selection of the excipients which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation.

Thermal analysis (Section 3) can be used to investigate and predict any physicochemical interactions between components in a formulation and therefore can be applied to the selection of suitable chemically compatible excipients. Primary excipients recommended for initial screening for table and capsule formulations are shown in Table 13.16.

**Table 13.16** Suggested primary candidates as excipients for tablet and capsule formulations

| *Excipient* | *Function** |
|---|---|
| Lactose monohydrate | D |
| Dicalcium phosphate dihydate | D |
| Dicalcium phosphate anhydrous | D |
| Calcium sulphate dihydrate | D |
| Microcystalline cellulose | D |
| Maize starch | B, T |
| Modified starch | B, T |
| Polyvinylpyrrolidone | B |
| Hydroxypropyl methylcellulose | B |
| Sodium starch glycollate | T |
| Sodium croscarmellose | T |
| Magnesium stearate | L |
| Stearic acid | L |
| Colloidal silica | G |

* B, binder; D diluent; G, glidant; L, lubricant; T, disintegrant.

*Method*

The preformulation screening of drug:excipient interactions only requires 5 mg of drug, in a 50% mixture with the excipient, to maximize the likelihood of observing an interaction. Mixtures should be examined under nitrogen to eliminate oxidative and pyrrolytic effects at a standard heating rate (2, 5 or 10 °C $min^{-1}$), on the DSC. apparatus, over a temperature range which will encompass any thermal changes due to both the drug and excipient. The melting range and any other transitions of the drug will be known from earlier investigations into purity, polymorphism and solvates. For all potential excipients (Table 13.16) it is sensible to retain in a reference file individual, representative thermograms for later comparison.

*Interpretation*

A scheme for interpreting the DSC. data from the individual components and their mixtures is shown in Fig. 13.7. Basically, the thermal properties of a physical mixture are the sum of the individual components, and this thermogram can be compared with those of the drug and the excipient alone. An interaction on DSC. will show as changes in melting point, peak shape and

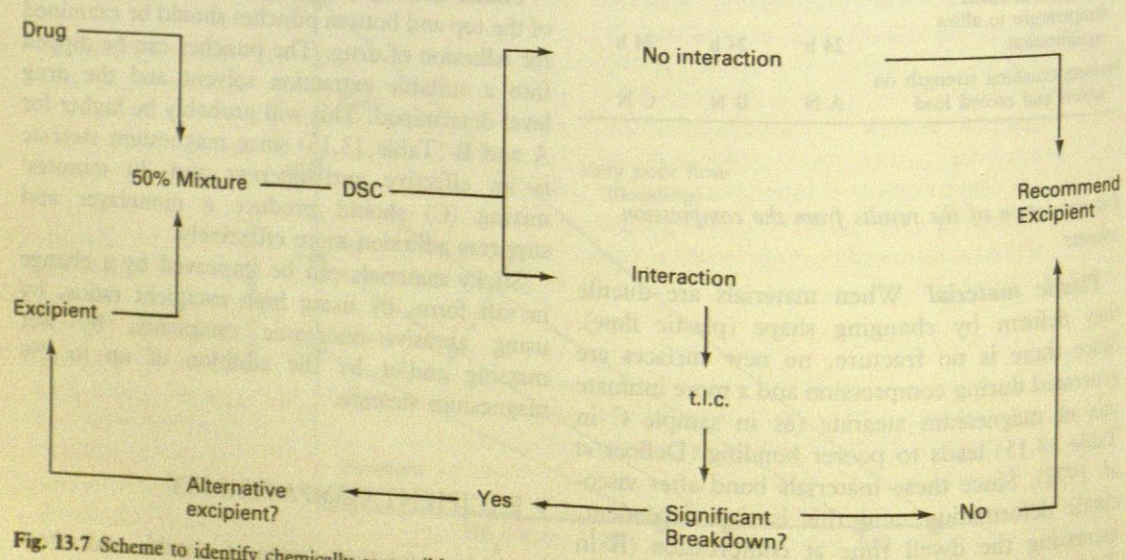


**Fig. 13.7** Scheme to identify chemically compatible excipients using DSC with confirmatory t.l.c.

area and/or the appearance of a transition. However, there is invariably some change in transition temperature and peak shape and area by virtue of mixing two components and this is not due to any detrimental interaction. In general, provided that no new thermal events occur or are lost by mixing the two components, no interaction can be assigned. Chemical interactions are indicated by the appearance of new peaks or where there is gross broadening or elongation of an exo- or endothermic change. Second order transitions produce changes in the baseline. Such observations may also be indicative of the production of eutectic or solid solution type melts. The excipient is then probably chemically reactive and incompatible with the drug and should be avoided. Where an interaction is suspected, but the thermal changes are small, the incompatibility can be confirmed by t.l.c.

The advantages of DSC. over more traditional, routine compatibility screens, typically t.l.c., is that no long-term storage of the mixture is required prior to evaluation nor is any inappropriate thermal stress (other than the DSC. itself, which has drug and excipient controls) required to accelerate the interactions. This, in itself, may be misleading if the mode of breakdown changes with temperature and elevated temperatures fail to reflect the degradative path occurring under normal (room temperature) storage.

Where confirmation is required by t.l.c., samples (50:50 mixtures of drug and excipient) should be sealed in small neutral glass test tubes and stored for either 3 days at 75 °C, 7 days at 50 °C or 14 days at 37 °C depending on whether it is likely, from earlier stability studies (Section 5), that degradation will be atypical at elevated temperatures.

It is important to view the results of such incompatibility testing with caution in cases where the additive is used at low concentration in the product. For example, magnesium stearate is notoriously incompatible with a wide range of compounds when tested as above. Yet, since it is only used at low levels, typically 0.5–1%, such apparent incompatibility rarely produces a problem in practice on long-term storage.

## 10 CONCLUSIONS

Preformulation studies, properly carried out, have a significant part to play in anticipating formulation problems and identifying logical paths in both liquid and solid dosage form technology (Fig. 13.8). The need for adequate drug solubility

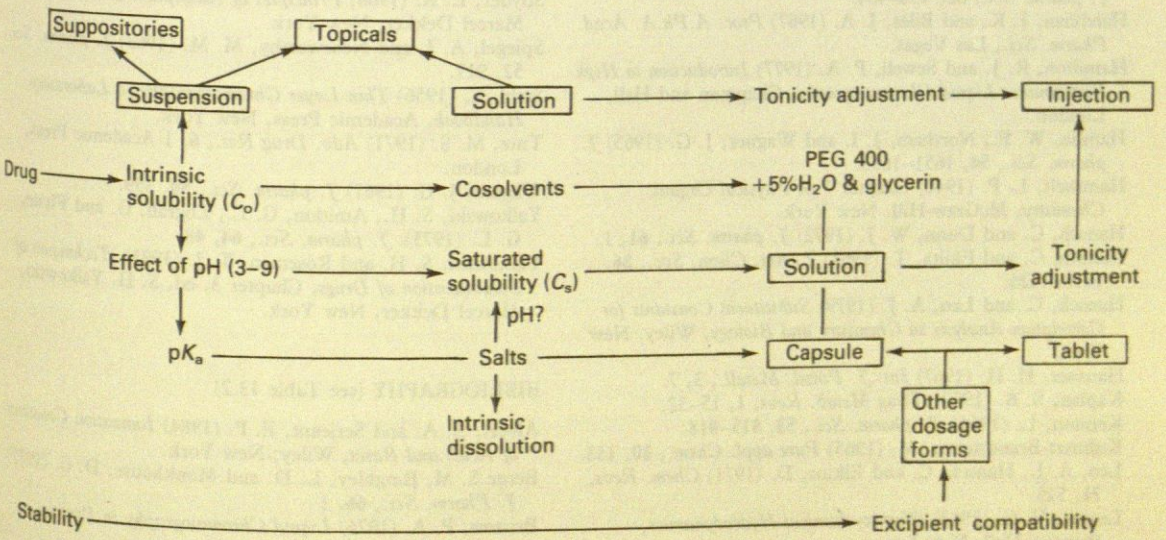


Fig. 13.8 A generic development pathway: the relationship between preformulation and formulation in dosage form development. The formulation stages are shown in boxes and the performulation stages are unboxed

cannot be overemphasized. The availability of sufficient solubility data should allow the selection of the most appropriate salt for development. Stability studies in solution will indicate the feasibility of parenteral, or other liquid, dosage forms and can identify methods of stabilization. In parallel, solid-state stability by DSC., t.l.c. and h.p.l.c. and in the presence of tablet and capsule excipients will indicate the most acceptable vehicles for solid dosage formulations.

Finally, by comparing the physicochemical properties of each drug candidate within a therapeutic group (using $C_s$, $pK_a$, melting point, $K_w^o$) the formulation scientist can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response and advise the bulk chemist about the selection and production of the best salt with appropriate particle size and morphology for subsequent processing.

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# Tablets



## TABLETS AS A DOSAGE FORM

In December 1843 a patent was granted to the Englishman, William Brockedon, for a machine to compress powders to form compacts. This very simple device consisted essentially of a hole (or die) bored through a piece of metal within which the powder was compressed between two cylindrical punches; one was inserted into the base of the die and at a fixed depth, the other was inserted at the top of the die and struck with a hammer. The invention was first used to produce compacts of potassium bicarbonate and caught the imagination of a number of pharmaceutical companies. Later, Wellcome in Britain was the first company to use the term tablet to describe this compressed dosage form. The *British Pharmacopoeia* defines tablets as being circular in shape with either flat or convex faces and prepared by compressing the medicament or mixture of medicaments, usually with added substances. Tablets are now the most popular dosage form, accounting for

some 70% of all ethical pharmaceutical preparations produced. Indeed the importance of tablets as a form of drug administration can be seen from the fact that the *British Pharmacopoeia* (BP) in 1932 included only one tablet monograph (glyceryl trinitrate), which rapidly increased to 82 in the 1953 BP. By 1963 the BP had 183 tablet preparations, and in 1973 this figure had risen to 310 and to 384 in the 1980 edition.

### Advantages of compressed tablets

The compressed tablet has a number of advantages as a dosage form. It enables an accurate dosage of medicament to be administered simply. It is easy to transport in bulk and carry by the patient. The tablet is a uniform final product as regards weight and appearance, and is usually more stable than liquid preparations. The release rate of the drug from a tablet can be tailored to meet pharmacological requirements. Finally, the major advantage of the compressed tablet as a dosage form is that tablets can be mass produced simply and quickly and the resultant manufacturing cost is therefore very much lower when compared with other dosage forms.

### Types of tablet

Several categories of tablet can be distinguished dependent on the mode of use. The commonest type are those intended to be swallowed whole. A less common type of tablet is that formulated to allow dissolution or dispersion in water prior to administration. Many tablets are formulated to be effervescent and have become increasingly wider used in recent years because of their more rapid release of medicament and reduced chance of causing gastric irritation. Some tablets are designed to be chewed and used where buccal absorption is desired. Alternatively they may be intended to dissolve slowly in the mouth, e.g. lozenges or under the tongue (sublingual). There are now available many types of tablets which provide for the release of the drug to be delayed or allow a controlled, sustained rate of release. Many of these preparations are highly sophisticated and are referred to as 'complete drug delivery systems'. Tablets can also be coated so as to protect the drug against decomposition or to disguise or minimize the unpleasant taste of certain medicaments (see Chapter 40 for further details). Coating also enhances the appearance of tablets and makes them more readily identifiable. In addition, coatings can be applied which are resistant to gastric juices but which readily dissolve in the small intestine. These 'enteric' coatings can protect drugs against decomposition in the acid environment of the stomach. The coating process has traditionally involved the application of surface layers of sucrose so as to build up a thick sugar coat around the tablets. This process can take several days. For this reason the spray application of a film of material is now becoming more popular. This film coating technique can be carried out in a coating pan or alternatively in specialized fluidized bed equipment. Compressed coating around a tablet core has also been developed. These compression machines can produce multilayer tablets with different ingredients in each layer, so that potentially incompatible ingredients can be formulated in the same tablet.

