TENSILE STRENGTH AND PLASTO-ELASTICITY OF PARACETAMOL FORMULATIONS IN RELATION TO TABLETING

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ABSTRACT

A study has been made of the tensile and plasto-elastic properties of paracetamol and Avicel powders and of their mixtures. A study- has also been made of the effects of interacting variables on the tensile strength and disintegration times of tablets made from the mixtures.

Measurements of the tensile properties were made on loosely consolidated beds of powders using a Warren-Spring Laboratory Tensile Tester. Two quantities were derived from the results ; m, a universal constant and a material constant which can be used to compare the 'strength' and 'range' of interparticle forces of different materials. The value of < for paracetamol was much larger than that for Avicel and increased slightly with increase in particle size. There was good agreement between the experimental results of the tensile strengths of both the single powders and the mixtures and those predicted from the tensile strength equations.

Measurements were also made using a DARTEG universal testing machine under various conditions of load, loading rate, sample composition, moisture, etc. of the stress relaxation (SR) and elastic recovery (ER) of mixtures of paracetamol and Avicel and of the tensile strengths (T) of their tablets. In all cases T was inversely proportional to ER/SR (plasto-elasticity) and this relationship could be used to predict whether a material would form good tablets or tend to laminate and cap during tableting.

The separate and combined effects of varying the packing fraction, the proportions of Avicel and alginic acid, disintegrant on the tensile strengths and disintegration times of paracetamol tablets were studied and explanations have been provided for the observed interactions of these variables.

DEDICATION

To my wife, Adunni and daughter, Ọmọṣẹkẹ

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CHAPTER 1

GENERAL INTRODUCTION

Powders are an agglomeration of particles which are of vital importance in many fields of science and technology including chemical engineering, metallurgy, ceramics and pharmaceutical technology. The definition of a powder is a collection of discrete particles less than 1 mm in diameter. Because powders are nonhomogeneous in structure consisting of particles of different shapes and sizes with interparticle voids and a multitude of interacting surfaces, they exhibit complex physico-chemical and mechanical properties (York 1983). They are similar to liquids in that they deform and flow when stressed and to solids in that they can exhibit both elastic recovery and brittle fracture. But unlike conventional solids, powders become appreciably compressed or consolidated by the application of pressure.

It is necessary to have knowledge about the fundamental properties of powders. These properties determine their behaviour during processing and during subsequent use. In this thesis the emphasis will be placed on the important properties of pharmaceutical powders which modify their compression into tablets and the subsequent performance of these during drug delivery.

There are two basically different approaches employed for studying the fundamental properties of powders : these are the continuum and the particulate approach.

CONTINUUM APPROACH

The powder bed is considered as a continuum without discrete structure and the relationships between stress and strain are investigated by using techniques similar to those employed for the mechanical properties of solids and liquids. This approach makes use of the theories and techniques of soil mechanics (Rankine 1857 ; Hvorslev 1937 ; Roscoe

et al 1958, 1963 ; Coulomb 1976). These authors showed that the strength and failure properties of moist soils were determined very largely by the amount of water in the sample and by the extent to which it had been compressed or consolidated. They derived equations relating the strength of a soil to its voidage.

Later Jenike (1961, 1964) and others (Brown 1961 ; Richmond and Gardner 1962) extended these theories to deal with dry powders. To do this, it was necessary to redefine some of the terms that had previously been used in soil mechanics and also to introduce new concepts that had not previously been considered. Thus while Rankine (1857) and Coulomb (1976) had been previously concerned with the "strength" of soils, that is with their resistance to failure or flow, Jenike (1964) was more interested in the design of hoppers through which dry powders of industrial importance could be made to flow without the occurence of "piping", "rat holing" or blocking of the orifice. Although Jenike provided solutions to various practical problems he did not attempt to derive a general equation for relating the stress and strain in powder beds subjected to particular test conditions. Instead he used the Mohr procedure (1940) to describe their flow and failure properties.

PARTICULATE APPROACH

In this approach, a powder is considered to consist of large but not infinitely large numbers of discrete particles which are separated from each other by void spaces. By summing the interactions of individual particles statistically, information about the bulk properties of the powder is obtained. However, the situation in powders is very complex since the factors associated with the particles and their surfaces (e.g. size, shape, surface morphology, packing condition and interparticle forces) must be taken into account. These properties

are difficult to define for real powder systems and interparticle forces are difficult to quantify. Nevertheless, the particulate approach has been applied successfully to real powders by Rowe 1962 ; Horne 1965 ; Cheng and Valentin 1968 ; Kočova and Pilpel 1973 a ; Chan et al 1983 who were able to make predictions of the tensile strengths of powders which compared reasonably with the experimental values.

Neither the continuum nor particulate approach gives completely satisfactory information about powders and it seems reasonable to employ both in studying the fundamental properties of powders ; this is the stance that has been adopted in the present work.

THE TENSILE STRENGTH OF POWDERS

The tensile strength is a parameter that is frequently used to study the fundamental mechanical properties of pharmaceutical powders.

The tensile strength of a powder is the force per unit area of broken face required to split the bed of powder. It may be determined experimentally using either the tilting table apparatus (Dawes 1952) or a tensile strength apparatus (Ashton et al 1964). The tilting table apparatus involves forming a bed of powder on a split metal plate, one half of which is free to move on ball bearings. By tilting the plate through an angle, θ_T with the horizontal the bed is caused to split under its own weight as the two halves of the plate separate. The disadvantage of this method is that the results are not reproducible (Thouzeau and Taylor 1962), θ_T varies considerable with the way in which the bed of powder has been packed (Morgan 1965), with the rate of tilting and with the relative humidity of the environment (Eisner et al 1960). Some of the difficulties are overcome in the Warren Spring Laboratory tensile tester (Ashton et al 1964). In this apparatus

the bed of powder is consolidated under controlled conditions and is then split in a vertical plane by causing the two halves of the cell to separate in a horizontal plane by means of a calibrated spring driven by a motor. Further details of this apparatus are given in Chapter 2. Despite certain errors which are inherent in the measurement of the tensile strength of a powder (e.g. the assumption that the fractured surface of the bed is smooth and that the sample has been packed uniformly throughout), the Warren Spring Laboratory tensile tester is considered to be the most satisfactory apparatus that is currently available for this type of measurement.

The tensile strength of a powder is a useful parameter to determine or predict its likely performance during handling and tableting. A powder with a very high tensile strength may form very hard tablets which may have extended disintegration times ; on the other hand, powders of low tensile strengths may form very weak and soft tablets which have a tendency to cap and laminate.

FORCES THAT OPERATE IN A POWDER

Several forces operate in a powder and it is considered relevant at this point to outline the interparticle forces which give rise to the tensile strengths of powders. These include :

1. Mechanical interlocking

Powder particles are irregularly shaped and have very rough surfaces which have a tendency to intermesh and mechanically interlock especially under load.

2. Plastic deformation

Bowden and Tabor (1957) and Tabor (1961) have shown that when two particles come into contact, only relatively small parts of their total surface area actually touch. When subjected to compaction, the pressures developed at these tips of their protrusions, referred to as asperities, are very high and this may cause plastic flow as well as elastic deformation to occur. Plastic deformation of the asperities will lead to greater true area of contact and hence to enhanced forces of adhesion between the particles.

3. Molecular forces.

These are generally referred to as van der Waals' forces. The electron clouds in the molecules vibrate in relation to the nuclei, setting up small instantaneous dipoles of defined orientation ; these then induce dipoles in neighbouring atoms, in this manner causing an attraction between molecules (London 1930). Van der Waals' forces vary inversely with the distance apart of the particles raised to the sixth power and they become considerable when the particles are less than 50 μm in diameter and are separated by less than 0.01 μm (Turba and Rumpf 1964).

4. Electrostatic forces

Electrostatic charges can arise on the surfaces of particles for two reasons :

a. if the particles have been in contact with an ionic substance (perhaps they have been washed in a solution, for example) then foreign ions may reside on the surface - leading to surface depolarisation.

b. electrons can transfer between the surfaces of particles by so-called "contact-charging" (Sutton 1976) which can take place with both conductors and insulators. Electrostatic forces thus arise from surface charges which are either permanent or acquired from adjacent surfaces, unlike van der Waals' forces which arise from random motion of the electrons in the surface molecules. Electrostatic forces are weaker forces but act over a larger range and become comparable to van der Waals' forces when the particles are less than 2 μm in diameter (Gold and Palermo 1965).

5. Solid bridge forces

Solid bridge formation may be due to mineral bridges, chemical reaction, partial melting and subsequent cooling and resolidification, binders which harden and crystallisation of dissolved substances and deposition of suspended colloidal particles (Rumpf 1958).

6. Liquid bridges

Surface tension forces can also arise in particles containing adsorbed moisture. The effect that moisture has on the interparticle forces depends on the state of water in the particles and is discussed in detail on pages 41-48. The effects of the presence of liquid films at the junctions of particles on their adhesion have been reviewed by Minty et al (1953) and Derjaguin (1961).

THEORY OF TENSILE STRENGTH OF POWDERS

A number of theoretical studies on the tensile strength of powders has been carried out on the basis of "ideal" models of uniform spheres, in particular numerous attempts have been made to express the tensile strength of a bed of powder in terms of fundamental properties of the bed such as its bulk density, size distribution, shape and packing

arrangement of the constituent particles (Rumpf 1962 ; Smalley and Smalley 1964 ; Pietsch and Rumpf 1967 ; Cheng 1968), van der Waals' forces, electrostatic and other forces between the particles (Krupp 1967) and the presence of liquid or adsorbed films on their surfaces (Pierce and Donald 1959 ; Rumpf 1962 ; Pietsch and Rumpf 1967 ; Daughlas 1967).

Rumpf, for example, derives an expression for the tensile strength of a granule of identical spheres. The basic equation is

$$T = \frac{9}{8} \frac{\ell_F}{\pi \bar{d}^2} cH \qquad (1)$$

where T = tensile strength

ℓ_F = packing fraction of bed

$\bar{d}$ = diameter of sphere

c = co-ordination number

and H is mean bonding force at point of contact and is the algebraic sum of the various types of force that act between the particles. For perfectly smooth, dry, spherical particles of chemically inert substances, it can be assumed that the van der Waals' forces predominate and the value of H is given as (Hamaker 1937)

$$H = \frac{g\bar{d}}{24\, t^2} \qquad (2)$$

where g is a constant whose value is about $10^{-11} Nm^{-2}$ and t is the interparticle separation between the spherical surfaces.

Eaves and Jones (1972a) substituted this value of H into Rumpf's basic equation (equation 1) and assuming that $\pi = c(1 - \ell_F)$ (Rumpf 1962) obtained the expression

$$t = \sqrt{\frac{9}{192} \quad \frac{\rho_F}{1 - \rho_F} \quad \frac{g}{T\,\bar{d}}} \qquad (3)$$

for estimating interparticle separation

Smalley and Smalley (1964) had earlier recalculated the tensile strength to allow for the dimensional anomalies in some of Rumpf's statements and obtained

$$T = \frac{4.6Bt_f}{\bar{d}^{\,3}} \qquad (4)$$

where B = H and t_f which is completely omitted by Rumpf is the thickness of the fracture zone, it being assumed that fracture occurs in a plane normal to the direction of the tensile force. However, Carr and Walker (1967) commented that the number of bonds and hence the tensile strength of uniform sized spheres in the fracture zone was likely to be inversely proportional to the particles' cross-sectional area instead of their volume as implied by equation 4.

On the assumption that a powder can be treated as a modified Mohr-Coulomb solid (Skepton and Bishop 1954) the criterion for failure in tension is that

$$T = \frac{3.6B}{\pi \bar{d}^{\,2}} \left(\frac{1 - \sin\Delta}{1 + \sin\Delta} \right) \qquad (5)$$

where Δ is the internal angle of friction of the material. This equation is similar to the equation proposed by Rumpf (1962) and others (Fisher 1926) who showed that if small amounts of water were present in the bed, the term B could be written as

$$B = \pi \bar{d}\, \gamma \left(1 + \tan\tfrac{1}{2}\delta\right) \qquad (6)$$

where 2δ is the angle subtended at the centre of the particle by

a lens of water and γ is the surface tension.

Similarly Pietsch and Rumpf (1967) modified equation 1 for particles containing moisture in the pendular state, in which the mean bonding force, H, is due to the presence of pendular bonds. Their expression for H was

$$H = \gamma_L \bar{d} f\left(\theta, \delta, \frac{t}{\bar{d}}\right) \qquad (7)$$

where γ_L is the surface tension of the liquid, f is a constant, θ is the contact angle and δ is the half centriangle (i.e. half the angle subtended at the centre of the sphere by the liquid bridge). The expression for tensile strength in equation 1 becomes (Eaves and Jones 1972a)

$$T = \frac{9}{8}\left(\frac{\rho_F}{1-\rho_F}\right)\frac{\gamma_L}{\bar{d}} f\left(\theta, \delta, \frac{t}{\bar{d}}\right) \qquad (8)$$

Ashton et al (1965) employed empirical equations to fit their experimental findings, they proposed a power law relationship between T and the bulk density, ρ , i.e.

$$T = A_1 (\rho)^{m_1} \qquad (9)$$

where A_1 and m_1 are empirically obtained constants.

Williams and Birks (1967) investigated titanium dioxide and penicillin while Kočova and Pilpel (1972) investigated α-lactose monohydrate and precipitated calcium carbonate ; they proposed that the tensile strength of the "simple" powders is a linear function of the load used for consolidation of the bed, i.e.

$$T = q\sigma_c \qquad (10)$$

where σ_c is the consolidating stress and q is the value of the

the tensile strength for unit consolidating pressure, or the so-called specific tensile strength.

In spite of the ability of the above cited expressions to fit a considerable amount of the experimental data they have several setbacks including the following :

1. the equations and others (Pierce and Donald 1959 ; Aitchison 1960 ; Daughlas 1967) primarily relate to granular beds in which the average size of the particles is of the order 150 μm or above. Thus there are considerable discrepancies between the values of the tensile strength predicted by the various equations and those obtained experimentaly by use of split plate or other types of tensile apparatus (Dawes 1952 ; Ashton et al 1964)

2. no allowance is made for the fact that powder beds are actually composed of particles of different sizes with irregular shapes and rough surfaces. In fact the theories (Rumpf 1962 ; Smalley and Smalley 1964) assume that the particles in an ideal powder are smooth and possess regular shapes.

3. they are unable to account adequately for the marked dependence of tensile strength on the powder packing fraction (Morgan 1965)

4. they are not derived from fundamental considerations and thus not universally applicable.

5. the significance of the physical constants associated with the empirical equations is often obscure.

In an attempt to improve on the previous theories and particularly

to offer a satisfactory explanation for the large variation of tensile strength that occurs when a small increase is made in the packing density of the material, Cheng (1968) has developed a theory for the tensile strength of powders in which he incorporated the effects of packing density, particle size distribution and the operation of interparticle forces.

He related the tensile strength, T, to the overall area of contact between the particles, A and interparticle force per unit area, h(t) by the expression

$$T = Ah(t) \qquad (11)$$

where t is the interparticle separation and is related to the effective particle diameter, $\bar{d}$ and the bulk density, ρ by the expression

$$t = t_o - \frac{\bar{d}}{3}\left(\frac{\rho}{\rho_o} - 1\right) \qquad (12)$$

where t_o is the average range of interparticle attractive forces and ρ_o is the bulk density at which the tensile strength, T is zero. Cheng then arrived at the following equation for the tensile strength of a powder bed :

$$T = \tfrac{1}{2}abc\frac{\bar{s}\rho}{\bar{v}\rho_s} H\left[t_o - \frac{\bar{d}}{3}\left(\frac{\rho}{\rho_o} - 1\right)\right] \qquad (13)$$

where a is the number of particle pairs per unit area divided by the number of particle pairs per unit volume ;

b is the true area of contact per particle pair divided by the surface area of the smaller particle ;

C is the mean co-ordination number ;

H is the interparticle force per unit area whose magnitude is dependent on the interparticle separation, t ;

t_o is the range of the attractive interparticle force ;

ρ is the bulk density and ρ_o is its value when T equals zero

$\bar{d}$ is the effective particle diameter ;

$\bar{s}$ is the mean surface area and

$\bar{V}$ is the mean volume per particle.

The Cheng theory has provided a satisfactory explanation for the marked dependence of the tensile strengths of powders on their packing fraction.

The theory has also enabled experimental results for different size fractions of a variety of materials to be correlated with their particle size distribution. However, in order to predict the tensile strengths of powders from knowledge of particle size distribution alone, values of ρ_o and t_o must be deduced by asymptotic extrapolation of the experimental data to zero tensile strength at which the separation between the particles is relatively large. This introduces uncertainty in the calculation and to overcome this difficulty Chan et al (1983) introduced the concepts of a reference state and a reduced tensile strength.

This modified theory of tensile strength and its extension for binary mixtures of powders has been tested in the present work and will now be derived in detail.

Latest theory of tensile strength

Cheng (1973a) assumed that the particles in a powder bed are spherical, rough and randomly distributed. Each particle is in contact with neighbouring particles at the points where their surface asperities touch (Fig 1.1) and the average coordination number, c is dependent on the density of the bed.

The tensile strength of all the particle pairs in unit area of split can be expressed by the simple equation

$$T = \sum \bar{F} \qquad (14)$$

where $\bar{F}$ is the mean effective value of the force F which acts between the particles in a pair. In general, F will be inclined at an angle θ' to the direction of the tensile force and it is the resolved component $F\cos\theta'$ that contributes to T. Assuming that all values of θ' are equally possible, $\bar{F}$ can be taken as

$$\bar{F} = \tfrac{1}{2}F \qquad (15)$$

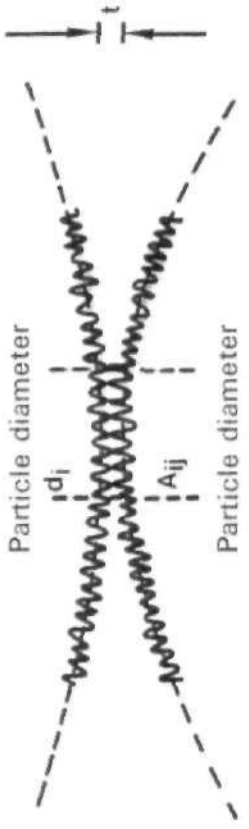
In an area of contact A_{ij} between particles (see Fig 1.1) F can be expressed as

$$F = HA_{ij} \qquad (16)$$

where H is the interparticle force per unit area of contact. The subscripts i, j refer to the two members of a particle pair whose diameters are d_i and d_j. The magnitude of the interparticle forces is dependent on the distance apart of the particles, i.e. H is a function of t :

$$H = H(t) \qquad (17)$$

Fig.1.1 Two particles of diameters d_i and d_j in contact over an area A_{ij}



Thus

$$F = H(t)A_{ij} \tag{18}$$

From Equations 16 and 18

$$T = \tfrac{1}{2}H(t) \sum A_{ij} \tag{19}$$

for all particle pairs in unit area of split. Now, when the bed splits, rupture occurs at the micro-points of contact between neighbouring particles in a pair. The fracture surface is rugged and the mean fracture plane is normal to the direction of the applied tensile force. Thus the tensile strength depends on the number of particle pairs per unit area of split, $N_{pp/a}$. Cheng (1968, 1973b) related $N_{pp/a}$ to the co-ordination number and packing density of the bed by

$$N_{pp/a} = \frac{c\bar{d}}{2\bar{V}} \quad \frac{\ell}{\ell_s} \tag{20}$$

The co-ordination number is related to the packing density of the bed by (Clark and Mason 1967)

$$c = \frac{K}{1 - \left(\frac{\ell}{\ell_s}\right)} \tag{21}$$

where K is a constant which for uniform sized spheres, is assumed to have an approximate value of 3 (Rumpf, 1962).

By combining Eqs. (20) and (21), one can write

$$N_{pp/a} = \frac{K\bar{d}}{2\bar{V}} \quad \frac{\ell/\ell_s}{1 - (\ell/\ell_s)} \tag{22}$$

Eq. (5) can now be written as

$$T = \tfrac{1}{2}H(t) \sum_{i,j} X_{ij} N_{pp/a} A_{ij} \tag{23}$$

where X_{ij} is the proportion of pairs of particles out of all possible pairs, that are composed of particles of sizes d_i and d_j.

In his modified theory, Cheng used a more rigorous procedure to evaluate the mean effective area of contact A_{ij} as illustrated in Fig. 1.2. This shows two particles of diameters d_i and d_j in contact with IJ as their common tangent. A_{ij} has to be found by integrating the forces of attraction over two surfaces, CI and CJ and it is related to the area R'^2. By Pythagoras' theorem

$$\left(2R'\right)^2 + \left(\frac{d_j - d_i}{2}\right)^2 = \left(\frac{d_i + d_j}{2}\right)^2 \qquad (24)$$

Hence

$$\pi R'^2 = \frac{\pi}{4} d_i d_j \qquad (25)$$

However , since H(t) decreases as t increases, it is the area near C that contributes most to the interparticle forces and A_{ij}must be very much smaller than $\pi R'^2$. The exact relationship between A_{ij} and R'^2 is not known but at present it can be taken as

$$A_{ij} = \xi \pi R'^2 \qquad (26)$$

and hence from (11)

$$A_{ij} = \xi \frac{\pi}{4} d_i d_j \qquad (27)$$

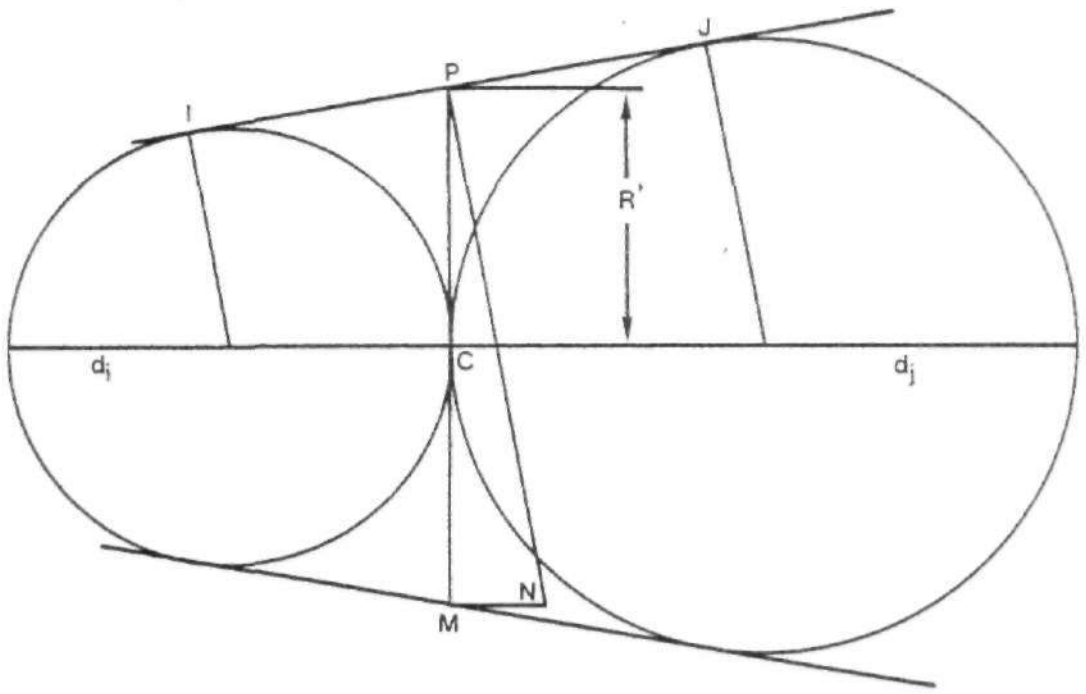
where ξ is a universal constant used in the enumeration of area of contact between paricles X_{ij}; the number fraction of particles of diameter d_i, d_j can be calculated from the size distribution of the powder. Assuming that N_p particles are present and the number fraction of diameter d_i is n_i, then the number fraction of particle-pairs of equal-sized particles can be written as

Fig. 1.2 Diagram used to determine A_{ij} (after Cheng (1973a))

$$PM = 2R'$$

$$PN = \frac{d_i + d_j}{2}$$

$$MN = \frac{d_i - d_j}{2}$$



$$X_{ii} = \frac{N_{ii}}{N_{pp}} = n_i^2 \left(\frac{1 - \frac{1}{n_i N_p}}{1 - \frac{1}{N_p}} \right)$$

and for unequal-sized spheres

$$X_{ij} = \frac{N_{ij}}{N_{pp}} = \frac{2 n_i n_j}{1 - \frac{1}{N_p}} \quad ; \text{ for } i < j$$

when N_p is large

$$\left.\begin{aligned} X_{ii} &= n_i^2 \quad \text{and} \\ X_{ij} &= 2 n_i n_j \quad \text{for } i < j \end{aligned}\right\} \tag{28}$$

and $\sum_i X_{ii} + \sum_{i<j} X_{ij} = 1$

Substituting Eqs, 22, 27, 28 into Eq. 23

$$T = K \ell \frac{\overline{ds}}{4 \overline{V}} \frac{\ell / \ell_s}{1 - (\ell / \ell_s)} H(t) \tag{29}$$

with

$$\overline{d} = \tfrac{1}{2} \sum_{i,j} n_i n_j (d_i + d_j)$$

$$\overline{s} = \frac{\pi}{4} \sum_{i,j} n_i n_j d_i d_j$$

$$\overline{V} = \frac{\pi}{6} \sum_i n_i d_i^3$$

The surface separation between particles, t can be related to the bed density. If it is assumed that no change in the type of packing of particles occurs as the density changes, the ℓ is proportional to $\frac{1}{L^3}$ where

$$L = \tfrac{1}{2}(d_i + d_j) + t \qquad (30)$$

For a small change in density $\left(\frac{\delta \rho}{\rho}\right)^{\frac{1}{3}}$ is proportional to $-\frac{\delta L}{L}$ or

$\left(\frac{\delta \rho}{\rho}\right)^{\frac{1}{3}}$ is proportional to $\frac{-\delta t}{\bar{d}}$

At any reference packing density

$$\left(\frac{\rho_r - \rho}{\rho}\right)^{\frac{1}{3}} = \frac{t - t_r}{\bar{d}}$$

Thus $t = t_r + \lambda \qquad (31)$

where

$$\lambda = \bar{d}\left\{\left(\frac{\rho_r}{\rho}\right)^{\frac{1}{3}} - 1\right\} \qquad (32)$$

The subscript r denotes a reference state and it is assumed that $t_r \ll \bar{d}$.

Rearranging Eq. 29, Chan et al (1983) introduced a new quantity R known as the "reduced tensile strength", which is a function of t.

$$R(t) = \frac{T}{\frac{\bar{d}\,\bar{s}}{4\bar{V}} \frac{\rho/\rho_s}{1-(\rho/\rho_s)}} \qquad (33)$$

It follows that when R is plotted against ρ, a similar R value for two size distributions would refer to the same but an unknown t value. By choosing a reference R value (R_r) such that data for the two distributions overlap, the value of ρ_r may be used to calculate λ in equation 32.

The Law of Corresponding States

The magnitude of the interparticle forces is dependent on the distance apart of the particles, i.e. H is a function of t. The relationship between H(t) and t can be written as analagous to the Lennard-Jones type of intermolecular potential (Hirschfelder et al 1954)

$$H(t) \text{ is proportional to } \frac{1}{t^m} \qquad (34)$$

where m is a positive index. This functional relationship preserves the intuitive concept that H(t) tends to zero as t tends to infinity but tends to infinity as t tends to zero. The law of corresponding states is a universal relationship between dimensionless variables. Hakala (1967) showed that any two-body intermolecular potential function could be put into a dimensionless form involving only one energy parameter ϵ_o, and only one length parameter t_o (defined as the "range" of interparticle force) in addition to any dimensionless intermolecular parameter that described the simplest form of this "potential function". Cheng (1968) made use of this result to derive a more general form of the law of corresponding states for the behaviour of single powder systems. He applied the law to relate H(t) and t, taking the parameter ϵ_o to be a measure of the "strength" of the interparticle force and t_o to be a measure of the "range" of this force and produced the relationship

$$\frac{t_o^3}{\epsilon_o} H(t) = \phi\left(\frac{t}{t_o}\right) \qquad (35)$$

where ϕ denotes a functional relationship. This has been used in correlating tensile strength data for a wide range of powders (Cheng 1968 ; Cheng et al ; Kočova and Pilpel 1972). The present concept

involves the use of an arbitrary t_r value which depends on the lie of the experimental data. To test its validity for comparison between different materials, a modification is necessary.

From Eq. 34 $\phi\left(\frac{t}{t_o}\right)$ can be expressed as $\left(\frac{t}{t_o}\right)^m$ and the law of corresponding states between H(t) and t may be written

$$H(t) = \frac{\epsilon_o}{t_o^3} \left(\frac{t_o}{t}\right)^m \tag{36}$$

with t_o as representative value of t, and m being a universal constant. Since H(t) has been related to the universal constants K and ϵ, See Eq. 29.

$$H(t) = \frac{R}{K\epsilon} \tag{37}$$

Equating the two expressions in Eqs, 36 and 37 gives

$$R = \frac{\alpha}{t^m} \tag{38}$$

where

$$\alpha = \frac{K\epsilon}{t_o^{3-m}} \tag{39}$$

and Eq. 33 becomes

$$T = \frac{\bar{d}\,\bar{s}}{4\,\bar{V}} \quad \frac{\ell/\ell_s}{1-\left(\ell/\ell_s\right)} \quad \frac{\alpha}{t^m} \tag{40}$$

where α denotes a parameter characteristic of each material.

BINARY MIXTURES OF POWDERS

Kočova and Pilpel (1973a, b) made an attempt to extend Cheng's earlier equations to mixtures. By considering different possible types of particle pairs in a binary mixture, they proposed the equation

$$T = \frac{1}{2}\frac{abc}{\bar{V}_{mix}}\frac{\ell}{\ell_s}M'\left(\bar{s}_{AA}w_A^2 + 2\,\bar{s}_{AB}w_Aw_B + \bar{s}_{BB}w_B^2\right)X$$
$$H\left[t_o - \frac{\bar{d}_{mix}}{3}\left(\ell/\ell_o - 1\right)\right] \qquad (41)$$

where the subscripts A and B denote the two components ; w is the weight fraction ; M' is the degree of mixing ; $\bar{d}_{mix}$, $\bar{V}_{mix}$, $\bar{s}_{AA}$, $\bar{s}_{AB}$ and $\bar{s}_{BB}$ are the particle size parameters of the mixtures. This equation is moderately satisfactory, giving $\pm$ 25% agreement between calculated and measured values of tensile strength for certain mixtures. However, it has theoretical weaknesses, notably in the use of a weight fraction for expressing composition and in making no distinction between interactions between like and unlike particles.

Recently Chan et al (1983) adopted the same basic approach as for single powders in attempting to develop a theory for the tensile strength of binary mixtures of powders. In this, they attempted to relate the tensile strength of the binary mixture to the parameters of the single components. It is of potential interest to see if the theory can be used to predict the tensile strength of other binary mixtures from the properties of the single components.

Equation 23 suggests that T depends on the number of particle pairs in contact, the interparticle forces, the distance of separation and the area of contact.

In a binary mixture of powders A and B three different pairings

of the two species of particles are possible : A-A, B-B and A-B or B-A. Their contribution to the tensile strength varies and depends on the number fractions of particles and the particle size of each species in the mixture.

If there are N_p particles in a mixture the composition can be described by the number fraction of particles of each species, U_A and U_B and this may be related to the weight fraction W_A, W_B of each species by

$$\left.\begin{aligned} U_A &= \frac{W_A}{\bar{V}\,\ell_{s_A}} \Bigg/ \left(\frac{W_A}{\bar{V}_A \ell_{s_A}} + \frac{W_B}{\bar{V}_B\,\ell_{s_B}} \right) \\ U_B &= \frac{W_B}{\bar{V}_B\,\ell_{s_B}} \Bigg/ \left(\frac{W_A}{\bar{V}_A\,\ell_{s_A}} + \frac{W_B}{\bar{V}_B\,\ell_{s_B}} \right) \end{aligned}\right\} \qquad (42)$$

The number of like particle pairs (A-A, B-B) formed by the species is

$$N_{AA} = N_A\,(N_A - 1)$$

$$N_{BB} = N_B\,(N_B - 1)$$

and the number of unlike particle pairs (A-B, B-A) formed by the two species is

$$N_{AB} = 2N_A\,N_B$$

The number fraction of the three different types of particle pairs is

$$Y_{AA} = \frac{N_{AA}}{N_{pp}} = U_A^2 \left(\frac{1 - \frac{1}{N_A}}{1 - \frac{1}{N_p}} \right)$$

$$Y_{BB} = \frac{N_{BB}}{N_{pp}} = U_B^2 \left(\frac{1 - \frac{1}{N_B}}{1 - \frac{1}{N_p}} \right)$$

$$Y_{AB} = \frac{N_{AB}}{N_{pp}} = 2U_A U_B \Big/ \left(1 - \frac{1}{N_p}\right)$$

and when N_p is large, then

$$\left.\begin{aligned} Y_{AA} &= U_A^2 \\ Y_{BB} &= U_B^2 \end{aligned}\right\} \qquad (43)$$

and $Y_{AB} = 2U_A U_B$

with $Y_{AA} + Y_{BB} + Y_{AB} = 1$

Extending the concepts of calculating the number fraction of particles in a size distribution for a powder with one species of particles to an idealy mixed binary mixture, Cheng derived the number fractions of the like particle pairs and unlike particle pairs.

If it is assumed that the particle sizes of the two species are discrete and the number distributions are n_i, n_j for species A and n_k, n_l for species B and their sizes are d_i, d_j and d_k, d_l respectively, then the number fractions for the like particle pairs (A-A, B-B) and unlike particle pairs (A-B, B-A) of diameters d_i and d_k are

$$\left.\begin{aligned} X_{ij} &= n_i n_j \quad \text{for all } i,j \\ X_{kl} &= n_k n_l \quad \text{for all } k,l \\ X_{ik} &= n_i n_k \quad \text{for all } i,k \end{aligned}\right\} \qquad (44)$$

Using a mass balance method, he found the relationship between the number of particle pairs per unit area, $N_{pp/a}$, coordination number c and packing density ρ/ρ_{smix} in the fracture plane of a binary mixture is similar to that described for a single component powder.

An extended form of Eq. 23 applies. He also calculated the effective area of contact between different particles

$$\left.\begin{aligned} A_{ij} &= \mathcal{E}\ \tfrac{\pi}{4} d_i d_j \\ A_{kl} &= \mathcal{E}\ \tfrac{\pi}{4} d_k d_l \\ A_{ik} &= \mathcal{E}\ \tfrac{\pi}{4} d_i d_k \end{aligned}\right\} \qquad (45)$$

and noted that they are independent of the exact chemical nature of the materials involved. Three different types of interparticle forces are present as a result of the possible particle pairing, namely, two of the like particles and one of the unlike particles. In a unit area of split

$$\left.\begin{aligned} F_{AA} &= H_{AA} A_{ij} \\ F_{BB} &= H_{BB} A_{kl} \\ F_{AB} &= H_{AB} A_{ik} \end{aligned}\right\} \qquad (46)$$

From Eq. 19, T can be written as

$$\begin{aligned} T &= \tfrac{1}{2} H_{AA} \lesssim A_{ij} + \tfrac{1}{2} H_{AB} \lesssim A_{ik} + \tfrac{1}{2} H_{BB} \lesssim A_{kl} \\ &= \tfrac{1}{2} N_{pp/a} \left[Y_{AA} H_{AA} \sum_{i,j} X_{ij} A_{ij} + Y_{AB} H_{AB} \sum_{i,k} X_{ik} A_{ik} \right. \\ &\qquad \left. + Y_{BB} H_{BB} \sum_{k,l} X_{kl} A_{kl} \right] \end{aligned} \qquad (47)$$

On grouping the total area of split,

$$\begin{aligned} T = \frac{K \mathcal{E}}{4} \frac{\bar{d}_{mix}}{\bar{V}_{mix}} \frac{\ell/\ell_{s_{mix}}}{1 - \left(\ell/\ell_{smix}\right)} \Big(& U_A^2\ \bar{s}_{AA}\ H_{AA} + \\ & 2 U_A U_B\ \bar{s}_{AB}\ H_{AB} + U_B^2\ \bar{s}_{BB} H_{BB} \Big) \end{aligned} \qquad (48)$$

where

$$\bar{d}_{mix} = U_A^2 \bar{d}_{AA} + 2U_A U_B \bar{d}_{AB} + U_B^2 \bar{d}_{BB}$$

$$\bar{d}_{AA} = \tfrac{1}{2} \sum_{i,j} X_{ij} (d_i + d_j)$$

$$\bar{d}_{AB} = \tfrac{1}{2} \sum_{i,k} X_{ik} (d_i + d_k)$$

$$\bar{d}_{BB} = \tfrac{1}{2} \sum_{k,l} X_{kl} (d_k + d_l)$$

$$\bar{S}_{AA} = \tfrac{\pi}{4} \sum_{i,j} X_{ij} d_i d_j$$

$$\bar{S}_{AB} = \tfrac{\pi}{4} \sum_{i,k} X_{ik} d_i d_k$$

$$\bar{S}_{BB} = \tfrac{\pi}{4} \sum_{k,l} X_{kl} d_k d_l$$

and $\bar{V}_{mix} = U_A \bar{V}_A + U_B \bar{V}_B$ where

$$\bar{V}_A = \frac{\pi}{6} \sum_i n_i d_i^3$$

$$\bar{V}_B = \frac{\pi}{6} \sum_k n_k d_k^3$$

It can be seen that when $U_A = 1.0$ (and $U_B = 0$) Eqs. 29 and 48 become identical, describing a single component powder. Similarly Eq. 48 can be written to give the reduced tensile strength.

$$R(t) = \frac{T}{\frac{\bar{d}_{mix} \bar{s}_{mix}}{4 \bar{V}_{mix}} \frac{\ell/\ell_{s_{mix}}}{1 - \left(\ell/\ell_{s_{mix}}\right)}} \qquad (49)$$

where

$$\bar{s}_{mix} = U_A^2 \bar{s}_{AA} + 2U_A U_B \bar{s}_{AB} + U_B^2 \bar{s}_{BB}$$

and R is a function of t.

The "average" surface separation between the particles in the mixture can be similarly described by Eqs. 31 and 32. Applying the law of corresponding states, the functional relationship between the interparticle force for different particle pairings i.e. H_{AA}, H_{AB} and H_{BB} and their distance of separation t_{AA}, t_{AB} and t_{BB} may be written as

$$\left.\begin{aligned} H_{AA} &= \frac{\epsilon_{AA}}{t_{AA}^{3}} \left(\frac{t_{AA}}{t}\right)^{m} \\ H_{BB} &= \frac{\epsilon_{BB}}{t_{BB}^{3}} \left(\frac{t_{BB}}{t}\right)^{m} \end{aligned}\right\} \qquad (50)$$

and

$$H_{AB} = \frac{\epsilon_{AB}}{t_{AB}^{3}} \left(\frac{t_{AB}}{t}\right)^{m}$$

Combining Eqs. 48 and 50, Eq. 49 becomes

$$R = \frac{\alpha_{mix}}{t^{m}} \qquad (51)$$

where

$$\alpha_{mix} = \frac{U_A^{2}\,\bar{s}_{AA}\,\alpha_{AA} + 2U_A U_B\,\bar{s}_{AB}\,\alpha_{AB} + U_B^{2}\,\bar{s}_{BB}\,\alpha_{BB}}{\bar{s}_{mix}} \qquad (52)$$

and

$$\alpha_{AA} = K\xi\frac{\epsilon_{AA}}{t_{AA}^{3-m}}$$

$$\alpha_{BB} = K\xi\frac{\epsilon_{BB}}{t_{BB}^{3-m}}$$

$$\alpha_{AB} = K\ell\frac{\epsilon_{AB}}{t_{AB}^{3-m}}$$

Substituting Eqs 51 and 52 in Eq. 48, T can now be written as

$$T = \frac{\bar{d}_{mix}\,\bar{s}_{mix}}{4\,\bar{V}_{mix}} \frac{\ell/\ell_{s_{mix}}}{1-\left(\ell/\ell_{smix}\right)} \frac{\alpha_{mix}}{t^{m}} \qquad (53)$$

It can be seen that Eqs. 52 and 53 reduce to Eqs. 39 and 40 respectively when U_A or U_B = 1.0 i.e. when the powder contains one species of particle.

THE EFFECT OF MOISTURE ON THE MECHANICAL PROPERTIES OF POWDERS AND TABLETS

In Chapter 5 of the present work the effect of moisture on the tensile strength and plasto-elastic properties of paracetamol tablet formulations has been studied. It is therefore considered appropriate to give a preliminary review of the relevant literature on the effect of moisture on the mechanical properties of powders and tablets.

