CHAPTER ONE

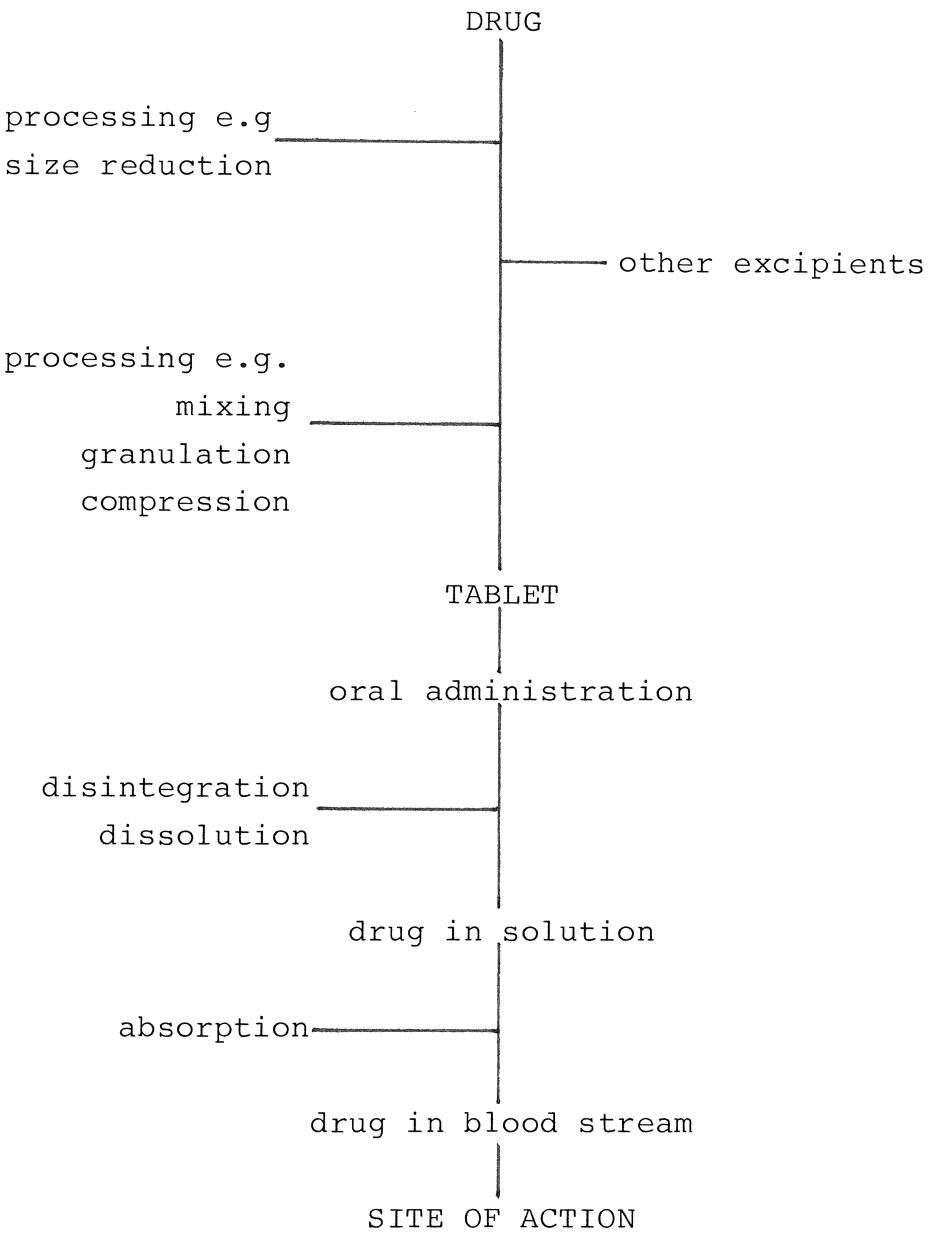
INTRODUCTION.

1.1 An Overview

The tablet is a well established, consistent and convenient drug delivery system. It can be modified to give slow, fast or controlled release of its active ingredients, and is relatively cheap to manufacture.

The biological efficacy of a drug administered as a tablet is affected by two major processes; the release of the drug from the tablet and the absorption of the drug into the body. Both of these processes are fairly complex and to some extent they interact. Figure 1.1 illustrates some of the possible steps in the delivery of a drug to its site of biological activity.

The processes involved in presenting a drug for biological absorption are not discrete events. Each step has the potential to modify the effect of other steps, the cumulative result being changes in the rate or extent of absorption. The intention of this study was to examine the effect of some of the possible changes in manufacturing conditions and their relative influence on the in vitro dissolution of a drug substance from a tablet. It should be appreciated that changes to the tablet may or may not influence the rate or extent of biological absorption. The bioavailability being dependent on the release of drug from the tablet and on the absorption of the drug, in solution, by the body. The latter being a highly variable and relatively uncontrollable process, the only scope for control in normal circumstances being the patients diet.



The Processes Involved in the Delivery of a Drug to its Site of Biological Activity

Figure 1.1

1.2 Tablet Manufacturing.

An examination of the index of the Extra Pharmacopoeia (Martindale 1982), or the pharmaceutical stock of any British pharmacy is all that is required to place the tablet as the most frequently used dosage form for the administration of drugs. The reasons for this popularity are economy, convenience and accuracy. As far as a manufacturer is concerned the tablet has the advantages of low unit cost of production, stability and ease of distribution. As far as the prescribing, dispensing and administration of medicinal compounds to humans is concerned, the tablet offers precise dosage and convenience with a concomitant likelihood of patient compliance. The only comparable form of presenting drugs to a patient is the capsule, which requires slightly more sophisticated machinery to manufacture.

J.R.Wood (1904) published the first major text on tablet manufacture where he noted the use of stamps by the Romans for certain medicaments, and describes the development of the compressed tablet from Brockendons patent of 1843 for the production of individual compressed tablets to 'high speed' (150-400 tablets/min.) production. The basic steps in the wet granulation method of producing tablets were also described by Wood (1904).

> "The ingredients are mixed, moistened, forced through a sieve to form granules, and dried. The dry granulation is then lubricated and compressed into tablets".

This process, with very little modification, remains in

common use today. The reasons for the granulation processes are the reduction of drug segregation in the bulk powder and to aid the flow of the drug and excipients into the die cavity of a tablet machine. For drugs or tablet mixes sensitive to moisture e.g. effervescent tablets, the technique of dry granulation has since been developed. This method consists of compressing the initial dry powder mix either between rollers (Chilsonating) or in large tablet dies under high compression forces (slugging), then breaking up the mass and treating it as the final stage of a wet granulation, (Sheth et al. 1980).

Since the early 1960´s these two granulation methods have been supplemented by a direct compression method whereby the active ingredients are dry mixed with a preprocessed excipient and any other necessary excipients prior to compression. This technique eliminates the need for the relatively expensive and time consuming wetting and drying of wet granulation or the extra heavy duty compression machinery of the dry granulation process. The three methods of preparing a drug for tabletting are summarised in Table 1.1 (Sheth et al. 1980).

The excipients used for the direct compression method are designed to substitute for the granules produced by the wet or dry granulation processes. As such, in addition to the overall excipient requirements of drug compatibility, stability and toxicological accept--ability, it has been suggested that they should also have certain additional attributes, (Staniforth and McCluskey 1982). That is, they should flow evenly and consistently without segregation (flowability); they should form suitable compacts on compression

Table 1.1

A Comparison of the Methods of Preparing Drugs for Tabletting.

