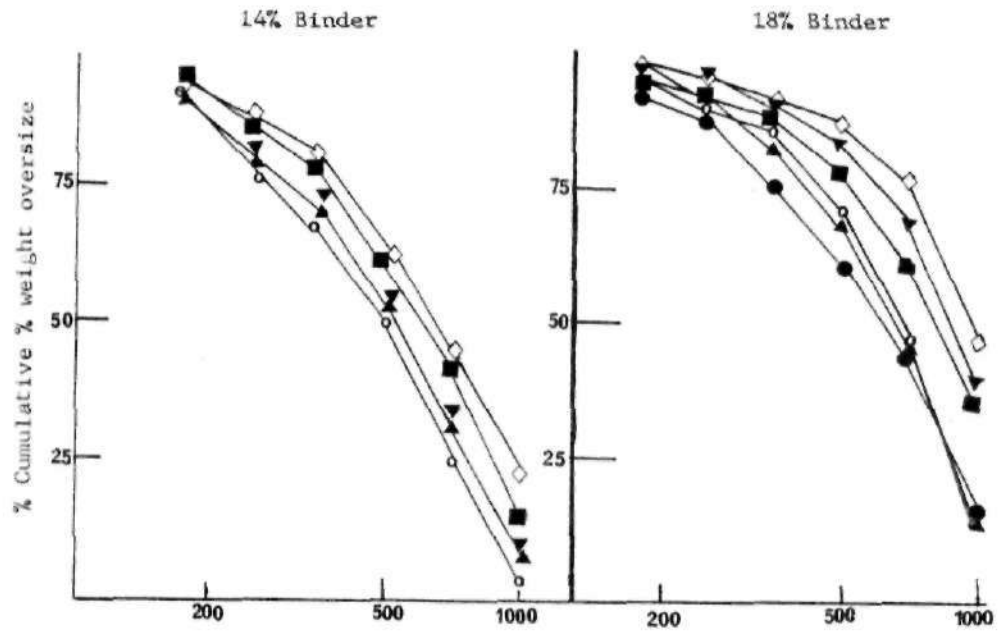
Granule size (μm mesh)	Concentration of sulphadimidine in granule (% w/w)			
	Concentration (% w/v) of PVP binder solution			
	25%	20%	15%	10%
1000	1.98	1.95	1.94	1.91
710	1.98	1.97	1.95	1.93
500	1.96	1.98	1.96	1.94
355	2.01	1.99	2.02	2.03
250	2.08	2.06	2.04	2.05
180	2.15	2.12	2.12	2.15
< 180 (fines)	2.17	2.14	2.11	2.11
conc. of dry mix in absence of binder	$\frac{2\%}{100\%-8.25\%} = 2.18$	2.14	2.10	2.07

Table 16. EFFECT OF PVP CONCENTRATION IN BINDER ON DRUG DISTRIBUTION IN GRANULES

Mesh size (μm) and order of screenings	% Cumulative weight of granules retained on sieve of a given mesh size (μm)						
	1000	710	500	355	250	180	<180
1680, —— , 1200 μm	22	45	64	81	88	95	100
1680, 1680, 1200 μm	15	40	61	78	86	95	100
1680, 1200, 1680 μm	8	33	54	70	86	91	100
1200, 1200, 1200 μm	3	25	50	68	89	93	100
1200, 1680, 1680 μm	9	32	55	72	90	95	100
1680, 1200, 1200 μm	7	31	51	70	79	90	100

Table 17 EFFECT OF MESH SIZE OF SIEVE AND INTERMEDIATE SCREENING ON GRANULE SIZE DISTRIBUTION OF GRANULES MASSED FROM 14% v/w BINDER

Figure 65 Effect of binder volume and sieve mesh size for wet screening, for intermediate screening after 30 minutes of drying and for dry screening on granule size distribution



▲	1680μm,	1200μm,	1200μm →	the granules were wet screened through sieve of mesh size 1680μm, rescreened through size 1200μm and dry screened through size 1200μm, and so on.
▼	1200μm,	1680μm,	1680μm	
■	1680μm,	1680μm,	1200μm	
●	1680μm,	1200μm,	1680μm	
o	1200μm,	1200μm,	1200μm	
◇	1680μm,	- ,	1200μm, i.e. no rescreening	

moisture content of the granules just after rescreening was in each case 7% v/w in granules prepared with 14% v/w water and 11% v/w in granules prepared with 18% v/w water.

The fraction of 1000 micrometre granules for each of the two binder contents was higher without rescreening during drying. This shows that the rescreening action caused some abrasion of the larger granules. The alternation of sieve mesh sizes was more sensitive to granule size distribution with the higher binder volume used for the massing. This is related to the higher binder volume remaining for migration and for binding action after the rescreening. The mesh size of the sieve for the intermediate screening was found to be important, a larger sieve mesh caused a higher quantity of large granules.

Drug Concentration in Granule Sizes

Figure 66 shows the distribution of borax in the sizes of granules when the mesh size of the sieve during the intermediate and dry screening is varied. In all cases the abrasion caused a higher borax concentration in the larger sized granules. A higher degree of abrasion takes place when the sieve mesh size used in the intermediate and dry screening is smaller than that used in the wet force-screening. This higher abrasion has been shown in the granule size distribution in Figure 65 and Table 17 and has been found to cause a higher borax concentration in the larger sized granules as is shown in Figure 66. The relative solubility of borax in the granulation is high. Therefore the granule periphery should be rich in borax concentration. Abrasion of the crust will reduce the

Figure 66 (a) Effect of binder volume and sieve mesh size for wet screening, for intermediate screening and for dry screening on borax concentration throughout the granule sizes.

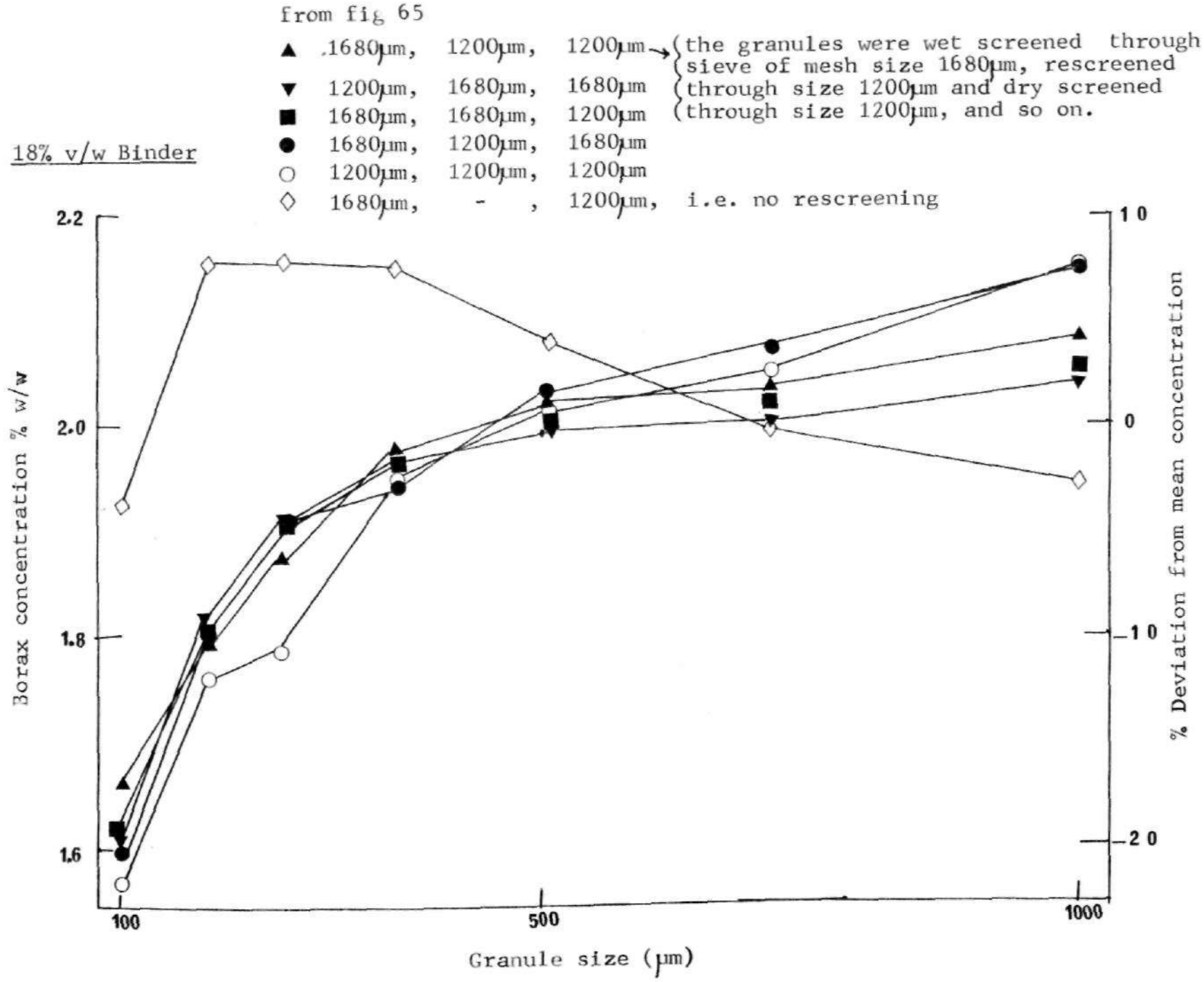
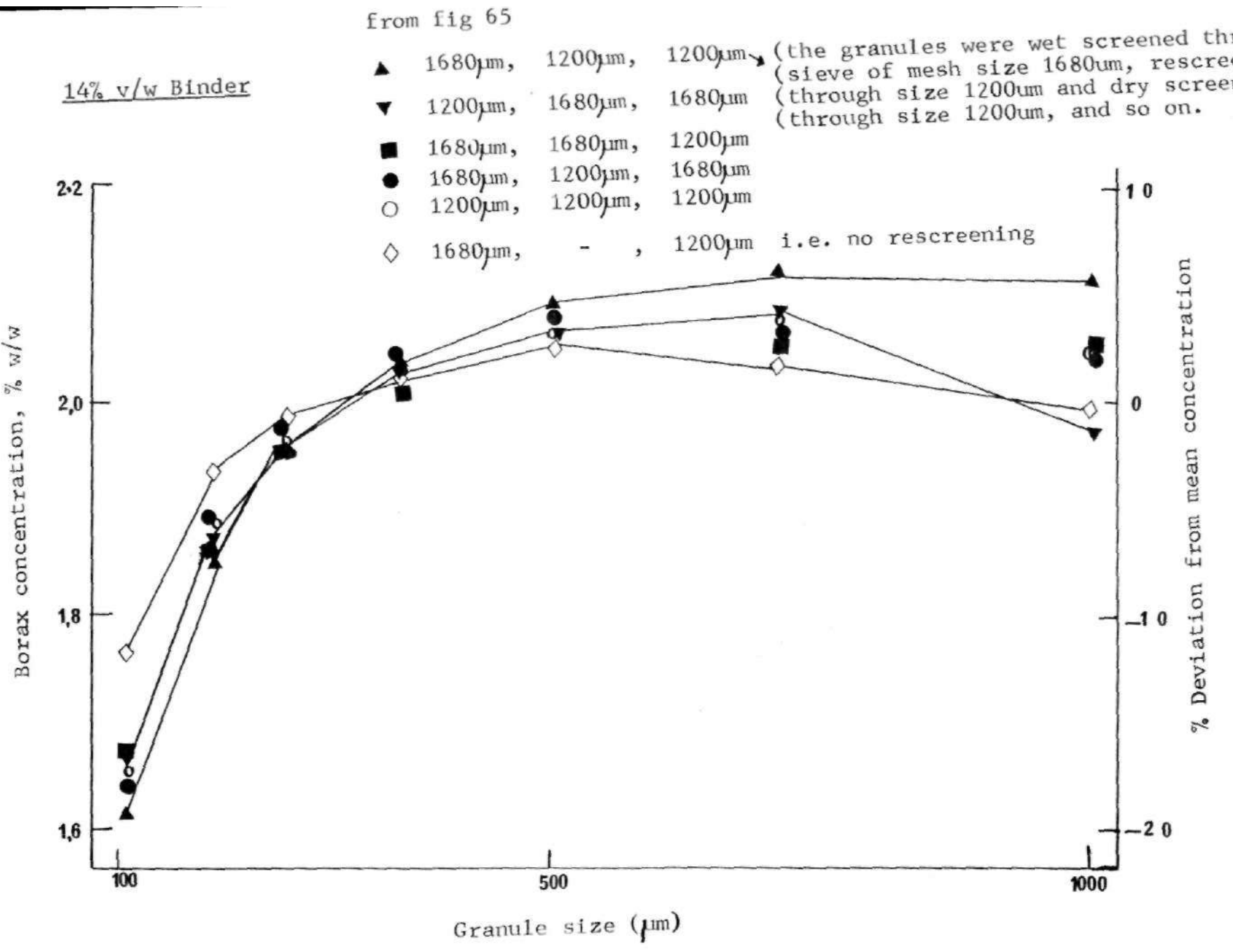
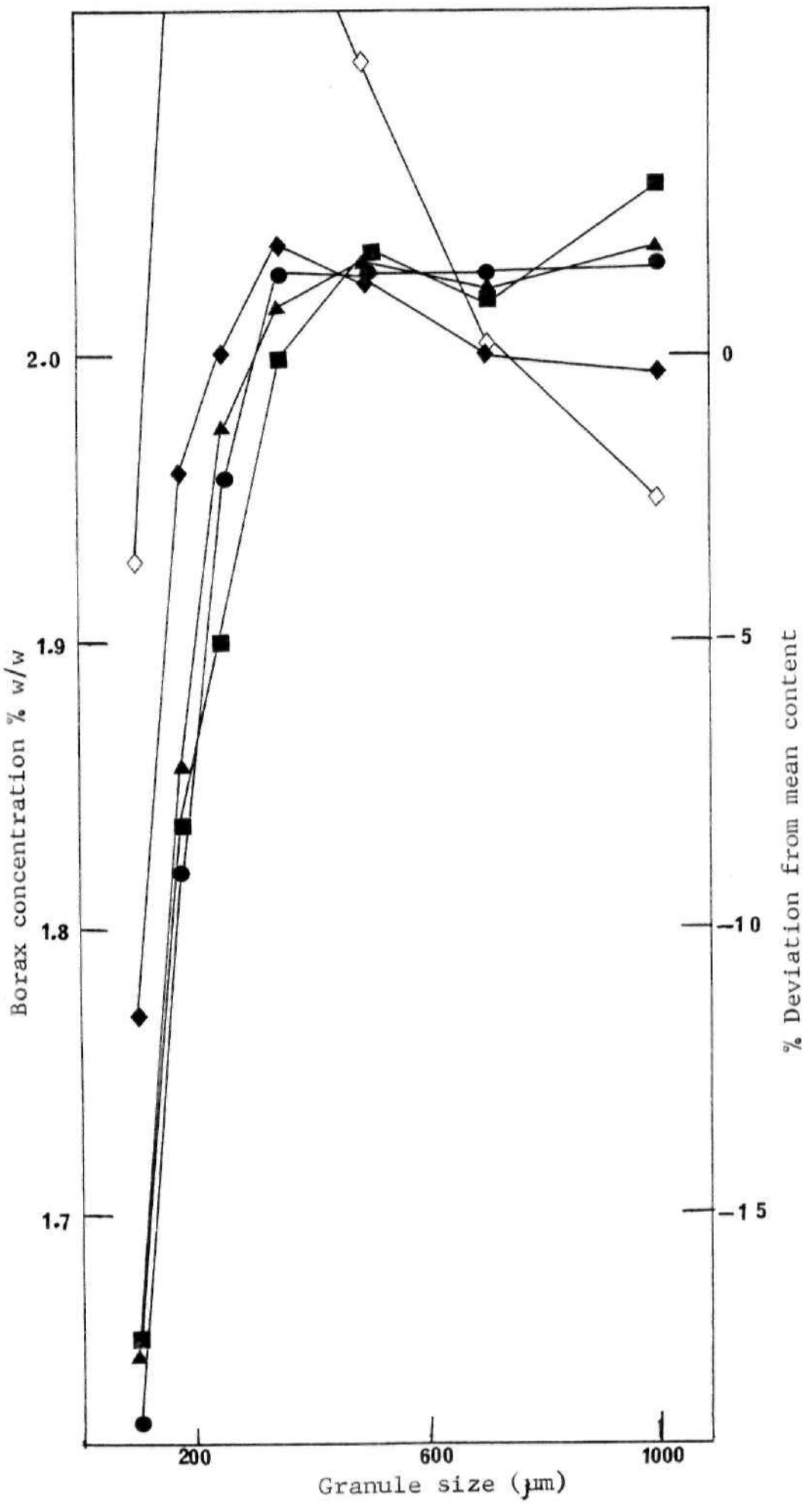