Several workers have reported their findings on the effects of moisture on the mechanical properties of powders and granulations. Shotton and Harbs (1966) and Eaves and Jones (1972a) found that the cohesion of starch and sodium chloride initially increased as the moisture was increased but beyond a critical level started to decrease. Walton and Pilpel (1972) reported that at low moisture levels (up to 3.6%), the tensile strength of procaine penicillin powder decreased with increasing moisture content. A similar effect was observed by Harwood (1969). Chan and Pilpel (1983) noticed that the presence of up to about 15% w/w moisture had little effect on the tensile strength and shear properties of sodium cromoglycate and 1 : 1 mixtures of sodium cromoglycate and lactose. Some of these results appear to be mutually contradictory.

The effects of moisture content on the mechanical properties of tablets have also been studied by some workers. Shotton and Rees (1966) have attributed the reduction in crushing strengths of

tablets at high moisture content to the hydrodynamic effects of moisture, hydrodynamic lubricants being able to reduce friction by forming a finite layer of low shear strength which prevents contact between adjacent surfaces. Similarly Rees (1970) has demonstrated that at low compression pressure the relative volume of material containing moisture is much lower than that of a dry compact and has 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) have noticed that breakage of tablets during ejection is accompanied by high ejection forces which can contribute to the problem of capping. They explained that the reduced tendency to cap in the presence of moisture is attributed to a decrease in tablet ejection force with increasing moisture content.

Esezobo and Pilpel (1976) using oxytetracycline tablet formulations have found that the tensile strengths of the tablets attain maximum values when they contain between 2.5 and 4.5% moisture. Similar results have been reported by Pilpel et al (1978) on chloroquine phosphate tablet formulations.

Various theories have been propounded to explain the effects of moisture content of powders on their tensile strengths. Fisher (1926) theorised that the multilayers of adsorbed moisture on the surface of particles could condense to form a lens-shaped ring of water, or liquid bridge, subtended across the points of contact between two particles. Later, workers (Newitt and Conway-Jones 1958 ; Rumpf 1958) termed this a pendular bond and proposed an equation

for the interparticle force :

$$H = \frac{\pi \bar{d} \gamma}{1 + \tan \delta} \qquad (54)$$

where γ is the surface tension of water, δ is half the angle subtended at the centre of each particle by lens of water and $\bar{d}$ is the mean effective particle diameter.

Read and Kitchener (1967) have suggested that in the absence of a chemical reaction moisture in a powder mass may form an adsorbed film one or a few molecules thick. The adsorbed layers of moisture tend to smooth out irregularities on the surfaces of neighbouring particles, increasing their areas of contact and the van der Waals' forces between them. An adsorbed monolayer may also affect the frictional forces between particles in a similar manner to that observed between sliding metal plates (Hardy 1936 ; Bowden and Tabor 1954, 1964).

For two rigid spheres of material A and B, in contact with particle diameters d_i and d_k respectively, Derjaguin (1961) has shown that the interparticle force, H could be written as

$$H = \frac{3\pi d_i d_k}{2(d_i + d_k)} \sqrt{\lceil A \rceil \lceil B \rceil} \text{ joules m}^{-2} \qquad (55)$$

where $\lceil A \rceil$ and $\lceil B \rceil$ are the surface free energies of molecules A and B respectively.

The adsorption of moisture causes the surfaces of some pharmaceutical powders to soften and under compression the area of contact between the particles is considerably increased. In such situations Derjaguin (1961) showed that the increased interparticle force is given by

$$H = \frac{3\pi d_i d_k}{2(d_i + d_k)} \sqrt{\overline{A}\ \overline{B}} \left(1 + \frac{3\pi K}{Y_p} \sqrt{\overline{A}\ \overline{B}}\right) \text{joules m}^{-2} \quad (56)$$

where Y_p is the yield pressure of the deformed layer and K is dependent on the area, shape and thickness of the deformed layer (Krupp and Sperling 1967). The deformation of the surfaces and the consequent increase in their areas of contact reduce the term Y and increase K in equation 56 and cause the increase in the adhesive/cohesive strength of the particles.

Pietsch and Rumpf (1967) and Pietsch et al (1969) modified the basic tensile equation due to Rumpf (1962), equation 1 for particles containing moisture in the pendular state in which the mean bonding force, H is due to the presence of pendular bonds. Their expression for H could be written as

$$H = \gamma \bar{d} f\left(\theta, \delta, \frac{t}{\bar{d}}\right) \quad (57)$$

where θ is the contact angle and f is a constant.

Substituting Equation 57 into Equation 1 the tensile strength of the moist granules can be written as

$$T = \frac{9}{8} \frac{\ell_F}{\Gamma \bar{d}} c\gamma f\left(\theta, \delta, \frac{t}{\bar{d}}\right) \quad (58)$$

Similarly Cheng (1970) extended his theory to cover powder systems containing pendular moisture in contrast to the idealised systems envisaged by Pietsch and Rumpf (1967) and derived an equation

$$T = \Phi_M{}^{0.995} \frac{\ell_{p/\ell_s}}{1 - \left(\ell_{p/\ell_s}\right)} f\left(\frac{t}{t_o}\right) \quad (59)$$

where Φ is a function incorporating the size distribution of the

particles, ρ_p is the total weight of particles per unit volume of powder and M is the moisture content. In deriving this equation, Cheng assumed that the powder mass behaves as a rigid solid and does not undergo appreciable tensile deformation before the point of rupture ; this assumption is not always valid for powders containing free moisture (Derjaguin 1961 ; Coulomb 1969 ; Pilpel 1970). In spite of this weakness, the equation reasonably well fitted the experimental results obtained on moistened polyvinyl chloride powder.

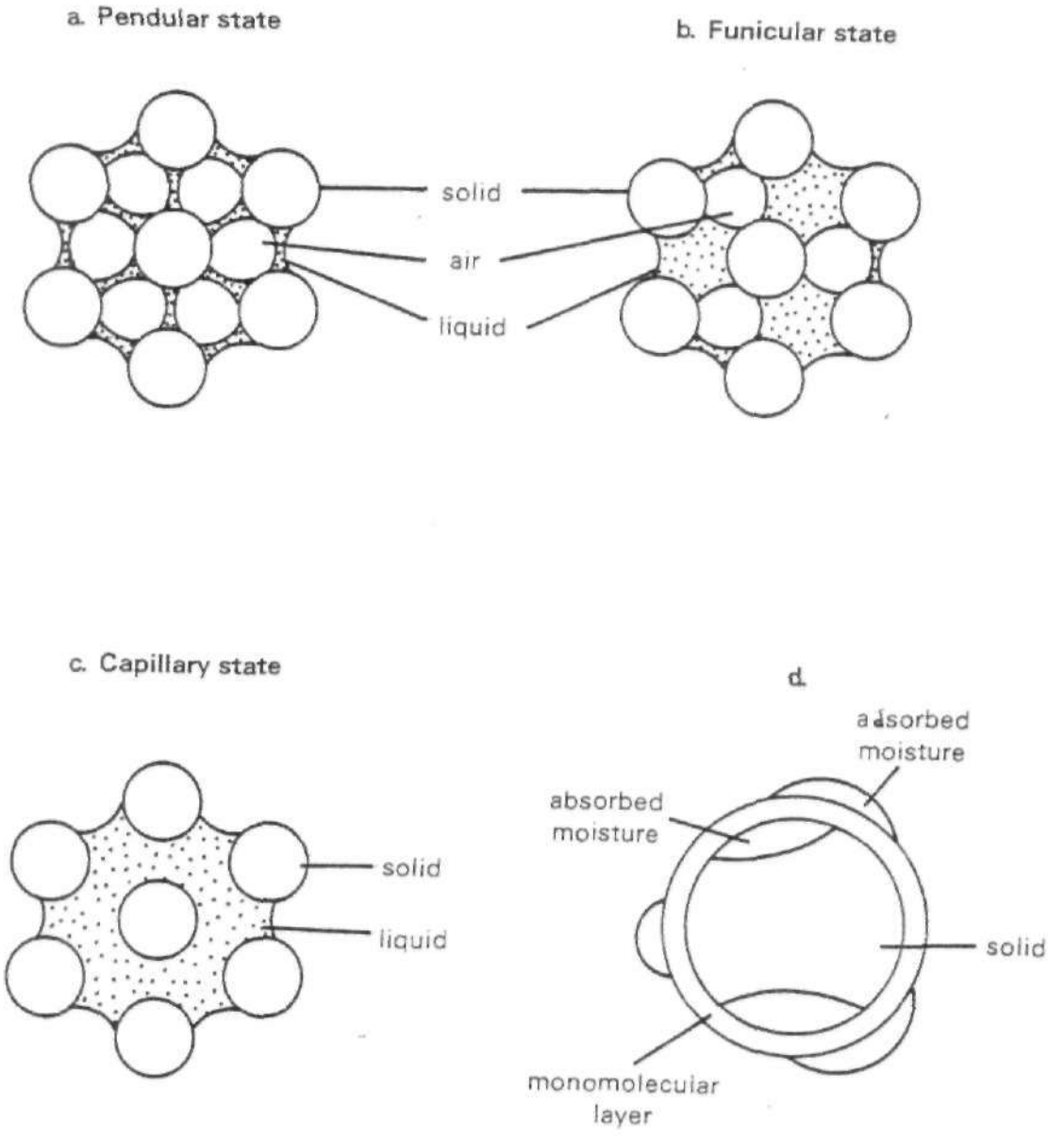
STATES OF WATER IN A POWDER

The apparent contradictions in the experimental findings of reported workers concerning the effect of water can be attributed to the variations in the moisture content of the powders that were investigated, the nature of the powder particularly whether or not it is hygroscopic and the possibility of moisture being present in different physical states.

Coelho and Harnby (1978 a and b) have reported that at low relative humidity, moisture is adsorbed on the surface of powder particles, but as the humidity increases the adsorbed layer of moisture grows in thickness until a critical value of humidity is reached when the layer condenses and forms lens-shaped rings of water between the points of contact of neighbouring particles.

Newitt and Conway-Jones (1958) had earlier postulated that three states of water may be distinguished. For low moisture content, water is held in the powder as discrete lens-shaped rings at the points of contact of the particles - Fig. 1.3a - this is known as the pendular state. At a somewhat higher moisture content the rings

Fig. 1.3 Diagrammatic representation of different types of moisture (after Newitt and Conway-Jones (1958 (a - c) and Young and Nelson (1967a and b) (d))



coalesce and there is a continuous network of liquid interspersed with air - this is the funicular state - Fig. 1.3b.

With further increase in the moisture content the capillary state is reached when all the pore spaces in the powder are completely filled - Fig. 1.3c.

Similarly Young and Nelson (1967 a and b) have reported that moisture can be present in three physical states - Fig. 1.3d; it can form an adsorbed monomolecular layer, an adsorbed multilayer which forms pendular, funicular or capillary bonds between particles or moisture can be absorbed into the interior of the particles. Using moisture adsorption and desorption isotherms of powders, Young and Nelson made improvements on the earlier theoretical equations proposed to determine the effect of moisture on the interparticle forces and tensile strength of powders. Based on this model and using the kinetic theory of gases they derived mathematical equations to describe moisture adsorption and desorption isotherms of powders. These equations have been applied, despite some disagreement (Zografi et al 1983), by York (1981) to explain the moisture sorption hysteresis in hard gelatin capsules, maize starch and mixtures of maize starch and drug powders and by Chan and Pilpel (1983) to show that the presence of up to about 15% w/w moisture has little effect on the tensile and shear properties of sodium cromoglycate and 1 : 1 mixtures of sodium cromoglycate and lactose because most of the moisture is located internally inside the particles.

Recently Zografi et al (1984) have investigated water vapour sorption of various starches and celluloses including microcrystalline cellulose and have concluded that water sorbed by such polymers most likely exists in at least three states ; tightly bound to anhydro-glucose units, less tightly bound and as bulk water.

It is considered that it would be of pharmaceutical interest to study in the present work the effect of moisture content on the elastic and plastic properties of paracetamol tablet formulations and the quality of the resulting tablets ; as far as can be ascertained this has not been previously reported.

TABLETS

Since they were first made more than a thousand years ago, the use of tablets as a dosage form has increased greatly and today tablets represent the most popular dosage form among the contemporary methods for administering drugs.

Tablets owe this popularity to several advantages which they offer, including ease of drug administration and therefore convenience to the patients, precision of dosage, durability of physical characteristics for extended periods of storage, stability of chemical and physiological activity of the drugs and amenability to automation and high speed commercial production and therefore less cost to the patients. However, very few drugs can be tableted on their own and problems occur such as capping, lamination, chipping, picking, variations in tablet weights. To ameliorate these problems, certain pharmaceutical compounds of diverse origin and chemical activity are usually incorporated with the active drug to aid the processing in one way or another. These compounds are important functional components usually referred to as tablet excipients and include inert diluents to provide bulk, binding agents to impart cohesiveness to the powder and structural strength to the formed tablets; disintegrants to ensure that they break up within a period of time in the presence of fluids for release of medicament ; glidants to improve and regulate flow properties

of the powder in the hopper and die thereby ensuring consistent and uniform weight ; and lubricants to prevent the tablet from sticking to the punches and die during compression and to facilitate tablet ejection. There are three main methods of tablet production : wet granulation, slugging and direct compression. In the traditional multistep wet granulation, a solution of binder is added to the powder mass either in a fluidised bed or prior to massing and screening and the granules are subsequently dried. In slugging (also called preliminary compression granulation) suitable powder flow is obtained by a preliminary compression step in the dry state using a heavy duty tablet press or rollers under controlled pressure. Compacted material so formed is then crushed to the optimum particle size for flow and compressibility. Direct compression generally involves only blending and compression, thus providing the possibility of increased product stability compared with wet granulation, and reduced costs by requiring fewer operations, less machinery, reduced personnel and considerably less time (Mendell 1972).

Powders and granules are compressed into tablets between punches and dies on single punch rotary tablet machines.

The number and diversity of tablet excipients make tablets a complex physico-chemical system. The selection of these excipients has been based mainly on trial and error 'artistic' (or rather empirical) methods and consequently the quality of tablets depends on the empiricism of their manufacture. Research in tableting during the past several decades has focussed mainly on how to increase the rate of tablet production but contemporary research is now aimed at correlating the fundamental properties of pharmaceutical powders with their tableting and at scientifically elucidating the mechanisms of powder consolidation during compaction .

Although there is uncertainty in the literature as to who pioneered the process (Barnel 1822 ; Wollaston 1829 ; Osann 1841), the first machine for the production of medicinal tablets by the compression process was patented by Brockendon (1843).

McFernen (1874) and Dutton (1876) developed and improved on Brockendon's idea and obtained further patents for the machine. Since then, many papers (Spring 1880, 1884 ; Hogan 1919) relating to the compaction of powder in dies and the quality of the resulting tablets have been published.

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 tableting and the physical and mechanical forces affecting the consolidation of powders during compaction. This followed immediately after Higuchi and his co-workers (1952) published the first series of papers relating to the physics of tablet compression.

The agglomeration of particles during compaction is well documented and many hypotheses have been proposed to describe the behaviour of the particles during tableting.

Rumpf (1962) proposed that the mechanism of bonding of powders in the formation of a tablet is related to inter particular van der Waals' forces of attraction. The cohesion between solid surfaces depends on forces of atomic attraction which manifest themselves at slightly greater distances than normal inter-atomic spacing (Versano and Lachman 1966). 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 tendency for plastic flow will attain a greater contact area under pressure and therefore a higher degree of bonding will result (Jones 1960).

Electrostatic forces may also 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 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.

When a powder is compressed, its density increases and the degree of consolidation may be monitored by the change produced in its volume. For various materials including lead shot, sodium chloride, potassium nitrate and ammonium chloride, Walker (1923 a and b) found a logarithmic relationship of the form

$$V_r = C' - K' \log P \qquad (60)$$

where V_r = relative volume defined as the ratio of the bulk volume at applied pressure, P to the volume at infinite pressure ; and C' and K' are constants for each material.

Higuchi et al (1952, 1954) obtained a similar relationship for sulphathiazole, aspirin and lactose which applied satisfactorily until the porosity of the material had been reduced to about 5%. But relationships of this type provide very little basic information on the obviously complex processes that are occuring when a powder

is subjected to increasing compression and finally forms into a compact.

To improve the situation, Seelig and Wulff (1947) carried out detailed studies on the effect of pressure on the volume of compressed powders and proposed that consolidation takes place in stages - the initial mechanism involves particle rearrangment and packing down, followed by elastic and plastic deformation and finally cold welding of the compact.

Similarly Train (1956) postulated a hypothesis which maintains that bonding is due to interparticular shearing and shearing along the die wall. The consolidation process is divided into four stages :

1. The application of axial pressure results in interparticulate slippage, re-organisation 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. Secondly, 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 3, 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 4 , 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 is

limited by the compressibility of the material.

Many experiments have validated this concept e.g. Higuchi et al (1953) working on suplhathiazole tablets observed that the porosity of the tablets progressively decreased as the pressure was increased but the specific surface 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 (Train 1956 ; Shotton and Ganderton 1960 a and b ; Rubinstein 1976).

More than fifteen different mathematical descriptions of the compression process have been compiled in the literature (Kawakita and Lüdde 1971) and several of these including those due to Heckel (1961 a and b), Cooper and Eaton (1962) and Kawakita and Lüdde (1970/71) have been validated for pharmaceutical systems.

THEORY OF ASPERITC MELTING

More recently, another theory describing a mechanism of powder consolidation was proposed by York and Pilpel (1972) 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. As a result frictional heat develops at points of contact due to a high degree of shear . The heat generated during tableting of formulated powders has been shown to raise the temperature between 5° and $30^{\circ}C$ above ambient (Nelson et al 1955 ; Hanus and King 1968 ; Harwood 1969 ; Juslin 1969 ;

Krogerus et al 1969 ; Travers and Merriman 1970). But much higher temperatures will have developed locally at the contact points between the asperities on the particles (Hanus and King 1968).

Also very high pressures are manifested at the localised points of contact or asperities. The combination of high pressures and high temperatures at asperities lowers the melting points of the materials according to Skotnicky's (1953) equation

$$\frac{\delta \theta_m}{\delta P_1} = - \frac{V_m \theta_m}{L_f} \qquad (61)$$

where $\frac{\delta \theta_m}{\delta P_1}$ is the change in melting point with pressure, V_m is the volume per mole of solid and L_f is the latent heat of fusion.

This differs from the well-known Claperyon thermodynamic equation which for most materials predicts an increase in melting point with applied pressure, because it is assumed that in a powder any liquid formed by melting would not be subjected to the same pressure as the solid.

This lowering of melting point under high pressure causes the materials to melt at the points of contact at temperatures below the conventional melting point. This phenomenon is termed asperitic melting.

This melting 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 and consequently some of the melted material may resolidify giving rise to bonding between particles.

The theory of asperitic melting has been confirmed experimentally by several workers who used materials coated with low melting point substances (York 1973 ; Britten and Pilpel 1978 ; Pilpel and Britten 1979 ; Malamataris and Pilpel 1983 ; Igwilo 1983).

The theories cited above and their related compression equations have contributed extensively to the elucidation of the mechanisms of powder consolidation during compaction but they have proved inadequate to explain some of the compression problems observed in routine production of tablets e.g. why some pharmaceutical powders and formulations form firm and satisfactory tablets, whereas others form weak and crumbly tablets which may tend to cap and laminate ; or why minor changes in the processing and formulation significantly affect the compression characteristics of powder formulations and the quality of their formed tablets.

The compression behaviour of multiparticulate systems is extremely difficult to characterise because there are several discrete mechanisms in operation which overlap and change as the compression proceeds. Most of the previous theories and equations describe only the compression stage of the tableting process whereas a complete tableting cycle involves the compression stage, when compression force is applied to the material, the relaxation (or decompression) stage when the material is relieved of the compression force and the ejection stage when the tablet leaves the die.

It is now realised that the decompression stage is at least as important but not independent of the compression stage in determining whether or not a tablet formulation will form firm and satisfactory tablets (Hiestand 1978).

In recent years much research has been conducted on intrumental tableting machines of both single punch (Higuchi et al 1954 ; Shotton and Ganderton 1960 ; Lewis and Shotton 1965 ; Leigh et al 1967) and multiple punch design (Shotton et al 1963 ; Knoechel et al 1967 ; Goodhert et al 1968) to study the work involved in tablet compression (Nelson et al 1955 ; Polderman and de Blaey 1971 ; Horikoshi et al 1974), the thermodynamic aspects of tablet formation (Coffin-Beach and Hollenbeck 1983), the distribution of the applied pressure (Higuchi et al 1954 ; Leigh et al 1967) and the effects of lubricants and moisture on these distributions (Lewis and Shotton 1965 ; Shotton and Rees 1966 ; Rees and Shotton 1971 ; Juslin and Krogerus 1971).

CAPPING OF TABLETS

Leigh et al (1967) have studied the axial and radial pressure cycles of several pharmaceutical systems. The curves obtained were compared with those of several ideal solid bodies, namely a perfectly elastic body, a body with constant yield stress in shear and a Mohr's body, i.e. a body in which there is a single relationship between the shear yield stress and the normal stress on the plane of shear. The results indicated that materials which tend to cap or laminate on decompression behave like a Mohr's body.

Paracetamol powder has been selected for investigation in the present work because it does not form satisfactory tablets - due to lamination and capping - without the addition of excipients (Leigh et al 1967 ; Krycer et al 1982).

Capping may be described as a phenomenon in which the top of the tablet (the 'cap') detaches partially or completely from the rest of the tablet during the decompression phase or after ejection of the tablet. Associated with capping are lamination and multilaminations

which are cracks in the tablet perpendicular to the compression axis. Several causes have been assigned to this common but difficult tableting problem and include high elastic recovery of the drug (Leigh et al 1967), polymorphic forms of drug (Fishburn 1948), particle size (Hersey and Rees 1970), transverse shearing at the die wall (Long 1960), air entrappment (Long and Alderton 1960 ; Mann et al 1982), inadequate binding (Elowe et al 1954 ; Obiorah and Shotton 1976), moisture content (Shotton and Harb 1966 ; Groenwold et al 1972), compression pressure (Elowe et al 1954 ; Shotton and Ganderton 1961) and shape of punches (Seth 1956).

The solutions are empirical in nature and it is only recently that researches have related the capping tendencies of tablet formulations to their plastic deformation during compression and elastic recovery during decompression and after tablet ejection.

Hiestand and his coworkers (1977, 1978, 1984) have extensively studied the effects of decompression for pharmaceutical systems and stated that whether or not tablet fracture occurs during the shear deformation which accompanies decompression depends on the ability of the material to relieve the stresses by plastic deformation without undergoing brittle fracture, and this ability is a time dependent phenomenon. Those materials that relieve stress rapidly are less likely to 'cap' and laminate. Hiestand has proposed several methods to assess the readiness of materials to laminate, ranging from measuring the speed at which the residual die wall pressure decays to a 'brittle fracture propensity' test which compares the tensile strength of a compact that contains a built-in stress concentrator 'defect' with one that does not.

Shlanta et al 1964 ; Okada and Fukumori 1974 and Travers et al 1983 have also studied time-dependent effects of powder compaction and Danielson et al (1983) have explained that the dependence of the viscous and elastic parameters on compression conditions is found to be predictive of conditions under which capping or lamination of the compact will occur.

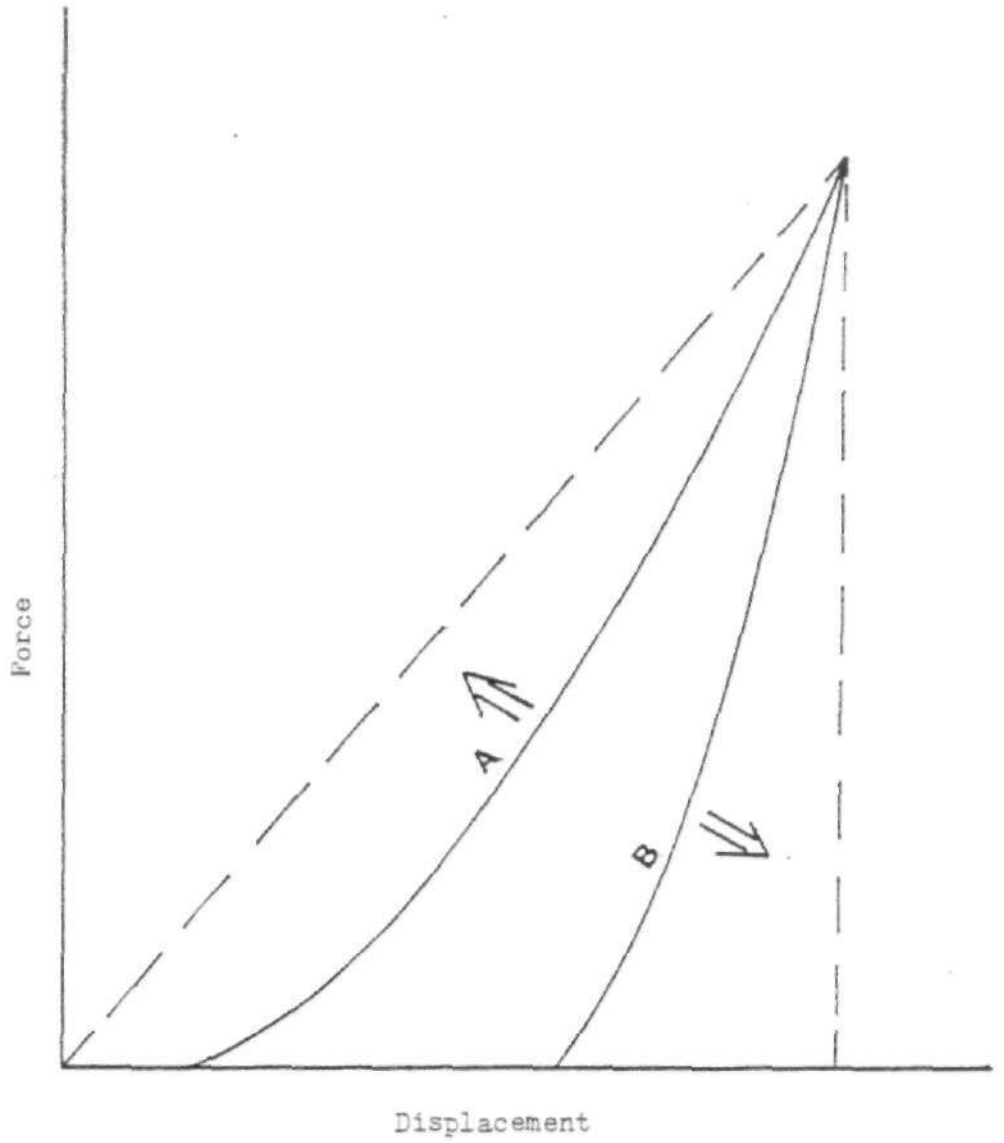
Guyot (1978) proposed a single method for characterising materials, based on the idea of Führer (1963) where the upper punch stress is plotted against its displacement during the compression cycle. Ideally, a right angled triangle is obtained, indicating perfect plastic behaviour with none of the disruptive effects of elasticity. A real material takes the form shown in Fig. 1.4 and excipients should be selected to move the profile for the mixture towards the ideal as indicated by the arrows.

In the present study similar force-displacement plots for various paracetamol and Avicel mixtures have been obtained under different tableting conditions and analysed to calculate their elastic recovery and stress relaxation. These paramaters are then used to derive an index of tableting performance termed the plasto-elastic ratio which is related to the tensile strength of the tablet. Details of these parameters are given in Chapter 2.

It is hoped that such measurements will contribute to the understanding of tableting in general and the problem of capping in particular.

Fig. 1.4. Optimisation of force-displacement compression profile (from Guyot 1978)

A = compression ; B = decompression



TESTING 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 elicit the required therapeutic responses when ingested. As a corollary, it is consistent with Good Pharmaceutical Manufacturing Practice (GPMP) that there should be uniformity in the quality of tablets produced from batch to batch. These are the basic principles justifying the design of quality control tests for tablets. While some of these tests are official and outlined in the relevant pharmacopoeias, a gamut of control tests are unofficial and serve as in-process control tests in pharmaceutical laboratories. Of much importance are two opposing tablet quality parameters : its mechanical strength and disintegration time. These tests have been applied to tablets made in the present work and it seems relevant to discuss them in detail.

MECHANICAL STRENGTH

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

The mechanical strength of tablets is an important property which plays a significant role in development and control procedures. It can be described by various terms including fracture resistance (Endicott et al 1961), friability (Burlinson and Pickering 1950) hardness (MacCallum et al 1955) , bending strength (Munzel and Kagi

1957), tensile strength (Nelson 1956 a ; Fell and Newton 1970 ; Ridgway et al 1972 ; York and Pilpel 1973 ; Newton and Stanley 1975) and crushing strength (Seitz and Flassland 1965). The latter has been linked by several workers with other properties of tablets (Higuch et al 1953 ; Nelson 1956 ; Kwan et al 1957 ; Shotton and Ganderton 1960) and is widely used in commercial production as a control test for tablet strength.

A convenient method for obtaining the tensile strength of a tablet is to apply diametrical compression and this method, which has been used in the present work has been reviewed by Ridgway (1970).

For flat faced cylindrical tablets, the tensile strength, T is given by (Timoshenko and Goodier 1951 ; Peliter 1954)

$$T = \frac{2P_b}{\pi D t_t} = \frac{2P_b}{\pi A_b} \qquad (62)$$

where P_b is the applied pressure, D is the diameter, t_t is the thickness of the tablet and A_b is the cross-sectional area of break.

Rowe et al (1973) considered that in the case of plastic matrix tablets containing nonporous spherical polymer particles of relatively narrow size distribution, the area of contact between the particles was linearly related to $(1 - \varepsilon)$ over the porosity ranges of 0.1 - 0.4. They therefore suggested that a porosity function should be incorporated into the tensile strength Equation 62 to give

$$T = \frac{2P_b}{\pi D t_t (1 - \varepsilon)} \qquad (63)$$

The validity of Equation 63 to other types of tablets is doubtful since the term $(1 - \varepsilon)$ does not express the area over which failure occurs. Moreover at porosities of 0.4 most of the powders will

be in too loose a state of packing to exhibit any tensile strength (Rowe et al 1973)

Recently other methods based on photoelastic and elastic theories have been used to measure the tensile strengths of tablets. Hiestand and Poet (1974) used a transverse compression method on square tablets and showed that for sucrose, aspirin and calcium carbonate, the tensile strength can be calculated using the equation

$$T = 0.16 \times \text{compressive stress} \qquad (64)$$

Similarly, David and Augsburger (1974) used a flexure (bending) test in which tablets were compressed at a constant rate between two knife edged fulcrums until fracture occured. The relevant flexure equation derived from elasticity theory

$$T = \frac{3 P_b b'}{4 D t_t^2} \qquad (65)$$

where b' is the distance from fulcrum to fulcrum and P_b, D and t_t have the same meanings as in equation 62, was used to calculate the tensile strengths of tablets.

Both these methods gave reproducible results which agreed well with the tensile strength values obtained from diametrical compression.

Some of the factors that have been shown to affect the tensile strengths of compressed tablets are : compression pressure (Higuchi et al 1953, 1954 ; Shotton and Ganderton 1960 ; Hersey et al 1967 ; Ridgway and Aulton 1974 ; Newton and Stanley 1975), binding agents (Bagster and Fitzgerald 1974 ; Shotton and Edwards 1974), temperature (York and Pilpel 1972, 1973 ; Britten and Pilpel 1978 ; Malamataris and Pilpel 1983), moisture content (Jaffe and Foss 1959 ; Shotton and Rees 1971 ; Eaves and Jones 1972a ; Cole et al 1975 ; Esezobo

and Pilpel 1976), size and shape of the particles/granules (Higuchi et al 1953 ; Newitt and Conway-Jones 1958 ; Shotton and Ganderton i960 ; Hersey et al I967 ; Harwood and Pilpel I968 ; Alpar et al 1970 ; Ridgway et al 1971). Very little work has been reported on the relationship between elastic recovery and stress relaxation of powder mixtures and the tensile strength of their resulting tablets. In Chapter *k* of the present work, some factors which affect this relationship have been investigated.

DISINTEGRATION TIME

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 processing conditions e.g. the effect of concentration of tablet disintegrant on its disintegration time.

Disintegration of a compressed tablet is the process by which a whole tablet breaks up into small pieces when in contact with fluid. Following oral administration, the tablet breaks down to granules and aggregates by a deaggregation process. The drug is brought into solution by a dissolution process which takes place from the intact tablet, the fragmented aggregates and the fine particles. The drug in solution is subsequently absorbed into the blood stream (Wagner est al 1971).

Complete tablet disintegration is defined by the National Formulary XIII as "that state in which any residue of the tablet, except fragments of insoluble coating remaining bn the screen, is a soft mass having no palpably firm core". The importance of tablet disintegration was recognized as early as 1879 when Richards obtained a patent

which recommended that pills be perforated to admit gastric juice for better disintegration. Subsequently a number of superior methods were proposed (Berry 1939 ; Prance et al 1946 ; Hoyle 1946) including that recommended by the British Pharmacopoeia which involves raising and lowering the tablet at a constant rate in a column of water at 37°C by means of a mechanical device and measuring the time taken for the particles to drop through a mesh of stated size.

Different methods and end-points are used in other pharmacopoeias and this interpharmacopoeial discordance has been criticized by French et al 1967. Moreover, for a particular pharmacopoeia, the guidelines in the disintegration test are still arbitrary. The choice of water as a disintegrating medium is open to criticism and Abbott et al have observed that the addition of mucoid substances to the test solution has 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 the drug is absorbed (Hartley 1950). Furthermore, 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 regard to dissolution. Rubinstein and Bodey (1976) have proposed a deaggregation test which utilizes an automated counter and measures the surface area generated per tablet during disintegration

Langenbucher (1974/75) has discussed means of an improved standardisation of the static and dynamic design of disintegration test equipment and has suggested tighter compendial specifications.

Despite these setbacks, the disintegration test in its present form is invaluable to tablet manufacturers because it provides a simple and useful means for monitoring and controlling the quality of tablets and more so because several workers have established quantitative correlation of disintegration times of tablets with their dissolution times (Schroeter et al 1962 ; Jacob and Plein 1968 ; Krowczynski and Stozek 1968 ; Smith et al 1971 ; Esezobo and Pilpel 1976 ; Pilpel et al 1978) and the physiological availability of the incorporated drugs (Chapman et al 1954, 1955 ; Levy 1961 ; Morrison et al 1964 ; Fraser et al 1973).

THEORIES OF DISINTEGRATION

It has been shown (Higuchi et al 1953 ; Wagner and Pernarowski 1971) that the majority of particles/granules in compressed tablets retain their individual identity and the disintegration of tablets takes place in two stages i.e. breaking up of the tablets into granules which then deaggregate to form small particles. Several mechanisms for tablet disintegration have been proposed by previous authors. They include :

a. Evolution of gas

If a gas is evolved by a chemical reaction when the tablet comes into contact with water, then the tablet will disintegrate. This is the basis for the manufacture of effervescent tablets. An example of such a reaction is sodium bicarbonate with citric and tartaric acids, which yields carbon dioxide. Peroxides incorporated in certain formulations decompose in the presence of moisture to release oxygen and this also causes disintegration.

b. Heat of Wetting

The heat produced when the tablet is immersed in water causes the entrapped air in the tablet to expand and exert sufficient pressure to disintegrate the tablet (Matsumaru 1958, 1959). He also showed that the heat of wetting of aluminium silicate decreased with compression pressure and this agreed with the observed increase in disintegration time.

c. Effect of water absorption

The water absorbed by the tablet initiates disintegration but this depends on the solubility of the drug and other ingredients present (Matsumaru 1959).

d. Swelling

The grains of the disintegrant, particularly starches, swell in the presence of water and exert pressure on the granules to force them apart (Berry and Ridout 1950 ; Jaminet 1964). Shteingart et al (1970) reported that tablets of water insoluble drugs disintegrated faster with starches than those of water soluble drugs due to the diminished water absorption capacity of the starches in the latter case.

Pharmaceutical factors which affect disintegration time of tablets

The physical properties of the drug, the pharmaceutical adjuvants employed in the tablet formulation and the manufacturing technique, procedure and equipment employed will more often than not affect the disintegration times of tablets. The following factors have been specifically shown to affect the disintegration time of tablets.

a. Surfactants

They increase the wetting of the surface of the tablet and its capillaries thereby promoting disintegration (Awe and Gelbrecht 1956 ; Cooper and Brecht 1957) but this depends on the concentration of the surfactant used (Aradi 1961 ; El-khalek and El-kader 1964). Surfactants decrease the hydrophobicity of the tablet thereby increasing the rate of water penetration into it (Awe and Gelbrecht 1956 ; Ritshcel and Rahman 1964). Duchene et al (1970) have shown that the more hydrophobic the tablet is, as observed when high concentrations of lubricants are used, the greater the disintegration time.

Compression pressure

Higuchi et al (1953) found among other things that there is a logarithmic relationship between the disintegration time and the compression force used to form the tablet. Manudhane et al (1969) obtained similar results with starches. It has been shown that penetration of water into a tablet is proportional to its pore diameter or porosity (Singh et al 1968 ; Ganderton 1969 ; Ganderton and Selkirk 1970 ; Selkirk and Ganderton 1970). The porosity and permeability of tablets decrease as the compression pressure is increased (Münzel and Kagi 1956 ; Ganderton and Fraser 1970) and as the porosity or pore diameter decreases, the disintegration time increases (Holstius and Dekay 1952 ; Fox et al 1963 ; Selmeczi and Kedvessey 1970). Though no quantitative relationships have been reported between disintegration and penetration times, generally short disintegration times are associated with rapid fluid penetration (Ganderton 1969).

Assuming that penetration of water into pores is affected by interfacial tension, contact angle, geometry of the solid surface and viscosity, Nogami et al (1967) developed an equation to calculate the penetration time for water

$$P_t = \frac{25\eta\bar{d}\, t_t}{\gamma d_p \cos\theta} \qquad (66)$$

where P_t is the penetration time, $\bar{d}$ is the diameter of the particles of the drug in the tablet, d_p is the average pore diameter, θ is the contact angle between water and drug particle and γ and η are respectively the surface tension and viscosity of the liquid.

Employing this equation, the authors calculated penetration times of water and a qualitative correlation was shown to exist between disintegration and penetration times.

The existence of pores and capillaries and the penetration of fluid into the tablets however, do not exclusively determine disintegration times since semi-polar and non-polar fluids have been shown to penetrate tablets (Nogami et al 1966 ; Patel and Hopponen 1966) yet do not cause them to disintegrate and certain tablets with very low porosities disintegrate rapidly (Bánó et al 1961 ; Patel and Hopponen 1966 ; Wood 1967).

The nature and proportion of binders (Huber et al 1966), lubricants (Alpar et al 1969) and disintegrants (Commons et al 1968) incorporated in tablet formulations and the moisture content of tablets (Kavarana and Burlage 1955 ; Esezobo and Pilpel 1976 ; Pilpel et al 1978) also modify the disintegration times of tablets in one way or another.

It can be seen that the disintegration of tablets is a complex phenomenon strongly dependent on the interaction of all the formulation

and processing variables ; therefore the making of sweeping generalisations about disintegration times of tablets may not only be misleading but hazardous.

In chapter 5 of the present work, the separate and combined effects of some of these variables on the disintegration times of paracetamol tablets have been investigated.

INTERACTION OF VARIABLES

The diversity of the origin and chemical activities of tablet excipients (diluents, binders, lubricants, disintegrants etc.) and the various methods of tablet manufacture as earlier discussed have made investigations into pharmaceutical tablets a complex subject. The compression characteristics of tablet formulations and the quality of the resulting tablets largely depend on the formulation and processing variables and these have preoccupied researchers in tableting technology and commercial manufacturers.

However the "isolationism" of many development projects is very obvious and has been criticised (Cooper 1971). There is a tendency to investigate one variable amongst many without consideration of the complex interactions that can occur between different ingredients of a formulation or between different processing variables. While the conclusions may be valid for a particular experimental design, they are often of little value in the advancement of the science of tablet formulation, processing and testing.

In attempts to improve the situation a few workers (Malinowski and Smith 1974, 1975 ; Dinçer and Özdurmus 1977 ; Newton and Razzo 1974, 1977 ; Kurup and Pilpel 1977 ; Adeyemi and Pilpel 1983, 1984 ; Sanderson et al 1984) have carried out factorially designed experiments to study the interaction of formulation and processing variables on

the quality of tablets and capsules. Results have been treated by the standard analysis of variance procedures.

An interaction, in terms of this type of analysis means that the effect of one variable on another is not simply additive (Snedecor and Cochran 1967). Hence it is possible to have an interaction in which one factor gives an increase in effect at one level of another factor and a decrease at another level ; or there may be an increase or decrease in both cases, but this cannot be predicted by simple addition of the individual effects (Newton and Razzo 1974). The essence of factorially designed experiments in formulation studies is to find out the nature of the interactions of the significant variables, show the emergence of some general patterns and draw general conclusions.