WET GRANULATION	DRY GRANULATION	DIRECT COMPRESSION
1. Size reduction of drug	Size reduction of drug	Size reduction of drug
2. Mixing of ingredients	Mixing of ingredients	Mixing of ingredients
3. Preparation of binder	High pressure compaction	Tablet compression
4. Wet massing	Dry screening	
5. Wet screening	Lubricant blending	
6. Drying and dry screen	Tablet compression	
7. Lubricant blending		
8. Tablet compression		

(compressibility), even in the presence of a large proportion of drug (capacity). Ideally these characteristics should not be lost if it is necessary to grind up and recompress a batch of tablets (reworkability) and excessive force should not be necessary to form a compact (strength profile).

The available direct compression excipients all have deficiencies in some respect, such as the discolour--ation of spray dried lactose in the presence of amines, the poor flow properties of microcrystalline cellulose or the alkaline and abrasive nature of dicalcium phosphate dihydrate. The whole group of direct compression excipients also has disadvantages. The excipients capacity (the amount of drug capable of being successfully tabletted with the excipient) is usually limited to about 30% of the compression weight (Gunsel and Kanig 1976). This means that the process is restricted to medium or low dose drugs to avoid very large tablets. The other major drawback with the direct compression technique is a potential for drug segregation. Ideally each granule of a wet granulation contains the drug and excipients in the correct proportions, whereas in a direct compression blend, the drug particle mobility is not restricted and aliquots of the blend may not contain the correct proportion of drug. Despite these considerations the advantages of the direct compression technique have led to considerable interest in the method.

Some of the most popular direct compression excipients are lactose, dicalcium phosphate, microcrystalline cellulose and modified starch. Table 1.2 lists some of the basic characteristics of these excipients.

Table 1.2

General Characteristics of Common Direct Compression Excipients.

EXCIPIENT	MICROCRYS. CELLULOSE	LACTOSE		DICALCIUM PHOSPHATE	STARCH
		SPRAY-DRY	ANHYDROUS		
TRADE NAME	AVICEL	FAST-FLO		EMCOMPRESS	STARCH1500
SIZE (um)	35	100	120	160-180	26-32
MOISTURE (%)	<5%	<1%	<1%	2-4%	9%
REPOSE ANGLE (^{o})	46-61	52-56	55	-	-
EFFECTIVE ANGLE OF FRICTION (^{o})	46.7	43.1	35-39	35.5	38.0
BULK DENSITY (g/ml)	0.3	0.7	0.46	0.49	0.49
TAP DENSITY (g/ml)	0.4	0.9	0.6-0.7	0.8-1.0	0.78
PARTICLE DENSITY (g/ml)	1.6	1.54	1.54	2.34	1.49
COMPRESSABILITY (%)*	25	19	21	15	19

* An empirical guide to flowability where lower values indicate better flow characteristics (Carr 1970).

The final tablet has characteristics which, whilst being determined by the excipients and manufacturing process, may be monitored independently. They are not easily predictable from the manufacturing information, though this is one of the topics to which this work is addressed. These characteristics include the tablet strength, friability, porosity, weight variation, disintegration and dissolution. Other factors such as the tablet weight and thickness are largely, but not wholly, determined by the initial compression machine settings.

1.3 Tablet Strength

The most common method of quantifying the resistance to crushing of a tablet is by some form of diametral compression. This method is employed industrially as a quality control procedure using such devices as the Monsanto, Pfizer or Schleuniger hardness testers. However for more precise determinations e.g. of the tensile fracture stress, machines with known compression speeds and calibrated load cells, such as the Instron, are necessary.

If a cylindrical tablet breaks in tension rather than in compression on being compressed across the diameter, then the tensile fracture stress can be calculated using Equation 1.1, (Fell and Newton 1970).

$$\sigma = \frac{2.P}{\pi.D.t} \qquad (1.1)$$

Where σ is the tensile fracture stress, P is the failure load, D is the tablet diameter and t is the tablet thickness.

Other parameters have been suggested for characterising tablet strength. For example, Rees and Rue (1978) advocated the use of tablet toughness or the work of failure calculated from the breaking load and platten movement by Equation 1.2. They suggest that this may give a better indication of the ability of a tablet to withstand handling than the tensile fracture stress. However their calculation was strictly invalid because the measured displacement was not in the same direction as the force causing fracture (Kennerley 1980).

$$W_f = \frac{2}{\pi.D.t} \int Fdx \qquad (1.2)$$

Where W_f is the work of failure, D is the tablet diameter, t is the tablet thickness and the integral Fdx is the area under the force displacement curve.

Alternative methods of quantifying tablet strength include indentation tests which measure the surface hardness of a compact. These may be static impression methods (Brinell or Vickers) or dynamic rebound tests. In either case the results may show large variations over a single tablet surface due to the lack of homogeneity of a tablet matrix (Aulton 1977).

The application of axial rather than radial force has also been used to determine tablet strength (Nystrom et al. 1977, Jarosz and Parrott 1982). It has been suggested that this test is more suitable for the study of capping tendencies as the applied force is in the same direction as the internal tensile stresses causing capping (Nystrom et al. 1977). Flexure tests have also been applied to tablets (David and Augsberger 1974).

1.4 Friability.

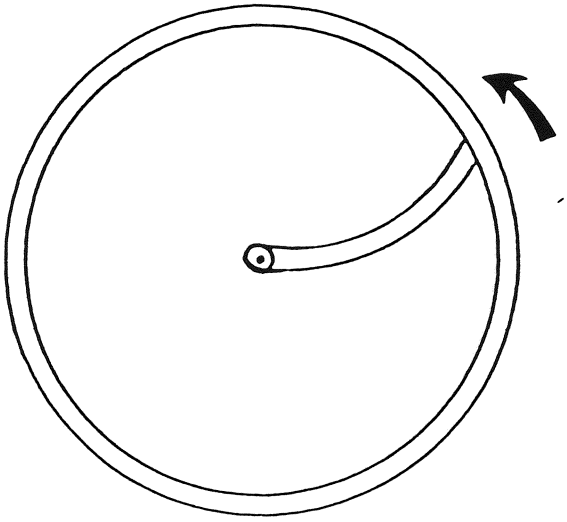
An alternative quality of tablet strength is the ability of a tablet to withstand mechanical handling measured by a friability test. This test involves the rotation of tablets in a drum, where the tablets are subjected to attrition and impact. There are two drum designs commonly available as shown in Figure 1.2, although other designs have been used (Gamlen et al. 1982, Fonner et al. 1970).

The weight loss after a number of revolutions allows the calculation of the friability as a percentage of the original weight. This test has been suggested to provide an index of capping (Nystrom et al. 1978) although other indices have also been proposed e.g. ratio of axial to radial tensile strength (Jarosz and Parrott 1982).

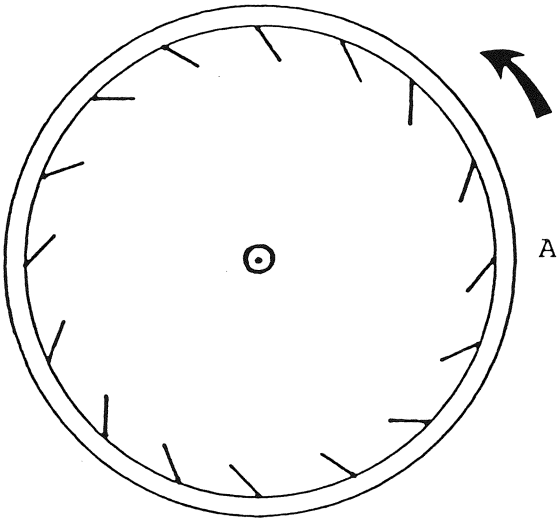
The tablet strength and moisture content are among the factors affecting tablet friability (Chowhan et al. 1982).

