# Modern Pharmaceutics

## Fourth Edition, Revised and Expanded

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# Chapter 10

# Tablet Dosage Forms

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## I. INTRODUCTION

During the past four decades, the pharmaceutical industry has invested vast amounts of time and money in the study of tablet compaction. This expenditure is quite reasonable when one considers how valuable tablets, as a dosage form, are to the industry. Because oral dosage forms can be self-administered by the patient, they are obviously more profitable to manufacture than parenteral dosage forms that must be administered, in most cases, by trained personnel. This is reflected by the fact that well over 80% of the drugs in the United States that are formulated to produce systemic effects are marketed as oral dosage forms. Compared to other oral dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package, and shipment; increased stability and virtual tamper resistance (most tampered-with tablets either become discolored or disintegrate).

## II. DESIGN AND FORMULATION OF COMPRESSED TABLETS

### A. General Considerations

The most common solid dosage forms in contemporary use are tablets, which may be defined as unit forms of solid medicaments prepared by compaction. Most consist of a mixture of powders that are compacted in a die to produce a single rigid body. The most common types of tablets are those intended to be swallowed whole and then disintegrate and release their medicaments in the gastrointestinal tract (GIT). A less common type of tablet that is rapidly gaining popularity in the United States is formulated to allow dissolution or dispersion in water prior to administration. Ideally, for this type of tablet all ingredients should be soluble, but frequently a fine suspension has to be accepted. Many tablets of this type are formulated to be effervescent, and their main advantages include rapid release of drug and minimization of gastric irritation.

Some tablets are designed to be masticated (i.e., chewed). This type of tablet is often used when absorption from the buccal cavity is desired or to enhance dispersion prior to swallowing. Alternatively, a tablet may be intended to dissolve slowly in the mouth (e.g., lozenges) so as to provide local activity of the drug. A few tablets are designed to be placed under the tongue (i.e., sublingual) or between the teeth and gum (i.e., buccal) and rapidly release drug into the bloodstream. Buccal or sublingual absorption is often desirable for drugs liable to extensive hepatic metabolism by the first-pass effect (e.g., nitroglycerin,

testosterone). Recently, a lozenge on a stick, or "lollipop," dosage form of fentanyl was developed for preoperative sedation in pediatric patients (Oralet®) and breakthrough cancer pain in adults (Actiq®). Active ingredient is released from the lozenge into the bloodstream from the oral mucosa.

There are now many types of tablet formulations that provide for the release of drug to be delayed or control the rate of the drug's availability. Some of these preparations are highly sophisticated and are rightly referred to as complete "drug-delivery systems." Since the concepts of controlled drug delivery are the subjects of Chapter 15, the strategies of these systems will not be discussed here. However, solid dosage formulators must be aware of the various options available to them.

For example, when prolonged release of a water-soluble drug is required, water-insoluble materials must be co-formulated with the drug. If the dose of the drug is high and it exhibits poor compactibility, purely hydrophobic agents, such as waxes, will exacerbate the inability of the material to form a compact. In such cases, formulators need to turn to other types of water-insoluble materials, such as polymers, to achieve both drug release and tableting goals.

Some tablets combine sustained-release and rapid disintegration characteristics. Products such as K-Dur® (Key Pharmaceuticals) combine coated potassium chloride crystals in a rapidly releasing tablet. In this particular instance, the crystals are coated with ethylcellulose, a water-insoluble polymer, and are then incorporated into a rapidly disintegrating microcrystalline cellulose (MCC) matrix. The purpose of this tablet is to minimize GI ulceration, commonly encountered by patients treated with potassium chloride. This simple but elegant formulation is an example of a solid dosage form strategy used to achieve clinical goals.

Thus, the single greatest challenge to the tablet formulator is in the definition of the purpose of the formulation and the identification of suitable materials to meet development objectives. In order to do this properly, the formulator must know the properties of the drug, the materials to be co-formulated with the drug, and the important aspects of the granulation, tableting, and coating processes.

Pharmaceutical compressed tablets are prepared by placing an appropriate powder mix, or granulation, in a metal die on a tablet press. At the base of the die is a lower punch, and above the die is an upper punch. When the upper punch is forced down on the powder mix (single station press) or when the upper and lower punches squeeze together (rotary or multiple station press), the powder is forced into a tablet. Despite the fact that powder compaction has been observed for hundreds of years, scientists still debate the exact mechanisms behind this phenomenon.