### Essential properties of tablets

The major advantage of tablets as a dosage form is that they provide an accurate dosage of medicament. Each tablet must contain a known amount of drug and this must be checked by content uniformity tests. Tablets must also be uniform in weight, appearance and diameter. Another prerequisite of tablets for oral use is that when they are swallowed whole they should readily disintegrate in the stomach. This property represents a great paradox in formulation, since tablets should be produced with sufficient strength to withstand the rigors of processing, coating and packing, yet be capable of rapid breakdown when administered in order to release the drug rapidly. This disintegration involves the bursting apart of the compact by aqueous fluids penetrating the fine residual pore structure of the tablet. These fluids come into contact with tablet components that either swell or release gases and so break apart the intact tablet. Perhaps the most significant property of tablets is that of dissolution rate. The active ingredient must be available pharmacologically

and since drugs cannot be absorbed into the blood stream from the solid state, the active ingredient must first dissolve in the gastric or intestinal fluids before absorption can take place (see Chapter 9 for further discussion). Thus dissolution of the drug from tablets into aqueous fluids is a very important property of solid dosage forms (Chapter 5). Tablets should also be stable to air and the temperature of the environment over a reasonable period of time and, in addition, light and moisture should not affect tablet properties. Finally tablets should be reasonably robust and be capable of withstanding normal patient handling and handling during transport. The formulation of a tablet is thus designed so that the final tablet has all these essential properties.

## TABLET FORMULATION

### Influence of tableting method on formulation

The majority of tablets are not composed solely of the drug. Various materials are usually added that make the powder system more compressible. Indeed powders intended for compression into tablets must possess two essential properties: fluidity and compressibility.

#### *Powder fluidity*

Fluidity is required so that the material can be transported through the hopper of a tableting machine. If adequate fluidity does not exist, this gives rise to 'arching', 'bridging' or 'rat-holing' (see Chapter 36). Fluidity is also essential so that adequate filling of the dies occurs in the tableting machine to produce tablets of a consistent weight. If the powder formulation does not flow satisfactorily, variable die filling will result, which will produce tablets that vary in weight and strength and therefore steps must be taken to ensure that fluidity is maintained. Powder flow can be improved mechanically by the use of vibrators. However, the use of these devices can cause powder segregation and stratification and much care needs to be exercised. A better method to enhance powder fluidity is to incorporate a glidant into the formulation (see later). Materials such as fumed silicon dioxide are excellent flow promoters even in concentrations of less than 0.01%. Another way to improve powder flow is to make the particles as spherical as possible, for example by spray drying or by the use of spheronization machines such as the marumarizor. The most popular method of increasing the flow properties of powders is by granulation. Most powdered materials can be granulated and the improvement in flow can be quite startling. Icing sugar, for example, will not flow, but if it is granulated with water it flows more easily.

#### *Powder compressibility*

Compressibility is the property of forming a stable, intact compact mass when pressure is applied. Paracetamol is poorly compressible whereas lactose compresses well. The physics of powder compression and why some materials compact better than others is a subject on its own and is described in Chapter 39. Much research work is in progress to characterize compaction behaviour but suffice to say that little is known about why some materials compress better than others. It is known, however, that in nearly all cases, granulation improves compressibility.

#### *The need for granulation prior to compression*

Granulation is the process of particle size enlargement of powdered ingredients (see Chapter 37 for details) and is carried out to confer fluidity and compressibility to powder systems. In addition the ideal properties of a granule include the following:

1 When compacted a tablet granulation should confer physical strength and form to the tablets. The granulation should be capable of being subjected to high compression pressures without defects forming.
2 A good granulation should have a uniform distribution of all the ingredients in the formulation.
3 The particle size range of the granulation should be log normally distributed. There should be a small percentage of both fine and coarse particles.
4 Granules should be as near spherical shape as possible and robust enough to withstand handling, without breaking down.

5 The granulation should be relatively dust free thus minimizing powder spread during tableting.

*Tableting methods*

The preparation of tablets can be divided into (a) dry methods and (b) wet methods. Dry methods include direct compression, slugging and roller compaction, and wet methods include wet granulation. The reader is referred to Chapter 39 for details.

*Direct compression*

Dry methods and in particular direct compression are superior to those methods employing liquids, since dry processes do not require the equipment and handling expenses required in wetting and drying procedures and can avoid hydrolysis of water-sensitive drugs. Some drugs, for example aspirin, can be tableted without further treatment, but the vast majority of drugs require the addition of a direct compression vehicle to aid compression. Great interest in direct compression has been evident in recent years and this has resulted in a wide range of direct compression tablet formulations being introduced. A direct compression vehicle is an inert substance which can be compacted with no difficulty and which may do so even when fairly large quantities of drugs are mixed with it. Materials currently available as direct compression diluents may be divided into three groups according to their disintegration properties and their flow characteristics:

1 disintegration agents with poor flow, e.g. microcrystalline cellulose, microfine cellulose and directly compressible starch,
2 free-flowing materials which do not disintegrate, e.g. dibasic calcium phosphate,
3 free-flowing powders which disintegrate by dissolution, e.g. spray-dried lactose, anhydrous lactose, spray-crystallized maltose, dextrose, sucrose, dextrose, mannitol and amylose.

Tablets are produced by mixing the drug with the compression vehicle in a blender. The powder mix is then compressed directly on a tableting machine. The process of direct compression is described in Chapter 39.

Direct compression vehicles should be free flowing, physiologically inert, tasteless, colourless, and have a good mouth feel. Vehicles should also improve the compressibility of poorly compressible drugs, be relatively inexpensive and be capable of being reworked with no loss of flow or compressibility. Finally, direct compression diluents should promote rapid disintegration, be white and able to produce tablets containing a high proportion of non-compressible material (known as *capacity*). In practice, no one single material fulfils all these criteria and it may be necessary to blend two or more compression aids together.

The quantity of medicament which can be mixed with the carrier so that direct compression properties are retained is governed by the capacity of the carrier. The more compressible the active ingredient, the greater the proportion that can be carried successfully by the vehicle. When considering the capacity potential, it is normal to consider the active ingredient as being non-compressible. Generally, unless the drug itself is easily compressible, the amount of drug present is limited to a maximum of about 25% of the tablet weight. Another potential problem with direct compression is static electricity.

The formulation and release of drugs from tablets prepared by direct compression has been extensively investigated. Fox *et al.* (1963) made a detailed study of the tableting properties of microcrystalline cellulose. It was found that extremely hard tablets could be made with ease with no sign of lubrication difficulties. Flowability was very good and tablets exhibited excellent friability and rapid disintegration time. The dissolution of phenobarbitone and prednisone from directly compressed tablets and from tablets prepared by wet granulation was investigated by Kim (1970). It was found that, in general, tablets prepared from soluble direct compression vehicles containing a disintegrant showed faster dissolution times than those prepared by wet granulation. Bolhuis and Lerk (1973) evaluated eleven excipients and found that microcrystalline cellulose and extra fine lactose had the best overall properties.

*Microcrystalline cellulose* (MCC) is perhaps the most widely used direct compression excipient. It exhibits the highest capacity and compressibility of all known direct compression vehicles (Mendell,

1972), however, its flow properties are relatively poor. MCC is chemically an inert material and is compatible with most drugs. Its high initial moisture content and its hygroscopicity may preclude its use with very moisture-sensitive drugs. However, there is some evidence that MCC may in fact stabilize drugs susceptible to hydrolysis, by perhaps acting as a moisture scavenging agent (Sixsmith, 1976). This has been demonstrated for ascorbic acid and aspirin. It has been reported that MCC has a specific stabilizing effect on nitroglycerine tablets (Richman *et al.*, 1965). It was later found by Goodhart *et al.* (1976), after a very comprehensive study, that nitroglycerine tablets formulated with MCC produced tablets with superior stability and more uniform content than tablets prepared by the popularly used moulded technique.

Another popular direct compression excipient is *dibasic calcium phosphate*, a comparatively cheap insoluble diluent with good flow properties. Khan and Rhodes (1972a, b) and Khan and Rooke (1976) have examined its compressional, disintegration and dissolution properties in the presence of various disintegrants. They have shown that a cationic ion exchange resin and sodium starch glycollate are effective disintegrants for dibasic calcium phosphate system even at low concentration. Dibasic calcium phosphate is slightly alkaline, so must not be used where the active ingredient is sensitive to pH values of 7.3 or above. Shah and Arambulo (1974) have shown from accelerated stability tests that dibasic calcium phosphate (Emcompress) was probably unsuitable for ascorbic acid and thiamine hydrochloride, since deteriorating crushing strength and disintegration properties resulted as well as chemical degradation in the case of ascorbic acid. Calcium salts in general have been shown to adversely effect the absorption properties of several drugs including tetracycline and they should not, therefore, be coformulated. Khan and Rhodes (1976) have shown that for directly compressing griseofulvin, dicalcium phosphate yielded tablets of better weight uniformity than MCC. Direct compression formulations of ampicillin have been successfully produced by Niazi *et al.* (1976) and shown to be better than similar tablets produced by moist granulation.

*Dry granulation*

Granulation by compression or slugging is one of the dry methods which has been used for many years for moisture- or heat-sensitive ingredients. The blend of powders is forced into dies of a large heavy-duty tableting press and compacted. The compacted masses are called 'slugs'. An alternative technique is to squeeze the powder blend into a solid cake between rollers. This is known as *roller compaction*. The slugs or roller compacts are then milled and screened in order to produce a granular form of tableting material which flows more uniformly than the original powder mix. These processes are described in more detail in Chapters 37 and 39.

Slugging has the advantage over direct compression in that once the slugs are formed, no segregation of drug and excipient can occur. In addition the method is useful for hydrolysable and thermolabile drugs. Although used, slugging is a lengthy process and involves a relatively high capital investment since heavy-duty presses are expensive. Compared with other granulation processes, the throughput is slow.

The effect of various tablet formulations and processing factors on the rate of dissolution of salicylic acid tablets prepared by slugging was investigated by Levy *et al.* (1963). It was found that the dissolution rate increased with decreasing granule size and starch content of the granules. Increasing the slugging pressure of granules caused an increase in dissolution rate due to fracturing of the harder granules into smaller particles with greater specific surface area. Langridge and Wells (1980) have recently shown that precompression or slugging of a mixture of microcrystalline cellulose and dicalcium phosphate dihydrate significantly reduced compressibility of both excipients. Although slugging is one of the oldest and most widely used processes for tableting, it has received very little scientific attention.

*Wet granulation*

Tableting by the wet granulation process is the most widely used method for pharmaceutical materials. The technique involves a number of

stages which are described in detail in Chapter 39. The wet granulation process has a number of advantages over the other granulation methods but it is not readily suitable for hydrolysable and/or thermolabile drugs such as antibiotics. During the development of a tablet formulation, all the physical variables which can affect the resultant granules have to be considered also so as to minimize the effect of process variation on the quality of the final product.