1.5 Porosity.

The porosity of a solid is analogous to its size in that the result obtained depends on the measuring technique employed. The porosity of a compacted powder may include the space between particles within the compact, the spaces due to the rugosity of the particle surface or the space enclosed within particles. The space totally contained by particles i.e. hollow particles, may only be estimated by comparison with similar but broken particles. This situation does not arise with recrystallised or milled particles but can



a.
´Roche´ Friabilator
Drum.



b.
Attrition Friabilator
Drum.

Figure 1.2.
Two commonly available designs of drum
used in friability tests.

occur with spray dried materials. Whether this is necessary depends on the reason the measurement is being made.

The simplest expression of the porosity of a compact is the percentage of the total compact volume, (determined from its external dimensions), not accounted for by the theoretical volume of the solids comprising the compact. Equation 1.3 expresses this in terms of the tablet density, (the weight of the tablet divided by the tablet volume), and the material density, (the weight of the tablet divided by the volume that weight would occupy at zero porosity).

$$\% E = 1 - \frac{\text{tablet density}}{\text{material density}} \times 100 \qquad (1.3)$$

The errors associated with the definition of the position of the surface of a compact are small compared to the volume of the compact and are therefore usually ignored. The estimation of the material density at zero porosity depends much more on precisely where a surface is located. The situation may be likened to the measurement of the length of a coastline, where a clear measurement may be made where there are cliffs but not on an estuary. The coastline question may be resolved by specifying the furthest extent of the penetration of salt water as the point where coastline becomes riverbank.

With particles the surface is similarly defined by the extent of penetration of a fluid. When the volume of solid is estimated by the displacement of water the derived material density is known as the specific gravity. A more convenient method uses air as the

displacement fluid, such as in an air comparison pycnometer. Small molecular weight gases may also be used on a similar basis to derive either the surface area (Armstrong and Griffiths 1970) or, in conjunction with the projected particle diameter, the surface roughness of powders (Staniforth 1984), the advantage of these fluids being their depth of penetration. Mercury under pressure has also been used to estimate pore sizes, (Stanley-Wood 1979).

1.6 Weight Variation.

The weight of an individual tablet is determined by a combination of the die fill volume and the bulk density of the feed material. The first of these is controlled by the tablet machine weight setting which may be altered manually or by automatic feedback monitoring equipment. The bulk density of the feed material is dependent on the flow characteristics at the time of filling. With direct compression excipients this flow may not be uniform over a given production run due to alterations in the particle packing state arising from machine vibration or hopper fill. This can result in bridging or surging of the powder bed in the hopper and consequent variations in tablet weight. These variations are generally less with coarser more spherical powders than with fine powders and is one of the major reasons for the popularity of the wet granulation method. Even with the coarser powders, until a uniform packing state of the powder is achieved in the hopper, the weight variation will be considerable. For this reason the tablets produced immediately after filling the hopper and those produced as the hopper is emptying, are routinely discarded. The

weight variation is thus a measure of a powders ability to flow consistently into a die cavity.

There have been many attempts to quantify flow either indirectly by measuring the internal friction of the powder or from Shear cell measurements, or directly by mass flow rates. These are summarised in Table 1.3.

There is some doubt over the value of the indirect methods of predicting tablet weight variation with some authors finding a relationship between flow parameters and tablet weight variation (Nyqvist 1982), and others finding none (Bagster and Crookes 1978). Varthalis and Pilpel (1976) have noted that the properties of mixed powders may not be proportionately intermediate between those of its constituents and, Varthalis and Pilpel (1977), that there may be optimum concentrations of glidants for minimum angles of internal flow. Chowhan and Yang (1983), in relating orifice flow rates to the tensile strength of powders, states that tensile strength measurements are limited to powder systems that are sufficiently cohesive to produce measurable tensile strengths of the consolidated powder yet sufficiently free flowing to produce a gravity flow under different consolidation states. Crookes et al. (1977) suggest that different modes of consolidation in different equipment may account for the lack of correlation between shear cell parameters and the tensile strength measured in a tensile tester. These changes in powder properties with different particle size distributions, in the presence of other substances, or under different testing conditions may explain the lack of correlations between the indirect determination of flow and tablet weight variation.

Table 1.3

Powder Measurements. Factors relating to powder flow.

METHOD	TYPICAL RANGE	COMMENT	REFERENCE
Angle of Repose	28-42°	Static or dynamic measure of internal cohesion	Train (1958)
Mass flow rate	50-100g/s	Direct measure which may show bridging or surging problems.	Gold et al. (1966)
Blocking Aperture	1-3cm	Maximum aperture preventing flow	Danish and Parrott (1971)
Ratio of Densities	5-40	Bulk density compared with density after consolidation by tapping.	Carr (1970) Hausner (1967)
Tensile Strength	0.2-1.5 kNm^{-2}	Strength of consolidated powder bed. Dependent on packing state.	Bangudu and Pilpel (1984)
Shear Cell Parameters.			
Angle of internal Friction	30-50°	Measure of difficulty of maintaining steady state flow.	Williams and Birks (1967)
Cohesion	2-20 gcm^{-2}	Yield stress at zero normal load	Peleg and Mannheim (1973)
Flow Function	1-20	Reciprocal possibly related to flow	York (1975) Crookes et al. (1977)

Direct measurements of mass flow rates may more closely represent the flow of powder into a die but can present practical difficulties. Dahlinder et al. (1982) found that flow rates through 30mm orifices could not be determined for cohesive powders. Jones and Pilpel (1966) described an equation relating particle size, density and flow rate to the flow orifice diameter. They limited their discussion to particles >0.2mm to eliminate effects due to electrostatic, van der Waals and other forces which may significantly influence small particle interactions. Danish and Parrott (1971) extended this relationship with similar restrictions on the minimum particle size but with different materials. Both studies used an equation similar to Equation 1.4.

$$D_o = A \left(\frac{4\,Q}{\pi \rho \sqrt{g}} \right)^{1/n} \qquad (1.4)$$

Where D_o is the orifice diameter for zero flow, Q is the mass flow rate, ρ is the powder density, g is the acceleration due to gravity, and A and n are functions of the particle size and shape.

Danish and Parrott (1971) also found that there was no correlation between mass flow rate and repose angle.

1.7 Liquid Penetration.

Before dissolution of a drug in a tablet can take place, the dissolution medium must, except for drug particles on the surface, pass through the tablet matrix. This penetration can cause the tablet to break up into discrete particles particularly in the presence of disintegrating agents. In this case the dissolution medium must still reach the disintegrant to have any effect. Thus the rate of liquid penetration into a tablet may exert a profound effect on drug dissolution. Groves and Alkan (1979) examined the application of the Washburn (1921) equation to pharmaceutical tablets. They found that the exponent m in Equation 1.5 could be taken as equal to 0.5 over a range of compaction pressures.

$$L^{1/m} = \frac{D\, y \cos\theta\, t}{4\eta} \qquad (1.5)$$

Where L is the length penetrated at time t, D is the capillary diameter, y is the surface tension of the liquid, θ is the contact angle between the liquid and solid and η is the liquid viscosity.

