THE INFLUENCE OF SOME FACTORS ON THE TECHNOLOGY AND QUALITY OF PARACETAMOL TABLETS

BY

AMOS BODUNRIN BANGUDU

A THESIS

presented to

Ahmadu Bello University in partial

fulfillment for the degree of

Master of Science

Department of Pharmaceutics

Faculty of Pharmaceutical Sciences

Ahmadu Bello University

ZARIA

1979

DEDICATION

Dedicated to my Parents.

ACKNOWLEDGEMENT

I wish to express my profound gratitude to Professor G.E. Osuide, Dean of the Faculty of Pharmaceutical Sciences for recommending the programme and for his advice and encouragement throughout the course.

I acknowledge my indebtedness to Dr. J.T. Porebski for his guidance and close supervision during the investigation I sincerely thank him for his constructive criticims which were of immense importance to the success of the work.

I am extremely grateful to the entire laboratory staff of the Faculty of Pharmaceutical Sciences for their co-operation and invaluable technical assistance.

My sincere gratitude goes to Mr. E.D. Ozizi for his high capability demonstrated in the typing of the thesis.

A B S T R A C T

The various categories of pharmaceutical materials necessary for the fabrication of tablets (functional components), their speciiic role and mechanisms of action have been reviewed.

The physics of tablet compression, the quality standards of tablets and the extent to which they can be interpreted an extrapolated to predict drug performance have been discussed.

Paracetamol has been shown to compress poorly into tablets due to lamination and capping and the pharmaceutical factors/processes which modify the severity of this problem have been investigated.

An investigation of the effect of binder type and concentration was conducted. The results show that fairly high concentrations of binder solutions are necessary to obtain satisfactory Paracetamol tablets. Gelatin solution and Polyvinylpyrolidone (PVP) solution when used at concentration of 5 - ϑ%ẅẅ and 10%w/w respectively have been found to impart enough cohesive strength to paracetamol to produce firm tablets.

It has been shown that using the wet granulation technique, paracetamol crystals do not offer any significant

advantages over paracetamol powder in reducing tendency towards capping of paracetamol tablets. However, the crystals have been found to form better tablets than the powder employing the direct compression method.

The incorporation of Tween 80 a non-ionic surfactant has been shown to exert no apparent influence on the consolidation of paracetamol and therefore irrelevant with respect to paracetamol tablet formulation.

The particle size of granules undergoing consolidation have been shown to modify the compression characteristics of paracetamol. The results of the investigation show that paracetamol forms satisfactory tablets when the size of granules falls within the range 250 um - 1000 um

An investigation of the effect of moisture content on quality of tablet was undertaken. It has been shown that the moisture content of granules plays a significant role in controlling the capping of paracetamol tablets and that to obtain satisfactory paracetamol tablets, the moisture content values should be within the range of 3 - 6%w/w.

The effects of shapes of punches, compression pressure were investigated in a qualitative manner. The results indicated that these factors modify the compression behaviour

of paracetamol.

The specific factors to be considered and steps to be taken consistent with the production of pharmaceutically acceptable paracetamol tablets are outlined for large scale potential exploitation.

CONTENTS

		Page
	Title	(i)
	Dedication	(ii)
	Acknowledgements	(iii)
	Abstract	(iv)
	Contents	(vii)
	CHAPTER ONE	
	INTRODUCTION:	
1.1	The manufacture of Compressed Tablets ...	4
1.1	Basic Composition of Tablets ...	9
1.2.1	Diluents (Fillers)	9
1.2.2	Binders	11
1.2.3	Lubricants	14
1.2.4	Disintegrants	26
1.2.5	Colouring Agents (Colourants) ...	35
	CHAPTER TWO	
2.	The theory of Tablet Compression ...	38
2.1	Interparticular van der waals forces ...	38
2.1.1	Train's Hypothesis	39
2.1.2	Theory of Asperitic Melting ...	42

		Page
2.2	The physics of tablet compression. Instrumentation - measurement of Tablet punch forces.	43
2.2.1	Transmission of forces through a powder.	49
2.2.2	Distribution of forces in a powder ...	51
	CHAPTER THREE	
	Quality Standards of Tablets ...	53
3.1	Uniformity of Diameter	53
3.2	Drug Content	54
3.3	Weight Variation Test	54
3.4	Mechanical Strength	55
3.5	Disintegration test	58
3.5.1	Factors Affecting Disintegration Time ...	63
3.6	Dissolution Test	67
3.6.1	Theory and Kinetics of Dissolution ...	69
3.6.1a	Energies of Dissolution	69
3.6.1b	Mechanism of Dissolution	74
3.6.2	Dissolution Apparatus	80
3.6.3	Factors that Affect Dissolution rate ...	83
3.6.4	Correlation of *In vivo* data with *in vitro* rate of Dissolution data	91

CONTENTS (Contd.)

		Page
	CHAPTER FOUR	
4.1	Scope of Work	94
4.2	Pharmacology of Paracetamol	96
4.2.1	Chemistry and Relation of Chemical Structure. ...	96
4.2.2	Pharmacological Effects	96
4.2.3	Absorption, Distribution, Biotransformation and Excretion.	98
4.2.4	Therapeutic Uses.	100
	CHAPTER FIVE	
	Materials and Methods of Investigation.	
5.1	Materials	101
5.2.1	Particle Size Analysis	101
5.2.2	Preparation of granules for compression.	102
5.2.3	Flow Test	104
5.2.4	Compression	104
5.2.5	Quality Control Tests	105
	CHAPTER SIX	
	RESULTS AND DEDUCTIONS	
6.1	Effect of Binders	107

CONTENTS (Contd.)

		Page
6.2	Use of Paracetamol crystals ...	113
6.3	Direct compression of Paracetamol tablets. ...	115
6.4	Effect of Concentration of binder ...	118
6.5	Effect of Tween 80 (Non-ionic surfactant)	120
6.6	Use of polyvinylpyrrolidone (PVP) ...	122
6.7	Effect of Lactose on the Consolidation of Paracetamol. ...	123
6.8	Effect of Particle Size ...	128
6.9	Effect of Moisture Content ...	130

CHAPTER SEVEN

GENERAL DISCUSSION AND CONCLUSIONS

7.1	Compression patterns of pharmaceutical materials. ...	134
7.2	Binders and binder concentration ...	135
7.3	Paracetamol Crystals and Direct compression. ...	138
7.4	Tween 80	140
7.5	Lactose	141
7.6	Particle size	142
7.7	Moisture	147

CONTENTS (Contd.)

		Page
7.8	Compression pressure and capping of Paracetamol tablets.	151
7.9	Shape of punches.	152
7.10	Single Punch and Rotary tablet presses. ..	154
7.11	Mechanical Hysterisis, Delayed Elasticity and capping of paracetamol tablets.	154
	R e f e r e n c e s.	157

CHAPTER ONE

INTRODUCTION

Tablets represent the most popular dosage form among the contemporary methods of administering drugs. A dosage form is the pharmaceutical gross form administered and therefore, it invariably represents a drug delivery system. Over 50% of the prescriptions given to the patients contain tablets as a dosage form. Tablets owe this popularity to a number of reasons including, ease of drug administration and therefore convenience to the patients, precision of dosage and the economically high production rate which can be extrapolated to less cost to the patient.[1 - 3]

In the manufacture of tablets, certain pharmaceutical compounds of diversed origin and chemical activities are usually incorporated with the active ingredient to aid the processing in one way or the other. These compounds are generally referred to as tablet excipients, additives or adjuvants and include fillers, lubricants, disintegrants binders etc. They are pharmaceutically important functional components for solid formulations in general and tablets in particular. They therefore represent the framework of the design for tablet formulations.

The diversed nature of the excipients incorporated in tablet formulations has made tablets as a dosage form, a very complex physico-chemical system. This situation has been aggravated by the proliferation of modern drugs in use consequent upon extensive research works in which derivatives of parent drugs which may be more potent and less toxic are chemically synthesized by molecular manipulation.

The minor disadvantages of tablets as a dosage form include patient's non-compliance with dosage regimen in some cases, inability to tablet drugs which are inactive orally and the episodes of local gastrointestinal tract irritation which frequently cause nausea and vomitting. While these defects can be circumvented, a major setback of tablets is chemical inequivalence and therapeutic inequivalence.

The fact that chemical equivalence does not always indicate therapeutic equivalence has been established for long and efforts have subsequently been made to investigate the determinants of physiological availability of administered drugs. In tablet formulations, two or more samples are said to be chemically equivalent but therapeutically inequivalent when they contain the same proportion of

active ingredient in the tablets but when ingested give different in vivo results e.g. plasma levels excretory rates of the drug and/or appropriate metabolites and therapeutic activities e.g. rate and extent of reduction of sugar in blood.

Generic inequivalence in many dosage forms and in tablets in particular, has contributed in no small measure to many therapeutic failures and rejection of potential drugs in clinical trials. It has also contributed to the development of the science of biopharmaceutics which may be defined as the study of the relationship between some of the physical and chemical properties of the drug and its dosage forms and the biological effects observed following the administration of the drug in its various dosage forms.[4] The realisation of the fact that tablet additives can interfere with or modify in one way or the other the performance of tablets and the activities of incorporated drugs has contributed to the catalogue of investigations of the influence of tablet formulation factors on tablet characteristics and some of these will be reviewed in detail in the next chapter.

Suffice is to indicate here however that not only

should each excipient contribute a necessary attribute to the essential processing requirements, but should also support the therapeutic objective of the drug substance and permit compliance with pharmacopoeial or manufacturer's quality standards; in other words it should enhance the production of tablets which will not only meet the pharmacopoeial specifications but will be pharmaceutically and clinically acceptable.

1.1 THE MANUFACTURE OF COMPRESSED TABLETS

A detailed account of the contemporary pharmaceutical materials and processes involved in the manufacture of compressed tablets will be given to appreciate:

(1) the technology of tablet formulations,

(2) the sources of problems associated with the tablet manufacture, tablet performance and how the problems are/may be ameliorated,

(3) the increasing importance of the science of biopharmaceutics.

Compressed tablets are made by compressing fine crystals, free flowing powders and granules in a die between punches. Materials to be tabletted must have

certain physical properties including:

a) ability to flow freely,

b) "cohesiveness" i.e tendency of its individual particles to stick together and

c) lubrication.

Very few of the pharmaceutical materials have some of these properties and methods of tablet formulation and preparation are being developed to impart these properties to materials being compressed. There are three principal methods of granulation:-

(1) DIRECT COMPRESSION METHOD

Some pharmaceutical materials are available in crystalline forms suitable for direct compression e.g. aspirin and potassium bromide. The crystals are broken and passed through sieves to select the required size. They are then mixed with diluents or disintegrants, if necessary, in the dry state and the mix is ready for compression. Excipients of significance in direct compression technique include anhydrous lactose, spray dried lactose microcrystalline cellulose, amylose, dicalcium phosphate dihydrate,

unmilled; pregranulated calcium sulphate and spray dried mannitol.

(2) PRECOMPRESSION METHOD (SLUGGING)

The drug and diluent are mixed as fine powders. The mix is subsequently fed into a heavy-duty compressing machine to form large tablets referred to as slugs. Their size is in the range $\frac{7}{8}$ to 1 inch. The compressed slugs are comminuted through the desirable mesh screen either by hand, or for large quantities through Fitzpatrick or similar comminuting mill. Compacting mills can be used to produce sheets as opposed to slugs produced by the slugging process. In the compaction method the powder to be densified passes between high-pressure rollers which compress the powder and remove the air. Excessive pressures which may be required to obtain cohesion of certain material may result in a prolonged dissolution rate.[5] Compaction mills available include the Chilsonator made by Fitzpatrick. The precompression method which is also referred to as Double Compression Method,

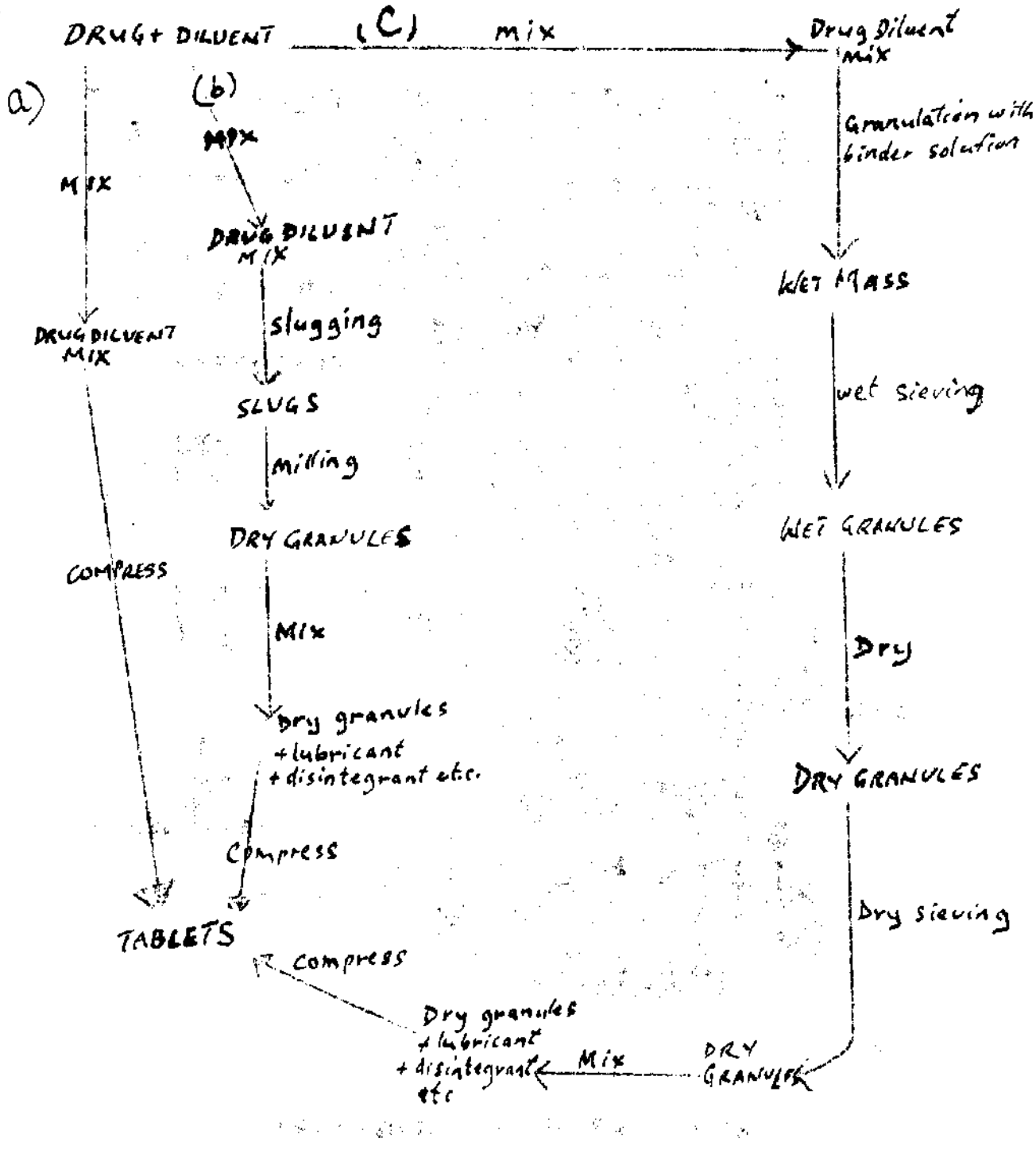
is extremely valuable for those materials which cannot be compressed directly and are at the same time thermolabile and/or moisture sensitive.

(3) WET GRANULATION METHOD

This is the traditional method of granulation and is still the most popular method. The mixed powders are moistened with a granulating fluid which is usually a solution of a binding agent. The moist mass is screened through a sieve, the size of which depends on the nature of particles to be produced. The granules are then dried in an oven on trays or in a fluidised bed dryer. The dry granules are sieved again to break down aggregates and to remove excess fines. The remaining excipients are then added to the granules before compression. The strength and quantity of the binding solution are of vital importance in determining the strength of the granules and the tablets produced.

The manufacture of tablets may be represented by the following flow diagram.

Fig. I



1.2 BASIC COMPOSITION OF TABLETS

1.2.1 DILUENTS (FILLERS)

Some drugs are very potent and may have a dose of a few milligrams or micrograms only. To produce a tablet of suitable size, a diluent or mixture of diluents must be added to such drugs. Ideally, the diluent should be cheap, non-toxic and inert with respect to the drug and its particle size should be approximately equal to that of the drug to facilitate mixing.

Diluents in current use include sucrose, conventional lactose, spray-dried lactose, powdered starch and dibasic calcium phosphate. Diluents are judiciously selected to avoid physico-chemical incompatibilities. Brownley and Lachman[6] demonstrated a difference in colour stability between the tablets prepared using spray-dried or conventional lactose in otherwise identical formulations. Tablets were found to discolour (brown) on aging especially with spray dried lactose, and has been attributed to the combination of amine salts with lactose in the presence of an alkaline lubricant. In an effort to

determine the cause of discoloration (browning) of spray dried lactose Brownley and Lachman, (1964)[7] utilized the Maillard reaction as a starting point. This carbonyl-amine type of reaction requires little energy for initiation and continues with autocatalytic assistance.[8] These workers found significant quantities of 5-(hydroxymethyl)-2-furaldehyde (HMF) in spray dried lactose while essentially no HMF was present in conventional lactose. They therefore attributed the browning of tablets containing spray dried lactose to the presence of HMF in this excipient.

Diluents can have significant effect on the performance of tablets and this has been investigated by several research workers.

Hirschorn et al (1971)[9] employed a direct compression method using spray dried lactose and poorly water soluble drug. They observed that an increase in excipient dilution of the hydrophobic drug with the hydrophilic diluent resulted in an increase in dissolution rate of the hydrophobic drug. Whereas Shalangwa[10] in his investigation of the

effect of concentration of diluents on the dissolution rate of sodium salicylate and salicylic acid determined that within the system used, an increase in the concentration of a hydrophilic diluent (lactose and sucrose) from 1:1 to 1:2 ratio decreased the dissolution rate of both the water soluble drug (sodium salicylate) and the poorly water soluble drug (salicylic acid). He also found that an increase in excipient dilution with magnesium carbonate had little or no effect on dissolution rate of both sodium salicylate and salicylic acid from their tablets. The differences in the results arrived at by these authors were accounted for by the difference in the method of granulation.

In an earlier work Boger et al[11] had found that calcium salts, when used as diluent for the broad spectrum antibiotic, tetracycline interfered with drug's absorption from gastro-intestinal tract.

1.2.2 BINDERS

These are substances incorporated in tablet formulations to impart cohesive qualities and

structural strength to the powdered material so that the tablets can withstand handling processes. The common binders in current use include gums such as veegum, celluloses such as methyl cellulose, carboxy-methyl cellulose; sugars such as glucose; polymers such as polyvinylpyrrolidone and copolymers like polyvinylpyrrolidone-vinyl acetate.

Binders are mostly used in solutions although some are used in the dry form. The binders in solutions usually possess more cohesive power and therefore are more effective than the dry binders. Among the most important dry binders are micro-crystalline cellulose (Avicel) amylose and polye-thyleneglycol (PEG).

The liquid binders are used in different concen-trations depending on the nature of the binder and the powdered material to be granulated. The nature, concentration and mode of incorporating the binder will influence the compression characteristics of given tablets; therefore these factors must be evaluated empirically for each formulation to prevent adverse effects. Thus, Jacob and Plein

(1968)[12] have shown that increasing the binder (gelatin solution) concentration caused an increase in the mechanical strength of phenobarbital tablets but simultaneously resulted in a decrease in the dissolution rate of the tablets.

Sakr and others (1972)[13] reported that as the concentration of gelatin binder increases in lactose tablets, the friability of the tablets decreases but disintegration and dissolution times increase.

Apart from the retardation effect which the use of excessive binder can have on the disintegration and dissolution rates of tablets, the sets of punches and dies will wear out prematurely by regular compression of such formulations. In extreme cases, high binder concentration can result in tablet capping. On the other hand inadequate incorporation of binders will cause inadequate binding and formation of extremely soft tablets. Thus the choice of binder solution and concentration for use in a wet granulation system can greatly affect the physicochemical properties of the resulting granules and compressed tablets.

Of interest and increasing importance is the use of dry binders for direct compression of tablets. The objective of direct compression is to produce pharmaceutically elegant tablets with a minimum of processing time and cost. Since many drugs cannot be compressed directly, one or more agents must be added to impart suitable compression properties. A major set back of this development is the fact that most of these additives are either too costly or react with the active ingredients to decrease stability or drug availability. Moreover the ratio of these additives to the drug necessary to effect compression may preclude use with higher dosage drugs. The most popular pharmaceutical dry binders are microcrystalline cellulose,amylose and polyethyleneglycol.

1.2.3 LUBRICANTS

The flow of granulation, adhesion of granules or powders to punches and dies and the release of tablet from its mould after compression are the three main problems associated with tablet compression which are ameliorated by a chemically diversed

group of substances collectively referred to as "lubricants". Cooper et al (1958)[14] defined lubricants in tablet technology as substances which facilitate the passage of a granulation through the various orifices of a tabletting machine.

Based on their ability to carry out certain functions "lubricants" may be classified into three groups: glidants, anti-adhesives and proper lubricants.[15]

(i) Glidants

These are also termed "flow regulators" and improve flow properties of the granules in the feed hopper thereby eliminating the problem associated with flow of materials from larger through smaller apertures in the tablet presses. The mechanism by which glidants improve flow has been thoroughly investigated,[16] Jones and Pilpel[17] have classified glidants into two categories:

a) those reducing van der Waal's type interparticle cohesive forces and

b) those reducing surface rugosity and hence

coefficient of interparticle friction. Examples are talc and silicondioxide.