In view of this it is considered appropriate to study in Chapter 5 of the present work the interactions of some variables and their effects on the tensile strengths and disintegration times of paracetamol tablets. It is hoped that this type of factorial study will contribute to an understanding of the basic mechanisms in tablet formulation and the relative importance of the individual interactions to the final tablet characteristics.

SCOPE OF THIS WORK

Paracetamol is a drug which it is very difficult to form into satisfactory tablets because they tend to cap and laminate. Avicel is a versatile tablet excipient which forms firm tablets and it is usually used as an adjunct in the tableting of paracetamol. No one seems to have offered a scientific explanation for their contrasting compressional properties. It was therefore considered appropriate

in the present work to study their fundamental mechanical properties in relation to tableting with the aim of contributing to an understanding of the consolidation of powders during compaction into tablets and of the basic mechanisms involved.

Simple mixtures have been used for most of the present work because there is much interest today in materials and formulas that permit the manufacture of tablets without the traditional and costly step of granulating.

The materials and equipment used and the experimental procedures that have been followed in this work are discussed in Chapter 2.

In Chapter 3 the tensile strengths of loosely consolidated powder mixtures have been measured. On the basis of the latest Cheng Theory, the results have been used to derive important parameters which can be used to predict the compressibility of pharmaceutical powders and their mixtures.

In Chapter 4, the powders were compressed into tablets on an instrumented test machine and their elastic recovery and stress relaxations were recorded. Results were used to derive a powder parameter - plastoelasticity, which is related to the tensile strengths of tablets. Some formulation and processing factors which modify the plastoelasticity of powders and their compressional characteristics were then investigated.

In Chapter 5, the separate and combined effects of selected formulation and processing variables on the tensile strength and disintegration times of paracetamol tablets were studied.

This detailed general introduction gives the relevant theoretical background to the present work. Detailed aims, results, discussion

and conclusions are given in each of the experimental chapters (i.e. 3, 4, 5) but for convenience the general conclusions of the work as a whole have been brought together and summarized in Chapter 6.

CHAPTER 2

CHARACTERISATION OF MATERIALS AND EXPERIMENTAL METHODS

This chapter deals with the materials, their classification and categorisation and the experimental techniques that have been employed in the present investigation for measuring the relevant physico-chemical and mechanical properties of the loosely consolidated powder beds and compressed tablets and disintegration times of tablets.

MATERIALS

The materials used in this work were Paracetamol powder (B.P. grade) supplied by Cambrians Chemicals Company, U.K. ; microcrystalline cellulose (Avicel PH 101) powder, supplied by Honeywill and Stein Ltd. U.K.) and alginic acid (HED grade) from Alginate Industries, U.K. All other chemicals employed were of good laboratory grades.

CLASSIFICATION OF MATERIALS

Paracetamol and Avicel powder were separately milled in a laboratory hammer mill (Micropul Ltd.) and classified into different size fractions using a Microplex zig-zag classifier (Alpine, Ausburg, W. Germany). The details of the equipment are shown in Figs 2. 1 A B C. The air volume,V and the classifier speed, S, required to produce different size fractions were obtained by reference to the manufacturers' standard curve for calcium carbonate and application of the following equations :

$$d_c = d_e \left(2.6 \times \frac{1}{\rho_s}\right)^{\frac{1}{2}} \qquad (67)$$

where :

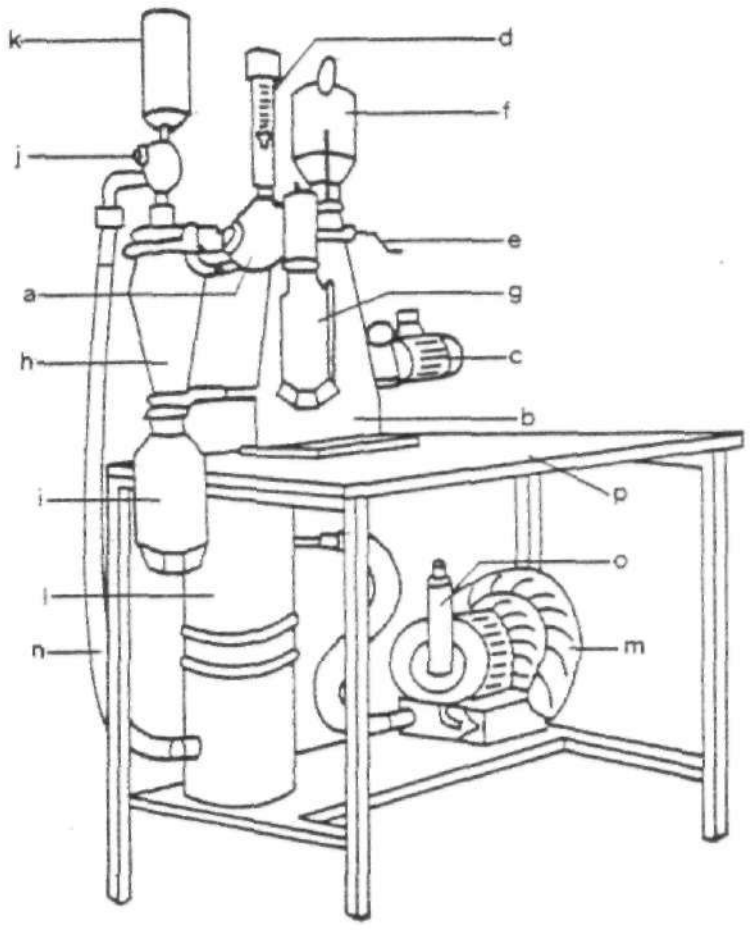
d_c = cut point diameter (diameter required)

d_e = diameter of calcium carbonate equivalent

ρ_s = particle density of powder

and $V = 55 - \frac{S}{1000}$ (68)

Fig. 2.1A Zig-Zag Classifier

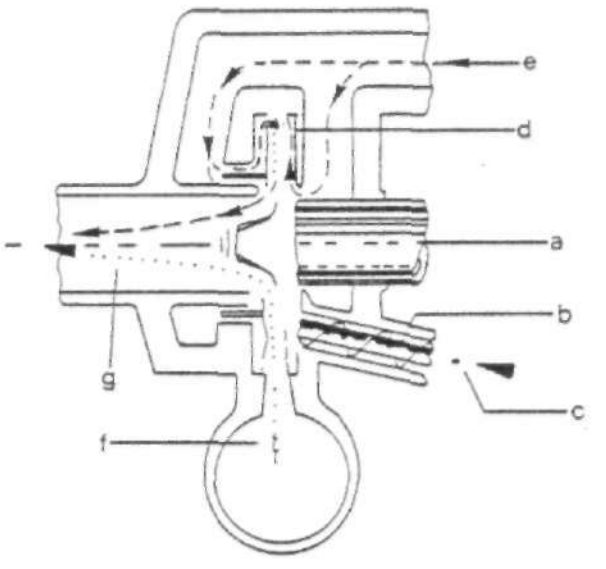


a. classifier
b. stand
c. regulable gear motor
d. flowmeter for classifying air
e. worm feeder
f. bottle for feed material
g. coarse product bottle
h. cyclone
i. fine material bottle
j. air throttle
k. secondary air silencer
l. small filter
m. side channel blower
n. air tubing
o. exhaust air silencer
p. mounting table

Fig. 2.1B Zig-Zag Classifying Rotor



Fig. 2.1C Operation of Classifier



a. drive shaft
b. worm feeder
c. feed material
d. classifying rotor
e. classifying air
f. coarse product
g. fine product

The standard curve gave the relationship between d_e and S. Eq. 67 was used to calculate the value of d_e which was then used to obtain the value of S from the curve. Finally Eq. 68 was used to calculate the value of V.

PARTICLE SIZING

Particle size analysis of powders was carried out by optical microscopy. Thin films of suspensions of the powders were prepared in light liquid paraffin using a fine haired brush to disperse aggregates before viewing under the microscope. Not less than 700 particles were counted to give a statistically significant mean value. As the particles were irregular in shape (paracetamol and Avicel were acicular), Heywood's equation (Heywood 1963)

$$d_a = \left(\frac{4}{\pi} \times \text{length} \times \text{breadth}\right)^{\frac{1}{2}} \qquad (69)$$

was employed to calculate the projected mean diameter, d_a, as the assumed geometric mean of the measured longest and shortest diameters. Although this assumption can be an oversimplification in certain circumstances (Walton and Pilpel 1972) it was considered an acceptable assumption for the present type of investigation. The size distributions of the fractions are given in Fig. 2.2.

PREPARATION OF BINARY MIXTURES

Various proportions of Avicel (mean projected diameter 16.8 μm) were mixed with paracetamol (mean projected diameter 7.7 μm) powder in a rotating cylinder mixer with baffle blades for 30 minutes to produce binary mixtures of different compositions which are shown in Table 2.1. To ensure uniformity of treatment the individual components were also tumbled in the mixer for 30 minutes.

Fig. 2.2.A. Particle size distribution of classified Avicel fractions

(● A_1 , ▲ A_2 , ■ A_3)

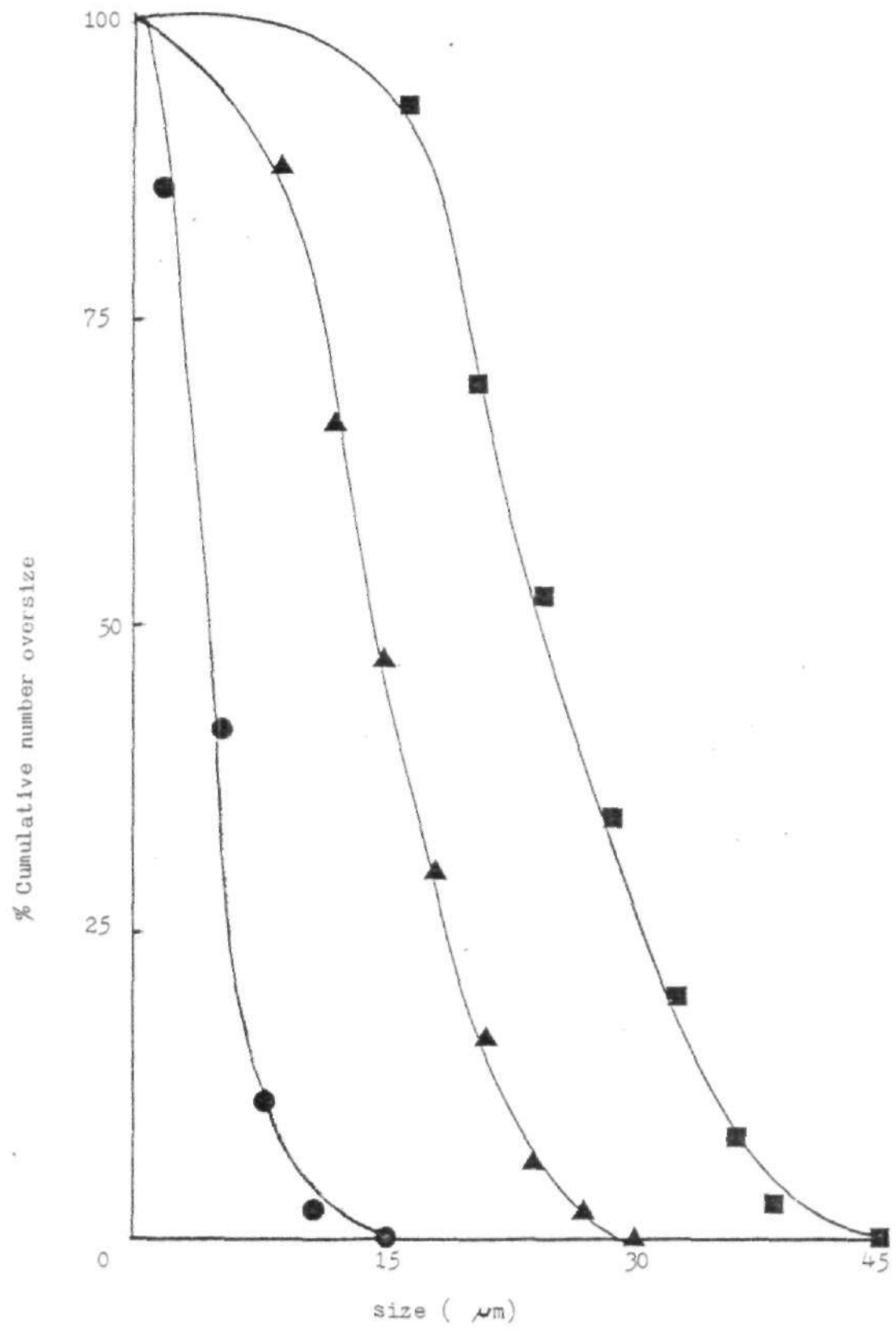


Fig. 2.2.B. Particle size distribution of classified paracetamol fractions

(▲ P_1 , ● P_2 , ■ P_3)

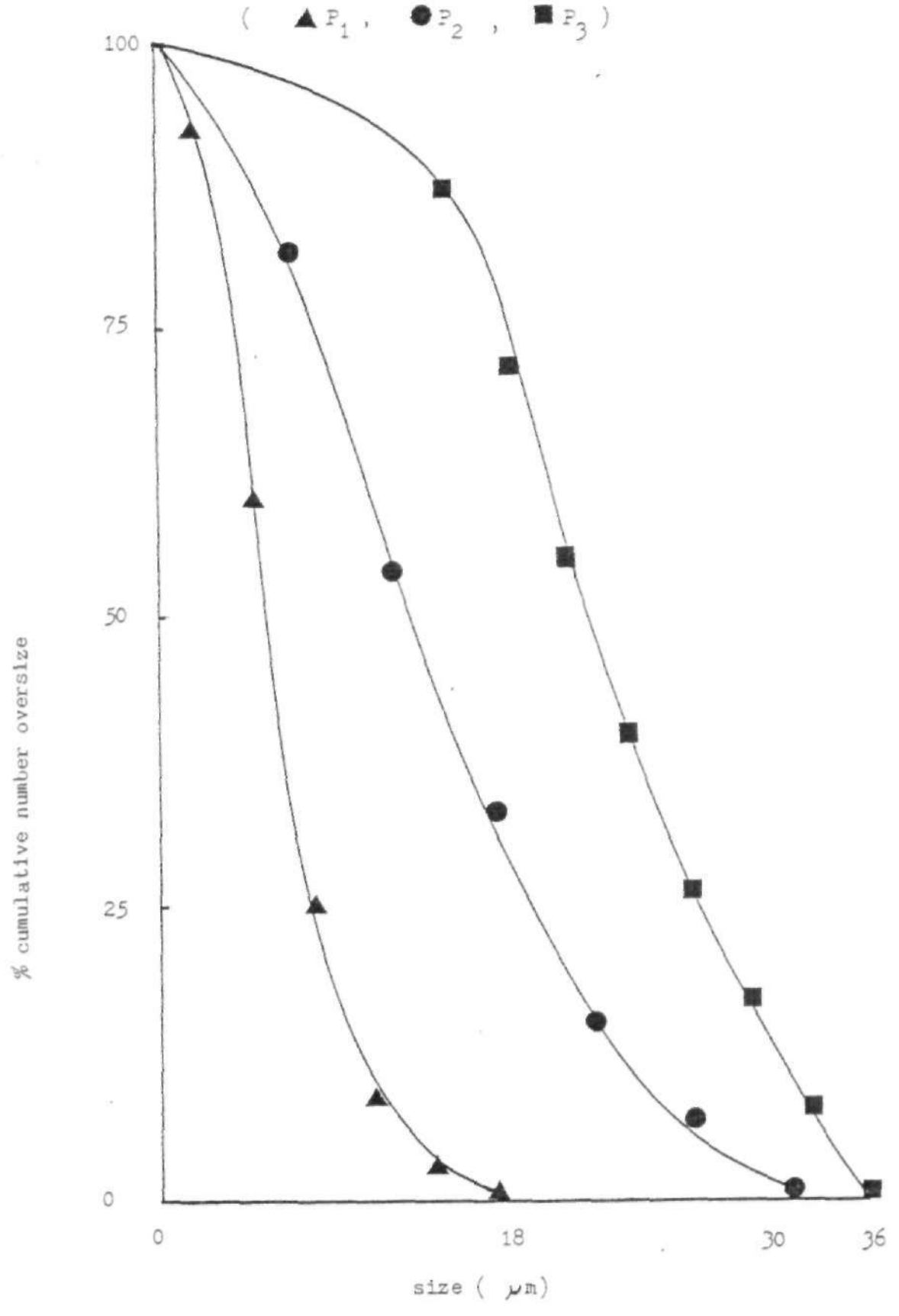


TABLE 2.1

Composition and Physical Parameters of Mixtures

CODE	% w/w Paracetamol	% w/w Avicel	Particle Density ($g\ cm^{-3}$)	Mean Projected Diameter (μm)	Mean Surface Area $(\mu m)^2$	Mean Volume $(\mu m)^3$
P_1	100	0	1.29	7.7	46.0	382.8
P_2	100	0	1.29	16.8	220.3	4186.8
P_3	100	0	1.29	24.2	458.8	8967.0
A_1	0	100	1.52	6.3	30.9	211.9
A_2	0	100	1.52	16.8	220.2	3270.0
A_3	0	100	1.52	27.7	604.4	13565.0
M_1	95	5	1.30	7.7	46.7	397.8
M_2	90	10	1.31	7.8	47.3	414.4
M_3	85	15	1.32	7.8	48.0	432.6
M_4	80	20	1.33	7.9	48.8	452.8
M_5	70	30	1.35	8.0	50.7	500.7
M_6	50	50	1.40	8.5	56.5	643.8
M_7	25	75	1.46	9.8	74.7	1045.8
M_8	10	90	1.49	12.0	112.2	1745.8

DEGREE OF MIXING

The amount of paracetamol in representative samples was measured by comparing its absorbance at 249 nm after suitable dilution of 450-500 mg, which is a scale of scrutiny (Ganderton 1968) appropriate for the dose of paracetamol with a calibration curve for pure paracetamol using a digital ultraviolet spectrophotometer (Cecil Instrumentations model CE 292). It was confirmed that the presence of Avicel did not affect the U.V. absorption of the drug. The degree of mixing, M' is expressed by (Rose 1959)

$$M' = 1 - \frac{\sigma}{\sigma_o} \qquad (70)$$

where σ is the standard deviation estimated from analysed samples and σ_o is the standard deviation of the completely unmixed system ;

i.e. $\sigma_o = \left[y - (1 - y)\right]^{\frac{1}{2}}$ where y is the proportion of paracetamol in the mixture, The degree of mixing was found in every case to be more than 0.93.

The mixtures were dried for 12 hr. at 60°C in a hot air oven and their moisture contents were less than 2%. They were then passed through a 40-mesh sieve and stored in airtight glass jars at 20°C and 40% relative humidity.

PARTICLE DENSITY

The Beckman air comparison pycnometer (model 930, Beckman Instruments, Limited) was used for measuring the particle densities of the individual components. This instrument measured the particle volume of a sample by air displacement at an applied pressure of 1-2 x 10^5 Pa and had an accuracy of 0.01 cm^3. The particle density was obtained from the expression

$$\text{Particle density} = \frac{\text{weight of sample}}{\text{particle volume}}$$

with a reproducibility better than 0.5% and the results are given in Table 2.1. These values were used to calculate the particle densities of the mixtures, $\ell_{s_{mix}}$ from equation (Farley and Valentin 1967/68)

$$\frac{1}{\ell_{s_{mix}}} = \frac{w_1}{\ell_{s_1}} + \frac{w_2}{\ell_{s_2}} \qquad (71)$$

where w is weight fraction, ℓ_s is particle density and the subscripts 1 and 2 refer to the two components. (See Appendix 2)

MOISTURE CONTENT

The moisture contents of samples were determined with an infrared vacuum moisture tester (Townson and Mercer, Limited, Croydon) operating at 90°C and 25 in. mercury pressure. The tester gives the % moisture content on a wet basis and its sensitivity is ± 0.1%

MOISTURE SORPTION AND DESORPTION ISOTHERMS

Several reagent grade salts from British Drug House were used to provide different humidity environments and they are listed in Table 2.2 (Winston and Bates 1960). Paracetamol and Avicel powders were initially dried over phosphorous pentoxide in a desiccator at 20°C. They were divided and transferred to desiccators of different relative humidities provided by the saturated salt solutions at 20°C taking the usual precautions to maintain the temperature constant and the desiccators leak-proof (Winston and Bates 1960 ; Young 1967). After standing for 5 days, their equilibrium moisture contents were determined. The results yielded the sorption isotherms. A similar procedure was followed for determining the desorption isotherms, this

Table 2.2.

Saturated salt solutions used to provide various humidity environments

(After Winston and Bates 1960)

Saturated salt solution	Relative Humidity (%) at 20°C
P_2O_5	0
$LiCl.\frac{1}{2}H_2O$	15
CH_3 COOK	20
$MgCl_2.6H_2O$	33
$K_2CO_3.6H_2O$	44
$Mg(NO_3)_2.2H_2O$	55
$NaNO_2$	65
NaCl	76
KCl	85

time initially equilibrating samples over saturated potassium chloride solution at RH 85% and 20°C.

PREPARATION OF GRANULES

300 gm batches of samples M_4 - M_8 and A_2 were granulated with controlled amounts of distilled water in a rotating cylinder for 10 minutes. The wet masses were then passed through a No. 16 mesh sieve and dried at 60°C for 12 hr. The rather loose and fragile granules were passed again through the No. 16 mesh sieve. They were then stored in airtight containers at 20°C and 40% relative humidity.

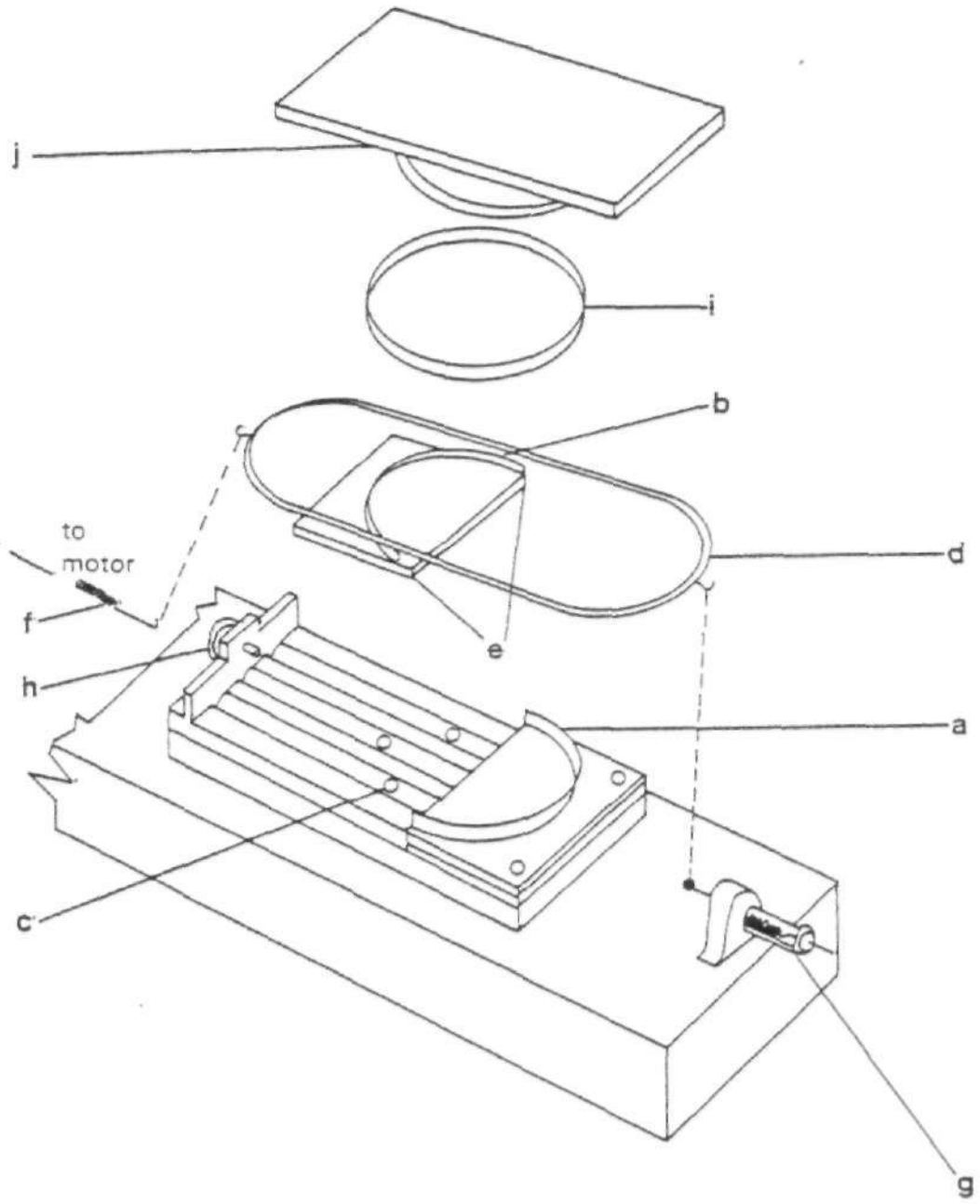
EQUIPMENT AND EXPERIMENTAL PROCEDURES

The mechanical and plastoelastic properties of the samples were measured with a powder tensile tester and a DARTEC Universal testing machine (DARTEC Limited) respectively.

POWDER TENSILE TESTER

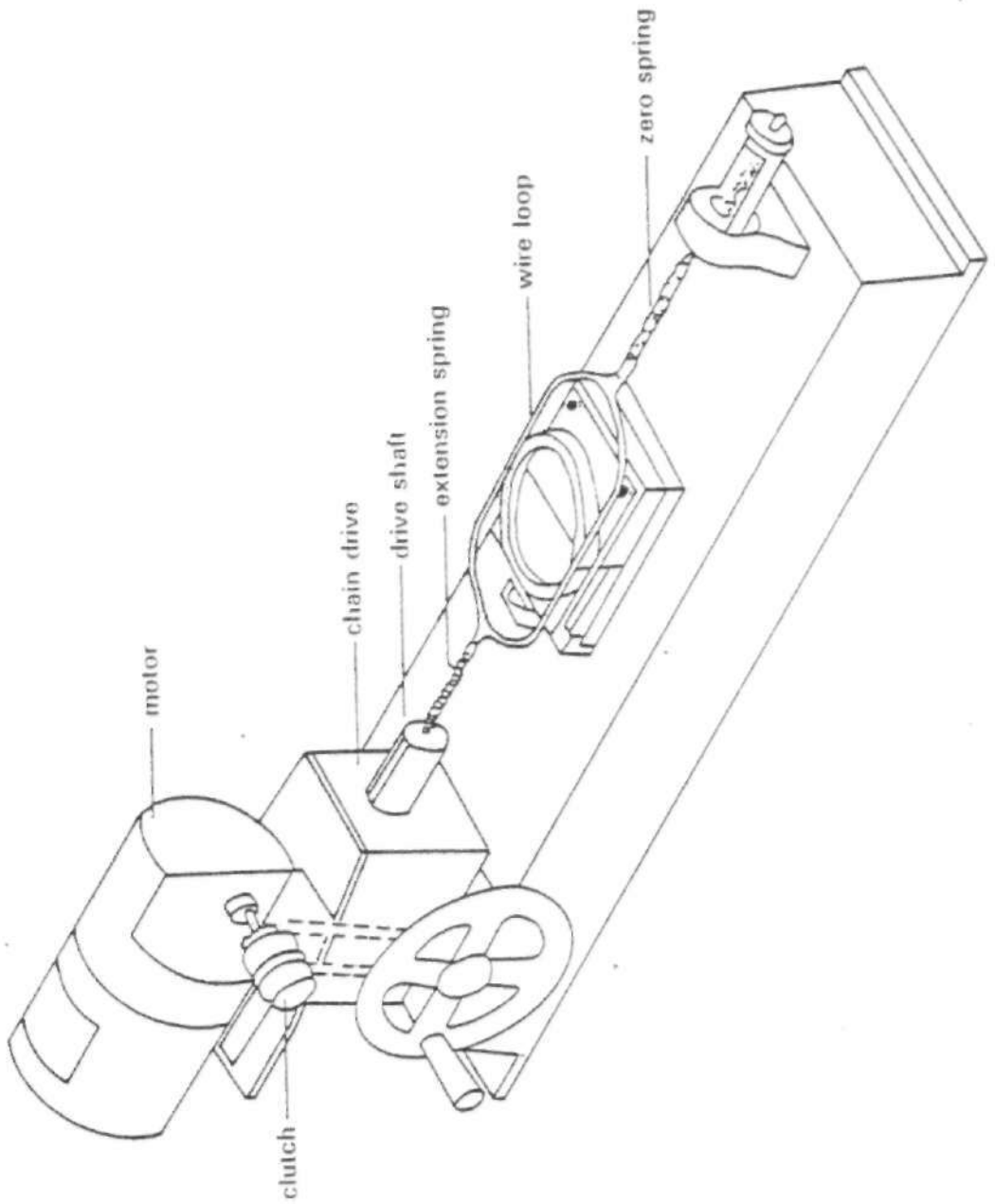
The tensile tester (shown schematically in Fig. 2.3 A B) was constructed by K.C. Productions Limited and was based on the design of Ashton et al (1964). It consisted essentially of a shallow cylindrical brass cell of 9.5 cm internal diameter and 1.0 cm deep with a serrated base to prevent slipping of powder within it. The cell was split vertically in half, one half, a, being fixed to the base, and the other, b, resting on steel ball bearings, c, which moved in V-shaped grooves. A horizontal wire loop, d, encircled the cell and was attached to projecting pins, e, on each side of the moveable half. Attached across the other diameter of the loop at right angles to the plane of separation of the cell were two springs, f and g acting in opposition. The former, the extension spring was first calibrated by hanging weights

Fig. 2.3A Tensile Tester Cell Assembly



a. fixed half-cell
b. movable half-cell
c. steel ball bearings
d. wire loop
e. locating pins
f. calibrated spring
g. zero spring
h. clamp screw
i. moulding ring
j. consolidation platform

Fig. 2.3B Tensile Tester Layout Sketch



from it and noting its extension ; the results showed perfectly Hookean behaviour. It was then connected to a motor driven shaft (Fig 2.3B) which extended it at constant rate of 0.125 cm per minute. The latter, the zero spring was employed to bring the two halves of the cell into touching contact, for zero adjustment. The clamp screw, h, held the two halves of the cell firmly together without tilting while filling it and consolidating the bed of powder. The depth of the cell was increased by means of a moulding ring, i, placed on its rim.

Measurement Procedure

The two springs were positioned and the two halves of the cell were clamped together after bringing them into touching contact by adjusting the zero spring. The moulding ring was placed on top of the cell which was then filled with successive layers of pre-dried powder, consolidating each layer by twisting the consolidating lid, j, back and forth 20 times through an angle of about $\pm$ 20°, using not more than 3.0 kg to avoid the possibility of fracturing individual particles and changing their size distribution. After consolidating the powder, the consolidating lid and the moulding ring were removed and the excess powder was scraped off level with the top of the cell using a nylon string. The movable half of the cell was unclamped and a constantly increasing tension was applied to it via the extension spring by switching on the motor. The time taken for the powder bed to split and the weight of powder in both halves of the cell were recorded. This procedure was repeated at least six times using several consolidation loads to obtain results at different packing fractions ; fresh samples were used for each measurement. The measurements were carried out in a room fitted with a Westair Drymatic dehumidifier (Westair Drymatic Ltd., Durham) at a relative humidity of 40 $\pm$ 5% and 20 $\pm$ 1°C.

The tensile strength which is the force per unit area of broken face required to split the bed at the packing fraction achieved during consolidation was calculated from knowledge of the extension of the calibrated spring when the powder bed split and from the weight of the bed and the cross-secional area of the fractured surface using the following relationship :-

$$T = \frac{R_g \times t_b \times L_g \times 9.81}{A_s} \qquad (72)$$

where T = tensile strength in Nm^{-2}

9.81 = equivalent of 1 Kg in Newtons

R_g = rate at which spring 'f' was extended in ms^{-1}

t_b = time in seconds to split the bed

L_g = Load in kg required for 1 m extension of the spring determined by calibration

A_s = area (m^2) of the split surface of the bed (i.e. diameter x depth of cell)

The value $\frac{R_g \times L_g \times 9.81}{A_s}$ $Nm^{-2}s^{-1}$ is called the spring constant ψ

therefore $T = \psi \times t_b Nm^{-2}$ (73)

The packing fraction of the bed defined by $\frac{\text{bulk density}}{\text{particle density}}$ was obtained from the weight of the powder filling the cell, the volume of the cell and the particle density of the sample.

PREPARATION OF TABLETS

Dartec Universal Test Machine

A specially adapted Dartec (100KNM2501) Universal testing machine (Dartec Limited) was used to determine the plasto-elastic properties of the powders while forming them into tablets. This machine was equipped with an electronic measurement and control panel and consisted

of a straining frame, fitted with a displacement transducer and a load cell, a control console, a hydraulic powder unit, a BRYAN X - Y recorder, a specimen holder adapted for holding a tablet punch and die and other accessories.

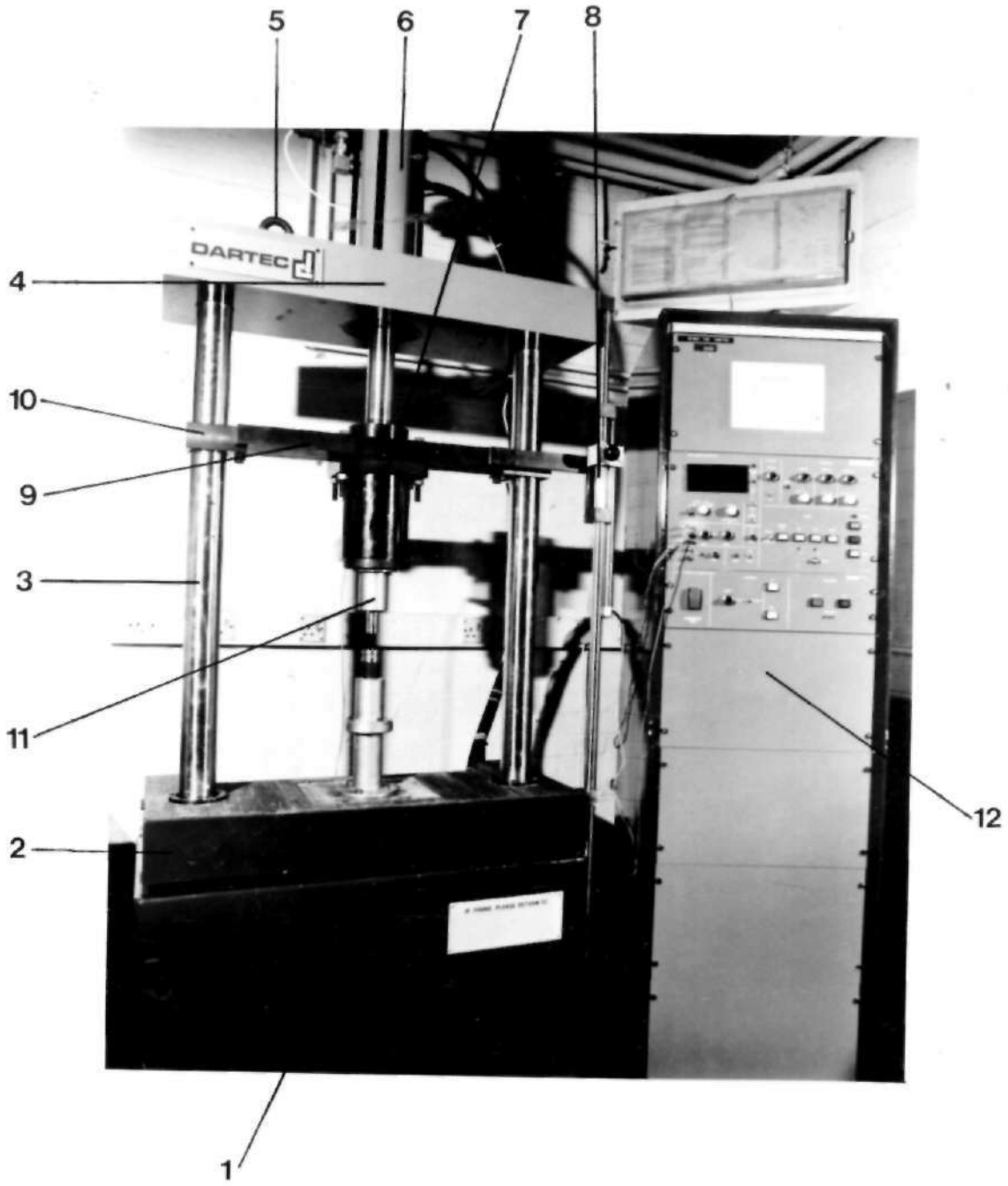
The straining frame (Dartec M1000/RF)

The test frame illustrated in Plate 1 was designed for routine static testing of materials in tension or compression, The unit consisted of a base (1) with lower beam (2). Two columns (3) were clamped in the lower beam and supported an upper crosshead (4). The columns extended through into the base to give some adjustment of frame height. A single ended long stroke servo-actuator (5) was mounted on the top crosshead. The servo-valve and associated filter (6) were attached to the actuator, The load cell (7) was mounted in the beam opposite the actuator. The travel of the actuator was measured by a displacement transducer (8) which sensed the movement of the piston. The end of the piston rod was guided on the columns by a moving crosshead (9) and bearings (10) which protected it against inadvertent side loads. Tools were mounted on the adaptor plates (11) fitted to the load cell and moving crosshead.

DISPLACEMENT TRANSDUCER

The displacement transducer (8) was a linearly variable differential transformer (LVDT) and operated at 5 kHz. It consisted of three windings on a long former. The centre winding was the primary and the other two were secondaries. A core couples the primary windings to both secondary windings in such a manner that as the core was moved from its central position, the voltage output from the transducer varied according to the amount and direction of movement. The output

Plate 1 DARTEC Universal Test Machine



from this device was demodulated in the electronic unit.

LOAD CELL

The load cell (7) was a resistance gauge device with a capacity of 100 kN and its calibration accuracy was better than 1% of reading down to 1 kN. The gauges were arranged in a four arm bridge with an equal number of active and dummy gauges. The load cell was sensitive to temperature change which could affect both the cell zero and output but these effects were minimised in the design by compensation techniques and need not be considered for normal room temperature operations as in the present work.

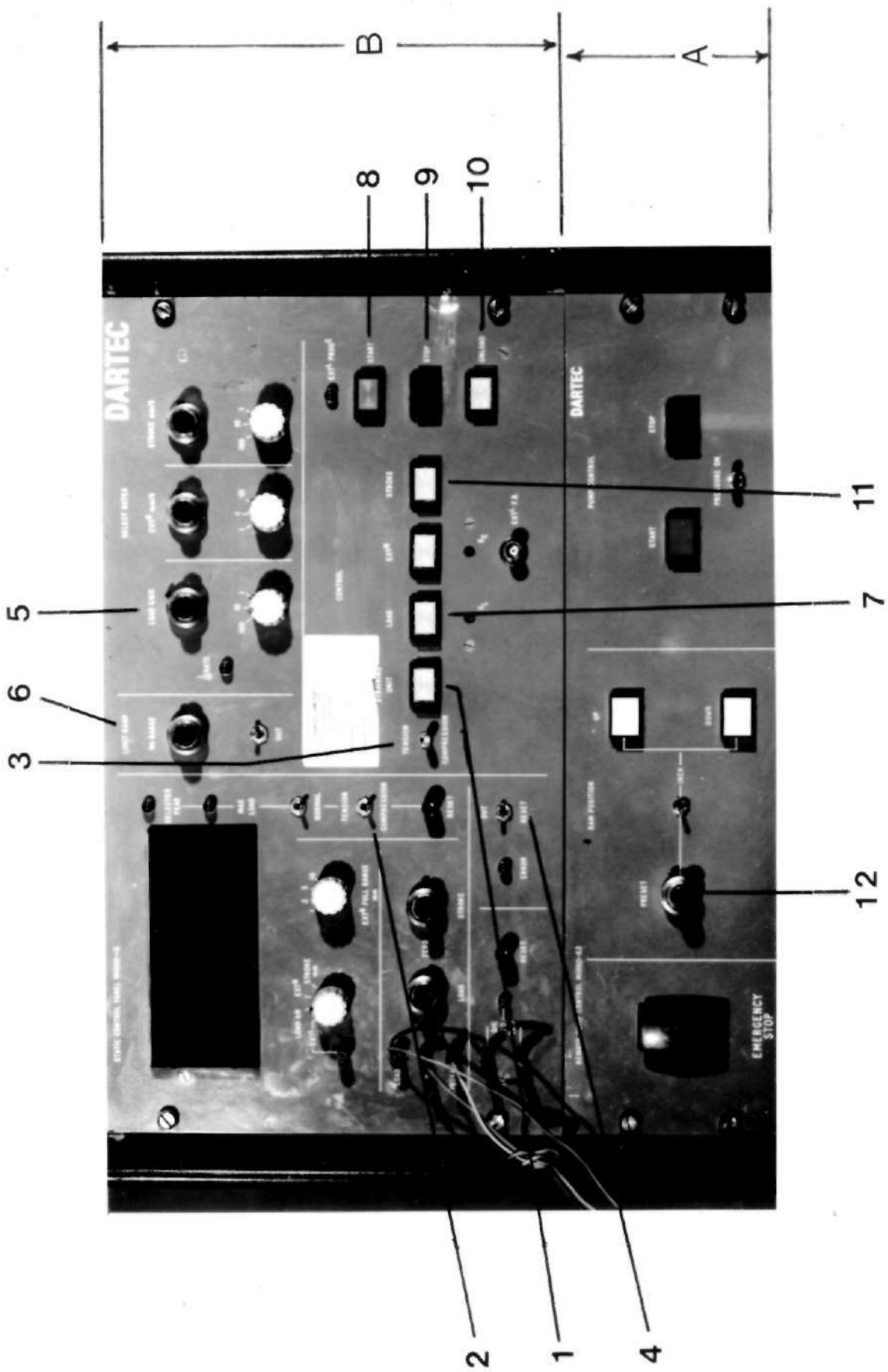
HYDRAULIC POWER SUPPLY

The straining frame was driven at a maximum straining speed of 3 m per minute by a servo-hydraulic activator mounted on the top crosshead The hydraulic power required to generate the motive force to drive the actuator was provided by a separate Dartec M1000/14 Hydraulic Power Supply Unit (not shown) which delivered a fixed flow of 23 litres/ min at a pressure of 207 bars. It had a water cooled heat exchanger fitted with a thermostatic water valve to ensure minimum water usage. The unit had trip circuits to shut down the system in the event of high oil temperature or low oil levels.