Where microcrystalline cellulose was used in a tablet formulation, Lerk et al. (1979) and Fukuoka et al. (1983) found that a value of m of 0.5 was not suitable to describe the liquid penetration. These authors found that m=1 gave a better description of the penetration and postulated that this was due to a change in pore size during liquid penetration. This was concluded to be caused by the breakage of hydrogen bonds in the microcrystalline cellulose by the liquid, allowing the

separated surfaces to move apart resulting in a 'V' shaped pore with the apex just behind the solvent front. It was also noted in both of these studies that the presence of magnesium stearate in the compact decreased the rate of penetration, presumably due to a change in the contact angle, i.e. the ability of the liquid to wet the next surface.

The contact angle between a liquid and a solid has been described as an index of the ability of a liquid to wet a solid (York 1983). However Fell and Efentakis (1978) have suggested that the adhesion tension (Equation 1.6) provides a better index for comparative purposes.

$$AT = y \cos\theta \qquad (1.6)$$

Where AT is the adhesion tension, y is the surface tension and θ is the contact angle between the liquid and the solid.

Table 1.4 shows the adhesion tension of some materials calculated from the figures published by Fell and Efentakis (1978) using methanol/water mixtures to vary the surface tension, and estimated from the work of Gissinger and Stamm (1980) using the assumption that the surface tension of the water used was $72.7 Nm^{-1}$ (Tennent 1971). The figures from Lerk et al. (1976) were based on saturated solutions of the materials.

The values for $\cos\theta$ or adhesion tension in Table 1.4 indicate that the paracetamol would be slightly more easily wetted than the aspirin, and that the starch or Avicel would be very easily wetted. The magnesium stearate would however, be difficult to wet with liquids with a surface tension similar to water.

Table 1.4

The adhesion tension of various materials. A higher value indicating an increased readiness for immersional wetting (Fell and Efentakis 1978).

solid		cosθ	surface tension Nm^{-1}	adhesion tension Nm^{-1}
aspirin		0.276	59.4	16.4
aspirin		0.389	55.0	21.4
paracetamol		0.559	55.0	30.7
paracetamol +		0.514	67.7	34.8
maize starch	0°	1.000*	72.7++	72.7
Avicel PH101	17°	0.956*	72.7++	69.5
magnesium stearate +		-0.520	72.3	-37.6

(++ estimated values; + from Lerk et al. 1976)

* Gissinger-Stamm (1980)

1.8 Disintegration.

Disintegration tests are most suitable for tablets manufactured from granulated material, where the test measures the time taken for a tablet to break up into granules or smaller particles. In the case of a tablet manufactured by direct compression the particles consist of the original powders or powder agglomerates. The standardised disintegration test measures the time taken for the tablet to disintegrate sufficiently to pass through a defined aperture on agitation in a liquid, the apparatus and operating conditions being specified, (British Pharmacopoeia 1980, United States Pharmacopoeia 1980).

Although early workers used the disintegration test extensively, the standardisation of the dissolution test, giving a better measure of drug release, has now superceeded it except as a quality control procedure. Several authors have found that drug release may bear little relationship to disintegration time, (Rubinstein and Price, 1977; Carlson et al. 1983). The disin--tegration process is however still important as a preliminary step in dissolution and may in some cases be determined from a dissolution profile (Nelson and Wang 1977, 1978). It may also be included in the analysis of dissolution as part of the lag time necessary to fit mathematical models to experimental dissolution results.

The action of disintegrants has been reviewed by many authors (Rudnic et al. 1982, Guyot-Herman and Ringard 1981, Lowenthal 1972, Kanig and Rudnic 1984) and the principal mechanisms are summarised in Table 1.5.

corn starch swells - Reduce by 15%
+ tab. ~ 0.8 - 1/g.

Table 1.5

Proposed Mechanisms for the action of Disintegrants.

1. Disintegrant Swelling.	Volume increase of disintegrant particle on hydration. The resultant forces are sufficient to overcome the bonds formed during compaction (or granulation)
2. Porous Capillary Network	Liquid uptake through disintegrant particles in tablet (wicking). This may result in an increase in internal hydrostatic pressure or the breakage of bonds within the disintegrant. (Khan and Rhodes 1975) vapour sorption
3. Particle Repulsion	Active repulsion between disintegrant particles on hydration. (Guyot-Hermann and Ringard 1981)
4. Heat of Hydration	The heat of hydration of the disintegrant causes expansion of entrapped air sufficient to destroy inter-granular bonds. (Matsumaru 1959)

A disintegrant in a formulation is often necessary to allow the drug to dissolve either by increasing the surface area i.e. separation of the particles in a tablet, or by increasing the amount of liquid inside the dosage form, i.e. wicking or capillary action. Where a tablet is manufactured from granules, the disintegrant may be intra or inter granularly distributed to make use of both of these mechanisms. The disintegration of a tablet may be influenced by many factors such as the proportion and type of disintegrant (Miller et al. 1980), the compaction pressure (Higuchi et al. 1953) or by the other excipients in a tablet (Bolhuis et al. 1981). The rate of liquid penetration may be modified by some of these factors but the response of a disintegrant to contact with the liquid will usually exert a greater effect.

Microcrystalline cellulose is of particular interest with regard to its action as a disintegrant, which may be due to the same mechanism as its effect on liquid penetration, (Section 1.7). Lerk et al. (1979) found that as liquid entered a microcrystalline cellulose tablet, the pore size increased. These authors postulated that this was due to the breaking of hydrogen bonds holding particles together which, besides facilitating liquid penetration, would also allow separation of particles i.e. destroying tablet coherence. Microcrystalline cellulose has also been stated to have a greater swelling capacity (70%) than maize starch (43%) in 0.1N HCl, (Caramella et al. 1984), although this seems to be in conflict with the swelling increases published by Gissinger and Stamm (1980) with water, (43% Avicel and 103% maize starch). The methods used for determining swelling capacity may account for these differences, with Gissinger and Stamm

(1980) measuring the expansion of a compact and Carmella et al. (1984) measuring the particle volume increase by a Coulter Counter determination.

1.9 Dissolution.

Tablets are intended to deliver drugs to a biological system and, to be absorbed systemically, the drug must pass through an aqueous phase. The drug must therefore pass from a solid tablet to a solution. The main steps in this process are shown in Figure 1.3.

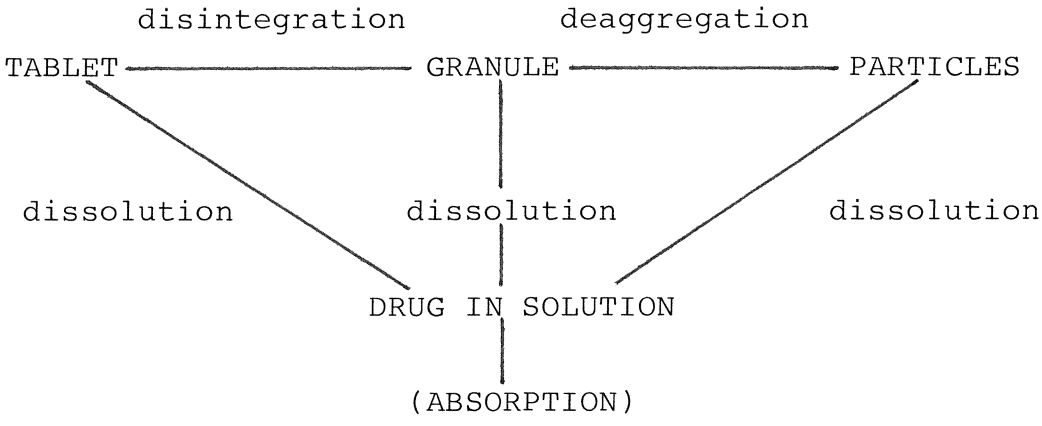


Figure 1.3.
The processes involved in the conversion of a drug contained in a tablet to a solution available for absorption.