Figure 66 (b) Effect of binder volume and sieve mesh size for wet screening, for intermediate screening and for dry screening on borax concentration throughout the granule sizes.



granule size of the granules. The moisture content of the abraded fines are capable of agglomerating to form larger sized granules. Some of these abraded fines are also capable of linking smaller granules together to form larger sized granules. These larger sized granules will contain a higher concentration of borax and will form part of the larger sized granules leading to a higher mean borax concentration in these granules. Thus an increase in the degree of abrasion due to the intermediate sieving will increase the number of abraded fines capable of forming a higher borax concentration in the larger sizes of granules formed. The moisture content of 14% remaining was still in the constant rate period, some smaller granules and the abraded fines would be capable of forming new granules. The concentration in the large granules increased at the expense of the initial content in the 180 micrometre granules from the batch left unscreened during the drying. However the peak borax concentration was contained in the intermediate sized granules.

The rescreening after 30, 45 and 60 minutes of drying in each case increased the concentration in the largest granules to such an extent that the peak concentration was obtained in these largest granules. Some measure of solute migration took place after the 30, 45 and 60 minutes of drying (already shown in Figure 26) as the moisture contents of 11, 8 and 6% v/w remaining were in the region of the falling drying rate and the latter content close to the pendular state (Figures 22 and 67). Thus the migration of the solutes after rescreening decreased with an increase


2.0
1.9
1.8
1.7
Borax concentration % w/w
0
5
10
15
% Deviation from mean content
200
600
1000
Granule size (μm)

in drying time as a consequence of diminishing moisture content. Also, the larger granules are more resistant to abrasion after a longer time of drying before the intermediate screening (Table 18).

It has been demonstrated (Figure 43 (a)) that a drug with a higher relative solubility would have a relatively greater proportion of solutes taking part in solute migration. Abrasion should then lead to a lower concentration in the large granules. The reverse is the case as obtained in Figure 67. This may show that the crystallised solutes were located in the crevices of the contact points within the granule periphery. Any abrasion in the latter case would not markedly affect the migrated solutes. On the other hand it is possible that crystallised solutes are themselves less prone to abrasion than the particles in the dry mix which are held inbetween these crystallised solutes. The proportion of borax dissolved in the binder is appreciably in excess of that remaining in the dry mix. This is 70% compared with the 30% of the total borax weight in the granulation. Therefore the dry mix particles located on the granule periphery would be more susceptible to the screening abrasion and would thus form the bulk of the fines consequential to the abrasion. The concentration of borax, as a result, would be low and that in the large granules left after the screening abrasion would be higher. This would therefore account for why the borax concentration in the large granules increased after the abrasion, a result consistent with that obtained by Selkirk (1976).

Granule size (μm)	% Weight of granule retained on sieves after the given time of intermediate screening				
	0 min	15 mins	30 mins	45 mins	60 mins
1000	46	32	29	34	38
710	29	29	27	26	24
500	12	18	18	14	12
355	5	11	11	10	9
250	2	6	8	7	8
180	2	2	3	4	3
<180	4	2	4	5	6

Table 18 EFFECT OF INTERMEDIATE SCREENING TIME OR RESIDUAL BINDER CONTENT ON GRANULE SIZE DISTRIBUTION OF GRANULES INITIALLY PREPARED BY MASSING BORAX/LACTOSE DRY MIX WITH 18% v/w WATER AS THE BINDER

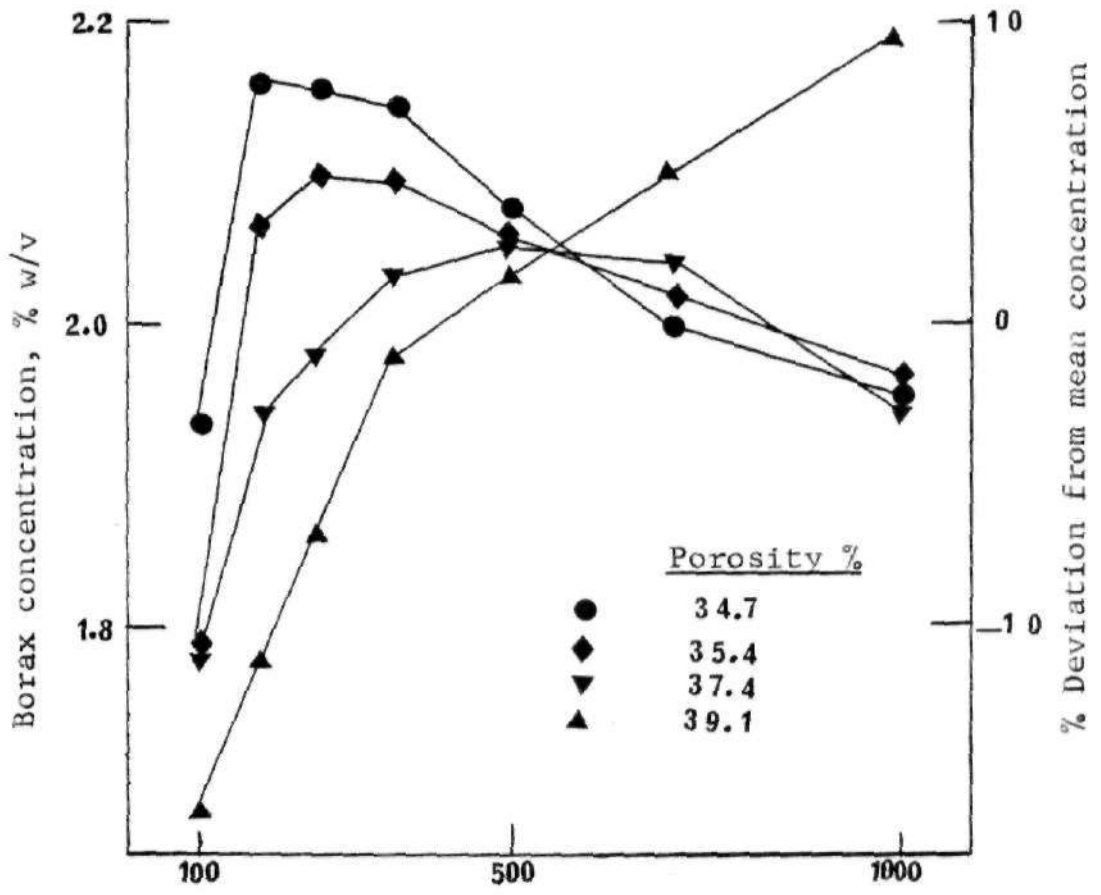
As already discussed in this section, another possibility accounting for the increase in borax concentration after the intermediate screening may be related to the agglomeration of the abraded fines as well as bonding of the smaller granules to form part of the larger sized granules. The fines even after the 60 minutes of drying before the intermediate sieving are capable of bonding smaller granules together. These fines contain an appreciable borax concentration as a result of migration of solute to the granule periphery. Thus the larger granules formed will contain a comparatively higher concentration of borax.

3.3.8 EFFECT OF EXCESSIVE MASSING

Figure 68 shows the result of borax concentration in sizes of granules prepared by massing the dry mix with 14% v/w water for 60 minutes. The peak concentration was shifted to and contained in granules finer than the mid-sized ones found with the 5 minutes massing. The concentration/granule size curves and porosities for the dry mix massed with a higher binder volume (18%) for 5 minutes massing and with a lower binder volume (14%) for 60 minute massing were similar.

Excessive massing will continue to increase the dissolution of the solutes in the binder with the result that a higher net concentration of borax in solution is being distributed to wet the particles in the drier portion of the wet mix. The continued massing action also steadily compacts the wet mass until the decreased

Figure 68 A comparison between borax distribution in granule sizes of a batch of granules prepared by massing a dry mix with 14% v/w water for 5 minutes, with 18% v/w water for 5 minutes, with 14% v/w water for 60 minutes and with a co-saturated borax/lactose solution, 14% v/w for 5 minutes.



	Binder concentration	Massing time (mins)
●	water 18% v/w	5
▲	co-saturated 14% v/w	5
▼	water 14% v/w	5
◆	water 14% v/w	60

granular pores are oversaturated giving rise to wetter granules with a lower porosity as shown in Table 15 (b).

With continued massing, agglomeration of the granular mass takes place due to the "spilled" binder being available on the granule surfaces to bind more granules together. Thus the excessive massing action serves a similar action as an increase in the binder volume.

The oversaturation of the granule pores will also cause the spilled binder, now much richer in borax, to coat or form a film round the granules. Under this condition, the smallest granule will contain the highest borax concentration. Dingwall and Ismail (1977) have shown that smaller glass beads had a higher binder uptake on account of the larger exposed surface area per unit volume. This is thus in agreement with the higher borax concentration in the smaller granules as obtained in Figure 68 in the excessively massed granulation.

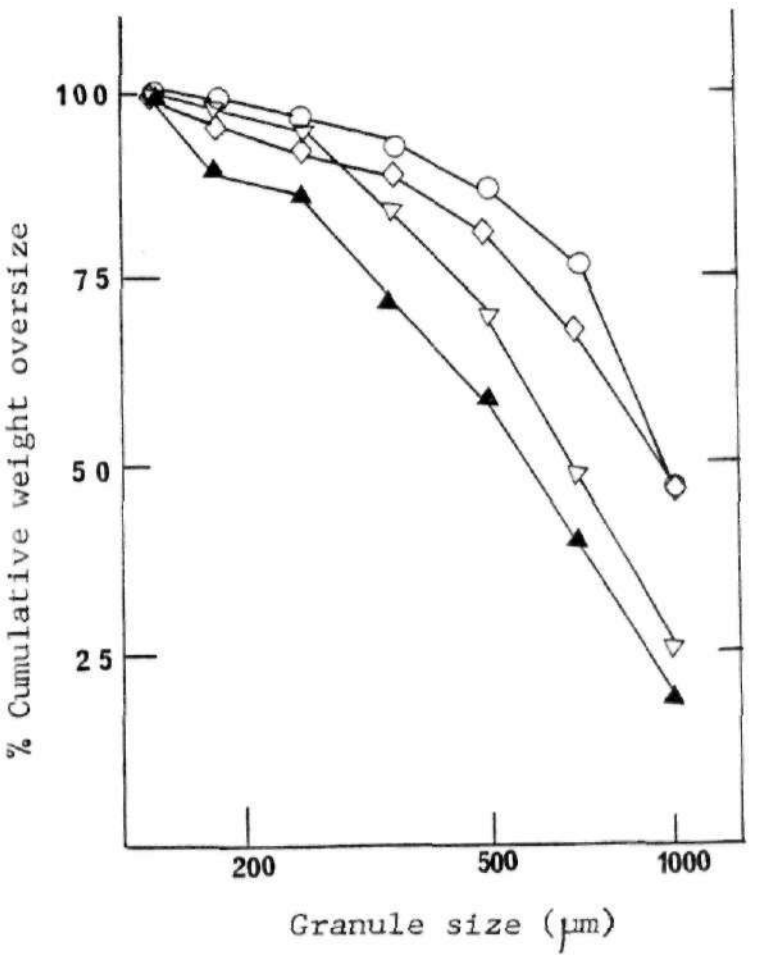
Figure 68 (b) shows the granule size distribution. The proportion of large granules was highest with 18% v/w binder content, followed closely by the excessively massed granules, then those massed with 14% v/w for 5 minutes and lowest in the granules prepared from the cosaturated binder. These results are thus in agreement with the above stated regime.