CONTROL CONSOLE (DARTEC M1000/C4)

This (12, plate 1) was a free-standing single bay standard rack mounting cabinet approximately 2 m high containing the following equipment (Plate 2) :-

Plate 2 DARTEC Control Console



A. Dartec M1000/K2 System Control Panel (A)

This provided remote push-button stop/start control of the hydraulic power supply unit and an emergency stop button. For repetitive tests the control panel allowed the ram position to be preset so that it would automatically return to the starting datum position after each test.

B. Dartec M1000/S Static Control Panel (B)

This provided the control systems for load, extensometer, and actuator stroke with digital indicator for read out of all three parameters and maximum load indication. The unit allowed "bumpless" transfer between control parameters and had rate controls enabling easy selection of constant load rate and constant strain rate testing.

RECORDER

A BRYAN X - Y recorder was used to measure the force-displacement plots of each compression cycle using the following sensitivities :-

X axis	displacement	12.5 mV/cm
Y axis	load	100 mV/cm

OPERATION OF THE DARTEC

The punches and die (10 mm diameter) were fixed into the respective adaptors. The punches were lubricated with 1% w/v magnesium stearate dispersion in acetone. Predetermined amounts of each sample were weighed and carefully introduced into the die resting on the lower punch. The hydraulic pump was started and the straining unit was adjusted so that the actuator would be about in the middle of its stroke when the sample was in position. The following operations were then carried out in chronological order :-

1. The controls to the straining unit (1) (Plate 2) were switched on and the upper punch was lowered into position until the compression dial read zero indicating that the upper punch was just entering the die ; the recorder pen was set to the origin of its trace. Referring to Plate 2, the following settings were made : (2) and (3) were switched to "compression".

2. The maximum "load indicator" (4) was switched to "Reset" position.

3. The rate of loading required (5) was set.

4. The maximum load required was set with the potentiometer (6).

5. The load control (7) was selected.

6. The start button (8) was pressed as soon as the load was registered by the display. The machine then loaded the powder at the preset rate.

7. The machine was left in the 'START' mode to subject the compact to the preset maximum load for a timed duration.

8. The 'STOP' button (9) was pressed to stop maximum loading and the "unload" button (10) was pressed and held to unload. The compact was then relieved of the load at the preset rate of loading.

9. The tablet was ejected by inverting the die on a support and by pressing the "stroke" button (11) and the start button (8). The upper punch then moved at the preset rate to eject the tablet.

10. The 'STOP' button (9) was pressed to stop movement of the upper punch.

11. Finally the "preset" button (12) was pressed to return the straining

unit to the initial position ready for another compression cycle.

Four tablets were prepared from each sample at each setting in order to obtain mean values of tensile strength and plastoelasticity.

ELASTIC RECOVERY AND STRESS RELAXATION

The elastic recovery(ER) and the stress relaxation (SR) of the samples were measured by monitoring the positions of the upper punch in the die during the compression/holding/decompression cycles at given settings. Fig. 2.4. is a schematic record of the behaviour of a powder sample while being formed into a tablet.

'0' = original positions of the upper punch at the top of the die before compression.

'a' = position of the upper punch at the selected maximum load.

'b' = position of the upper punch after being held for a selected period of time at the maximum load.

'c' = position of the upper punch after decompression.

'd' = maximum displacement of upper punch i.e. the distance between the two punches.

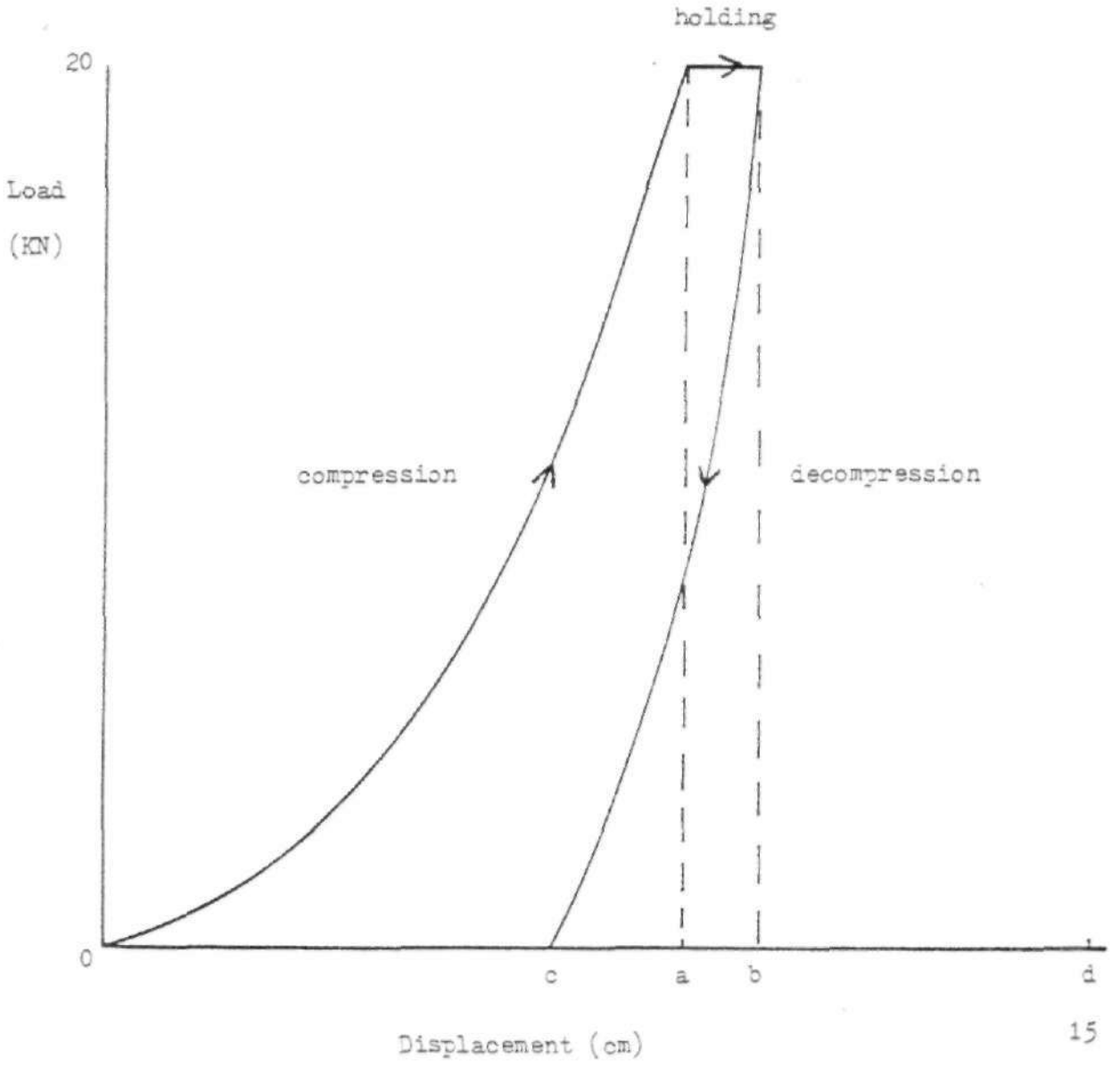
Knowing the distance apart between the two punches, the percentage of the ER can be calculated according to the Armstrong and Haines-Nutt (1972) expression

$$ER = \left[\frac{(H_o - H_p)}{H_p}\right] \times 100\% \qquad (74)$$

where H_p and H_o are the thicknesses of a tablet respectively at maximum pressure, and after decompression.

$H_p \equiv d-a$; $H_o \equiv d-c$ see Fig. 2.4.

Fig. 2.4. Schematic Representation of Force-Displacement plot



$$\therefore \quad ER = \left[\frac{[(d - c) - (d - a)]}{(d - a)}\right] \times 100\%$$

$$= \left[\frac{(a - c)}{(d - a)}\right] \times 100\%$$

Similarly, the amount of stress relaxation (SR) can be calculated from the expression (Malamataris et al 1984)

$$SR = \left[\frac{H_p - H_t}{H_t}\right] \times 100\% \qquad (75)$$

where H_t is the thickness of a tablet after being held for a given period of time at maximum load.

$$H_t \equiv d - b$$

$$\therefore \quad SR = \left[\frac{[(d - a) - (d - b)]}{(d - b)}\right] \times 100\%$$

$$= \left[\frac{(b - a)}{(d - b)}\right] \times 100\%$$

The stress relaxation of the powder, SR, is the percentage reduction in force that occurs when, as a result of plastic compression, the applied force decays with time. The value of SR will be influenced by a number of experimental variables including the rate of loading, the magnitude of the applied force, the length of time for which it is held, the dimensions and state of the punches and die employed. While it could be argued that the stress relaxation or "plasticity" of a powder is unlikely to be related only to changes in tablet thickness and that the expression for elastic recovery does not allow for the possibility of recovery in the radial direction, nevertheless it seems reasonable to expect that ER and SR as defined above should provide some comparative measure of the changes that occur in the "plastoelastic" properties of a powder as increasing amounts of a second ingredient

are added to it. The values may not be absolute values but they should be comparative and they will depend on the experimental conditions employed.

Preparation of tablets using a tablet press

A single punch (Manesty F3 model) tablet press fitted with a 10 mm diameter die and flat faced punches was used to form the granules prepared from samples M4 - M8 and A_2 into tablets at the rate of 40/min using different compression pressures in order to achieve packing fractions between 0.80 and 0.91. 40 - 50 tablets were prepared from each sample at each pressure setting. Since the samples contained high proportions of Avicel it was found unnecessary to employ a lubricant which might otherwise have complicated interpretation of the test results.

DISINTEGRATION TIMES OF TABLETS

The disintegration times of the tablets prepared on the single punch tablet press were measured in a Manesty disintegration tester using the standard B.P. (1973) method in distilled water thermostated at 37 $\pm$ 1°C. The tablets were considered completely disintegrated when all the particles passed through the wire mesh.

DIAMETRAL COMPRESSION TEST

The tensile strengths of the tablets prepared by both techniques were measured after 24 hr. of storage over silica gel in a desiccator (unless otherwise stated) to allow for hardening and elastic recovery by diametral compression using a CT 40 tablet mechanical strength tester (Engineering System, Nottingham) shown in Plate 3. It consisted of an upper flat horizontal plate which was driven vertically downwards by a motor at constant speed of 0.1 cm/min onto the tablet plate. The lower plate was connected through an amplifier system to a digital scale which showed the force required to break the tablet. 0.35 mm thick cardboard strips were positioned at the contact points

Plate 3 CT 40 Diametral Compression Tester

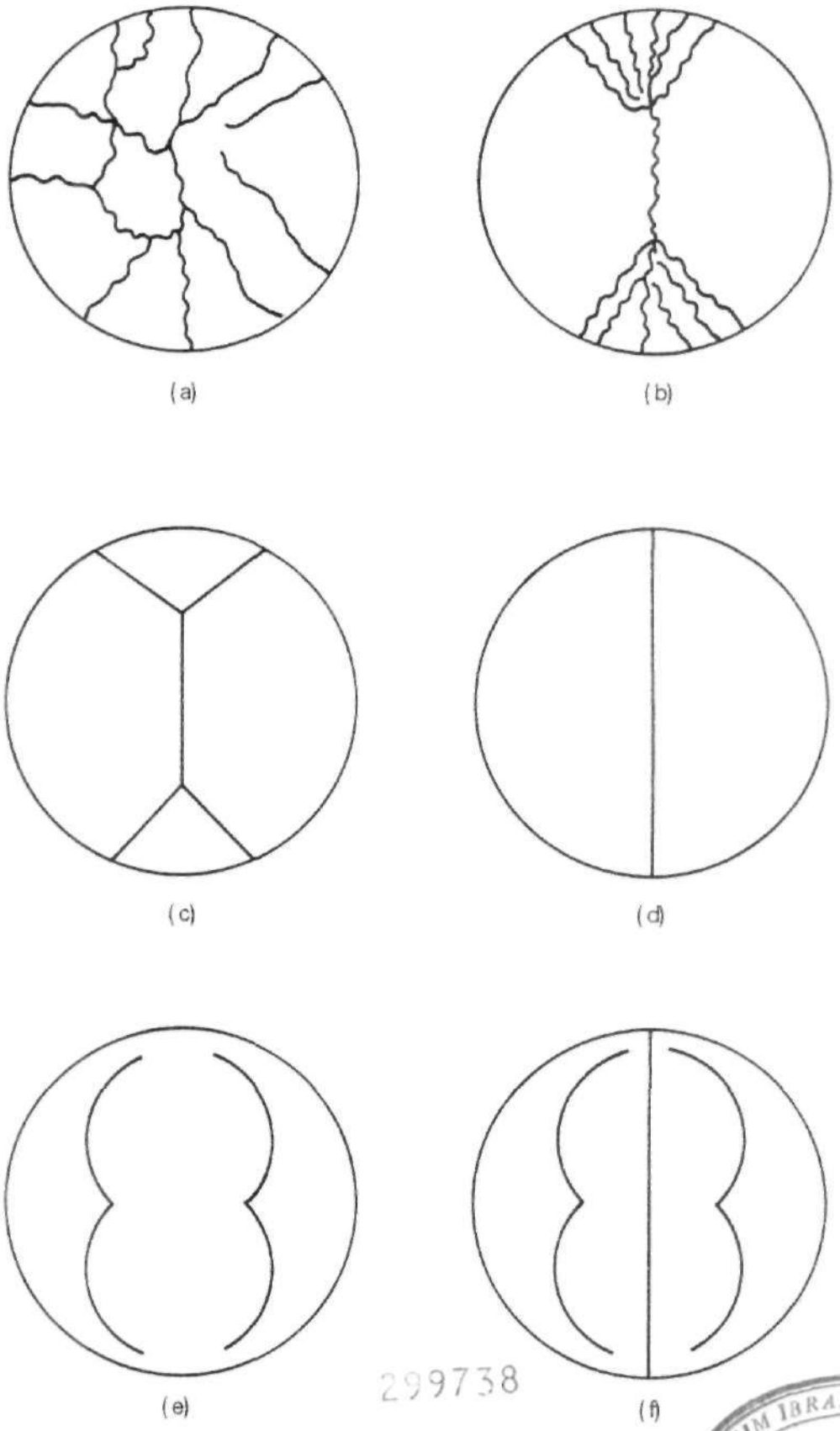


between the tablet and the plates to ensure even distribution of the applied stress across the edge of the tablet. The tablet was placed on its edge on the lower padding strip and the upper plate was lowered carefully to touch and hold it in position. An increasing force was then applied by switching on the motor until the tablet broke into two symmetrical halves along the loaded diameter. The force required to break the tablet was automatically registered on the digital scale.

When a tablet is diametrically compressed between two platens, failure can occur in one of six ways shown in Fig. 2.5. depending on the experimental conditions (Mitchell 1961 ; Rudnick et al 1963 ; Fell and Newton 1970 ; Ridgway 1970 ; Bagster and Fitzgerald 1974). Without a padding strip, localised crushing, cracking or even shattering of the material occurs at the point of contact, due to the high localised compressive stresses. This produces irregular fragments as shown in (a) and (b). If the padding strip is too large the localised compression is spread out and the tablet breaks into four fragments as in (c) by two shearing wedges initiating a tensile failure through the centre of the tablet. With the correct padding strip, the tablet breaks cleanly along its loaded diameter into two symmetrical halves (d). In the fifth type of failure (e), the tablet breaks into three, following a photo-elastic fringe pattern of a loaded disc. Finally the triple cleft failure in (f) is characterised by a tensile break on the vertical centre line and each half then breaks into two, following the photo-elastic fringe pattern of a loaded half disc.

Measurements were made in quadruplets and the results accepted only if the samples split into two halves following the type (d) or (f) modes of failure. In these two circumstances, it has been shown from elastic theory (Timoshenko and Goodier 1951 ; Peliter 1954 ; Rudnick et al 1963 ; Fell and Newton 1970) that the maximum tensile strength, T of a flat faced tablet is given by Eq. 62.

Fig. 2.5 Failure patterns of tablets subjected to diametral compression



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CHAPTER 3

TENSILE STRENGTHS OF SINGLE POWDERS AND THEIR BINARY MIXTURES

Purposes of Chapter 3

Paracetamol on its own is very difficult to compress into firm tablets as they tend to cap and laminate. Avicel (microcrystalline cellulose) powder is a versatile tablet excipient which forms hard tablets and which is usually incorporated with paracetamol in the tableting of the latter. It was therefore considered appropriate to study the mechanical properties of these powders with a view to offering a scientific explanation to their contrasting behaviour during tableting.

It is also now realised that attempts to scientifically elucidate and accurately predict the behaviour of pharmaceutical powders may have to follow a radical (rather than empirical) approach. The theory of tensile strength of powders proposed by Cheng is a pointer in this direction. In view of this it seems reasonable to verify the recently modified version of the theory which is based on the concepts of a "reference state" and a "reduced tensile strength".

The purposes of this chapter have been :

1. to measure the tensile strengths of paracetamol and Avicel powders and of their binary mixtures.
2. to test the validity of Cheng's modified theory of tensile strengths of single powders and of binary mixtures of powders and to assess its application to the present mixtures.
3. to examine the potentialities of the theory for predicting the tensile strength of single powders and binary mixtures of powders
4. to contribute to the understanding of the fundamental mechanical properties of pharmaceutical powders in relation to tableting.

RESULTS

Table 3.1 gives the values of the particle densities and size parameters $\bar{d}$, $\bar{s}$ and $\bar{v}$ of the single components and of their binary mixtures calculated from their size distributions.

The tensile strength, T and the reduced tensile strength, R data at different packing densities calculated from Eq. 33 for single components and from Eq. 49 for binary mixtures are give in Table 3.2. The equations of best-fitting lines obtained by linear regression for log T against packing fraction of single powders and mixtures are given in Table 3.3. Figs. 3.1 and 3.2 show respectively how the T and R values of samples at selected packing densities vary with the % w/w of Avicel in the mixtures. Fig. 3.3 a,b show the plots of R versus ε for the materials and their mixtures. The reference R value (R_r) depends on the lie of the experimental data. An R_r value of 8000 Nm^{-2} was chosen for samples P_1 and P_2 and M_1 - M_6 and of 4000 Nm^{-2} for all the Avicel fractions and P_3, M_7 and M_8. These R_r values were used to determine the corresponding ε_r values from the plots in Fig. 3.3 a,b and the results were used to calculate the appropriate λ values using Eq. 32. The results are given in Table 3.4.

Plots of R against λ are shown in Fig. 3.4 for Avicel and representative mixtures. It is observed that the curves exhibit asymptotic behaviour. Invoking the concept that as t tends to zero, T tends to infinity and hence similarly for R, it may be possible to estimate the t_r value by extrapolating the R versus λ curve to $R = \infty$. The asymptotic value of λ must equal $t_o - t_r$, since at $R = \infty$, $t = t_r + \lambda = 0$. The practical difficulty in assessing the asymptotic behaviour of the curves by extrapolation causes inaccuracy and introduces

Table 3.1 Calculated Particle Size Parameters

SAMPLE	ρ_s or ρ_{mix} ($g\ cm^{-3}$)	U_A	U_B	$\bar{d}$ or $\bar{d}_{mix}$ (μm)	$\bar{s}$ or $\bar{s}_{mix}$ $(\mu m)^2$	$\bar{V}$ or $\bar{V}_{mix}$ $(\mu m)^3$
P_1	1.29	1.000	0.000	7.66	46.0	382.8
P_2				16.75	220.3	4186.8
P_3				24.17	458.8	8967.0
A_1	1.52	0.000	1.000	6.27	30.9	211.9
A_2				16.76	220.2	3270.0
A_3				27.74	604.4	13565.0
M_1	1.30	0.995	0.005	7.71	46.7	397.8
M_2	1.31	0.989	0.011	7.76	47.3	414.4
M_3	1.32	0.983	0.017	7.82	48.0	432.6
M_4	1.33	0.976	0.024	7.88	48.8	452.8
M_5	1.35	0.959	0.041	8.04	50.7	500.7
M_6	1.40	0.910	0.090	8.49	56.5	643.8
M_7	1.46	0.770	0.230	9.75	74.7	1045.8
M_8	1.49	0.528	0.472	11.96	112.2	1745.8

For $M_1 - M_8$

$\bar{d}_{AA} = 7.66\ \mu m$ $\quad \bar{d}_{AB} = 12.21\ \mu m$

$\bar{d}_{BB} = 16.76\ \mu m$ $\quad \bar{S}_{AA} = 46.1\ (\mu m)^2$

$\bar{S}_{AB} = 100.8\ (\mu m)^2$ $\quad \bar{S}_{BB} = 220.2\ (\mu m)^2$

$\bar{V}_A = 382.8\ (\mu m)^3$ $\quad \bar{V}_B = 3270.0\ (\mu m)^3$

Table 3.2 Tensile Strength and Reduced Tensile Strength Results

SAMPLE	ρ ($g\ cm^{-3}$)	ρ/ρ_s	$T \times 10^{-3}$ (Nm^{-2})	$R \times 10^{-3}$ (Nm^{-2})
	0.282	0.218	0.457	7.067
	0.315	0.244	0.881	11.827
	0.296	0.230	0.659	9.580
P_1	0.333	0.258	1.338	16.666
	0.336	0.260	1.389	17.107
	0.349	0.270	1.548	18.108
	0.279	0.217	0.449	7.041
	0.370	0.287	0.461	5.209
	0.387	0.300	0.604	6.405
	0.435	0.337	1.316	11.761
P_2	0.375	0.291	0.429	4.742
	0.378	0.293	0.646	7.071
	0.401	0.311	0.826	8.318
	0.413	0.321	0.935	8.996
	0.382	0.296	0.457	3.512
	0.459	0.355	0.957	5.616
P_3	0.426	0.330	0.757	4.964
	0.454	0.352	1.031	6.150
	0.406	0.314	0.566	3.989
	0.437	0.339	0.839	5.290
	0.289	0.190	0.064	1.197
	0.342	0.225	0.226	3.400
	0.353	0.232	0.332	4.797
A_1	0.326	0.214	0.203	3.255
	0.347	0.228	0.278	4.108
	0.361	0.237	0.360	5.058
	0.302	0.199	0.120	2.122

Table 3.2 (cont)

SAMPLE	ρ ($g.cm^{-3}$)	ρ/ρ_s	T x 10^{-3} (Nm^{-2})	R x 10^{-3} (Nm^{-2})
	0.361	0.238	0.072	0.821
	0.404	0.265	0.253	2.480
A_2	0.399	0.262	0.193	1.920
	0.413	0.271	0.250	2.379
	0.393	0.259	0.183	1.860
	0.377	0.248	0.095	1.019
	0.423	0.278	0.255	2.147
	0.413	0.272	0.181	1.564
A_3	0.440	0.289	0.444	3.533
	0.411	0.270	0.135	1.181
	0.432	0.284	0.369	3.009
	0.435	0.286	0.449	3.624
	0.298	0.229	0.282	4.197
	0.380	0.292	1.114	11.936
	0.334	0.257	0.733	9.375
M_1	0.365	0.281	1.074	12.132
	0.307	0.236	0.546	7.800
	0.325	0.250	0.344	7.800
	0.387	0.297	1.005	10.497
	0.339	0.261	0.648	8.135
	0.308	0.237	0.599	8.540
	0.391	0.298	1.046	11.091
	0.350	0.267	0.643	7.959
M_2	0.370	0.282	0.920	10.554
	0.321	0.245	0.455	6.317
	0.352	0.269	0.695	8.519
	0.298	0.226	0.263	4.166
	0.380	0.288	0.955	10.896
M_3	0.331	0.251	0.679	9.354
	0.366	0.277	0.744	8.969
	0.321	0.243	0.525	7.533
	0.343	0.260	0.620	8.150

Table 3.2 (cont)

SAMPLE	ρ (g cm^{-3})	ρ/ρ_s	T x 10^{-3} (Nm^{-2})	R x 10^{-3} (Nm^{-2})
	0.308	0.232	0.340	5.298
	0.388	0.292	0.931	10.653
M_4	0.348	0.262	0.669	8.873
	0.368	0.276	0.941	11.603
	0.378	0.284	0.826	9.782
	0.301	0.226	0.400	6.447
	0.295	0.218	0.318	5.605
	0.362	0.268	1.102	14.809
	0.332	0.246	0.580	8.750
M_5	0.320	0.237	0.504	8.002
	0.344	0.254	0.677	9.758
	0.358	0.265	0.886	12.087
	0.308	0.228	0.384	6.389
	0.343	0.246	0.279	4.606
	0.392	0.281	0.833	11.467
M_6	0.361	0.259	0.511	7.851
	0.349	0.250	0.380	6.108
	0.374	0.268	0.642	9.398
	0.368	0.253	0.187	3.175
	0.383	0.263	0.278	4.477
M_7	0.404	0.277	0.397	5.947
	0.404	0.277	0.435	6.508
	0.381	0.262	0.257	4.154
	0.354	0.243	0.124	2.207
	0.370	0.248	0.123	1.942
	0.413	0.276	0.370	5.050
M_8	0.399	0.267	0.233	3.320
	0.371	0.249	0.136	2.148
	0.388	0.260	0.183	2.710
	0.407	0.273	0.282	3.921

Table 3.3 Equations of Best-fitting line for log T against packing fraction of single powders and mixtures.

SAMPLE	EQUATION	CORRELATION COEFFICIENT
A_1	$\log T = 14.70\ell_F - 0.908$	0.979
A_2	$\log T = 17.99\ell_F - 2.430$	0.978
A_3	$\log T = 27.22\ell_F - 5.176$	0.986
P_1	$\log T = 10.66\ell_F + 0.349$	0.994
P_2	$\log T = 9.13\ell_F + 0.054$	0.962
P_3	$\log T = 5.98\ell_F + 0.888$	0.989
M_1	$\log T = 7.06\ell_F + 0.972$	0.964
M_2	$\log T = 9.14\ell_F + 0.352$	0.961
M_3	$\log T = 7.71\ell_F + 0.785$	0.913
M_4	$\log T = 6.68\ell_F + 1.054$	0.958
M_5	$\log T = 10.17\ell_F + 0.275$	0.991
M_6	$\log T = 12.97\ell_F - 0.690$	0.979
M_7	$\log T = 15.18\ell_F - 1.579$	0.994
M_8	$\log T = 15.16\ell_F - 1.661$	0.988

Fig. 3.1. Tensile Strength Vs % w/w of Avicel at selected packing fractions (○ ρ_F 0.20, ● ρ_F 0.25, □ ρ_F 0.30, ■ ρ_F 0.35)

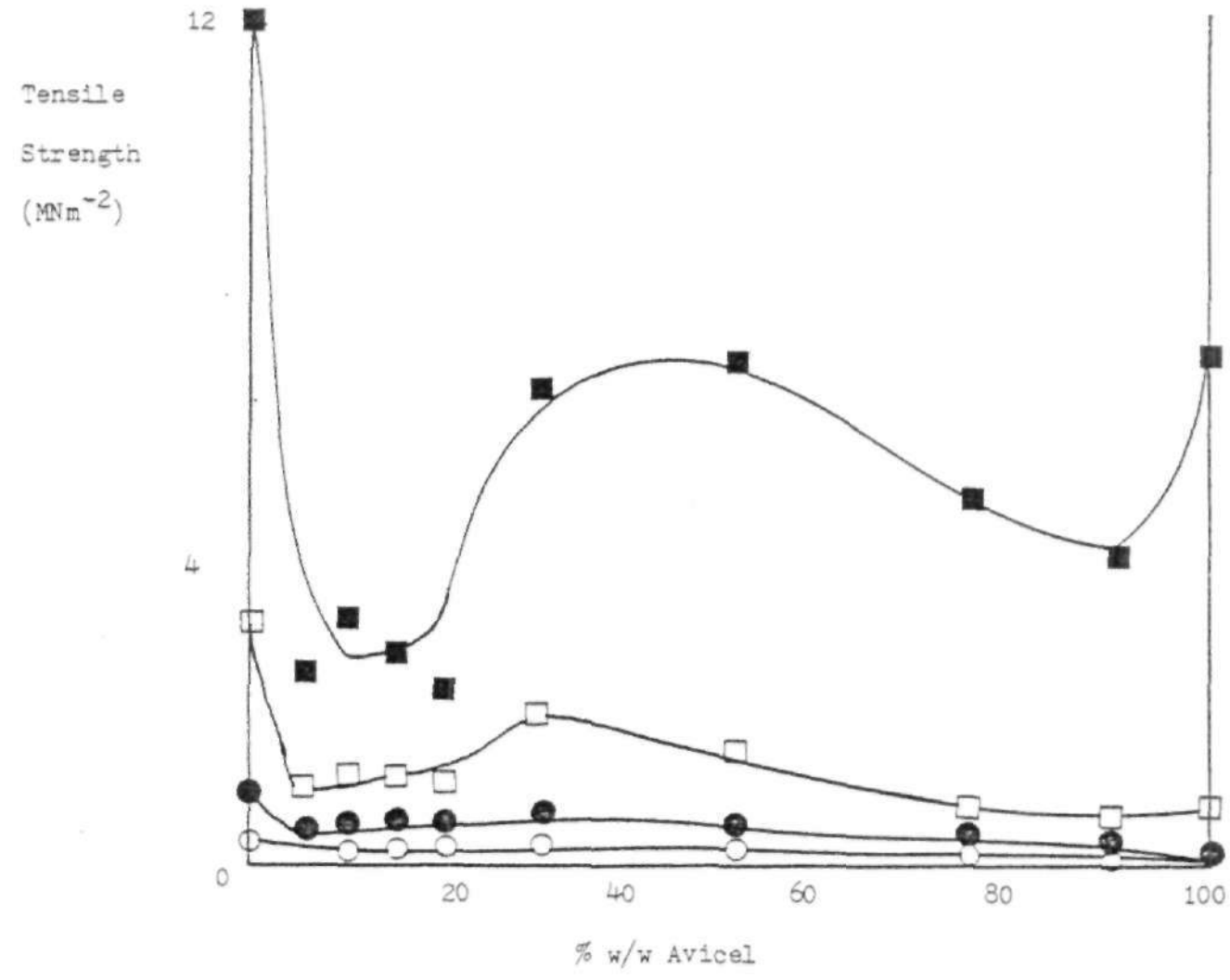


Fig. 3.2. Reduced tensile strength Vs % w/w of Avicel at selected packing fractions.
(○ ρ_F 0.20, ● ρ_F 0.25, □ ρ_F 0.30, ■ ρ_F 0.35)

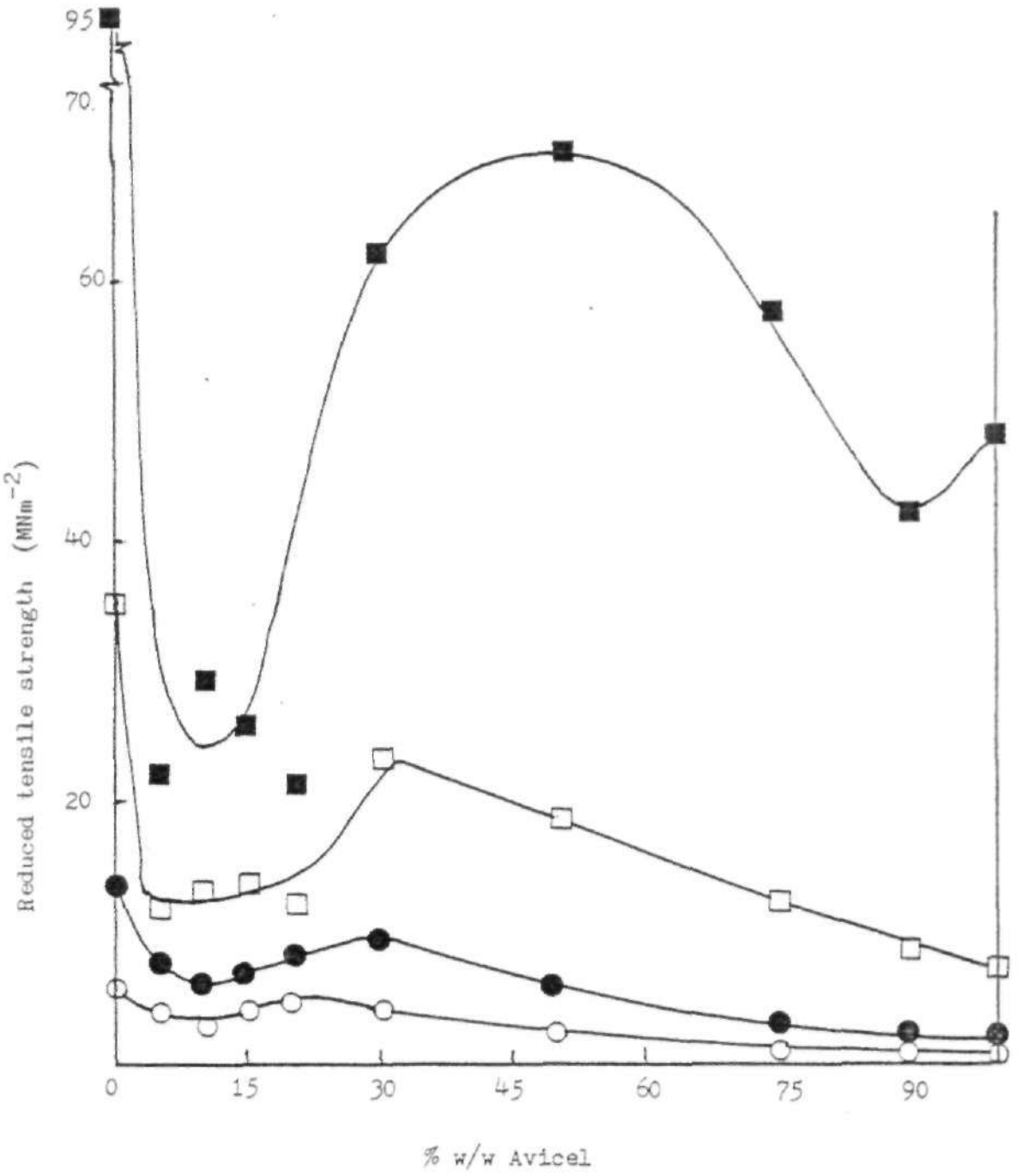


Fig. 3.3a. Plot of R against ρ for different size fraction of single powders

(○ P_1 , ● P_2 , ★ P_3 , □ A_1 , ■ A_2 , ▲ A_3)

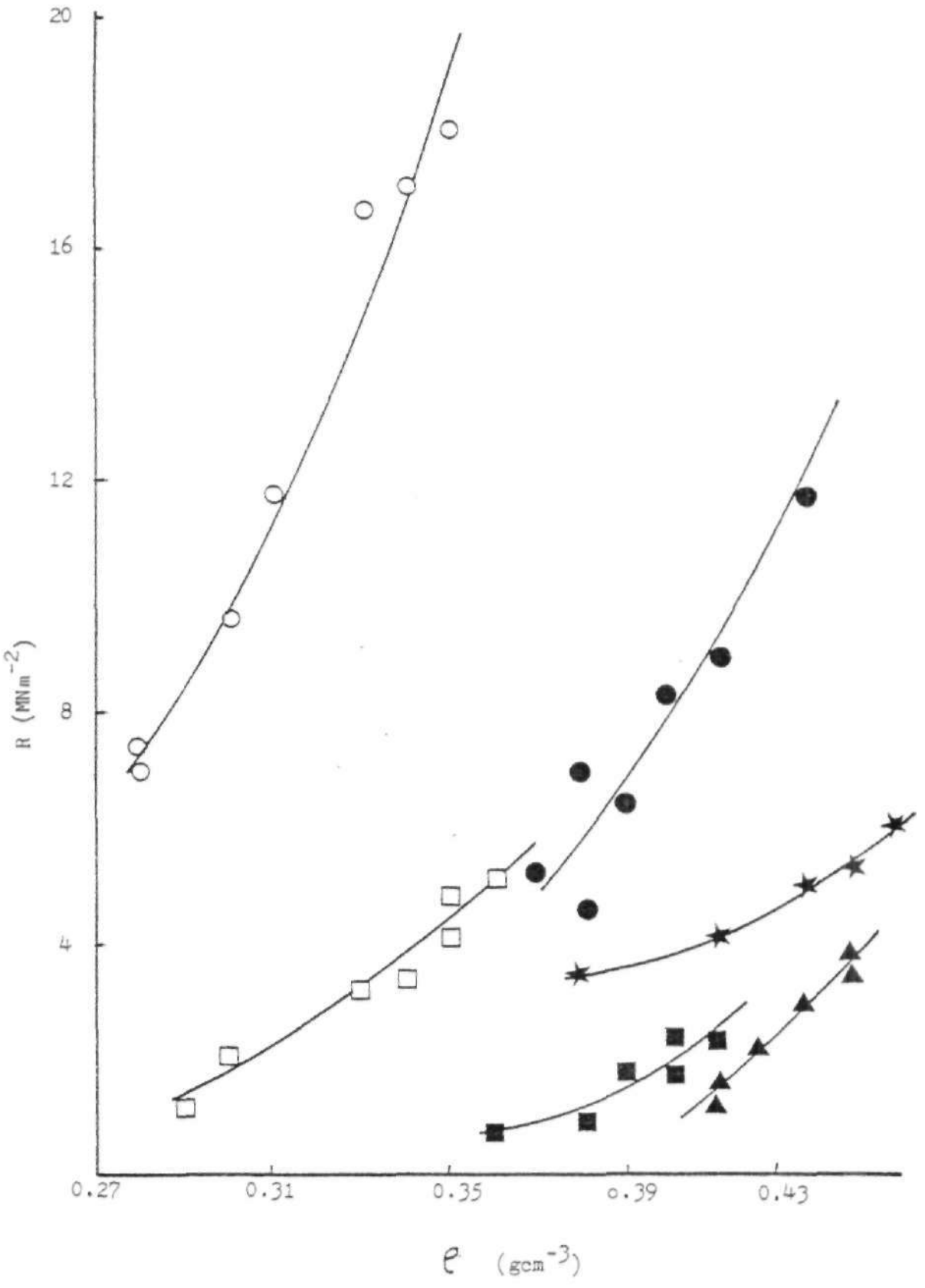


Fig. 3.3b. Plot of R against ρ for representative mixtures

(★ M_3, ▲ M_5, ○ M_6, ● M_7)