Gold et al[16] have proposed another mechanism of glidant action-filling void spaces between large particles by fine particles which may be chemically similar (in which case they are referred to as "fines") or chemically dissimilar to the material with which they are admixed.

Angle of repose, angle of spatula and timed delivery from an orifice are the simplest and most popular methods of studying flow rates.[18] Gold et al (1966)[19] have criticized these methods, especially angle of repose as index of flowability. They reported that many widely used glidants actually decreased flow rate and that glidants which lowered the angle of repose did not necessarily increase the flow rate and marked changes in flow rate were not always detectable by angle of repose measurement. They therefore concluded that angle of repose measurement is not a reliable method for evaluating flow properties. They suggested a

more reliable method and designed an apparutus called Recording Powder Flowometer which consists basically of various hoppers with and without vibrations, a strain gauge balance and a recorder. There is a limit to the concentration of fines and other glidants to be added to a specific tablet formulation to improve flow properties above which granule flow rate decreases and becomes irregular. This has been explained by the theory of "cohesive bridging" of the fine particles.[20]

(ii) Antiadhesives (Antisticking Agents)

These easily deformed substances prevent adhesion of the tablet surface to the punches and dies during compression thereby reducing the incidence of binding or sticking in the die. Examples of antisticking agents are stearic acid and soaps.

(iii) Lubricants (Proper)

These are the proper lubricants which reduce interparticular friction during compression and friction between tablet and die wall

during ejection cycle, thereby facilitating tablet ejection. The most popular lubricants include talc and the metallic stearates such as calcium stearate and magnesium stearate.

The most commonly used tablet lubricants are hydrophobic substances. Therefore the primary problem in the preparation of a water soluble tablet is the selection of a satisfactory lubricant. Where hydrophobic water-insoluble lubricants are used to prepare water soluble tablets, formulations represent a number of compromises between compression efficiency and water solubility[21] and therefore, the optimum proportion of lubricant must be empirically selected. The most efficient lubricants are materials that are water insoluble due to the relationship that exists between degree of lipophilic properties and general effectiveness as tablet lubricants. Since hydrophobic lubricants, by their water-repellant properties can markedly interfere with disintegration and dissolution of tablets,

it is axiomatic that a sufficient quantity of a lubricant should be used to optimize tablet manufacture but its concentration in a compressed tablet should be as low as practical to prevent a marked slowing of dissolution and absorption.

Levy, G. and Gumtow, R.(1963)[22] determined that hydrophobic lubricants (magnesium stearate) can retard the dissolution of drugs from compressed tablets and attributed this to inhibition of penetration of solvent. The mechanism by which hydrophobic lubricants in general and magnesium stearate in particular, retard dissolution rate is complex and has been reviewed.[23] It is thought magnesium stearate modifies the mechanism of bonding during compression and therefore break up of a tablet in water. It is also conceivable that changes in the shape and size distribution of the capillaries which conduct water into tablet may result from volumetric distribution of a powder like magnesium stearate which compacts with ease.since

it has a very low shear strength.

A major mechanism contributing to the dissolution rate inhibiting effect of magnesium stearate is inhibition of penetration of solvent. Ganderton (1969)[23] has shown that inhibition of penetration by liquids is roughly proportional to the concentration of magnesium stearate. The inhibition of penetration is due to the high contact angle with water.

The force driving a liquid into a tablet is derived from the pressure difference ΔP existing across the curved menisci of the liquid entering the capillaries of the tablet. Carman (1941)[24] gives this pressure difference as

$$\Delta P = \frac{\gamma \cos \theta}{m} \quad \text{.....equation (1)}$$

where γ = the surface tension of the penetrating liquid, θ is the contact angle between the penetrating liquid and the capillery surface, and m is the ratio of the cross-sectional area

of the capillary and its perimeter. If $\theta < 90^{\circ}$, ΔP is positive and the liquid moves through the capillary. The contact angle of water with magnesium stearate is $> 90^{\circ}$ so that water will not penetrate a tablet composed of this material only. When magnesium stearate is incorporated in a tablet formulation, capillaries composed of some proportion of magnesium stearate will not transmit water and the proportion of capillaries so affected will depend mainly on the concentration of magnesium stearate. Higher concentration yield an increase in the non-wetting surface and the number of capillaries not contributing to the transport of water, hence the slower rate of dissolution.

In the light of the major set back in incorporating hydrophobic lubricants in tablet formulating, extensive investigations are being carried out on the potential use of hydrophilic lubricants for future exploitation.[25] Examples of soluble lubricants are sodium benzoate,

sodium laurylsulphate, sodium acetate, polyoxyethylene monostearates etc.

Sodium laurylsulphate, a surfactant having high lubricating activity has been found to enhance dissolution rate of salicylic acid tablets.[22] This was attributed to increased wetting and to better solvent penetration into the tablets and granules as a result of the interfacial tension lowering effect of the surfactant. The possibilities of solubilization of drug by micelles and an increase in micro-enviromental pH, which are other mechanisms of dissolution enhancement, have been ruled out because sodium laurylsulphate has no effect on the dissolution rate of salicylic acid from the surface of non-disintegrating disks. However Song-Ling [26] and others in a series of in vitro experiments showed that the presence of physiological concentrations of lysolecithin (a naturally occuring biosurfactant) exhibited micellar solubilising properties on griseofulvin and gluthethimide. The data obtained from the

dissolution rate studies showed that aqueous lysolecithin solution caused significant enhancement of the extent as well as the rate of dissolution of the drugs investigated. This derives from the fact that the concentration of surfactants above the critical micelle concentration (CMC) may markedly increase the apparent solubility of the drug in the medium by means of micellar solubilisation and thereby effect an increase in the dissolution rate.

The dissolution rate of a drug can be increased by a surfactant if the latter increases the micro-enviromental pH of the dissolution medium surrounding the drug. This is more likely with weakly acidic drugs which dissociate more completely and therefore dissolve more readily with increasing pH.

The intrinsic surface activity found with surfactants may be the major factor contributing to the mechanism of dissolution rate enhancement of this group of pharmaceutical materials. Roller, P. (1931)[27] speculated that surface

activity may play apart in the dissolution process if spontaneous release from the crystal controls dissolution. A surfactant may decrease interfacial energy barrier between the drug and the dissolution medium, allowing the drug to be "wet" more completely and thereby effectively increase the available surface area of the solid. The term "wetting" means that the contact angle, θ between a liquid and a solid approaches zero. According to the Dupre equation.

$$\text{Cos } \theta = (\gamma_s - \gamma_{SL})\gamma_L \quad \text{.....Equation 2}$$

where γ_S and γ_L refer to the surface tension of the solid and liquid respectively and γ_{SL} refers to the solid-liquid interfacial tension.

Adamson (1960)[28] notes that if good wetting is to be observed, both γ_{SL} and γ_L should be made as small as possible and this is effected by a surfactant. Finhort, P. and Solvang, S. (1968)[29] studied the effect of a surfactant polysorbate 80 on the rate of dissolution of phenacetin (a hydrophobic drug).

The dissolution rate enhancement by polysorbate 80 was attributed to its ability to decrease interfacial tension between the substance and the dissolution medium.

Methods of Incorporating Lubricants

There are two principal ways of incorporating the lubricant into the tablet formulation:-

(1) The lubricant is usually added in the form of fine powder (passed through 60 - 85 mesh sieve) to the dried granules prior to compression. These "external lubricants" are thought to function by coating the surface of the granules with a film which reduces interfacial friction between the granules and the compressing surfaces. Magnesium stearate and calcium stearate are well known examples.

(2) Internal lubricants - stearic acid and hydrogenated oil can be dissolved in organic solvent such as isopropanol or chloroform and added during the moist granulation process. Cooper et al (1958)[30] found that it was possible

to add the lubricant to the initial powdered mixture of therapeutic agent and excipients and then subject it to wet granulation without loss of lubricating properties. The impression that the lubricant would be enclosed within the granule and covered by the binder, thereby losing its function, proved to be unfounded since tablets prepared by this method had good physical properties and additionally exhibited a reduced disintegration time. This notwithstanding external lubricants remain the more popular form of incorporating lubricants in tablet formulations.

1.2.4 DISINTEGRANTS

The importance of a disintegrating agent in a conventional peroral tablet formulation cannot be overemphasized. Basically, it is the function of the disintegrant to cause the compressed tablet to break apart or disintegrate within a limited period of time when in presence of fluids to allow for a more favourable condition for the dissolution and absorption of the contained medicament.

Feinsteinward et al[31] have classified disintegrants into starches, cellulose, algins, gums and clays based on their natural sources. Fakouhi[32] based his classification on the mechanism of action of the disintegrants viz

a) agents that react with moisture to constitute a foam,
b) Effervescent substances that react with moisture to form a gas, and
c) Substances that react with moisture to swell.

Those of the "absorb moisture and swell" type are by far the most commonly employed in research and industry today.

The starches among which are corn, potato, wheat and rice starch are undoubtedly the most popular class of disintegrants in research and industry. Cornstarch has been used in compressed tablets as a disintegrant for decades and is still the disintegrant of choice. Many authorities consider starch as the best tablet disintegrating agent and infact corn starch frequently serves as standards in evaluations of other disintegrating.

agents.[33 - 35]

Other disintegrating agents of less importance ~~and~~ are the gums e.g. veegum magnesium alluminium silicate, alginic acid, cellulose derivatives carboxymethylcellulose, ethylcellulose, microcrystalline cellulose, polymers, cation exchange resins and synthetics like cross linked polyvinylpyrrolidone.

Incorporation of Disintegrants in the Tablet Formulation

The disintegrant is usually added to the active ingredient and diluent during the preparation of the granules. The utilization of intragranular disintegrant is based on the assumption that much finer particles are recovered during disintegration than when the disintegrant is incorporated extragranularly.[36]

It is advantageous in some cases to add part of the disintegrant to the powder formula prior to granulation. The other part is added to a lubricant and added prior compression.

Michael, H. Rubinstein et al[37] in their study

of disaggregation of compressed tablets prepared tablets of dibasic calcium phosphate containing varying proportions of intra to extra granular maize starch. They arrived at the conclusion that the optinium starch combination that produced maximum disintegration rate and maximum surface area in a tablet formulation was either 2.5% intra to 12.5% extra granular or 15% intragranular starch alone.

Depending on the particular formulation different proportions of the specific disintegrant are incorporated in the tablet fabrication. In general, the higher the percentage of the disintegrant in the tablet composition the shorter is the disintegration time - but there seems to be an optimum concentration above which disintegration time increases with further increase in proportion of disintegrant.[31,38]

Gums usually dissolve in aqueous medium to cause increased viscosity or form a mucilagenous layer over the tablets which inhibits water penetration during disintegration.[39]

Mechanism of Action of Disintegrants

Much controversy has been generated among research workers on the issue of the exact mechanism of action of disintegrants in current use. The resultant effect of this is the development of new and more effective disintegrating agents.

The following are some of the theories that have been put forward to explain how disintegrants act:

(1) Evolution of gas

The basis of effervescent tablets is the evolution of gas - carbondioxide the product of the reaction of sodium bicarbonate with citric and tartaric acids in the presence of water. As carbondioxide is released within the tablet, an internal pressure developes until the tablet breaks apart and carbondioxide dissolves or disappears from the reaction vessel.

(2) Water Absorption - Capillary Theory

This theory maintains that a disintegrant especially starch by virtue of relative incom-

pressibility forms chains around granules. These chains form a capillary net work within the tablet and the higher the concentration of starch, the greater the number of capillaries formed. The capillaries are thought to promote the rapid absorption of water into the tablet and the subsequent disintegration of the tablet.

Crisafi and Becker[40] have shown that starch will absorb about 20% of its weight of water in 24 hours when exposed to an atmosphere of 95% relative humidity at 27°C.

Kerr[41] in his book on starch states that in the natural state, starch is insoluble in cold water but appears to absorb 25 - 30% and does not swell appreciably. Curlin[42] has suggested that the disintegrating effect is due to capillary action rather than swelling. Korublum and others postulated that capillarity of cross linked polyvinylpyrrolidone for water appears responsible for its tablet disintegration property.

Capillarity per se. may not have a disintegrating effect, although under certain conditions related to pore size, it may play a part in increasing the rate at which water is introduced into the tablet matrix. Many fluids e.g. alcohol and glycerin have been found to penetrate tablets without causing disintegration.[44]

(3) Swelling - Rupture Theory

Most disintegrants have ability to absorb water and swell to several times their own size.[45 - 46] If for example starch is added to the dry granules before compression, the tablet will absorb gastric fluid causing starch to swell and mechanically distrupt the tablet. This is called the Rupture Theory. W. Lowenthal et al (1972)[46] postulated that water hydrates the hydroxyl groups of the starch molecules causing them to move apart. They indicated that the slight swelling that occurs is due to the rapid hydration step and slower sorption of addition water step. The swelling which takes

a few seconds would result in significant increase in volume. The combined effect of the attachment of water molecules and the increase in volume of the grain cause sufficient force to break up the tablet. The antagonists of the Rupture theory have exposed the observation that while many substances swell to a greater degree than the starches but are poor disintegrants, other materials do not swell but have good disintegrating properties e.g. amylose[47].

In tablets containing disintegrants which are adhesive in the hydrated state (e.g. sodium carboxymethyl cellulose) the positive forces of penetration of water and swelling of particle must overcome the opposing forces of adhesion within the particles to produce tablet disintegration. When the opposing forces are equal to or greater than the positive forces the result is a longer disintegration time.[48] Because the extent of hydration increases with the number of polar groups, one would expect higher grades (of viscosity) to produce greater

swelling of particles, thus causing faster disintegration at low concentration. At higher concentrations, however, the higher grades, because of their higher viscosities may also become more adhesive in the hydrated state. Thus, the opposing forces of adhesion within the particles would become dominant, resulting in a longer disintegration time of tablets. The mechanism of action of disintegrating agents is complex and mediated through several unrelated phenomena. In most cases, however, the principal mechanism of disintegrants, especially starch is pressure exerted by increased volume in the presence of water although capillarity may facilitate rate of penetration of water.

1.2.5 COLOURING AGENTS (COLOURANTS)

The use of dyes in tabletting has increased considerably since the discovery of the first synthetic aniline dye.

There are three main reasons for incorporating colours in tablet formulations:

(1) to improve the tablet appearance by making it more aesthetic or elegant;

(2) for manufacturing control and identification during processing and quality control in laboratories which manufacture different drugs concurrently;

(3) to serve as a means of identification by the user.

In general colours used in tabletting must be safe for human consumption and therefore must comply with the requirements of the legally controlling body in the particular country.

In the United States the amended regulations (1940) of the Food, Drug and Cosmetic (FD & C) Act required batch certification of any colours used in products covered by the Act. The chemical proper-

ties of the colours must be fully understood to avoid chemical incompatibilities with the active ingredients and/or tablet excipients.

Colours and coloured tablets fade on storage usually by photochemical degradation.[49] The complexes formed by the reaction of water-soluble dyes with aluminium hydroxide are called "lakes" and are thought to be more stable especially to light than the corresponding dyes. Lachman et al (1961)[50] have however demonstrated that this expression is unfounded. The workers found in the course of their investigation that all the lakes exhibited less photostability than their corresponding dyes.

A major problem in the manufacture of coloured tablets is the phenomenon of mottling. Mottling is defined as "an unequal distribution of colour on the surface of a tablet, with light or dark areas standing out in an otherwise uniform surface".[51] Mottling has been attributed to the migration of dye with the granulation fluid during drying.[52] Methods have been investigated to obtain appropriate tablet manufacture procedure which would reduce mottling.[52; 53]

N.A. Armstrong and others[52] have outlined some suggestions to minimize mottling since it cannot be eliminated completely:

(1) Granules should be dried by a method that prevents intergranular migration of the dye e.g. fluid bed drying as opposed to tray drying.

(2) Granules should not be subjected to a comminution process after drying; otherwise, the dye deficient interior of the granule will be exposed.

(3) As far as commensurate with granule flow properties, the granule size should be as small as possible. The authors theorized that in such granules, the amount of dye available for migration is minimized and the colour contrast between the periphery and the interior is reduced.

CHAPTER TWO

THE THEORY OF TABLET COMPRESSION

A considerable amount of research has been carried out in an attempt to determine quantitatively the mechanism of powder consolidation during tabletting and the physical and mechanical factors affecting the consolidation of powders during compaction. This followed immediately after Higuchi and his research workers published the first series of paper relating to the physics of tablet compression.[54]

The agglomeration of pharmaceutical material particles during compaction is well documented and many hypotheses have been proposed to describe the behaviour of the particles during tabletting.[55, 56]

2.1 INTERPARTICULAR VAN DER WAALS FORCES

Rumpf, H. (1962)[55], proposed that the mechanism of bonding of powders in the formation of a tablet is related to interparticular van der waals forces of attraction. The cohesion between solid surfaces depends on forces of atomic attraction which demonstrate themselves at distances slightly greater than normal inter-atomic spacing.[57] The degree of bonding will generally directly depend on the contact area

of the solid surfaces. The greater the effective surface area of contact the greater is the degree of bonding. Therefore, pharmaceutical solids with a greater tendency for plastic flow will attain a greater contact area under pressure and therefore a higher degree of bonding will result.[58]

Electrostatic forces may arise from friction or particle size reduction during the granulation process. the charge developed depending on the materials and type of motion encountered, whereas with ionic materials there is the added possibility of surface polarisation

Mechanical interlocking, especially when dealing with fibrous or spongy particles, and the formation of solid bridges by friction and junction growth all contribute to the additional strength of the compressed tablet over that of the granules from which it is formed.

2.1.1 TRAIN'S HYPOTHESIS

The hypothesis maintains that bonding is due to interparticular shearing and shearing along the die wall.[56] The consolidation process is divided into stages:

(1) The application of axial pressure results in interparticulate slippage, re-organization and re-arrangement of the powder particles. The consequence of this is a decrease in the relative volume of the compact i.e. closer packing and increased bulk density.

(2) There is formation of temporary struts, columns, vaults and bridges (as a result of friction) and increased resistance of the powder to compression.

(3) In Stage III there is failure of these temporary structures as they can no longer resist the increasing compressional force. The failure of the structure is due to crushing of particles - (mechanical fragmentation) or plastic flow.

(4) In Stage IV, rebonding is taking place more quickly than particle fracture and the decrease in relative volume of the compact becomes quite small as compared to the former stages and are limited by the compressibility of the solid. Many experiments have validated this concept. Higuchi et al (1953)[59] working on sulphathiozole

tablets determined that the porosity of the tablets progressively decreased as the pressure was increased but the specific area rose to a maximum at about 1600 Kg cm^{-2} and subsequently decreased. This was attributed to fragmentation of granules during the initial stages of compaction followed by bonding of the freshly formed surfaces at higher pressures. Similar results were obtained with magnesium carbonate aspirin and lactose by different workers.[60 - 63]

The reduction in volume of compact with increase in compaction pressure can be represented by a single equation.

$$V_r = C - K\ln P \qquad \text{.....Equation 3.}$$

where V_r = relative volume defined as the ratio of the bulk volume at Pressure P to the volume at infinite Pressure. P is the compression pressure and C and K are constants.

Heckel (1961)[64] considered that the consolidation or decrease in porosity with increased pressure could be likened to a first order chemical reaction. He obtained a relation between apparent density, D and compression pressure, P.

$$\ln\left(\frac{1}{1-D}\right) = KP + A \quad \therefore \text{ Equation 4.}$$

where K and A are constants relating to the yield pressure and original compact volume respectively.

2.1.2 THEORY OF ASPERITIC MELTING

More recently another theory describing the mechanism of powder consolidation was proposed by York and Plpel (1972)[65] and relates to the asperitic melting of the local surfaces of powder particles. During the compression of powders the bigger particles are broken down while the smaller particles are forced to fill the voids since they cannot be broken down further. In the latter case, frictional heat develops at points of contact due to a high degree of shear. Very high pressures are also manifested at these points of contact known as asperities. Consequently the melting points of the materials decrease according to thermodynamics and Stotnicky's Equation (1953).[66]

$$\frac{d\theta}{dP} = \frac{-V\theta}{H} \quad \text{.....Equation 5,}$$

where $d\theta/dP$ = change in melting Point with pressure

H = latent heat of fusion (Cal. g^{-1})

V = volume per gramne of solid (Cm^3 g^{-1})

Θ = melting point of solid (^{o}K).

The lowering of melting point under higher pressure causes the materials to melt at the points of contact below the conventional melting point - asperitic melting.

Melting of the asperities causes an increase in the area of contact between particles and hence, a reduction in pressure that is acting between them. Pressure is also reduced on releasing the load consequently some of the melted material may resolidify giving rise to strongly bonded particles.