Perhaps the most significant factor in the tableting of materials for use as drug products is the need to produce tablets of uniform weight. This is achieved by feeding constant volumes of homogeneous material to the dies. Such an approach is necessary because direct weighing at rates commensurate with modern tablet press operation is impossible. This requirement immediately places demands on the physical characteristics of the feed and on the design of the tablet press itself. In the case of the former, precompression treatment of the granulation is one of the most common ways of minimizing difficulties arising from this source.

The great paradox in pharmaceutical tableting is the need to manufacture a compact of sufficient mechanical strength to withstand the rigors of processing and packaging that is also capable of reproducibly releasing the drug. In most cases, the release of the drug is produced by the penetration of aqueous fluids into the fine residual pore structure of the tablet and the contact of these fluids with components that either swell or release gases.

The selected precompression treatment, if any, markedly affects the manufacture of tablets. In particular, one must determine whether a mixture of powdered ingredients is to be tableted directly or if an intervening wet granulation step is to be introduced. This decision is influenced by many factors, including the stability of the drug to heat and moisture; the flow properties of the granulation; and the tendency of the granulation to segregate. At the present time there are also two conflicting considerations that tend to play a major role in this choice. These are the reluctance to change methods employed traditionally by the company versus the economic advantages of omitting complete stages in the production sequence.

In wet granulation, the components of the formulations are mixed with a granulating liquid, such as water or ethanol, to produce granules that will readily compress to give tablets. Wet granulation methods predominate in the manufacture of existing products, while the trend for new products is to use direct compression procedures. Although many steps are eliminated when using direct compression, some formulators have found that wet granulated products are more robust and able to accommodate variability in raw materials and tableting equipment. Thus, for some

companies, the trend is reverting to the formulation of tablets by wet granulation.

## B. Desirable Properties of Raw Materials

Most formulations are composed of one or more medicaments plus a variety of excipients. Irrespective of the type of tablet, general criteria for these raw materials are necessary. In order to produce accurate, reproducible dosage forms, it is essential that each component be uniformly dispersed within the mixture and that any tendency for component segregation be minimized. In addition, the processing operations demand that the mixture be both free-flowing and cohesive when compressed.

### *Particle Size*

In general, the tendencies for a powder mix to segregate can be reduced by maintaining similar particle size distribution, shape, and, theoretically, density of all the ingredients. Flow properties are enhanced by using regular-shaped, smooth particles with a narrow size distribution together with an optimum proportion of "fines" (particles 50 μm). If such conditions cannot be met, then some form of granulation should be considered.

Particle size distribution, and hence surface area of the drug itself, is an important property that has received considerable attention in the literature. For many drugs, particularly those whose absorption is limited by the rate of dissolution, attainment of therapeutic levels may depend upon achieving a small particle size [1]. In fact, it has been suggested that for such drugs, standards for specific surface areas and the number of particles per unit weight should be developed. However, the difficulty in handling very fine powders, as well as the possibility of altering the material in other ways, has shifted the emphasis towards producing an optimum, rather than a minimum, particle size. For instance, several researchers have found that decreasing particle size produces tablets of increased strength that also have a reduced tendency for lamination [2–5]. This is probably due to the minimization of any adverse influences that a particular crystal structure may have on the bonding mechanism. On the other hand, samples of milled digoxin crystals prepared by a number of size-reduction techniques have been reported to elicit different equilibrium solubilities [1]. This suggests that the method of grinding may well affect the dissolution behavior of certain drugs.

The effect of particle size on the compaction characteristics of two model sulfonamide drugs, one exhibiting brittle fracture and the other being compressed chiefly by plastic deformation, has been reported [3]. In particular, it was shown that the tensile strength of tablets made from the brittle material were more sensitive to the drug's particle size than that of tablets made from the plastically deforming material. In addition, larger granules possess better flow, while small aggregates deform during compaction (e.g., spray-dried lactose) [6].

An alternative approach aimed at reducing the segregation tendencies of medicaments and excipients involves milling the former to a small particle size and then physically absorbing it uniformly onto the surface of the larger particles of an excipient substrate. By these means "ordered," as opposed to "random," mixing is realized and dissolution is enhanced as a result of the fine dispersion [7].