The mechanical properties of tablets previously discussed have very little effect on the dissolution of pure drug particles but may have considerable effect on the availability of the drug surface to the dissolution medium. The disintegration test gives some indication of the rate of formation of particles available for dissolution, (a combination of the rate of penetration of liquid and the effect of any disintegrants present in the formulation), but the in vitro dissolution test gives a better indication of the availability of a drug from a tablet.

1.9.1 Dissolution from a surface.

The rate of solution of cylinders of lead chloride and benzoic acid in water was studied by Noyes and Whitney in 1897, and forms the basis of modern dissolution theory. They derived a relationship between the rate of change of concentration (dC/dt) and the difference between saturation solubility (C_s) and the concentration at some time t (C_t), Equation 1.7.

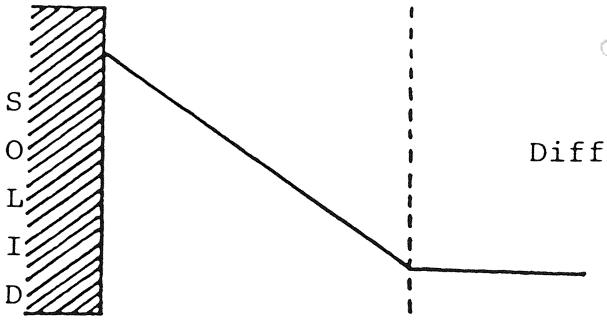
$$dC/dt = K(C_s - C_t) \qquad (1.7)$$

This relationship was expanded by Nernst and Brunner (1904) by differentiating between the instantaneous chemical solvation of the solid and the transport of the solvate across a stationary layer of liquid according to Ficks Law of diffusion. This may be expressed as Equation 1.8.

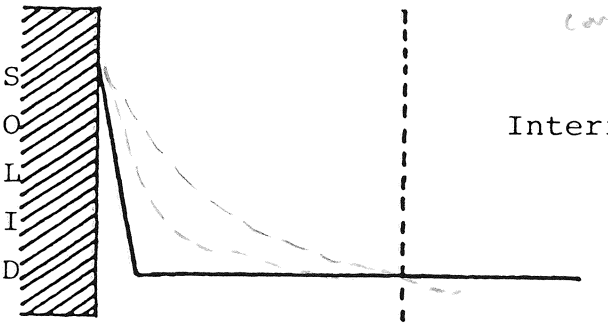
$$dW/dt = DS(C_s - C_t)/h \qquad (1.8)$$

Where dW/dt is the rate of change of mass; D is the diffusion coefficient; S is the surface area; h is the thickness of the diffusion layer and C_s,C_t are as in Equation 1.7.

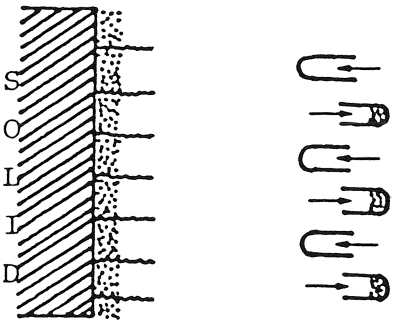
These relationships and the later work of Dankwerts (1951) were summarised by Higuchi (1967) as the diffusion layer model, the interfacial barrier model and the Dankwerts model as shown in Figure 1.4. The applicability of a given model depending on the characteristics of the dosage form and the conditions in the dissolution system. Essentially the choice of a dissolution model is empirical in that the parameters of a model only adequately describe a dissolution process when the experimental data fits the model. Carstensen (1980) provided a more comprehensive review of the models which are likely to be associated with various types of dissolution behaviour as well as discussing model derivation in greater depth.



Diffusion Layer Model.



Interfacial Barrier Model.



Dankwerts Model.

Figure 1.4.

Diagramatic representation of three models describing the dissolution of a solid from a surface.

1.9.2 Dissolution of Powders.

The models for dissolution described above (Equations 1.7 and 1.8) were derived on the basis of a constant surface area during the dissolution process. Unfortunately as a powder dissolves the available surface area changes. Hixson and Crowell (1931) modified the basic diffusion models above to take account of the surface of a monodisperse powder thus,

$$W_o^{1/3} - W^{1/3} = K't \qquad (1.9)$$

Where $K' = 2 D C_s/h\rho \ (\pi N\rho/6)^{1/3}$; W_o is the initial weight of powder available for dissolution; W is the weight of powder not in solution; D is the diffusion coefficient; C_s is the saturation solubility; ρ is the particle density; h is the thickness of the diffusion layer and N is the number of particles.

The above equation defines the intrinsic dissolution rate constant under sink conditions (i.e. the concentration of dissolved solid is much less than the saturation solubility), with agitation.

Modifications have been made to this cube root equation (1.9) to compensate for non-sink conditions (Pothsiri and Carstensen 1973), and for differences in boundary layer thickness or agitation (Niebergall et al. 1963). Even with these modifications the models still contain the assumption of a spherical monodisperse powder, an exception rather than the rule.

Higuchi and Hiestand (1963) studied the situation relating to the dissolution of a log-normally distributed powder but found that the equations became unmanageable and required the use of approximations for the number of particles. Higuchi et al. (1963) used a similar approximation in an experimental study, but still found deviations from theoretical. These deviations were considered to be due to the effects of agitation, sedimentation, particle shape and variation of solubility with particle size. Carstensen and Musa (1972) used a computer simulation of a polydisperse powder system and Brooke (1973) used a simpler simulation, but the assumption of an initial log-normal spherical powder distribution remains a major obstacle to the fitting of these models to experimental data.

1.9.3. Dissolution from a tablet.

The relationships discussed above describe the dissolution of pure substances either from homogenous surfaces or a known surface distribution. The release of a drug from a tablet, although dependent on dissolution from the drug particle, is complicated by the disintegration process, the presence of other substances and by the hydrodynamics of the test apparatus. This means that although the basic equations successfully describe some experimental dissolution curves, in many cases the data may only be described by empirical equations. The primary aim of these mathematical models is to quantify a tablet dissolution profile to allow comparisons between profiles. Table 1.6 lists some of the most common models and their factors for comparison. Other methods such as plots based on probability or dissolution efficiency have

Table 1.6.

DISSOLUTION MODELS.

MODEL EQUATION	COMPARISON FACTOR	REFERENCE
$\log (100\%-M\%) = -K(t-t_i)$	dissolution rate constant (K)	Wagner 1969
$M^{1/3} - M_o^{1/3} = -K(t-t_i)$	cube root dissolution rate constant (K)	Hixson and Crowell 1931
$M = 1 - \exp[-(t-t_i)^b/a]$	a - time scale of process b - shape parameter dissolution time (63.2%)	Langenbucher 1972

Where M represents the cumulative fraction of material in solution at time, t. t_i represents the time lag before onset of the dissolution process, which may be zero, and M_o represents the initial amount of material available for dissolution.

also been used (Wagner 1969, Langenbucher 1972, Khan 1975). Goldsmith et al. (1978), in a comparison of several methods of presenting dissolution data, concluded that the work involved in these manipulations was not justified by the additional information obtained.