3.3.9 EFFECT OF PARTICLE SIZE OF DRUG AND DILUENT

Drug Particle Size

The effect of the particle size of a soluble drug when it is present as a low dose will mirror the effect of the rat

Figure 68 (b) A comparison between the size distribution of a batch of granules prepared by massing a dry mix with 14% v/w water for 5 minutes (▽), with 18% v/w water for 5 minutes (○), with 14% v/w water for 60 minutes (◇) and with 14% v/w of co-saturated borax/lactose solution for 5 minutes (▲).

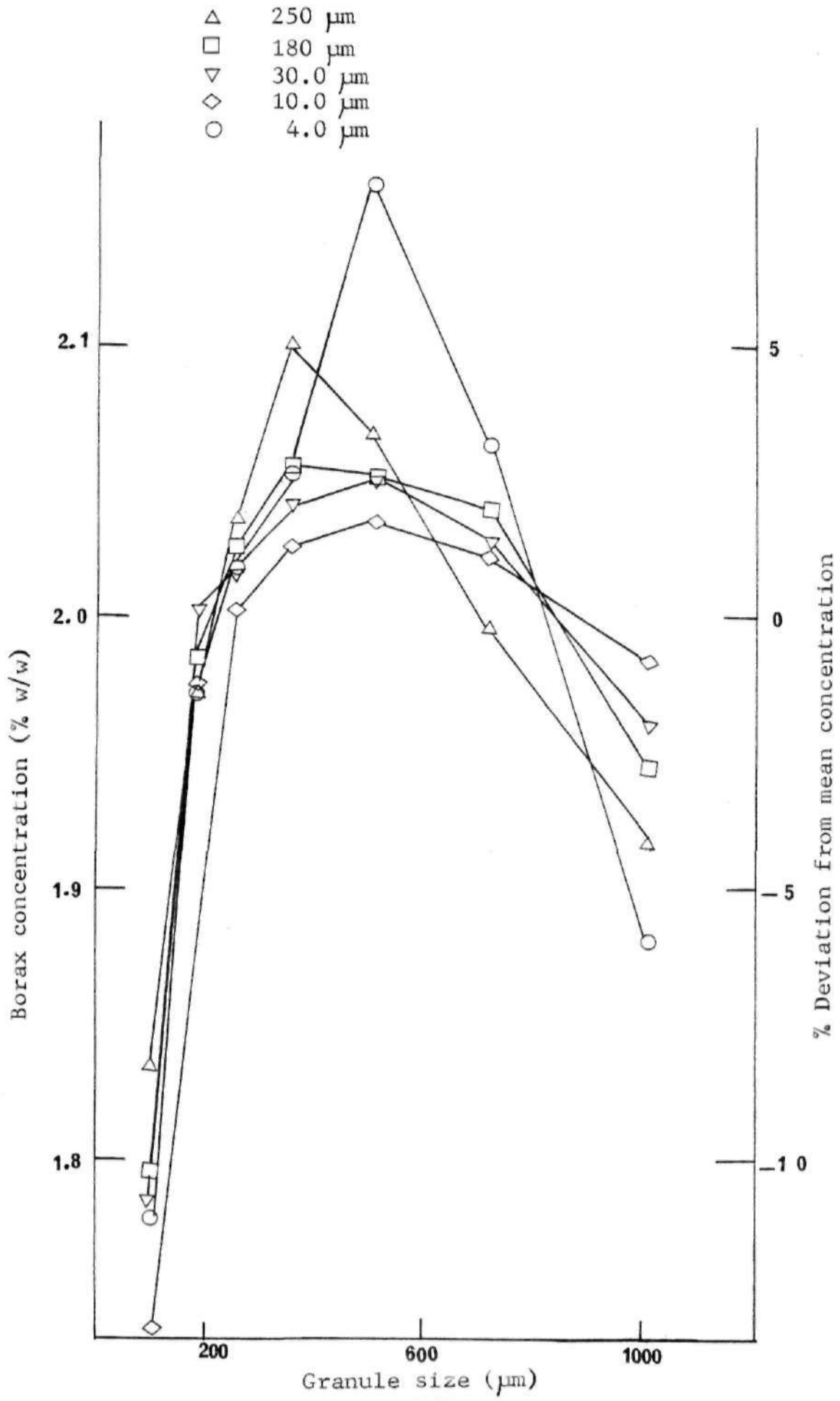


of wetting and dissolution of the drug particles during massing (Figures 18 and 19) and during drying.

Figure 69 shows the effect of borax particle size on its distribution in borax/lactose granules. The concentration of borax in the biggest granules is inversely proportional to its particle size (with the exception of the 4 micrometre size) employed in the granulation. However, the concentration in the finest granules is directly related to the particle size. This is attributed to the rate of dissolution of the borax particles which has been shown to be inversely related to the particle size (Figures 18 and 19). As a result of the mutual increase in the solubilities of borax and lactose in the binder (Figure 11), a slower rate of dissolution of larger particles of borax will in turn slow the dissolution rate of lactose. It will thus be expected that borax concentration in the largest granules will increase with an increase in its mean particle size as less borax and also lactose will be removed during massing from the overwetted agglomerates. The contrary is the case with the results obtained in Figure 69.

There are two reasons for the lower borax concentration in the larger granules massed from a larger borax particle size. The first arises from the greater proportion of the particles not being granulated due to lack of adequate wetting necessary for agglomeration. Some of these dislodged particles will be granulated with subsequently formed granule size by the massing input. The rest of these solids will form part of the fines and will therefore be retained during granule size fractionation on mesh sizes smaller than their diameters.

Figure 69 Effect of borax particle size on its distribution throughout the sizes of borax/lactose granules



The second factor accounting for the lower borax concentration in the large granules massed from the larger mean size of borax is related to the binder composition forming the cementing bridges. The appreciably slower rate of dissolution of the larger particles will cause the solutes dissolved in the binder to consist virtually of lactose only. The largest granule size contains the highest binder content (Opakunle and Spring, 1976; Dingwall and Ismail, 1977) and therefore contains a predominantly lactose solute which will dilute the borax concentration in the larger granules. This second possibility is less likely as this cannot explain the marked peak concentration in the granule sizes about equal to the initial borax particle size.

The appreciable lowest concentration with the 4 micrometre borax in the largest granules is a consequence of a marked increase in its dissolution rate. Thus the binder distributing to the drier area of the wet mix, ultimately forming the finer granules, contains the highest borax concentration as shown in Figure 69. The results with the use of 10 and 4 micrometre sizes in relation with the rate of dissolution in the binder during massing are as predicted. These results also point to the problem of using drug particles excessively larger than the diluent particle size resulting in the failure of granulation of most of the drug particles.

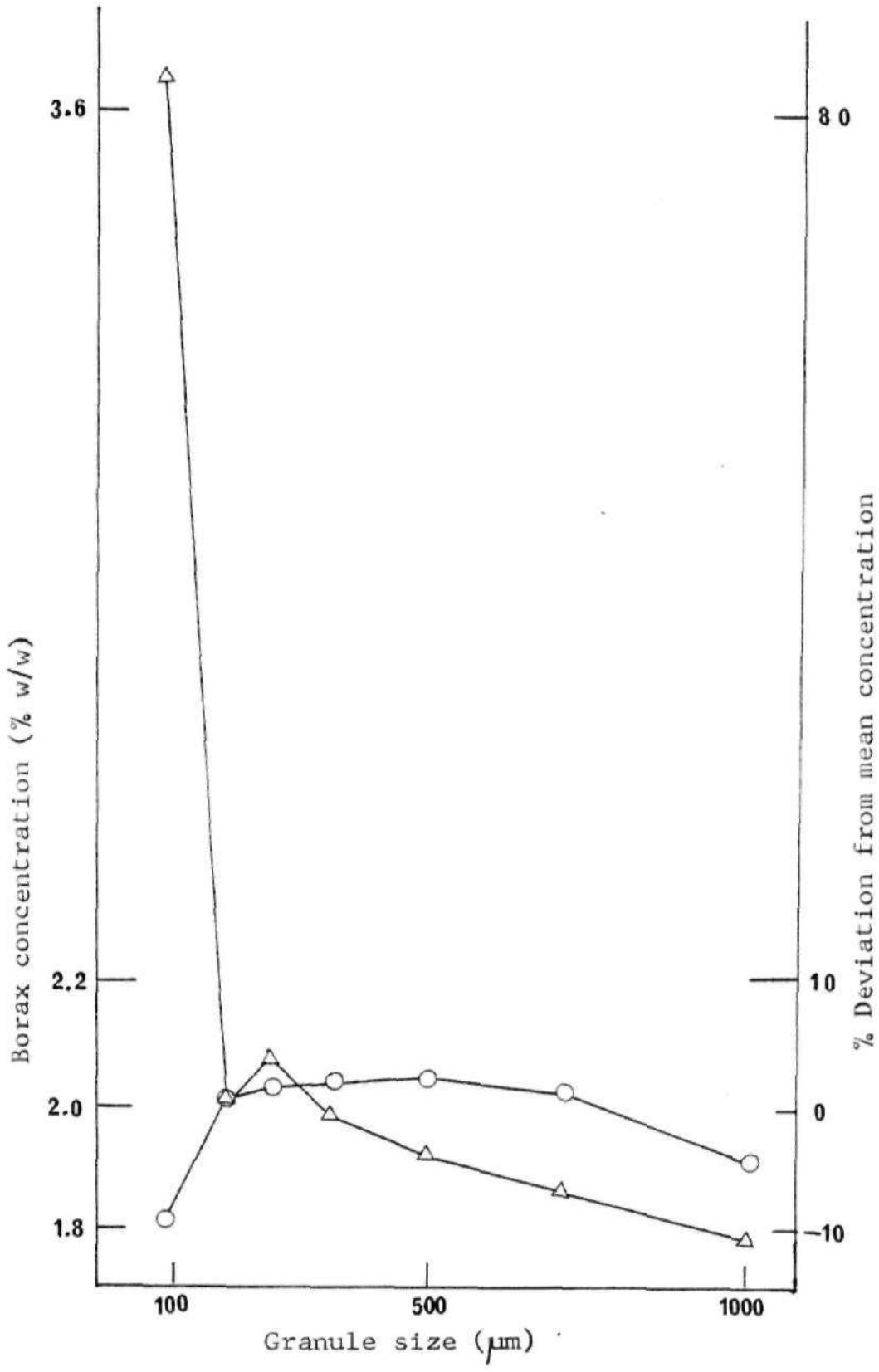
Initially the 5 minute massing was made continuous without stopping to scrape in the dead zones of the mass. Thus some sizeable quantity of the larger borax particles

in these dead zones were not sufficiently subjected to the massing input. Consequently, most of these larger particles were not incorporated in the granules and therefore form part of the fines, resulting in a substantially high concentration in the fines (Figure 70). This clearly shows the importance of minimising the dead zones during massing.

The granule size distribution is shown in Figure 71. The quantity of large granules was lower with the use of the larger borax particles in the granulation due to a decreased quantity of dissolved borax from the larger particles and thus lactose.

With the normal massing procedures (i.e. where the entire mass was reasonably subjected to the massing input by the intermittent stopping and turning in the dead zones) the granule size distribution is not appreciably different with the change in the initial borax particle size in the dry mix before massing (Table 19). However there is still an inverse relationship between the initial dry mix borax particle size and the percentage of largest granules. This pertains to the differences in the dissolution rate which is inversely related to the initial borax particle size.

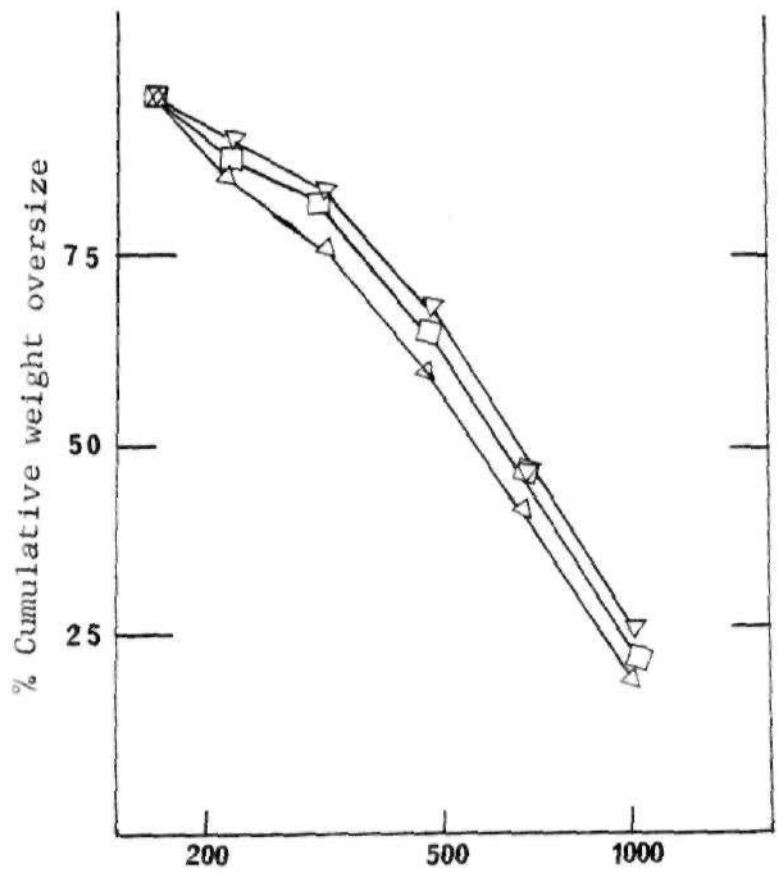
On the whole, Table 16 shows that for each formulation the initial drug particle size did not divergently alter the granule size distribution especially if the presence of the components soluble in the binder does not alter their respective solubilities as with borax and lactose. Thus the granule size distribution of a low dose drug is not markedly affected by the drug particle size.



o 5 minutes of continuous massing

Δ 5 minutes massing exclusive of scrapping and turning after 2 and 4 minutes of massing

Figure 70 Effect of minimisation of dead zones during massing on distribution of borax in sizes of granules by massing 30 micrometre borax dry mixed with lactose.