***Influence of granulation media*** In wet granulation, the binder is normally incorporated as a solution or mucilage. The choice of the liquid phase will depend upon the properties of the materials to be granulated. *Water* is the most widely used binder vehicle but non-aqueous granulation using *isopropanol*, *ethanol* or *methanol* may be preferred if the drug is readily hydrolysed. Changes in drug solubility resulting from a change in solvent have been shown by Wells and Walker (1983) to affect granule strength due to solute migration.

In wet granulation, granule growth is initiated by the formation of liquid bridges between primary particles (see Chapter 37). Soluble excipients will dissolve in the binder solution to increase the liquid volume available for wet granulation, consequently granules of large mean size are formed. The soluble components recrystallize on drying to form a greater number of solid bridges. If one of the components absorbs water, this reduces the volume of binder liquid available to form wet granules and so smaller granules will result (Jaiyeoba and Spring, 1980). Thus the choice of binder vehicle can affect the characteristics of the dry granules.

***Influence of binder concentration and volume*** Techniques of binder addition to powders include the incorporation of a concentrated binder solution followed by additional fluid, which maintains a standard binder content. Shubair and Dingwall (1976) studied the rate of release of erythrosine from lactose tablets without disintegrant or lubricant. It was found that release rate was inversely related to starch binder content. Release rates decreased progressively from 2 to 10% w/w mucilage, but an unexpected rapid release followed use of 20% w/w starch mucilage. Further research did not indicate that poor binder distribution gave a complete explanation, since addition of water to dilute the 20% w/w mucilage to 10% w/w did not reduce the dissolution rate. Therefore the method of incorporation of the binder may also have an effect on drug release. The effect of increasing the volume of binder fluid used to granulate blends of lactose and boric acid, has been investigated by Opakunle and Spring (1976). Increasing the volume of binder fluid produced stronger granules, thought to be due to the formation of more binder bonds and the presence of more recrystallized bridges. Thus the amount of binder fluid must be very closely controlled in order to produce granules of a consistent hardness.

## Tablet excipients

A tablet does not just contain the active ingredient but also includes other substances, known as excipients, which have specific functions. The various classes of excipients which are normally incorporated into tablet formulations are discussed here.

### *Diluents*

Diluents or 'bulking agents' are 'inert' substances which are added to the active ingredient in sufficient quantity to make a reasonably sized tablet. This agent may not be necessary if the dose of the drug per tablet is high. Generally, a tablet should weigh at least 50 mg and therefore very low dose drugs will invariably require a diluent to bring the overall tablet weight to at least 50 mg. The principal substance employed as a diluent is *lactose*. It has a pleasant taste, rapidly dissolves in water, absorbs very little moisture and is fairly neutral in reaction. Its main disadvantage is that it is somewhat expensive and has poor flow characteristics. Lactose deforms easily under pressure and, as a result of this ductility, good tablets are normally produced. The spray-dried form of lactose flows much more readily and is used as a direct compression vehicle. *Dicalcium phosphate* is another diluent that is used extensively as a tablet diluent. It is insoluble in water and makes good hard, white granules. It absorbs even less moisture than lactose and is therefore used with hygro-

scopic drugs such as pethidine hydrochloride. The *starches* are used as diluents and as binding agents. They are available as finely divided powders and aid the disintegration process. Starches contain up to 14% moisture and can therefore lead to stability problems for a moisture-sensitive drug. Another very popular diluent is *microcrystalline cellulose*. This substance is supplied as a free-flowing ingredient and is normally used as a direct compression vehicle. It has disintegrating properties and requires less lubricant in the formulation than other diluents. *Dextrose* has been used as a bulking agent, but the granules produced are much softer and not very white. In addition, dextrose absorbs moisture. *Sucrose* is very hygroscopic and goes sticky on exposure to moisture. Its pleasant taste makes it especially useful in lozenges. *Mannitol* is another sugar which, although expensive, is very quick dissolving and is therefore used for tablets that have to be dissolved, e.g. glyceryl trinitrate tablets. Since it has a negative heat of solution, it is used for chewable tablets because it imparts a pleasant taste and a cooling sensation when sucked or chewed. Table 18.1 summarizes the commonly used diluents.

**Table 18.1** Tablet diluents used in the wet granulation process

| *Diluent* | *Comments* |
|---|---|
| Dextrose | Hygroscopic |
| Dicalcium phosphate | Inexpensive, insoluble in water |
| α-Lactose BP | Inexpensive, relatively inert; the most frequently used diluent |
| Mannitol | Freely soluble; used particularly for chewable tablets |
| Microcrystalline cellulose | Excellent compression properties; has some disintegrating ability |
| Sodium chloride | Freely soluble; used for solution tablets |
| Sucrose | Sweet taste but hygroscopic; may be diluted with lactose |

Courtesy of N. A. Armstrong.

### *Adsorbents*

Adsorbents are substances included in a formulation that are capable of holding quantities of fluids in an apparently dry state. Oil-soluble drugs, fluid extracts or oils can be mixed with adsorbents and then granulated and compressed into tablets. *Fumed silica*, *microcrystalline cellulose*, *magnesium carbonate*, *kaolin* and *bentonite* are examples of adsorbents commonly employed.

### *Moistening agents*

In wet granulation, a moistening agent is required which is usually *water*. If the formulated powder contains sucrose, for example, it may only be necessary to add water, since sucrose rapidly dissolves and acts as its own binding agent. In cases where water cannot be used because the drug is hydrolysed, then alcohol is often substituted. Absolute alcohol is expensive and thus *industrial methylated spirits* is used. Care must be taken to remove all traces of the solvent during drying or the tablets will possess an alcoholic odour. *Isopropyl alcohol* is an alternative moistening agent. It is difficult, however, to remove the last traces from granules and it possesses an objectionable odour.

### *Binding agents (adhesives)*

The substances that act as adhesives to bind powders together in the wet granulation process are known as binders. They also help to bind granules together during compression. If too little binding agent is included in a formulation, soft granules result. Conversely, too much binding agent produces large, hard granules.

Binding agents can be added in two ways depending on the method of granulation:

1 as a powder in the formulation as in 'slugging' or in dry granulation methods,
2 as a solution to the mixed powders as in wet granulation.

There are not many examples of (1) since most substances require some moisture present to make them adhesive.

Common binding agents include starch mucilage and gelatin solution. *Starch* is a good and popular binder and needs to be present in an amount equal to 2%. It is incorporated as a mucilage in water. When dry, the starch binder is insoluble in water, unlike gelatin which remains soluble in the dry state. *Gelatin* is often used as a binder in lozenges. Among the other most

important binders is *polyvinylpyrrolidone* (PVP). This substance is soluble both in water and in alcohol and has been shown to release drugs faster than with other binders. Rubinstein and Rughani (1978), using four binders in a tablet formulation of frusemide, showed how the choice of binder affects dissolution rate. They observed $t_{50}$ values between 3.65 minutes with PVP to 117 minutes with starch mucilage. Other less common binders include *hydrolysed gelatin*, derivatives of seaweed (such as *alginic acid*, *sodium alginate* and calcium alginate) and cellulose derivatives (in particular *ethyl cellulose* and *hydroxypropylmethylcellulose*).

Common binders used in the wet granulation process are listed in Table 18.2.

**Table 18.2** Adhesives (binders) used in the wet granulation process

| *Adhesive* | *Concentration in granulating fluid (% w/v)* | *Comments* |
|---|---|---|
| Acacia mucilage | up to 20 | Yields very hard granules |
| Gelatin | 5–20 | Forms gel in cold, therefore warm solution used; strong adhesive, often used in lozenge granules |
| Glucose | up to 50 | Strong adhesive; hygroscopic, so tablet may weaken in humid conditions |
| Polyvinyl pyrrolidone (PVP) | 2–10 | Soluble in water and in some organic solvents; therefore can be used for anhydrous granulation |
| Starch mucilage | 5–10 | Often used warm; a very commonly used adhesive |
| Sucrose | up to 70 | Hygroscopic; tablets may harden on storage |

Courtesy of N. A. Armstrong.

### *Glidants*

Glidants are materials which are added to tablet formulations in order to improve the flow properties of the granulations. They act by reducing interparticulate friction. The most commonly used and effective glidant is *fumed* (or *colloidal*) *silica*. Flow of granules can be dramatically improved by the addition of less than 0.1% w/w of this material to powders and granules. Fumed silica is thought to act by lodging in the surface irregularities of the particles or granules, which effectively smooths the particle surface.

### *Lubricants*

These agents are required to prevent adherence of the granules to the punch faces and dies. They also ensure smooth ejection of the tablet from the die. Many lubricants also enhance the flow properties of the granules. Talc and magnesium stearate appear to be more effective as punch lubricants than stearic acid, which is more effective as a die lubricant.

*Magnesium stearate* is the most popular lubricant used and is normally effective on its own as both a die and a punch lubricant. It is incorporated by blending with the dry granules prior to compression, up to a concentration of about 1% w/w. A thin layer of magnesium stearate around the granule is just as effective as a thick layer from the lubrication point of view, but increased magnesium stearate quantities reduce the disintegration time, retard drug dissolution and also reduce the bonding forces between granules to produce soft tablets. The reduction in drug release properties is due to the hydrophobic nature of magnesium stearate preventing drug dissolution. It has been shown (Bolhuis *et al.*, 1975) that the extent of mixing time greatly affects the distribution of magnesium stearate around the tablet granules. An increase in mixing time produces a more uniform distribution of lubricant, but adversely affects tablet hardness and dissolution. For many drugs, magnesium stearate is chemically incompatible (e.g. aspirin) and therefore *talc* or *stearic acid* is often used. Microcrystalline cellulose requires less lubricant for effective lubrication of granules, since to some extent it acts as its own lubricant.

Table 18.3 lists the commonly used tablet glidants and lubricants.

### *Disintegrating agents*

Disintegrants are always added to tablets to promote breakup of the tablets when placed in an

**Table 18.3** Commonly used tablet glidants and lubricants

| *Substance* | *Lubricant or glidant* | *Concentration in tablet (% w/w)* | *Comments* |
|---|---|---|---|
| Stearates, e.g. magnesium, calcium, stearic acid | Lubricant | 0.25–1 | Reduce tablet strength; prolong disintegration; insoluble in water; excellent lubricant properties; magnesium stearate is very widely used |
| Talc | Lubricant and glidant | 1–2 | Insoluble but not hydrophobic; only a moderate lubricant |
| Polyethylene glycol | Lubricant | 2–5 | Molecular weights 4000–6000; soluble in water; moderately effective |
| Liquid paraffin | Lubricant | up to 5 | Dispersion problems; inferior to stearates |
| Sodium lauryl sulphate | Lubricant | 0.5–5 | Moderate lubricant with wetting properties; often used in conjunction with stearates |
| Colloidal silica | Glidant | 0.1–0.5 | Excellent glidant |
| Starch | Glidant | 2–10 | Primary function is that of a disintegrant |
| Magnesium lauryl sulphate | Lubricant | 1–2 | Water soluble |

Courtesy of N. A. Armstrong.

aqueous environment. The object of a disintegrant is to cause the tablet to disintegrate rapidly so as to increase the surface area of the tablet fragments and so promote rapid release of the drug. Wagner (1969) proposed a scheme which related tablet breakup to drug dissolution and absorption (Fig. 18.1) which had been referred to previously in Chapter 9. Release rate of the drug is greater from disintegrated particles than from the intact tablet or tablet fragments. Thus, a good disintegrant will quickly break up a tablet into primary particles and ensure that the drug is assimilated at a fast rate. The disintegration test, which is included in all pharmacopoeias, measures the time it takes for a tablet to break down and pass through a standard screen.