The rate of solution of drug from a surface or multiparticulate powder has already been considered. The rate of solution being dependent on the surface area of the solid, the concentration of the solid in solution, the properties of the liquid and the testing conditions. Of these, under standardised testing conditions, the factor most likely to vary in a tablet is the surface area. The surface area of a particle is proportional to its size but the number of particles per unit mass is inversely proportional to particle size. This is illustrated for a spherical monodisperse powder in Table 1.7. Thus, according to Equation 1.8, as the particle size is decreased the dissolution rate should increase. However, dissolution from a tablet has already been stated to be a composite process (Figure 1.3), and it should be noted that the effective surface area may be considerably different from the apparent surface area. Thus the particle size determined by, for example, microscopy, may bear little relationship to the rate of solution of the same powder. This is particularly true of particles below about 10μm where the particles may agglomerate due to an increase in surface bonding, or with particles which are difficult to wet. In these cases the area of powder available to the solvent (effective surface area), is less than the area of powder determined under other conditions (apparent surface area).

Table 1.7

The change in particle surface with size reduction.

No. of particles	particle radius	surface area per particle	weight of powder	total surface
1	0.5	3.142	0.5237	3.14
2	0.397	1.979	0.5237	3.96
4	0.315	1.247	0.5237	5.00
8	0.25	0.786	0.5237	6.28

One spherical particle diameter 1 unit, density 1 unit broken down into a number of spherical particles having the same total weight as the initial particle.

Yen (1964), Johansen (1972), Finholt (1974) and others have reported the expected increase in dissolution rate with decreasing particle size. Other reports describe the opposite effect (Al-Saieq 1983, Finholt 1974, Newton and Bader 1980). The latter effect has been attributed to the surface characteristics of the drug involved, with hydrophobic surfaces resisting wetting or entrapping air. The reduced dissolution rate may be reversed by incorporating a surfactant in the dissolution medium i.e. reducing surface tension, or by altering the drug surface by intimate proximity of hydrophilic excipients (Lerk et al. 1978), or by granulation (Solvang and Finholt 1970). In each case the ability of the liquid to pass a hydrophobic surface barrier is enhanced. The 'wicking' action of hydrophilic excipients enables the solvent to wet the drug surface prior to dissolution. Unfortunately the ability of the solvent to pass through or around the

hydrophilic excipients adds another step to the process of dissolution from an intact or disintegrated tablet. The penetration of a liquid into a tablet will depend on both the nature of the excipients and the manufacturing process.

The manufacturing process alters drug release by changing the proximity of the drug and excipients. This may be the spreading of hydrophobic lubricants by mixing, the location of binders in granulation, or the bonding or fragmentation induced by compaction.

Lerk et al. (1979) and others have studied the effects of the mixing of lubricants on dissolution and found that increased mixing time, i.e. an increased distribution of lubricant in the powder mix, caused a decrease in the dissolution rate. This was less pronounced with more potent disintegrants and in the presence of brittle materials capable of disrupting the lubricant film on compaction. Lubricants also interfere with bonding on compaction again dependent on the distribution of lubricant (Shotton and Lewis 1964).

In studies of the effect of lubricant mixing on the dissolution rate, disintegration time and tablet strength, the individual effects are difficult to isolate because changes in lubricant distribution affect all the factors. That is, the presence of interparticulate lubricants may reduce tablet strength and altering the strength may modify the dissolution process. However, changing the lubricant distribution may also directly affect the dissolution process.

Finholt (1974) reviewed the types of relationship between dissolution rate and compression force. He described five different responses as shown in Figure 1.5. Figure 1.5e could be interpreted as a composite of the other four relationships. The section of Figure 1.5e which is derived from an experiment being dependent on the experimental conditions, the formulation and the compaction pressures chosen. Khan and Rooke (1974) also found that the relationship between dissolution efficiency and compression force depended on the excipients used.

The effect of tablet formulation factors on the dissolution of a drug may be summarised as a combination of the effects on liquid penetration, the response of the excipients to the liquid, the changes induced in the drug surface and the intrinsic dissolution rate of the drug. The interpretation of the effects of individual factors should ideally be considered in the context of the effect of the factor on the formulation as a whole, rather than the effect on dissolution alone. The influence of the apparatus and test conditions should also be considered.

1.9.4 Dissolution Methods.

Pernarowski (1974) stated that there were more than 100 published dissolution methods. Various classifications of the methods have been used, for example Hersey (1969) based his review on agitation and sink conditions. Stricker (1976) identified three main categories of apparatus, closed compartment, open flow through and dialysis-diffusion methods. The closed compartment (non-sink) type is typified by the

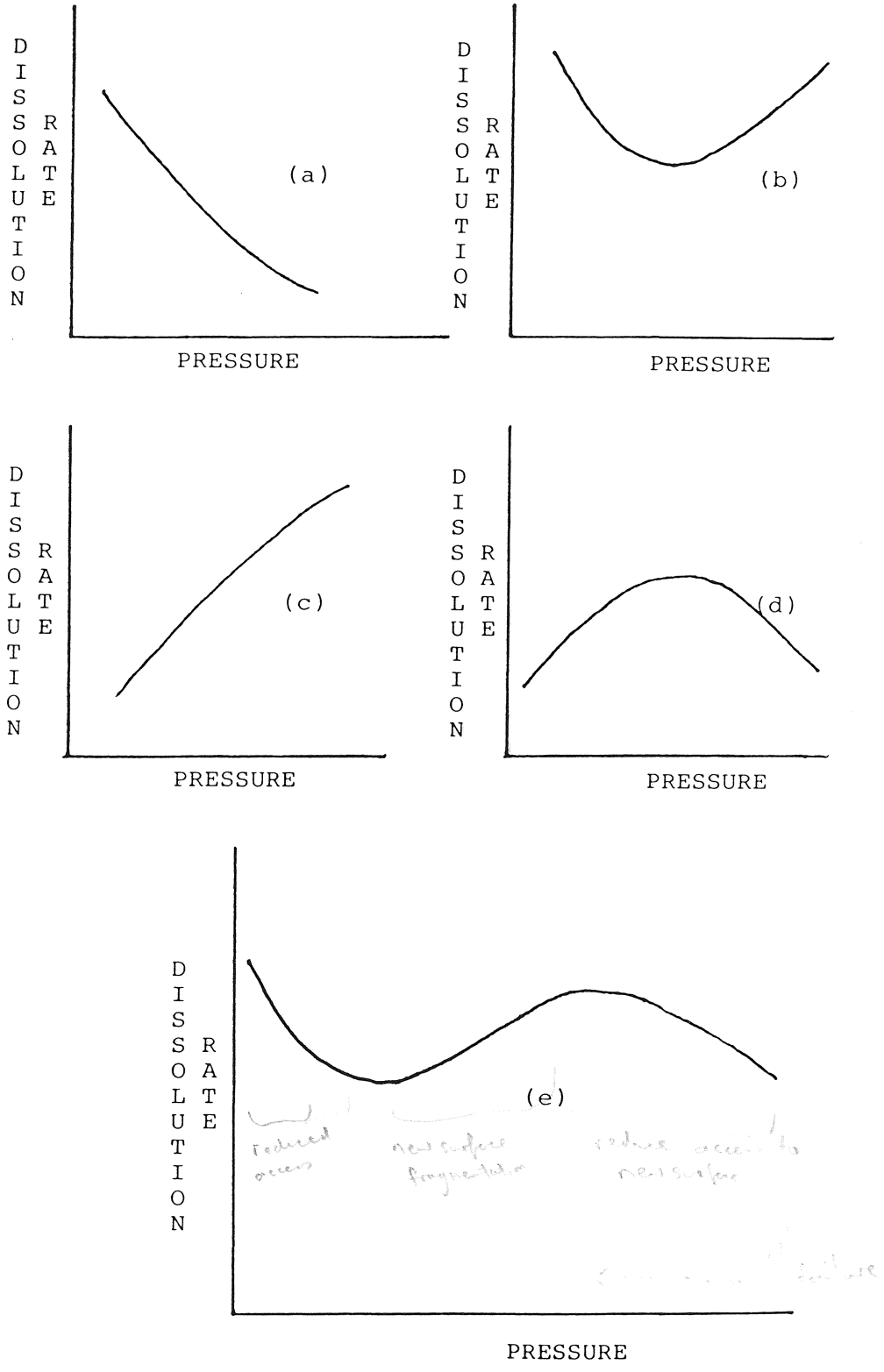


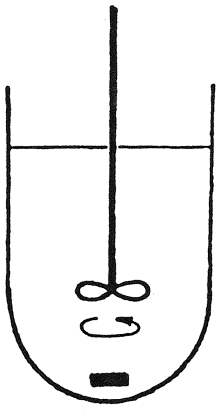
Figure 1.5

The effect of the compaction pressure on the dissolution of a drug from a tablet.