### *Moisture Content*

One of the most significant parameters contributing to the behavior of many tablet formulations is the level of moisture present during manufacture as well as that residual in the product. In addition to its role as a granulation fluid and its potentially adverse effects on stability, water has some subtle effects that should not be overlooked. For example, there is increasing evidence to suggest that moisture levels may be very critical in minimizing certain faults, such as lamination, that can occur during compression. Moisture levels can also affect the mechanical strength of tablets and may act as an internal lubricant. For example, Fig. 1 illus-

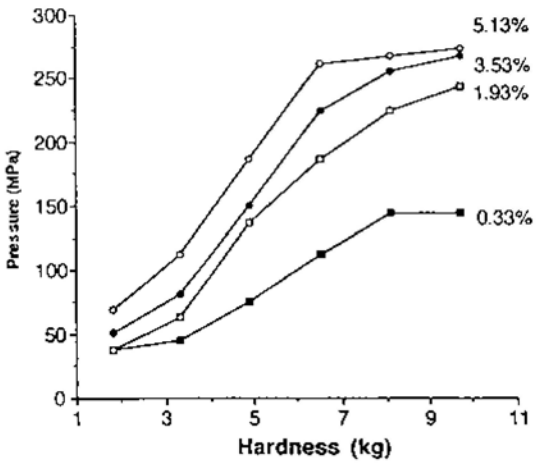


**Fig. 1** The effect of moisture content on the compactibility of anhydrous beta lactose tablets. (From Ref. 8.)

trates the effect of moisture content on the compactibility of anhydrous lactose [8]. As the moisture content increases, it is adsorbed by the lactose, thereby converting it from the anhydrous to the hydrous form. During this transformation, the β-form of lactose most probably changes to the α-form and thus produces changes in compactibility.

Accelerated aging and crystal transformation rates have also been traced to high residual moisture content. Ando et al. studied the effect of moisture content on the crystallization of anhydrous theophylline in tablets [9]. Their results also indicate that anhydrous materials convert to hydrates at high levels of relative humidity. In addition, if hygroscopic materials (e.g., polyethylene glycol 6000) are also contained in the formulation, needle-like crystals form at the tablet surface and significantly reduce the release rate of the theophylline.

In many products it seems highly probable that there exists a narrow range of optimum moisture contents that should be maintained. More specifically, the effect of moisture on MCC-containing tablets has been the subject of an investigation that demonstrates the sensitivity of this important excipient to moisture content [10]. These researchers found that differences exist in both the cohesive nature and the moisture content to two commercial brands of MCC. A very useful report on the equilibrium moisture content of some 30 excipients has been compiled by a collaborative group of workers from several pharmaceutical companies and appears in the *Handbook of Pharmaceutical Excipients* [11,12].

### *Crystalline Form*

Selection of the most suitable chemical form of the active principle for a tablet, while not strictly within our terms of reference here, must be considered. For example, some chloramphenicol esters produce little clinical response [13]. There is also a significant difference in the bioavailability of anhydrous and hydrated forms of ampicillin [14]. Furthermore, different polymorphic forms, and even crystal habits, may have a pronounced influence on the bioavailability of some drugs due to the different dissolution rates they exhibit. Such changes can also give rise to manufacturing problems. Polymorphism is, of course, not restricted to active ingredients, as shown, for example, in an evaluation of the tableting characteristics of five forms or sorbitol [15].

Many drugs have definite and stable crystal habits. Morphological changes rarely occur in such drugs as the formulation process is scaled up. However, some drugs exhibit polymorphism or have different identifiable crystal habits. Chan and Doelker reviewed a number of drugs that undergo polymorphic transformation when triturated in a mortar and pestle [16]. Some of their conclusions are listed in Table 1 and illustrated in Fig. 2. In addition, a number of researchers have concluded that both polymorph and crystal habit influence the compactibility and mechanical strength to tablets prepared from polymorphic materials [16–21]. York compared the compressibility of naproxen crystals that had been spherically agglomerated with different solvents and found that significant differences existed between the various types of agglomerates (see Fig. 3) [21]. Other investigators have found that, in some instances, there is a correlation between the rate of reversion to the metastable form during dissolution and the crystal growth rate of the stable form [22]. These polymorphic changes may have a profound effect on tablet performance in terms of processing, in vitro dissolution and in vivo absorption. Thus, formulators of solid dosage forms must be aware of a subject compound's propensity for polymorphic transition so that a rational approach to formulation can be followed.

**Table 1** Some Drugs That Undergo Polymorphic Transition When Triturated

| Drug | Number of polymorphs before trituration | Number of polymorphs after trituration |
|---|---|---|
| Barbitone | 2 | 1 |
| Caffeine | 2 | 1 |
| Chlorpropamide | 3 | 2 |
| Clenbuterol HCl | 2 | 3 |
| Dipyridamole | 2 | 1 |
| Maprotiline HCl | 3 | 1 |
| Mebendazole | 4 | 5 |
| Nafoxidine HCl | 4 | 3 |
| Pentobarbitone | 3 | 2 |
| Phenobarbitone | 2 | 1 |
| Sulfabenzamide | 2 | 1 |

*Source*: Ref. 16.