△ 30.0 μm
□ 13.0 μm
▽ 10.0 μm

Figure 71 Effect of borax particle size on size distribution of granules prepared by massing the dry mix without minimisation of dead zones.

Table 19 EFFECT OF INITIAL DRUG PARTICLE SIZE ON GRANULE SIZE DISTRIBUTION

Drug/Diluent	Drug Particle Size (μm)	% Cumulative weight of granules retained on given sieve mesh size (μm)							% weight of fines (∠180 μm)
		1000	710	500	355	250	180	∠180	
Borax/Lactose	250	26	45	61	76	88	94	100	6
	180	27	46	62	78	90	96	100	4
	30	30	47	64	79	90	96	100	4
	10	31	50	66	81	91	96	100	4
	4	33	52	69	84	93	97	100	3
Sodium salicylate/Lactose	29	28	46	60	72	82	89	100	11
	9	28	45	59	71	81	89	100	11
	co-saturated binder	27	46	60	73	83	90	100	20
Sulphadimidine/Lactose	17.6	23	40	54	65	74	83	100	17
	14.6	26	42	56	68	78	86	100	14
	8.6	27	46	59	70	78	84	100	16
	4.4	27	45	58	70	79	86	100	14
Sodium salicylate/d.c.o.	29	34	54	69	81	89	94	100	6
	9	37	58	73	85	91	95	100	5
Sulphadimidine/d.c.o.	17.6	27	41	54	65	73	79	100	21
	14.6	25	40	53	64	72	78	100	22
	8.6	28	45	58	69	77	82	100	18
	4.4	30	45	58	67	76	80	100	20

Figure 72 shows that, for a readily soluble drug such as sodium salicylate, the rate of dissolution is sufficiently rapid to make it a non-rate determining step (Figure 18). Consequently the drug distribution in the granules prepared from different particle sizes in the dry mix is similar.

The distribution of sulphadimidine in sulphadimidine/lactose granules prepared from different particle sizes of sulphadimidine is presented in Figure 73. The concentration in the fines is directly related to the initial drug particle size. This is due to failure of incorporation of some of the larger sulphadimidine particles into the granules. The distribution of the sulphadimidine in the granules is similar for the two larger drug particle sizes with the 14.6 micrometre size giving a higher displacement. The similar shape is a consequence of the higher quantity of encapsulated particles in the larger granules (Lachman and Sylwestrowic, 1964). However this encapsulation of sulphadimidine particles by the wetted lactose particles is more difficult with the smaller drug particles due to the higher number of particles in smaller particles. Therefore the shape of the curves of the drug distribution with the initial smaller particle sizes is an inversion compared with the distribution curve for the two larger drug particle sizes. This steady change in shape is by virtue of the dissolution of lactose in the binder and its distribution during massing (Figure 16) and migration during drying (Figure 35). Thus the nature of the drug distribution is as described before (Figure 46 for sulphadimidine/lactose). The concentration

Figure 72 Effect of sodium salicylate particle size on its distribution in sizes of granules prepared by massing sodium salicylate/dibasic calcium orthophosphate dry mix with PVP solution

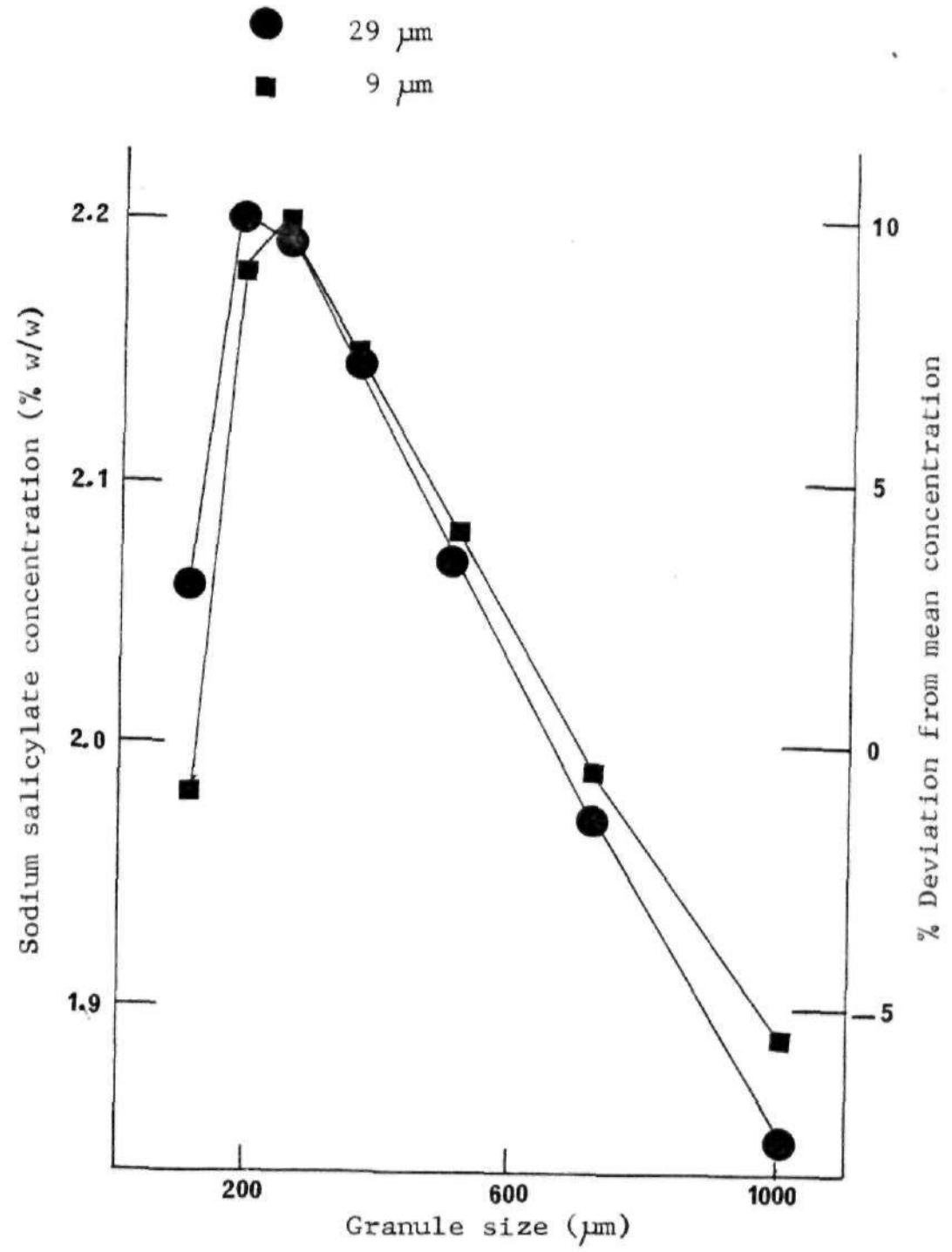
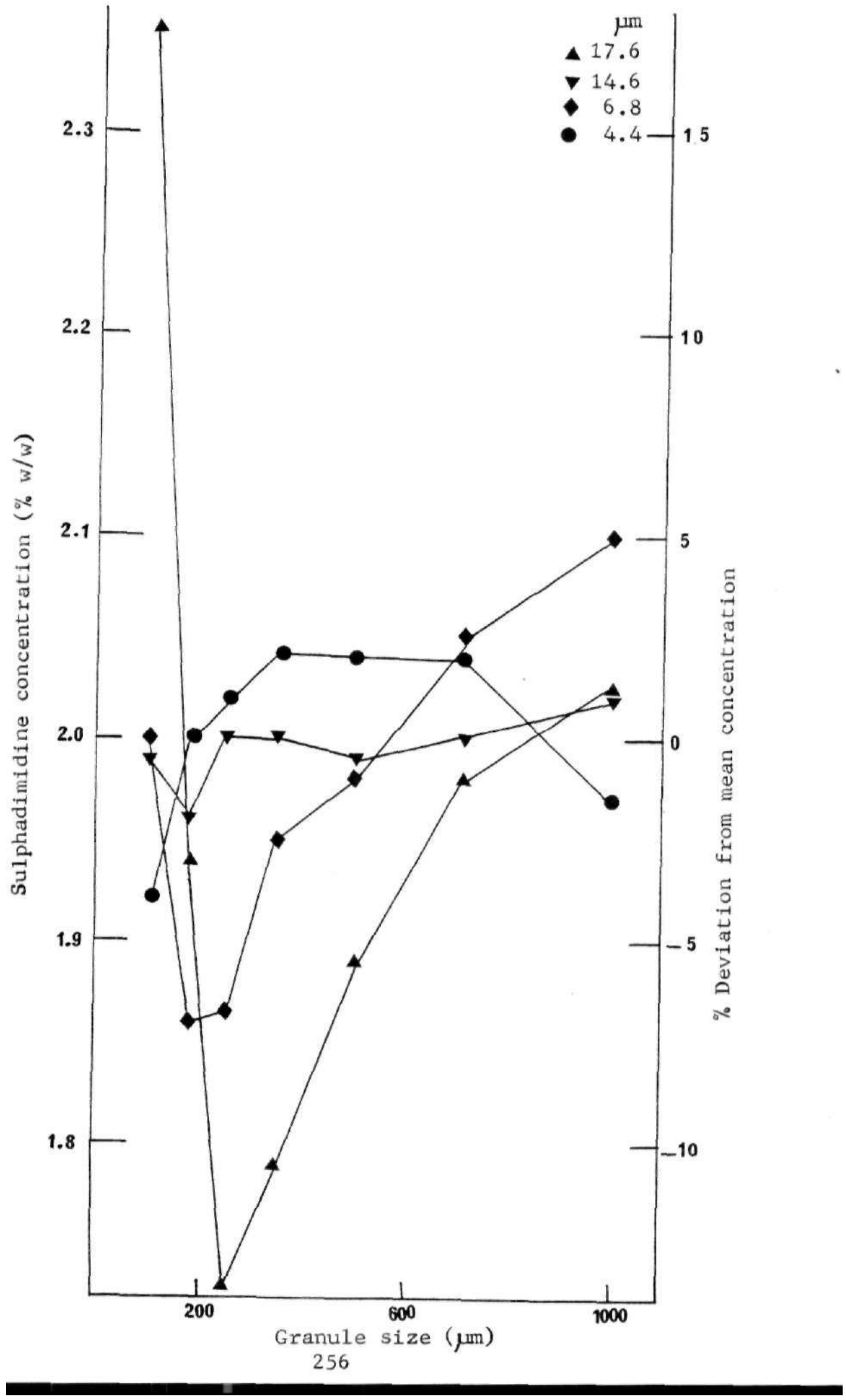


Figure 73 Effect of sulphadimidine particle size on its distribution in sizes of sulphadimidine/lactose granules



of sulphadimidine in the granule sizes containing these initial smaller sizes of the drug was more uniform, i.e. ± 4% deviation from the dose.

On the whole, the use of a larger particle size of a poorly soluble drug in the granulation raises the concentration of that drug in the fines as a result of ungranulated particles.

Granules derived from a poorly soluble drug and diluent mix e.g. sulphadimidine/dibasic calcium orthophosphate show a general trend. The smaller initial drug particles contain a higher drug content in the larger granules (Figure 74). The higher displacement of the similarly shaped curves for a lower particle size results from a smaller quantity of ungranulated particles and a correspondingly higher concentration in the granules. The shape of the typical curve has already been discussed (Figure 46).

Effect of Diluent Particle Size

It has been shown earlier (Table 11) that the granule packing density increased as the mean particle size of the diluent increased. This was more pronounced with a soluble diluent like lactose. It has also been shown (Figure 41) that appreciable migration of solutes take place with an increase in the diluent mean particle size as a result of the availability of a higher volume of binder in the pores.

The effect of lactose particle size on granule size distribution is shown in Figures 75 and 76. Generally, larger particle sizes of diluents gave rise to a higher percentage of large granules and less fines (Figures 75 to 76). However there was not a direct relationship between the initial particle size and the proportion of the largest

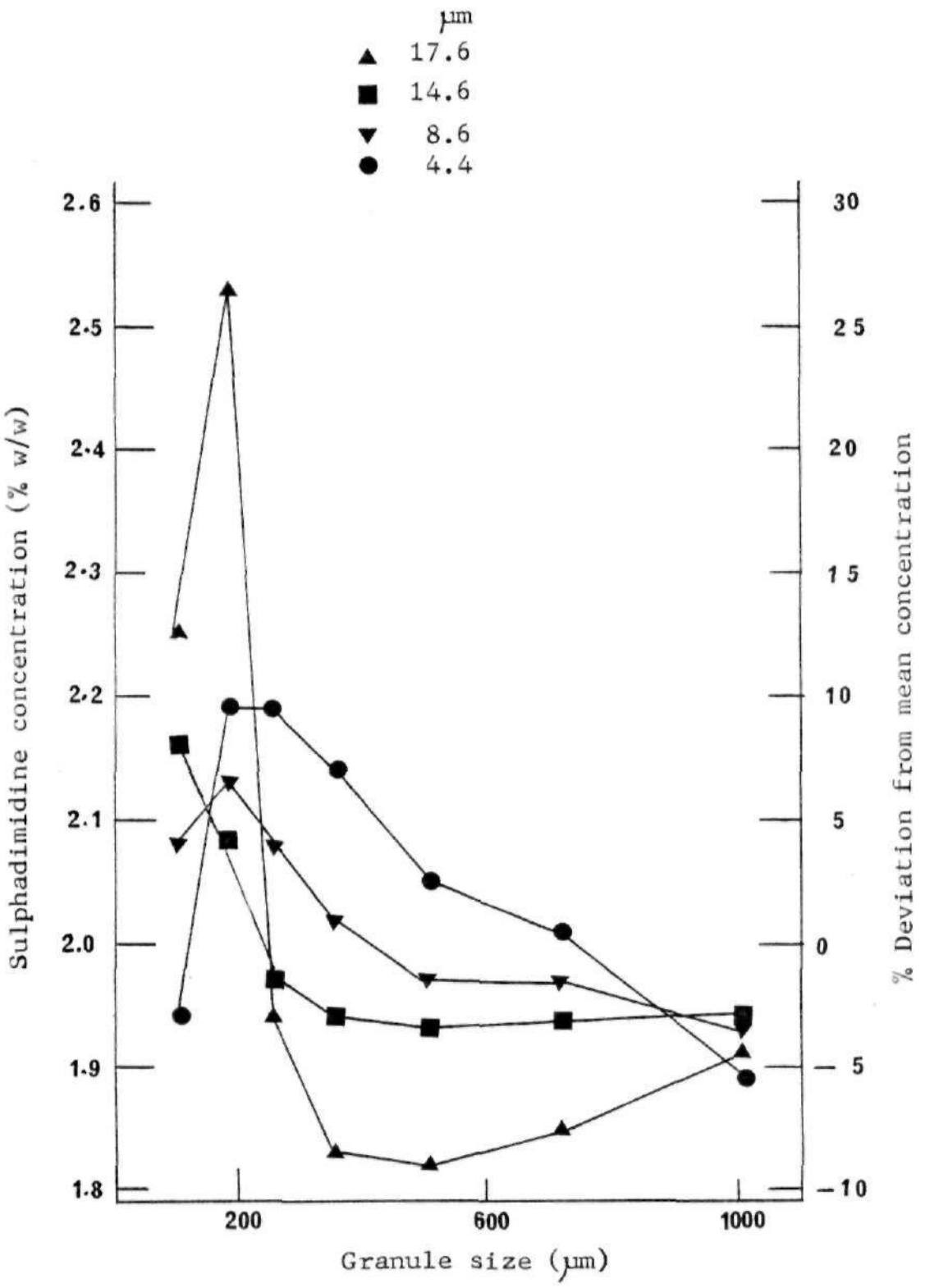


Figure 74 Effect of sulphadimidine particle size on its distribution in sizes of sulphadimidine/dibasic calcium orthophosphate granules.