Disintegrants can act by swelling in the presence of water to burst open the tablet. Starch is the commonest disintegrant in tablet formulation and is believed to act by swelling. However, other effective disintegrants do not swell in contact with water and the mechanisms by which disintegrants act is the subject of some controversy. It is believed that disintegrants that do not swell exert their disintegrating action by capillary action. Liquid is drawn up through capillary pathways within the tablet and ruptures the interparticulate bonds. This action serves to break the tablet apart. Lowenthal (1973) has discussed in detail the various mechanisms of disintegration.

*Starch* can be incorporated in many ways into a formulation. For example, all the starch can be added to the other ingredients and the homogenous mix wet granulated. Alternatively, about two-thirds of the starch can be added before wet granulation and the remainder added in dry form to the dried granules. Starch can be added in dry form all at once to the dried granules. This last method is not popular because too much starch between the granules inhibits bonding, with the result that a soft tablet is produced. The advantage of incorporating some of the starch outside the dry granules, is that the disintegration time is improved in tablets possessing water repellant drugs, since the surrounding starch acts as a pathway for water penetration into the tablet and for the pushing apart of granules due to the expansion of a localized high concentration of starch.

Other common disintegrants include *cation exchange resins* (Amberlite IRP 88), *cross-linked polyvinylpyrrolidone* (Polyplasdone XL), *modified starches* (sodium starch glycollate) and *cellulose materials* (Avicel) (see Table 18.4).

## Specific formulation requirements of other compressed dosage forms

### *Lozenges*

Lozenges are compressed tablets, usually at least 18 mm in diameter, which do not contain a disin-

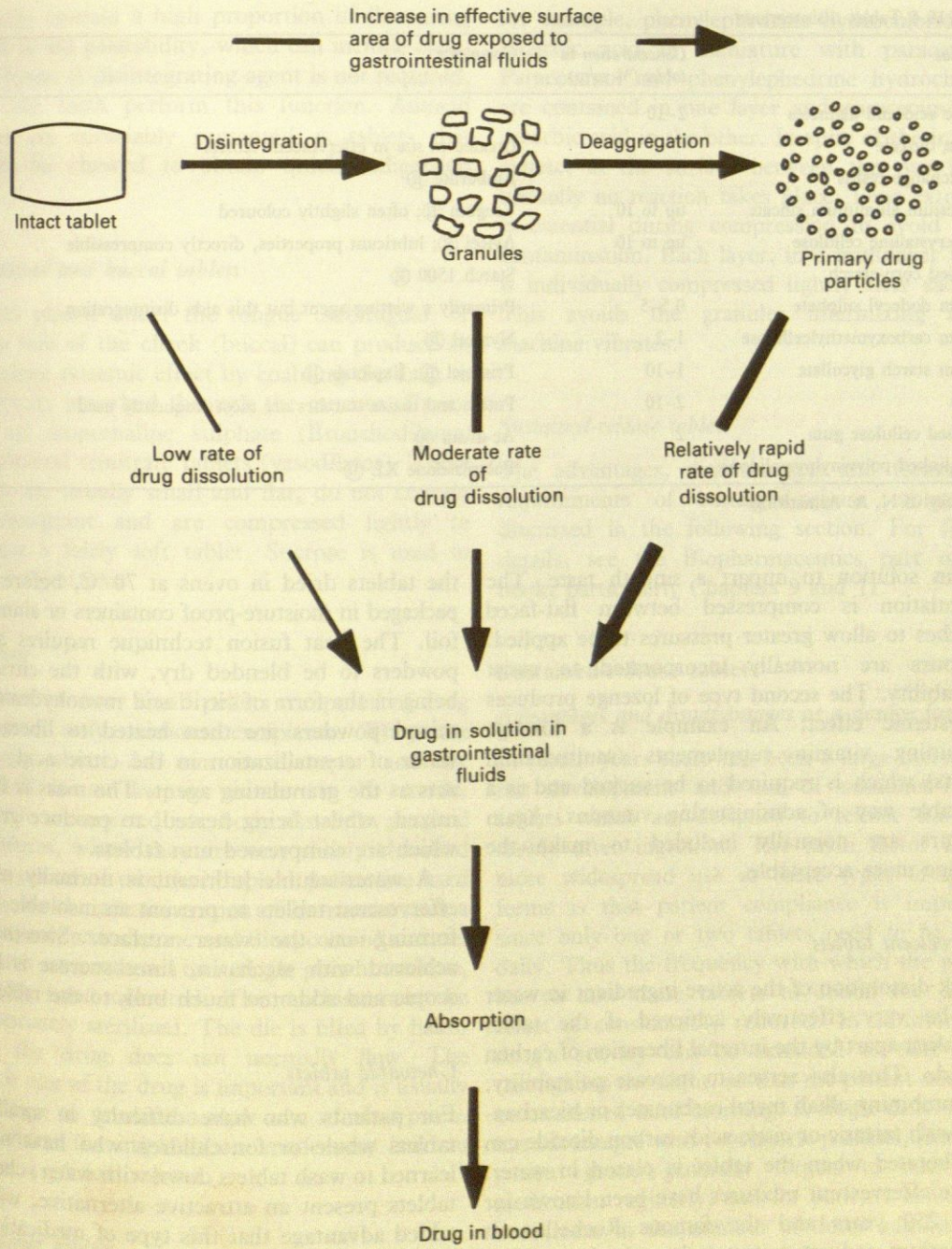


Fig. 18.1 Diagrammatic representation of the disintegration and dissolution steps prior to absorption of a poorly soluble drug from a tablet. (After Wells and Rubinstein, 1976)

tegrant and which are sucked to dissolve in the mouth. Generally there are two types, depending on the required action. The first type produces a local effect in the mouth or throat. Usually this type of lozenge contains an antiseptic (e.g. benzalkonium) or antibiotic. These lozenges must be palatable and slowly soluble. The formulation thus contains some sucrose in fine powder, lactose and

**Table 18.4** Tablet disintegrants

| *Material* | *Concentration in tablet (% w/w)* | *Comments* |
|---|---|---|
| Alginic acid and alginates | 2–10 | |
| Carbon dioxide | | Created *in situ* in effervescent tablets |
| Ion exchange resins | | Amberlite ® |
| Magnesium aluminium silicate | up to 10 | Veegum ®; often slightly coloured |
| Microcrystalline cellulose | up to 10 | Avicel ®; lubricant properties, directly compressible |
| Modified corn starch | | Starch 1500 ® |
| Sodium dodecyl sulphate | 0.5–5 | Primarily a wetting agent but this aids disintegration |
| Sodium carboxymethylcellulose | 1–2 | Nymcel ® |
| Sodium starch glycollate | 1–10 | Primojel ®; Explotab ® |
| Starch | 2–10 | Potato and maize starches are most frequently used |
| Modified cellulose gum | 2 | Ac-di-sol ® |
| Cross-linked polyvinylpyrrolidone | | Polyplasdone XL ® |

Courtesy of N. A. Armstrong.

gelatin solution to impart a smooth taste. The formulation is compressed between flat-faced punches to allow greater pressures to be applied. Flavours are normally incorporated to assist palatability. The second type of lozenge produces a systemic effect. An example is a lozenge containing vitamin supplements (multivitamin tablets) which is required to be sucked and is a palatable way of administering vitamins. Again flavours are normally included to make the lozenge more acceptable.

### *Effervescent tablets*

Quick dissolution of the active ingredient in water can be very effectively achieved if the tablet is broken apart by the internal liberation of carbon dioxide. This also serves to increase palatability. By combining alkali metal carbonates or bicarbonates with tartaric or citric acid, carbon dioxide can be liberated when the tablet is placed in water. These effervescent mixtures have been known for over 250 years and the famous Rochelle salt (potassium sodium tartrate) dates back to 1731. Effervescent tablets can be produced by wet fusion and heat fusion. With the wet fusion technique, citric acid is moistened and added to sodium bicarbonate and granulated in a suitable mixer, the moist citric acid acting to partially fuse the powders. The granules are then tableted and the tablets dried in ovens at 70 °C, before being packaged in moisture-proof containers or aluminium foil. The heat fusion technique requires all the powders to be blended dry, with the citric acid being in the form of citric acid monohydrate. The mixed powders are then heated to liberate the water of crystallization in the citric acid, which acts as the granulating agent. The mass is further mixed, whilst being heated, to produce granules which are compressed into tablets.

A water-soluble lubricant is normally used in effervescent tablets to prevent an insoluble 'scum' forming on the water surface. Sweetness is achieved with saccharin, since sucrose is hygroscopic and adds too much bulk to the tablets.

### *Chewable tablets*

For patients who have difficulty in swallowing tablets whole or for children who have not yet learned to wash tablets down with water, chewable tablets present an attractive alternative, with the added advantage that this type of medication can be taken at any time or place when water is not available. Mannitol is normally used as a chewable base diluent, since it has a pleasant, cooling sensation in the mouth and can mask the taste of some objectionable medicaments.

Chewable tablets are prepared by wet granulation. The granules should not be too hard and

normally contain a high proportion of flavouring agents to aid palatability, which can include chocolate bases. A disintegrating agent is not required, since the teeth perform this function. Antacid tablets are invariably presented as tablets that should be chewed to obtain quick indigestion relief.

*Sublingual and buccal tablets*

Tablets placed under the tongue (sublingual) or in the side of the cheek (buccal) can produce an immediate systemic effect by enabling the drug to be directly absorbed through the mucosa. Examples are isoprenaline sulphate (Bronchodilator) and glyceryl trinitrate tablets (vasodilator). These tablets are usually small and flat, do not contain a disintegrant and are compressed lightly to produce a fairly soft tablet. Sucrose is used to impact sweetness.

*Implants*

Implants are very small pellets composed of drug substance only without excipients. They are normally about 2–3 mm in diameter and are prepared in an aseptic manner to be sterile. Implants are inserted into body tissues by surgical procedures, where they are very slowly absorbed over a period of months. Implant pellets are used largely for the administration of hormones such a stilboestrol, testosterone and dioxycortone acetate. Implants are produced on a single punch machine, normally hand operated. The machine must be appropriately sterilized. The die is filled by hand, since the drug does not normally flow. The particle size of the drug is important and is usually kept large to produce a slow rate of absorption. In addition the implants are made very hard to achieve a gradual release.

*Multilayer tablets*

A multilayer tablet consists of several different granulations that are compressed, on top of each other, to form a single tablet composed of two or more layers. Each layer is fed from a separate feed frame with individual weight control. Multilayer tablets are mainly used for incompatible substances, for example, phenylephedrine hydrochloride and ascorbic acid in admixture with paracetamol. Paracetamol and phenylephedrine hydrochloride are contained in one layer and paracetamol and ascorbic acid in the other. In spite of the intimate contact at the surface between the two layers, virtually no reaction takes place. Dust extraction is essential during compression to avoid cross-contamination. Each layer, in a multilayer tablet, is individually compressed lightly after each fill. This avoids the granules intermixing if the machine vibrates.