### *Hiestand Tableting Indices*

Materials that do not compress well produce soft tablets. In addition, brittle crystalline materials will yield brittle tablets. Hiestand was the first pharmaceutical scientist to quantify rationally the compaction properties of pharmaceutical powders [23–28]. The results

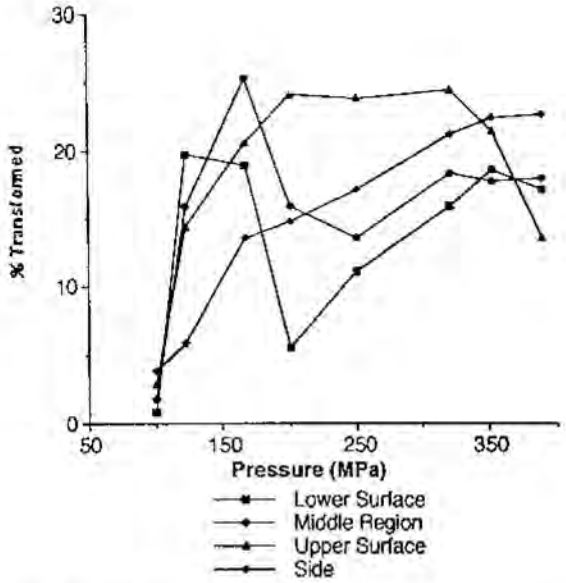


**Fig. 2** Percentage of caffeine "form A" transformed vs. applied pressure. (From Ref. 16.)

of this work are three indices known as the Hiestand Tableting Indices. The strain index (SI) is a measure of the internal entropy, or strain, associated with a given material when compacted. The bonding index (BI) is a measure of the material's ability to form bonds and undergo plastic transformation to produce a suitable tablet. The third index, the brittle fracture index (BFI), is a measure of the brittleness of the material and its compact. Table 2 lists these indices for a number of drugs and excipients. For most materials, the strength of the tablet is a result of competing processes. For example, erythromycin is a material known for its tendency to cap and laminate when tableted. On the basis of its BI value, one might expect relatively good bonding. However, the very high strain index associated with this drug appears to overcome its bonding abilities. MCC, on the other hand, has very high strain index, but its bonding index is exceptionally high and compensates for this effect.

Other investigators have evaluated the potential for these indices. In their studies, Williams and McGinnity have concluded that evaluation of single-material systems should precede binary or tertiary powder systems [29]. A full discussion of compaction mechanisms is given later in this chapter.

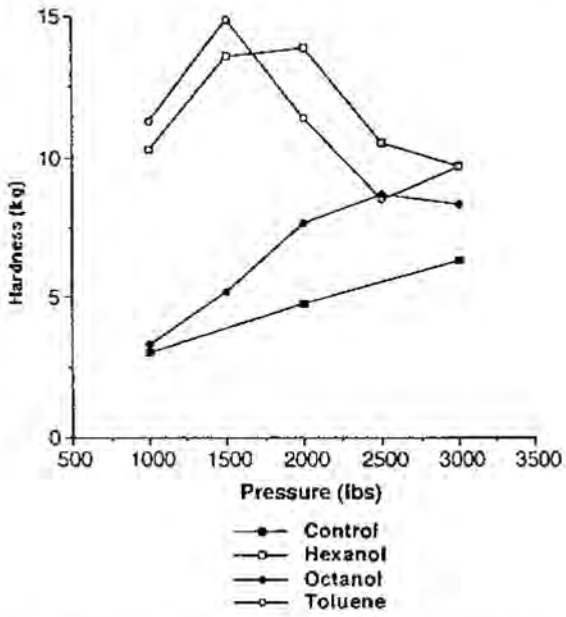


**Fig. 3** Intrinsic compressibility of nonagglomerated naproxen (control) and of naproxen that has been spherically agglomerated with different solvents. (From Ref. 21.)

### *Variability*

The effect of raw material variability on tablet production [2,30,31] and suggestions for improving tableting quality of starting materials [21] has been the subject of several publications. Table 3, which lists the characteristics of different sources of magnesium stearate, clearly illustrates the variability of this material [32]. Phadke and Eichorst have also confirmed that significant differences can exist between different sources, and even different lots, of magnesium stearate [33]. Given the fact that the effectiveness of magnesium stearate is due, in large part, to its large surface area, these variations should not be overlooked. In addition, studies assessing raw material variability emphasize the need for physical as well as chemical testing of raw materials to ensure uniformity of the final product.