Figure 75 Effect of initial lactose particle size on size distribution of borax/lactose granules

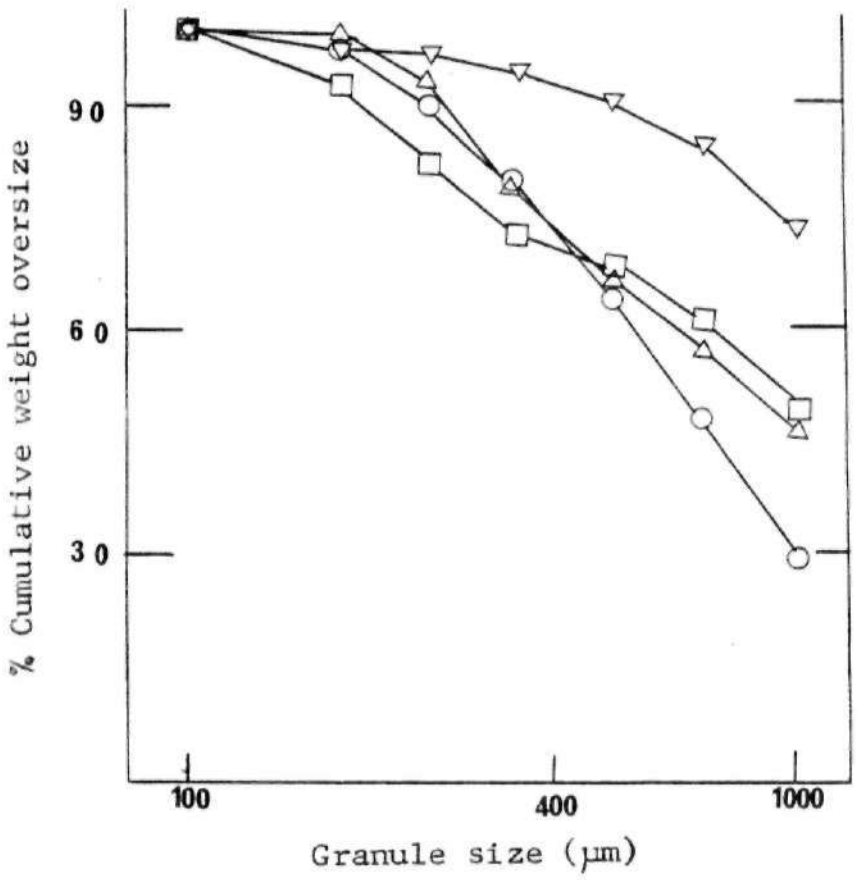
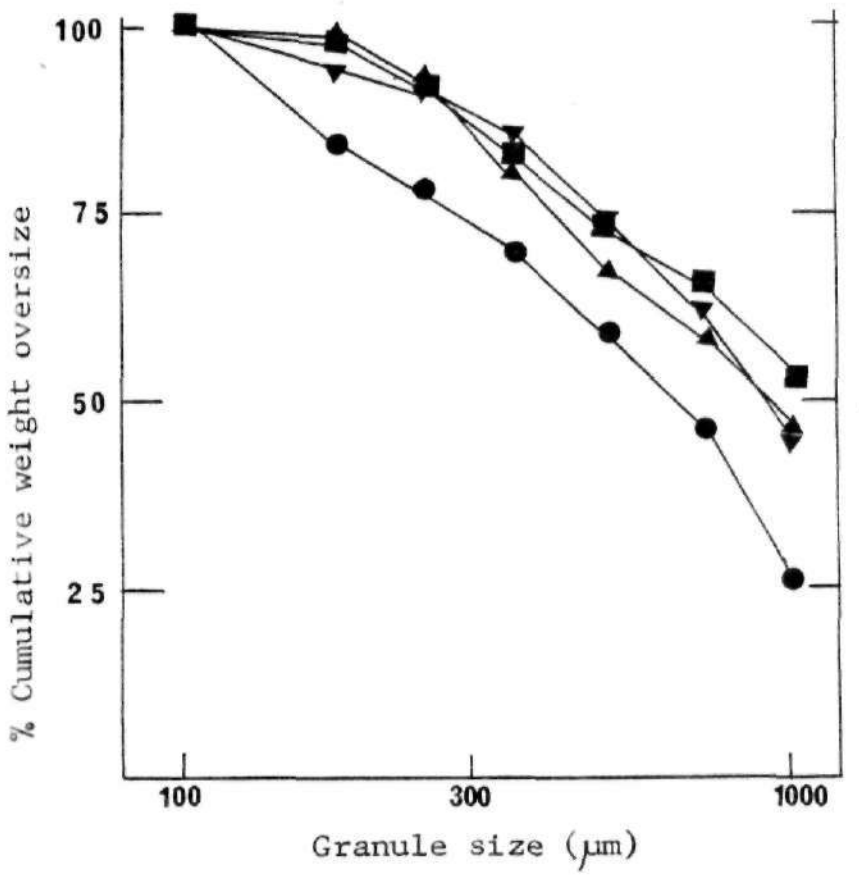


Figure 76 Effect of initial lactose particle size on size distribution of sulphadimidine/lactose granules

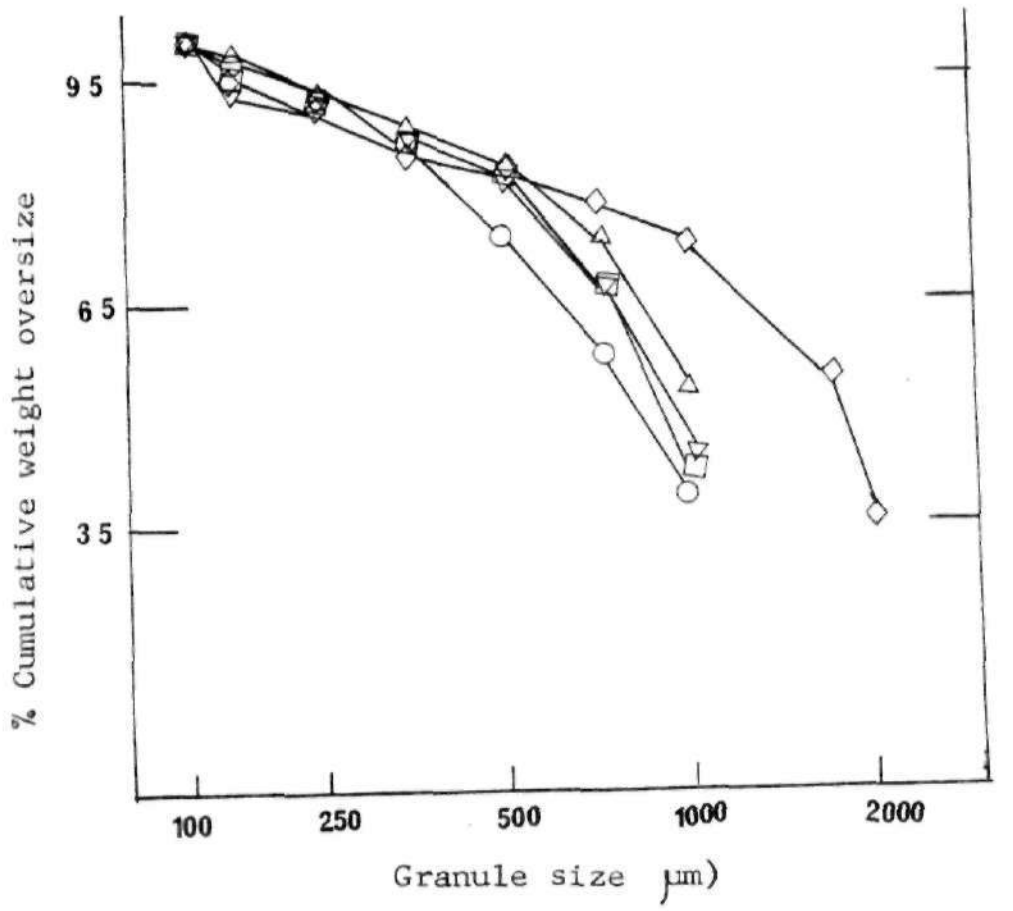


granules. This is due to the presence of larger pores in the initially large lactose particles. In this regard, the portion of the binder entrapped in these pores has less effect on intra-particulate binding leading to a lower fraction of large granules. The use of a diluent having large variations of particle sizes as obtained in e.g. size unfractionated Emcompress leads to more compact granules as a result of entrapment of the smaller particles within the pores. Thus the granules will be expected to contain less pores. This will lead to a much higher fraction of large granules as a consequence of a higher volume of binder available for intra-particulate bonding (Figures 77 and 78).

Granule Sizes in a Batch

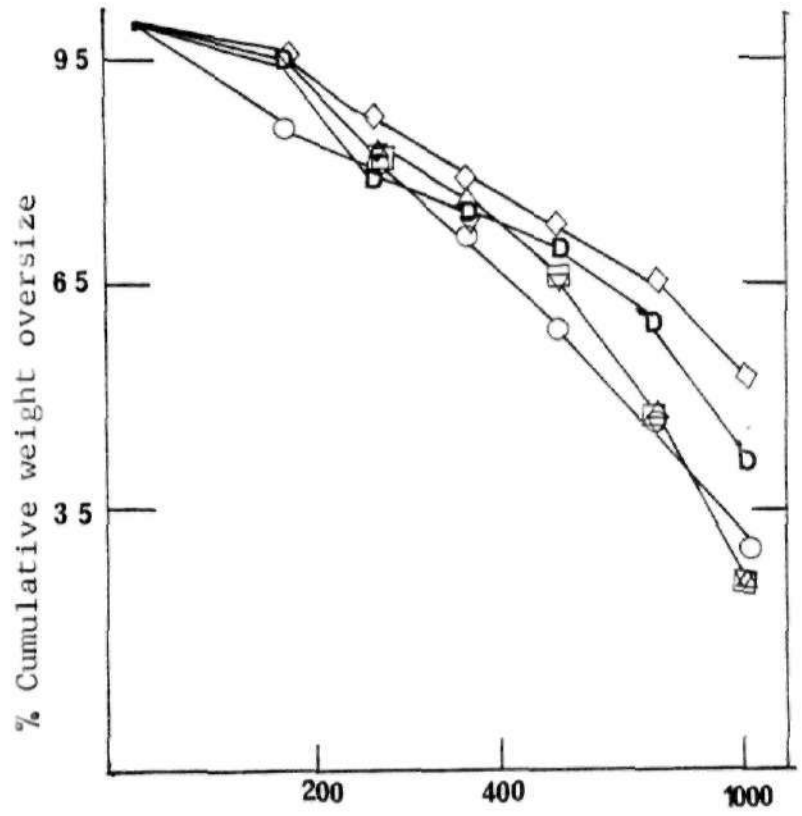
Figure 79 shows that the two larger particle sizes, 350 and 180 micrometres, of lactose produced granules with a borax concentration which is directly related to the granule size. During massing, binder distribution by the massing action would take place leading to a peak concentration of borax in the intermediate granules (Figure 46 for borax/lactose). During the drying process, since a larger diluent particle size gives rise to higher packing density (Table 11), intergranular migration was shown to be appreciable (Figure 41). During this migration, the binder solution containing a considerable quantity of dissolved borax, will be transported to and through the granules including the larger granules. Larger granules have larger pores (Nicholson and Enever, 1974) which are

Figure 77 Effect of the initial particle size of dibasic calcium orthophosphate (d.c.o.) on size distribution of sodium salicylate/d.c.o. granules