2.2.0 THE PHYSICS OF COMPRESSION OPERATION. (INSTRUMENTATION - MEASUREMENT OF TABLET PUNCH FORCES).

During tabletting, the compression forces exerted by the punches on the material undergoing consolidation cause, elastic deformation of the material. An interesting criterion for assessment of the compression behaviour of powders is the progress of the force in the machine depending on the compression. The measurement of punch forces may be

achieved by the use of strain gauges or piezo-electrical devices. A typical strain gauge consists of a coil of high resistance wire mounted on a paper backing. They are available in various shapes and sizes to cover a wide range of resistances. The gauge must be firmly bonded to the punch shank so that it is deformed simultaneously with the punch as a force is applied. The bonded strain gauge is similarly deformed so that the length of the resistance wire decreased and its diameter increased. resulting in a decrease of electrical resistance. To measure the variation in resistance a Wheatstone bridge may be used with suitable recording of the bridge output, either by an oscilloscope or by an ultraviolet spot galvanometer used in conjunction with photographic paper. A typical assembly of the strain gauge elements is illustrated in Fig. 2. The compression resulting from the moment-to-moment position of the punches in relation to one another may be examined continuously when transformed into an electrical signal by these inductive displacement gauges. A typical Force-Displacement diagram[68],

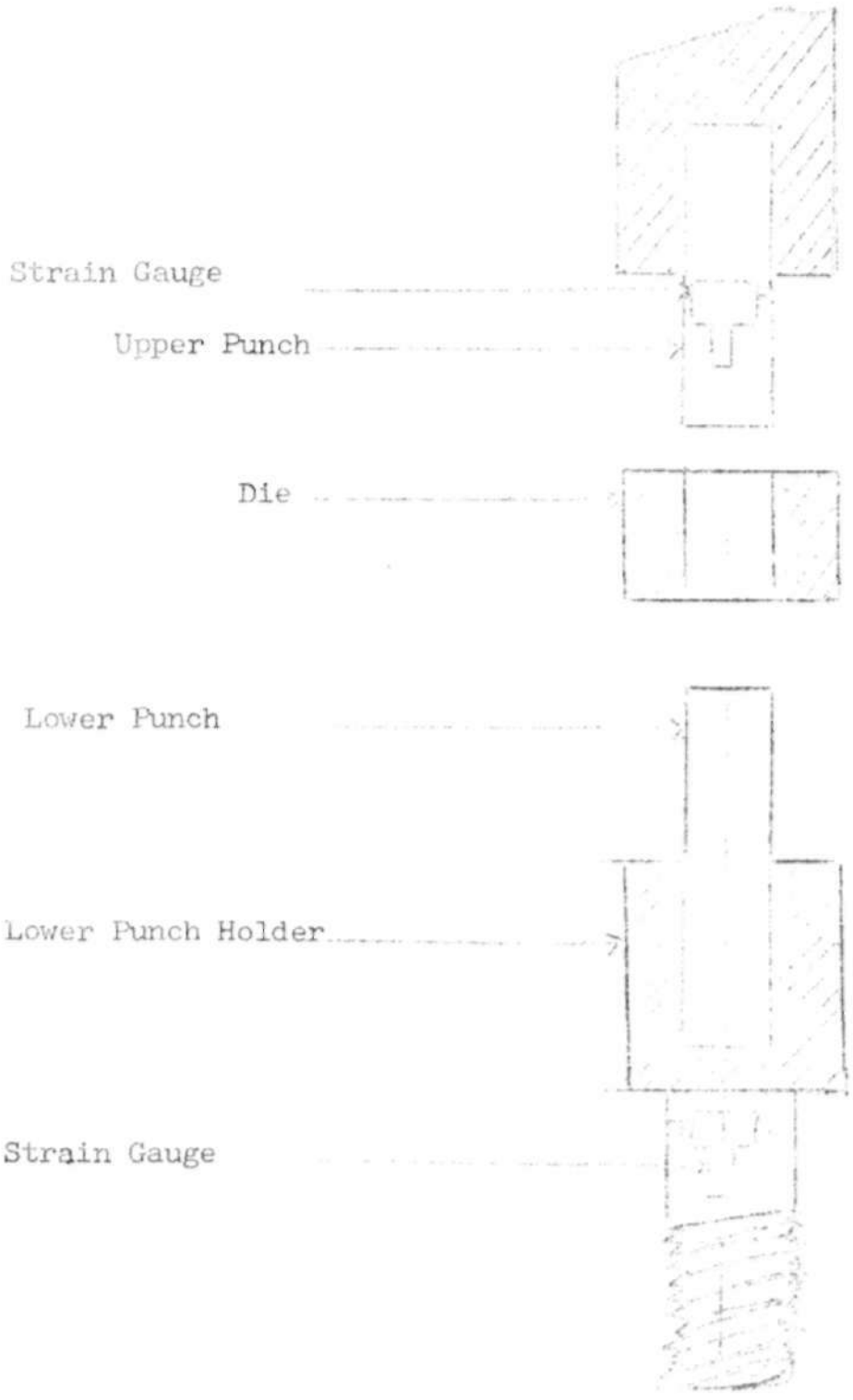


Fig. 2 - Typical assembly of strain gauge elements bonded to shank of upper punch and to lower punch holder. Ref. 67.

which represents theforce in the top punch in relation to the distance between the two punches, is shown in Fig. 3. The initial penetration of the upper punch does not produce any increase in force. Only after a certain compression is the precompression phase completed and the resistance of the particles becomes recognisable.

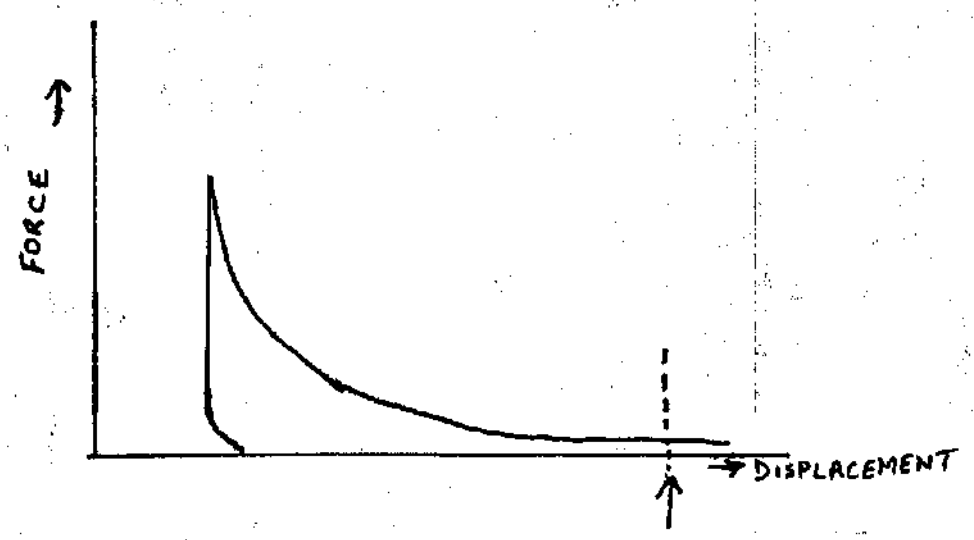


Fig. 3: Force-Displacement diagram of the formation of a tablet. The abscissa shows the distance between the upper and lower punches. The zero of the coordinate corresponds to the position of the lower punch. The ordinate shows the force exerted by the upper

punch. The position of the top edge of the die is indicated on the abscissa.

Measurement of the fringe pattern developed in materials such as polymethacrylate or gelatin using polarized light, enables calculation of the compression forces. The use of this photoelastic techniques for simmlation studies of the tabletting operation in which the punches and/or die are made of photoclastic materials has been used for the elucidation of force patterns in the tabletting operation and are useful to assess the radial force on the die wall.

Application of Instrumentation

The instrumentation of single punch machines, enabling the measurement of the applied and transmitted punch forces, Fa and Fb has led to a greater understanding of the physics of tabletting process. It is useful in evaluating the necessary properties of powders, granules and lubricants.

Knoechel et al (1967)[69] have instrumented high-speed rotary presses to measure and record compressional and ejectional forces during actual tabletting operation. They suggested that the general relation ships between compression force and the weight,

thickness, density and ejection force were relatively independent of the material being compressed and quite similar for all materials studied. They found that large punch-to-punch variations in compressional and ejectional force levels were apparently due to unequal filling in the dies, having found that formulations with good flow properties exhibited less variation. The authors concluded that instrumented rotary tablet presses could be used to compare lubricants and lubricant concentrations, to compare flow properties of granulations and to check experimental formulations at pre-selected force levels.

From their investigations on the instrumentation of a Manesty Rotapress, Goodhart et al (1968)[70] have concluded that formulation characteristics and defects are better understood with the use of tablet machine instrumentation.

The compression force signal and its relation with tablet weight has been used to activate relays operating both a servo-mechanism on the weight adjuster mechanism of the tablet machine and a tablet rejection system. Thus direct automatic control of tablet weight can be maintained throughout an entire batch.

Thus, with the development of the instrumentation techniques the operation and adjustments inherent in tabletting process can be completely automated.

2.2.1 TRANSMISSION OF FORCES THROUGH A POWDER

The applied force, Fa is through the upper punch. The force exerted to the lower punch through the powder is Fb. In the single punch machine Fa $>$ Fb but in the rotary press where the upper and lower punches approach one another at the point of maximum compression Fa is approximately equal to Fb.

The force pattern within the powder mass is such that the axial force causes compression of powder and a radial force (Fx) is exerted upon the die wall.

A frictional force Fd between the solid and the die wall tends to resist consolidation of the compact. If μ is the coefficient of friction between the particulate solid and the die wall, then

$$Fd = \mu Fx \quad \text{.....Equation 6}$$

Fx can be measured by using calibrated strain gages. Fa and Fb and their corresponding pressures Pa and Pb, are apprxomately linear but where depth of the powder varies Shaxby and Evans[71] have found a logarithmic

relationship
~~relatively~~;

$$Pa = Pb \exp. \frac{4LK}{D} \quad \text{.....Equation 7.}$$

where L is the length of the compact

D is the Diameter

and K is a material constant

K could be replaced by the product of coefficient of frictions (μ) and the ratio of radial to axial stress in the compact, η

Thus

$$Pa = Pb \exp. \frac{4L\mu\eta}{D} \quad \text{.....Equation 8}$$

This shows that the rate of decline of pressure (i.e. pressure decay) in a column of powder is exponential ~~experimental~~ since from Equation 8 it follows that

$$\ln \frac{Pa}{Pb} = 4\mu\eta\frac{L}{D} \quad \text{..... Equation 8a}$$

Equation 8a is important in that the L : D ratio of the tablet may determine the degree of consolidation of the material. There may be poor compaction if L : D ratio is high since the further the material is away from the punch face the lower is the degree of compaction especially in the single punch machine du

to pressure decay. The Equation 8a also shows the influence coefficient of friction between the powder and the die wall and this equation is used to evaluate tablet lubricants.

2.2.2 DISTRIBUTION OF FORCES IN A POWDER

The distributions of forces within the powder mass is not homogeneous. When compression has reached such a point that the packing density achieved no longer permits displacement of the particles against each other and diminition of the pore volume to a significant extent, then further compression may be achieved only by a simultaneous deformation of the particles. The loose particles are exposed to bending and shear forces resulting in deformation so that they are impressed into the spaces still present in the column of the substance. The contact surfaces of the particles through which the forces are transferred are very small in relation to the total surface area of the particles. For this reason, very limited regions of extremely high load occur - these are referred to as "hot spots". These zones of high pressure and density occur at the

periphery near the moving punch, and on the axis near the stationary punch. The latter zone may account for the failure of some tablets to disintegrate completely when immersed in water.

Train[72] measured the pressure distribution in a powder mass while compression was taking place by incorporating a number of pressure-sensitive resistance ganges encapsulated with glycogelatin in heavy magnesium carbonate mass.

Fig 4.

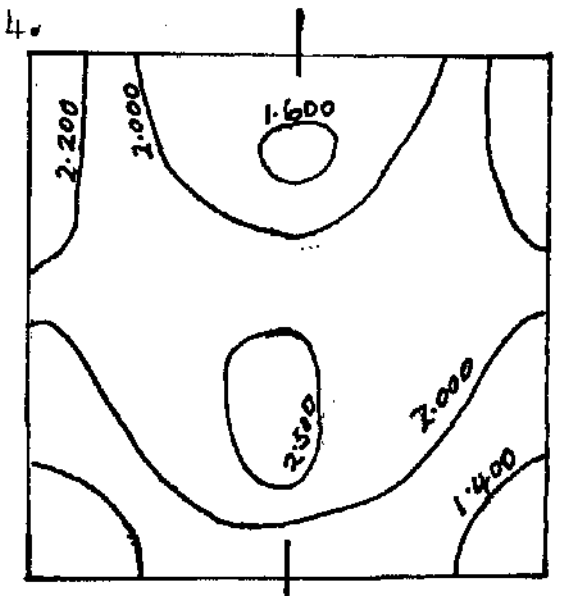


Fig. 4 - Distribution of pressure in magnesium carbonate compact. Contour levels in Kg/sq cm. Applied pressure 2040 Kg/sq cm.

(From Train D. Ref. 72.)

CHAPTER THREE

QUALITY STANDARDS OF TABLETS

The advantages which tablets have over other dosage forms will be nullified if steps are not taken to ensure that tablets perform very well and elicits the therapeutic responses when ingested. Apart from the therapeutic implications, it is consistent with Good Manufacturing Practice that there should be uniformity in quality of tablets produced from batch to batch. These are the basic principles justifying the design of quality control tests for tablets. While some are official a gamut of control tests are unofficial but serve as in process control tests in pharmaceutical laboratories.

3.1 UNIFORMITY OF DIAMETER

This is an attempt to rationalise the diameter of uncoated tablets containing a certain dose of drug, hence the use of punches of specified diameter for the compression of a given tablet. This measure ensures that tablets of given strength and weight are of approximate size which could otherwise be frowned at by some patients and other users. Tablets which have very uniform diameter present no problem during packaging.

3.2 DRUG CONTENT

This is an attempt to detect dose variation in tablets and this may arise from uneven distribution of the active ingredient throughout the tablet mass. The composite assay test in which a number of tablets are ground into powder together and assayed does not always detect dose variation. It is conceivable that half of the tablets may fall below the tolerance limit while the other half are above; there will be a masking of the drug contents of the tablets.

Single assay, undoubtedly is a more reliable method although it can be costly and time consuming. The development of Autoanalyzers[73] and automatic spectrophotometers[74] for assaying a large number of individual tablets will solve these problems.

3.3 WEIGHT VARIATION TEST

If a drug is uniformly dispersed throughout the tablet mix, variation in tablet weight results in variation in doseage. This is particularly true in formulations containing a high proportion of drug. For tablets containing relatively small proportion of active medicament, there may be no significance

between the tablet weight and drug content. This quality parameter is therefore not of vital importance. A sample of tablets (usually 20) is taken and their average weight determined. The tablets are then weighed individually and deviations in tablet weight from the mean must be within the official limits.

3.4 MECHANICAL STRENGTH

Tablets must be firm enough to withstand without breaking, chipping or crumbling, the normal processes of handling during packaging, transportation, storage etc. The quality test of the tablet which determines the resistance of the tablet to these forces is referred to as mechanical strength.

The mechanical strength of tablets is an important property which plays significant role in development and control procedures. It has[75] been described by various terms including:

1) fracture resistance
2) friability
3) hardness
4) bending strength, and
5) crushing strength.

Measurement of crushing strength is the most widely used technique and may be precisely defined as "that compressional force which, when applied diametrically to a tablet, just fractures it". There are a variety of hardness testers and their performance has been reviewed by Brook and Marshall[75] (1968) and by Ritschel et al (1969)[76]. In most cases the tablet is placed upon a fixed anvil and the force is transmitted to it by means of a moving plunger. In the Monsanto Hardness Tester, Pressure is applied to a spring by rotating a screw. The instrument has a calibrated gauge on the bottom with a zero adjustment. The Pfizer tester operates on the plier mechanism and with the Erweka Tester, compressional force is applied by a loaded beam. The Srong-Cobb operates pneumatically and registers the air pressure in Kg cm^2 required to crush the tablet.

Brook and Marshall (1968) have found that variations in crushing strength values obtained from different types of tester are due to inaccuracies in instrument scale values, zero-errors and varying methods of applying force (load). They suggested

that calibration is therefore necessary where a high degree of accuracy is required or when comparing results from different type of testers. The determination of tablet breaking strength has become an important measurement in the formulation and manufacture of compressed tablets.

FRIABILITY

This is resistance to abrasion due to falling or rolling in contact with similar tablets and therefore a measure of interparticulate cohesiveness. In the Roche Friabilator tablets drop through a fixed distance during each revolution of a horizontally disposed plastic drum. After a number of revolutions loss of weight as a percentage of original weight provides the numerical value.

Hardness, as a surface property can also be evaluated by the use of a microindentation test of the Vickers type. In this test the penetration of a diamond shaped point, under a known force, is measured. The difficulty in applying this test is that a tablet is not homogeneous and even for tablets compressed from a single material, it is apparent that there would be considerable variation owing to

crystal face orientation and to differences between indentation of a crystal face and indentation of a boundary between crystals.

3.5 DISINTEGRATION TEST

The fundamental importance of absorption problems in therapy derives from the fact that a drug must be absorbed in order to be effective. On the other hand, absorption processes are extremely dependent on external conditions e.g. disintegrant concentration effect on disintegration rate.

Disintegration of a compressed tablet is the process by which a whole tablet breaks up into small pieces when in contact with fluid. Fig. 5 depicts the processes involved when a tablet or capsule is exposed to fluid under *in vitro* or *in vivo* conditions conditions following oral administration. The tablet breaks down to granules and aggregates by a disintegration process; the granules and aggregates break down into fine particles by deaggregation process. The drug is brought into solution by a dissolution process which takes place from the intact tablet, the fragmented aggregates and fine particles. The drug in solution is subsequently absorbed into

the blood stream.[77]

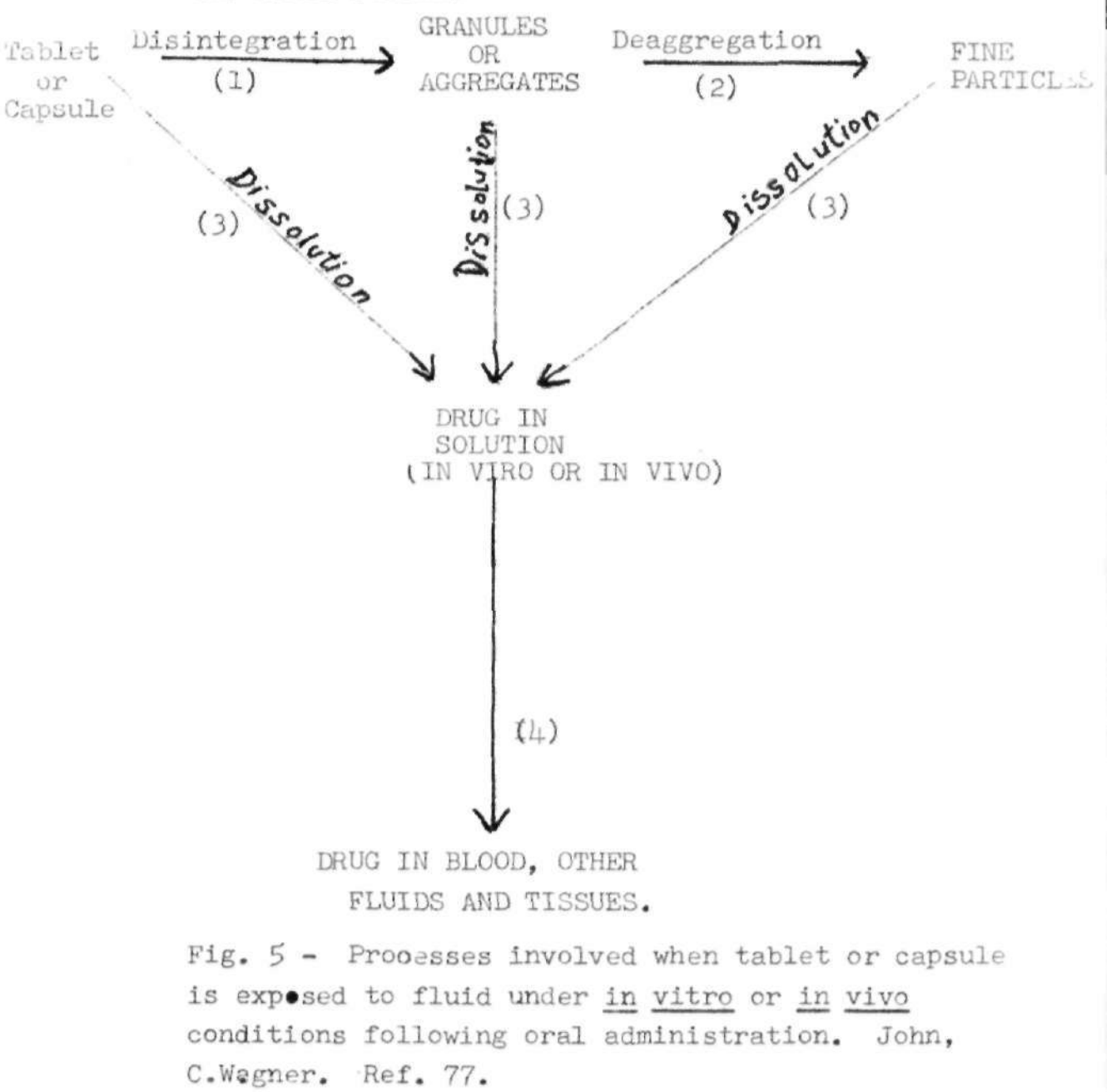


Fig. 5 - Prooesses involved when tablet or capsule is exposed to fluid under in vitro or in vivo conditions following oral administration. John, C.Wagner. Ref. 77.

It is assumed that disintegration of a tablet takes place in two steps:

(1) first the tablet breaks into granules

(2) the granules fragment or break into smaller particles.[78]

Complete tablet disintegration is defined by NF XIII[79] as ".....that state in which any residue of the tablet, except fragments of insoluble coating, remaining on the screen is a soft mass having no palpably firm core". This often makes tablet disintegration a necessary first step to achieve rapid availability of the active ingredient(s). The importance of the disintegration test as a parameter in quality control of tablets cannot therefore be overlooked.

Today's emphasis on the availability of drugs highlights the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited drug dissolution behaviour.[80] When the disintegration process is slower than the deaggregation, dissolution and absorptive processes, then disintegration will be rate-limiting and one might

expect a reasonable correlation between disintegration time, measured *in vitro*, and some *in vivo* parameter such as physiological availability ..... The quantitative correlation of physiological availability of drugs with disintegration times have been established by several workers.[80 - 82]

DISINTEGRATION TEST

The design of the apparatus for disintegration test differs within pharmacopoeias. The most common techniques for the disintegration test of tablets, coated tablets and capsules are those described in USP XVIII[83] and B.P 1973.[84] The specimen to be tested is contained in a vertical cylindrical tube which is closed at the bottom by a wire cloth and is periodically moved up and down through a liquid medium; the disappearance of larger particles from the wire cloth is taken as criterion of the completeness of disintegration.