*Sustained-release tablets*

The advantages, disadvantages and formulation requirements of sustained-release tablets are discussed in the following section. For further details, see the Biopharmaceutics part of this book, particularly Chapters 9 and 11.

## Sustained-release tablets

*Advantages and disadvantages as a dosage form*

In recent years there has been a large increase in the development and use of sustained-release tablets which are designed to release the drug slowly after ingestion. The main factor in the more widespread use of these types of dosage forms is that patient compliance is improved, since only one or two tablets need to be taken daily. Thus the frequency with which the patient has to take these tablets to obtain the desired effect is considerably reduced. In addition, the drug's activity can be extended to take effect throughout the night, so that the patient need not be awakened until morning. A single daily dosage has advantages with psychiatric patients, since this patient group generally forgets to take their medication regularly, and for patients in hospital a decrease in the number of doses administered can result in a time saving for nurses. Another advantage sometimes expressed for sustained-release tablets is that this type of medication reduces the severity or frequency of untoward side effects. Aspirin, for example, has been shown to produce less gastric bleeding when formulated as a sustained-release formulation than conventional

aspirin preparations (Treadwell *et al.* 1973). Generally, a sustained-release tablet produces a more constant blood level of drug than repeated doses of a conventional tablet and this may be clinically very significant (see Chapter 11). Aminophylline has a very narrow therapeutic blood level range and many daily dosages must be given in order that the correct therapeutic blood level can be maintained. In practice, this means that conventional tablets must be administered at precise time intervals, which is very inconvenient for the patient. Formulating aminophylline as a sustained-release tablet has resulted in a 12-hourly dosage regimen and the constant blood level that has been achieved has reduced the incidence of toxicity due to blood level peaking. Thus a more efficient utilization of the drug in the body can be effected with some sustained-release formulations.

Although there is no doubt that sustained-release tablets have many advantages to the patient, there are disadvantages with this type of medication. The cost of prolonged action tablets is more per unit dose than conventional dosage forms. Some drugs, such as riboflavin and ferrous sulphate, are more efficiently absorbed in particular regions of the gastrointestinal tract and therefore sustained-release tablets are not very useful, because they release the drug throughout the intestinal tract. Accidental poisoning with sustained-release dosage forms does present special treatment problems not seen with conventional oral tablets. The slow release of the drug into the gastrointestinal tract and its extended absorption, often results in slow clearance of drug from the body. The physical size of the dosage form may present problems. Some patients do experience difficulty in swallowing a 600–650 mg sustained-release tablet and it is often difficult to formulate the tablets so that the overall tablet weight is very much lower than this. In isolated cases, large tablets have been reported lodged in the oesophagus. Sustained-release tablets of potassium chloride have been known to cause ulceration due to delayed gastrointestinal transit time (McCall, 1975). Variability of absorption can be a troublesome problem with sustained-release tablets. After ingestion the tablet should release quantities of drug at much later times to maintain drug absorption over an extended period. This involves a triggering mechanism and the mechanism may exist in the dosage form itself or in the gastrointestinal tract of the patient. Sustained-release tablets can fail because poor formulation can result in all the drug being released at once, or they fail because inconsistent amounts of drug are released. It has been known for sustained-release tablets to be recovered from the faeces of some subjects.

### *Types of sustained-release tablets*

Attempts have been made to classify sustained-release dosage forms according to their mode of release or the blood level–time profiles that they produce. These differences are discussed in Chapter 11. Suffice it to say here that the BNF presently refers to all such preparations as 'sustained release'.

### *Formulation of sustained-release tablets*

Sustained-release tablets can consist of two parts: an immediately available dose and a sustaining part, containing many times the therapeutic dose, for protracted blood drug levels. The immediately available dose is normally directly added to the sustaining part of the tablet or alternatively is incorporated in the tablet coating with the sustaining portion in the core of the tablet. The heart of the system resides with the sustaining portion of the tablet and various methods have been used to retard drug release.

### *Methods of achieving sustained-release*

***Diffusion-controlled release*** Diffusion entails the movement of drug molecules from a region of high concentration in the tablet to one of a lower concentration in the gastrointestinal fluids. The rate at which diffusion occurs will depend upon the surface area, the diffusional pathway, the drug concentration gradient and the diffusion coefficient of the system. In any one dosage form these factors will be kept constant so that a predetermined diffusion rate of drug out of the tablet will be achieved. In practice, diffusion-controlled release can be produced by formulating the drug

in an insoluble matrix. The gastrointesinal fluids penetrate the matrix and drug diffuses out of the matrix and is absorbed. Alternatively, the drug particles can be coated with a polymer coat of defined thickness. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of fluid into the surrounding liquid. In both cases a constant concentration of drug and a constant area of diffusion, together with a constant diffusional pathway, are essential to achieve a constant drug release rate.

With matrix tablets the initial dose is normally placed in the coat of the tablet. The coat and the matrix can be tableted together by compression coating or the coat can be applied using a coating pan or air-suspension technique. In non-coated systems the initial dose is normally tableted with the matrix granulation. Matrices can be compoed of polymeric materials such as methylcellulose or insoluble plastic inert substances such as methyl methacrylate. Higuchi (1962) found that for matrix tablets a plot of the square root of time against amount of drug released produced a straight line and this square root plot is often used to record the dissolution rate of matrix tablets.

***Dissolution-controlled release*** Dissolution can be employed as the rate-limiting step in sustained-release tablets. Drugs with poor dissolution rates are inherently prolonged, but with water-soluble drugs it is possible to incorporate a water-insoluble carrier into the tablet formulation to reduce dissolution. Prolonged drug action can also be achieved by leaving out the disintegrating agent in the tablet formulation. Encapsulated drug products also utilize dissolution to control release. With these products, individual drug particles or granules are coated with a slowly soluble coating material such as polyethylene glycol of varying thickness. The time required for dissolution of the coat is proportional to the coating thickness. The coated particles can be compressed directly into tablets. A pulsed dosing effect is obtained by tableting a small number of different thickness coated particles or more usually by utilizing a spectrum of different thickness coatings.

***Release controlled by ion exchange*** Ion exchange materials are water-insoluble resinous materials containing salt-forming groups. Either anionic or cationic groups can be used to produce the desired ion exchange resin. The drug-charged resin is prepared by mixing the resin with drug solution, then washing to remove contaminant ions and then dried to form beads or particles which are tableted. Drug release is achieved in the presence of a high concentration of appropriately charged ions in the gastrointestinal tract; the drug molecule is exchanged and diffused out of the resin to the gastrointestinal fluids. The method is attractive because it relies only on the ionic environment of the resin and not on pH, enzyme content, etc. at the absorption site. The main disadvantage with this type of sustained-release product is that whereas in theory the ionic content of the gastrointestinal tract should remain constant, in practice the ionic content varies with diet and water content, and therefore variable drug release results.

***Release controlled by osmotic pressure*** With this technique, a semipermeable membrane is placed around a tablet or drug particle which allows transport of water into the centre of the tablet by osmosis. As a result of increased internal pressure, drug solution is then pumped out of the tablet through a small hole in the tablet coating. The delivery rate is contant provided that excess drug is present inside the tablet but rapidly declines parabolically to zero once the concentration drops to below saturation. The size of the delivery orifice is very important and this is bored with the use of a laser beam. Since the mechanism is based on osmotic pressure, the system delivers drug at a rate independent of stirring rate and environment pH, factors which make this system an attractive proposition for prolonged drug release from the gastrointestinal tract.

## FORMULATION FACTORS AFFECTING THE RELEASE OF A DRUG FROM TABLETS

### The effective surface area of the drug

The dissolution rate of a drug is directly related to the surface area exposed to the dissolution media. In order therefore to increase the dissolution rate for a given amount of drug, the effective surface area has to be increased. This can

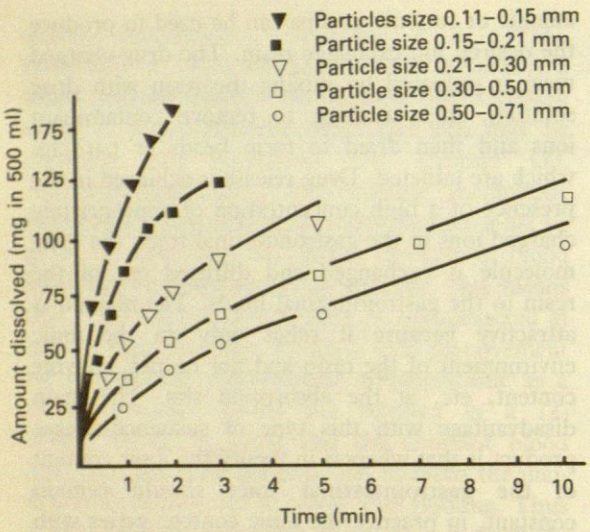


**Fig. 18.2** Effect of particle size of phenacetin on dissolution rate. (Finholt, P. (1974) Influence of formulation on dissolution rate. In *Dissolution Technology*, L. J. Leeson and J. T. Carstenson, eds, pp. 106–146, Academy of Pharmaceutical Science, American Pharmaceutical Association, Washington, DC).

simply be accomplished by decreasing the particle size of the drug. See earlier discussion under 'Disintegrating agents' and Fig. 18.1.

Figure 18.2 clearly depicts this phenomenon. For the five size ranges examined, the amount of drug dissolving increases as the particle size decreases and surface area increases. However, if the drug is hydrophobic a reduction in particle size may produce a smaller effective surface area and a reduction in dissolution rate. Many *in vivo* studies have also demonstrated the importance of the effective surface area of drug particles. Figure 18.3 shows the effect of administering three different particle sizes of phenacetin on the plasma levels of healthy adult volunteers. Both the rate and extent of phenacetin availability increase as particle size decreases. The effect of particle size reduction on the bioavailability of nitrofurantoin in shown in Fig. 18.4. The microcrystalline form, particle size less than 10 $\mu$m, is more rapidly and completely absorbed from tablets than is the macrocrystalline form (74–177 $\mu$m) from capsules.

## Effect of binding agents

Binding agents are incorporated into tablets during granulation in order to improve the flowability of the drug and to enhance compressibility. These agents coat the drug particles and therefore the rate of solution of the binder in water can determine the release rate from the tableted drug.