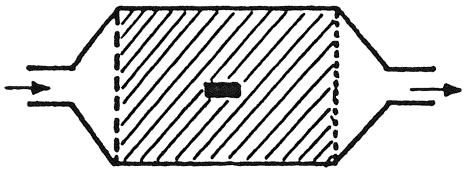
compendial methods e.g. United States Pharmacopoeia (1980) methods 1 and 2, where the tablet dissolves in a fixed volume of solution. The open flow through method typically involves passing solvent over a fixed position tablet (Smolen and Weigand 1976). This may be fresh solvent (sink conditions) or recirculated (non-sink conditions, Meyers 1960). Dialysis methods involve the separation of the tablet from its bulk (receptor) solution by a membrane (Marlowe and Shangraw 1967). Figure 1.6 illustrates the basic types of apparatus. These methods include such variations as rotating bottles (Higuchi et al. 1963, NF XII 1967), oscillating tubes (Levy 1963) and the simultaneous measurement of particle size (Edmundsen and Lees 1965) or partition coefficients (Gibaldi and Feldman 1967).

The beaker and paddle method originally used by Levy and Hayes (1960) has been developed and modified by many authors, notably Poole (1969). This method, modified to locate the tablet more precisely, was incorporated in the United States Pharmacopoeia (USP) XVIII (1970) as the basket method. Compendial standardisation following inclusion of the rotating basket method in the USP XVIII (1970) and other methods (USP XIX 1975, USP XX 1980) has resulted in a concentration on these methods in the interests of international comparability of results. It should be noted that a disintegration apparatus modified for dissolution testing remained in the USP XX (1980) as method 3.

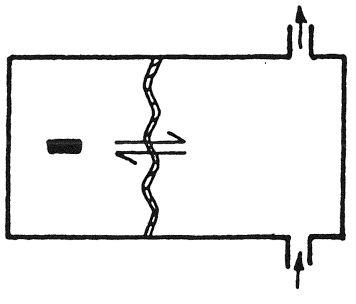
Criticism of the basket method of the USP XIX (1975) by Carstensen et al. (1977) and others (Tingstad 1981) probably resulted in the modifications to the method and the inclusion of other methods in the USP XX (1980).



Closed Compartment Apparatus



Open Flow Through Apparatus



Dialysis-Diffusion Apparatus

Figure 1.6.

The common designs of apparatus for in-vitro dissolution testing.

Despite these changes the Federation International Pharmaceutique (FIP) working party on dissolution in 1981 recommended that the basket method be discarded as 'technically unsound', and that future compendial standards be concentrated on the paddle and flow cell methods.

The USP XX (1980) dissolution test method 2 (paddle) is not free from criticism. Cox et al. (1982) has studied the effect of vessel shape on the dissolution of prednisone tablets and found bias dependent on the degree of flattening of the base, and in a later study (Cox and Furman 1982) differences due to shaft alignment. These studies would obviously apply similarly to the basket method and indicate the need, as mentioned in the FIP (1981) report, for a tighter specification on apparatus and methodology.

The flow cell or column method may well provide an alternative standard to the basket or paddle methods although it may have drawbacks in multiple testing procedures. It has been claimed to have the advantages of low agitation intensity (Baun and Walker 1969), versatility and liquid homogeneity. The method has been used and modified by several authors including Tingstad and Riegelman (1970), Langenbucher (1969) and Seth (1972). Smolen and Weigand (1976) advocated its use as a flexible method potentially capable of mimicking a variety of biological absorption profiles. The mathematics of the hydrodynamic flow conditions may also be easier to define in this method than the complex situation in a stirred beaker (Grijseels et al. 1981).

The concentration on dissolution testing as both a control and research method has led to another development, that of automated testing. This brings the additional problem of the presence in the test vessel of a sampling device (Wells 1981). The flow cell method has an advantage in this respect in that sampling may be carried out without influencing the hydrodynamic conditions at the dissolution site and without the need to maintain liquid volume by sample return. Automation does however offer the advantages of the possibility of more frequent sampling with less operator time and reduced operator variability. One of the simplest means of achieving this for the beaker methods, is by continuous or intermittent pumping of the vessel contents to a UV-spectrophotometer. This may be done by means of a valve control mechanism through a single UV flow cell or, eliminating the problems of residual fluid in the tubing, through multiple flow cells with a cell changing mechanism. These two variations require that the solution to be measured absorbs satisfactorily under the assay conditions, and does not need to be diluted or otherwise modified before testing. The improvement in spectrophotometer wavelength control has enabled many drugs to be assayed without recourse to their λmax (Wahlich 1980), thus expanding the range of drugs capable of being reliably measured by UV absorption. Retention sampling may also be automated, this is particularly valuable where destructive analysis is necessary.

1.10 Statistical Methods in Formulation.

The complexity of the influence of excipients and manufacturing processes on dissolution make its study difficult. The normal experimental procedure of assessing the effect of a single variable whilst keeping the remainder constant can yield misleading results if there are interactions between variables.

The application of statistical methods to the study of pharmaceutical formulations, besides allowing the calculation of means, measures of distribution and confidence limits, can also enable individual aspects of complex interactions to be examined. These techniques may also be used in formulation optimisation and model fitting.

1.10.1 Optimisation Methods.

Sequential optimisation procedures have an intrinsic appeal in industrial formulation. The process consists of a series of experiments, the next experiment depending on the result of the preceding experiments until some defined endpoint is reached or no further improvement is possible. One such method is the simplex search technique. This method, in its simplest two dimensional form, consists of the reflection of a geometric figure in axes defined by preceeding experimental points to define the co-ordinates of the next experiment. The least satisfactory point after each step is then discarded and the next axis for reflection is defined by the remaining points. Gould and Goodman (1983) used this technique to optimise the solubility of caffeine in a three component solvent and Shek et al. (1980) used a similar method to optimise a

capsule formulation with respect to its dissolution and compaction rates. These authors also used the data generated in the simplex search in a polynomial expression of the response surface. One of the simplest forms of this expression is given in Equation 1.10.