Different methods and end-points are used in these pharmacopoeia and this has been severely criticized by many authors among whom are French and his co-workers (1967)[85] who have described it as a classical example of interpharmacopoeial discordance

Moreover for a particular pharmacopoeia, the guidelines in the disintegration test are arbitrary. The choice of water as a disintegrating medium is open to criticism also. Abbott et al (1959)[86] observed that the addition of mucoid substances to the test solution had a marked effect on disintegration time. The selection of 15 minutes for the disintegration time is itself arbitrary and may be unrelated to the rate at which drug is absorbed.[87]

Although a tablet may comply with official requirements, the particles freely passing the mesh of the disintegration tube may remain intact for periods in excess of 15 minutes. In other words the surface areas generated by the tablets having the same disintegration time may not be equal and this is of utmost importance with regards to dissolution. A new disaggregation method, has therefore been proposed by Michael Rubinstein et al.[37] The authors consider that the official disintegration test is only sufficiently sensitive to detect gross differences between tablets. The more sensitive deaggregation test utilizes an automated counter and measures the surface area generated per tablet during dis-

integration.

Langenbucher[88] has discussed means for an improved standardization of the static and dynamic design of disintegration equipment and suggested tighter compendial specifications.

Apart from the inadequacies inherent in the official disintegration test apparatus, the lack of correlations between disintegration times and drug blood levels or *in vivo* activity has been disclosed by several authors.[89,90]

3.5.1 FACTORS AFFECTING DISINTEGRATION TIME

The factors that affect disintegration time of tablets are complex and diversed. They have been divided into namely those variables involved in the disintegration test and those variables involved in the doseage forms i.e. pharmaceutical factors.[91]

VARIABLES INVOLVED IN THE DISINTEGRATION TEST

1. The Apparatus

The type of apparatus will determine the intensity of agitation (rate of stirring) and this is governed by the geometry of the apparatus, the presence or absence of turbulence, use of plastic disks etc. The use of plastic disks stems from the desire to

obtain increased solid-to-solid contact (as in the stomach) and to take care of the problem of tablets, which, because of specific gravity or air imprisonment terd to float in the test fluids. However, the disks may introduce errors or deviations in the test because many tablets may adhere to the rising and falling disks, or adhere to the bottom of stainless steel wire cloth. The result may be a flattening out of the tablet core caused by the constant action of the falling disk on the same point of the tablet surface.

2. The Composition of the test media will determine the pH, ionic strength, viscosity, surface tension etc. of the fluids and each of these properties will affect test results in most cases. Addition of gastric mucin to the disintegrating fluid caused disintegration times to increase and this increase was proportional to the viscosity of the mucin or methylcellulose.[92] It has been shown that acidic solution and simulated gastric, juice resulted in faster disintegration ~~time~~ rate than water.[93]

3. Effect of Temperature

The temperature of the disintegration medium

is usually held constant at 37°C and may therefore not be considered as a variable.

PHARMACEUTICAL FACTORS

The physical properties of the drug, the pharmaceutical adjuvants employed in the tablet formulation and the manufacturing technique, procedure and equipment employed will move often than not affect the disintegration times of tablets.

Surfactants, by their wetting properties will generally enhance water penetration into tablets, by reducing contact angle, and therefore reduce disintegration time although this is not always the case. The diluent may affect the disintegration time.[47]

Binders may have significant effect on disintegration and this effect will depend on the nature of the basic materials, binder concentration and pressure. For example, gum type binders may form a gel barrier around the tablet to inhibit disintegration. If the binder concentration is sufficiently large delayed drug release is obtained.[94]

Lubricants especially the hydrophobic types will lengthen disintegration time if present in the tablet formulation in high proportion. Magnesium stearate

has been found to lengthen disintegration time.[95]

Common et al[38] have determined a critical concentration of starch (as a disintegrant) for lowest disintegration time for tolbutamide tablets contrary to the general assumption that disintegration time decrease with increase in starch concentration.

Compressional force is one of the most important determinants of tablet disintegration time and was first investigated in a quatitative series by Higuchi, T. et al (1953).[59] They investigated the influence of compressional force on the apparent density, porosity, hardness, disintegration time and average particle size of compressed tablets. Among other things, they found that there was a logarithmic relationship between the disintegration time and compressional face. A plot of logerithmic disintegration time versus compressional force was linear with positive slope indicating that disintegration time increased rapidly with little increase in compaction pressure. Manudhane et al (1969)[47] obtained similar results with starches.

The foregoing discussion indicates that the disintegration of tablets is a complex phenomenon

depending on the interactions between all of the variables of formulation and processing, therefore, the making of sweeping generalisations may not only be misleading but hazardous. The routine application of disintegration test and proper evaluation of the data present a simple and useful form of production control. When correlated with *in vivo* test parameters, the disintegration test can be used to predict physiological availability and *in vivo* tablet performance.

3.6 DISSOLUTION TEST

The inherent faults in disintegration test have made the control of the quality of tablets by this parameter rather arbitrary and the prediction of tablet performance unequivocal in many cases.

Implicit in the disintegration test is the assumption that the rate of tablet break up is directly related to the rate of surface area generation of the disintegrating tablet. This assumption can be misleading since for adequate evaluation of surface area, the size and the number of tablet fragments must be determined rather than size alone which is the basis of the official disintegration

test. Moreover disintegration does not imply dissolution of the tablet or even of its active ingredient. It is the realisation of this that has warranted the necessity for design and operation of more informative tests and the development of the dissolution test measurements.

Dissolution is the act of dissolving a process whereby solid particles are brought into solution when in contact with a solvent. The rate of dissolution is the rate of dissolving of the medicament from the intact dosage form or fragments of the disintegrated form. Drug absorption and physiological availability is largely dependent upon having the drug in the dissolved state, therefore dissolution is an important process which a solid dosage form must undergo when administered before it can systemically elicit its pharmacological and/or therapeutic action. There is adequate evidence to conclude that the rate at which a drug dissolves from its intact or fragmented dosage form in the gastrointestinal tract often partially or completely controls therate at which the drug appears in blood i.e. rate of absorption. This is particularly true of drugs which are poorly soluble say

less than 1% in acqueous fluids in the physiological pH range.[96]

THEORY AND KINETICS OF DISSOLUTION

Fig. 5 indicates the processes involved when a tablet or capsule is exposed to fluid under suitable conditions *in vitro* or in the gastrointestinal contents *in vivo* after oral administration. Dissolution takes place from the fine particles as well as the aggregated particles and the intact dosage form. When the dissolution process is much slower than the other processes i.e. disintegration, deaggregation and absorption then dissolution becomes the rate limiting process which controls the absorption rate.

3.6.1 ENERGIES OF DISSOLUTION

The dissolution of a solid immersed in a solvent is considered as a consecutive process:[97]

1. primary surface interaction leading to the production of a new surface at the solid-liquid interface.
2. solvation of the solid at the interface and
3. transfer of the solvated solid into the bulk of the solution.

Solid $\xrightarrow[\Delta E_1]{}$ Solvent .....solid $\xrightarrow[\Delta E_2]{\text{solvation}}$

solvated solid $\xrightarrow[\Delta E_4]{\text{mass transfer}}$ solution

at solid surface

The energy required to produce a new surface or to remove a molecule from the surface of a solid is

$$E_1 = \gamma_{SL} \Delta A \quad \text{.....equation 9}$$

where ΔA represents the exposed surface area of a mole of solid and γ_{SL} is the interfacial tension. According to these authors[97], the heat of solvation consists of two energy terms:

1. ΔE_2, which is the energy required to break the solid lattice energy and is equal to the heat of fusion ΔH_f of the solid.
2. and E_3, energy released or required during the solvation. If the interaction energy between the solvent and solid is greater than that between the solid molecules, energy is released. If the interaction energy is less than that existing

between solid molecules energy is required.

ΔE_3 cannot be determined experimentally but can be calculated from E_1, ΔE_2 and ΔH_s heat of solution.

$$\Delta Hs = \Delta E_s + P\Delta V \quad \text{.....Equation 10.}$$

V is negligible if amount of solid dissolving is small.

$$\therefore \Delta Hs = \Delta E_s = \Delta E_1 + \Delta E_2 + \Delta E_3 \quad \text{.....Equation 11}$$

ΔH_s is the energy difference between two equilibrium states i.e. the energy of the system before and after the solid is dissolved and can be obtained from a Van't Hoff plot of logarithic solubility ~~is~~ versus reciprocal of absolute temperature

Rearranging equation 8 gives

$$\Delta E_3 = \Delta H_s - \Delta E_1 - \Delta E_2 \text{.....Equation 12}$$

If ΔE_3 is positive, energy is required for the solvation step in addition to the heat of solution.

The activation energy of mass transfer or dispersion is the energy required to transfer the solvated solid from interfacial region to the bulk of the

solution, ΔE_4.

ΔE_4 can be determined experimentally from the temperature dependence of the liquid-liquid dispersion rate of the solution into the pure solvent:

$$D = Do\ e^{-\Delta E_4/RT} \quad \text{.....Equation 13}$$

assuming dispersion coefficient is related to temperature like diffusion coefficient

where

D = dispersion coefficient

Do = a constant related to molecular dimensions

ΔE_4 = activation energy for dispersion

R = gas constant

T = Absolute temperature.

The heat of dissolution ΔEd is the energy of activation associated with solid dissolution and is given by

$$\Delta E_d = \Delta E_1 + \Delta E_2 + \Delta E_3 + \Delta E_4 \text{ .....Equation 1}$$

The energy diagram for the dissolution of a solid is shown in Fig. 6.

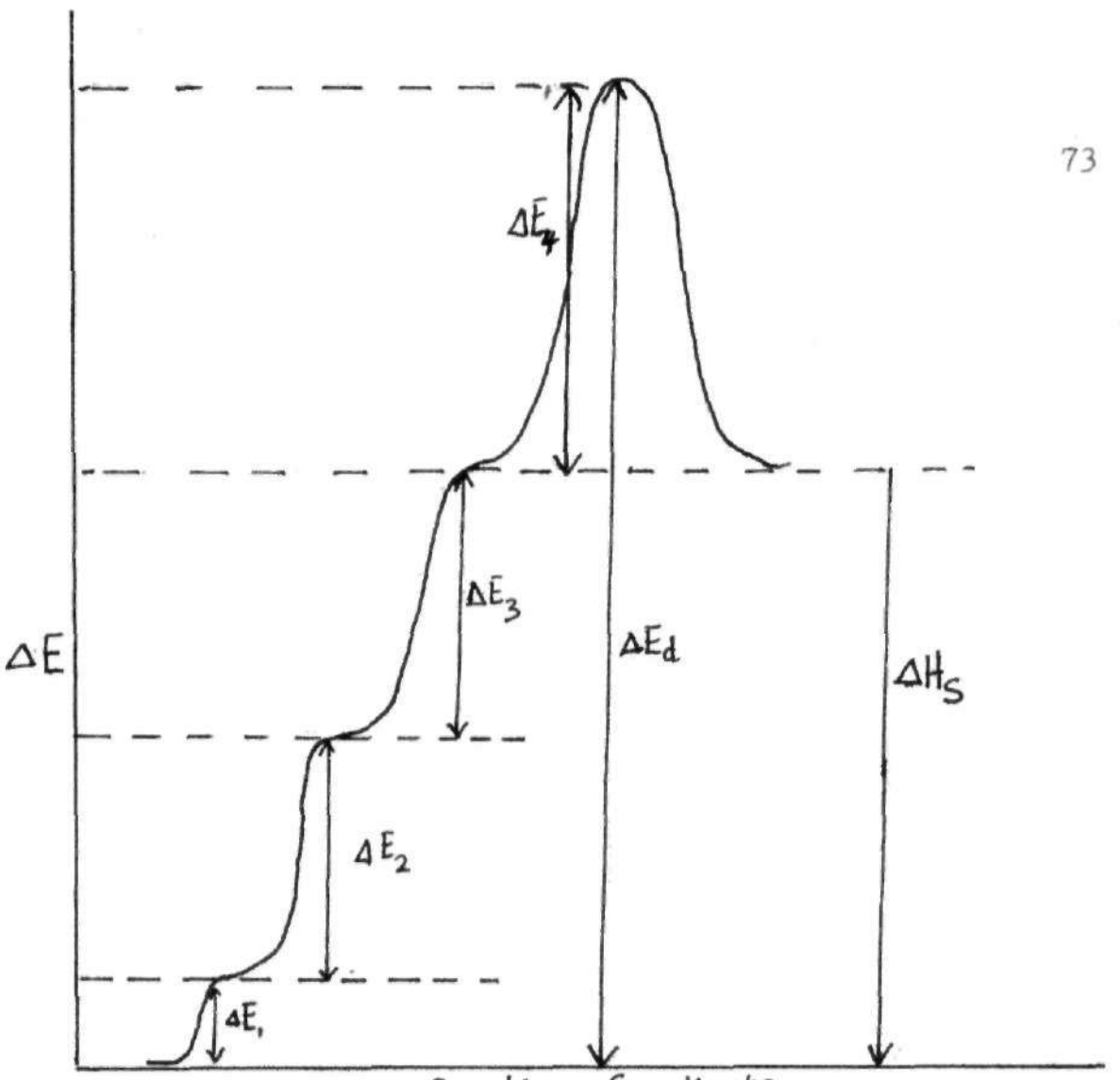


Fig. 6.

Reaction Coordinate

Energy diagram for the dissolution of a solid (David et al. J. Pharm. Sci. 66 1977).

3.6.1b. MECHANISM OF DISSOLUTION

In order for the dissolution of a solid to occur solute must first escape from the surface of the solid into the immediate layer of solvent and then diffuse into the bulk of the solvent. Either of these operations may be the rate limiting one for dissolution. According to Higuchi (1967)[98] there are three processes which, either alone or in combination can be used to describe dissolution rate mechanism.

1. Diffusion Layer Model

This is the simplest approach and proposes that a static film is adjacent to the solid surface area. It is assumed that the reaction at the solid/liquid film interface is rapid, so that the rate of dissolution is governed by the diffusional transport of the solute molecules through the liquid film. Once the solute molecules pass the liquid film/bulk film interface rapid mixing occurs and the concentration gradient is destroyed. See Fig. 7.

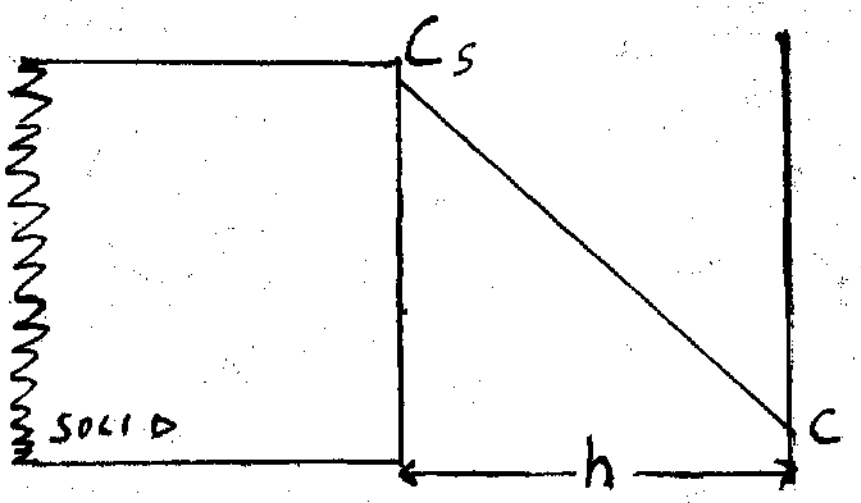


Fig. 7 - h = thickness of diffusion layer.

Cs = solubility of the solid in the liquid.

C = concentration of the solution at any time, t.

When dissolution is studied using rotating disk method, the diffusion layer model is not completely valid, since it does not account for the additional effect of a centrifugal force on diffusion.

2. Interfacial Barrier Model

It is assumed that the reaction at the solid surface is not instantaneous due to a high free energy of activation required; thus process at the

solid/liquid film interface now becomes rate limiting step with respect to the transport process. Fig. 8.

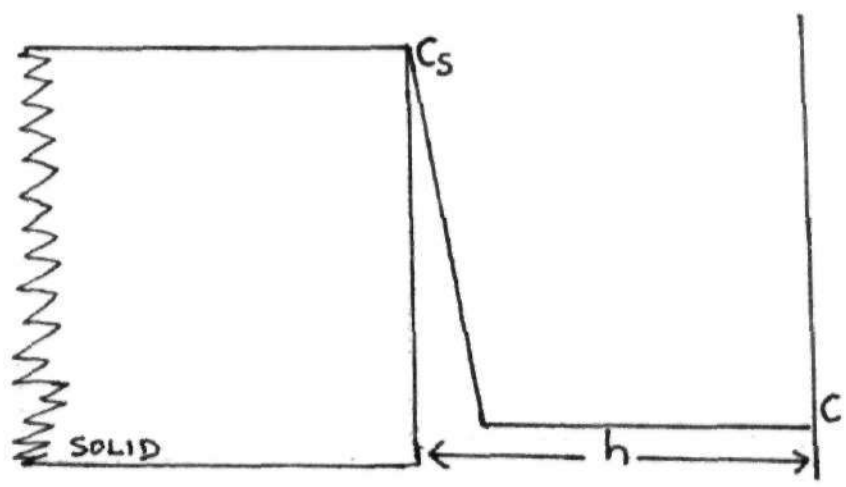


Fig. 8 - Graph of concentration against thickness.

3. Danckwerts' Model

In this model one imagines macroscopic packets of solvent reaching the solid-liquid interface by eddy diffusion in some random fashion. During its residence at the interface the packet is able to absorb solute according to the laws of diffusion. These surface elements are continuously

replaced by new packets of solvent. Assuming the solid surface reaction to be instantaneous, the rate at which this process occurs is related to the solute transport rate. Fig. 9.

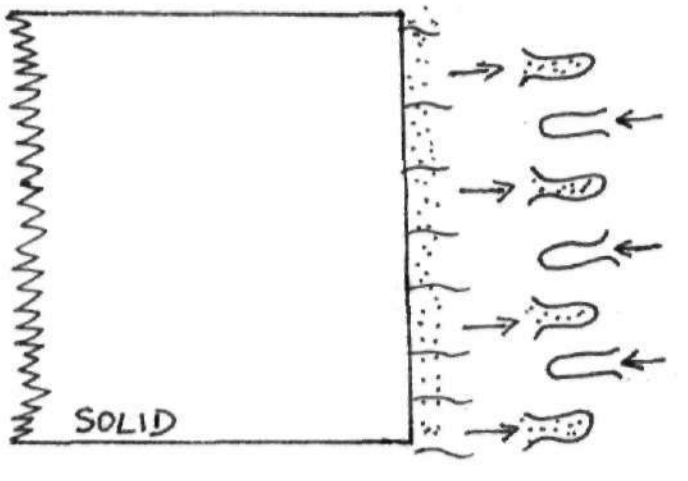


Fig. 9

If a very simple case is considered e.g. a single component non-disintegrating single phase solid dissolving into a chemically non-reactive solvent under mild to hard agitation conditions, then the diffusion layer model predicts that

$$G = \frac{D}{h} (C_S - C) \quad \text{.....Equation 15.}$$

where G is the dissolution rate per unit area of solid,

D is Diffusion coefficient

C_s is solubility of the solid in the liquid and

C is the concentration of the solution at anytime t.

The interfacial barrier model predicts that

$$G = K_1 (C_s - C) \quad \text{.....Equation 16.}$$

where K_1 is the effective interfacial transport rate constant.

Danckwerts' model predicts that

$$G = S^{\frac{1}{2}} D^{\frac{1}{2}} (C_s - C) \quad \text{.....Equation 17.}$$

where S = mean rate at which new surface is produced

The earliest equation expressing dissolution rate in a quantitative manner was proposed by Noyes and Whitney (1897)[99] when studying the rate at which solids dissolve in their own solutions:

$$G = x (C_s - C) \quad \text{.....Equation 18.}$$

where x is a proportionality constant. This equation is usually expanded to give

$$\frac{dw}{dt} = KS (C_s - C) \quad \text{.....Equation 19.}$$

where W is the amount of drug that dissolves in time, t.

dw/dt is the rate at which the substance is dissolving across a surface area, S and $(C_s - C)$ is the concentration gradient between C_s, the concentration of substance in a thin saturated liquid film adjacent to the dissolving surface and C is the concentration in the surrounding bulk medium.

K is a rate constant, incorporating the diffusion coefficient and the film thickness - diffusion barrier.

Equation 19 can be seen to be very closely connected to the diffusion layer model equation (equation 15) and the former is the equation generally used for measuring dissolution rate. This is rather unfortunate as such a model may not be applicable for all physical and chemical conditions of dissolution especially under different conditions of agitation. Thus efforts to achieve in vitro-in vivo correlation may be frustrated because the in vitro test conditions are different to those encountered in vivo.

From the work done on this topic, it would seem that the diffusion layer model is operative when a

stirred dissolution medium flows over the surface of a solid disc of material. Under static conditions Danckwerts' model appears the best explaining the result.

3.6.2 DISSOLUTION APPARATUS

There are a number of reasons for measuring dissolution tests. When a successful model that adequately mimics the in vivo situation has been developed, it is likely that the physico-chemical properties existing in the model may also be of significance in the in vivo process. Dissolution tests can therefore be used for research purposes to elucidate the mechanisms of dissolution and the relative importance of the various variables in the processes. Better understanding of the in vivo environment can be achieved by the design and operation of a well characterised in vitro model.

Secondly, dissolution tests are useful to pinpoint formulations which are unsatisfactory and to guide the pharmaceutical formulator in the preparation of optimum dosage forms of drugs for clinical trial. The screening of potential drugs for their dissolution

and absorption characteristics is an asset of dissolution test.