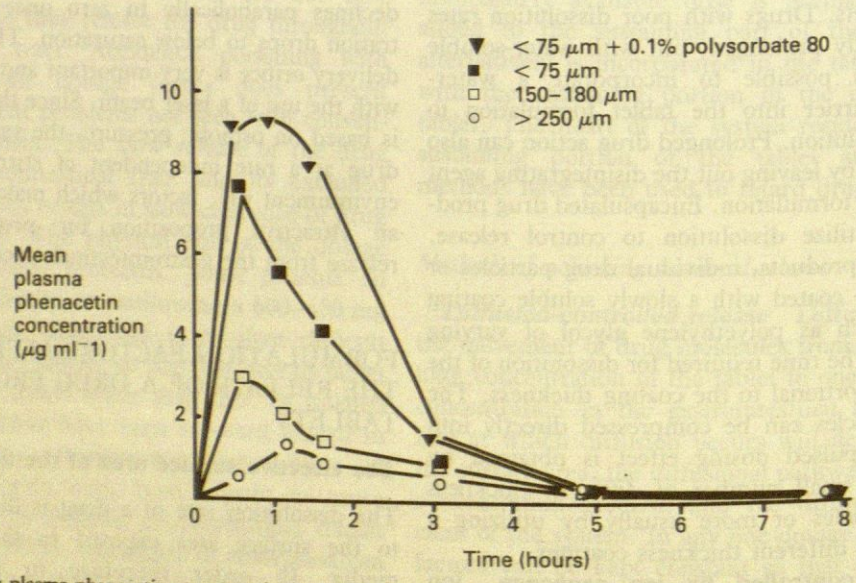


**Fig. 18.3** Mean plasma phenacetin concentration in six adult volunteers following administration of 1.5 g doses (Prescott, L. F., Steel, R. F. and Ferrier, W. R. (1970) The effect of particle size on the absorption of phenacetin in man. *Clin. Pharmac. Ther.*, **11**, 496–504)

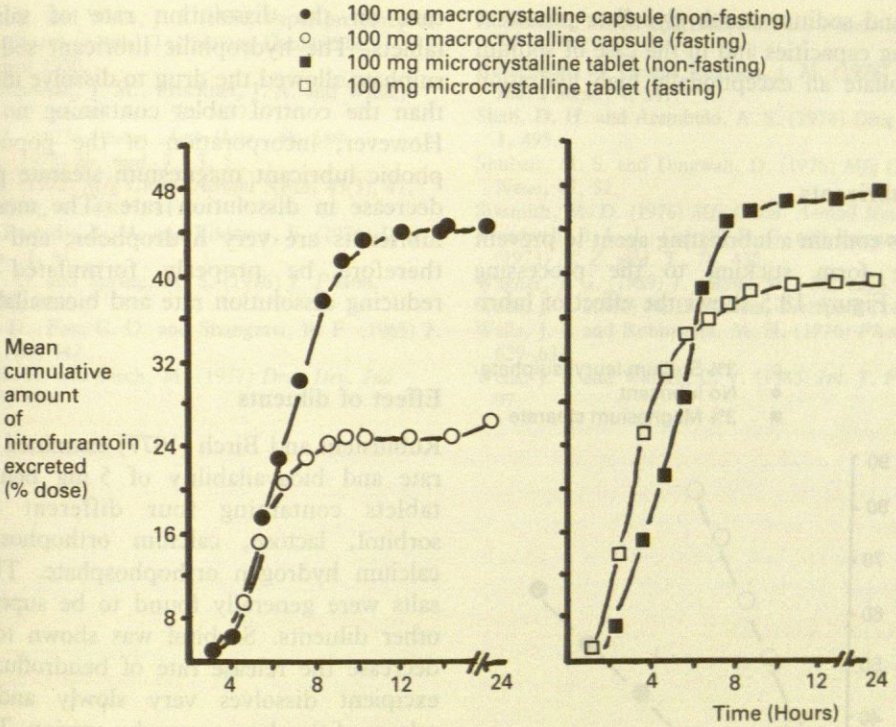


Fig. 18.4 Mean cumulative urinary excretion of nitrofurantoin after oral administration of a 100 mg capsule or tablet. (Bates, T. R., Sequeria, J. A. and Tembo, A. V. (1974) Effect of food on nitrofurantoin absorption. *Clin. Pharmac. Ther.*, **16**, 63–68

Wells (1980) measured the dissolution rates of chlorpropamide tablets containing starch, hydrolysed gelatin, methylhydroxyethylcellulose (MHEC) and polyvinylpyrrolidone (PVP) as binders. It was found that tablets containing soluble binders (hydrolysed gelatin and PVP) had rapid dissolution rates whereas slow and incomplete disintegration of tablets formulated with starch paste led to protracted release of drug. MHEC produced macrogranular breakdown which gave rise to very slow release rates.

### Effect of disintegrants

In order for a drug to be released rapidly from a solid dosage form, the tablet or capsule must disintegrate quickly to liberate a large effective surface area of drug to the dissolving medium. Disintegrants act by either bursting open the tablet and/or by promoting the rapid ingress of water into the centre of the tablet or capsule. In many cases capillarity and therefore the rate of water penetration predominates in causing disruption. Wells (1980) has found that chlorpropamide tablets containing sodium starch glycollate were superior in dissolution properties from similar tablets containing microcrystalline cellulose and cross-linked polyvinylpyrrolidone. The ion exchange resin Amberlite was found to promote rapid disintegration of chlorpropamide tablets, but dissolution rates were found to be inferior to sodium starch glycollate. Measurement of the swelling capacity and hydration capacity of the disintegrants (Table 18.5) indicated that

**Table 18.5** Swelling and hydration characteristics of tablet disintegrants

| *Disintegrant* | *Swelling capacity* | *Hydration capacity* |
|---|---|---|
| Starch | 1.025 | 1.5620 |
| Microcrystalline cellulose (Elcema) | 1.020 | 4.1778 |
| Cross-linked polyvinylpyrrolidone | 1.780 | 4.8099 |
| Amberlite | 2.048 | 3.7443 |
| Sodium starch glycollate | >3 | ∞ |

Amberlite and sodium starch glycollate possesses high swelling capacities and in the case of sodium starch glycollate an exceptionally high hydration capacity.

### Effect of lubricants

Most tablets contain a lubricating agent to prevent the dosage form sticking to the processing machinery. Figure 18.5 shows the effect of lubricant on the dissolution rate of salicylic acid tablets. The hydrophilic lubricant sodium lauryl sulphate allowed the drug to dissolve more rapidly than the control tablet containing no lubricant. However, incorporation of the popular hydrophobic lubricant magnesium stearate produced a decrease in dissolution rate. The most effective lubricants are very hydrophobic and they must therefore be properly formulated to avoid reducing dissolution rate and bioavailability.

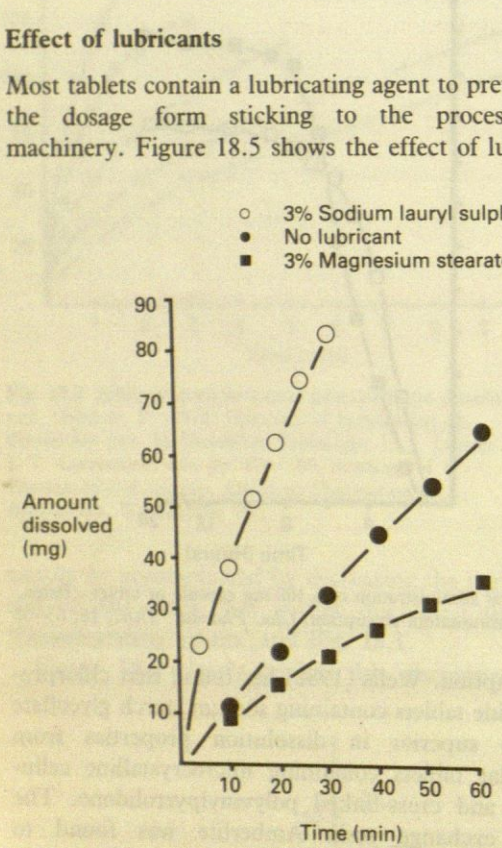


**Fig. 18.5** Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets. (Levy, G. and Gumtow, R. H. (1963) Effect of certain tablet formulation factors on dissolution rate of the active ingredient. III: Tablet lubricants. *J. pharm. Sci.*, **52**, 1139–1141)

### Effect of diluents

Rubinstein and Birch (1977) examined the release rate and bioavailability of 5 mg bendrofluazide tablets containing four different excipients: sorbitol, lactose, calcium orthophospahte and calcium hydrogen orthophosphate. The calcium salts were generally found to be superior to the other diluents. Sorbitol was shown to markedly decrease the release rate of bendrofluazide. This excipient dissolves very slowly and therefore release of the drug occurs by erosion. The calcium salts on the other hand were shown to promote the rapid disintegration of the tablets and therefore to liberate the drug quickly from the dosage form.

### Effect of granule size

Rubinstein and Blane (1977) examined the effect of granule size on the *in vitro* and *in vivo* properties of bendrofluazide tablets 5 mg. Extensive investigations showed that in general granule size was not a critical factor affecting the pharmaceutical properties of the tablets.

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# Tableting



## INTRODUCTION TO TABLETING

The earliest reference to a dosage form resembling the tablet is to be found in arabic medical literature, in which drug particles were compressed between the ends of engraved ebony rods, force being applied by means of a hammer. However details of the tableting process as it is now known were first published in 1843, when Thomas Brockedon was granted a patent for 'manufacturing pills and medicinal lozenges by causing materials when in a state of granulation, dust or

powder, to be made into form and solidified by pressure in dies'. In this case too, force was applied by a hammer.

The use of the tablet rapidly increased, especially in the USA, where the demand for large quantities of medical supplies during the civil war spurred its development. Powder-driven presses replaced Brockedon's hammer, and by 1874, there existed both rotary and eccentric presses which in their mode of operation were fundamentally similar to those in use at the present time.

A monograph for Glyceryl Trinitrate Tablets was included in the *British Pharmacopoeia* of 1885. No other tablet monograph appeared until 1945; this, however, was due to the absence of acceptable quality control standards rather than lack of popularity of the dosage form itself. Despite this, the tablet did not meet with the unqualified approval of the pharmaceutical profession. 'Apprentice', writing in the *Pharmaceutical Journal* asked what his future would be if after 3 years' training, his duties would consist chiefly of counting factory-made tablets, whilst in 1895, an editorial in the *Pharmaceutical Journal* predicted that 'tablets have had their day and will pass away to make room for something else'. Notwithstanding these predictions, the 1980 Pharmacopoeia has nearly 300 monographs for tablets, far in excess of any other dosage form.

The reason for the popularity of the tablet is that it provides advantages for all those involved in the production and consumption of medicinal products. For the manufacturer, though initial capital outlay is high, tablets can be produced at a much greater rate than any other dosage form. Furthermore the fact that the tablet is a dry dosage form promotes stability, and in general, tablets have shelf lives measured in years.

From the viewpoint of the pharmacist, tablets are easy to dispense, whilst the patient receives a concentrated and hence readily portable and consumed dosage form. Furthermore if properly prepared, tablets provide a uniformity of dosage greater than, for example, a liquid medicine, and appropriate coating can mask unpleasant tastes and improve patient acceptability.

The tablet also provides a versatile drug delivery system. Whilst most tablets are intended to be swallowed intact, the same basic manufacturing process, associated with appropriate formulation, provides dosage forms for sublingual, buccal, rectal and vaginal administration, lozenges and solution tablets.

Naturally, tablets only possess these advantages if they are properly formulated and manufactured. It thus becomes possible to specify the qualities which a well prepared tablet should possess.

1 It should contain the stated dose of drug within permitted limits.
2 It should be sufficiently strong to withstand the stresses of manufacture, transport and handling, so as to reach the patient intact.
3 It should deliver its dose of drug at the site and at the speed required.
4 Its size and appearance should not detract from its acceptability by the patient.

Tablets as a dosage form are considered in detail in Chapter 18.

## Processes of tablet production

Though the detailed operation of tablet presses will be considered later, the basic principle of manufacture is common to all types. The tablet ingredient, in particulate form, is fed into a die, and is then compressed between punches. Following this, the compacted mass is ejected from the die. Thus for a particulate system to be made into tablets, three vital properties are demanded.

1 The particles must be sufficiently free-flowing that they will uniformly flow into the relatively small volume in the die in a very short time.
2 The particles, when subjected to a force from the punches, cohere to form a compact of adequate strength.
3 Whilst the particles must cohere, adhesion by the tablet to the punches and dies must be avoided, otherwise damage to both tablet and press will ensue when attempts are made to remove the tablet from the die.