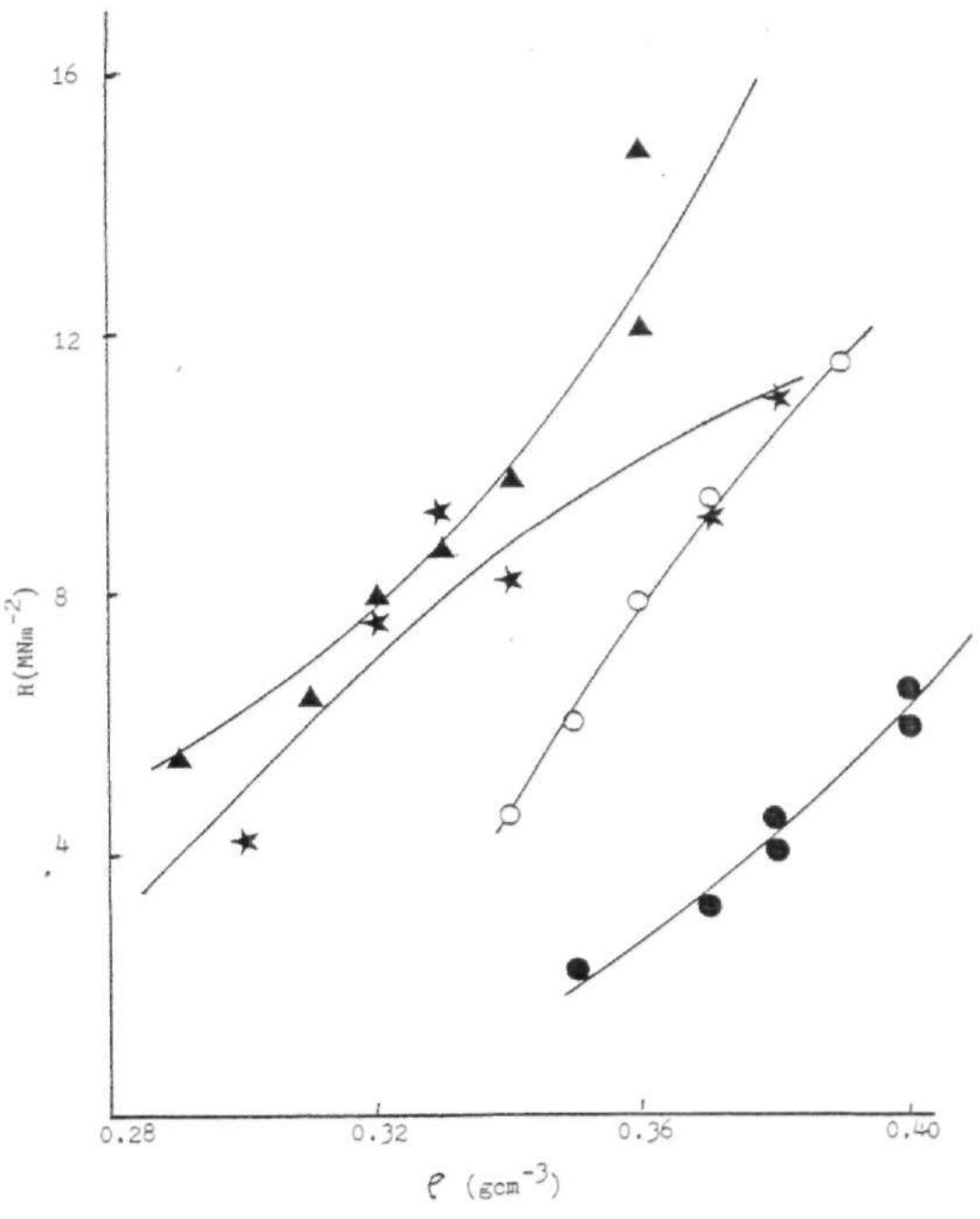


Table 3.4 Calculation of λ values

SAMPLE	$\bar{d}$ or $\bar{d}_{mix}$ (μm)	ρ (g cm^{-3})	ρ/ρ_s	$R_r \times 10^{-3}$ (Nm^{-2})	ρ_r (gcm^{-3})	λ (μm)
	7.66	0.282	0.218	8.000	0.29	0.05
P_1		0.315	0.244			-0.22
		0.296	0.230			-0.07
		0.333	0.258			-0.36
		0.336	0.260			-0.38
		0.349	0.270			-0.47
		0.279	0.217			0.08
	16.75	0.370	0.287	8.000	0.40	0.45
P_2		0.387	0.300			0.19
		0.435	0.337			-0.45
		0.375	0.291			0.36
		0.378	0.293			0.32
		0.401	0.311			-0.01
		0.413	0.321			-0.18
	24.17	0.382	0.296	4.000	0.41	0.53
P_3		0.459	0.355			-0.92
		0.426	0.330			-0.35
		0.454	0.352			-0.84
		0.406	0.314			0.05
		0.437	0.339			-0.55
	6.27	0.289	0.190	4.000	0.34	0.37
A_1		0.342	0.225			0.01
		0.353	0.232			-0.06
		0.326	0.214			0.11
		0.347	0.228			-0.02
		0.361	0.237			-0.10
		0.302	0.199			0.28

Table 3.4 (cont)

SAMPLE	$\bar{d}$ or $\bar{d}_{mix}$ (μm)	ℓ (g cm^{-3})	ℓ/ℓ_s	$R_r \times 10^{-3}$ (Nm^{-2})	ℓ_r (g cm^{-3})	λ (μm)
	16.76	0.361	0.238	4.000	0.43	1.06
A_2		0.404	0.265			0.41
		0.399	0.262			0.48
		0.413	0.271			0.29
		0.393	0.259			0.56
		0.377	0.248			0.80
	27.74	0.423	0.278	4.000	0.44	0.44
A_3		0.413	0.272			0.65
		0.440	0.289			0.07
		0.411	0.270			0.71
		0.432	0.284			0.23
		0.435	0.286			0.16
	7.71	0.298	0.229	8.000	0.33	0.23
M_1		0.380	0.292			-0.39
		0.334	0.257			-0.07
		0.365	0.281			-0.30
		0.307	0.236			0.15
		0.325	0.250			0.00
		0.387	0.297			-0.43
		0.339	0.261			-0.10
		0.308	0.237			0.14
	7.76	0.391	0.298	8.000	0.35	-0.28
M_2		0.350	0.267			0.00
		0.370	0.282			-0.14
		0.321	0.245			0.23
		0.352	0.269			-0.02

Table 3.4 (cont)

SAMPLE	d or d_{mix} (μm)	ℓ (g cm^{-3})	ℓ/ℓ_s	$R_r \times 10^{-3}$ (Nm^{-2})	ℓ_r (g cm^{-3})	λ (μm)
	7.82	0.298	0.226	8.000	0.34	0.38
M_3		0.380	0.288			-0.26
		0.331	0.251			0.10
		0.366	0.277			-0.17
		0.321	0.243			0.18
		0.343	0.260			0.00
	7.88	0.308	0.232	8.000	0.34	0.26
M_4		0.388	0.292			-0.33
		0.348	0.262			-0.05
		0.368	0.276			-0.19
		0.378	0.284			-0.26
		0.301	0.226			0.35
	8.04	0.295	0.218	8.000	0.32	0.26
M_5		0.362	0.268			-0.29
		0.332	0.246			-0.06
		0.320	0.237			0.04
		0.358	0.254			-0.15
		0.358	0.265			-0.22
		0.308	0.228			0.16
	8.49	0.343	0.246	8.000	0.37	0.18
M_6		0.392	0.281			-0.20
		0.361	0.259			0.03
		0.349	0.250			0.13
		0.374	0.268			-0.11

Table 3.4 (cont)

SAMPLE	$\bar{d}$ or $\bar{d}_{mix}$ (μm)	ℓ (g cm^{-3})	ℓ/ℓ_s	$R_r \times 10^{-3}$ (Nm^{-2})	ℓ_r (g cm^{-3})	λ (μm)
	9.75	0.368	0.253	4.000	0.38	0.06
M_7		0.383	0.263			-0.07
		0.404	0.277			-0.24
		0.404	0.277			-0.24
		0.381	0.262			-0.06
		0.354	0.243			0.19
	11.96	0.370	0.248	4.000	0.35	0.38
M_8		0.413	0.276			-0.06
		0.399	0.267			0.08
		0.371	0.249			0.37
		0.388	0.260			0.19
		0.407	0.273			0.00

Fig. 3.4a. Plot of R Vs λ for size fractions of Avicel

(○ A1 , ● A2 , ★ A3)

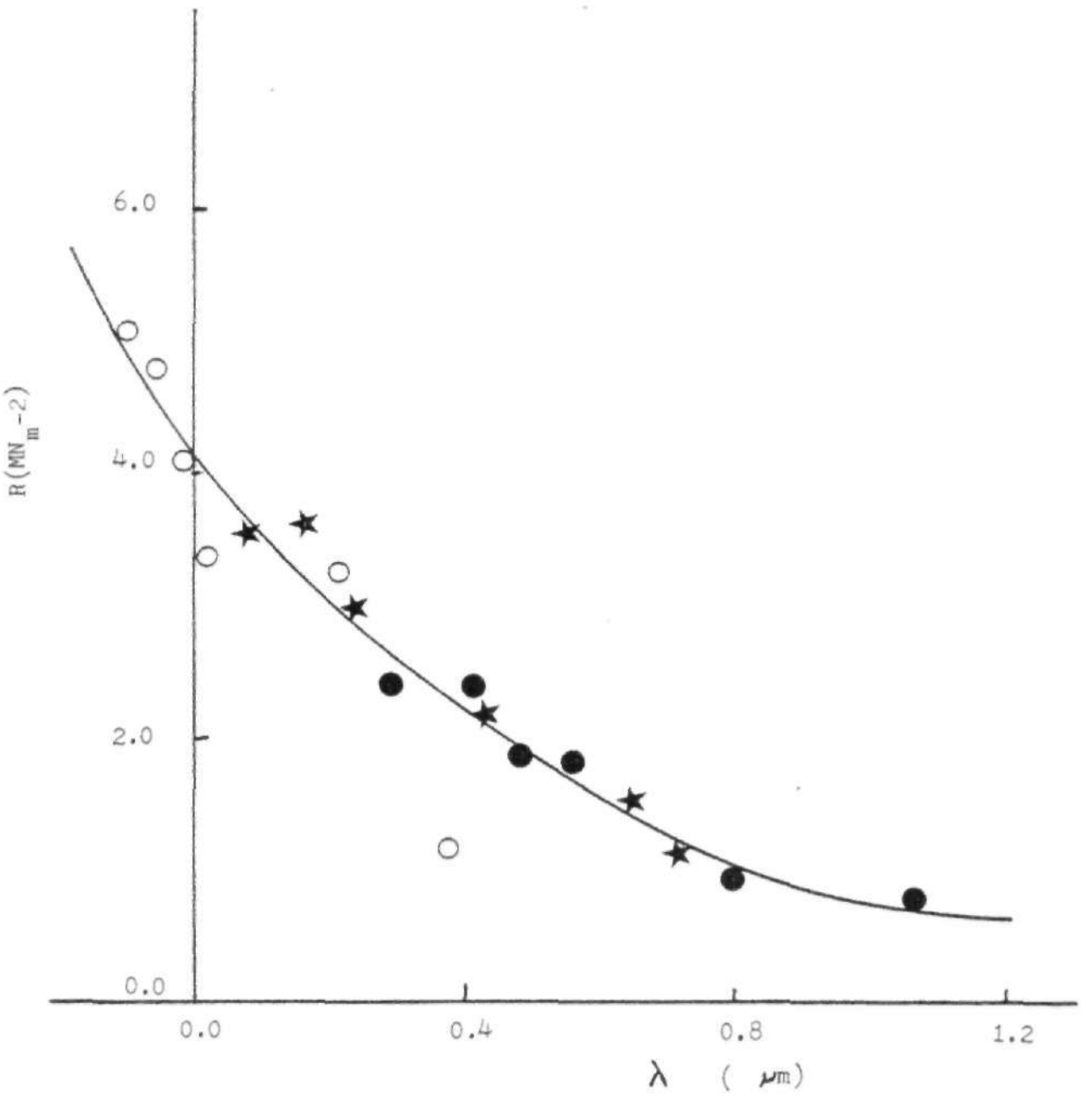
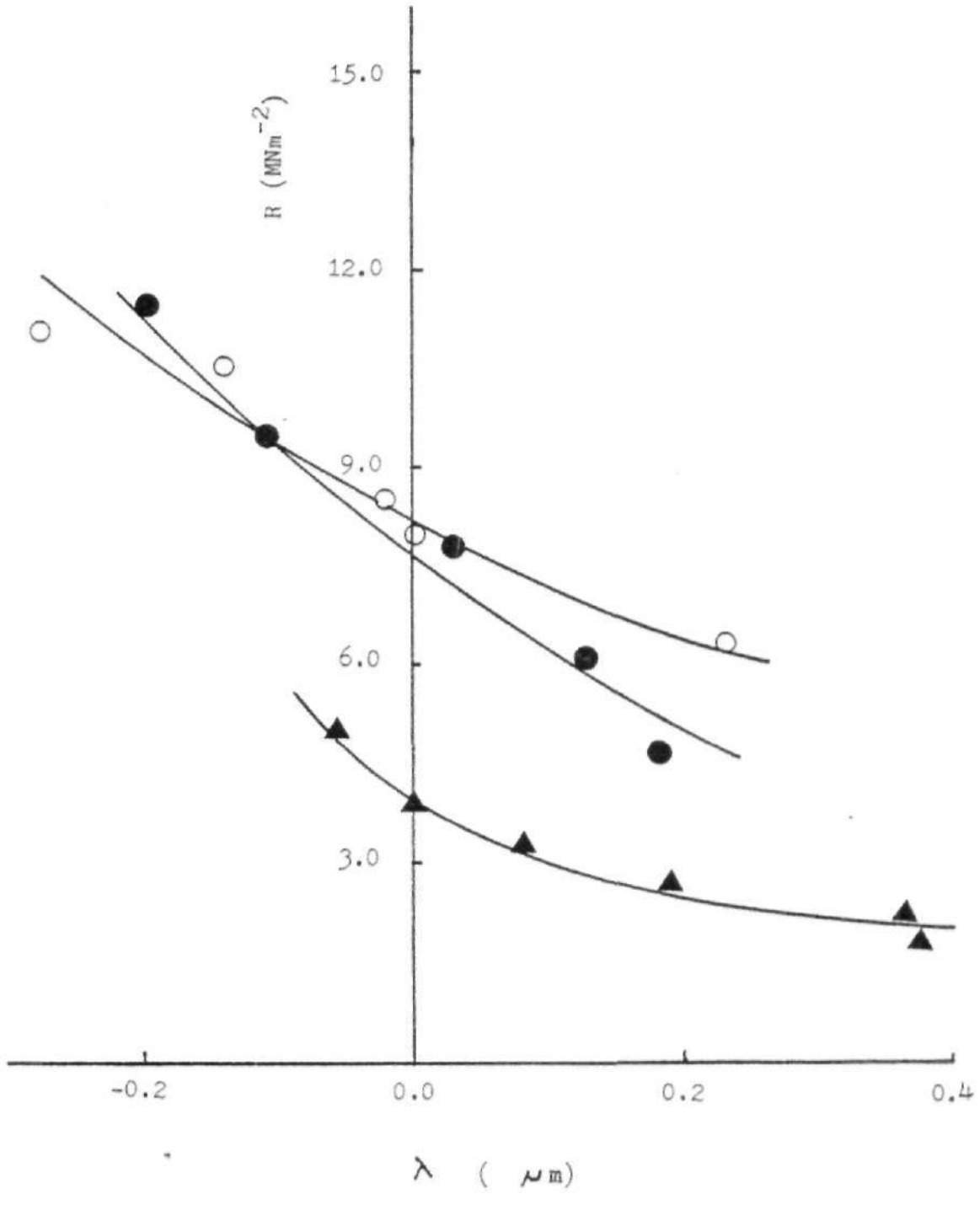


Fig. 3.4b. Plot of R against λ for representative mixtures
(○ M_2 , ● M_6 , ▲ M_8)



uncertainty in the results. By employing Eqs. 33 and 38 and by assuming that $t_r \ll d$ and that the law of corresponding states holds, log R may be plotted against log t using different values of t_r by a trial and error method until a straight line is obtained. [This procedure allows for variation in the value chosen for R_r (Chan et al 1983)] . The slope gives m and the intercept on the ordinate when $t_r + \lambda = 1$ is α. This is shown in Fig. 3.5. Fig. 3.6 shows how the values of α vary as the % w/w of Avicel in the mixtures is increased.

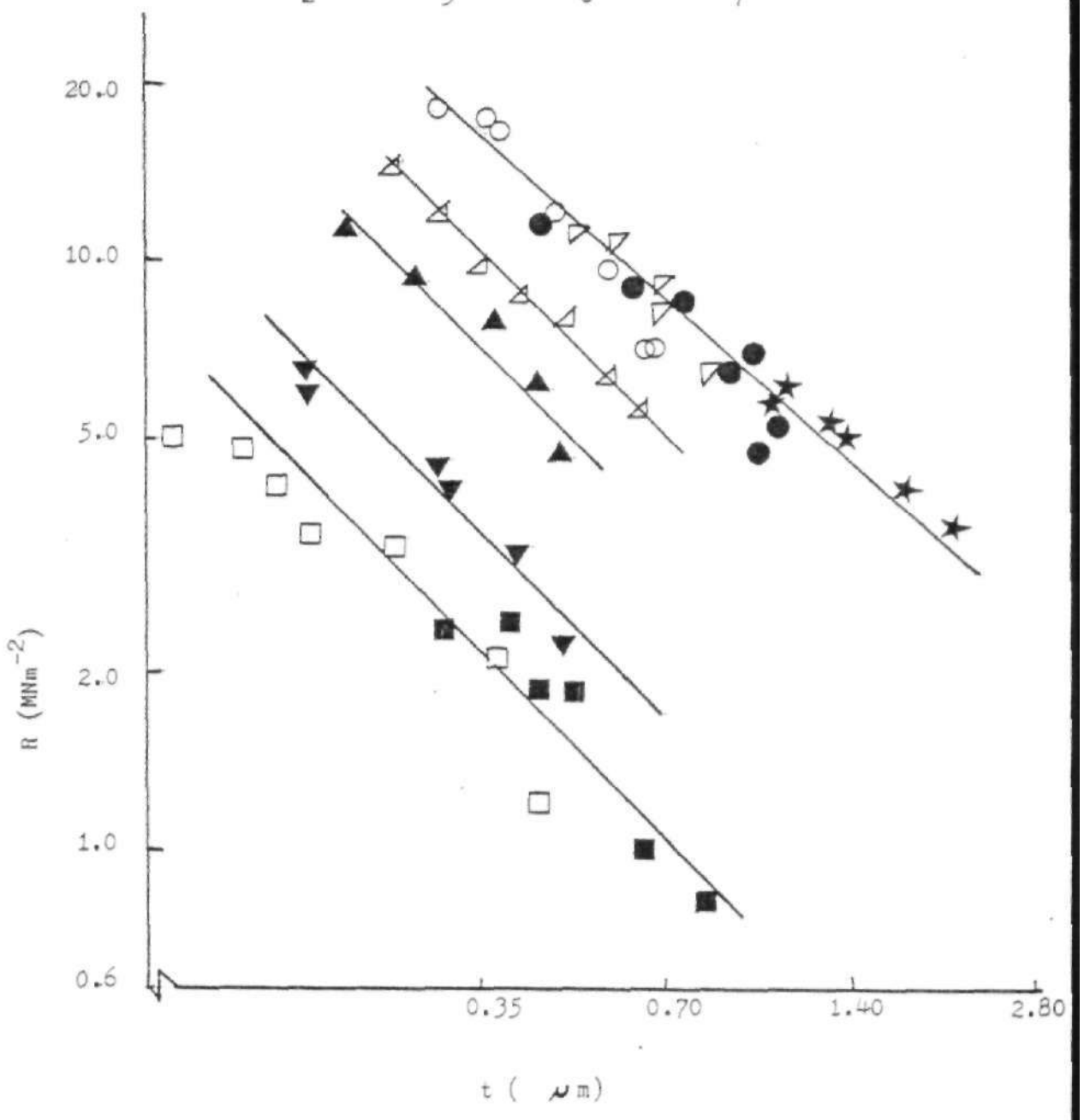
DISCUSSION

The tensile strengths and reduced tensile strengths of the mixtures at selected packing fractions are not proportionally intermediate between those of the components as illustrated in Fig. 3.1 and Fig. 3.2. This type of anomalous behaviour has been observed by some workers (Heywood 1961 ; Varthalis and Pilpel 1976) and is attributed to changes in the packing arrangements of the particles presumably due to the differences in the shape and size distribution of particles of different species in the mixturs ; these changes may alter the 'range' and magnitude of the interaction forces that operate between the particles.

Table 3.2 and Fig. 3.3 show that as the packing densities of all samples are increased, their values of T and R both increase. This is due to the enhancement in the van der Waals', electrostatic, frictional mechanical interlocking and other forces (Krupp 1967 ; Cheng 1968) that operate between the particles as they are brought into closer contact.

Fig. 3.5. Plot of log R against log t for representative samples.

(○ P_1 , ● P_2 , ✶ P_3 , □ A_1 , ■ A_2 ,
▽ M_2 , ◿ M_5 , ▲ M_6 , ▼ M_7)



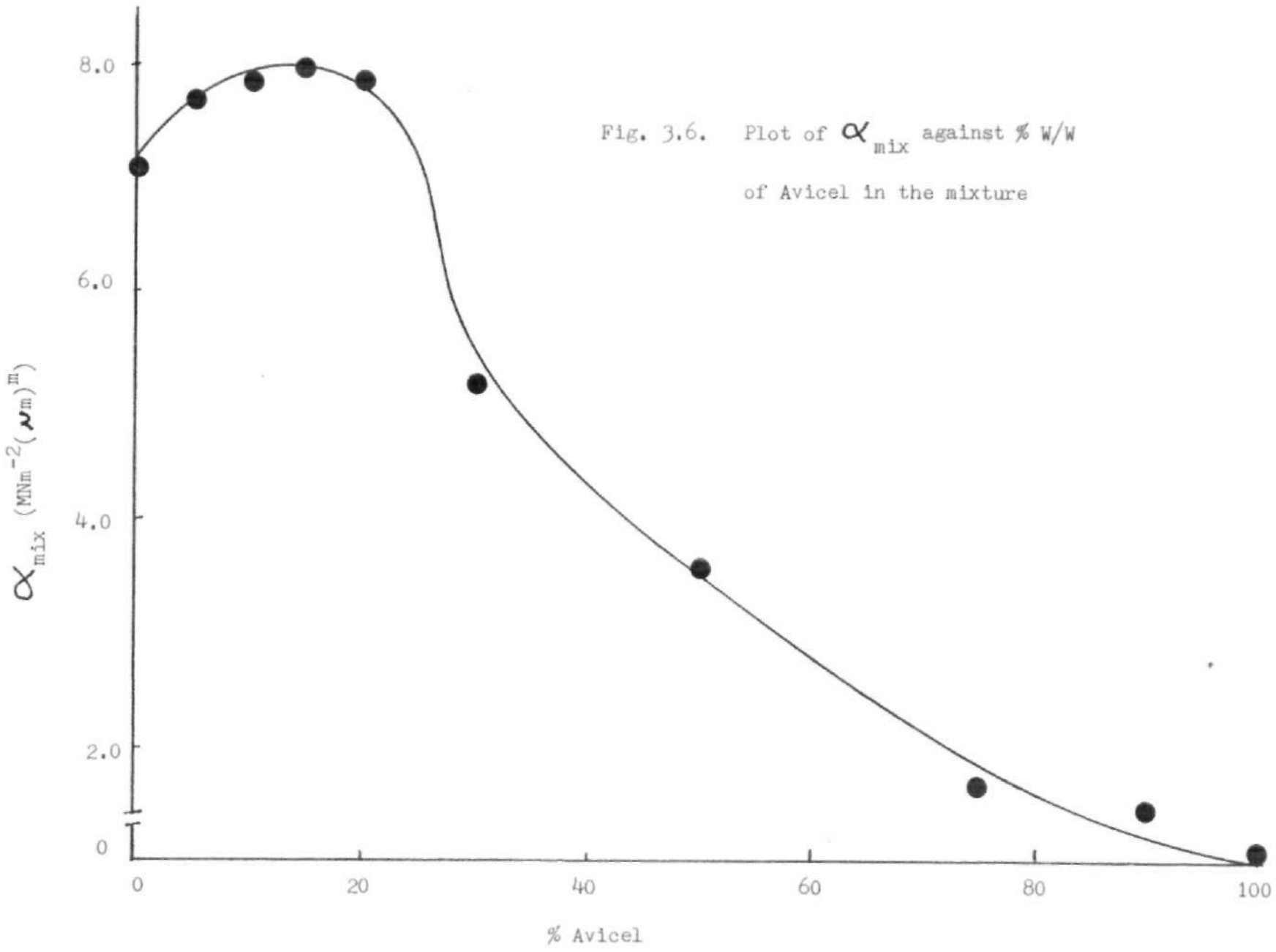
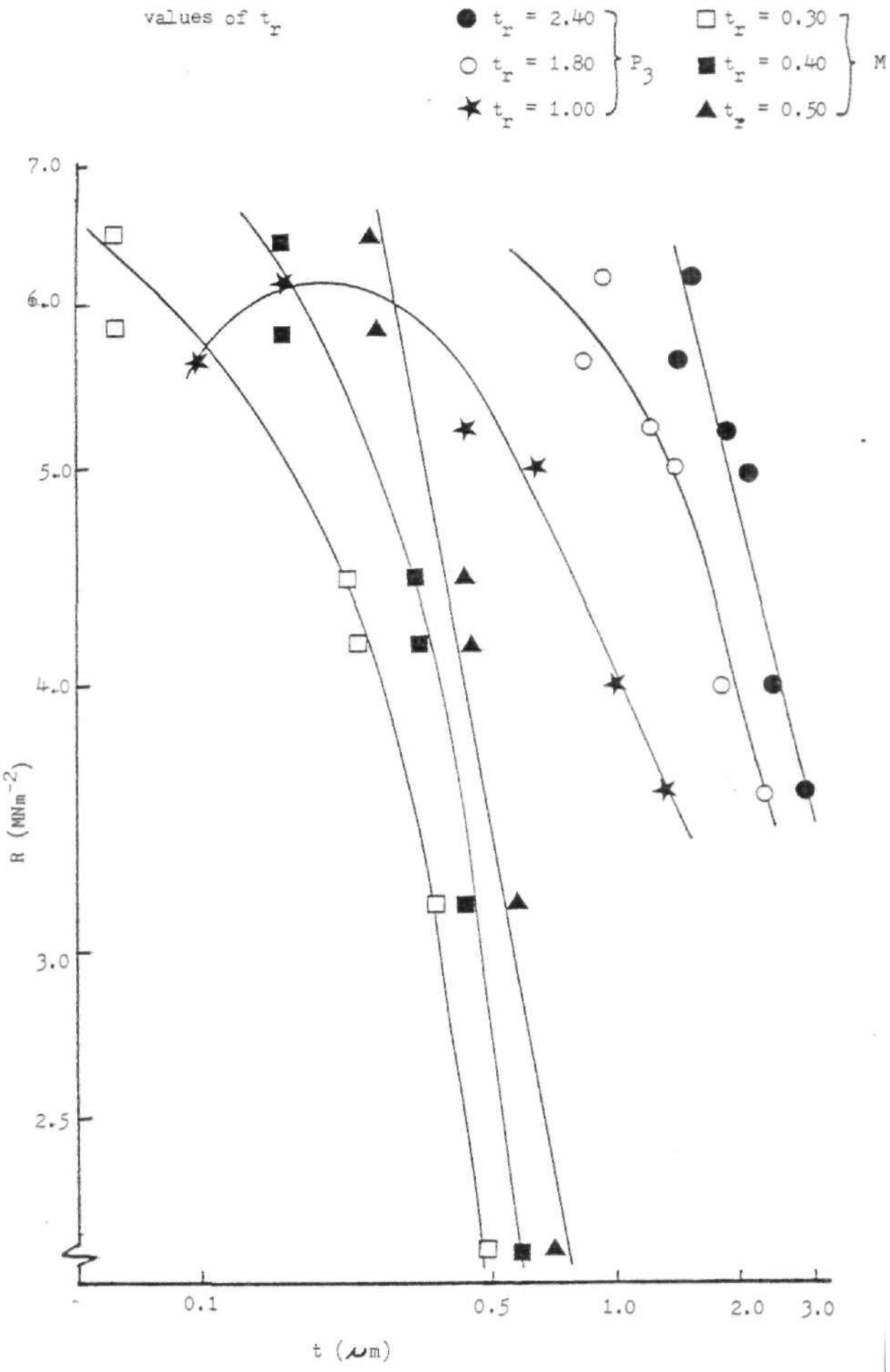


Fig. 3.6. Plot of α_{mix} against % W/W of Avicel in the mixture

Fig. 3.7 shows that the relationship between log R and log t is a curve at low trial values of t_r. It becomes rectilinear as it approaches the correct t_r value ; for P_3 this value is 2.40 μm and for M_7 it is 0.50 μm. In principle when the trial value of t_r used is larger than the correct one, the plot of log R versus log t should become concave upwards. In practice, however, because of experimental scatter it may be difficult to determine when the log R versus log t plot becomes a straight line and so it is difficult to obtain the correct value of t_r. One way of avoiding too large a value for t_r is to recall the assumption made in deriving Eq. 31 namely that $t_r \ll \bar{d}$. By using the above trial and error method, a series of lines almost parallel to each other was obtained when R was plotted against t on log-log paper for all samples (Fig. 3.5). The slopes of these lines give the value of m and their intercepts at log t = 0, i.e. t = 1.00 m, give α or α_{mix}. The values are given in Table 3.5 : m ranges from 0.77 to 1.23 but considering the assumptions made in the derivation of the theory it can be reasonably concluded that m is a universal constant, as implied by Eq. 36 with an (average) value of 1.00 $\pm$ 0.23.

The values of R_r chosen to obtain ℓ_r for use in Eq . 32 are dependent on the lie of the experimental data. As has been shown earlier, the values of R_r varied with the particle shape, density and size distributions of the materials used. This implies that they also have different t values (see Eqs. 31 and 32). However this fact will not affect the values obtained for α and m because as has been shown in Fig. 3.5, there is only one set of (R,t) i.e. $\{R,(t_r + \lambda)\}$, that gives a straight line plot. Therefore any change in λ produced by using different values of ℓ_r in Eq . 32 will be compensated for by the choice of t_r. In fact,

Fig. 3.7. Plot of log R against log t using different trial values of t_r



the consistency of the α (or α_{mix}) and m values has been tested by using various R_r values and thereby obtaining different t_r values. When log R is plotted against log t, the α (or α_{mix}) and m values obtained were respectively within $\pm$ 5% and 15% of those listed in Table 3.5. This suggests that values of α, α_{mix} and m are independent of the choice of R_r and also of the material employed and supports the idea that they are in fact constants. The parameters α, t_r and m are related by the equation

$$R_r = \frac{\alpha}{t_r^m} \qquad (76)$$

because at R_r, $\ell = \ell_r$ and $t = t_r$. Thus a check of consistency is possible. In Table 3.5 $\frac{\alpha}{(t_r)^m}$ and $\frac{\alpha_{mix}}{(t_r)^m}$ are tabulated for both the experimental m obtained at the chosen R_r values and for the average m = 1.00. In view of the scatter in the results and the difficulty of determining t_r, it is considered that the agreement is on the whole satisfactory and so both the theory and the universality of m are confirmed by the experiments. One could rework the data to obtain improved values of α and t_r if so desired.

Fig. 3.5 shows that all the points for the different size fractions of paracetamol and Avicel can be accomodated approximately on two different straight lines [The correlation coefficients are reasonably high and the scatter especially as the particles become large can be ascribed to the intrinsic scatter of experimental results associated with tensile strength experiments (Sutton 1976), to the assumptions in the theory employed (Cheng 1968 ; Chan et al 1983) and also possibly to variations in particle shape between the different

Table 3.5 Derived values of α and m obtained from graph of log R versus log t

Sample	ℓ_r ($g\ cm^{-3}$)	t_r (μm)	Correlation Coefficient	m	α or α_{mix} $\times 10^{-3}$ $[Nm^{-2}(\mu m)^m]$	$\frac{\alpha}{(t_r)^m}$ or $\frac{\alpha_{mix}}{(t_r)^m}$ using $\times 10^{-3}$	
						experimental m (Nm^{-2})	average m = 1.00 (Nm^{-2})
P_1	0.29	0.90	-0.982	1.23	7.1	8.08	7.89
P_2	0.40	1.10	-0.929	0.94	8.2	7.50	7.45
P_3	0.41	2.40	-0.968	0.79	8.3	4.16	3.46
A_1	0.34	0.25	-0.945	0.93	1.0	3.63	4.00
A_2	0.43	0.15	-0.953	1.19	1.1	10.52	7.33
A_3	0.44	0.15	-0.950	0.81	1.3	6.04	8.67
M_1	0.33	1.00	-0.953	0.86	7.7	7.70	7.70
M_2	0.35	1.00	-0.967	1.12	7.9	7.90	7.90
M_3	0.34	1.00	-0.950	1.22	8.0	8.00	8.00
M_4	0.34	1.00	-0.904	0.96	7.9	7.90	7.90
M_5	0.32	0.65	-0.993	1.01	5.2	8.03	8.00
M_6	0.37	0.50	-0.955	1.01	3.6	7.25	7.20
M_7	0.38	0.50	-0.972	1.00	1.7	3.40	3.40
M_8	0.40	0.35	-0.994	0.96	1.5	4.11	4.29

samples (Pilpel and Walton 1974)] . The derivation of Cheng's tensile strength theory assumed the particles to be spherical. However, optical microscopy of the present material revealed them to be acicular and the larger particles to be less spherical than the smaller ones. Frictional forces and mechanical interlocking may, therefore contribute significantly to the tensile strengths of beds made from larger particles. More stringent enumeration of the particle size parameters may be necessary to accomodate the effects of particle shape to the present theory.

The α value for paracetamol is very much greater than that for Avicel (Table 3.5). Although the term compressibility is interpreted in different ways by different authors, α appears to be a measure of the compressibility of a material. Paracetamol with a high value of α is very difficult to compress and compacts formed from it immediately cap and laminate (Leigh et al 1967 ; Shotton and Obiorah 1978). Avicel with a low value of α is soft and readily compressible (Lamberson and Raynor 1976 ; Esezobo and Pilpel 1977) and it is therefore used as an excipient for tableting paracetamol and other pharmaceutical drugs. At least 25% w/w of Avicel has to be mixed with paracetamol before the α value of the mixture is substantially reduced below that of the pure drug (Fig. 3.6). This provides a scientific explanation for the empirical observation that in production it is necessary to incorporate 25 - 30% w/w of Avicel in paracetamol (Avicel Bulletin, FMC Corporation 1975) if it is to be compressed on a commercial scale into firm and satisfactory tablets that do not cap or laminate (Carless and Leigh 1974 ; Leiberman and Lachman 1980).

The slight difference between the α value of the smaller fraction of paracetamol (P_1) and the bigger fractions P_2 and P_3 may be attributed to the effect of particle shape. Microscopy shows all the fractions to be acicular but the P_1 particles were more 'spherical' than those of P_2 and P_3. It is possible that the shape factor may not be constant between different sizes of non-spherical particles and these may influence tensile strength and α values. Walton (1972) has observed that the greater the departure from sphericity the higher the rise in tensile strength of particles of the same material for small changes in their packing densities. However, the shape factor effect will require further experimental confirmation.

An alternative explanation is that sample P_1 possesses a different character from the rest of the paracetamol fractions. Carless and Leigh (1974) suggested that by micronising paracetamol, one may improve its compressibility. They ascribed this to a decrease the elasticity of the material. Since P_1 had been micronised to less than 10 μm it may be less elastic than the other paracetamol fractions, and hence more compressible. In fact, as will be seen in the next chapter, the % elastic recovery of tablets formed from P_1 was slightly less than that of those from P_2 and P_3 but further work on the compressibility of this sample would be necessary to confirm this suggestion.

Table 3.6 shows the experimental values of α_{mix} and α_{AB} calculated according to Eq. 52 for the mixtures. The values of α_{AB} are not constant and in some cases take negative values. A negative value indicates a negative force of attraction, that is a force of repulsion between the two unlike particles of species A and B [This could arise as a result of the deformation of the surface

Table 3.6 α_{AB} values for the mixtures

SAMPLE	U_A	U_B	$\alpha_{mix} \times 10^{-3}$ $\left[Nm^{-2}(\mu m)^m\right]$	$\alpha_{AB} \times 10^{-3}$ $\left[Nm^{-2}(\mu m)^m\right]$
M_1	0.995	0.005	7.7	36.1
M_2	0.989	0.011	7.9	24.7
M_3	0.983	0.017	8.0	20.3
M_4	0.976	0.024	7.9	15.7
M_5	0.959	0.041	5.2	-4.7
M_6	0.910	0.090	3.6	-4.2
M_7	0.770	0.230	1.7	2.2
M_8	0.528	0,472	1.5	0.5

protrusions of particles (Krupp 1967 ; Greenwood and Tripp 1967 ; Cheng and Valentine 1968) but seems rather unlikely] . By the law of corresponding states, one would expect α_{AB} to be a constant relating $H_{AB}(t)$ and t because ϵ_{AB} and t_{AB} (Eq. 50) are parameters that describe the intrinsic properties of these unlike particles in the pair. The variation in the values of α_{AB} may be attributed to the following reasons :

Firstly, in Cheng's approach to the theory, the tensile strength of a powder is calculated by statistically summing all the interparticle forces between the particle pairs at the fracture zone. In a tensile test, it is assumed that failure occurs on a predetermined plane. However, when the powder fails, it is likely that certain zones of structure will be weaker than others and failure will occur in the weakest zone first. In practice, the results of the test are normally rejected if the failure surface is generally rough and is a few particles thick especially when the particle size of the powder is less than 100 μm. For a single powder with a narrow size distribution, the errors involved will be acceptable as there is only one type of interparticle force. However, in a binary mixture, as mentioned earlier, there are three types of particle pairs and their interparticle forces may be of different magnitudes. If this is the case, then when the powder fails, failure may occur along a plane which contains the greatest number of particle pairs which have the weakest interparticle forces. This will result in a lower measured tensile strength and as a consequence in a smaller α_{AB} value than expected. The presence of such a plane of weakness could well account for the negative α_{AB} values obtained for some samples in the present study. This possibility of a plane of weakness in the powder compact when it failed was not considered by Cheng.

The second possible reason for the variations in α_{AB} and for the inability to relate α_{mix} to the α values of the single components might be due to physical changes produced in the particles during the process of mixing. During mixing, comminution and smoothing out of surface irregularities may occur (Hersey 1976). Frictional attrition may cause the particles to become electrostatically charged. These changes in the surface characteristics may alter the type and magnitude of the interparticle forces.

Thirdly, there is the possibility that the variation in α_{AB} values of the mixtures may be due to experimental errors which will affect the evaluation of particle size and interparticle force parameters. This is thought to be unlikely in view of the care and precautions taken over the experimental work and the frequent rechecking of results.

Finally, the non-constancy of the values of α_{AB} and the inability to relate α_{mix} to the α values of the single components could be due to the simplifications made in the statistical approach to the Cheng's theory. It is assumed that the particles in a bed are randomly distributed but this is known to be very difficult to achieve practically (Williams et al 1972). Moreover, ideal mixing is rarely achieved (Hersey 1976) invalidating the theory's assumption that any given bed will show the property of the statistical "average" bed. Also the theory does not allow for the possibility of non-spherical particles which could have different surface characteristics ; nor for the possibility that not all the particle pairs are equally likely. There is therefore room for appropriate modifications of the theory.

Although Cheng's theory for binary mixtures is only moderately successful in relating α_{mix} to the values of α for the single components, provided α_{mix} and ϱ_r are known, Eq. 53 can be used in conjunction with Eqs. 31 and 32 to calculate the tensile strengths of the mixtures with reasonable accuracy as depicted in Table 3.7.

Finally, a further practical application of the theory would be to see if the tensile strength equations can be used to predict the tensile strengths of single powders and their binary mixtures at given packing densities from knowledge of their particle size distributions and compositions.

SINGLE POWDERS

For a single powder, of known particle size distribution, with a material constant α, knowledge of ϱ_r and t_r would be required if its tensile strength at a chosen bulk density were to be predicted according to Eq. 40 . Although ϱ may be predicted from knowledge of particle size distribution (Gupta and Larson 1979). the values of ϱ_r is dependent on the choice of reference reduced tensile strength used in the evaluation of t_r. It seems likely that ϱ_r, being a measure of packing structure will depend on the shape of the size distribution of particles rather than on the absolute values of size. Predictions have been attempted in soil science and in suspensions. (Fedors 1979 ; Fedors and Landel 1979).

To overcome the uncertainty in the choice of ϱ_r the concept of maximum bulk density, ϱ_{max} (Chan 1982) was invoked ; ϱ_{max} represents a state of packing of particles when the distance of separation, t becomes zero. This allows t to be calculated from the particle size alone without a knowledge of ϱ_r.