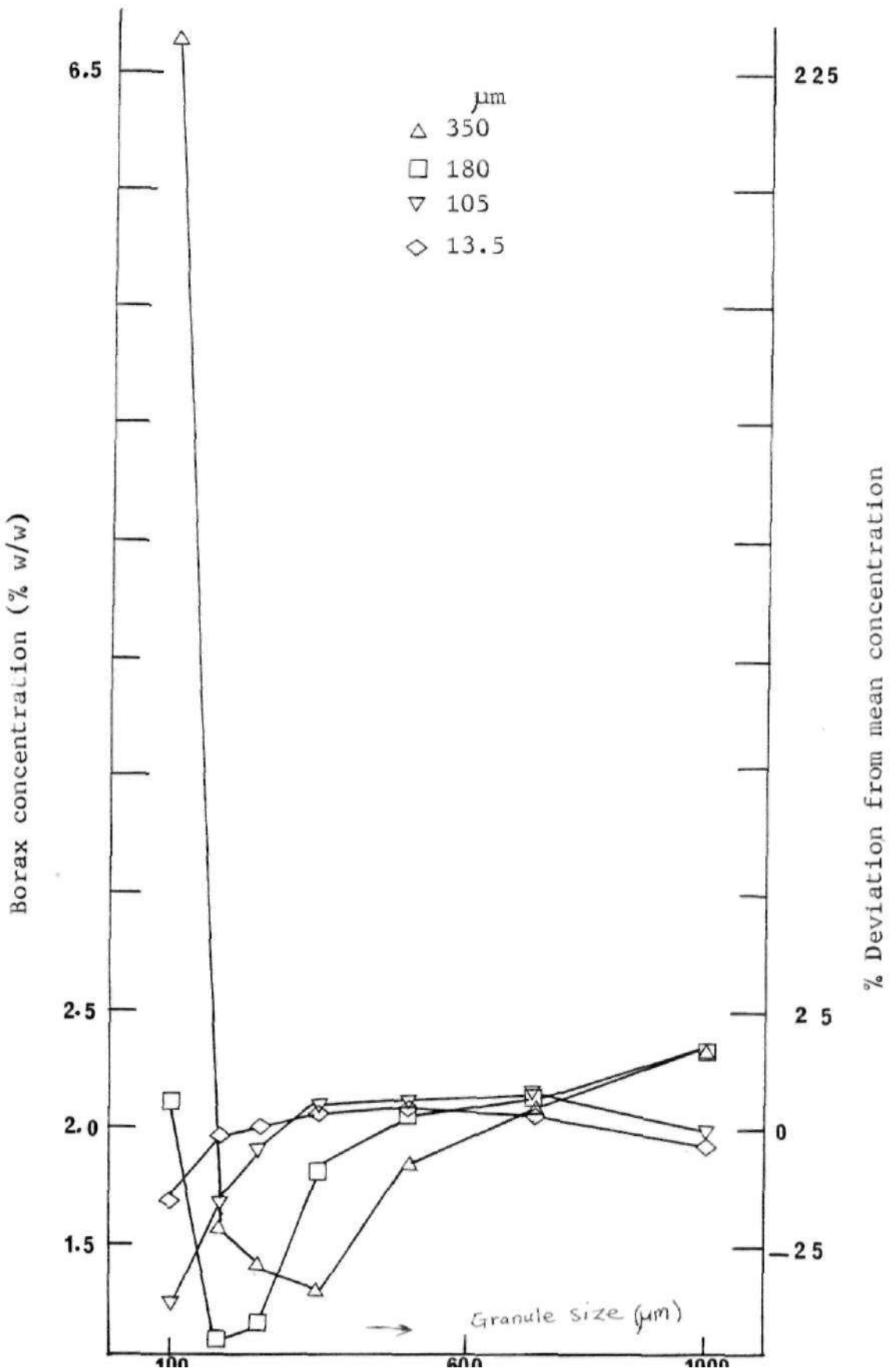
◇ Unfractionated from -315 + 40 um
△ -350 + 200 µm
□ -200 + 160 µm
▽ -160 µm
○ 2.4 µm

Figure 78 Effect of the initial particle size of dibasic calcium orthophosphate (d.c.o.) on size distribution of sulphadimidine/d.c.o. granules



◇	Unfractionated from -315 + 40 μm	
D	-350 + 200 μm, binder volume	41% v/w
△	-350 + 200 μm	33% v/w
□	-200 + 160 μm	33% v/w
▽	-160 μm	33% v/w
○	2.4 μm	33% v/w

Figure 79 Effect of the initial lactose particle size on borax distribution throughout the sizes of the borax/lactose granules



expected to be far marked in these granules composed of some few particles. The deposition of borax-rich solutes in the binder after drying the moisture entrapped as pendular liquid phase will therefore lead to a higher borax concentration in the larger granules.

Another mechanism which would account for the higher drug concentration in the larger than the intermediate granules prepared from the initially large lactose particles is related to the agglomeration of particles which will encapsulate some of the borax. The intermediate granules contain some single, ungranulated lactose particles. These intermediate granules will thus be mainly lactose particles with some borax adsorbed on the particles by an ordered mixing process.

The two larger sizes of lactose particles give rise to a higher borax concentration in granules finer than their initial respective sizes. Any ungranulated lactose particle would not pass through a sieve aperture which is less than its diameter. However borax particles resulting from either abrasion or granule fracture will pass through all the sieve apertures to the pan. Thus by a concentration effect the content of borax in granule sizes and fines less than the initial lactose particles will be appreciably high.

The peak concentration of borax in the intermediate granules massed from the two smaller particle sizes, 105 and 14 micrometres, is in agreement with the distribution of binder containing higher dissolved solutes from the overwetted to drier areas of the mix (Figures 17 and 79). The appreciable lower concentration in the finer granules

prepared from the 105 micrometres of lactose appears to be a consequence of migration during drying and a higher volume of binder at pendular phase in the larger granules at the expense of the finer ones.

Figures 79 to 82 show that an appreciable concentration of a drug is contained in fines from granules prepared from diluent particle sizes larger than the fines. This is more prominent with moderately soluble and poorly soluble drugs e.g. borax and sulphadimidine respectively with low values of dissolution ratios. Sodium salicylate which is readily soluble, i.e. with a much higher dissolution ratio, is capable of being reasonably granulated, thereby leaving little or no ungranulated particles which normally form part of the fines (Figure 81).

It has been pointed out above that the presence of smaller particles in unfractionated Emcompress reduced the size of the pores and thus increased the binder volume taking part in binding the particles together. Larger initial particle sizes of a material gave rise to a higher porosity (Hunter and Ganderton, 1972). It is therefore logical that a higher amount of the fine particles of sulphadimidine would be located within the larger pores created by these larger lactose particles within the granules (Figure 80). Since larger granules also have larger pores (Nicholson and Enever, 1974) the sulphadimidine concentration for larger lactose particles as expected was directly related to granule size.

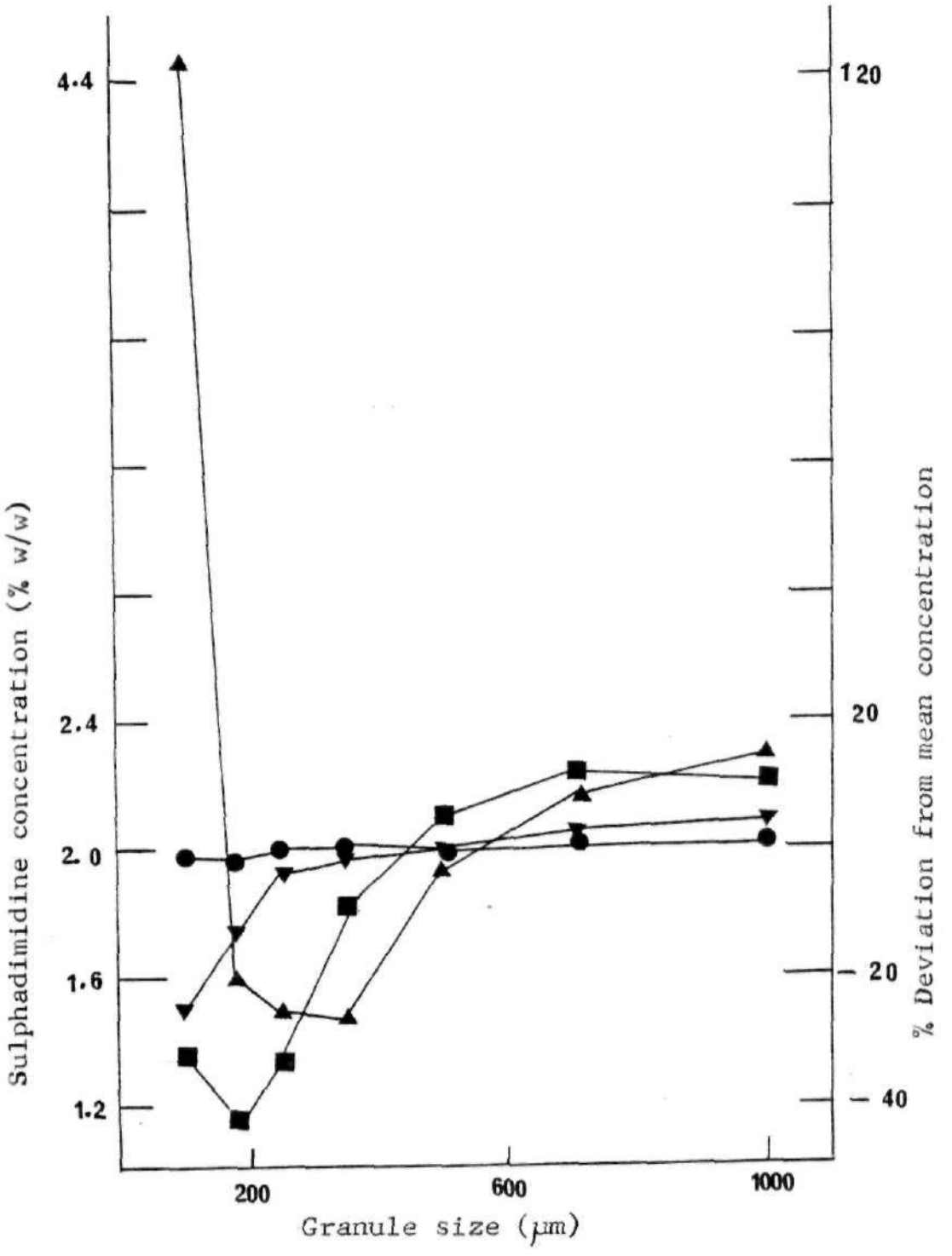
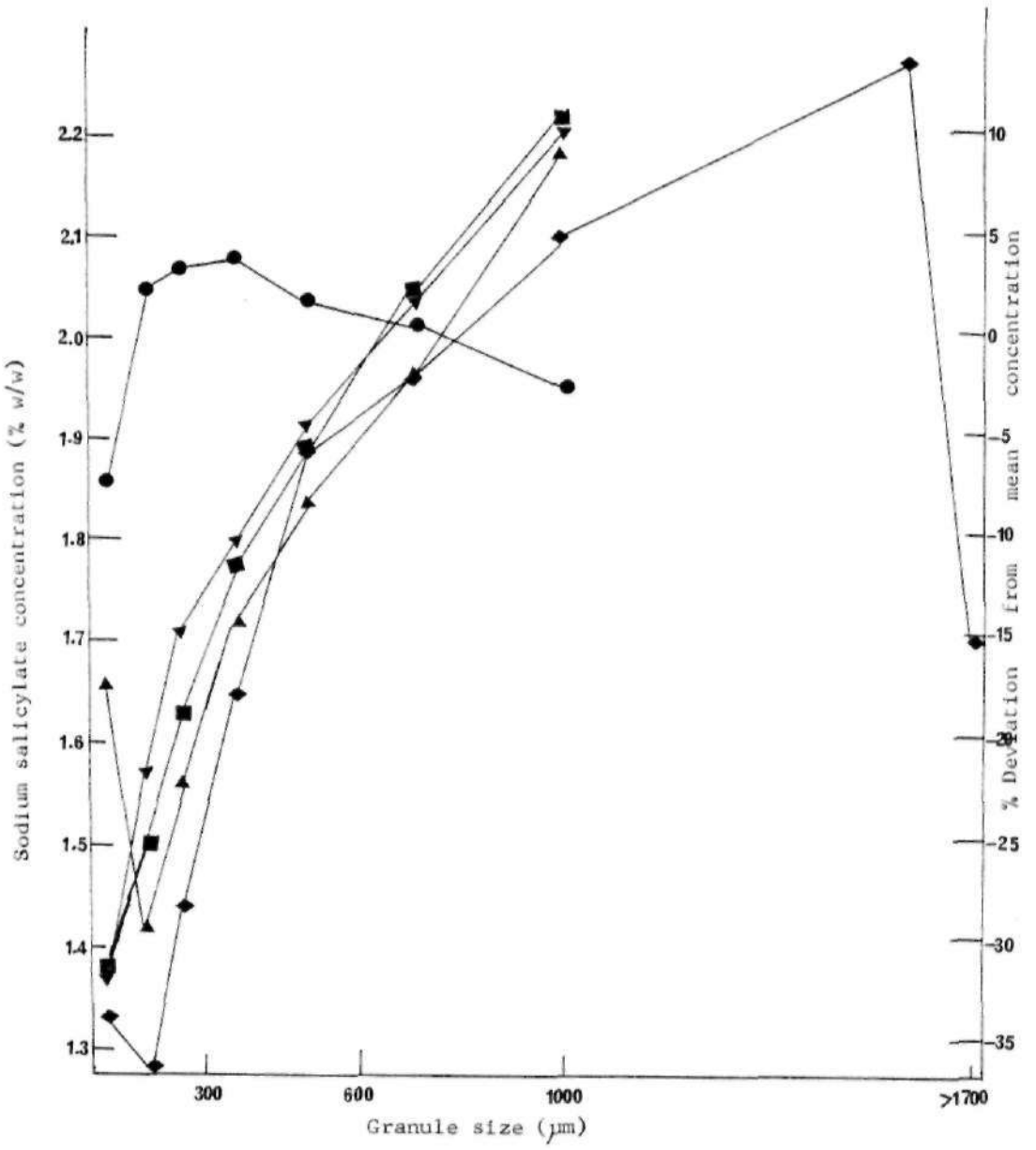
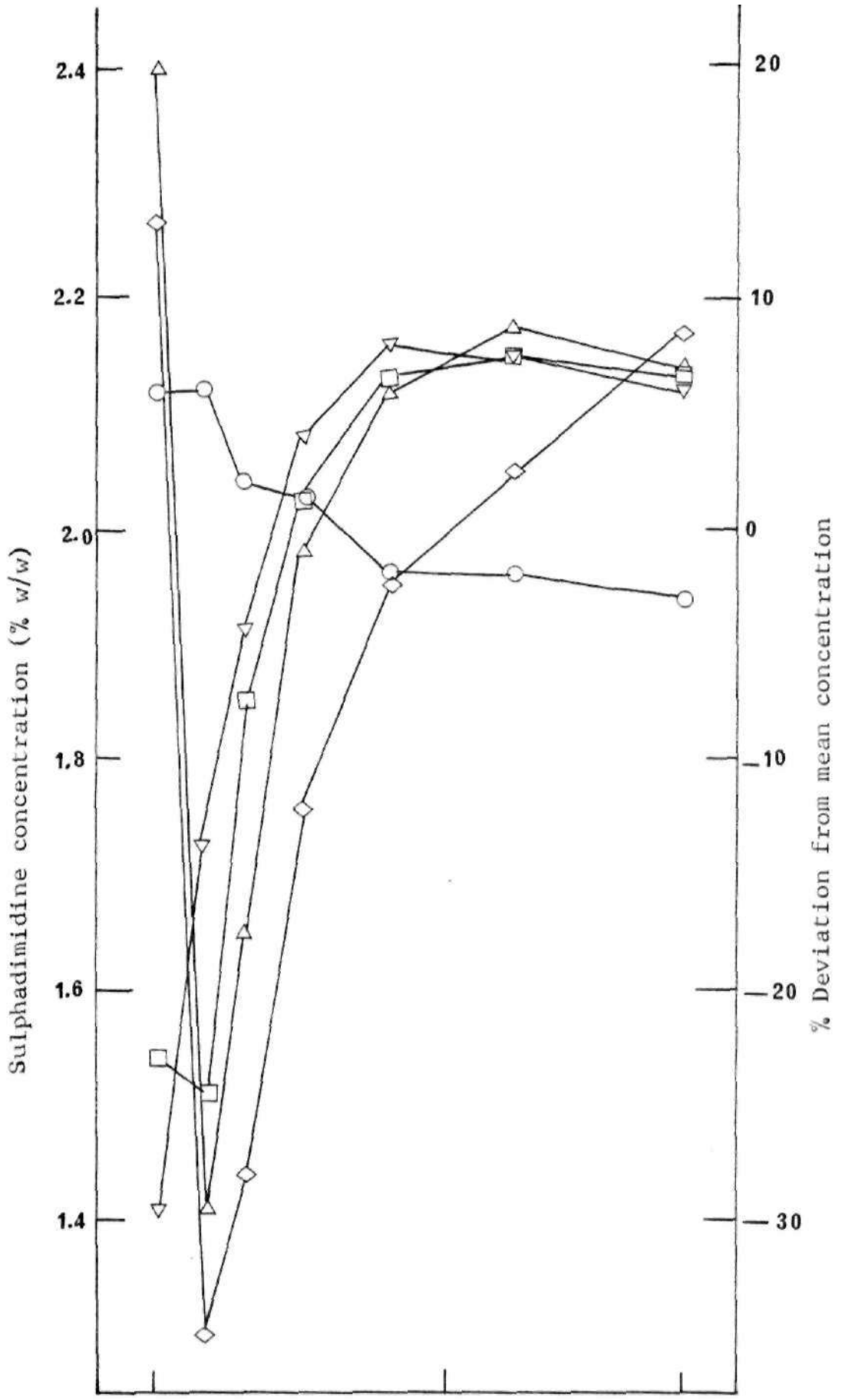