Unfortunately, relatively few substances possess these essential properties without some preliminary treatment. Thus two major stages of tableting are considered in this chapter:

1 preliminary (precompaction) treatment of powders,
2 compression of this material into tablets.

The assessment of the quality of the finished tablets follows.

## Tablet formulation

The formulation of a tablet is governed by a number of factors:

1 the drug substance involved, its chemical and physical propertes and route of administration,
2 the manufacturing process to be employed,
3 the method by which the tablet is to be used, i.e. swallowed whole, chewed, dissolved in water, etc.

These three factors are inter-related.

### *The drug substance*

This must be the most important consideration. Properties of the drug substance which are relevant in this context are as follows.

***Site and extent of absorption of drug in the gastrointestinal tract*** If the drug is satisfactorily absorbed in the stomach or intestine, then a tablet can be designed which is to be swallowed and which disintegrates in the stomach. If absorption is dissolution-controlled, then the particle size of the drug may need to be reduced, or dissolution promoted in some other way. If the drug is unstable in any of the fluids of the gastrointestinal tract, then either some form of protection must be afforded, e.g. by enteric coating, or a tablet formulated for buccal or sublingual absorption. A similar solution may be adopted for substances which undergo extensive first-pass hepatic metabolism, e.g. glyceryl trinitrate.

***Stability of the drug to heat or moisture*** Substances which would undergo appreciable hydrolysis in the conditions of the wet granulation process obviously cannot be made into tablets by this means, and alternatives such as precompression or direct compression must be used, or another dosage form chosen.

***Compatibility of the drug*** The compatibility of the drug with other tablet ingredients in the solid state, for example magnesium stearate, lactose, microcrystalline cellulose and starch, must be considered, since this will govern those additives which can be used in the production of the tablet.

***Dose of the drug*** The dose of the drug will decide the necessity of the filler. If a filler is not used, then there is little possibility of the direct compression method of tablet preparation being available.

***Solubility of the drug*** The solubility of the drug, together with the proportion of drug in each tablet, will govern the need for a disintegrating agent.

### *The method of production*

This may well be governed by the drug substance, but where a choice is available, economic factors will play an important role. The process of direct compression with its savings in time, apparatus, energy costs and space is obviously attractive, but against this must be set higher material costs.

### *The type of tablet*

Having decided on a route of administration and method of production, a formulation must now be designed which will enable the manufacturer to produce tablets which satisfy pharmacopoeial and 'in-house' standards for performance and appearance. Thus for a tablet designed to disintegrate after swallowing, and to be made by a wet granulation process then:

1 A granulating agent must be chosen with adequate adhesive properties, and giving a granule which compresses to form tablets of acceptable strength and friability.
2 A lubricant is chosen so as to enable ejection from the die to occur without unacceptably prolonging the disintegration time or reducing tablet strength.
3 A sufficient concentration of disintegrant is used.

It must be stressed that these points are all inter-related. Thus, for example, disintegration time is not only governed by disintegrant concentration, but also by the lubricant, the compression

pressure and the solubility of drug and diluent. Whilst many tablets are formulated on an *ad hoc* basis, optimum levels of additives can be determined using factorially designed experiments and computer-assisted analysis of the resulting data. The reader is referred to Schwartz (1979) for a detailed discussion of this approach.

If the tablet is not to be swallowed intact, then other formulation considerations arise. For example, if the tablet is to be dissolved in water before use, then all ingredients must be soluble. A variety of solution tablet is the effervescent tablet in which an acid (usually tartaric or citric acid) reacts with a bicarbonate (usually sodium or potassium) on the addition of water to produce carbon dioxide. In addition to solubility considerations, this type of preparation cannot be prepared with an aqueous-based granulating agent. A non-aqueous granulation or a totally dry method of tablet production is mandatory.

There are other types of tablet designed for oral administration but which are not to be swallowed. Chewable tablets are often used for children and geriatric patients who have difficulty in swallowing tablets. Since the disintegrated tablet is present in the mouth, the taste of the preparation is important in this case. Taste masking can be achieved by choice of diluent but obviously this problem becomes more acute with drugs of unpleasant taste, after-taste and high dose. A frequently used diluent is mannitol, which has a pleasant cooling sensation in the mouth, effectively disguising many taste problems.

The lozenge and the sublingual or buccal tablet are also designed to be kept in the mouth but pose opposite formulation problems. The lozenge, often containing a small amount of antibacterial substance, is designed to be kept in the mouth for long periods. Hence it should remain intact and dissolve slowly, since the patient will have difficulty in retaining fragments in the mouth. Flavour is also important, and a mixture of lactose and sucrose is often used as filler. The sublingual tablet also should not disintegrate but in this case it must dissolve rapidly. Hence a highly soluble formulation must be selected.

Further consideration of the formulation of tablets is given in Chapter 18.

## PRECOMPACTION TREATMENT

### Tablet production via wet massing and screening

This is the traditional method of giving a particulate solid those properties needed for it to produce satisfactory tablets. The process essentially consists of sticking the particles together using an adhesive material, thereby increasing the particle size and improving flow properties. These enlarged particles are termed granules. Other additives are also usually incorporated at some stage of the process.

The process is represented in Fig. 39.1, and each stage will be discussed in some detail.

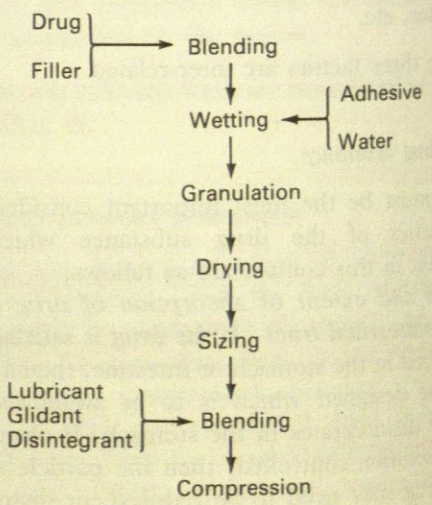


**Fig. 39.1** Flow sheet of the wet granulation process of tablet production

#### *Initial powder blending*

In this stage, the drug substance is mixed, if needed, with the diluent or filler. Tablets weighing much less than 50 mg are so small as to be difficult to pick up and manipulate with the fingers, yet many drug substances are active in far lower doses. Accordingly it is necessary to dilute the drug to make a tablet of reasonable size. The ideal diluent should be inert, both chemically and pharmacologically, pose no problems on compression and should be cheap. Commonly used diluents are given in Chapter 18. The

powders are blended in a powder mixer, the design and size of which is governed by the masses of powder involved. The aim is to produce a uniform dispersion of the drug in the filler. A detailed description of powder mixers, and of methods of assessing the uniformity of a powder blend is given in Chapter 32.

*Wetting*

The mixture of powders is now wetted and it is at this stage that the adhesive is introduced, usually as an aqueous solution or dispersion. A wide variety of adhesives (also known as binders or granulating agents) are available and some details are given in Chapter 18. The choice of granulating agent will often be governed by the intended use of the tablet. Though the more obvious role of the adhesive is to form granules, it also plays an important role in the compressive behaviour of the formulation. This point is discussed later in this chapter.

Though size enlargement takes place primarily with the adhesion of particles by a film of granulating agent, a second mechanism is available if the solid particles are soluble in the granulating fluid. Partial dissolution occurs, yielding a saturated solution of the solid. On subsequent drying, recrystallization occurs and the resultant crystal bridges between particles can contribute significantly to granule strength (see Chapter 37).

In the case of drugs which are unstable in the presence of water, a small number of non-aqueous systems, notably polyvinyl pyrrolidone in isopropanol, are available. These are not used unless absolutely necessary because of expense and the environmental problems caused by handling large volumes of flammable vapour.

The wetting stage is usually carried out in the same apparatus in which the dry powders were blended. Sufficient adhesive is added to form a damp, coherent mass, though overwetting should be avoided.

*Granulation*

The damp mass is now passed through a coarse sieve, usually of mesh size 1–2 mm, yielding roughly spherical particles or granules. This product is usually achieved mechanically, often by means of an oscillating granulator, in which a rotor, oscillating about its horizontal axis, passes the damp material through the screen. Alternatively, a comminutor, containing a number of rapidly revolving blades, may be used. Chapter 37 describes some commonly used granulation equipment.

*Drying*

The granules are now dried, the apparatus used being either a tray drier or, more usually, a fluidized bed drier. The resultant product will be a coarse, free-flowing solid. The process of drying is discussed in detail in Chapter 38.

*Sizing*

The size of granules at this point will usually be considerably larger than the size required for tableting. Also for the latter process, a relatively uniform size is needed to ensure that a constant weight flows into the die of the tablet press. Hence a comminution stage, followed by sieving, will normally be needed, the usual granule size for tableting being 350–700 $\mu$m.

*Second blending*

A second blending stage is now required, since at this point other important additives are incorporated.

***The role of lubricants*** A lubricant is almost invariably needed in a tablet formulation. As the granules are compressed and thus deformed, they exert a radial stress on the die wall, the magnitude of which can be great enough to prevent ejection of the tablet from the die. A lubricant is a substance which deforms easily when sheared between two surfaces and hence, when interposed between the tablet and die wall, provides a readily deformable film. Details of commonly used lubricants are given in Chapter 18.

The most effective are substances based on stearic acid and especially magnesium stearate, the hydrocarbon chains of which provide the deformable property. A consequence of this is that the granule surface is covered with a hydrophobic

material, and this may lead to retarded disintegration of the tablet after ingestion. However, this can usually be counteracted by adding a wetting agent, e.g. sodium lauryl sulphate, to the formulation. In addition, the formation of interparticulate bonds, on which the integrity of the tablet depends, can also be decreased by the presence of a film of lubricant, and thus the tablet is weakened. For both these reasons therefore the minimum amount of lubricant is used.

Inadequate lubrication can be the cause of a number of tablet faults. Frictional forces at the die wall resist ejection of the tablet from the die. This can often be recognized by vertical scratches on the tablet edges. It can lead to tablet fragmentation on ejection and in extreme cases to damage to the press. Alternatively the tablet may tend to stick to the punch faces. This causes a build-up of powder on the faces which in turn will lead to a matt, dimpled appearance of the tablet face. This phenomenon, known as picking, may also occur with moist or sticky granules, a humid environment and is especially prone to happen if the tablet punches are engraved or embossed.

***The role of glidants*** One of the main reasons for granulation is to improve flow properties. However, the requirements for adequate flow are high, since the granules are required to fall uniformly into a confined space in a very short time. The purpose of the glidant is to promote flow. The most commonly used glidant is silica. It is believed to act by lodging in the surface irregularities of the granule, effectively smoothing its surface. Hence a finely divided grade of silica must be used. Details of this and other glidants are given in Chapter 18. Inadequate glidant action is detected by an unacceptable variation in tablet weight.

***The role of disintegrants*** In the course of compression, a particulate system with a high surface area is transformed into a solid mass of low porosity. Yet if the tablet is to liberate its active principle in the gastrointestinal tract, it is essential that the lumenal fluids gain access to the drug. If the bulk of the tablet is fairly soluble in water this is not difficult, but if not, it is possible that the tablet may pass through the gastrointestinal tract without yielding up the drug. The function of the disintegrant is to prevent this. It acts by causing the tablet to break up into small fragments, thereby increasing the surface area to which the dissolving fluid has access. The most commonly used disintegrants are described in Chapter 18.