Furthermore, dissolution tests are used for in-process quality control procedures to ensure that a given pharmaceutical product is uniform from batch to batch.

Lastly, in vitro dissolution rate measurements enable prediction of approximate rates of absorption in vivo and/or availability of drug for absorption in man. For this purpose, the in vitro and in vivo results must have been carefully correlated.

APPARATUS

There is a proliferation of dissolution methods and apparatus in an attempt to characterise the role of dissolution in predicting drug availability. Hersey[100] has commented that "the number of dissolution rate methods described in the literature is almost equal to the number of workers in the field".

The crucial test of any in vitro model is the correlation to the in vivo situation. In the design and use of a reliable in vitro dissolution test model, it is essential that the model is capable of simulating in vivo dissolution process. One such

condition is the maintenance of nearly perfect sink conditions during *in vitro* dissolution rate determinations i.e. the drug concentration in the dissolution medium does not exceed 10 - 20% of drug solubility This condition is required because in a dissolution rate limited drug absorption process, there is no appreciable build-up of drug concentration in the gastro-intestinal fluids which act as infinite sink. It is therefore conceivable that unless similar sink conditions are embodied in the *in vitro* dissolution test model, *in vitro* results will bear little or no relation to the *in vivo* observations.

The various dissolution apparatus in current use, both official and unofficial have been reviewed by Wagner (1971)[96] and Swarbrick (1970)[101]. They range from the Beaker method of Levy and Hayes (1960). Rotating Disk method of the National Formlary to the oscillating tube method.

These methods differ in intensities of agitation of the dissolution medium, geometry of apparatus, surface area generation, sink or non-sink conditions etc. It is interesting to note that no single dissolution apparatus has been designed that completely

simulates the in vivo conditions.

3.6.3 FACTORS THAT AFFECT DISSOLUTION RATE

The factors affecting therate of dissolution of drugs from solid dosage forms in general, and tablets in particular in vivo and in vitro are diversed and interwoven in a complex manner as to require considerable effort to analyse and elucidate. The physicochemical factors that control the rate of dissolution may be deduced from the discussion on dissolution mechanism and equations. These include pH, degree of agitation, temperature, solubility, concentration gradient, composition and viscosity of dissolution medium and its potential for micellar solubilisation drug polymorphism particle size and effective surface area. These factors which can be used to modify drug dissolution have been reviewed by Wurster and Taylor[102] (1965) and by Wood (1967).[103]

Intensity of Agitation, rate and type of flow of fluids and geometrical factors. The constant in the Noyes-Whitney's equation incorporates the diffusion co-efficient and the thickness of the diffusion layer and can be equated to D where D is the diffusion coefficient and h is the thickness of the barrier

layer. Generally the higher the intensity of stirring or agitation of the dissolution medium, the smaller is the thickness of the barrier layer and therefore the greater is the rate of dissolution. This difference in type and intensity of agitation is partly responsible for the discrepancies in the dissolution rate results obtained by research workers. Wurster and Taylor (1965) proposed an equation describing the dependence of dissolution rate on agitation intensity.

$$K = a\,(N)^{b} \quad \text{.....Equation 20}$$

where K = reaction rate, 'a' and 'b' are constants and N = agitation rate. In diffusion controlled processes b = 1.

An increase in agitation intensity (rate of stirring or velocity of the dissolution medium across the surface of the dissolving substance) will increase the dissolution rate of the system in which the transport of solute molecules from the solid-solution interface is wholly or partially the rate determining step. If the rate determing step is the rate of the interfacial reaction, the over-all dissolution rate

will be independent of agitation.[104]

The influence of agitation on the transport process is thought to be a result of its effect on the thickness of the diffusion layer. Levich (1942) calculated that for a disc rotating in a volume where wall effects are minimal, the thickness of the diffusion layer "h", should be related to the angular velocity of the disc "w" by the expression.

$$h = 1.61\ D^{\frac{1}{3}}V^{1/6}w^{-\frac{1}{2}} \quad \text{.....Equation 21.}$$

where D is the solute molecule diffusion coefficient and V is the viscosity. Therefore for laminar flow

$$K_t \quad w^{\frac{1}{2}}$$

where K_t is the rate constant for the transport process = D/h.

For other types of stirring $K_t \propto w^a$ where the value of "a", which has between 0 and 1 depends on type of agitation (laminar or turbulent), the geometries of the stirrer and vessel and the position of the stirrer with respect to the dissolving substance. The authors concluded that the rule that dissolution rates are functions of stirring may not be applicable

to micronised drug particles since a micronised drug particle generally has a radius of approximately 10 µm (10 microns) any stirring (hydrodynamic) effects are felt to be minimal.

Levy et al (1967)[105] reported a study of the dissolution characteristics of two aspirin formulations differing only in drug particle size. Using the beaker method, it was shown that the ratio of the time for dissolution of one third the drug content from each of the tablet batches varies from less than unity at 50 r.p.m to almost 15 at 75 r.p.m. It was only at 55 r.p.m. that the ratio of the two *in vitro* dissolution rates was similar to the ratio of the *in vivo* absorption rates. The need to choose correct agitation rate so as to achieve correlation between *in vivo* and *in vitro* data is thus apparent. By means of X-rays pictures Levy (1963)[106] has concluded that the normal agitation of gastric contents is "mild".

DRUG SOLUBILITY - C_S

This determines the concentration gradient and is the driving force enhancing dissolution rate. The greater the solubility of the drug, C_S, the greater

is the driving force and therefore the higher is the dissolution rate, all other things being equal. Many factors determine the solubility of a drug. Salts of acidic or basic drugs have solubilities different from those of the parent compounds and will therefore show different dissolution rates. The sodium salts of weak acids are able to increase the micro-environmental pH, thereby increasing solubility They re-precipitate in the bulk fluid i.e. gastric environment but in very fine forms causing increased surface area which enhances dissolution.

Crystal form and state of Solvation

Many drugs can exist in two or more crystalline forms with different space-lattice arrangements. This is termed polymorphism. Different polymorphs of a given drug can exhibit marked differences in dissolution rates and therefore in absorption characteristic.

Crystalline and amorphous varieties of drugs generally have different thermodynamic activities. Orally administered crystalline novobiocin yields no detectable plasma levels in dogs while the amorphous form of this antibiotic is absorbed rapidly. This is so because the amorphous novobiocin dissolves

much more rapidly in acqueous media than the crystalline form. Other examples are the chloramphenicol stearate and palmitate.

SURFACE ACTIVE AGENTS

Surface Active Agents at strengths in excess of critical micelle concentration have been used and enhanced dissolution rates have been observed.[107,108] The increased dissolution rate is attributed to the solubilisation of the drug in micelles of the surface active agents at a concentration above critical concentration for the formation of micelles. However, increased dissolution rate in the presence of the surfactants may not always mean increased absorption because some of the drugs may be trapped in the micelles and therefore made unavailable for absorption. Also some surfactants can interfere with the physiology of the gastrointestinal tract e.g. lowering of gastric emptying rate. This will definitely complicate necessity of incorporating surface active agents in the formulations.

SURFACE AREA

The Noyes-Whitney Equation predicts that an increase in the surface area of solid drug in contact with the dissolution medium will enhance dissolution rate. By reducing the particle size of the drug in milling or micronising, the effective surface area is increased and

dissolution rate is enhanced. The superior clinical efficacy and low dosage requirements of the fine particle type of griseofulvin, an artifungal agent have been confirmed. In order to improve dissolution, the micronised material is widely used.[109] Other popular examples are spironolactone, chloramphenicol and sulphadiazine. There are exceptions however, where reduction in particle size is not desirable and this may reduce absorption of the drug. These are drugs which are unstable in the gastric fluid e.g. erythromycin. The degradative effect of the gastric fluids is minimized if dissolution is sufficiently slow so that most of the drug passes through the stomach in the undissolved state.

Enhanced dissolution rates in the presence of surfactants below the critical micelle concentration have been reported and attributed to an increase in effective surface area, resulting from a lowering of interfacial tension and increased wetting of the solid particles.[22,29]

TEMPERATURE

An increase in temperature will increase the rates of both the interfacial reaction and transport

processes. Solubility of some drugs also increase with temperature. For a transport controlled dissolution process, the dependence of K_t, on temperature can be expressed by the Arrhenius equation.

$$K_t = Z_t\, e^{-Et/RT} \quad \text{.....Equation 22.}$$

where K_t = the ratio of dissolution rate and solubility, C_s provided the experimental conditions are such that the concentration of dissolved solute is negligible compared with C_s.

E_t = Activation energy of the transport process.

R = gas constant, T = Absolute Temperature

Z_t = a constant.

PHARMACEUTICAL FACTORS

The biopharmaceutical factors which affect the performance of drugs incorporated in tablet formulating have been discussed previously, the factors which modify disintegration characteristics of tablets will influence in one way or the other, their rates or extent of dissolution.

Compressed tablets are complex multi-component systems in which the formulation adjuvants (fillers,

binders, disintegrants, lubricants etc.) and processing factors (compression pressure, moisture content etc.) can superimpose significant effects on the intrinsic dissolution characteristics of the active ingredients The amount and type of filler or diluent and other adjuvants like flavours and colourants; the type of the tablet manufacture employed i.e. whether dry granulation wet granulation or direct compression; the granule size and size distribution, amount and type of disintegrants and surfactants and methods of incorporating them; compression force and speed of compression - all these factors affect dissolution of tablet. The environmental factors involved in the manufacture of tablets which can affect dissolution rate include the humidity during manufacture, storage conditions of the tablets and age of tablets.

3.6.4 CORRELATION OF IN VIVO DATA WITH IN VITRO RATE OF DISSOLUTION DATA

One of the main reasons for designing and operating in vitro dissolution testing is to predict physiological availability from compressed tablets and therapeutic efficacy of the incorporated drug. Clinical efficacy is very difficult to quantify for two reasons:

Firstly, there is the invariable subject to subject variation, indicating that large scale experiment is required; this is not easy taking cognizance of the fact that human volunteers are used. Secondly, clinical trial is extremely costly and a time consuming exercise. It is therefore desirable to develop *in vitro* tests which can reflect the rate of dissolution-rate limited gastrointestinal absorption.

Due to the proliferation of different dissolution testers, use of different dissolution methods has produced significantly different amounts of drugs dissolved at specified times in a dissolution profile.[110] Despite this apparent setback, many research workers have been able to correlate *in vivo* results with *in vitro* dissolution rate data.

In 1961, Levy[111] reported a linear correlation between the amount of salicylate excreted following the oral administration of two aspirin tablets and the *in vitro* dissolution rate of the same tablets.

A correlation between the dissolution rate of seven oral dosage forms of p-aminosalicylic acid and its sodium salts and biological availability has been established by Middleton et al (1968).[112]

Gilhadi and Weintraub (1970)[113] using rotating flask apparatus were able to demonstrate qualitative correlation between *in vivo* absorption and the *in vitro* dissolution data of aspirin.

Symchowicz and Katchen (1968)[114] were able to show correlation between absorption and dissolution rate following the administration of seven daily 500mg doses of griseofulvin. These authors therefore concluded that the absorption characteristics of griseofulvin preparations can be predicted on the basis of dissolution rate data.[114]

The foregoing summarily indicate that dissolution testers are useful for predictive purposes once they can be correlated with *in vivo* data and as long as such apparatus are relatively cheap and highly reproducible.

4.1 SCOPE OF WORK

The formulation factors which affect the quality of tablets and the physiological availability and therapeutic action of the incorporated drug(s) are static, dynamic, widely diversed and interwoven with a high degree of complexity.

The tablet as a dosage form is a complex multi-component system. It is therefore conceivable that many processing problems and faults will attend its pharmaceutical formulation and manufacture.

A prominent problem in tabletting is the incidence of capping, a situation in which the top of the tablet detaches from the rest of the tablet during or after ejection of the tablet. Associated with capping are lamination and multi-laminations which are cracks in the tablet perpendicular to the compression axis. Paracetamol and phenacetin are examples of drugs which tend to cap when compacted during tabletting. In this work, the factors which affect the compression characteristics of paracetamol tablets were qualitatively and/or quantitatively investigated with a view to exhausting the various causes of tablet capping. Paracetamol is also a common

drug in use. It was selected because of the difficulty encountered in its production at a local manufacturing unit. The steps taken in ameliorating the problem of capping associated with the compression of paracetamol at this unit include the incorporation of a considerably high proportion of microcrystalline cellulose (Avicel PH 101) in the tablet formulation. Considering the fact that microcrystalline cellulose is an extremely expensive tablet adjuvant, it is felt that following this practice in the large scale production of paracetamol tablets may not be economically feasible. An important aim of this project was to design an expedient alternative formulation.

4.2 PHARMACOLOGY OF PARACETAMOL

4.2.1 Chemistry and Relation of Chemical Structure

The structural formulae of major Para-aminophenol phenol derivatives and their inter-relations are depicted in table A

The Antipyretic effect of the compounds resides in the aminobenzene structure, but aniline itself is too toxic for clinical use.

Introduction of other radicals into the OH of para-aminophenol and into the free amino group of aniline reduces toxicity without loss of antipyretic action. Best results are obtained when an alkyl group is substituted in the OH (ethyl in phenacetin) and /or an acid group is introduced in the NH_2 of aniline (acetyl in acetanilid, phenacetin and acetaminophen).

4.2.2 Pharmacological Effects

The main therapeutic effects of phenacetin and acetaminophen are antipyresis and analgesia.

Antipyresis

The antipyretic action resembles that of the salicy-

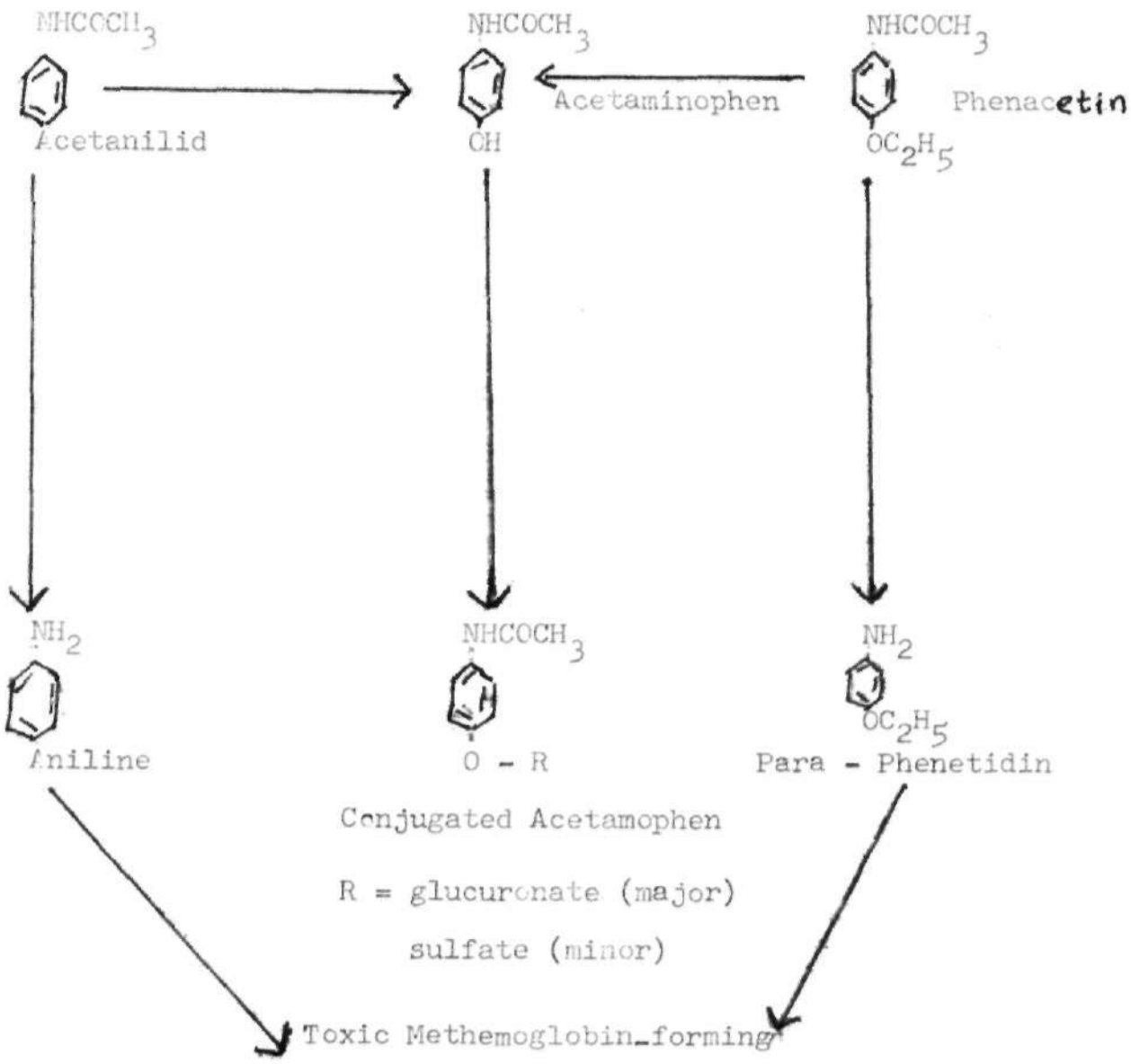


Table A

Structural formulae of Major Para-Aminophenol Dérivatives and their Inter-relations.

lates. Acetaminophen acts on the hypothalamic heat regulating centres of the central nervous system in febrile individuals to bring about a greater dissipation of body heat through cutaneous vasodilation.

Analgesia

It is similar to that of the salicylates. The type of pain relieved is that of moderate intensity, such as usually occurs in headache, dysmenorrhoea and in many muscle joint and peripheral nerve affections.

Intense pain or that arising from smooth muscle spasm in hollow viscera is not alleviated. The analgesic effect of paracetenol is over in about 3 - 4 hours. Paracetamol is devoid of anti-imflammatory and anti-rheumatic properties.

4.2.3 Absorption, Distribution, Biotransformation and Excretion

Paracetamol is a weak acid pKa 9.5, of low molecular weight, soluble in both acqueous and lipid media; these properties indicate that under the conditions found in the gastrointestinal tract, rapid and efficient absorption might be expected.

Paracetamol is metabolized mainly by the hepatic microsomal enzymes. Major pathways of distribution are dipicted in table A . It is rapidly and practically completely absorbed from the gastrointestinal tract. Plasma concentrations reaches a peak in ½ to 1 hour; the plasma half-time is 1 to 3 hours. Acetaminophen is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma protein is variable; 20 - 50% may be bound at the concentrations encountered during acute intoxication.

About 3% of acetaminophen is excreted unchanged in the urine and about 80% is excreted in the urine after conjugation in the liver predominantly with glucuronic acid and to a small extent with sulfuric acid.

A conjugate with cysteine and metabolites produced by hydroxylation and deacetylation have also been detected. The hydroxylated metabolites are responsible for methenoglobin formation, haemolysis of red blood cells and hepatotoxicity.

Toxicity

In recommended therapeutic dosage acetaminophen is usually well tolerated. Skin rash and other allergic

reactions may occur. Neutropenia, pancytopenia and leukopenia may occur in rare cases. The most serious adverse effect of acute overdosage of paracetamol is dose-dependent, potentially fatal hepatic necrosis.

Paracetamol produces less methemoglobin formation and has not been incriminated in the haemolytic reactions but it has caused thrombocytopenia.

4.2.4 THERAPEUTIC USES

Paracetamol is a suitable substitute for aspirin for its analgesic and antipyretic uses in patients who are allergic to aspirin or when aspirin is contraindicated, as in patients with gout or peptic ulcer.

The Adult dose is 0.5g to 1g every 3 or 4 hours to a maximum of 3gm daily.

For children aged upto 1 year, 120mg, 1 to 5 years 250mg and 6 to 12 years, 500 mg.

If ordinary doses are ineffective, larger amounts as a rule do not give relief.

CHAPTER FIVE

MATERIALS AND METHODS OF INVESTIGATION

5.1 MATERIALS

Paracetamol Powder - Quality Control No. PQCU 53550

Paracetamol crystals.

Lactose (Conventional) - Analar analytical Reagent

$C_{12}H_{22}O_{11}.H_2O$: 360.32

BDH chemicals Ltd. Poole England.

Gelatin Powder BDH.

Maize starch BDH laboratory reagents

Magnesium stearate Technical

approximately $(C_{17}H_{35}.COO)_2$ Mg BDH

Tween 80 - (Polyoxyethylene (20) sorbitan mono-oleate)

Glycerin B.P

Polyvinnylpyrollidone PVP - Poland.

Microcrystalline Cellulose (Avicel/Powder PH 101.

Quality Control No. 6223801

5.2.1 PARTICLE SIZE ANALYSIS

The microscopic technique was employed at the first instance; the sieve method was also followed as

a comparative measure. The size distribution of paracetamol powder particles determined by the sieve method was found to be similar to the size distribution by the microscopic technique. Since the sieve technique is shorter and less laborious than the microscopic technique, the former was employed in subsequent analysis.

Sieving tests were performed through a nest of sieves (laboratory test sieves) of standard sizes 180, 250 μ, 355 μ, 500, 600, 710, 1mm 2mm and pan and shaken for 10 minutes using the Endecotts Test Sieve Shaker. The weights of the granules or powder retained on the screens were determined and particle size distributions were calculated as % oversize.

5.2.2 PREPARATION OF GRANULES FOR COMPRESSION

The Wet Granulation method was employed unless otherwise stated.

The batch size was small and therefore mixing was done in a mortar. The "Doubling-up" technique was used in the mixing of drug powders.

BINDER SOLUTIONS

Starch Paste

Starch paste of the appropriate strength was made

in a steam-heated vessel by adding cold distilled water to the starch and heating it under stirring until it became translucent. After cooling the freshly prepared paste was added to the powder mix and Kneaded.