Figure 80 Effect of the initial lactose particle size on sulphadimidine distribution throughout the sizes of sulphadimidine/lactose granules



◆ -315 + 40 μm unfractionated
▲ -315 + 200 μm
■ -200 + 160 μm
▼ -160 μm
● 2.4 μm

Figure 81 Effect of the initial particle size of dibasic calcium orthophosphate on the distribution of sodium salicylate throughout the granule sizes in the batch


2.4
2.2
2.0
1.8
1.6
1.4
Sulphadimidine concentration (% w/w)
20
10
0
-10
-20
-30
% Deviation from mean concentration
100
600
1000
Granule size (μm)
◇ -315 + 40 μm unfractionated
△ -315 + 200 μm
□ -200 + 160 μm
▽ -160 μm
○ 2.4 μm

The smaller lactose particles produced concentration results which are more governed by the phenomenon of the binder distribution during massing (Figure 16, 46 and 80 for sulphadimidine/lactose granulation).

The behaviour of the concentration of sodium salicylate in 2.4 micrometres of pure dibasic calcium orthophosphate has laready been discussed (Figure 46 (b)). In Figure 81 the concentration of sodium salicylate in the granules appears to be related to the migration of a sodium salicylate binder during drying. The appreciable binder volume and marked relative solubility of sodium salicylate dictate that all the sodium salicylate particles are capable of dissolving in the PVP binder. At the pendular liquid phase the moisture in the binder located within the pores, after solute migration, is evaporated leaving deposits of the solutes which are in greater amounts in the large pores. Thus the sodium salicylate concentration is directly related to the granule size excluding the fines. The difference in the shape of the curves as compared to that with the micronised diluent has obviously shown different mechanisms of the drug distribution. The mechanisms for the drug distribution containing the initial micronised diluent were shown before (Figure 46 (b)).

Figure 82 shows that the packing of fine sulphadimidine possibly by encapsulation during the formation of granules prepared from the larger Emcompress particles causes a direct relationship between granule size and the sulphadimidine concentration. However the slight decrease in

the largest granules is due to the dilution effect of the highest concentration of PVP in the largest granules by virtue of the highest binder content (Dingwall and Ismail, 1977). Again, there is a marked decrease in the fines with a decrease in the initial particle size due to a failure of complete incorporation of the particles in the granules.

The similar shapes of the curves in Figures 81 and 82 suggest that the mode of incorporation of the drugs, sodium salicylate in Figure 81 and sulphadimidine (poorly soluble) in Figure 82, is more of an encapsulation process. The amount of drug particles encapsulated depends on the quantity of particles making up the granule. A larger granule would be expected to encapsulate a higher quantity of the drug particles. The concentration of sulphadimidine with micronised d.c.o. diluent has already been discussed (Figure 46 (b)).

In general terms it would be concluded that the use of a large initial size of diluent particle would allow a higher drug concentration in large granules irrespective of the solubilities of the drug/diluent components. The concentration in the fines is normally appreciably higher with particle sizes larger than the fines. This behaviour is more prominent with drugs having low values of relative dissolution ratios but less marked in readily soluble drugs.

Granule Size Distribution

In general terms, the sequence of granule size distribution containing the same diluent of the same size

variations but different low dose drugs is similar.

For example in Figures 75 and 76, the granulation of lactose as a dry mix with either borax or sulphadimidine produced the highest proportion of largest granules with 180, then 350 and 105 together, and lowest with 13.5 micrometre sizes.

In Figures 77 and 78, the same sequence is followed with dibasic calcium orthophosphate diluent granulated with sodium salicylate or sulphadimidine. In both cases, the largest particle size of the diluent did not necessarily produce the highest proportion of the largest granules due to the presence of pores in the larger particles. The entrapment of some of the binder volume within these pores which are relatively larger in larger particles (Nicholson and Enever, 1974) would reduce the effective action of the volume of binder necessary to form granule sizes. This is in agreement with the results obtained by Jaiyeoba and Spring (1979) using starch particles.

Another reason why a larger initial particle size of the diluent does not necessarily cause a higher fraction of large sized granules may be that there is an optimum initial particle size beyond which most of the particles fail to granulate.

3.4

GENERAL CONCLUSIONS

3.4 GENERAL CONCLUSIONS

The factors which affect the distribution of a drug in a batch of granules were related to the relative solubilities of the components and their relative dissolution ratios, R. Formulation and processing variables have been found to modify the relative solubility and R values.

Variations in the drug distribution in granules was linearly related to the relative solubility of the low dose drug in the binder.

The wet mixing action and solute migration during drying governed the drug distribution in granules. This massing action dissolved some of the solutes present in the part of the powdered mix overwetted by the binder. The subsequent distribution of the solute-laden binder from the overwetted region wetted the drier area of the mix which subsequently form the intermediate granules and the bulk of the fines. Thus a drug with a high R value produced a peak concentration of the drug in the intermediate sized granules. Although a diluent may have an appreciable relative solubility, it produced only a slightly higher drug concentration in the largest granules formed from the initially overwetted region, due to the lower R value. Thus when the R values of the drug and the diluent were respectively equal to unity, the drug distribution was uniform irrespective of the granule size or the depth of the granule layer. The co-saturation of the binder with part of the components for massing with the rest of the mix produced a direct relationship between the granule size

in the batch and the drug concentration as a consequence of the distribution of the binder which had a constant composition during the massing. Massing a granule formulation with a binder, e.g. PVP solution in which both components were poorly soluble, i.e. a binder of constant composition, produced an inverse relationship between the granule size and the drug concentration due to a dilution effect of the PVP binder content which was directly related to the granule size.

The rate of dissolution of a moderately soluble drug in the binder was inversely proportional to its particle size. For a readily soluble drug the dissolution rate was sufficiently rapid that the particle size had a less effec Some of the larger drug particles not easily wetted in the overwetted region failed to bind to the agglomerates to cause a lower drug concentration in the larger granules.

Any action which affected the capillarity of the granules during drying affected solute migration. Such factors include the increase in the packing density which increased migration. The increase in the diluent particle size increased the packing density and thus increased migration. A longer massing time which compacted the intra-granular pores also increased the solute migration. In addition, any factors which increased the amount of component solutes dissolving in the binder enhanced solute migration. These include the mutual increase in the solubilities of borax and lactose and a larger diluent particle size which decreased intra-particulate bridging

and thus made available a higher binder volume in the pores. For tray dried granules, a higher drying temperature paradoxically decreased solute migration. The higher borax concentration in the fines in the batch dried at the higher temperature was more of the breaking rather than an abrasive action on the weaker granules during dry screening.

Tray dried borax/lactose granules produced the peak concentration in the intermediate granules but the granule size from the batch dried in a thick-bed was directly related to the borax concentration.

The effect of an intermediate screening of granules during drying increased the concentration of borax in the larger granules.

An increase in the binder volume decreased the concentration of borax in the largest granules but increased and shifted the peak concentration to finer granules. An excessive massing action had a similar effect to the increase in binder volume. An increase in the PVP concentration in the binder solution increased the concentration of sulphadimidine in the larger sized granules.

The hot air oven dried granules produced the highest solute migration, followed by vacuum dried granules. Solute migration was absent in freeze dried granules. Thus the largest granules contained the highest borax concentration in freeze dried granules, followed by vacuum oven and by hot air oven. Migration of solutes depleted the solutes from the larger granules to the intermediate granules.

The lowest concentration of borax in the large sized granules from the batch dried by fluidisation was more of the consequence of fluidised abrasion of mostly the softer granules formed by wetting of the mix with the solute-laden binder.

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SOME FACTORS AFFECTING SOLUTE MIGRATION IN GRANULAR BEDS

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SUMMARY

The intergranular migration of soluble materials during drying in thick beds has been studied. This migration has been shown to be a function of the packing of the bed, the moisture content at commencement of drying and the method of drying. Factors which enhance the transport of moisture through the bed by capillarity also increase the extent of solute migration.

INTRODUCTION

Uneven drug distribution throughout a batch of granules is one source of dose variation in tablets. One way in which this drug distribution may be affected is by migration of soluble constituents to the drying surface during the drying operation, (Selkirk, 1976). Various factors such as particle size (Warren and Price, 1977), method of drying (Travers, 1975) and binder viscosity (Chaudry and King, 1972) have been shown to affect solute migration in pharmaceutical granulations. We have examined solute migration in thick-bed drying and have studied the effects of drying conditions, binder volume and particle packing on this migration.

MATERIALS AND METHODS

The lactose and borax used were both of BP quality.

Preparation of granules

Since dose uniformity problems are generally more serious with low dose drugs, the lactose and borax were mixed in the ratio 50 : 1 in a planetary mixer. Samples were taken at various time intervals and the mixing index of Ashton and Valentin (1966), was used to determine the optimum mixing time. This was found to be 5 min and was then kept constant throughout the study.

The lactose/borax mix was wet massed with water as a binder. Massing water concen-

trations of 14% or 18% volume per dry weight of powder were used in the study. These were lower volumes than may be expected and were due to a mutual increase in solubility of borax and lactose in each other presence (Fig. 1). The mix was massed with the appropriate volume of water for 5 min and the resultant mass force screened through a number 10 mesh to form the granules. These were allowed to fall from the granulator into the appropriate containers for drying.

Drying of granules

The granules fell into and were dried in containers 4.265 cm in diameter and 7 cm deep in a hot air oven. One further batch was dried in a container 8.5 cm in diameter and 14 cm deep.

Drying rates were determined by suspending the containers in the oven from a load cell situated in the roof of the oven. Decrease in weight with drying could then be followed without interference with the oven. A typical drying curve is shown in Fig. 2.

In a number of cases the granules were partially dried in thin layers on large trays in the hot air oven. Once a certain moisture content had been reached they were rescreened through the granulator into the cylindrical containers as described above and drying was continued as before. This enabled granules of a fixed initial moisture content to be dried in the cylindrical containers.

The effect of the method of drying used was also studied by drying batches of granules by vacuum- and freeze-drying methods. Vacuum-drying was carried out at 48°C and at a pressure of 6.8 kNm^{-2}. Freeze-drying was accomplished using a freeze-drier, (Model EF6, Edwards, England).

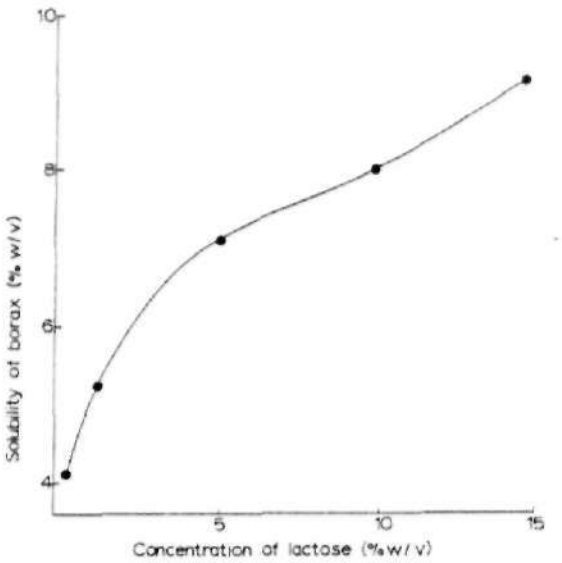


Fig. 1. The effect of lactose concentration on the solubility of borax.