The mechanism by which disintegrants act has in the past been the subject of some controversy. The various types of starch, which are still the most commonly used disintegrants, were believed to act by swelling when they came into contact with water. This disrupted the interparticulate bonds holding the tablet together and hence disintegration occurred. Whilst this may account for the disintegrant action of starch, it cannot explain the fact that certain other effective disintegrants do not swell in contact with water. These are believed to act by providing hydrophilic pathways within the tablet structure. When the tablet is immersed in water, the liquid is drawn up through these pathways by what is termed a 'wicking' mechanism, with the consequent rupture of interparticulate bonds. It is probable that the action of starch can also be attributed to this latter mechanism, the swelling of the starch grains being of secondary importance. A detailed discussion of disintegrant action is given by Lowenthal (1973).

***Flavours*** Taste masking in tablets is often achieved by using a sweet-tasting substance as diluent or by coating the tablet. However, it may be necessary to incorporate a flavouring agent, and as these are often thermolabile, they cannot be added prior to an operation involving heat. They are often added as spray-dried beads or, if oily, sprayed on to the granules as an alcoholic solution.

***Colorants*** Many tablets are coloured to aid identification and patient compliance. Whilst this is often achieved by coating the tablets, dyes can be added at the final mixing stage, usually as a water-insoluble precipitate with aluminium hydroxide, i.e. as the lake of the dye. Alternatively the water-soluble dye can be added to the granulating fluid, but this can lead to colour variation in the tablet (mottling) caused by migration of the dye during the drying stage.

## Tablet production via fluidized bed granulation

Though a high proportion of all tablets are made by the wet massing process, there are a number

of drawbacks to it. First, there are many stages involved, and hence the product must be moved from one piece of apparatus to another on several occasions. Thus production costs are increased. Second, the process involves the addition and subsequent removal of water. This too is an expensive procedure, but in addition the presence of water and heat can cause deterioration of substances susceptible to hydrolysis.

An attempt to reduce handling costs in the wet granulation process has been the introduction of fluidized bed granulation. In this, the drug and filler are loaded into a chamber through which a current of warm air is passed, which thoroughly blends the mixture. The binder solution is sprayed as a stream of droplets on to the fluidized powder, and thus granulation takes place as the particles are suspended in air. After granulation is complete, the spray is stopped but the fluidizing hot air is continued and the product dried as in a fluidized bed drier. Whilst this speeds up the process, it is still one which involves water and heat. Granules can be produced very effectively in this type of equipment and to some extent the granule size can be controlled.

### Tablet production via spray drying

Granules can be produced directly from the spray-drying process. All the components of the formulation, diluent, binder, disintegrant and lubricant are suspended in a suitable vehicle to achieve a concentration of about 50–60% w/w. The slurry is then spray dried to produce nearly spherical granules of uniform diameter, 10–250 $\mu$m in size. The spray-dried product is usually free flowing. Spray-drying is normally only used on the very large scale and due to the very high capital cost, the advantages of this process are usually outweighed by the high investment involved in installing this specialized piece of equipment. As a consequence this process is little used except for the production of diluents.

### Tablet production via precompression

This is an alternative to wet granulation and is employed where heat- or moisture-sensitive materials are involved. It is not widely used. The process, sometimes known as slugging, is shown schematically in Fig. 39.2.

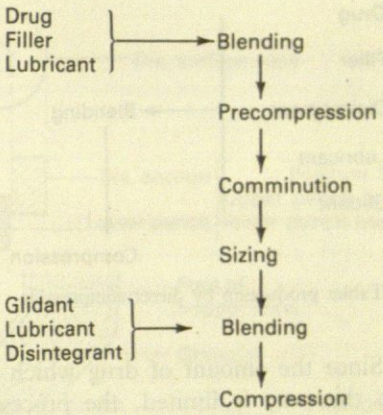


**Fig. 39.2** Flow sheet of the precompression method of tablet production

The constituents, after blending with some of the lubricant, are compressed into large tablets on a heavy duty press. These tablets (or slugs), which will lack the uniformity of weight and appearance normally required of tablets, are then broken down to granule-sized particles which are subsequently recompressed into the finished product. A variation on this technique is to squeeze the powder particles into a cake between rollers (roller compaction). Thus the process essentially replaces the wetting and drying stages of wet granulation with a preliminary compression stage.

### Tablet production by direct compression

It has been repeatedly stressed that the great majority of solids need some preliminary treatment before they can be made into tablets. However, for those relatively few substances which need no prior manipulation, tableting is a simple matter. The steps are shown schematically in Fig. 39.3. The number of medicinal substances which can be tableted in this way is very small. Sodium and potassium chlorides and aspirin are the most common, but the promise of this method lies in the discovery of directly compressible fillers or diluents which produce good quality tablets without prior manipulation. The filler can be mixed with the drug without significantly reducing the compressional properties of the

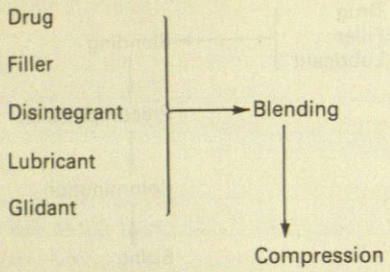


**Fig. 39.3** Tablet production by direct compression

former. Since the amount of drug which can be added in this way is limited, the process is of greatest promise with potent substances where perhaps only a few milligrams are present in each tablet. In the last few years, a considerable number of direct compression diluents have been introduced. Details of some, together with their proprietary names, are given in Table 39.1.

**Table 39.1** Direct compression diluents

| *Diluent* | *Proprietary name* | *Comments* |
|---|---|---|
| Microcrystalline cellulose | Avicel PH | Very compressible; no lubricant needed |
| Microfine cellulose | Elcema | |
| Lactose; spray-dried | Zeparox | Highly compressible; good flow properties; high bulk density |
| Modified starch | Starch 1500 | More useful as a disintegrant |
| Sucrose–dextrin coprecipitate | Dipac | Good flow properties; moisture-sensitive |
| Dextrose–maltose | Emdex | |
| Dicalcium phosphate | Emcompress | Insoluble in water; good flow properties |

### *Advantages*

The advantages of this process are obvious. Very few stages are involved, with a consequent reduction in appliance and handling costs. Furthermore as heat and water are not involved, stability is not affected. Also though additives such as lubricant and disintegrant are usually necessary, some direct compression diluents such as microcrystalline cellulose need neither, and hence costs are further reduced.

### *The requirements of a direct compression diluent*

1 It should have good flow properties, so that uniform flow into the die is facilitated.
2 It should have a high bulk density. If the solid is light and fluffy, a relatively low weight of powder will fill the die, and after compression, the resultant tablet will be correspondingly thin.
3 The particle size should be such as to minimize segregation of the powder blend prior to compression. With wet granulated systems, the constituents of the mixture are stuck together during the blending stage, and hence cannot subsequently separate. In direct compression systems, separation may occur due, for example, to vibration. This is particularly prone to happen if the components of the mixture differ widely in particle size, and hence where possible the sizes of drug and diluent particles should be approximately equal. This matter is explored more fully in Chapters 32 and 37.
4 The substance should have a high capacity in that it is capable of considerable dilution with drug substances. There is no universally recognized method of measuring capacity, and consequently published data must be viewed with caution.
5 It should have a good compression pressure–tablet strength profile so that strong tablets are obtained at relatively low pressures.
6 The diluent should be physiologically inert, should not interfere with bioavailability, and should be compatible with the drug substance.
7 In the event of a defective batch of tablets being produced, the tablets should be capable of being broken down and recompressed. The structure of some direct compression diluents, e.g. spray-dried lactose, is lost on compression, and hence reworking may not be feasible.
8 The diluent should not be so expensive as to nullify the economic advantages of the direct compression process.

### *Disadvantages*

Although the method is simple there are, however, limitations to the use of direct compression formulations. In particular, differ-

ences in particle size and bulk density between the diluent and the active ingredient may result and this can easily lead to stratification in handling and variation in drug content of the resultant tablets. From a quality control point of view, it is never certain how the powder mix will be handled before compression takes place, and if the mix is subjected to any form of vibration, e.g. on the back of a lorry, powder segregation could occur which would produce drug content variability. Static charges may develop on the drug during mixing which may prevent uniform distribution and inadequate mixing may result. Good earthing of mixers and blenders is thus essential.

## TABLET COMPRESSION

Tablets are prepared by compressing a particulate solid in a die by the application of forces via two punches. The punches are termed the lower punch, the tip of which moves up and down within the die, but never actually leaves it, and the upper punch, which descends to penetrate the die and apply the compressive force, and then withdraws to permit ejection of the tablet. The die and punches are almost invariably made of hardened steel.

### Compression sequence

Irrespective of the type of tablet press, the process of compaction can be divided into three distinct stages (Fig. 39.4).

1 The lower punch falls within the die, leaving a cavity into which particulate material can flow under the influence of gravity.
2 The upper punch descends, and the punch tip enters the die, confining the particles. Further punch movement applies the compressive force to the particles, which aggregate to form a coherent tablet.
3 The upper punch withdraws from the die and simultaneously the lower punch rises until its tip becomes level with the top of the die. The tablet is thus ejected from the die and removed from the tablet press.

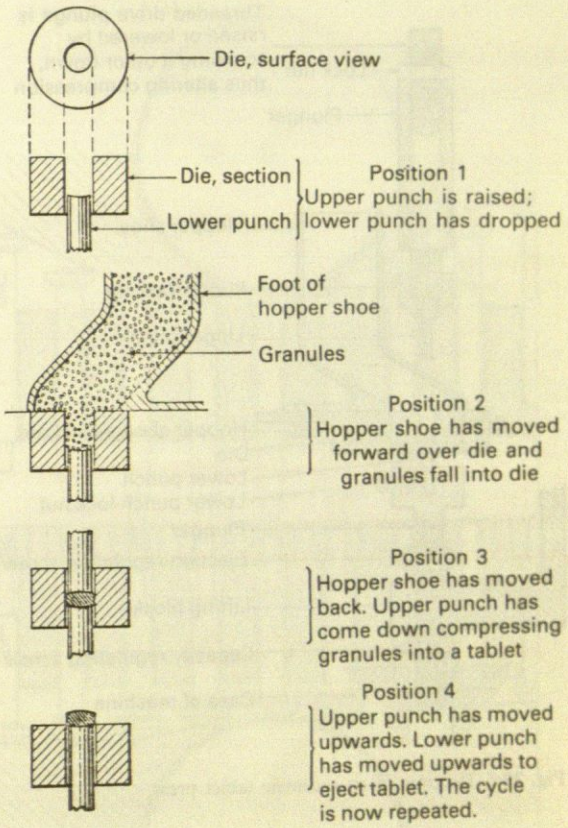


**Fig. 39.4** Movements involved in tablet compression

This process demands that the particulate solid possesses good flow properties, is coherent, and yet will not adhere to the die wall and the punches of the press. As stated earlier, few substances possess all these properties, and so prior manipulation is almost always necessary.

### Tablet compression machinery

There are two types of tablet press in common use.

#### *The single stroke or eccentric press*

This type possesses one die and one pair of punches. The particulate solid, contained in a hopper, is fed into the die by means of a shoe which moves to and fro over the die. The output of this type of press is 150–200 tablets per minute