GELATIN SOLUTION

The calculated weight of gelatin was hydrated by adding cold purified water for 15 minutes. It was then warmed in a water bath to dissolve the gelatin and the solution was made to the required weight with enough purified water. The gelatin solution used as the granulating fluid was freshly prepared.

GELATIN SOLUTION AND STARCH

Cold purified water was added to weighed starch. Hot gelatin solution was then added to the cold starch slurry and the mixture was stirred to make a homogeneous solution.

PVP SOLUTION

PVP is readily soluble in water. The weighed PVP was simply dissolved in some cold purified water and the weight of the solution made up to required value with enough cold water.

WET MIXING

The calculated amount of the binder solution was added in portions to the powder mix and kneaded thoroughly in a mortar. The wet mix was passed through a 1.25mm screen in an oscillating granulator (Erweka Type FGS). The granulations were dried in an oven (Gallenkamp size three oven BS with safety thermostat) at 45°C for appropriate number of minutes. To produce good blending and uniform dispersion the lubricants/ disintegrants were passed through a 250 um screen before blending with the granules. Blending was performed in a closed plastic container by gentle rotation or tumbling about different axes.

5.2.3 FLOW TEST

The time required for a given volume (100 ml) of granules to pass through an orifice was automatically determined in a flowability tester (Erweka Type GDT).

5.2.4 COMPRESSION

Tablets were compressed on a power driven single punch (eccentric) tablet press (Erweka Type Eko) using a single set of 12.5mm (½ inch) flat bevelled edge punches and die at a production rate of fourty tablets per minute.

The pressure and die fill settings were held constant for each set of formulations unless otherwise indicated. Tablets were compressed in a controlled humidity area (65 % ± 10 relative humidity) where temperature was maintained at 30°C ± 2°.

5.2.5 QUALITY CONTROL TESTS

DISINTEGRATION TEST

The Disintegration times were determined on a Manesty Disintegration Test Unit (TD - 96T167) USP method No discs were used in any instance and disintegration medium was distilled water thermostated at 37°C ± 1° Times of at least two sets of determinations were averaged.

CRUSHING STRENGTH TEST

Hardness (crushing strength) of at least 10 tablets were measured on an Erweka Hardness tester (Type TB24); the mean values were obtained.

FRIABILITY

10 tablets were subjected to abrasion test in the Roche Friabilator (Erweka Type TA3R) operated at 25 rpm for 4 minutes. Friability was expressed as % weight lost of the original weight of the 10 tablets. In some

cases the time taken for a friable tablet to break into pieces was noted.

CHAPTER SIX

RESULTS AND DEDUCTIONS

6.1 EFFECT OF BINDERS

The ability of some binders at certain concentrations to reduce or eliminate capping and lamination of paracetamol tablets and therefore produce satisfactory tablet was investigated.

Granules of paracetamol were prepared following the formulae shown in Table I. In this experiment the influence of binders e.g. maize starch paste and 5%w/w gelatin solution was compared with an original formula i.e. Formula I.

The granules were tested for particle size distribution, and flow properties. The granules were compressed into tablets after adding 7% microcrystalline cellulose (Avicel PH 101).

The results of the granule tests are shown in Tables 2 and 3. It could be observed that the granules made from 5%w/w gelatin solution contained the highest proportion of fines (indicating inadequate binding) and had the fastest flow rates among the different granules.

The incorporation of Avicel considerably improved the rates of granules especially those that had longer flow times before the addition of Avicel. This confirms the good lubricating property associated with microcrystalline cellulose.

TABLE X FORMULATIONS USED FOR THE PREPARATION OF PARACETAMOL TABLETS

	* Unit Size	I	II	III
Paracetamol Powder	35kg	250g	250g	250g
Maize starch	2.1kg	15g	15g	15g
Maize starch	1.3kg	9.3g	-	-
Gelatin solution (5%w/w)	11.7kg	83.5g	100g	-
Maize Starch Paste (10%w/w)	-	-	-	100g
Maize Starch	2.0kg	14.3g	14.3g	14.3g
Avicel	2.8kg	20g	20g	20g

* Large Scale batch of Formula I used at a manufacturing Unit.

TABLE 2 PARTICLE SIZE ANALYSIS OF PARACETAMOL GRANULES MADE WITH DIFFERENT BINDERS

FORMULA		SIZE OF SCREEN												% < 180um	% < 250 ("FINES")
		1000um	710	600	500	355	250	180	150	125	106	75	53		
I	Amount Retained on Screen	0.0953	5.7622	4.2486	5.1529	7.2075	7.0483	4.3135	5.5056	-	-	-	-	14.00	24.97
	%	0.24	14.65	10.80	13.10	18.32	17.92	10.97	14.00	-	-	-	-		
II	Amount Retained on Screen	0.0110	2.4046	3.9484	4.667	6.8491	6.8974	5.5411	6.5355	2.6156	0.8702	0.4739	-	23.89	37.61
	%	0.028	6.06	9.94	11.75	17.24	17.37	13.72	13.93	6.58	2.19	1.19	-		
III	Amount Retained on Screen	0.1600	6.1531	5.5815	5.3411	6.6621	6.3508	3.5800	5.7853	-	-	-	-	14.60	23.64
	%	0.40	15.53	14.09	13.48	16.82	16.03	9.04	14.6	-	-	-	-		

TABLE 3 EFFECT OF AVICEL ON FLOW RATES OF PARACETAMOL GRANULES PREPARED FROM DIFFERENT BINDERS

FORMULA	MEAN TIME OF FLOW, SECONDS			
	WITHOUT AVICEL		WITH 37% AVICEL	
I	6.30, 7.71, 7.52, 6.04, 6.14	AVERAGE 6.74	3.62, 3.68, 3.58, 3.60	AVERAGE 3.62
II	4.11, 3.74, 3.72, 3.51, 3.78	3.77	3.54 3.64, 3.66, 3.68	3.63
III	5.18, 7.24, 7.12, 7.12, 6.98	6.73	3.48, 3.85, 3.70 3.50	3.63

Table 4 shows the compression characteristics of the paracetamol tablets produced from different binders. It is observed that all tablets were firm and had no tendency towards capping. They are therefore referred to as "satisfactory" or "good" tablets.

An important observation is that the incorporation of maize starch with gelatin solution caused the tablets prepared at the same level of compression pressure to be relatively very hard indicating good binding capacity of the combination binding solution.

In addition, all tablets disintegrated within one minute this reflects the powerful disintegrating property of microcrystalline cellulose. An additional investigation was carried out to find the actual role of Avicel in the paracetamol formulation. The mixture of Avicel and maize starch used in the final mixing operation of the granules was replaced by the commonly used mixture containing 0.5% magnesium stecrate and 2% maize starch. The granules were compressed.

The tablets capped and laminated in the three cases. Tablets produced using starch paste as the binder (Formula III) capped only at high compression pressures. At lower

TABLE 4 COMPRESSION CHARACTERISTICS OF PARACETAMOL TABLETS PREPARED FROM DIFFERENT BINDERS USING AVICEL AS LUBRICANT

FORMULA	Calculated mean weight per tablet	Practical mean weight	Hardness (Kg)	Disintegration Time	REMARKS
I	626mg	615mg	11.1	60 Seconds	"Good" tablets No tendency to cap
II	610mg	600	5.8	53 Seconds	-do-
III	620mg	610	5.7	38 Seconds	"

pressures, fairly good tablets were formed (hardness 6.0kg), but the disintegration time was prolonged (> 15 minutes).

It may be concluded from this investigation that Avicel at the concentration used acted as a lubricant as well as a binder. Also it is indicated that good paracetamol tablets can be produced without necessarily incorporating Avicel.

6.2 USE OF PARACETAMOL CRYSTALS

To find if paracetamol crystals would give better properties of granules and tablets than the paracetamol powder, paracetamol crystals were granulated with 5% gelatin solution following Formula II of Table I. The properties of the compressed tablets are depicted in Table 5.

While the tablets were equally hard or firm when compared with those made from paracetamol powder, the friability of the tablets produced from paracetamol crystals was very high since an average of one tablet broke in the Roche drum during the friability test.

This experiment suggests that the use of paracetamol crystals may not solve the problems associated with the compression of paracetamol tablets especially capping and lamination.

TABLE 5 COMPRESSION CHARACTERISTICS OF PARACETAMOL TABLETS PREPARED FROM PARACETOL CRYSTALS

AVERAGE WEIGHT OF TABLET	DISINTEGRATION TIME	HARDNESS	FRIABILITY
605mg	55 Seconds	7.0Kg	A tablet broke in the friabilator during the friability test

6.3 DIRECT COMPRESSION OF PARACETAMOL TABLETS

An attempt was made to prepare paracetamol tablets by the direct compression and pre-compression methods, using paracetamol powder and crystals and varying concentrations of lactose as shown in Table 6. 20% Avicel was blended with each formulation. The ingredients were mixed thoroughly and compressed. The properties of the tablets are shown in Table 7. Tablets were generally soft i.e. low hardness, and exceedingly friable, resulting in severe capping of the tablets. Increasing the proportion of lactose in the formulation did not improve the strength and capping of the tablets. This indicates that lactose, in the dry state has little or no effect on the consolidation of paracetamol.

Only in one case (Formula B) were the tablets fairly hard (crushing strength = 5kg), but all tablets disintegrated within 5 minutes.

To prepare paracetamol tablets by the pre-compression method, friable tablets produced from the direct compression investigation were used as slugs and crushed in the comminuting mill. They were separated into fractions. The fraction $\geq 250\ \mu m$ was compressed. All tablets were unsatisfactory by virtue of their low hardness and high friability.

TABLE 5 FORMULATIONS USED FOR THE DIRECT COMPRESSION OF PARACETAMOL POWDER AND CRYSTALS

FORMULA	A	B	C	D	E	F
Paracetamol Powder	250g	-	250	-	-	250g
Paracetamol Crystal	-	250g	-	250g	250g	-
Lactose	-	-	15g	15g	25g	25g
Avicel	50g	50g	-	-	-	-
Magnesium Stearate	-	-	0.5%	0.5%	0.5%	0.5%

TABLE 7 COMPRESSION CHARACTERISTICS OF PARACETAMOL TABLETS PREPARED FROM POWDER AND CRYSTALS USING DIFFERENT PROPORTIONS OF LACTOSE

FORMULA	DISINTEGRATION TIME	HARDNESS	FRIABILITY	REMARKS
A	1min. 22seconds	Very low < 2kg	Very high	Soft tablets
B	2 - 2½ minutes	5Kg	0.5 - 0.8%	Good tablets
C	2 - 3 minutes	Very low	Capping	Bad tablets
D	2½ - 3½ minutes	Very low	Very high	Bad tablets
E	4 - 5 minutes	4Kg	Very high	Bad tablets
F	3 minutes	3Kg	Very high	Bad tablets

Thus the preparation of paracetamol tablets by direct compression or pre-compression method is not potentially feasible with the use of ordinary tablet excipients.

6.4 EFFECT OF CONCENTRATION OF BINDER

As the direct compression results were not satisfactory the wet granulation method was reverted to. The following formulation was prepared.

a) Paracetamol powder - 250g
   Maize starch - 15g

b) Gelatin solution - 70g

c) Magnesium stearate - 0.5% weight of granules
   Maize starch - 2% weight of granules.

The effect of the concentration of binder solution i.e. gelatin solution on the properties of paracetamol granules and tablets was investigated using 2%w/w, 5%w/w and 10%w/w gelatin solution as granulating fluid. The results of the analysis of granules are shown in Table 8. Increasing the concentration of gelatin solution from 2% to 10% increased considerably the extent of wetting and binding of the granules and reduced the percentage of fines. Thus the higher the concentration of a solution of binding agent the greater is its adhesive and

TABLE 8 EFFECT OF THE CONCENTRATION OF GELATIN SOLUTION (BINDER) ON SOME PROPERTIES OF GRANULES

% OF GELATIN SOLUTION w/w	AVERAGE FLOW TIME THROUGH AN ORIFICE (SEC.)	PARTICLE SIZE ANALYSIS								% FINES
			SCREEN SIZE um							
			1000	710	600	500	350	250	180	<100	
2	6.20	Amount Retained on Screen gm.	0.3024	1.4664	2.5908	3.6734	7.7869	0.5269	4.7575	3.0104	34.40
		%	0.81	3.95	6.98	9.90	20.98	22.97	12.82	21.58	
5	3.77	Amount Retained on Screen gm.	0.0110	2.4046	3.9484	4.667	6.8491	6.8974	5.5411	10.5052	37.61
		%	0.028	6.06	9,94	11.75	17.24	17.37	13.72	23.89	
10	4.10	Amount Retained on Screen gm.	10.0744	6.5542	4.1542	2.8942	3.8442	3.7108	2.3466	4.0705	22.31
		%	26.20	17.05	10.80	7.53	10.13	9.65	6.10	12.66	

binding property. An Examination of Table 8 shows that the granules prepared from 5% gelatin solution had the fastest flow rate and contained the highest proportion of fines. There is therefore an apparent relationship between the proportion of fines in a granulation and the rate of flow of granules within the various orifices of the tabletting press This will be of utmost importance in weight variation and/or drug content tests.

The tablets produced from all granules showed severe capping and were therefore unsatisfactory.

6.5 EFFECT OF TWEEN 80 (NON-IONIC SURFACTANT)

Tween 80 is a non-ionic surfactant and was incorporated in the gelatin formulation in various concentrations (Table 9) to determine its effect on the wetting characteristics of the powder mix and strength of the resulting granules.

The calculated amount of Tween 80 was added to freshly prepared gelatin solution.

Results indicated that at all the concentrations of Tween 80 used there was better wetting of the mass and an easier wet sieving operation. However, after drying the granules broke down producing fine particles. The compression of these granules gave very soft tablets with high friability and

TABLE 9 FORMULATIONS CONTAINING VARYING PROPORTIONS OF TWEEN 80 USED IN THE PREPARATION OF PARACETAMOL GRANULES

FORMULA	A	B	C	D
Paracetamol Powder	250g	250g	250g	250g
Maize Starch	15g	15g	15g	15g
Gelatin Solution 5%w/w	99.9g	99.5g	99.0g	100g
Tween 80	0.1g	0.5g	1.0g	-
Maize Starch	2% granular wt.	2% granular wt.	2% granular wt.	2% granular wt.
Magnesium Stearate	0.5% granular wt.	0.5%	0.5%	0.5%

tendency towards capping.

It is concluded that the incorporation of Tween 80 in paracetamol formulations may not serve any important or useful purpose.

6.6 USE OF POLYVINYLPYRROLIDONE (PVP)

PVP is a polymer which is very soluble in water, insoluble in acetone and can be used as a binder in solution. The strength of binding solution used for most drugs is in the range of 0.5 - 5% although stronger concentrations are necessary for other materials.

PVP solution was used as the binder instead of gelatin solution according to the following formula:

a)	Paracetamol powder	-	250g
	Maize starch	-	15g
b)	PVP solution	-	40g
c)	Magnesium stearate	-	0.5%
	Maize starch	-	2%.

The mixture of powders was wetted and kneeded using 5% and 10% solutions of PVP in two batches. After drying the granules, maize starch and magnesium stearate were added and the granules were compressed into tablets. The granules were not separated into size fractions before compressing and the

characteristics of the tablets produced are depicted in Table 10.

Tablets produced from 5% PVP solution were very soft and highly friable indicating inadequate binding. Those prepared from 10% PVP solution were harder and less friable and therefore the latter formulation is potentially better. Increasing the concentration of binder solution (PVP) increased the strength of the granules and tablets of paracetamol due to an increase in the binding power of the granulating fluid.

By compressing granules of size $\geq$ 250 µm better tablets were produced with reduced friability especially the tablets produced from 10% PVP as shown in Table 11.

This suggests that the particle size of the granules compressed has an effect on the consolidation and friability of paracetamol tablets.

6.7 EFFECT OF LACTOSE ON THE CONSOLIDATION OF PARACETAMOL

Lactose powder was incorporated in the paracetamol formulations in different proportions as shown in Table 12. Gelatin solution (5%) was used as the granulating fluid. The tablet quality parameters were tested and the result are shown in Table 13.

Lactose makes paracetamol tablets harder, the extent of

TABLE 10 COMPRESSION CHARACTERISTICS OF PARACETAMOL TABLETS PREPARED FROM DIFFERENT CONCENTRATIONS OF PVP(BINDER)

FORMULA	HARDNESS	FRIABILITY	REMARKS
5% PVP. 40 gm	< 3.0Kg.	Capping at all levels of compression	Inadequate Binding
10% PVP	7.2Kg.	2 - 4% (Reduced tendency to cap)	Potentially Better tablets

TABLE 11 COMPRESSION CHARACTERISTICS OF PARACETAMOL TABLETS USING PVP AS BINDER AND GRANULES ≥ 250 um

Concentration of PVP Solution % w/w	Hardness Kg		Friability
7.5	Compression Setting at 7	5.1	Most tablets broke
	Setting at 7½	6.0	high incidence of capping.
10	Setting at 6½	5.3	1.4%.
	Setting at 7	7.9	5.2%

TABLE 12 PARACETAMOL FORMULATIONS CONTAINING VARIOUS CONCENTRATIONS OF LACTOSE

FORMULATION	I	II	III	IV	V
Paracetamol Powder	125g	125g	125g	125g	125g
Lactose	2.5g	5.0g	7.5g	12.5g	12.5g
Maize Starch	5.0g	2.0g	-	-	5.0g
Gelatin Solution 5%w/w	35g	35g	35g	35g	35g
Maize Starch	2% weight of granules	2% weight of granules	2% weight of granules	2% weight of granules	2% weight of granules
Magnesium Stearate	0.5% weight of granules	0.5% weight of granules	0.5% weight of granules	0.5% weight of granules	0.5% weight of granules

TABLE 13 COMPRESSION CHARACTERISTICS OF PARACETAMOL TABLETS CONTAINING DIFFERENT PROPORTIONS OF LACTOSE

FORMULATION	HARDNESS Kg	DISINTEGRATION Time	FRIABILITY
I	5.3	5 minutes	Severe Capping
II	4.6	6 minutes	Severe Capping
III	5.9	7 minutes	Capping
IV	10Kg.	> 60 minutes	reduced tendency to cap
V	9.5	< 15 minutes	No capping

the effect being proportional to the concentration of lactose in the formulation. Lactose (10%) reduced the tendency for the tablets to cap but caused prolongation of disintegration times. Lactose has good flow properties and deforms under stress thereby leading to the formation of "cold bonds". This enhances low permeability of the formed tablets and may explain the extended disintegration time.

Intragranular incorporation of maize starch (4% the weight of paracetamol powder) plus the normal 2% extragranular starch used in this investigation) reduced the disintegration time to acceptable values.

6.8 EFFECT OF PARTICLE SIZE

Formula V of Table 12 gave the best tablets among formulations containing lactose. It was therefore repeated for the investigation of effect of particle size as the compression characteristics of paracetamol tablets.

Three size fractions of granules were used viz, fraction < 250 µm, fraction ≥ 250 µm and fraction containing particules of different sizes. Table 14 indicates the properties of tablets prepared from granules of different sizes and size distributions. Generally only the tablets produced from granules ≥ 250 µm were satisfactory. Tablets produced from other

TABLE 14 EFFECT OF PARTICLE SIZE ON COMPRESSION OF PARACETAMOL

PARTICLE SIZE	HARDNESS Kg.	DISINTEGRATION Time minutes	R e m a r k s
Whole	10	8	The tablets broke
<250 um	9.3	<10	The tablets broke
>250 um	7.1kg	<15	None of the tablets broke

sizes of granules showed marked capping the defect being worst with tablets prepared from granules < 250 µm.

There were no significant differences in the disintegration times and crushing strengths of the tablets.

From the results obtained from earlier investigations and this experiment on particle size, it is suggested that to obtain satisfactory paracetamol tablets, only paracetamol granules ≥ 250 um should be compressed.

6.9 EFFECT OF MOISTURE CONTENT

The moisture content of granulations very often modifies the consolidation of granules and the quality of the resulting tablets.

To determine the effect of moisture on the consolidation of paracetamol tablets the following formula was used.

	I	II
Paracetamol powder	125g	125g
Maize Starch	7.5g	7.5g
Gelatin Solution (5%)	35g	-
Gelatin Solution (6%)	-	35g
Magnesium stearate	0.5%	0.5%
Maize Starch	2%	2%

After mixing the powders, the binder solution was

incorporated and the wet mass was passed through 1.25mm screen. The wet granules were dried and passed through 1.00 mm screen. Granules that were required to contain high moisture content were dried for shorter time and vice versa. In addition the granules were separated into three size fractions as in the previous investigations.

Granules were compressed immediately after taking samples for moisture content determination to avoid loss or absorption of moisture and consequent discrepancies in moisture contents.

Table 15 depicts the properties of tablets prepared from granules of different physical parameters.

Generally tablets produced using 6% gelatin solution were better than those produced from 5% gelatin solution; this may derive from the greater binding capacity of 6% gelatin solution.

Tablets prepared from granules of size < 250 µm showed non - tolerable degree of capping irrespective of moisture content. The compression of granules containing different sizes of particles gave tablets which had high friability and were prone to capping.