Table 3.7 Test for Equations 40 and 53 and the constancy of m

SAMPLE	Packing Density ℓ/ℓ_s	$T_{calculated}$ x 10^{-3} (Nm^{-2})	$T_{observed}$ x10^{-3} (Nm^{-2})	% difference
	0.218	0.487	0.457	6.56
	0.244	0.762	0.881	-13.51
	0.230	0.590	0.659	-10.47
P_1	0.258	1.067	1.338	-20.25
	0.260	1.108	1.389	-20.23
	0.270	1.411	1.548	-8.85
	0.217	0.472	0.449	5.12
	0.287	0.478	0.461	3.69
	0.300	0.602	0.604	-0.33
P_2	0.337	1.436	1.316	9.12
	0.291	0.507	0.429	18.18
	0.311	0.747	0.826	-9.56
	0.321	0.927	0.935	-0.86
	0.296	0.376	0.457	-17.72
	0.355	0.978	0.957	2.19
P_3	0.330	0.618	0.757	-18.36
	0.352	0.888	1.031	-13.87
	0.314	0.472	0.566	-16.61
	0.339	0.716	0.839	-14.66
	0.225	0.264	0.226	16.81
	0.232	0.362	0.332	9.04
A_1	0.214	0.170	0.203	-16.26
	0.228	0.299	0.278	7.55
	0.237	0.484	0.360	34.44
	0.199	0.108	0.120	-10.00

Table 3.7 (cont)

SAMPLE	Packing Density ℓ/ℓ_s	$T_{calculated}$ x 10^{-3} (Nm^{-2})	$T_{observed}$ x 10^{-3} (Nm^{-2})	% difference
	0.238	0.081	0.072	12.50
	0.265	0.205	0.253	-18.97
A_2	0.262	0.173	0.193	-10.36
	0.271	0.261	0.250	4.40
	0.259	0.154	0.183	-15.85
	0.248	0.109	0.095	14.74
	0.278	0.265	0.255	3.92
	0.272	0.186	0.181	2.76
A_3	0.270	0.173	0.135	28.15
	0.284	0.411	0.369	11.38
	0.286	0.530	0.449	18.04
	0.292	1.165	1.114	4.58
	0.257	0.657	0.733	-10.37
M_1	0.281	0.967	1.074	-9.96
	0.236	0.478	0.546	-12.45
	0.261	0.679	0.648	4.78
	0.237	0.482	0.599	-19.53
	0.298	1.049	1.046	0.29
	0.267	0.652	0.643	1.40
M_2	0.282	0.797	0.920	-13.37
	0.245	0.478	0.455	5.05
	0.269	0.665	0.695	-4.32
	0.288	0.954	0.955	-0.10
	0.251	0.524	0.679	-22.83
M_3	0.277	0.810	0.744	8.87
	0.243	0.462	0.525	-12.00
	0.260	0.607	0.620	-2.10

Table 3.7 (cont)

SAMPLE	Packing Density ρ/ρ_s	$T_{calculated}$ x 10^{-3} (Nm^{-2})	$T_{observed}$ x 10^{-3} (Nm^{-2})	% Difference
	0.232	0.393	0.340	15.59
	0.292	1.026	0.931	10.20
M_4	0.262	0.622	0.669	-7.03
	0.276	0.808	0.941	-14.13
	0.284	0.884	0.826	7.02
	0.226	0.372	0.400	-7.00
	0.218	0.327	0.318	2.83
	0.268	1.085	1.102	-1.54
	0.246	0.597	0.580	2.93
M_5	0.237	0.483	0.504	-4.17
	0.254	0.704	0.677	3.99
	0.265	0.908	0.886	2.48
	0.228	0.389	0.384	1.30
	0.246	0.328	0.279	17.56
	0.281	0.869	0.833	4.32
M_6	0.259	0.444	0.511	-13.11
	0.250	0.354	0.380	-6.84
	0.268	0.635	0.642	-1.09
	0.253	0.177	0.187	-5.35
	0.263	0.243	0.278	-12.59
M_7	0.277	0.446	0.397	12.34
	0.277	0.446	0.435	2.53
	0.262	0.238	0.257	-7.39
	0.243	0.136	0.124	9.98
	0.248	0.132	0.123	7.32
	0.276	0.389	0.370	5.14
M_8	0.267	0.249	0.233	6.87
	0.249	0.134	0.136	-1.47
	0.260	0.189	0.183	3.28
	0.273	0.306	0.282	8.51

As mentioned earlier, the theory assumes that the particles are spherical with a mean effective diameter $\bar{d}$ and are separated by a distance t due to the operation of interparticle forces. The weight of a particle whose mean volume is $\bar{V}$ is $\rho_s \bar{V}$ and the volume it effectively occupies is $(\bar{d} + t)^3$. Thus the bulk density of a powder containing a large number of particles can be related to $\rho_s \bar{V}$ and $(\bar{d} + t)^3$ i.e.

$$\rho \quad \text{is proportional to} \quad \frac{\rho_s \bar{V}}{(\bar{d} + t)^3} \tag{77}$$

Rearranging Eq. 77

$$\frac{\rho}{\rho_s \bar{V}} \quad \text{is proportional to} \quad \frac{1}{(\bar{d} + t)^3} \tag{78}$$

and when t is zero, a maximum bulk density is reached and Eq. 78 becomes

$$\frac{\rho_{max}}{\rho_s \bar{V}} \quad \text{is proportional to} \quad \frac{1}{\bar{d}^3} \tag{79}$$

Combining Eqs. 78 and 79

$$\frac{\rho_{max}}{\rho} = \frac{(\bar{d} + t)^3}{\bar{d}^3} \tag{80}$$

or

$$t = \bar{d}\left\{ \left(\frac{\rho_{max}}{\rho}\right)^{1/3} - 1 \right\} \tag{81}$$

Substituting Eq. 81 into Eq. 40 the tensile strength, T, is

$$T = \frac{\bar{d}\,\bar{S}}{4\,\bar{V}} \quad \frac{\rho/\rho_s}{1 - \left(\rho/\rho_s\right)} \quad \frac{\alpha}{\left[\bar{d}\left\{ \left(\frac{\rho_{max}}{\rho}\right)^{1/3} - 1 \right\}\right]^m} \tag{82}$$

If the particle size parameters, α and m are known it should be possible to predict the tensile strength of a powder at a chosen bulk density once its ρ_{max} value is known.

Fig. 3.8 is interpolated to get the value of the ordinate $\ell_{max} / (\ell_s \bar{V})$ for a particular diameter $\bar{d}$ of the powder. Since $\bar{V}$ and ℓ_s are known, ℓ_{max} of the powder can be obtained. Using this method, the ℓ_{max} values of different size fractions of paracetamol and Avicel powders were obtained. Using the experimental α values listed in Table 3.5 and an average m value of 1.00, Eq. 82 was used to predict the tensile strength of the powders at different bulk densities. It is seen from Table 3.8 that the agreement between $T_{predicted}$ and $T_{observed}$ values is satisfactory.

The linear relationship between $\log \frac{\ell}{\ell_s \bar{V}}$ and $\log (\bar{d} + t)$ in Fig. 3.8 for the different size fractions of paracetamol and Avicel which have very different characteristics suggests that this graph is a "universal" plot and that it might be used to obtain ℓ_{max} values of other powders from a knowledge of their particle size parameters. This suggestion however is subject to further confirmatory work.

BINARY MIXTURES

The tensile strength of a binary mixture of powders is given by Eq.53 and like single powders, knowledge of ℓ_r and t_r is required. One may equally apply the concept of maximum bulk density to overcome uncertainty in the choice of ℓ_r and re-write Eq. 81 as

$$t = \bar{d}_{mix} \left\{ \left(\frac{\ell_{max}}{\ell} \right)^{1/3} - 1 \right\} \qquad (83)$$

Similarly Eq. 53 becomes

Fig. 3.8. Plot of $\log \frac{\rho}{\rho_s \bar{V}}$ Vs $\log (\bar{d} + t)$ for single powders

(● P , ○ A)

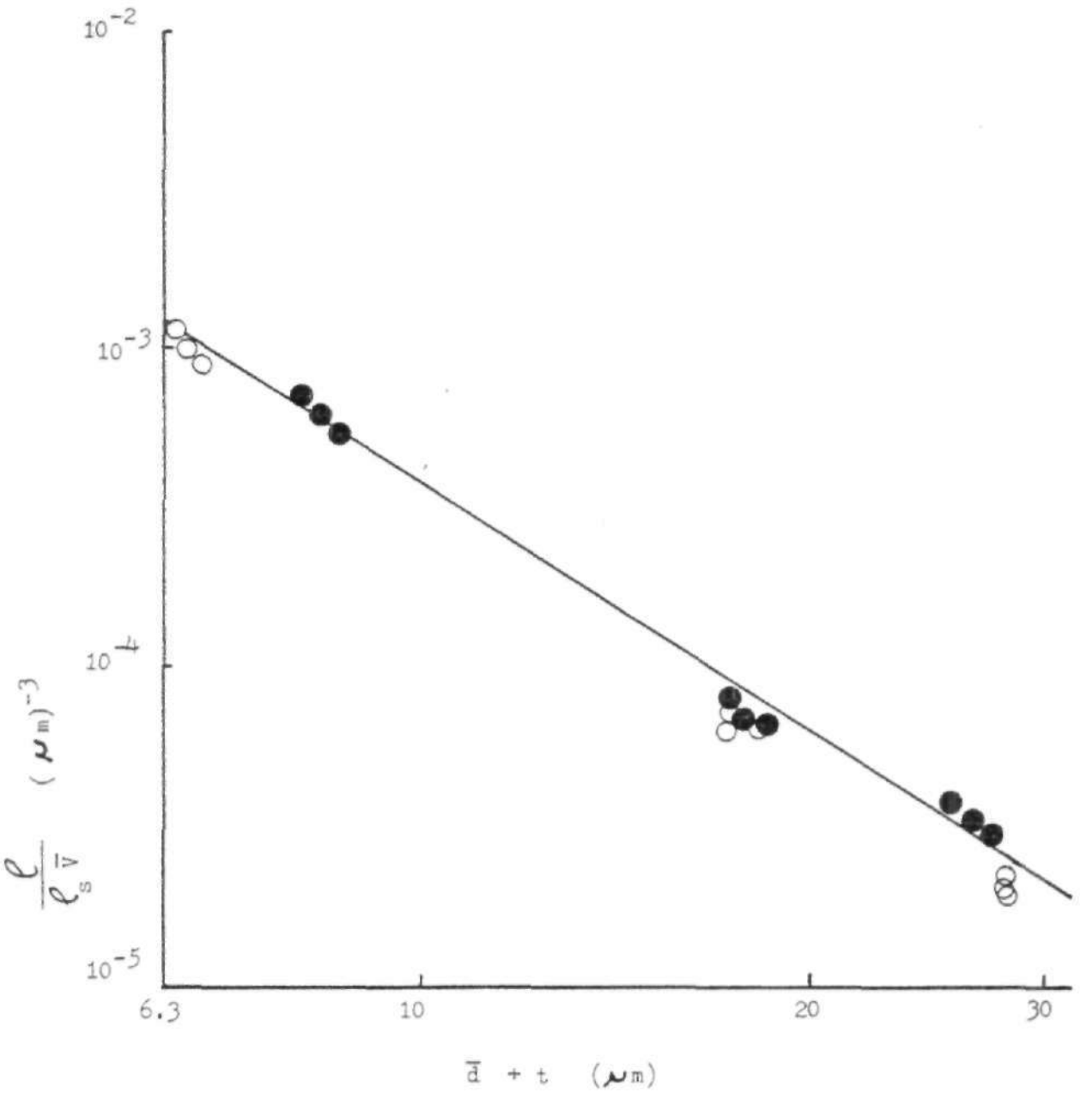


Table 3.8 Test for Equation 84

SAMPLE	ℓ_{max} ($g\ cm^{-3}$)	ℓ ($g\ cm^{-3}$)	$T_{predicted}$ (Nm^{-2})	$T_{observed}$ (Nm^{-2})	% difference
P_1	0.399	0.282	480	457	5.03
		0.333	1147	1338	-14.28
		0.349	1767	1548	14.15
P_2	0.488	0.370	453	461	-1.74
		0.387	591	604	-2.15
		0.413	841	935	-10.05
P_3	0.522	0.382	388	457	-15.10
		0.406	596	566	5.30
		0.454	1127	1031	9.31
A_1	0.383	0.302	108	120	-10.00
		0.326	202	203	-0.49
		0.353	358	332	7.83
A_2	0.444	0.413	256	250	2.40
		0.361	81	72	12.50
		0.393	148	183	-19.13
A_3	0.458	0.411	143	135	5.93
		0.423	194	255	-23.92
		0.435	447	449	-0.45

$$T = \frac{\bar{d}_{mix}\,\bar{S}_{mix}}{4\,\bar{V}_{mix}} \quad \frac{\ell/\ell_{smix}}{1-\left(\ell/\ell_{smix}\right)} \left\{ \frac{\alpha_{mix}}{\bar{d}_{mix}\left\{\left(\frac{\ell_{max}}{\ell}\right)^{1/3}-1\right\}} \right\}^{m} \quad (84)$$

The values of $\bar{d}_{mix}$, $\bar{S}_{mix}$ and $\bar{V}_{mix}$ may be calculated from knowledge of the particle size parameters of the two powders and the composition of the mixture, and similarly ℓ_{smix} can be obtained from $\ell_{s\,A}$ and $\ell_{s\,B}$ (see Chapter 2 page 82). If the tensile strength of a binary mixture at a chosen bulk density is to be predicted, one would require knowledge of ℓ_{max} and α_{mix}.

The value of ℓ_{max} may be obtained by the method described for single powders (pages 132 - 138). A graph of $\log\left\{\ell/\left(\ell_{smix}\,\bar{V}_{mix}\right)\right\}$ against $\log\left(\bar{d}_{mix}+t\right)$ could be plotted and the value of $\ell_{max}/\left(\ell_{smix}\,\bar{V}_{mix}\right)$ could be read off the ordinate at a particular value of $\bar{d}_{mix}$. Knowing ℓ_{smix} and $\bar{V}_{mix}$, ℓ_{max} could be calculated.

From Eq. 52 α_{mix} may be calculated from the values of α_{AA} α_{BB} and α_{AB}, which are parameters describing interactions between two like particles A-A or B-B or two unlike particles A-B. One would expect these values to be constant because they are related to the intrinsic properties of the materials. However, Table 3.6 shows that α_{AB} is not constant and so Eq. 52 gives different values for α_{mix}. The reasons for this have been outlined in the discussion on page 128 to page 131 . It must be concluded that in its present form the theory is not entirely satisfactory for predicting

the tensile strengths of binary mixtures from knowledge of the particle size distributions of the powders concerned.

CONCLUSIONS

Using the concept of a reference state, equations have been derived to relate the tensile strength of single powders and their binary mixtures to their particle size parameters and composition.

For a single powder :

$$T = \frac{\bar{d}\,\bar{S}}{4\,\bar{V}} \cdot \frac{\ell/\ell_s}{1-(\ell/\ell_s)} \cdot \frac{\alpha}{t^m}$$

m is a universal constant and α is a material constant which can be used to compare the 'strength' and 'range' of interparticle forces of different materials.

For binary mixtures :

$$T = \frac{\bar{d}_{mix}\,\bar{S}_{mix}}{4\,\bar{V}_{mix}} \cdot \frac{\ell/\ell_{s_{mix}}}{1-(\ell/\ell_{s_{mix}})} \cdot \frac{\alpha_{mix}}{t^m}$$

where $$\alpha_{mix} = \frac{U_A^2\,\bar{s}_{AA}\,\alpha_{AA} + 2U_A U_B \bar{s}_{AB}\,\alpha_{AB} + U_B^2\,\bar{s}_{BB}\,\alpha_{BB}}{\bar{S}_{mix}}$$

and α_{AA}, α_{BB} and α_{AB} are parameters describing the interactions between type A-A, type B-B and type A-B particles.

Good agreement has been found between the measured tensile strengths of powders and of their binary mixtures and those predicted from the equations.

The value of α for paracetamol has been found to be much larger than that for Avicel and to increase slightly with increase in particle size. At least 25% of Avicel has to be mixed with

paracetamol to reduce the α value of the mixture below that of the pure drug and this provides a scientific explanation for the inclusion of 25 - 30% w/w Avicel in the tableting of paracetamol.

The evaluation of t by the concepts of a reference state and a reduced tensile strength overcomes the previous uncertainty in extrapolating the value of ℓ_o at which the tensile strength is zero.

A concept of maximum bulk density has been applied to enable the prediction of the tensile strength of a single powder with a known α value from the knowledge of its particle size parameters. It is suggested that further work should be undertaken to improve the accuracy of the prediction of the tensile strengths of binary mixtures of powders.

CHAPTER 4

THE PLASTO-ELASTIC PROPERTIES OF PARACETAMOL TABLET FORMULATIONS

Purpose of Chapter 4

The range of packing fractions that is achieved during the measurement of the tensile strengths of powders is 0.2 - 0.5. In order to achieve packing fractions comparable to those of commercial tablets, 0.7 - 0.9, the same powder samples as used in the experiments described in Chapter 3 were compressed into tablets on the DARTEC test machine under various processing conditions. The force-displacement plots were simultaneously recorded as depicted in Fig. 1.4 These plots were used to calculate the elastic recovery (ER), stress relaxation (SR) and hence the plasto-elasticity (ER/SR) of the samples using equations 74 and 75.

Specifically the main objectives of this chapter have been to investigate :

1. the effects of processing variables e.g. duration of compression cycle, thickness of tablets, etc. and formulation factors e.g. sample composition and moisture content on the plasto-elasticity of the samples and the tensile strengths of the resulting tablets.

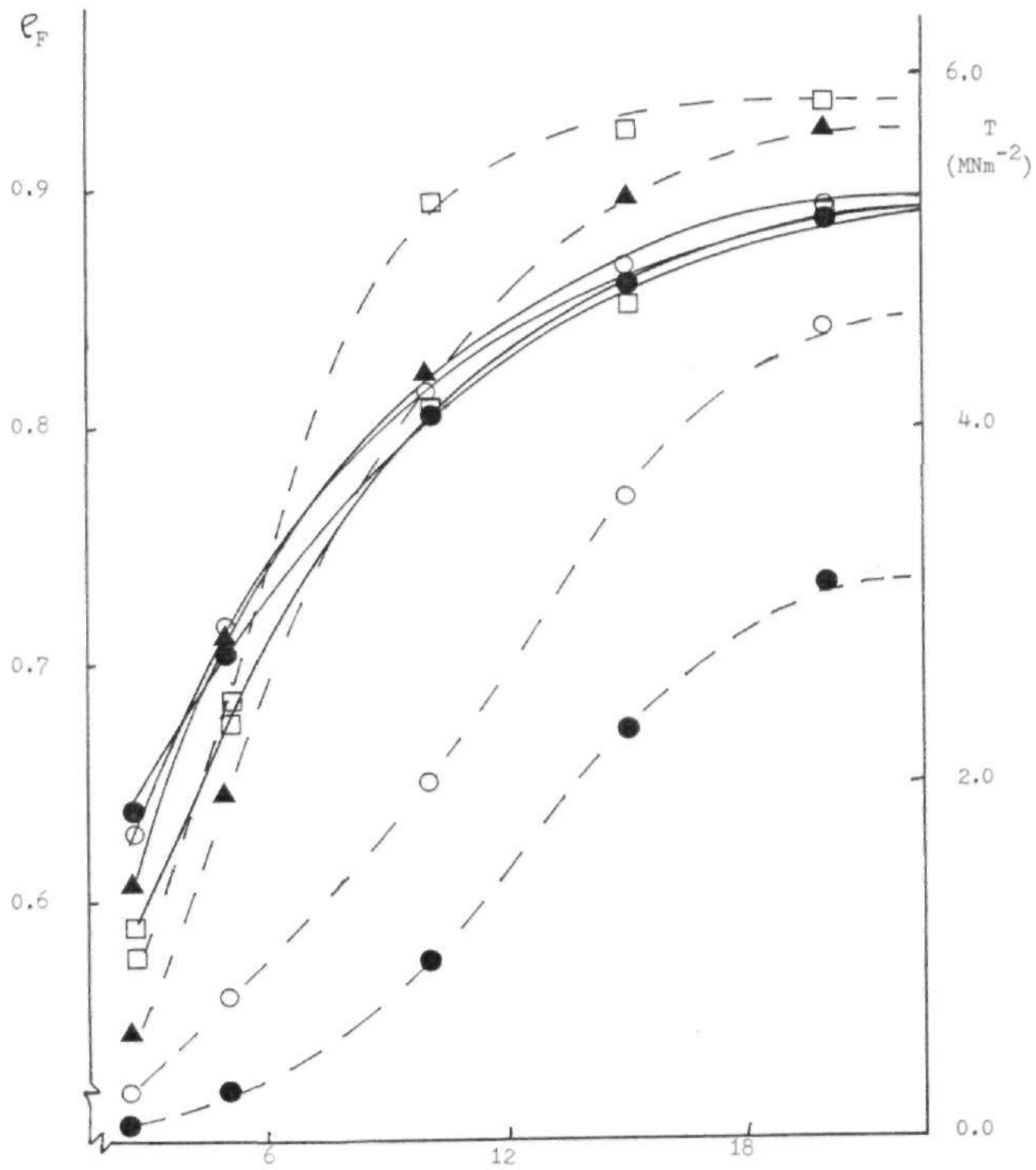
2. any correlation between the plasto-elasticity of samples and their material constant α (see Chapter 3).

It was hoped that the findings would contribute to a better understanding of the mechanism operating during consolidation and compaction of powders and subsequently be of value in the development of new solid dosage products.

RESULTS

Fig. 4.1 shows that the packing fractions of typical samples weighing about 450 mg approach an asymptotic value of about 0.90, the usual commercial value - at the compression load of 20 KN. This

Fig. 4.1. Packing fraction and tensile strength Vs Compression load. (— ϱ_F , --- T , ● M_5 , ○ M_6 , ▲ M_7 , □ M_8)



is expected from the theory of the mechanisms operating during compression (Heckel 1961). The tensile strengths of the resulting tablets each also approach a limiting upper value at this load. In view of this, it seemed reasonable to select a compression load of 20 KN for all the subsequent compression experiments. Typical results are given in Table 4.1.

The packing fraction and the tensile strength results on tablets made from various samples at different compression loads are listed in Table A.2 Appendix 3 on page 211. Representative graphs of tablet tensile strength versus packing fraction for some of the samples are illustrated in Fig. 4.2.

Data on the effect of the weight of sample used (and therefore the thickness of the resulting tablet) on the tablet strength and plasto-elasticity are listed in Table A3 Appendix 3 on page 213. The values that are obtained for ER, SR and the ratio ER/SR depend on the thickness of the tablets as illustrated typically in Fig. 4.3 ; therefore in all subsequent tests the weight of sample employed was that which gave a tablet thickness of between 4.2 and 4.6 mm.

Fig. 4.4 shows that the values of ER, SR and ER/SR are also dependent upon the duration of the compression/decompression cycle and that the values of ER/SR become minimal when compression/holding/decompression occupies 90 s. This was therefore selected for for the subsequent tests. Additional results on the effects produced by varying the compression/decompression cycle are given in Table A.4 Appendix 3 on page 214 and Table A.5 Appendix 3 on page 215.

Fig. 4.5 shows how the values of ER/SR and tensile strength of tablets vary with the % w/w of Avicel incorporated into the mixture.

Table 4.1

Composition, tensile strength and plasto-elasticity of samples

CODE	% w/w of Avicel	Elastic Recovery (%)	Stress Relaxation (%)	Plasto-elasticity (ER/SR)	Tensile Strength at ℓ_F 0.89 [MNm^{-2}]
P_1	0	11.74	0.83	14.14	cap
P_2	0	12.03	0.79	15.34	
P_3	0	12.18	0.80	15.23	
A_1	100	8.20	2.08	3.94	>6
A_2	100	9.02	2.19	4.12	
A_3	100	9.08	2.26	4.02	
M_1	5	11.31	0.92	12.29	1.44
M_2	10	11.22	1.12	9.86	2.20
M_3	15	11.04	1.16	9.52	2.02
M_4	20	10.49	1.17	8.97	2.32
M_5	30	10.33	1.56	6.62	3.12
M_6	50	9.69	1.81	5.36	4.56
M_7	75	9.30	1.94	4.80	>6
M_8	90	9.20	2.14	4.30	

Fig. 4.2. Tensile strength Vs packing fraction of some samples

(● M_5 , ○ M_6 , ★ M_7 , □ M_8)

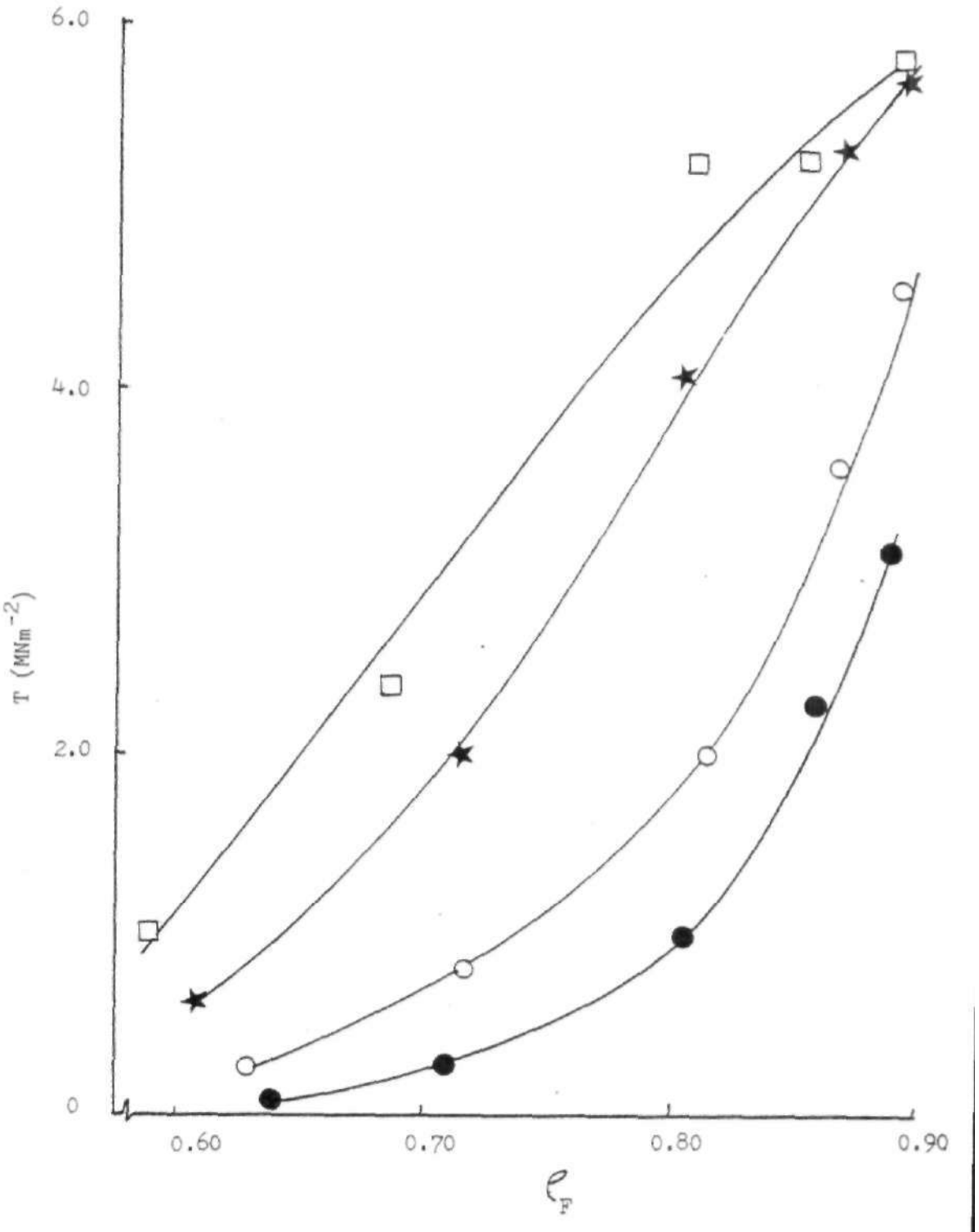


Fig. 4.3. $ER/_{SR}$ Vs Tablet thickness

(● M_5 , ■ M_6 , ▲ A)

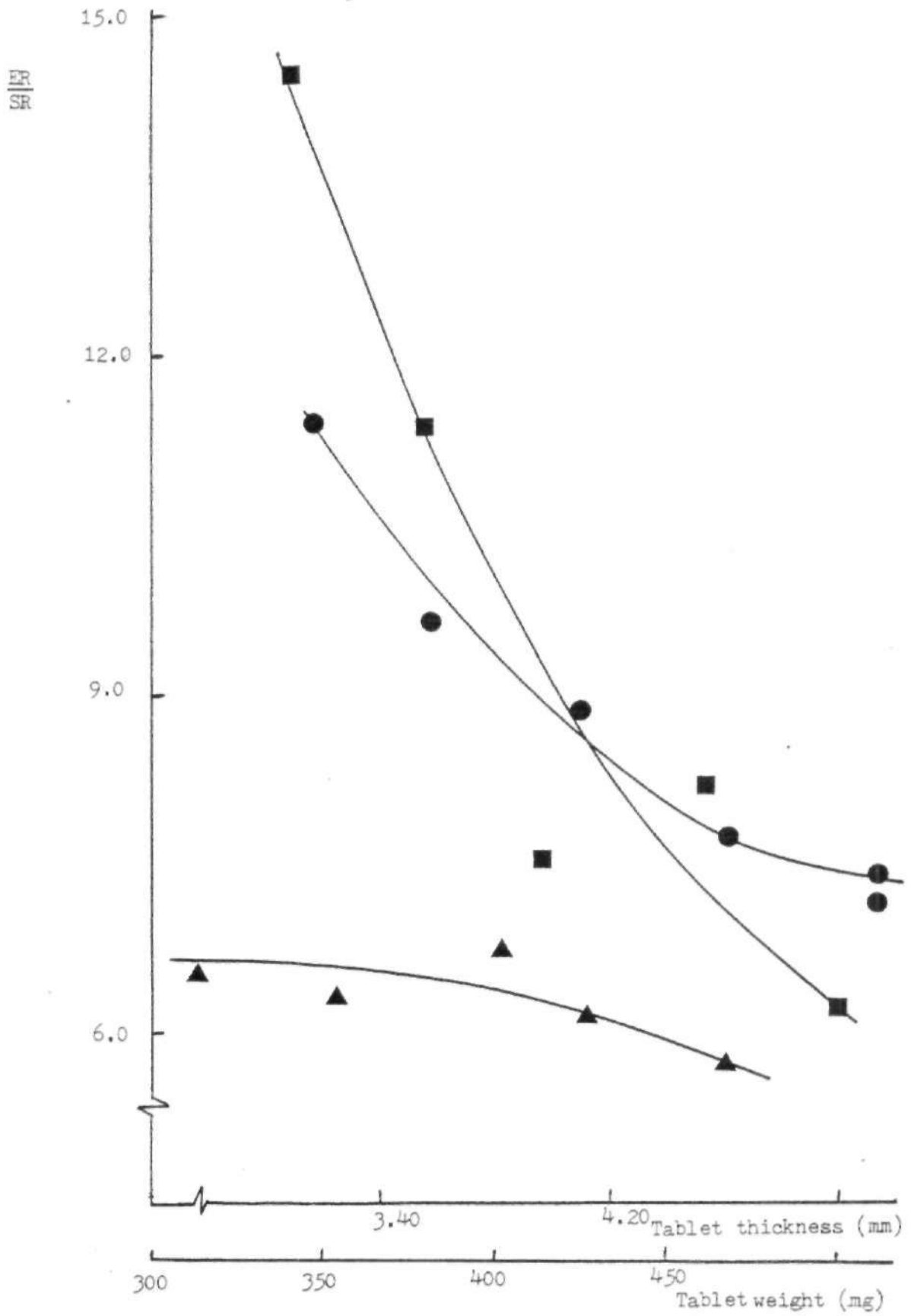


Fig. 4.4. $\frac{ER}{SR}$ Vs Duration of compression/decompression cycle

(■ M_4 , ● M_6 , ▲ A)

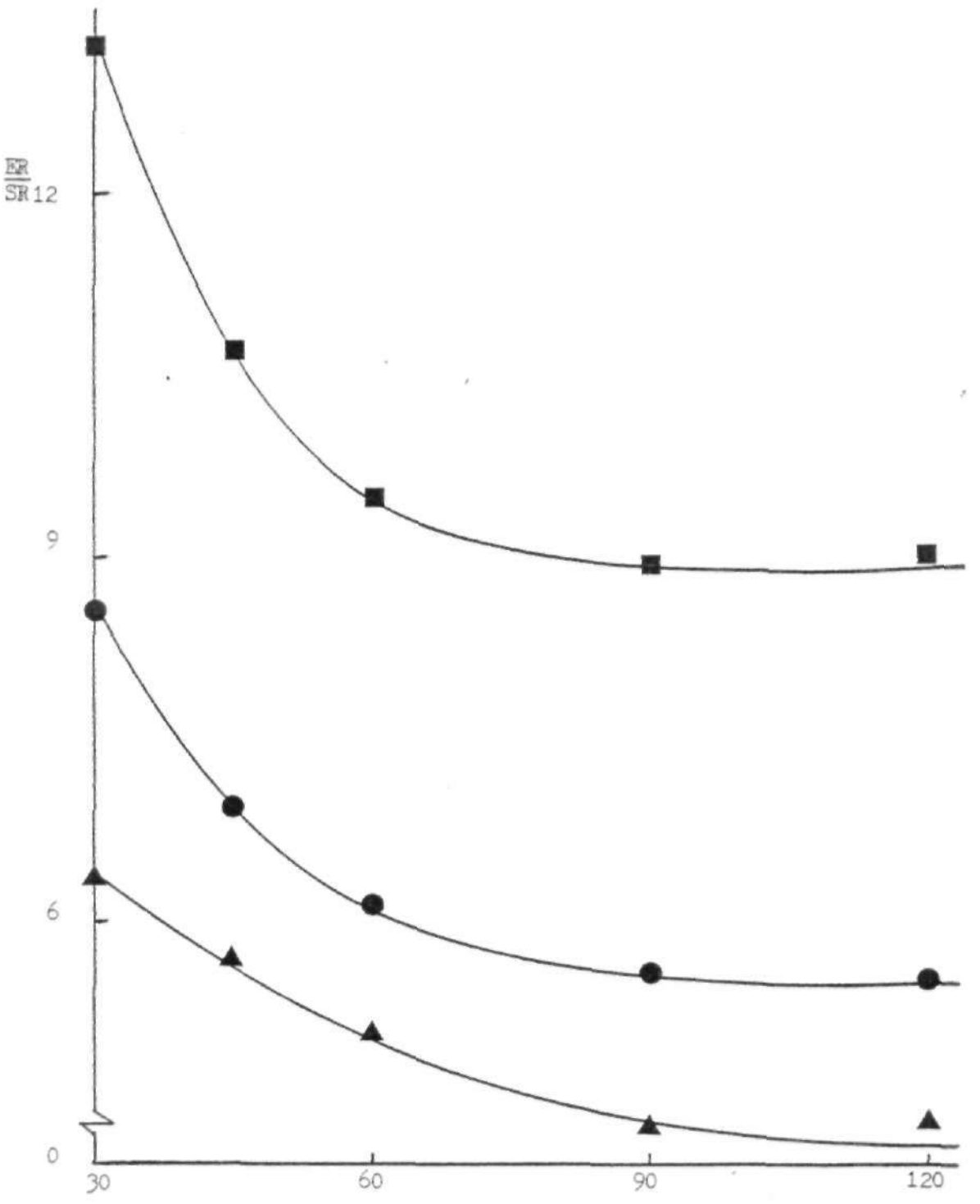


Fig. 4.5. Tensile Strength and Plasto-Elasticity Vs % w/w of Avicel

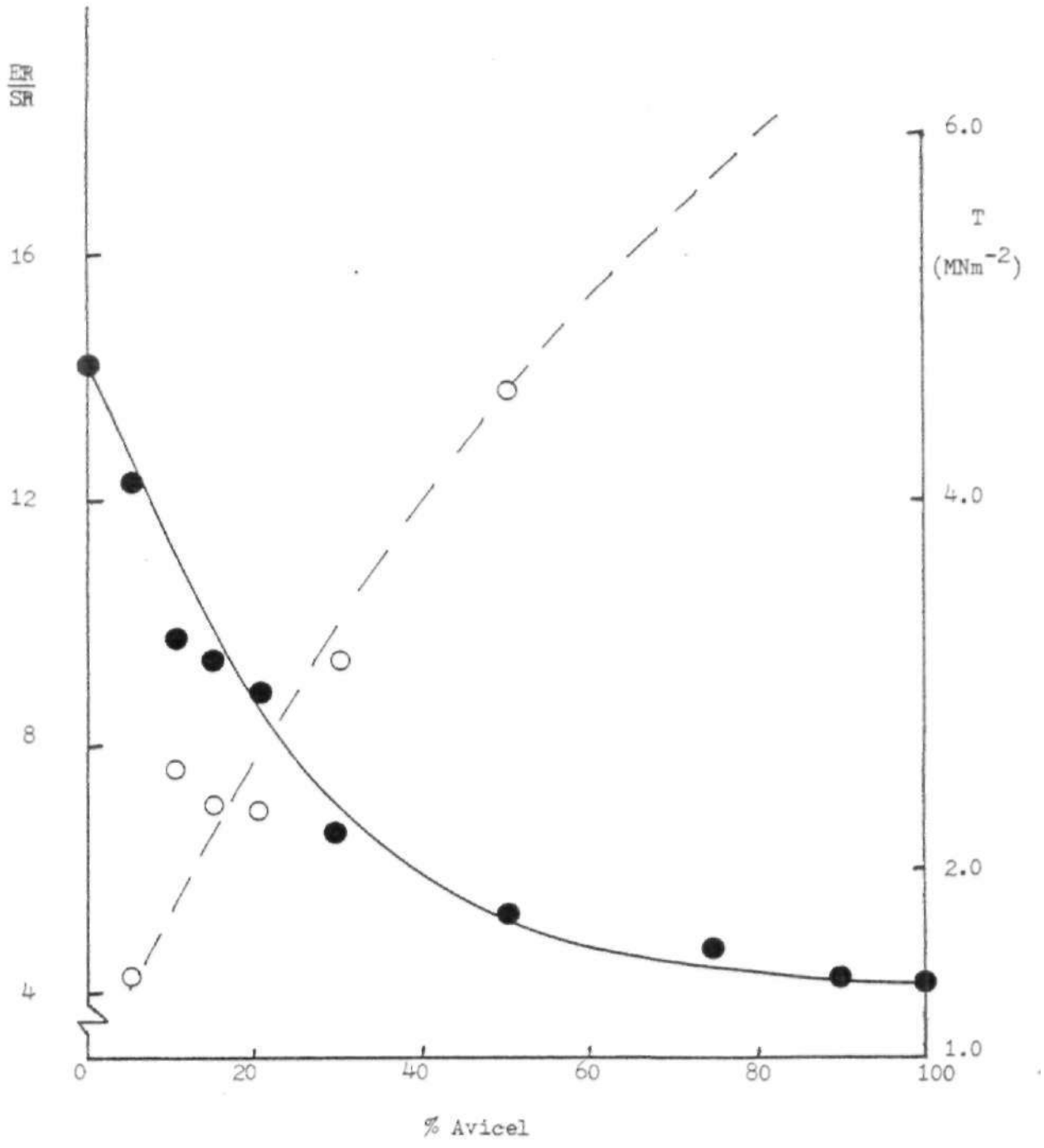


Fig. 4.6 shows that there is an inverse relationship between the values of ER/SR for samples and the tensile strengths of their tablets at a fixed packing fraction of 0.89.