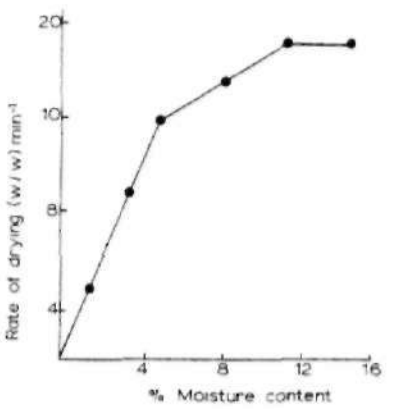


Fig. 2. Drying rate of borax granulation.

One further batch of granules was prepared by tapping down the granules in their container as it was filled from the granulator. The granules were then dried in the hot air oven as before. The tapping was done to determine the effect of particle packing on solute migration.

Analysis of granules

After drying the granules in the containers to a constant weight, the contents were separated into a number of layers. Seven layers each 1 cm deep were separated for the small containers (4.265 × 7 cm) and 3 layers for the large containers (8.5 × 14 cm).

Each layer was analyzed for its borax content by titration with hydrochloric acid using an automatic titrimeter (model TTT IC, Radiometer, Copenhagen).

In addition, the 3 layers of granules separated from the large container were each sized by sieve analysis. The borax content of each size of granule in each layer was then determined as above.

Bulk density determination

Bulk density determinations were made on the dried granules, with and without tapping during filling from the granulator. As expected the tapped granules showed a higher bulk density, 0.7 g cm^{-3}, when compared to the untapped, 0.5 g cm^{-3}, indicating closer packing with the former.

RESULTS AND DISCUSSION

The system studied is complex in as much as both the borax and lactose are soluble in water. Therefore both may migrate on drying. However, the ratio of borax/lactose in the solution phase is considerably higher than in the solid state. Solute migration will then be shown as an increase in borax concentration. Fig. 3 shows the effect of temperature on the migration of the borax. The results are plotted as the percentage deviation from the mean borax content, i.e. 2%. In both cases solute migration is seen. It is, however, considerably more marked for granules dried at the lower of the two temperatures. This is somewhat unexpected as the slower drying rate with the lower temperature may have been expected to allow more time for back diffusion of the borax. Such back diffusion has been shown to occur during the migration of PVP solution used as a binder (Rubinstein and Ridgway, 1974). In this case, however, the binder solution is completely saturated with borax. This saturation will therefore prevent back diffusion under these conditions, the slower rate of drying would allow longer for an equilibrium situation to be established and therefore result in a greater degree of migration.

The effect of drying method is shown in Fig. 4. As might be expected freeze-drying produced no evidence of solute migration. Vacuum-drying gave results similar to that found by Travers (1975) using sodium chloride and Kaolin, and supports his theory of flash-drying with such systems. Drying in a hot air oven showed a steady decrease in borax concentrations with a maximum at the topmost granule layer, a result again in agreement with Travers (1975). Considerable solute migration occurs with this system.

This migration will only continue while there is sufficient moisture to maintain the system in a capillary or funicular state. Such a state is a function of the size of the capil-

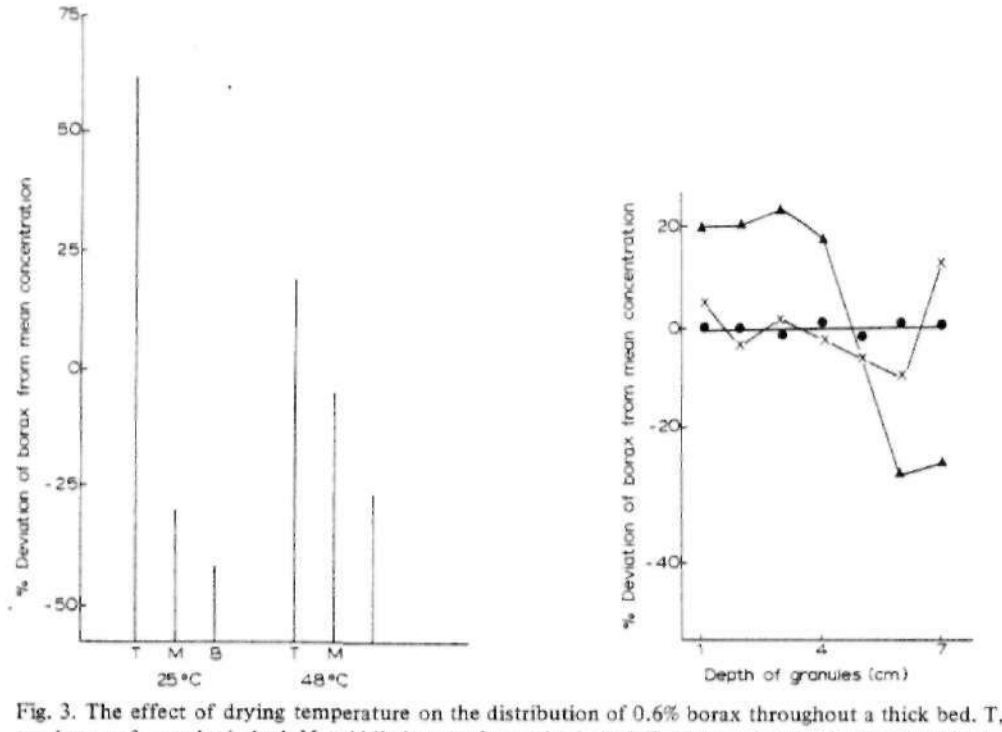


Fig. 3. The effect of drying temperature on the distribution of 0.6% borax throughout a thick bed. T, top layers of granules in bed; M, middle layers of granules in bed; B, bottom layers of granules in bed.

Fig. 4. The effect of the method of drying on the distribution of 2% borax through a thick bed. Tray drying in hot air oven, ▲; freeze-drying, ●; and vacuum-drying, X.

laries in the bed. The smaller the capillaries, the greater the head of liquid they can support and therefore the greater the amount of liquid which can be transported to the drying surface before the surface layers enter the pendular state and the drying plane recedes into the bed. As a consequence of this, the closer the granules are packed in a bed, the greater the solute migration of the soluble constituents. This is shown in Fig. 5. The granules which were tapped during filling from the granulator have a greater bulk density and show a more marked solute migration.

If the premises stated above are correct then solute migration to the surface of the drying bed will be most marked during the constant rate period of drying. The migration will then recede into the bed as the first falling rate period proceeds. Finally when all moisture in the bed is in the pendular state, no migration will be found.

The effect of moisture content on solute migration is shown in Fig. 6. The granules in this case were all dried at 48°C. As can be seen from Fig. 2, granules with a moisture content of over 11% lay within the constant rate drying period. A steady reduction in borax concentration with distance from the drying surface was observed with these granules. This is consistent with the concept that sufficient moisture is being transported to the

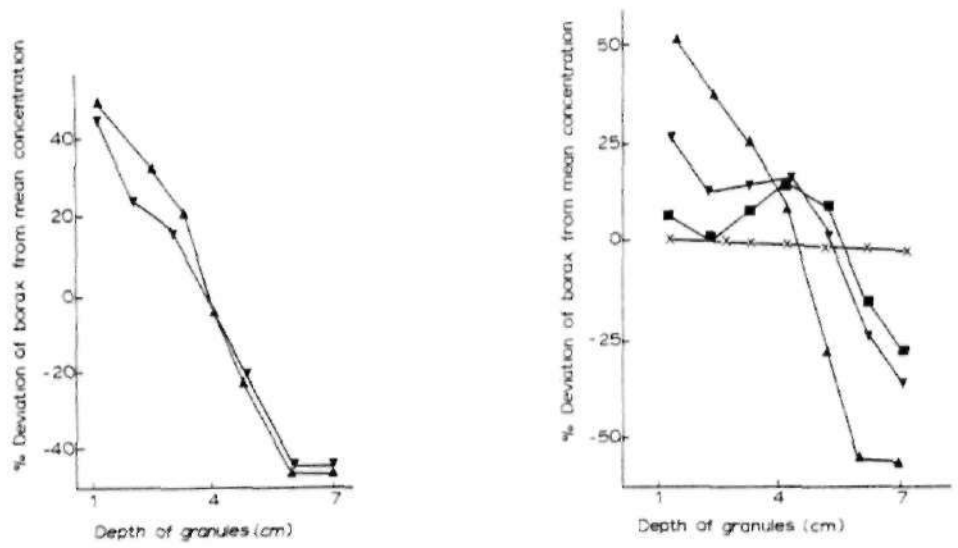


Fig. 5. The effect of packing density on the distribution of 2% borax throughout a thick bed. High density (0.7 g cm^{-3}), ▲; low density (0.5 g cm^{-3}), ▼.

Fig. 6. The effect of initial moisture content on the distribution of 2% borax throughout a batch of granules. ▲, 18% initial moisture content; ▼, 14% initial moisture content; ■, 11% initial moisture content; ♦, 6% initial moisture content.

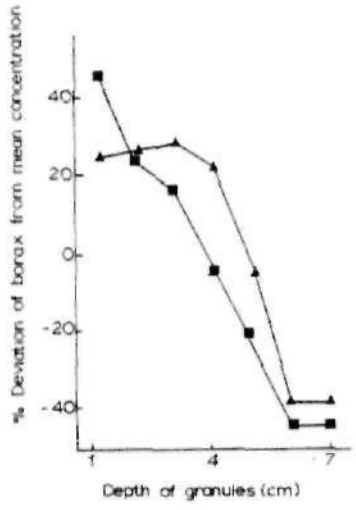


Fig. 7. The effect of massing water concentration on the distribution of 2% borax throughout a batch of granules. ■, 18% massing water concentration. ▲, 14% massing water concentration.

TABLE 1

GRANULE SIZE DISTRIBUTION OF GRANULES DRIED IN A THICK BED

Size of sieve (μm) retaining granules	% cumulative weight of granules			
	Top layer of thick bed	Middle layer	Bottom layer	Whole layer of thick bed
1000	33	30	33	32
710	55	53	56	55
500	72	70	72	71
355	85	84	85	85
250	94	93	93	93
180	97	97	97	97
<180	100	100	100	100

surface to allow saturation of the air immediately above the surface layer.

However, if the granules are dried to a moisture content within the first falling rate period and are then rescreened and repacked into the beds, the capillary forces are now insufficient to saturate the surface air layer and the drying front will recede into the bed at certain points. This will result in a reduction in migration to the surface but with an increase in migration to layers immediately below the surface. This is shown in Fig. 6 by a reduction in the borax concentration of the surface layers with a secondary peak appearing at lower levels in the bed. The lower the initial moisture content, the more marked this effect becomes. Eventually the initial moisture content is so low that all moisture in the bed exists in the pendular state. At this stage there is no evidence of solute migration.

While the initial moisture content of the bed can be controlled by rescreening of the granules after a given period of drying, a more practical control is by varying the binder volume. A lower binder volume would give a lower initial moisture content and therefore less marked solute migration. Such an effect is shown in Fig. 7.

Since solute migration to the drying surface of granular beds does take place, it is of importance to know how it affects granule size distribution in the bed and drug concentration for different sized granules. Binding in granules is considered to take place by crystalline bridges of material forming from solution during drying. Most of this material will migrate to the upper bed layers with these larger granules having a disproportionate amount of drug in them.

The sieve analysis from the 3 layers is shown in Table 1 along with a sieve analysis from an overall unsectioned batch. No significant difference in granule size was found at the different depths or with the bed as a whole.

The effect of granule size on drug concentration for each of the section is shown in Fig. 8.

Migration is shown by the vertical displacement of the curves from each of the sections. However, the shape of each of the curves was similar, each showing a slight drop in drug concentration with the smallest granules. Thus, intergranular solute migration neither influences granule size distribution nor the variation in drug concentration with granule size.

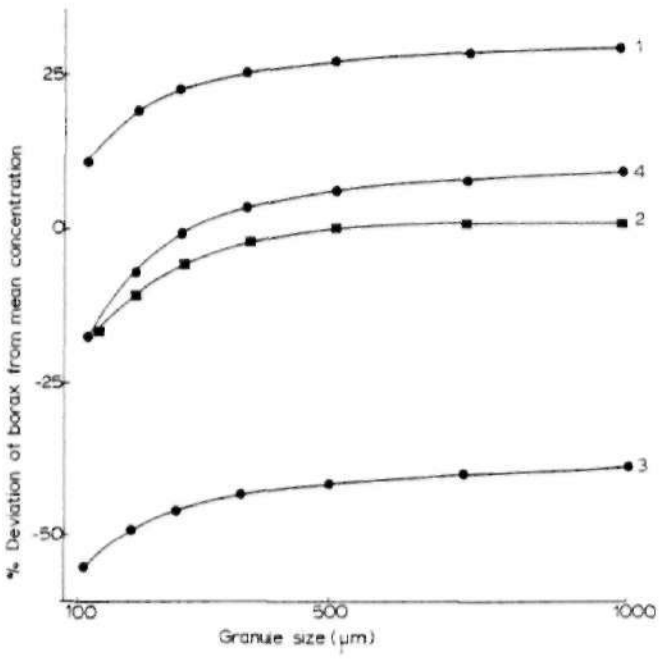


Fig. 8. The effect of thick-bed drying on the distribution of 2% borax in sized granules from the top, middle and bottom of bed compared to overall distribution of bed. 1, top of bed; 2, middle of bed; 3, bottom of bed; 4, overall.

CONCLUSIONS

The results show that solute migration can be a serious problem in drug distribution in a granule bed. The extent of migration is related to the capillary forces occurring during drying. Any factors affecting these capillary forces markedly alters the migration of soluble constituents during drying.

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