Tablets prepared from granules of size ≥ 250 um were satisfactory in some cases and unsatisfactory in others depending on the moisture contents. Generally paracetamol

TABLE 15 EFFECTS OF PARTICLE SIZE AND MOISTURE CONTENT OF GRANULES ON THE COMPRESSION OF PARACETAMOL

	Moisture Content %w/w	Particle size um	Average weight of each tablet (Mg)	Hardness(Kg)	Disintegration Time	Friability	Remarks
FORMULA I 5%w/w Gelatin Solution	2	Whole	555	4	2' 30"	Capping	Very friable tablets
		< 250	560	3½	2' 20"		
		> 250	550	4	2' 35"		
	3	Whole	554	6	2' 42"	1.2%	Capping
		< 250	550	5	2' 40"	1.3%	Severe Capping
		> 250	550	8	2' 40"	1.2%	No tendency to cap
	6	Whole	553	6½	2' 30"	1.4	Capping
		< 250	550	5	2' 40"	1.4	Severe Capping
		> 250	545	8	2' 25"	1.3%	No tendency to cap
	10	Whole	550	4	2'	Breaking of Tablets	Extremely soft tablets
		< 250	555	2	1' 50"		
		> 250	550	3	2' 20"		
FORMULA II 6% w/w Gelatin Solution	2	Whole	560	5	3'	Capping	Unsatisfactory tablets
		< 250	565	5	2' 40"	Severe Capping	Unsatisfactory tablets
		> 250	560	6	2' 40"	Capping	Unsatisfactory tablets
	3	Whole	557	6	3' 20"	1.2%	Tendency to cap
		< 250	560	6	3' 10"	2.0%	Tendency to cap
		> 250	565	8½	3' 30"	0.7%	Good tablets
	6	Whole	560	6½	3'	1.1%	High friability
		< 250	563	6	2' 45"	1.3%	High friability
		> 250	555	9	3' 10"	0.6%	Good tablets
	10	Whole	565	4	1' 37"	2%	Extremely Soft
		< 250	560	3	1' 32"	Capping	and friable
		> 250	560	5	1' 40"	1.5%	tablets

tablets were good and satisfactory when the granules had a moisture content within the range of 3 - 6%w/w. Below a moisture content of 3%w/w, tablets were highly friable, whereas above 10% the tablets were very soft and friable. In the latter case, there was hardening of the tablet after 24 hours of storage and this is attributed to moisture loss.

CHAPTER SEVEN

GENERAL DISCUSSION AND CONCLUSIONS

7.1 COMPRESSION PATTERNS OF PHARMACEUTICAL MATERIALS

It is well known that pharmaceutical materials like phenacetin and paracetamol on compression tend to cap and laminate and therefore are very difficult to compress into firm tablets.

Leigh, Carless and Brutt (1967)[117] have studied the compression characteristics of some pharmaceutical materials. Using a commercial single punch tablet machine instrumented with strain gauges to monitor the forces simultaneously on the upper punch and the die wall, the authors were able to study the complete pressure cycles of a number of pharmaceutical materials at various levels of compression. The materials were sucrose granules and crystals, acetaminophen granules, aspirin crystals and sodium chloride crystals. It has been found that these materials conform to three different types of compression pattern. Importantly materials which laminate or cap on compression behave like a Mohr's body e.g. acetaminophen granules without binder. During the compaction of a Mohr's body, after yield has taken place, the shearing stress in a plane of slip depends on the value of the

normal stress acting in the same plane. In other words, the yield stress in shear is a function of the normal stress on the plane of shear.

Materials which form "good" tablets e.g. acetaminophen granulated with 3% PVP are thought to have a compression pattern similar to that of a body with constant yield stress i.e. the yield stress (during deformation) is independent of the magnitude of the principal stresses to which it is subjected. Although the tablet press used in this investigation was not instrumented to monitor pressure cycles, it could be inferred from previous investigations that the ability of some binders at certain concentrations to reduce or eliminate capping and lamination of paracetamol tablets stems from their ability to modify the interparticulate bonding of the particles during compaction. The net result is a change from the compression pattern of the Mohr's body type to the constant yield in shear pattern.

7.2 BINDERS AND BINDER CONCENTRATION

The pharmaceutical factors which affect the compression characteristics of paracetamol tablets are numerous and intricately interwoven. In general the flow rates

of granulations were fast and uniform. This property promotes good uniformity of tablet weight and/or active ingredient. The incorporation of a strong glidant might therefore be unnecessary. It is of course considered that flow rates of granulations can vary considerably depending upon the degree of wetting and upon the granulating agent used. For example Gold et al (1968)[118] have reported that granulating agents increased in effectiveness with respect to flow rate enhancement of lactose granulations in the order 10% starch, 2% methyl cellulose, 10% PVP, 10% gelatin and 10% methylcellulose.

The nature of excipients in a tablet formulation can modify the compression characteristic of the drug. Binders in particular behave differently during compaction and influence the consolidation of granules. It seems that to obtain satisfactory paracetamol tablets, high concentration of binding agents must be used. This has been the trend in overcoming the capping which frequently occurs in tablets during compression.[119]

Hardwood and Pilpel (1968)[120] have observed that granule strength in a particular size group depends on the PVP content when used as a granulating fluid, and attri-

buted the increased granule strength to increased viscosity. It is necessary for granules to have sufficient strength to withstand handling and mixing, but is generally thought that they should break down on compaction in the die.[121] Healey, Rubinstein and Walters (1974)[122] have studied the mechanical properties of some binders used in tabletting by determining their tensile strengths. Gelatin was found to possess the highest values of Young's elastic modulus and tensile strength although it was brittle. The high elasticity and low plasticity may resist deformation and the brittleness may make tablets containing gelatin relatively friable. Generally paracetamol tablets produced from gelatin are hard and this is attributed to its high tensile strength. PVP was found to have a low value of modulus and tensile strength and therefore it has high deformability which will aid consolidation during compaction. Starch on the other hand is intermediately tough and ductile. Addition of starch to gelatin solution should improve the binding property of gelatin. It is therefore interesting to note that paracetamol tablets produced from gelatin-starch combination did not show an observable relative decrease in capping. However

from analysis of the results of the investigation of binders, it could be concluded that subject to the careful control of moisture content and other granule parameters, either 6% gelatin solution or 10% PVP solution could be used to produce satisfactory paracetamol tablets by the wet granulation method. By viture of the higher cost of PVP, gelatin may be preferred for large scale manufacture of paracetamol tablets. Generally the higher the concentration of a solution of binding agent the greater is its adhesive and binding property. In a given formulation the appropriate strength of the solution should be empirically determined. Use of extremely high concentrations of binder may result in excessive wetting and the screen may merely act as an extruder during wet sieving. On drying, the granules produced from such wet mass will be extremely hard and may contain high proportion of fines. Furthermore, the frequent compression of such formulation will accelerate the premature wear of the sets of punches and dies.

7.3 PARACETAMOL CRYSTALS AND DIRECT COMPRESSION

The substitution of paracetamol powder with paracetamol crystals did not alleviate the problem of capping

and lamination of the tablets prepared by the wet granulation method. However, better tablets were produced from the crystals when the direct compression method was utilized. A recent trend in pharmaceutical technology is to use excipients that permit making tablets by direct compression. The direct compression technique in many instances affords the distinct advantages of lower costs and improved product stability compared to tablets prepared by slugging or wet granulation. The use of direct compression paracetamol which is reputed to contain 4% of gelatin hydrolysate is a pointer in this direction.[123] Gelatin hydrolysate is obtained by hydrolysing high quality grade gelatin under carefully controlled conditions. Its incorporation with paracetamol crystals has been found to produce satisfactory tablets. Gelatin hydrolysate can also be used as a binding solution where upon there is increased adhesiveness attributed to the increased power of penetration of its solution with decreasing viscosity and particle size.[124] E. Shotton and B.A. Obiorah (1974)[125] have reported that satisfactory i.e. non-capping tablets were produced from paracetamol formulations containing 4% BYCO (gelatin hydrolysate) whereas

crystals without additives gave unsatisfactory tablets. The mixtures containing the hydrolysate and moisture (2%) gave the strongest tablets. The presence of moisture was thought to have activated the binding properties of gelatin hydrolysate when used as a water-soluble binder. The authors concluded that the inclusion of the hydrolysate in a formulation could be useful in converting material which is only tabletted with difficulty into a directly compressible form.

7.4 TWEEN 80

Paracetamol granules which contained Tween 80, on drying had excess fines although they were easy to wet-sieve. The control formulation which contained no surfactant produced granules which had less fines. The ability of Tween 80 to enhance easier wet sieving may be attributed to increased granule porosity. The addition of Tween 80 to aqueous PVP solution (binder solution for lithium carbonate crystals) has been reported and the effect of surface tension on the tensile strength of liquid bridges joining particles in moist aggregates has been considered.[126] The authors also reported that the addition of Tween 80 to PVP solution did not have a

significant effect on granule strength. In this investigation the addition of Tween 80 to paracetamol formulations has been shown to be unnecessary.

7.5 LACTOSE

Lactose powder had little or no effect on the consolidation of paracetamol when incorporated in the direct compression method. When lactose was added to paracetamol powder and then subjected to wet granulation, the tablets produced from the compression of such granules were hard and elicited less capping; there was however a prolongated disintegration time. Lactose makes paracetamol tablets harder due to the formation of "cold bonds". Shotton and Obiorah (1975)[127] found materials such as lactose show plastic flow from the pressure profiles give correspondingly good tablets due to a greater contact area being formed, whereas materials in which recovery was mainly elastic produced weak tablets. In the manufacture of paracetamol tablets, the incorporation of lactose in the formulation may be indicated where the use of a particular binding agent may not impart sufficient cohesive strength to the tablets. Otherwise lactose can be eliminated from the formula since its presence necessi-

tates the use of high proportion of starch as a disintegrant.

7.6 PARTICLE SIZE

Generally paracetamol tablets produced from small granules, irrespective of nature of binder showed extreme capping immediately after ejection from the die. Granules ≥ 250 um when compressed gave tablets which had fairly good surface strength and showed little or no capping. From the analysis of the results of investigations of particle size of paracetamol granules, it may be concluded that the presence of fines (particles < 250 um) does not favour the good compression of paracetamol tablets.

The particle size of a drug is not a new consideration. Down through the ages the state of sub-division of a drug was and still is a primary factor to be considered in the preparation of aesthetical and stable dosage forms. In the preparation of tablets the effect which particle size of the granules or powder being compressed will have on compression characteristics of the tablets depends mainly on the nature and proportions of the drug and excipients.

Alan and Sciarra[128] using placebo, sulfadiazine

(poorly soluble drug) and sodium saccharin (very soluble drug) tablets investigated the relationship and effect of granule size upon the physical properties of granules and the tablets produced from those granules. In the range of the granule size studied 250 μ - 2380 μ - compression range - they determined that the physical properties of the granules were interrelated and for the most part related to the granule size. They found among other things, that both the degree of granule friability and flowability increased as the size of the granule decreased and there was no defined or observable relationship between granule size and the hardness of the corresponding tablets. Forlano and Chavkin[129] reported a definite relationship among particle size, disintegration time and degree of capping. Using sodium bicarbonate granulation, tablets compressed with granules in the 8 - 40 mesh range exhibited a rise in disintegration time and a decrease in capping. Tablets compressed using granules of 60 mesh or smaller exhibited a decreased disintegration time and an increase in capping. It was found that the optimum granule size of the granulation they used was in the range 16 - 60 mesh.

On the other hand Carless and Leigh (1974)[130] found that finer sucrose particles had greater yield pressure and higher residual die wall pressure than the bigger particles. The increased transmission of smaller particles was attributed to:

a) more numerous point contacts which increase the total contact areas, facilitating transmission of applied forces.

b) increased shear strength at the die wall. Increased residual die wall pressure in finer particles was explained on increased number of junctions in the fine powder which resulted in more cohesive structure that would relax to a lesser extent than that formed from coarser particles. Also the increased transmission of the finer particles resulted in higher frictional forces at the die wall which would restrain recovery of the compact in the die.

Long[131] considered that separation took place within the die when the axial load was removed by axial relaxation of the material in order to relieve the residual pressure exerted by the die wall. As the compact is pushed out of the die, radial relaxation also occurs and

may cause a series of radial cracks. With substances exhibiting a weak particle-particle bond (e.g. Aspirin) the radial stress may be relieved by the elastic recovery of the particles axially by the partial separation of the bonding surfaces. However, with a strong particle-particle bond (e.g. paracetamol) elastic recovery in the axial direction may cause capping. At a given pressure the use of smaller particles increases the chances of capping. This may result from a high elastic recovery of the material due to larger number of particle-particle contacts which carry the load.

Long and Alderton (1960)[132] demonstrated that trapped gas could produce cracks. During a rapid compression cycle using punches and dies with a small clearance air may be entrapped within the compact and considerable pressures built up. This may accentuate the axial separation of the tablet when faults arise especially if the surface of the tablet is sealed by shear at the die wall and punch faces. Since the number of pores and therefore the volume of air entrapped increases with decrease in particle size, the presence of excessive fines in the tablet formulations may aggravate the problem of capping. However, air entrapment

is not the sole cause of capping since hexamine tablets which capped readily at atmospheric pressure still capped when compression was repeated under vacuum (6mm, pressure). The weight variation may exceed limits if the granulation contains an excess of large granules and may laminate if the particles are too fine. A specification relating to the range of granule size could be maintained as a guide and control during the manufacture of tablets. In this investigation, the compaction of granules of size $\geq$ 250 u has been found to give satisfactory tablets. The proportion of"fines" i.e. particles $<$ 250 um should be maintained at very low level. "Fines" are necessary in granulations because they serve as glidants filling void spaces between coarser particles. While 10 - 20% fines has occasionally been set as the maximum amount permissible, it has been pointed out that there is no general limit to the amount of fines that can be present in a granulation and that excessive fines should be determined for each formulation.[133] Lamination of tablets could result from the difference in particle size of the drug and tablet matrix (excipients), vibration in the hopper tending to cause separation. In the case of paracetamol formulatio

the amount of fines produced as a result of the incorporation of extragranular disintegrant and lubricant appears to be the maximum proportion that favours the production of satisfactory tablets.

7.7 MOISTURE CONTENT

The moisture content of granulations may affect granule consolidation and the quality of tablets produced from them. In this investigation paracetamol granules which had moisture content within the range of 3 - 6%w/w were found to give good tablets using 5% and 6% gelatin solution as binder. Granules which had < 3% moisture content gave extremely friable and capping tablets. High moisture contents above 6%w/w produced extremely soft tablets which picked at the punch surfaces during tabletting; the latter tablets hardened within 48 hours of storage.

The effect of moisture on the compression characteristics of drugs has been investigated by several workers.

Esezobo and Pilpel (1976)[134] using uncoated oxytetracycline tablets have found that the tensile strength, disintegration and dissolution times all

increase with the gelatin content and maximum tensile strength occurs when the tablets contain between 2.5 and 4.0%w/w of moisture. They suggested that at relatively low packing fractions, any moisture present is in the form of pendular, funicular or capillary bonds and contributes immensely to the tensile strength of the mass. At higher moisture content the water begins to act as a lubricant or dispersion medium reducing the cohesive forces between the particles, and hence the tensile strength of the mass.

Earlier Shotton and Rees (1966)[135] have attributed the reduction in crushing strengths of tablets at high moisture content to the hydrodynamic effect of moisture. Hydrodynamic lubricants are able to reduce friction by forming a finite layer of low shear strength which prevents contact between adjacent surfaces.

During the initial stage of compaction, consolidation occurs mainly by the relative movement of intact particles. J. E. Rees (1970)[136] has demonstrated that at low pressure, the relative volume of material containing moisture is much lower than that of a dry compact. He suggested that the formation of temporary struts, columns and vaults is

increase with the gelatin content and maximum tensile strength occurs when the tablets contain between 2.5 and 4.5%w/w of moisture. They suggested that at relatively low packing fractions, any moisture present is in the form of pendular, funicular or capillary bonds and contributes immensely to the tensile strength of the mass. At higher moisture content the water begins to act as a lubricant or dispersion medium reducing the cohesive forces between the particles, and hence the tensile strength of the mass.

Earlier Shotton and Rees (1966)[135] have attributed the reduction in crushing strengths of tablets at high moisture content to the hydrodynamic effect of moisture. Hydrodynamic lubricants are able to reduce friction by forming a finite layer of low shear strength which prevents contact between adjacent surfaces.

During the initial stage of compaction, consolidation occurs mainly by the relative movement of intact particles. J. E. Rees (1970)[136] has demonstrated that at low pressure, the relative volume of material containing moisture is much lower than that of a dry compact. He suggested that the formation of temporary struts, columns and vaults is

minimized by a lubricant effect of moisture at the die wall and interparticulate boundaries.

Groenwold et al (1972)[137] have determined that breakage of tablets during ejection is accompanied by high ejection forces. This can therefore contribute to the problem of capping. The reduced tendency to cap in the presence of moisture is attributed to a decrease in the tablet ejection force with increasing moisture content.

Bowder and Taylor (1954)[138] have proposed that moisture is a lubricant and Rumpf (1958)[139] has stated that interparticulate distance is reduced in the presence of adsorbed film and this can be used to explain the experimental observations.

The crushing strengths of tablets especially those having high moisture content (> 6%) increased considerably within 48 hours of storage and this applied to all tablets produced from small and big granules. Loss of moisture may be responsible for hardening of tablets since the soluble components can recrystallise and form a harder compact.

Lazarus and Lachman (1966)[140] reported that the surface of potassium chloride crystals was altered by

moisture due to surface dissolution and recrystallisation on drying. Obiorah and Shotton (1976)[141] have pointed out that this may play but a small part in the improved consolidation of paracetamol crystals as the solubility is low. However, this may be sufficient to produce clean surfaces for binding and surface tension forces will bring crystals into close proximity. Also Chowhan et al (1978)[142] have attributed the tablet hardness increase induced by partial moisture loss to re-crystallisation of water soluble components or a water soluble drug that is expelled into void spaces on compression - formation of bridges. The extent of hardness increase is thought to depend on the specific combination of the drug and excipients and their physical properties such as aqueous solubility, crystalline properties and hygroscopicity. Recrystallisation of soluble components may reinforce strength of compact but several dissolution recrystallisation of solids in a compact can produce an increased number of discontinuities which can propagate failure of the compact and will contribute appreciably to a pronounced decrease in strength. In conclusion, moisture improves consolidation by virtue of its hydrodynamic lubricating property

but high moisture content may have a deleterious effect in producing soft tablets. It should be recognized therefore that the granulation moisture content should be adjusted to an optimal range to obtain desirable compaction properties. The increased tendency to cap of paracetamol tablets compressed during the dry season in a local laboratory may be attributed to low relative humidity and loss of moisture from the granulation beyond good consolidation values.

7.8 COMPRESSION PRESSURE AND CAPPING OF PARACETAMOL TABLETS

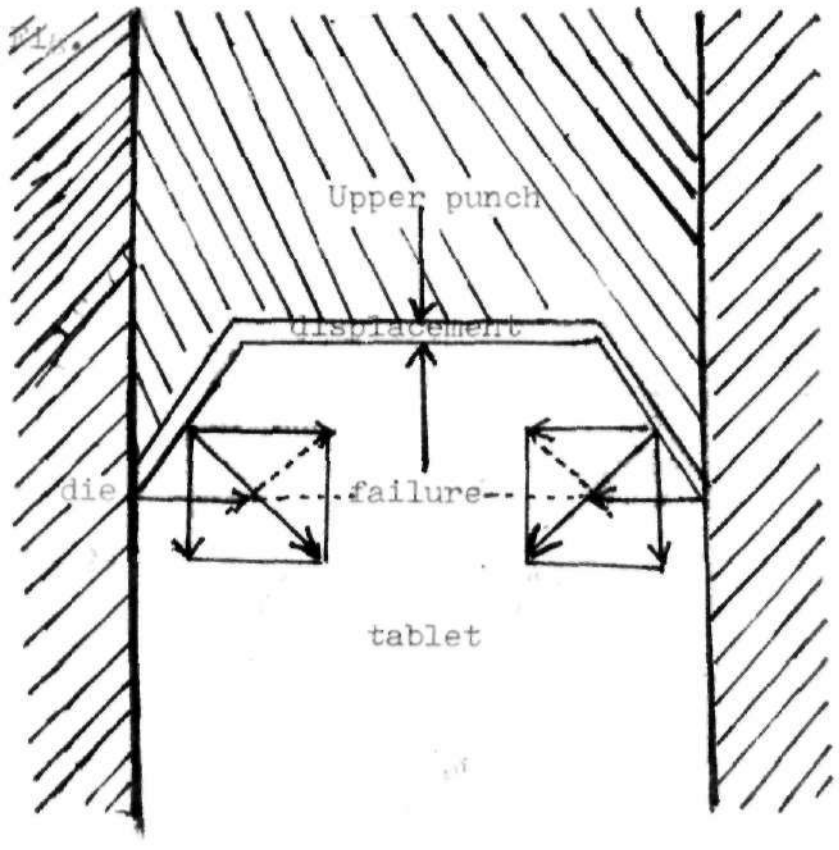
In this work the behaviour of paracetamol granules has been shown though qualitatively to be very sensitive to the level of compression pressure at which they are compacted. Generally boarderline formulations and tablets which had tendency to cap or laminate capped severely at higher compression pressures. At the last stage of compression, the extent to which the compact is consolidated depends on the elastic compressibility of the material. Materials that are elastic will laminate at high compression pressure due to strong axial relaxation of the material after the removal of applied load. Thus compression beyond the maximum density of the compact serves

only to increase the elastic strains already present in the compact. It is therefore extremely important to empirically determine the minimum compression pressure necessary to give satisfactory tablets. Apart from the adverse effect of extreme compression pressure on tabletting, high pressures may also form extremely hard tablets which may have prolonged disintegration and dissolution times due to reduced porosity and retardation of rate of penetration of water.