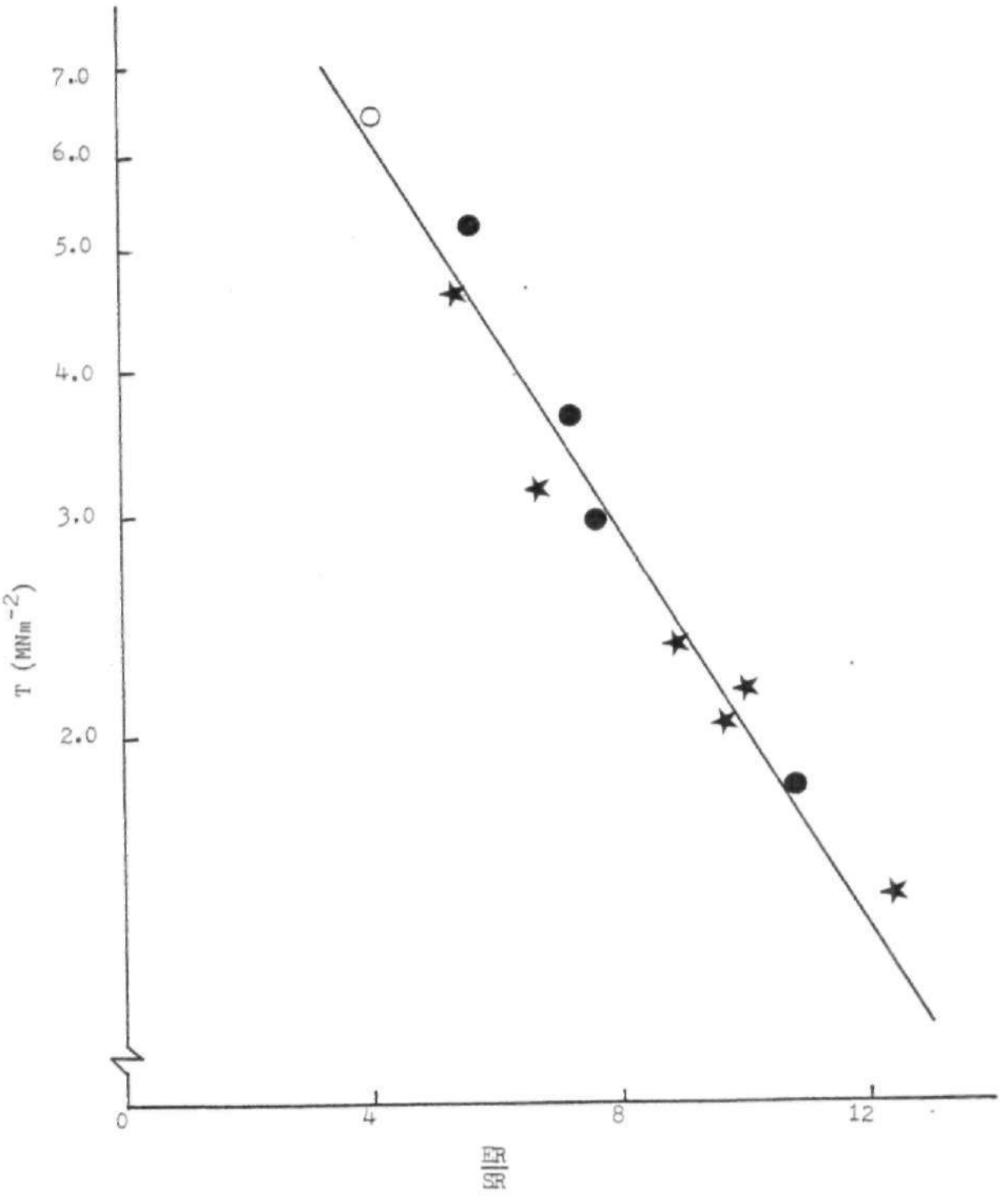
DISCUSSION

Effect of duration of compression/decompression cycle

The dependency of the values that are obtained for ER, SR and the ratio ER/SR on the duration of the compression/decompression cycle is consistent with the results of previous studies (Shlanta and Milosovich 1964 ; David and Ausburger 1977 ; Rue and Rees 1978 ; Armstrong et al 1982 ; Danielson et al 1983). Since low values of ER/SR correspond to high tensile strength tablets, it may be inferred that these will be best produced by using relatively slow rates of compression allowing opportunity for elastic and plastic deformation and for bond formation between particles. The successful production of a pharmaceutical tablet by the compression of solid particles depends on the formation of bonds across particle-particle interfaces. The areas of actual contact, necessary for bonding, are both formed and destroyed during the compression and decompression phases and possibly also during ejection from the die. The net area of such interparticle contacts during and after injection is therefore expected to depend on the time-dependent flow of material which occurs in conjuntion with instantaneous elastic deformations. This explains the observation that the slower tablets expand during decompression the more they will tend to cap and the well-known experience that the tendency for capping can be lessened by lowering the speed of the tablet machine so that more time for expansion is available before ejection of the tablet from the die.

Fig. 4.6. T versus $\frac{ER}{SR}$ at ρ_F 0.89

(○ A_2 , ★ $P_1 + A_2$, ● $P_1 + A_2$ + Stearic acid)



Effect of composition

Table 4.1 shows that while the elastic recoveries of paracetamol and Avicel are comparable, the latter has a much bigger value of stress relaxation. This greater plasticity results in the formation of strong (hydrogen) bonds during compression. Fig. 4.5 shows that as the proportion of Avicel in the mixture is increased, the values of ER/SR decrease and the tensile strengths of the tablets increase. It was also observed that paracetamol on its own could not be made into satisfactory tablets as they tend to cap, laminate or crumble whereas pure Avicel produced very strong tablets at relatively low compression pressures. This accounts for the need in practice to incorporate a number of additives e.g. Avicel into paracetamol tablets to enhance plastic deformation. The plastic Avicel will permanently deform and establish large areas of true contact with the harder paracetamol and will do so at relatively low pressures. Thus, during recovery, the stored elastic energy will be inadequate to separate extensive areas of contact, and strong bonding will result.

Fig. 4.6 shows the inverse relationship between the ER/SR values and the tensile strengths of tablets at packing fraction 0.89. A similar observation was recently made by Malamataris et al (1984). The linear relationship can be expressed empirically by

$$\log T = Q - G\left(ER/SR\right) \qquad (85)$$

where Q and G are constants which are related to the experimental conditions and which for these now employed have the values of 13.9 and 12.4 respectively and T is the tensile strength in MNm^{-2}. The correlation coefficient of the straight line plot in Fig. 4.6 is 0.981. It was noticed that tablets were very weak and had a tendency to cap and laminate when their tensile strength values (if measurable) were less than 2.5 MNm^{-2} and their values of ER/SR were greater than 9.0.

The proportion of Avicel in these tablets was less than 25% and this may therefore account for the commercial use of a minimum of 25% Avicel as an excipient for paracetamol tablets. The establishment of a correlation between the ER/SR values of powders and the tensile strengths of the resulting tablets suggests that ER/SR which is a measure of the plasto-elasticity of a material can be used to predict its tabletability. As mentioned on pages 97-98 the ratio ER/SR is not an intrinsic property of a pharmaceutical powder but nevertheless provides an index for assessing its likely performance during tableting.

Effect of moisture

Fig. 4.7 shows that paracetamol has little tendency to absorb moisture, but that Avicel absorbs up to 14% w/w at relative humidity of 85% and at 20°C. The relative ease with which this can be desorbed (shown by the narrow hysteresis loop) accounts for the ready reversibility of the softening that occurs at high relative humidities in tablets containing more than 25% w/w of Avicel when they are subsequently dried (Reier and Shangraw 1966).

Fig. 4.8 shows that for all the mixtures adding small (< 4% w/w) amounts of water causes a decrease in the ratio ER/SR but that at higher levels there is an increase. With Avicel alone, there is only an increase. The initial decrease is presumably due to the development of surface tension and pendular bonds which hold the particles together (Newitt and Conway-Jones 1958 ; Young and Nelson 1967 a, b). It can be inferred from Figs. 4.6 and 4.8 that mixtures of paracetamol and Avicel containing between about 2 and 4% w/w of water (depending on their composition) will form stronger tablets than those without moisture. The reason why the values of ER/SR increase when more

Fig. 4.7. Moisture sorption and desorption isotherms of paracetamol and Avicel powders at 20°C

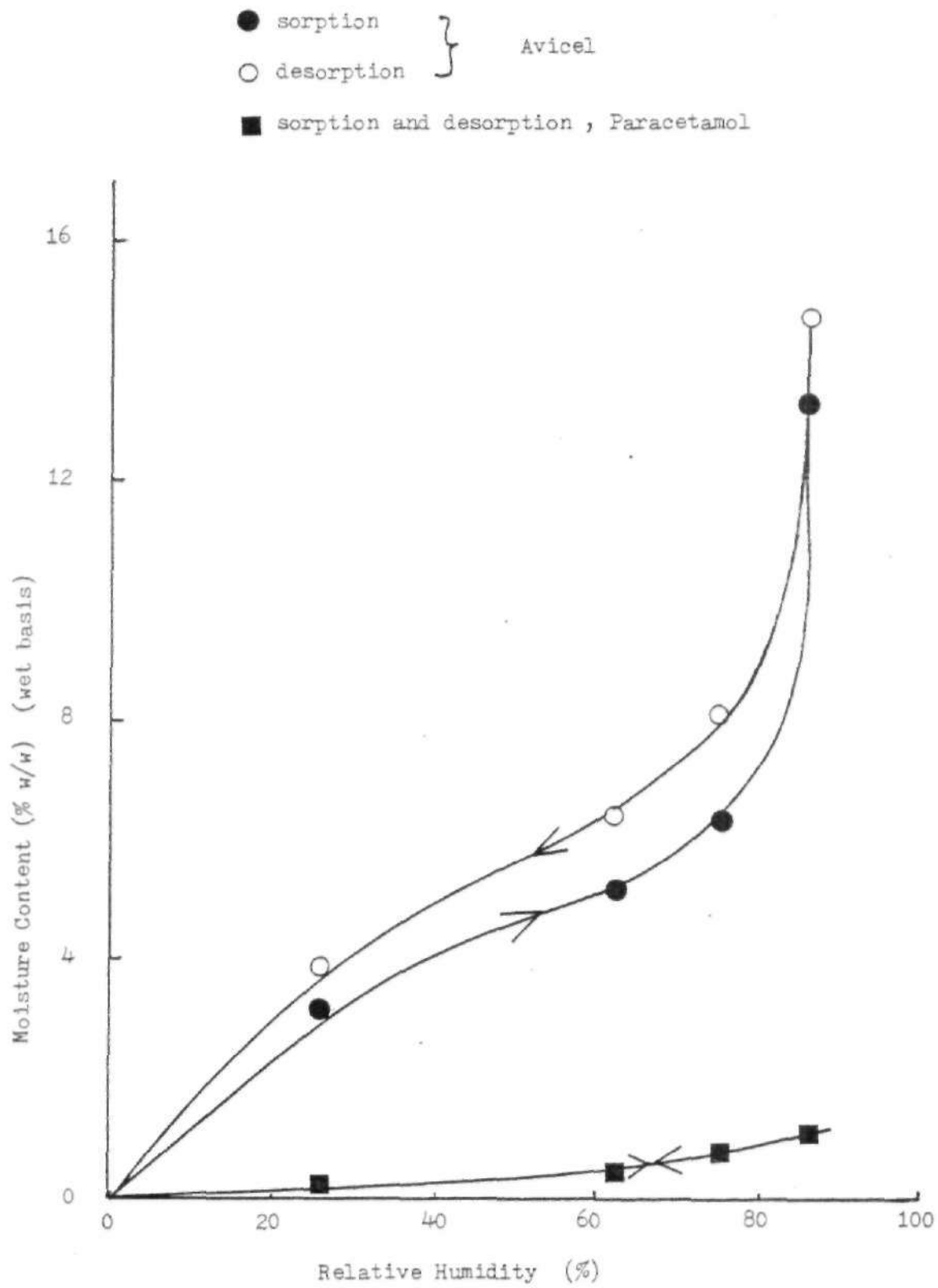
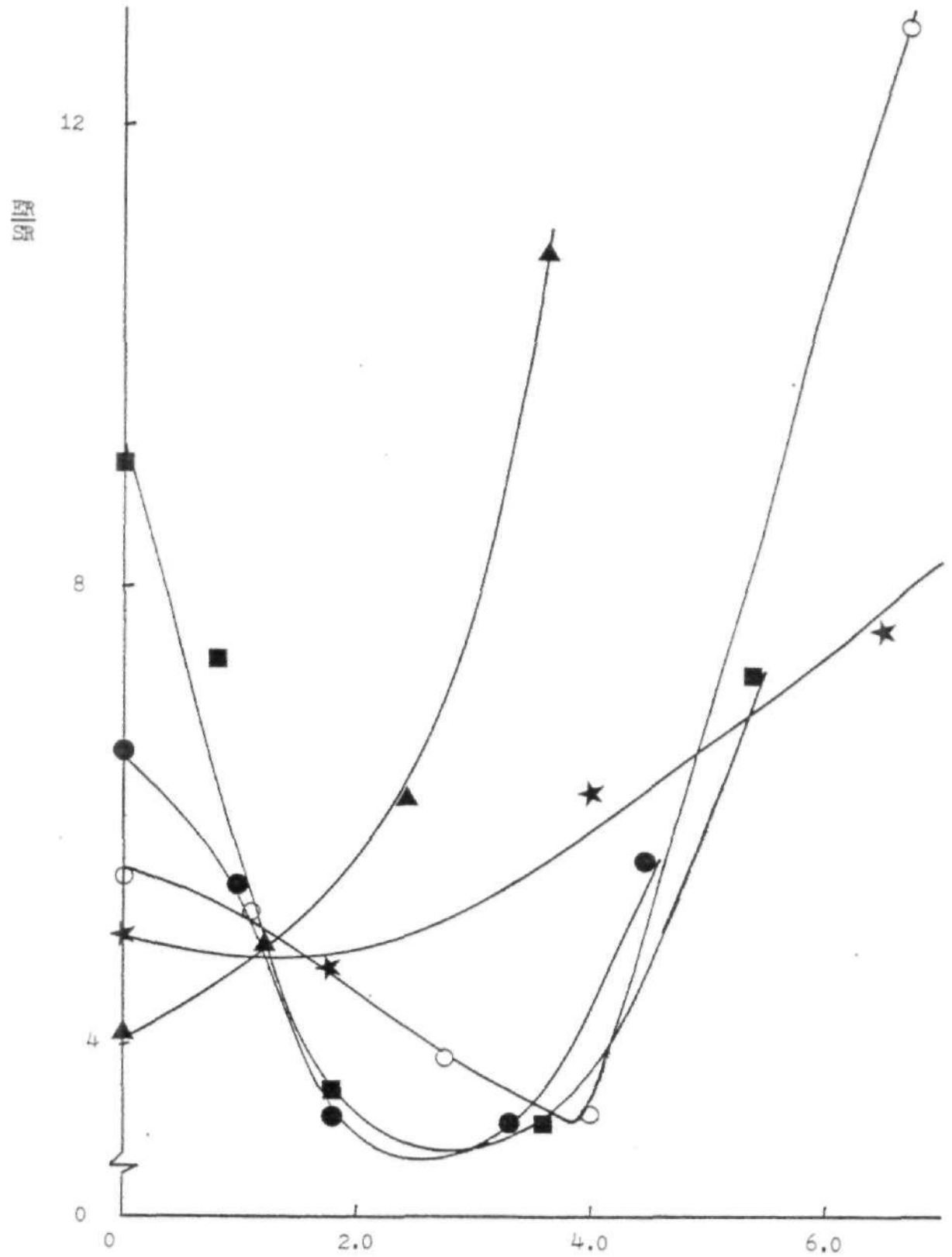


Fig. 4.8. $\frac{ER}{SR}$ Vs % moisture content of some samples

(■ M_4 , ● M_5 , ○ M_6 , ★ M_7 , ▲ A_2)



water is added and why the tensile strengths of the tablets then decrease is that at these levels the water is probably beginning to form multi-layers on the surfaces of the particles (Zografi et al 1984) acting as a lubricant and therefore reducing the frictional forces responsible for attraction between particles (Coelho and Harnby 1978). Liquid water also tends to rupture the hydrogen bonds between Avicel particles (Reier and Shangraw 1966) which contribute to its tensile strength. This explains why samples containing 75% w/w or more of Avicel exhibit virtually no decrease in the ratio ER/SR (and consequent increase in tensile strength) when up to 2% w/w is added to them.

Effect of lubricant

To further justify the explanation that water in excess of 4% w/w in samples was acting like a lubricant, stearic acid was added to Avicel alone and to some mixtures of paracetamol and Avicel. Figs. 4.9 and 4.10 show that adding up to 10% w/w of stearic acid, which is frequently used as a lubricant in tablet formulations (Strickland 1959 ; Little and Mitchell 1963) and which because of its hydrophobicity can also affect disintegration and dissolution rates (Levy and Gumtow 1963 ; Colaizzi and Pitlick 1982) caused increases in the values of ER/SR and reduced the tensile strengths of all the present mixtures. This is because stearic acid is a lubricant and is inherently less cohesive than the two other materials at a fixed packing fraction. The presence of such a lubricant in the form of a surface film or as particles could influence the bonding mechanism between particles and thus account for the changes observed in T and in ER/SR.

Fig. 4.9. $\frac{ER}{SR}$ and tensile strength versus % w/w of added stearic acid

(—— $\frac{ER}{SR}$, - - - T , ■ M_4 , ● M_5 , ○ M_6 , ▲ A_2)

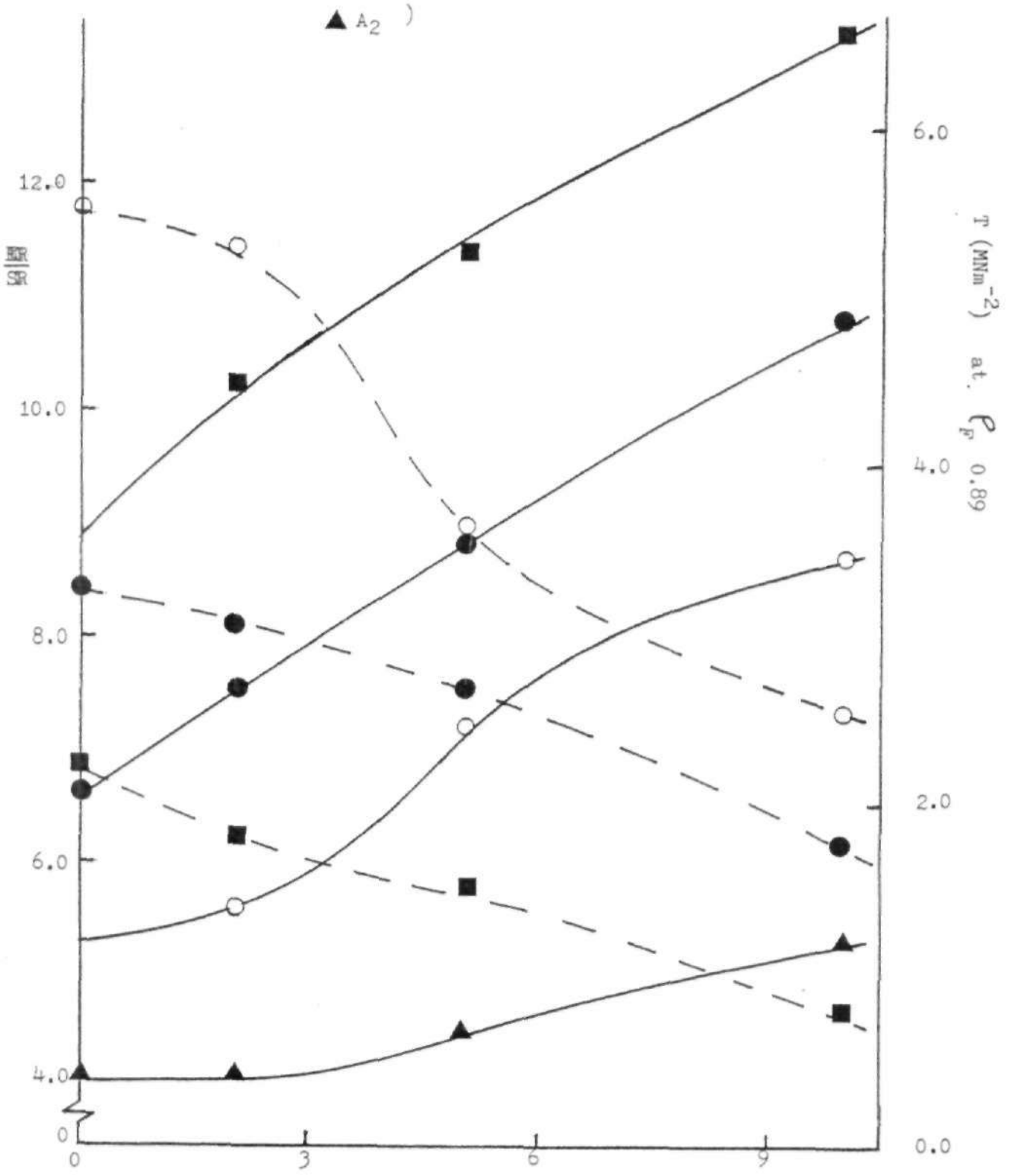
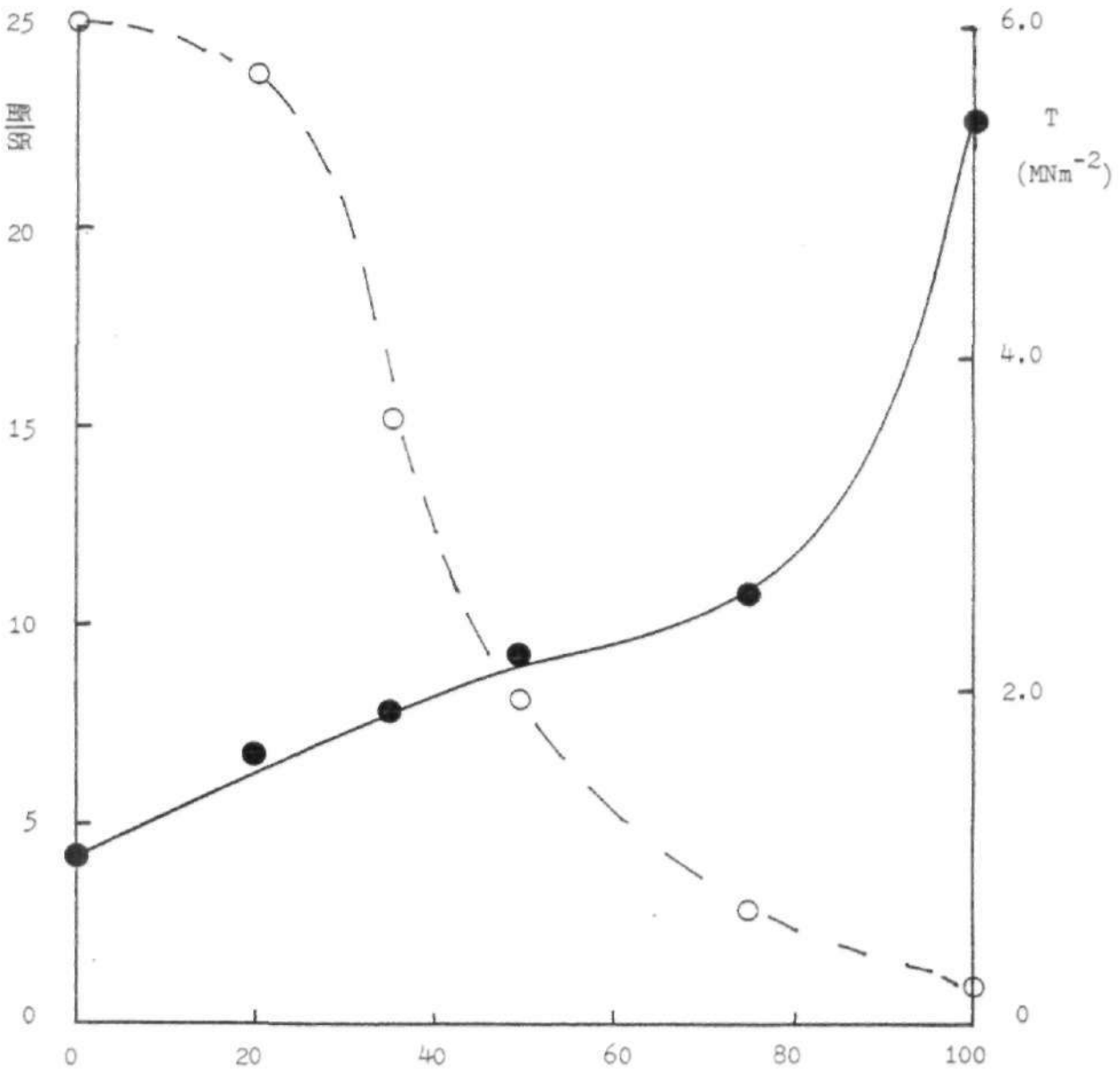


Fig. 4.10. Plasto-elasticity and tensile strength Vs % w/w of stearic acid added to Avicel

(●—● $\frac{ER}{SR}$, O---O T)



Relationship between α and ER/SR

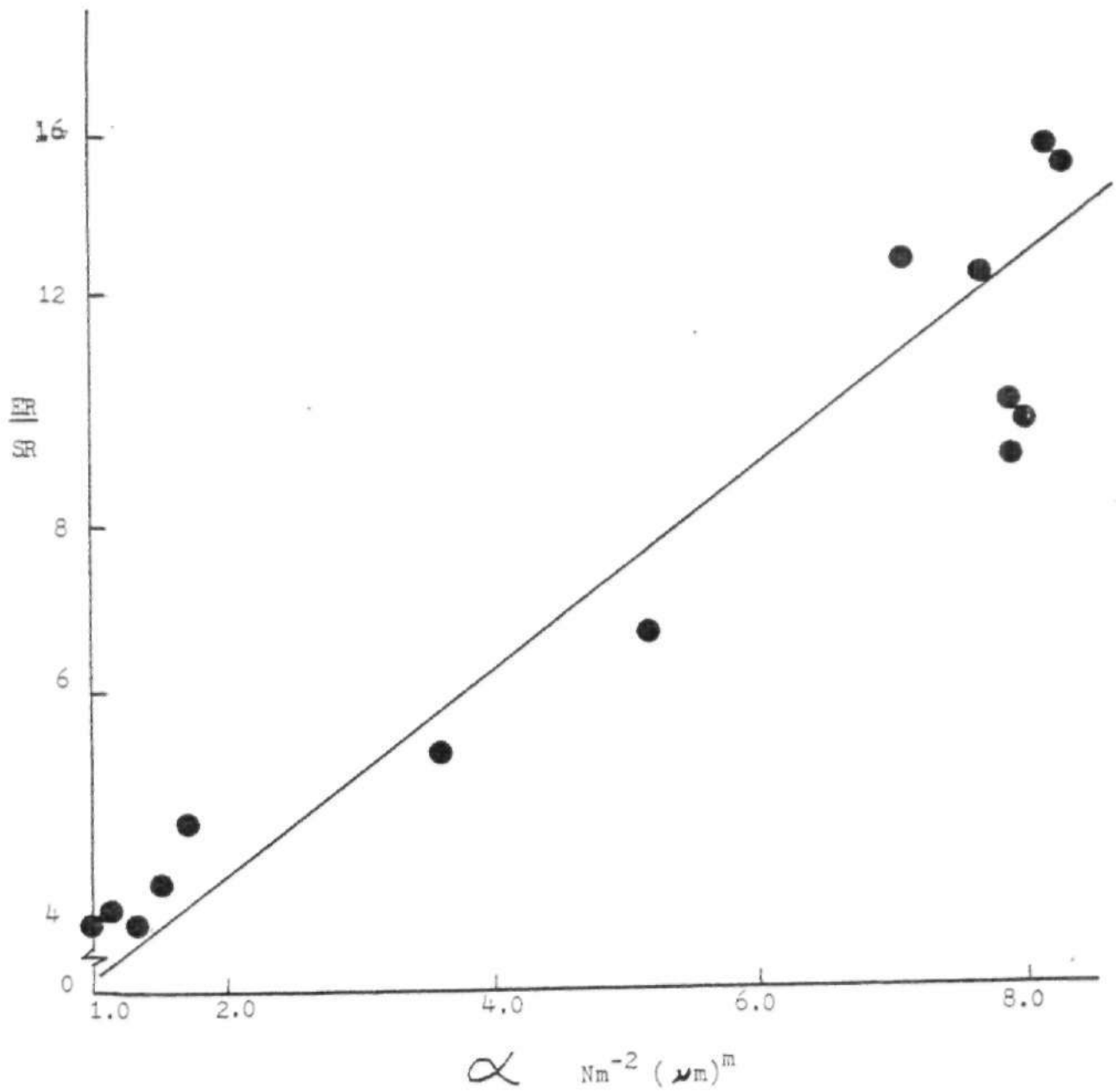
Finally, it will be recalled that in Chapter 3 a relationship was established between a material constant, α and the compressibility of the material concerned. The observation now that the plasto-elasticity ratio, ER/SR may be used to predict whether or not the material will form firm and satisfactory tablets suggests that there may also be a relationship between α and ER/SR. This is tested in Fig. 4.11, which shows that the relationship is semi-logarithmic, namely

$$\log \left[\frac{ER}{SR}\right] = Y'\alpha - Z \qquad (86)$$

with a correlation coefficient of 0.945. Y' and Z are constants whose values are 12.9 and 6.2 respectively.

It can be seen that samples containing $< 25\%$ Avicel have values of $\alpha > 6.0$ and values of ER/SR > 9.0 and form very weak tablets (whose tensile strength, T $< 2.5\ MNm^{-2}$). In practice such tablets will cap and laminate. It may be concluded that the α and ER/SR are indices which can be used to predict the tableting performance of tablet formulations.

Fig. 4.11. $\frac{ER}{SR}$ versus α



CONCLUSIONS

1. The elastic recovery (ER)and stress relaxation (SR) of the powders and their mixtures have been measured under various experimental conditions. The value of the plasto-elasticity (defined as ratio ER/SR) depends on the processing variables and formulation factors.

2. A correlation has been established between the plasto-elasticity (ER/SR) of a powder or mixture of powders and the tensile strength (T) of the resulting tablets. This is

$$\log T = Q - G\left[\frac{ER}{SR}\right]$$

where Q an G are empirical constants.

3. The plasto-elasticity (ER/SR) of a material has been shown to be useful for predicting its likely performance during tableting.

4. The plasto-elasticity of Avicel is much less than that of paracetamol and this explains why it is used as an excipient in the tableting of paracetamol.

5. The effect that moisture has on the plasto-elasticity and tensile strengths of formulations depends on its level and the presence and level of other tablet excipients in the formulation. This is attributed to the different states of moisture in a sample.

6. Stearic acid increases the plasto-elasticity of powders and reduces the tensile strengths of their tablets by interrupting the bonding mechanisms between particles.

7. A correlation has also been established between the material constant, α and the plasto-elasticity (ER/SR) of the material. This is expressed by

$$\log \left[\frac{ER}{SR} \right] = Y' \alpha - Z$$

where Y' and Z are experimental constants.

CHAPTER 5

EFFECTS OF INTERACTING VARIABLES ON THE TENSILE STRENGTHS AND DISINTEGRATION TIMES OF PARACETAMOL TABLETS

Pharmaceutical tablets may contain several different ingredients whose proportions determine the mechanical properties of the tablets and their disintegration and dissolution characteristics. Processing variables such as granulation, temperature, rate of compression and packing fraction achieved can also affect the properties of the tablets. Much research in tableting technology has concerned the relationship between these independent controllable formulation and process variables and the compression characteristics and quality of the resultant tablets. The independent variables have usually been studied separately by successively changing one of them at a time (Levy et al 1963 ; Chalmers and Elworthy 1975 ; Esezobo and Pilpel 1976). However, an accurate interpretation of the individual effects of the variables or of their interactions is not possible with this approach since the influence of a given variable is often dependent on the other variables. These interdependencies take the form of either a variation in the extent of an effect or the reversal of an effect.

The inaccuracy inherent in investigating only the separate effects of variables has been realised and recently some workers (Kurup and Pilpel 1977; Adeyemi and Pilpel 1983 ; Sanderson et al 1984) have studied the combined effects of formulation and processing variables with the objective of optimising the production and therapeutic performance of various tablet formulations.

The aim of this chapter has been to determine how packing fraction and addition of microcrystalline cellulose (Avicel) and alginic acid to paracetamol separately and in combination affect the tensile strengths and disintegration times of the resulting tablets.

It is hoped that this type of analysis on the separate and

combined effects of variables will prove useful in the future development of commercial tablet formulations.

EXPERIMENTAL DESIGN

Experiments were performed in a factorial design using some of the binary mixtures of paracetamol and Avicel in Table 2.1 on page 80 They were granulated and compressed into tablets on a single punch tablet press and their tensile strengths and disintegration times were determined as detailed in Chapter 2.

Each of the three variables, packing fraction, P, proportion of Avicel, A, and proportion of alginic acid, D was employed at a "low" level (denoted by subscript L), a "medium" level (subscript M) and a "high" level (subscript H), see Table 5.1.

By grouping the results into a number of sets, it is possible to assess the effect that each variable has separately on the properties of the tablets and also to determine the extent of interaction, if any, between any two variables (Woolfall, 1964). The effects of increasing, say A from its "low" level to its "high" level on say, tensile strength is found by summing all tensile strength results from samples containing high levels of A and subtracting the sum of the tensile strength results from the samples containing "low" levels of A and then dividing by 4. That is

$$\tfrac{1}{4}\left[(A_HP_HD_H + A_HP_LD_H + A_HP_HD_L + A_HP_LD_L) - (A_LP_HD_H + A_LP_LD_H + A_LP_HD_L + A_LP_LD_L)\right]$$

and

Table 5.1

Levels of variables

VARIABLE	"LOW" LEVEL	"MEDIUM" LEVEL	"HIGH" LEVEL
Packing fraction	0.80	0.85	0.91
% w/w Avicel	20	30	50
% w/w Alginic Acid	1.0	2.0	3.0

$$1/4 \left[(A_H P_H D_H + A_L P_H D_H + A_H P_L D_H + A_L P_L D_H) - (A_H P_H D_L + A_L P_H D_L + A_H P_L D_L + A_L P_L D_L)\right]$$

The separate effects produced by going from a "low" to a "medium" and a "medium" to a high" level are treated in the same way (Adeyemi and Pilpel 1983).

To determine the extent of interaction between any two variables say A and P (at "low" and "high" levels) on say, tensile strengths, the procedure is to treat the results as follows :-

$$1/4 \left[(A_L P_L D_L + A_L P_L D_H + A_H P_H D_L + A_H P_H D_H) - (A_L P_H D_L + A_L P_H D_H + A_H P_L D_L + A_H P_L D_H)\right]$$

and for A and D :

$$1/4 \left[(A_L P_L D_L + A_L P_H D_L + A_H P_L D_H + A_H P_H D_H) - (A_L P_L D_H + A_L P_H D_H + A_H P_L D_L + A_H P_H D_L)\right]$$

and for D and P :

$$1/4 \left[(A_L P_L D_L + A_H P_L D_L + A_L P_H D_H + A_H P_H D_H) - (A_L P_L D_H + A_H P_L D_H + A_L P_H D_L + A_H P_H D_L)\right]$$

and similarly for the other levels (Adeyemi and Pilpel 1983).

A result of zero indicates no interaction ; departure from zero provides a quantitative measure of the amount of interaction (Woolfall 1964).

RESULTS/DISCUSSION

Results of the tensile strengths and disintegration times of the tablets are given in Appendix 5 on page 219.

As expected (Heckel 1961 ; York and Pilpel 1973 ; Kurup and Pilpel 1977) the tensile strengths and disintegration times of the tablets increase with packing fraction, Fig. 5.1 ; at any particular P between 0.80 and 0.91 they also increase with the Avicel content as illustrated typically in Fig. 5.2.

Addition of alginic acid reduces the disintegration time to a minimum at about 2% w/w but has little effect on tensile strength, Fig. 5.3. The results follow logically from the known properties of Avicel as an excipient for improving compression and bond formation between drug particles (Lamberson and Raynor 1976 ; Esezobo and Pilpel 1977) and of alginic acid as a disintegrant which acts by swelling in water and rupturing the bonds (Khan and Rhodes 1972).

The relative effects of the variables at all three levels both on the tensile strengths and on the disintegration times of the tablets are P >> A >> D, see Table 5.2. The packing fraction is a measure of the extent to which particles are brought together during consolidation to form bonds resulting in hard tablets. At any particular packing fraction, P it is known that the tensile strengths of different materials are comparable and do not differ by a factor of more than about 3 (Malamataris et al 1984). It is also known that the tensile strengths of materials increase exponentially with packing fraction (York and Pilpel 1973) so that a small increase in packing fraction has a very large effect on tensile strength. This explains why increasing the packing fraction has a much larger effect on tensile strength (and incidentally on disintegration time which

Fig. 5.1. Tensile strength and disintegration time Vs packing fraction of tablets.