$$\text{response} = b_o + b_1 X1 + b_2 X2 + b_{12} X1X2 \qquad (1.10)$$

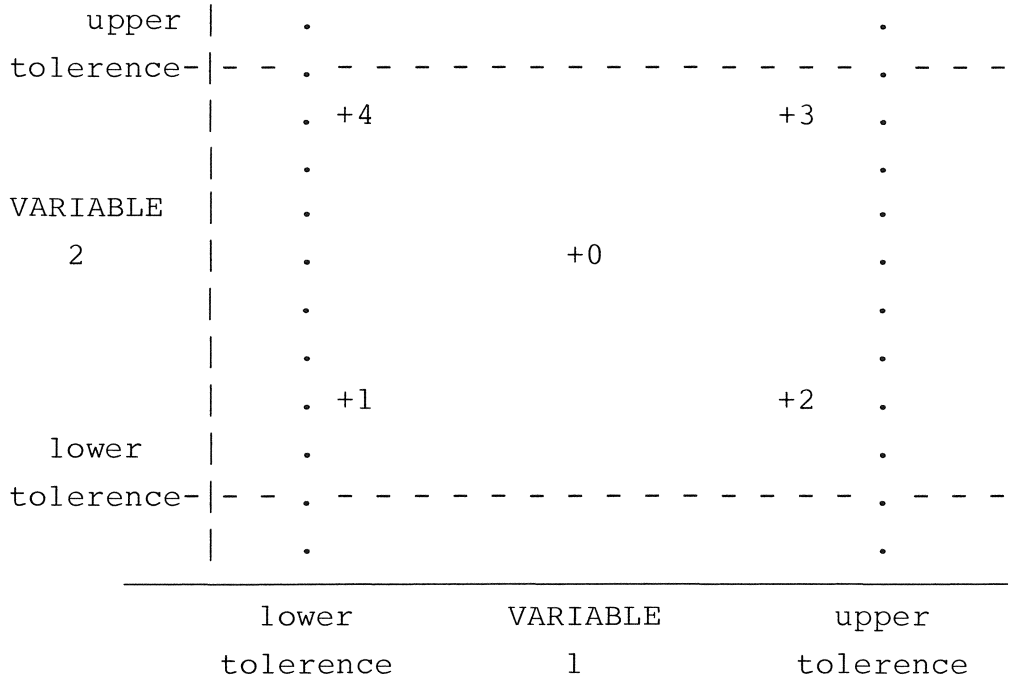
Where X1 and X2 represent the control variables and b_o, b_1 and b_{12} represent constants.

Higher order polynomials would include the squares of X1, X2, and their combinations.

The steepest ascent method of analysis is somewhat similar to the simplex method. A limited polynomial equation is derived from the response surface, the first order coefficients being calculated from an initial experimental design centred around some postulated maximum. This linear polynomial is used to determine the incremental changes in the factors to follow the response surface in the required direction. As the response surface becomes less steep, that is, as it approaches a maximum or minimum, the linear polynomial tends to describe the surface less adequately. Other methods of identifying the actual peak are more suitable, one of these is Canonical Analysis. This technique locates the maximum by partial differentiation of the response surface polynomial followed by solution of the resultant simultaneous equations. This point is then used as the origin for a new set of axes such that the general form

of the canonical equation describes the type of response surface being examined. The initial regression coefficients are then used to derive a more manageable quadratic canonical equation.

Evolutionary operation is another optimisation technique. It has been developed for use by production staff in a repetitive (batch) processing situation where the scope for change is low. The method is really a fine-tuning technique for established processes. Rubinstein (1975) described the basic concepts but a clearer discussion of its application and statistical theory is to be found in Anderson and McLean (1974), who pointed out that a straight forward analysis of variance technique would be more efficient. However, the method is orientated to use by operators unfamiliar with statistical manipulations and has the appeal of simplicity. The basic idea is that, starting from an origin within the existing working parameters, two variables are examined by systematically altering them within the working tolerances, keeping any other conditions constant. This is illustrated in Figure 1.7. The sequence (1-4) is repeated over several cycles and the response recorded. An on-going calculation of the effect at each point and its significance then indicates whether or not a new origin should be chosen, calculated by some other technique, e.g. steepest ascent. The process is then repeated using either new variables or a new location of the existing study variables or both, until no further improvement is noted.



Where 0 is the existing setting of the variables and 1-4 are the new settings in sequence for subsequent batches.

Figure 1.7.
The Test Conditions for Evolutionary Operation.

The method of Principal Component Analysis is not an optimisation procedure as such. It is concerned with the responses rather than the control variables. The technique is essentially a comparison of the variance of the response with the covariance of other responses under the same experimental conditions. Bohidar et al. (1975) applied this method to data generated by Schwartz et al. (1973) to establish the response with the maximum information content and thus derive the response which should be followed in an experimental design.

The statistical techniques discussed so far have all been optimisation procedures, that is they are ways of locating a maximal response within the constraints of the controlling variables. This type of approach is more suitable for the solution of a specific rather than a general problem. The exploration of the interrelationships between control variables has most often, in the pharmaceutical field, been by means of a factorial design experiment (Newton and Bader 1980, Newton and Razzo 1977a, El-Banna and Sautin 1980, Marlowe and Shangraw 1967, Bolton 1983). This method enables the effect of changing one variable to be assessed independently of the other variables. If sufficient levels of variables are used then predictive equations of the type given in Equation 1.10 may be used to define response surfaces, however the number of experiments increases exponentially with the number of levels of the variable factors.

The advantages of the factorial design method have been stated by Davies (1967) to be:-

a) When there are no interactions - maximum efficiency in the estimation of effects.
b) When interactions exist - factorial design necessary to avoid misleading conclusions.
c) Conclusions hold over a wide range of conditions.

The basis of the technique is an analysis of variance on the results of a complete experimental design of all the combinations of the factors and levels of the factors studied. Partial or confounded designs may be used particularly where the number of individual trials would otherwise be large or where prior knowledge of the effect of some factors is known. Some examples of the application of the technique are listed in Table 1.8. The increasing availability of computers has meant that the method is very easy to use particularly with established statistical packages such as Genstat (1980).

Table 1.8

Some examples of factorial design experiments.

Factors examined	Design / Response	Reference
particle diameter, liquid velocity initial mass load	3 X 4 X 4 Dissolution Time	Langenbucher (1969)
disintegrant type, concentration compression pressure;	3 X 4 X 3 Disintegration,	Lowenthal and Burruss (1971)
drug type, compression pressure, disintegrant concentration	Pore size, porosity 4 X 3 X 4	as above
particle size, temperature lactose concentration	2^3 Tensile Strength	Adeyemi and Pilpel (1983)
diluent, lubricant and wetting agent concentrations	5 X 4 X 5 Dissolution Time	Newton and Razzo (1977a)
drug type, diluent concentration, lubricant or wetting agent inclusion	6 X 3 X 2^3 Dissolution Time	Newton and Razzo (1977b)
granulation and mixing methods additive type	2 X 2 X 3 Dissolution Efficiency	Nath and Borcar (1979)
water content, spheronizer and extruder speed, screen size, time	2^5	Malinowski and Smith (1975)

1.11 Aims and Objectives.

The aim of this study was to examine how four factors, drug particle size, disintegrant concentration, mixing time and compaction pressure, influenced the in-vitro dissolution of drug from a direct compression tablet. The first two factors representing model changes in formulation and the last two factors representing changes in the manufacturing procedure. A factorial design experiment was considered to be a suitable way of assessing the contribution of the individual factors at levels likely to be encountered under normal manufacturing conditions. The contribution of other tablet parameters such as strength, porosity, liquid uptake and friability to the dissolution process were similarly examined. The final result bringing together the individual processes in a consideration of a tablet as a whole. Predictive analysis, whilst being desirable in the elucidation of particular aspects of the mechanics of formulation and necessary to an understanding of the processes involved, are only useful where the relative importance of the mechanisms is known. It was on this last aspect that this study was concentrated.