7.9 SHAPE OF PUNCHES

Another factor which should be considered in tabletting difficult pharmaceutical materials is the shape of the set of punches. Seth (1954)[143] stated that deeply biconvex tablets show a greater tendency toward capping because the applied pressure is not uniformly distributed throughout the tablet granulation in the die cavity during compression. As a result, the more deeply biconvex shaped tablets are in general relatively weaker in strength than the flat shaped or conventional biconvex tablets. Because of the convexity of the tablet, the pressures reaching the centre of the tablet at its maximum diameter would be expected to be minimum. It

It has also been demonstrated that tablets with an upper bevelled edge capped at high applied forces unlike those prepared with a flat upper face.[131] An explanation may be that interparticulate bonds formed during compression are broken down at the end of the compression cycle by high radial forces in the bevelled top caused by the displacement of the bevelled edge on the upper punch. See



Capping of tablet compressed with bevel-edged upper punch

7.10 SINGLE PUNCH AND ROTARY TABLET PRESSES

The type of tablet press used in compressing granules is also a matter of consideration i.e. whether it is a single punch (eccentric) or a rotary machine. In a single punch machine, the lower punch is stationary and only the upper punch exerts the pressure at the time of maximum compression. In a rotary press, both the upper and the lower punches approach one another simultaneously up to the point of maximum pressure. Consequently the strains induced in tablets produced on a single punch machine would be different than those obtained from a rotary press. Since there is a gentle squeezing action of the tablet during compression in a rotary press, it is conceivable that tablets which laminate on a single punch machine may be firm and satisfactory when compressed on a rotary press; this will be more important when compressing small particles where lamination and capping may result from air entrappment.

7.11 MECHANICAL HYSTERESIS, DELAYED ELASTICITY AND CAPPING OF PARACETAMOL TABLETS

It is not uncommon to observe tablets which do not laminate or cap immediately after ejection from the die

crack and break on storage. This is attributed to creep or delayed elasticity phenomenon. In the case of non-linear elastic materials, only a proportion of the energy stored during compression is recoverable, the remainder being dissipated as internal friction; this is referred to as mechanical hysterisis. D.N. Travers et al[144] have studied the thermoelastic properties of preformed compacts. They showed that paracetamol and vitamin yeast powder which show a marked tendency to crack on storage have appreciable internal friction and wide mechanical hysterisis. This enhances large residual strains in the compact (caused by compression) which disappear slowly after compression and during storage. This delayed elasticity is known as thermo-elastic-after-effect. Raymond Myers and J.S. Long[145] have described creep in quantitative terms - the response (strain) of the elastic component of a material is considered to be instantaneous. It may be delayed or retarded by the viscous component. For this case, the time for the response (strain) to reach $\frac{1}{e}$ of the initial strain is a characteristic parameter and is called the retardation time. This slower response in the presence of large viscous component is

known as creep or delayed elasticity. The creep strain developed at constant stress plotted against the time yields the creep curve. On removal of the stress the transient recovery may be partial or complete; that part of the recovery which is retarded by a viscous component is known as the elastic-after-effect. According to Long's (1960)[131] theory of capping, laminar stress concentrations are produced as the tablet is ejected from a die and it is possible that high creep rates could precipitate cracking at these sites. Thus tablet formulations should be designed such that tablet produced do not laminate or cap not only immediately after manufacture but on storage for a specified period of time. In this investigation, paracetamol tablets designated as good or satisfactory were still firm and intact after nine months of storage.

REFERENCES

1. BURLINSON, H.,
   "Tablets and Tabletting" London: Heinemann Medical (1968).

2. "REMINGTON PHARMACEUTICAL SCIENCES"
   Mack Publishing Company, Easton, PA, 1970, P. 1655

3. "THE THEORY AND PRACTICE OF INDUSTRIAL PHARMACY".
   Edi. Leon Lachman, Herbert, A. Lierberman and Joseph L. Kanig; 2nd Edition; Lea and Febiger, Philadelphia, 1976; P. 321.

4. WAGNER, J.,
   "Biopharmaceutics and relevant pharmacokinetics"; Drug Intelligence Publications, Hamilton, Illinois 62341, 1st Edition, 1971, P.2.

5. KOVAC, G.M.,
   Drug Cosmetic Ind. 91, 171 (1962).

6. BROWNLEY, C.A. and LACHMAN, L.
   J. Pharm. Sci. 52, 86 (1963).

7. BROWNLEY, C.A. and LACHMAN, L.
   J. Pharm. Sci. 53 452, (1964).

8. J. COOPER,
   "Recent Advances in Pharmaceutical Sciences" Vol.3 Academic New York, 1971, P.6.

9. HIRSCHORN, O.J. and KORN-BLUM, S.S. (1971)
   J. Pharm. Sci. 60 445.

10. SHALANGWA, E.A. (1974)

B.Sc. Thesis. "The Effect of Concentration of Diluents on the Dissolution Rates of Sodium Salicylate and Salicylic Acid Tablets", Ahmadu Bello University, Zaria.

11. BOGER, W.P. and GAVIN, J.J.

Evaluation of Tetracycline Preparations. New Eng. J. Med. 261 827 (1959).

12. JACOB, J.T. and PLEIN, E.M. (1968).

J. Pharm. Sci. 57 802 - 805.

13. SAKR, A.M., KASSEM, A.A., AZIZ, S.A.A. and SHALABY, A.H.(1972

Manuf. Chem. and Aerosol News. (Nov.) 38 - 44.

14. COOPER, J. and PASQUALE, D. (1958)

Pharm. J. 181 397.

15. GUMSEL, W.C. and Others (1970).

"The Theory and Practice of Industrial Pharmacy" Edited by Lachman, L. Lee and Febiger, Philadelphia 305 - 345.

16. GOLD, G., R.N. DUVALL., B.T. PALERMO and J.G. SLATER;

J. Pharm. Sci. 57 667 (1968).

17. JONES, T.M. and PILPEL, N.J.

J. Pharm. and Pharmadol. 18 429 (1966).

18. GOLD, G. et al.

J. Pharm. Sci. 55, 1133 (1966).

19. GOLD, G. et al.

J. Pharm. Sci. 55 1291 (1966).

20. TREVOR, M. JONES,
J. Pharm. Sci. 57 2015 (1968).

21. KING, E.R. (1970).
"Remington's Pharmaceutical Sciences" 14th Edition, Easton, Pennsylvania Mack Publishing Company, P. 1652

22. LEVY, G. and GUMTOW, R. (1963).
J. Pharm. Sci. 52 1139 - 1144.

23. GANDERTON, D. (1969).
J. Pharm. Pharmacol. 21 Suppl. 95 - 185.

24. CARMAN, P.C. (1941).
Soil Sci. 52 1 - 14.

25. STRICKLAND, W.A. Jr., HIGUCHI, T., and BUSSE, L.W.
J. Pharm. Sci. 49 35 (1960).

26. SONG-LING, LIN., JOHANNE MENIG and LEON LACHMAN,
J. Pharm. Sci. 57 2143 (1968).

27. ROLLER, P. (1931).
J. Phy. Chem. 35, 1133.

28. ADAMSON, A.W. (1960),
"Physical Chemistry of Surfaces", Interscience New York, N.Y. P. 356.

29. FINHOLT, P. and SOLVANG, S. (1968).
J. Pharm. Sci. 57 1322.

30. COOPER, J. and PASQUALE, D. (1958).
Pharm. J. 181 397.

31. FEINSTENWARD,BARTILUCCI, A.
J. Pharm. Sci. (1966) 55 332.

32. TAGHI, AFAKOUGH, NORMAN, F. BILLUPS and ROBERT, W. SAGER.
J. Pharm. Sci. 52 700 (1963).

33. BURLINSON, H. and PICKERING, C.
J. Pharm. and Pharmacol. 2 630 (1950).

34. H.C. MITAL and J. OCHRAN.
Pharma. Acta. Helmet. 43, 493 (1968).

35. K.A. KHAN and C.T. RHODES,
Pharma. Acta Helmet 47 153, (1972).

36. E. SHOTTON and G.S. LEONARD.
J. Pharm. Pharmacol. 24, 798 (1972).

37. MICHAEL, H. RUBINSTEIN and DOROTHY, M. BODEY;
J. Pharm. Sci. 65 1749 (1976).

38. K.C. COMMONS, A. BERGEN and G.C. WALKER,
J. Pharm. Sci. 57, 1253 (1968).

39. H.M. GROSS and C.H. BECKER,
J. Pharm. Sci. 41 157 (1952).

40. CRISAFI, R.C. and BECKER, C.H.
J. Am. Pharm. Assoc., Sci. Ed. 47, 363 (1958).

41. KERR, R.W.,
"Chemistry and Industry of Starch" 2nd Ed. Academic Press Inc. New York N.Y. (1950), P. 10.

42. CURLIN, L.C.,
J. Am. Pharm. Assoc. Sci. Ed. 44, 16 (1955).

43. SAUL, S. KORNBLUM and SAMULE, B. STOOPAK.
J. Pharm. Sci. 62, 43 (1973).

44. N.R. PATEL and R.E. HOPPONEN,
J. Pharm. Sci.. 55, 1065 (1966).

45. H. SPRENGLER and E. SCHENKER,
Pharm. Acta Helv, 12 337 (1937).

46. W. LOWENTHAL and JOHN, H. WOOD.
J. Pharm. Sci. 61 455 (1972).

47. K.S. MANUDHANE, A.M. CONTRACTOR, H.Y. KIM and R.F. SHANGRAW.
J. Pharm. Sci. 58 616 (1969).

48. K.A. KHAN and C.T. RHODES,
Pharm. Act. Helv. 50 4 (1975).

49. URBANYI, T., SWARTZ, C.J. and LACHMAN, L.
J. Am. Pharm. Assoc., Sci. Ed. 49 344 (1960).

50. LACHMAN, L., WEINSTEIN, S., SWARTZ, C.J. URBANYI, T. and COOPER, J. (1961).
J. Pharm. Sci. 50 142.

51. GUMSEL, W.C. and Others (1970).
"The Theory and Practice of Industrial Pharmacy"
Ed. Lachman, L., Lee and Febiger, Philadelphia, P.331.

52. N.A. ARMSTRONG,and G.A. MARCH.
J. Pharm. Sci. 65 198 - 204 (1976).

53. R.E. KING
in "Remington Pharmaceutical Sciences" Mack Publishi... Company, Easton Pa, 1970, P. 1653.

54. HIGUCHI, T., ARNOLD, R.D., TUCKER, S.J. and BUSSE, L.W.(19[illegible])
J. Am. Pharm. Assoc., Sci. Ed. 41 93.

55. RUMPF., H. (1962)
"Agglomeration" New York, John Wiley and Sons.

56. TRAIN, D. and LEWIS, C. (1962)
Trans. Int. Chem. Eng. 40 235 - 240.

57. JACOB VARSANO and LEON LACHMAN
J. Pharm. Sci. 55 1128 (1966).

58. JONES, W.D.,
"Fundamental Principles of Powder Metallurgy", E. Arnold Ltd. London, England, (1960) P. 245.

59. HIGUCHIT, RAO, A.N., BUSSE, L.W. and SWINTOSKY, J.V.(1953).
J. Am. Pharm. Assoc., Sci. Ed. 43 344.

60. TRAIN, D. (1956).
J. Pharm. and Pharmacol. 8 745.

61a. SHOTTON, E. and GANDERTON, D. (1960).
J. Pharm. and Pharmacol. 12 87T.

61b. SHOTTON, E. and GANDERTON, D.
J. Pharm. and Pharmacol. 12 Suppl. 93T. (1960).

62. SHOTTON, E. and GANDERTON, D. (1961).
J. Pharm. and Pharmacol. 13 Suppl. 144T.

63. MICHAEL, H. RUBINSTEIN,
J. Pharm. Sci. 65 376 (1976).

64. R.W. HECKEL,
Trans. Metall. Soc. A.I.M.E. 221 671, 1001 (1961).

65. YORK, P. and PILPEL, N. (1972).
J. Pharm. and Pharmacol. 24 47P - 56P.

66. STOTNICKY, J. (1953).
Czech. J. Phys. 3 225 - 230.

67. E. SHOTTON, J.A. HERSEY and P.E. WRAY
in "The Theory and Practice of Industrial Pharmacy" 2nd Edition. Edited by Leon Lachman, Herbert, A. Lierberman and Joseph L. Kanig Lea and Febiger, Philadelphia 1976, Page 298.

68. C. FUHRER.
Processes Involved in Tablet Formation. Paper on Formulation and Preparation of Dosage forms - Proceedings of the 37th International Congress of Pharmaceutical Sciences of F.I.P. held in the Hague, The Netherlands, 1977, Editor J. Polderman, Publi. Elsevier/North-Holland Biomedical Press Amsterdam, New-York and Oxford, 1977.

69. KNOECHEL, E.L., SPERRY, C.C. and LINTNER, C.J. (1967).
J. Pharm. Sci. 56 109, 116.

70. GOODHART, F.W., MAYORGA, G., MILLS, M.N. and NINGER, F.C.(19
J. Pharm. Sci. 57 1770.

71. SHAXBY, J.H. and EVANS, J.C.
Trans. Faraday Soc. 19, 60, (1923).

72. TRAIN, D. (1957).
Trans. Instn. Chem. Engrs. 35 258.

73. BEYER, W.F. (1966).
J. Pharm. Sci. 55 200.

74. REHM, C. (1968).
Ann. N.Y. Acad. Sci. 153 (2) P. 640.

75. DAVID, B. BROOK and KEITH MARSHALL (1968).
J. Pharm. Sci. 57 481.

76. RITSCHEL, W.A., SKINNER, F.S. and SCHLUMPF, R. (1969).
Pharm. Act. Helv. 44 547.

77. JOHN, G. WAGNER.
"Biopharmaceutics and Relevant Pharmacokinetics"
Drug Intelligence Publications, Hamilton Illinois
62341 1st Edition, 1971, P. 66.

78. BERGMAN, L.A. and BANDELIN, F.J.
J. Pharm. Sci. 54 445 (1965).

79. "THE NATIONAL FORMULARY"
13th Ed. Mack Publishing Company - Easton Pa 1970,
P. 878.

80. E.J. MIDDLETON, J.M. DAVIES and A.B. MORRISON,
J. Pharm. Sci. 53 1378 (1964).

81. CHAPMAN, D.G., CRISAFIO, R. and CAMPBELL, J.A. (1954).
J. Am. Pharm. Assoc., Sci. Ed. 43 297.

82. MORRISON, A.B., PERUSSE, C.P. and CAMPBELL, J.A.
J. Pharm. Sci. 51 623 (1962).

83. "THE UNITED STATES PHARMACOPOEIA"
ed. 18 P. 932 (1970).

84. BRITISH PHARMACOPOEIA, P. A131 (1973).

85. FRENCH, W.N. MATSUI, F., COOKS, D., LEVI, L. (1967).
J. Pharm. Sci. 56 1622.

86. ABBOTT, D.D., PACKMAN, E.W., REES, E.W. and HARRISON, J.W. (1959).
J. Am. Pharm. Assoc., Sci. Ed. 48, 19.

87. HARTLEY, F. (1950).
J. Pharm. Pharmacol. 2 628.

88. LANGENBUCHER, F:
Improved Standards for The Disintegration Test of Soli Products., Drug Development Communications 1(4), 287 - 301 (1974 - 75).

89. W.M. GRIM and W.E. GORDON Jr.
Amer. J. Pharm. 124 410 (1952).

90. G. LEVY,
J. Pharm. Sci. 50 388 (1961).

91. WAGNER, JOHN.
"Biopharmaceutics and Relevant Pharmacokinetics"
Drug Intelligence Publications, Hamilton Illinois 62341, 1st Edition 1971, P. 89.

92. K. MUNZEL and T. KUHN.
Pharm. Acta Helv. 37 509 (1962).

93. G. HECHT and C.L. HUYCK.
J. Pharm. Sci. 53 112 (1964).

94. H.E. HUBER, L.B. DALE and G.L. CHRISTENSON.
J. Pharm. Sci. 55 974 (1966).

95. O. ALPAR, J.J. DEER, J.A. HERSEY and E. SHOTTON,
J. Pharm. Pharmacol. 21 65 (1969).

96. WAGNER, J.G.
"Biopharmaceutics and Relevant Pharmacokinetics" Drug Intelligence Publications Hamilton Illinois 62341, 1st Edition 1971, P. 98.

97. DAVID, C. HSIA, CHONG-KOOK KIM and DANE. O. KILDSIG.
J. Pharm. Sci. 66 961 (1977).

98. HIGUCHI, W.I.
J. Pharm. Sci. 56 315 (1967).

99. NOYES, A.A. and WHITNEY, W.R.
J. Am. Chem. Soc. 19 930 - 934 (1897).

100. J.A. HERSEY,
Mfg. Chem. Aerosol News. 1969, 32.

101. SWARBRICK, J.
Current Concepts in pharmaceutical Sciences: Biopharmaceutics. Lead and Febiger. Philadelphia, 1970, 276 - 288.

102. WURSTER, D.E. and TAYLOR, P.W. (1965).
J. Pharm. Sci. 54 169.

103. WOOD, J.H. (1967).
Pharm. Acta. Helv. 42 129.

104. A.G. MITCHELL and DOROTHY J. SAVILLE
J. Pharm. Pharmacol. 21 29 (1969).

105. LEVY et al (1967).
J. Pharm. Sci. 56, 1365

106. LEVY, G. (1963).
J. Pharm. Sci. 52 1039.

107. SINGH, P., DESAI, S.J., FLANAGAN, D.R., SIMONELLI, A.P. HIGUCHI, W.I. (1968).
J. Pharm. Sci. 57 959.

108. TAYLOR, P.W. and WURSTER, D.E.
J. Pharm. Sci. 54 1654 (1965).

109. B.A. MATTHEWS and C.T. RHODES.
J. Pharm. Sci. 56 838 (1967).

110. T.E. NEEDLAM and L.A. LUZZI.
J. Pharm. Sci. 63 925 (1974).

111. LEVY, G. (1961).
J. Pharm. Sci. 50 388.

112. MIDDLETON, E.J., CHANG, H.S. and COLE, D. (1968).
Can. J. Pharm. Sci. 3 97.

113. GILBADI, M. and WEINTRAUB, H. (1970).
J. Pharm. Sci. 59 725.

114. SYMCHOWICZ, S. and KATCHEN, B. (1968).
J. Pharm. Sci. 57 1383.

115. MARTINDALE THE EXTRA PHARMACOPOEIA
26th Edition Edited by Norman, W. Blacow Assistant Editor Ainley Wade, 1972, London The Pharmaceutical Press, P. 245.

116. "THE PHARMACOLOGICAL BASIS OF THERAPEUTICS"
5th Edition. Editors: Louis S. Goodman and Alfre Gilman, MacMillan Publishing Co. Inc. New York 343 - 347.

117. S. LEIGH, J.E. CARLESS and B.W. BURT.
J. Pharm. Sci. 56 888 (1967).

118. G. GOLD et al (1968).
J. Pharm. Sci. 57, 667.

119. ELOWE, L.N., HIGUCHI, T. and BUSSE, L.W. (1954).
J. Am. Pharm. Assoc. Sci. Ed. 43 718 - 721.

120. GOLD, G; DUVALL, R.N., PALERMO, B.T. and HURTLE, R.L.
J. Pharm. Sci. 60 922 (1971).

121. C.F. HARDWOOD and N. PILPEL
J. Pharm. Sci. 57 478 (1968).

122. J.N. HEALEY, M.H. RUBINSTEIN and V. WALTERS
J. Pharm. and Pharmac. (1974) 26 Suppl. 41P - 46P.

123. B.A. OBIORAH and E. SHOTTON
J. Pharm. and Pharmac. (1976) 28 629 - 632.

124. ROSSER KISSLING et al (1917)
"The Adhesiveness of Gelatin". Chemical Abstracts 19, 10644.

125. E. SHOTTON and B.A. OBIORAH (1974)
J. Pharm. and Pharmac. 26 Suppl. 108P.

126. HEALY J.N.C., J.F. HUMPHREYS and V. WALTERS (1972).
J. Pharm. and Pharmac. 24 Supp. 121P.

127. SHOTTON,E. and OBIORAH, B.A. (1975)
J. Pharm. Sci. 64 1213 - 1216.

128. ALAN M. MARKS and JOHN S. SCIARRA
J. Pharm. Sci. 57, 497 (1968).

129. FORLANO, A.J. and S. LEIGH (1974).
J. Am. Pharm. Assoc. Sci. Ed. 49, 67.

130. J.E. CARLESS and S. LEIGH (1974).
J. Pharm. and Pharmac. 26, 287.

131. LONG, W.M., POWDER METALLURGY 6 73 (1960).

132. LONG, W.M. and ALDERTON, J.R. (1960).
Powder Metallurgy 6 52 - 72.

133. TUCKER, S.J. and HAYS, H.M.
J. Am. Pharm. Assoc. Sci. Ed. 48 362 (1959).

134. S. ESEZOBO and N. PILPEL.
J. Pharm. and Pharmac. 28 8 - 16 (1976).

135. SHOTTON, E. and REES, J.E. (1966).
J. Pharm. and Pharmac. 18 1605 - 1705.

136. J.E. REES.
J. Pharm. and Pharmac. 22 245 (1970).

137. H. GROENWOLD, C.F. LERK and R.J. MULDER.
J. Pharm. and Pharmac. 24 352 - 356 (1972).

138. BOWDER, F.P. and TABOR, D. (1954).
"The Friction and Lubrication of Solids" Oxford, Clarendon Press.

139. RUMPF, H. (1958).
Chemine Ing. Techn. 30 146 - 158.

140. LAZARUS, J. and LACHMAN, L. (1966).
J. Pharm. Sci. 55 1121 - 1127.

141. B.A. OBIORAH and E. SHOTTON,
J. Pharm. and Pharmac. (1976) 28 629 - 632.

142. Z.T. CHOWHAN and L. PALAGYI,
J. Pharm. Sci. 67 1385 (1978).

143. SETH, P.L.
"The Influence of Physical and Mechanical Factors in Tablet Making" Tent House, Calcutta, India (1956)

144. D.N. TRAVERS, P.J.P. WHITE and C.J. LEWIS.
J. Pharm. and Pharmac. (1972) 24 Suppl. 57P - 66P.

145. RAYMOND, R. MYERS and J.S. LONG.
Treatise on Coatings, Volume 2 (in two parts), Characterisation of Coatings; Physical Techniques Part II. P. 126.