——— Disintegration time , DT

– – – – Tensile strength , T

○ M_5 without alginic acid

● M_5 containing 2% alginic acid

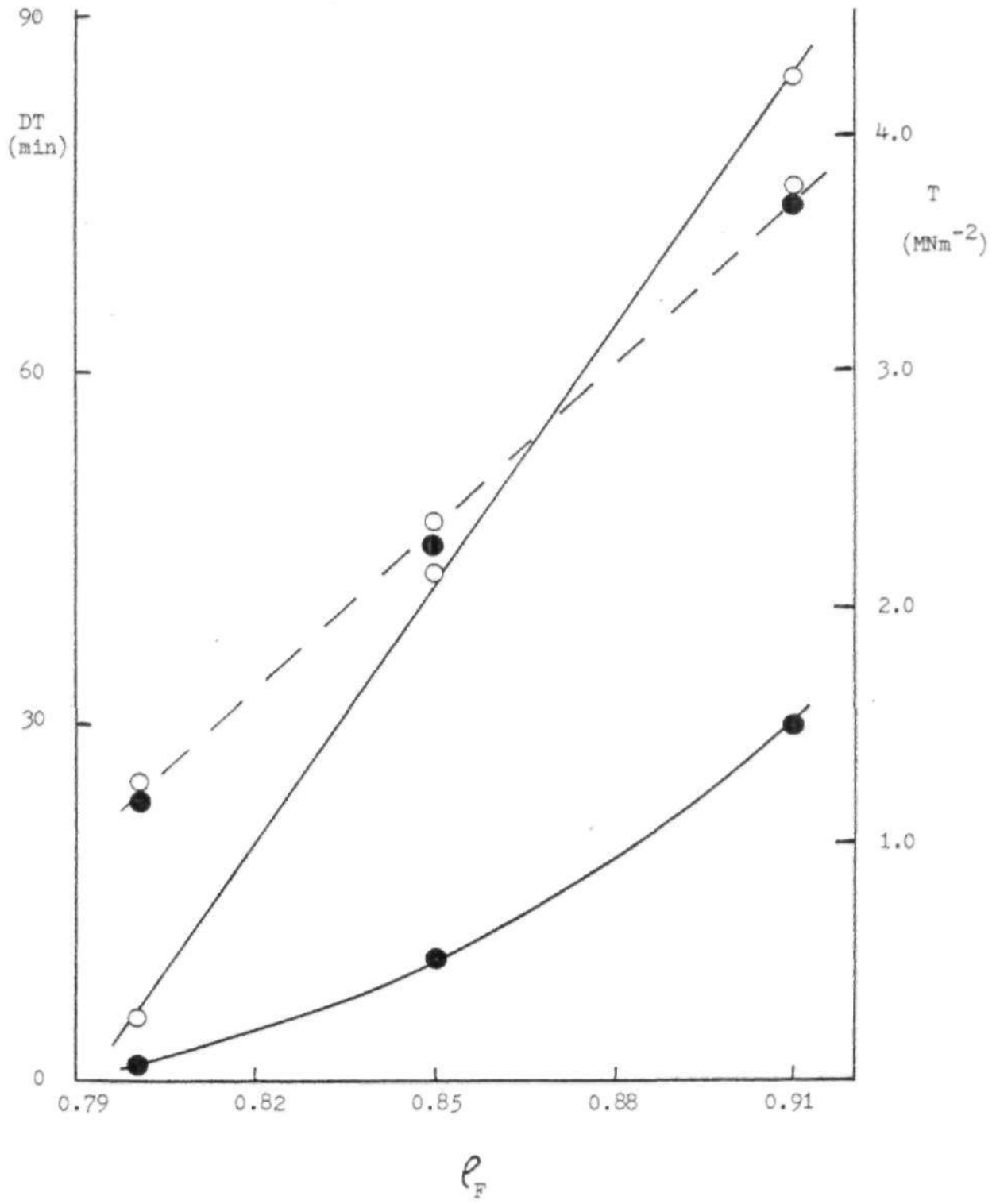


Fig. 5.2. Tensile strength and disintegration time, DT of tablets containing no alginic acid versus % content of Avicel at different packing fractions.
(—— T , - - - - DT , ϱ_F = 0.80 , ϱ_F = 0.85 , ϱ_F = 0.91)

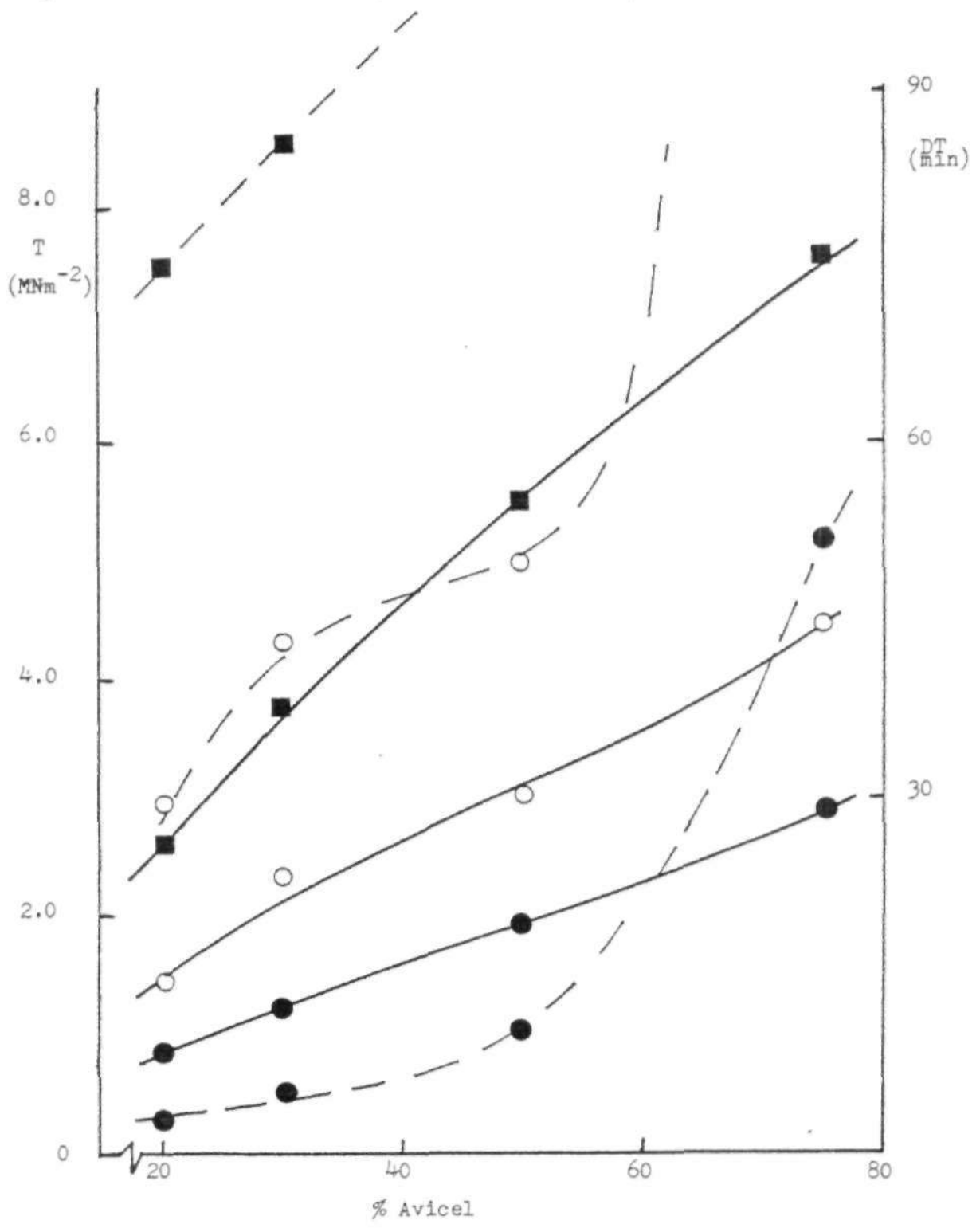


Fig. 5.3. Tensile strength and disintegration time, DT of tablets containing 30% w/w Avicel Vs % content of alginic acid at different packing fractions (—— T , - - - - DT , ● ρ_F = 0.80, ○ ρ_F = 0.85, ■ ρ_F = 0.91)

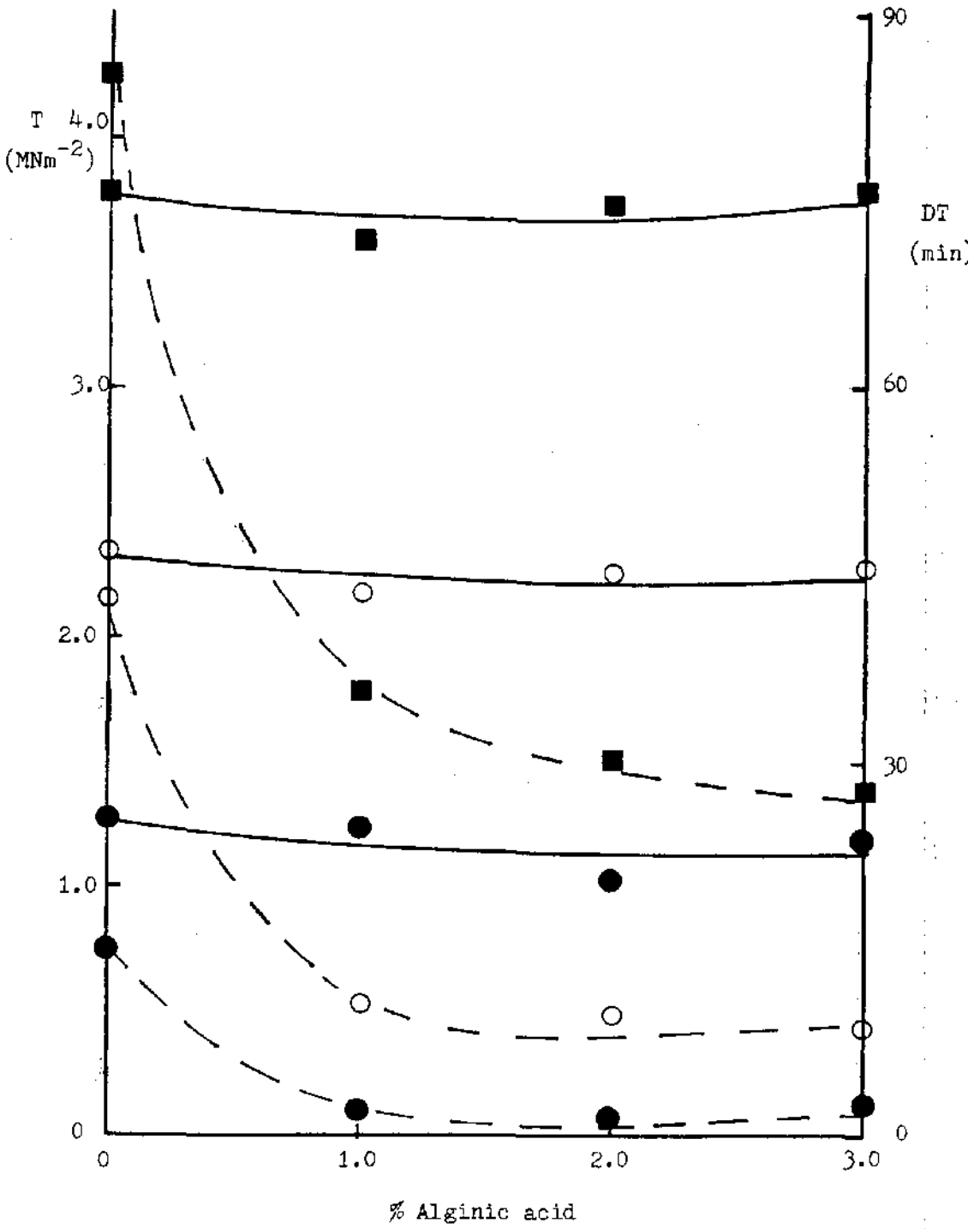


Table 5.2

Effect of packing fraction and composition on the t
and disintegration time of tablets

Effect on Tensile Strength (MNm^{-2}) of increasing from LOW to HIGH level of			Effect on Di (minutes) of LOW to HIGH l		
Packing fraction	Avicel	Alginic Acid	Packing fraction	Avicel	Alginic Acid
P	A	D	P	A	D
2.40	1.77	-0.11	60.75	29.75	-10.50

Effect on Tensile Strength (MNm^{-2}) of increasing from LOW to MEDIUM level of			Effect on Disintegration Time (minutes) of increasing from LOW to MEDIUM level of		
Packing fraction	Avicel	Alginic Acid	Packing fraction	Avicel	Alginic Acid
P	A	D	P	A	D
0.80	0.53	-0.05	11.55	-4.45	-6.80

Effect on Tensile Strength (MNm^{-2}) of increasing from MEDIUM to HIGH level of			Effect on Disintegration Time (minutes)of increasing from MEDIUM to HIGH level of		
Packing fraction	Avicel	Alginic Acid	Packing fraction	Avicel	Alginic Acid
P	A	D	P	A	D
2.04	1.02	-0.06	55.43	35.08	-1.58

is also known to be directly related to it) than changing the amount of Avicel or alginic acid that has been incorporated in the mixture. Since the disintegration time is directly related to the tensile strength, Fig. 5.4 [because although both are measured in quite different ways, both involve the rupture of bonds between particles (Kurup and Pilpel 1977)] , the same argument applies to the greater effect of packing fraction, P on disintegration times than those of A and D.

The greater effect of the proportion of A than that of D on both tablet properties is consistent with the use of Avicel as a tablet excipient for improving the compressibility of materials and producing strong, hard tablets. Their rate of disintegration appears to depend primarily on their hardness and on the rate at which water can penetrate them and rather less on the amount of alginic acid present as a disintegrant.

Table 5.3 shows that the three variables are also interacting with each other at the three levels employed. The ranking order of the interactions for both parameters is A x P >> D x P > A x D. It would be expected that the combined effect of any two variables would depend to some extent on their separate effects and since, as we have already seen, these are in the order P>> A >> D the above result seems reasonable.

Fig. 5.4. Disintegration time versus tensile strength of tablets

(● M_4 + 2% alginic acid

▲ M_5 + 2% alginic acid

★ M_6 + 2% alginic acid)

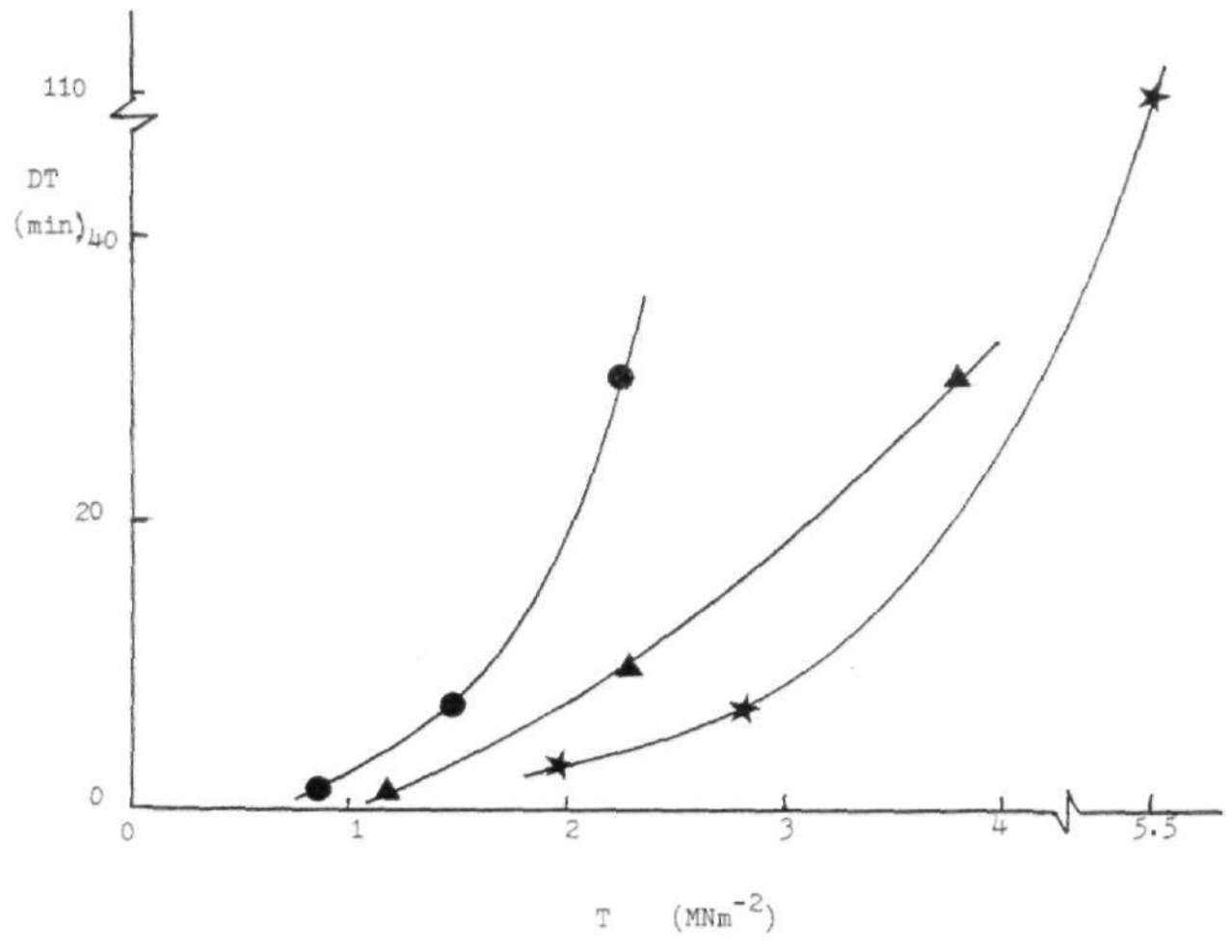


Table 5.3

Interaction coefficients.

TRANSITIONAL LEVEL	Interaction Coefficients for Tensile Strength (MNm^{-2}) between			Interaction Coefficient for Disintegration Time (minutes) between		
	Avicel and Alginic acid	Avicel and Packing fraction	Alginic acid and Packing fraction	Avicel and Alginic acid	Avicel and Packing fraction	Alginic acid and Packing fraction
Low-High	0.04	0.71	-0.08	1.00	29.75	-9.00
Low-Medium	0.05	0.21	0.05	5.80	-2.55	-4.20
Medium-High	-0.22	0.44	-0.15	-5.58	35.93	-8.93

CONCLUSIONS

1. Using a factorial experimental design, the tensile strengths and disintegration times of paracetamol tablets at different packing fractions and containing different proportions of Avicel and alginic acid have been measured.

2. The effects of separately varying the variables (i.e. packing fraction, P, the proportions of Avicel (A) and alginic acid, disintegra nt D) on both the tensile strengths and disintegration times of the tablets are in the order P >> A >> D.

3. These variables are interacting with each other and their combined effects on both tensile strength and disintegration time are A x P >> D x P > A x D. Explanations have been provided for the results.

4. It is hoped that this type of factorial analysis will prove useful in future product development studies to identify the significant variables and to predict the effects of changes in processing conditions on selected tablet properties.

CHAPTER 6

GENERAL CONCLUSIONS

In summary, the following are the main conclusions of this work :

1. Measurements have been made of the tensile strength and plasto-elasticity of paracetamol tablet formulations.

2. Using the concept of a reference state, equations have been derived to relate the tensile strengths of single powders and their binary mixtures to their particle size parameters and composition.

For a single powder

$$T = \frac{\bar{d}\,\bar{s}}{4\,\bar{V}} \cdot \frac{\ell/\ell_s}{1 - (\ell/\ell_s)} \cdot \frac{\alpha}{t^m}$$

where m is a universal constant and α is a material constant which can be used to predict the compressibility of a material.

For binary mixtures,

$$T = \frac{\bar{d}_{mix}\,\bar{s}_{mix}}{4\,\bar{V}_{mix}} \cdot \frac{\ell/\ell_{s_{mix}}}{1 - (\ell/\ell_{s_{mix}})} \cdot \frac{\alpha_{mix}}{t^m}$$

Good agreement has been found between the measured tensile strengths of single powders and of binary mixtures with those predicted from the equations.

3. The value of α for paracetamol is much larger than that for Avicel. At least 25% of Avicel has to be mixed with paracetamol to reduce the α value of the mixture below that of the pure drug and this provides a scientific explanation for the inclusion of 25 - 30% Avicel in the tableting of paracetamol.

4. The evaluation of t by the concepts of a reference state and

a reduced tensile strength overcomes the previous uncertainty of using extrapolation to obtain the value of ρ_o i.e. the packing fraction at which the tensile strength is zero.

5. A concept of maximum bulk density has been applied to enable the prediction of the tensile strength of a single powder with a known α value from knowledge of its size parameters. It is suggested that further work should be undertaken to improve the accuracy of the prediction of the tensile strengths of binary mixtures.

6. The plasto-elasticity of a material (defined as the ratio of its elastic recovery, ER to its stress relaxation, SR), has been shown to be useful for predicting its likely performance during tableting. A correlation has been established between the plasto-elasticity of a powder or mixture of powders and the tensile strength, T of the resulting tablets. This is

$$\log T = Q - G \left(\frac{ER}{SR} \right)$$

where Q and G are empirical constants.

7. A correlation has also been established between the material constant, α and the plastoelasticity $\left(\frac{ER}{SR} \right)$ of the material. This is expressed by

$$\log \left(\frac{ER}{SR} \right) = Y'\alpha - Z$$

Where Y' and Z are experimental constants.

8. The effect that moisture has on the plasto-elasticity and the tensile strengths of formulations depends on the level and the presence and the level of other tablet excipients in the

formulations. This is attributed to the different states of moisture in a sample.

9. Stearic acid increases the plasto-elasticity of powders and reduces the tensile strengths of their tablets by interrupting the bonding mechanisms between particles.

10. Using a factorial experimental design, the tensile strengths and disintegration times of paracetamol tablets have been shown to depend on their packing fraction and on the proportions of Avicel and alginic acid incorporated and that there are significant interactions between these variables.

11. It is hoped that the results of this work will contribute to the understanding of the fundamental mechanical properties of powders in relation to tableting and will prove useful in future product development studies.

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LIST OF SYMBOLS

LIST OF SYMBOLS

a	Ratio of particle pairs per unit area to the same per unit volume.
A	Overall area of contact between particles.
A_b	Area of the cross-section of tablet break.
A_{ij}	Area of contact between two particles of species A with diameters d_i and d_j.
A_{kl}	Area of contact between two particles of species B with diameters d_k and d_l.
A_{ik}	Area of contact between two particles of species A and species B with diameters of d_i and d_k.
A_s	Area of the split surface of the powder bed.
A_1	Constant in Eq. 9.
b	Ratio of true area of contact between two particles to the surface area of the smaller particle.
b'	Distance between two fulcrums.
c	Mean co-ordination number.
c'	Constant in Eq. 60.
$\bar{d}$, $\bar{d}_{mix}$	Mean effective particle diameter of single powder and binary mixture.
d_a	Projected area diameter in Heywood equation.
$\bar{d}_{AA}$, $\bar{d}_{BB}$, $\bar{d}_{AB}$	Mean effective particle diameter between type A-A B-B and A-B particles respectively.
d_c	Classifier cut point diameter.
d_e	Equivalent diameter of calcium carbonate.
d_i, d_j	Particle diameters of species A.
d_k, d_l	Particle diameters of species B.
D	Diameter of tablet.
e	Porosity.
ER	Elastic recovery.
ER/SR	Plasto-elasticity.
f	Constant in Eq. 7

F, $\overline{F}$ Tensile force and mean tensile force between two particles in contact.

$\mathfrak{G}$ Constant in Eq. 2.

G Constant in Eq. 85.

H Interparticle force per unit area.

H_{AA}, H_{BB}, H_{AB} Force between particles of type A-A, B-B and A-B respectively per unit area.

H_o Thickness of tablet at zero load after decompression.

H_p Thickness of tablet at maximum compression pressure.

H_t Thickness of tablet after holding for a given time at maximum compression pressure.

k Constant in Eq. 21.

K' Constant in Eq. 60.

L Distance between the centres of two particles.

L_f Latent heat of fusion.

L_g Load in kg required for a 1 m extension of the spring determined by calibration.

m Universal constant.

m_s Constant in Eq. 9.

M Moisture content of powder.

M' Degree of mixing.

n_i, n_j, n_k, n_l Number fraction of particle diameters d_i, d_j, d_k, d_l respectively.

N_{ii}, N_{ij} Number of particle pairs between equal-size and unequal-size particles of a species in a mixture.

N_p Total number of particles.

N_{pp} Total number of particle pairs.

$N_{pp/a}$ Number of particle pairs per unit area of split.

P Applied pressure.

P_b Applied load causing breakage of tablet.

P_t Penetration time of water.

q Specific tensile strength.

Q	Constant in Eq. 85
R, R_r	Reduced tensile strength, and at reference state.
R_g	Rate at which extension spring 'g' was extended.
RH	Relative humidity.
$\bar{s}$, $\bar{s}_{mix}$	Mean effective surface area per particle of single powder and binary mixture.
$\bar{s}_{AA}$, $\bar{s}_{BB}$, $\bar{s}_{BB}$	Mean effective surface area of particle pair of type A-A, A-B and B-B.
S	Classifier speed.
SR	Stress relaxation.
t	Distance of separation between two particles.
t_b	Time to split powder bed.
t_o, t_r	Distance of separation between two particles when tensile strength is zero and at reference state.
t_t	Thickness of tablet.
T	Tensile strength
U_A, U_B	Number fraction of particles of species A and species B in binary mixture.
$\bar{V}$, $\bar{V}_{mix}$	Mean effective volume per particle of a single powder and binary mixture.
V	Air volume for classifier.
V_m	Volume per mole of solid.
V_r	Ratio of bulk volume at applied pressure to the volume at infinite pressure.
w_1, w_2	Weight fraction of component 1 and component 2 in a binary mixture.
X_{ii}	Number fraction of particle pairs in contact of diameter d_i.
X_{ij}	Number fraction of particle pairs in contact of diameters d_i and d_j.
X_{ik}	Number fraction of particle pairs in contact of diameters d_i and d_k.
Y_{AA}, Y_{AB}, Y_{BB}	Number fraction of particle pairs in contact consisting of type A-A, A-B and B-B particles respectively in binary mixtures.
Y_p	Yield Pressure

Y' Constant in Eq. 86

Z Constant in Eq. 86

α, α_{mix} Parameter characteristic of a single powder and a binary mixture.

α_{AA}, α_{AB}, α_{BB} Parameter characteristic between interacting particles of type A-A, A-B and B-B respectively

γ Surface tension.

Γ Surface energy.

δ Half the angle subtended at the centre of a particle by a lens of water.

Δ Angle of internal friction

ϵ_o Parameter of "strength" of interparticle force when $T = 0$

ϵ_{AA}, ϵ_{AB}, ϵ_{BB} Parameters of "strength" of interparticle force of particle type A-A, A-B and B-B respectively.

θ Contact angle.

θ_m Melting point.

θ_T Angle of split plate with the horizontal.

θ' Angle of inclination of Force F to the direction of the tensile force.

λ Functional relationship between ρ and $\bar{d}$.

ξ Universal constant in enumeration of area of contact between two particles.

ρ Bulk density of powder bed.

ρ_o, ρ_r Bulk density of powder bed when $T = 0$ and at reference state.

ρ_F Packing fraction.

ρ_{max} Maximum bulk density of powder bed.

ρ_P Total weight of particle per unit volume of powder.

ρ_s, $\rho_{s_{mix}}$ Particle density of single powder and binary mixture.

ρ_{s_A}, ρ_{s_B} Particle density of species A and species B.

ψ Spring constant

$\overline{\Phi}$ Function related to particle size parameters in a distribution.

φ Functional relationship between ϵ and t.

σ	Standard deviation estimated for analysed sample.
σ_c	Compressive stress.
σ_o	Standard deviation of completely unmixed system.
η	Viscosity.

APPENDICES

APPENDIX 1

CALCULATION OF SIZE PARAMETERS

APPENDIX 1

Table A.1. Calculation of Size Parameters.

Sample P_1

$d_{\mu m}$	n_i	n_i^2	$n_i d_i^3$	$n_i d_i^2$	$n_i^2 (d_i + d_i)$
2.0	0.074	0.0055	0.5920	0.0220	0.0220
5.0	0.330	0.1089	41.2500	2.7225	1.0890
8.0	0.339	0.1149	173.5680	7.3536	1.8384
11.0	0.174	0.0303	231.5940	3.6663	0.6666
14.0	0.057	0.0032	156.4080	0.6272	0.0896
17.0	0.026	0.0007	127.7380	0.2023	0.0238
	$\sum = 1$	$\sum = 0.2635$	$\sum = 731.1500$	$\sum = 14.5939$	$\sum = 3.7294$

Table A.1. (cont)

$n_i n_j$	$n_i n_j (d_i + d_j)$	$n_i n_j d_i d_j$
0.0244	0.1709	0.2442
0.0251	0.2509	0.4014
0.0129	0.1674	0.2833
0.0042	0.0675	0.1181
0.0019	0.0366	0.0654
0.1119	1.4543	4.4748
0.0574	0.9187	3.1581
0.0188	0.3574	1.3167
0.0086	0.1888	0.7293
0.0590	1.1207	5.1908
0.0193	0.4251	2.1642
0.0088	0.2204	1.1987
0.0099	0.2480	1.5274
0.0045	0.1267	0.8460
0.0015	0.0459	0.3527
$\sum$ = 0.3682	$\sum$ = 5.7993	$\sum$ = 22.0711

Mean effective diameter, $\bar{d}$

$$= \frac{1}{2} \sum_{ij} n_i n_j (d_i + d_j)$$

$$= \frac{1}{2} \left[\sum 2 \times n_i n_j (d_i + d_j) + \left(\sum n_i^2 (d_i + d_i) \right) \right]$$

$$= \frac{1}{2} \left[(2 \times 5.7993) + 3.7294 \right]$$

$$= 7.7 \mu m$$

Mean effective surface area, $\bar{s}$ =

$$\frac{\pi}{4}\left[2 \times \sum n_i n_j d_i d_j + \sum n_i^2 d_i^2\right.$$

$$= \frac{\pi}{4}\left[(2 \times 22.0711) + 14.5939\right]$$

$$= 46.1\ (\mu m)^2$$

Mean effective volume, $\bar{V}$ =

$$\frac{\pi}{6} \sum n_i d_i^3$$

$$= \frac{\pi}{6} \times 731.1500$$

$$= 382.8\ (\mu m)^3$$

APPENDIX 2

CALCULATION OF PARTICLE DENSITY OF A BINARY MIXTURE OF POWDERS

APPENDIX 2

When mixing a mass m_A of particles of density

$$\rho_{s_A} = \frac{m_A}{V_A}$$

with a mass m_B of particles of density

$$\rho_{s_B} = \frac{m_B}{V_B}$$

Weight fraction of species A, w_A is given by

$$\frac{m_A}{m_A + m_B}$$

and weight fraction of B, w_B is

$$\frac{m_B}{m_A + m_B}$$

and the total volume, if no interactions occur is

$$V = V_A + V_B$$

The particle density of the mixture is given by

$$\rho_{s_{AB}} = \frac{m_A + m_B}{V_A + V_B}$$

or

$$\rho_{s_{AB}} = \frac{m_A + m_B}{\frac{m_A}{\rho_{s_A}} + \frac{m_B}{\rho_{s_B}}} = \frac{(m_A + m_B)\,\rho_{s_A}\,\rho_{s_B}}{\rho_{s_B}\,m_A + \rho_{s_A}\,m_B}$$

or

$$\frac{1}{\ell_{s_{AB}}} = \frac{\ell_{s_B} m_A + \ell_{s_A} m_B}{(m_A + m_B)(\ell_{s_A} \ell_{s_B})}$$

$$= \frac{\ell_{s_B} m_A}{(m_A + m_B)(\ell_{s_A} \ell_{s_B})} + \frac{\ell_{s_A} m_B}{(m_A + m_B)(\ell_{s_A} \ell_{s_B})}$$

$$= \frac{\ell_{s_B} w_A}{\ell_{s_A} \ell_{s_B}} + \frac{\ell_{s_A} w_B}{\ell_{s_A} \ell_{s_B}}$$

$$= \frac{w_A}{\ell_{s_A}} + \frac{w_B}{\ell_{s_B}}$$

APPENDIX 3

Effects of some variables on the tensile strength and plasto-elasticity of Paracetamol tablet formulations

Table A.2

Effect of compression load on the packing fraction, tensile strength and plasto-elasticity of some samples.

Compression load (KN)	CODE	Packing fraction	Elastic recovery (%)	Stress relaxation (%)	Plasto-elasticity (ER/SR)	Tensile Strength MNm^{-2}
	A_2	0.587	2.92	3.79	0.77	1.43
	M_8	0.590	2.66	3.37	0.79	1.00
2.5	M_7	0.608	3.51	2.97	1.18	0.62
	M_6	0.629	3.42	2.01	1.70	0.26
	M_5	0.640	4.48	1.42	3.15	0.08
	P_1	0.662	4.45	1.20	3.71	cap
	A_2	0.699	2.29	4.01	0.57	4.13
	M_8	0.686	3.95	3.35	1.18	2.36
	M_7	0.716	3.08	3.02	1.02	1.95
5.0	M_6	0.719	4.18	1.98	2.11	0.80
	M_5	0.708	5.03	1.70	2.96	0.28
	M_4	0.699	5.15	1.38	3.73	0.09
	M_3	0.703	5.43	1.42	3.82	cap
	P_1	0.679	5.57	1.19	4.68	cap
	A_2	0.821	6.04	2.93	2.06	5.15
	M_8	0.809	5.57	2.39	2.33	5.26
	M_7	0.805	6.24	2.12	2.94	4.08
10.0	M_6	0.815	5.93	2.02	2.94	2.01
	M_5	0.804	7.28	1.23	5.92	1.00
	M_4	0.786	6.59	1.44	4.58	0.62
	M_3	0.798	6.96	1.49	4.67	0.44
	P_1	0.769	8.17	1.03	7.93	cap

Table 2 (cont.)

Compression load (KN)	CODE	Packing fraction	Elastic recovery (%)	Stress relaxation (%)	Plasto-elasticity (ER/SR)	Tensile Strength MNm^{-2}
15.0	A_2	0.864	8.31	2.72	3.06	5.38
	M_8	0.854	6.99	1.91	3.66	5.26
	M_7	0.869	7.64	2.09	3.66	5.33
	M_6	0.867	7.63	1.75	4.36	3.61
	M_5	0.859	8.78	1.75	5.02	2.31
	M_4	0.857	9.16	1.62	5.65	1.73
	M_3	0.840	8.95	1.32	6.78	0.78
	M_2	0.856	9.78	1.24	7.89	0.72
	M_1	0.839	9.25	1.37	6.75	cap
	P_1	0.815	9.46	0.91	10.40	cap
20.0	A_2	0.902	9.02	2.19	4.12	6.09
	M_8	0.895	10.56	2.16	4.89	5.83
	M_7	0.893	8.95	2.08	4.30	5.69
	M_6	0.892	9.69	1.81	5.35	4.56
	M_5	0.890	10.49	1.58	6.64	3.12
	M_4	0.891	10.33	1.16	8.91	2.32
	M_3	0.889	11.22	1.17	9.59	2.02
	M_2	0.879	11.04	1.12	9.86	2.20
	M_1	0.881	11.31	0.92	12.29	1.45
	P_1	0.882	11.74	0.83	14.14	cap

Table A.3

Effect of tablet weight and tablet thickness on the tensile strength and plasto-elasticity of some samples.

Tablet weight (mg)	CODE	Tablet thickness (mm)	Packing fraction	Elastic recovery (%)	Stress relaxation (%)	Plasto-elasticity (ER/SR)	Tensile Strength (MNm^{-2})
	A	2.76	0.875	14.21	2.18	6.52	8.96
300	M_6	3.08	0.871	13.92	0.96	14.50	4.57
	M_5	3.16	0.862	13.90	1.22	11.39	2.00
	A	3.24	0.874	13.56	2.15	6.31	7.63
350	M_6	3.54	0.874	12.54	1.10	11.40	4.79
	M_5	3.58	0.882	13.03	1.35	9.65	3.37
	A	3.82	0.873	12.14	1.80	6.74	6.47
400	M_6	3.98	0.883	11.09	1.47	7.54	4.81
	M_5	4.08	0.872	12.60	1.42	8.87	3.14
	A	4.12	0.889	11.79	1.92	6.14	6.00
450	M_6	4.54	0.883	10.58	1.29	8.20	4.41
	M_5	4.60	0.884	11.31	1.46	7.75	2.79
	A	4.60	0.880	11.13	1.93	5.74	5.34
500	M_6	5.00	0.878	9.73	1.55	6.28	4.47
	M_5	5.14	0.881	11.10	1.50	7.40	2.96

Table A.4

Effect of duration of compression/holding/decompression cycle on the tensile strength and plasto-elasticity of some samples

Duration of compression cycle (s)	CODE	Packing fraction	Elastic recovery (%)	Stress relaxation (%)	Plasto-elasticity (ER/SR)	Tensile strength (MNm^{-2})
30	A_2	0.880	12.00	1.90	6.32	5.50
	M_6	0.871	9.75	1.14	8.55	4.55
	M_5	0.875	10.32	1.12	9.21	1.59
	M_4	0.868	13.73	1.04	13.20	1.11
	P_1	0.836	11.76	0.86	13.67	0.46
45	A_2	0.891	10.96	1.93	5.68	5.50
	M_6	0.879	8.50	1.50	6.95	4.12
	M_5	0.866	10.73	1.12	9.58	1.69
	M_4	0.868	12.31	1.15	10.70	0.85
	M_3	0.845	9.61	1.04	9.24	0.71
	P_1	0.840	9.80	0.85	11.53	0.52
60	A_2	0.887	9.36	1.83	5.11	5.50
	M_6	0.883	9.50	1.54	6.17	4.25
	M_5	0.865	9.42	1.47	6.41	1.49
	M_4	0.851	8.93	1.39	9.50	0.95
	M_3	0.833	8.61	1.34	6.43	0.91
90	A_2	0.903	9.58	2.23	4.30	5.50
	M_6	0.885	9.07	1.54	5.89	4.14
	M_5	0.866	8.87	1.44	6.16	1.59
	M_4	0.846	10.38	1.16	8.95	1.01
	M_3	0.852	8.84	1.07	8.26	0.72
	P_1	0.857	9.69	1.20	8.08	0.58
120	A_2	0.909	9.93	2.21	4.49	5.5
	M_6	0.902	9.24	1.56	5.92	4.80
	M_5	0.884	9.44	1.50	6.29	2.80
	M_4	0.869	12.74	1.40	9.10	1.67
	M_3	0.878	9.65	1.29	7.48	1.76
	P_1	0.844	9.96	1.20	8.30	cap

Table A.5

Effect of duration of holding at maximum compression pressure on the tensile strength and plasto-elasticity of some samples.

Duration of holding (s)	CODE	Packing fraction	Elastic recovery (%)	Stress relaxation (%)	Plasto-elasticity (ER/SR)	Tensile strength (MNm^{-2})
	A_2	0.884	12.91	0.97	13.31	5.50
5	M_6	0.882	12.23	0.88	13.90	5.02
	M_5	0.861	11.03	0.82	13.45	2.30
	M_4	0.878	12.45	0.85	14.65	2.15
	A_2	0.891	12.08	1.44	8.39	5.50
10	M_6	0.890	10.33	1.09	9.48	4.76
	M_5	0.881	11.57	1.26	9.18	2.82
	M_4	0.851	11.28	0.78	14.46	1.45
	A_2	0.892	12.20	1.70	7.18	5.50
15	M_6	0.886	11.69	1.32	8.86	4.97
	M_5	0.887	11.49	1.29	8.91	2.34
	M_4	0.857	11.85	0.82	14.45	2.16
	A	0.903	11.00	2.20	5.00	5.50
20	M_6	0.894	10.96	1.33	8.24	5.66
	M_5	0.875	10.20	1.24	8.23	2.45
	M_4	0.858	10.61	0.79	13.43	1.38
	A	0.908	12.49	1.74	7.18	5.50
25	M_6	0.900	10.62	1.32	8.05	5.54
	M_5	0.880	10.79	1.26	8.56	2.15
	M_4	0.867	11.59	1.24	9.35	1.67
	A	0.902	12.64	2.02	6.26	5.50
30	M_6	0.903	10.85	1.35	8.04	5.70
	M_5	0.865	10.64	1.29	8.25	2.80
	M_4	0.846	10.33	1.16	8.91	2.32

Table A.6

Effect of moisture on the tensile strength and plasto-elasticity of some samples

CODE	Moisture content % w/w (wet basis)	Packing fraction	Elastic recovery (%)	Stress ratio (%)	Plasto-elasticity (ER/SR)	Tensile strength (MNm^{-2})
M_4	0.0	0.899	8.74	1.08	8.09	2.93
	0.8	0.895	10.41	1.39	7.49	2.66
	1.8	0.905	8.24	2.30	3.58	3.32
	3.6	0.949	7.31	2.24	3.26	3.41
	5.4	0.931	9.38	1.30	7.22	2.32
M_5	0.0	0.884	10.19	1.54	6.62	2.84
	1.0	0.888	9.64	1.78	5.42	3.36
	1.8	0.917	9.54	2.80	3.41	4.83
	3.3	0.943	10.06	3.06	3.29	4.59
	4.5	0.952	10.86	1.93	5.63	3.92
M_6	0.0	0.892	11.26	1.87	6.02	4.71
	1.1	0.902	9.52	1.85	5.15	5.36
	2.7	0.934	9.55	2.45	3.90	5.83
	4.0	0.929	9.53	2.80	3.40	5.64
	6.7	0.909	11.84	0.92	12.87	3.81
M_7	0.0	0.890	9.64	1.92	5.01	5.81
	1.8	0.900	8.94	1.92	4.66	5.80
	4.0	0.943	10.88	1.76	6.18	6.02
	6.5	0.938	11.14	1.47	7.58	5.95
A_2	0.0	0.907	11.79	2.52	4.68	>6
	1.2	0.927	9.84	2.01	4.90	
	2.4	0.928	10.30	1.67	6.17	
	3.6	0.928	10.33	0.95	10.87	

Table A.7

Effect of stearic acid on the tensile strength and plasto-elasticity of some samples.

CODE	% w/w of added stearic acid	Elastic recovery (%)	Stress relaxation (%)	Plasto-elasticity	Tensile strength (MNm^{-2})
	0	10.32	1.16	8.90	2.20
M_4	2	10.05	0.98	10.26	1.80
	5	10.59	0.93	11.39	1.53
	10	9.08	0.68	13.35	0.81
	0	10.49	1.58	6.64	3.32
M_5	2	10.06	1.33	7.56	3.08
	5	10.30	1.17	8.80	2.68
	10	11.03	1.02	10.81	1.77
	0	9.69	1.81	5.35	5.50
M_6	2	10.02	1.79	5.60	5.30
	5	11.32	1.57	7.21	3.60
	10	11.53	1.33	8.67	2.53
	0	9.02	2.19	4.12	> 6
	2	9.02	2.19	4.12	
	5	9.05	2.01	4.50	
	10	9.19	1.73	5.31	
A_2	20	9.90	1.43	6.92	
	35	9.90	1.25	7.92	3.80
	50	9.42	1.01	9.33	2.04
	75	9.06	0.83	10.92	0.73
	100	9.52	0.42	22.67	0.22

APPENDIX 4

Table A.8

Moisture sorption and desorption isotherms at 20°C of paracetamol and Avicel powders.

Relative Humidity (%)	Moisture content at sorption, % w/w (wet basis)		Moisture content at desorption, % w/w (wet basis)	
	AVICEL	PARACETAMOL	AVICEL	PARACETAMOL
26	3.2	0.2	3.9	0.3
64	5.2	0.4	6.4	0.5
75	6.3	0.8	8.1	0.9
87	13.4	1.1	14.8	1.1

APPENDIX 5

Table A.9

Composition, tensile strength and disintegration time of tablets at different packing fractions.

SAMPLE	% w/w Alginic Acid Added	Tensile Strength [MNm^{-2}]			Disintegration Time [Minutes]		
		ℓ_F 0.80	ℓ_F 0.85	ℓ_F 0.91	ℓ_F 0.80	ℓ_F 0.85	ℓ_F 0.91
M_4	0	0.85	1.46	2.61	2.8	29.6	75.0
	1	0.96	1.53	2.72	5.5	28.0	45.0
	2	0.84	1.45	2.24	1.3	7.0	30.0
	3	0.88	1.19	2.49	2.5	5.0	25.0
M_5	0	1.27	2.35	3.78	5.0	43.0	85.0
	1	1.27	2.19	3.60	2.0	11.0	36.0
	2	1.18	2.27	3.75	1.0	10.0	30.0
	3	1.20	2.32	4.03	2.0	9.0	28.0
M6	0	1.93	3.00	5.45	10.5	50.0	175.0
	1	1.97	2.95	5.16	4.0	14.0	104.0
	2	1.96	2.81	5.70	3.5	6.3	115.0
	3	1.98	2.94	5.01	4.0	11.0	85.0
M7	0	2.90	4.48	7.56	52.0	*	*
	1	2.97	5.27	7.10	45.0	*	*
	2	2.99	4.52	6.41	28.0	*	*
	3	2.89	5.04	7.01	26.0	*	*

* Disintegration time > 180 min.