### *Purity*

Raw material purity, in general, must also be given careful attention. Apart from the obvious reasons for a high level of integrity, as recognized by the regulatory requirements, one should be aware of more subtle implications that are perhaps only just beginning to emerge. For instance, small proportions of the impurity acetylsalicylic anhydride have been shown to reduce the dissolution rate of aspirin itself (see Fig. 4) [34].

Another area of interest is that of microbiological contamination of solid dosage forms, which is thought to arise chiefly from raw materials rather than the

**Table 2** Hiestand Compaction Indices for Some Drugs and Excipients

| Material | Bonding index | Brittle fracture index | Strain index |
|---|---|---|---|
| Aspirin | 1.5 | 0.16 | 1.11 |
| Caffeine | 1.3 | 0.34 | 2.19 |
| Croscarmellose sodium NF | 2.7 | 0.02 | 3.79 |
| Dicalcium phosphate | 1.3 | 0.15 | 1.13 |
| Erythromycin dihydrate | 1.9 | 0.98 | 2.13 |
| Hydroxypropyl cellulose | 1.6 | 0.04 | 2.10 |
| Ibuprofen | | | |
| A | 1.9 | 0.05 | 0.98 |
| B | 1.8 | 0.57 | 1.51 |
| C | 2.7 | 0.45 | 1.21 |
| Lactose USP | | | |
| Anhydrous | 0.8 | 0.27 | 1.40 |
| Hydrous Fast-Flo | 0.4 | 0.19 | 1.70 |
| Hydrous bolted | 0.6 | 0.12 | 2.16 |
| Hydrous spray process | 0.6 | 0.45 | 2.12 |
| Spray-dried | | | |
| A | 0.6 | 0.18 | 1.47 |
| B | 0.5 | 0.12 | 1.81 |
| Mannitol | | | |
| A | 0.8 | 0.19 | 2.18 |
| B | 0.5 | 0.15 | 2.26 |
| Methenamine | 1.6 | 0.98 | 0.84 |
| Methyl cellulose | 4.5 | 0.06 | 3.02 |
| Microcrystalline cellulose NF | | | |
| Avicel PH 102 (coarse) | 4.3 | 0.04 | 2.20 |
| Avicel PH 101 (fine) | 3.3 | 0.04 | 2.37 |
| Povidone USP | 1.7 | 0.42 | 3.70 |
| Sorbitol NF | 0.9 | 0.16 | 1.70 |
| Starch NF | | | |
| Corn | 0.4 | 0.26 | 2.48 |
| Pregelatinized | 1.8 | 0.14 | 2.02 |
| Pregelatinized compressible | 1.2 | 0.02 | 2.08 |
| Modified (starch 1500) | 1.5 | 0.27 | 2.30 |
| Sucrose NF | | | |
| A | 1.0 | 0.35 | 1.45 |
| B | 0.8 | 0.42 | 1.79 |
| C | 0.5 | 0.53 | 1.55 |

*Source*: Refs. 23–28.

manufacturing process [35,36]. Ibrahim and Olurinaola monitored the effects of production, environment and method of production, as well as microbial quality of starting materials, on the microbial load during various stages of tablet production [35]. Although high levels of contamination were present during the wet granulation process, these levels were significantly reduced during the drying process. The investigators also found that products derived from natural origins, such as gelatins and starch, can be contaminated heavily.

**Table 3** Average Particle Data for Different Sources of Magnesium Stearate

| Source | Size (μm) | Surface area ($m^2/g$) | Pore radius (Å) |
|---|---|---|---|
| United States | 1.5–3.2 | 13.4 | 50 |
| Great Britain | 2.1–5.2 | 12.2 | 68 |
| Germany | 4.1–6.9 | 7.4 | 61 |
| Italy | 5.5–9.1 | 4.6 | 36 |

*Source*: Ref. 32.

### *Compatibility*

One final area that should be considered when choosing the excipients to be used in the tablet formulation is that of drug-excipient interactions. There is still much debate as to whether excipient compatibility testing should be conducted prior to formulation [37–39]. These tests most often involve the trituration of small amounts of the active ingredient with a variety of excipients. Critics of these small-scale studies argue that their predictive value has yet to be established and indeed do not reflect actual processing conditions [37]. Instead, they suggest a sound knowledge of the chemistry of the materials used in conjuncture with "mini-formulation" studies as a preferable method for investigation of drug-excipient interactions.

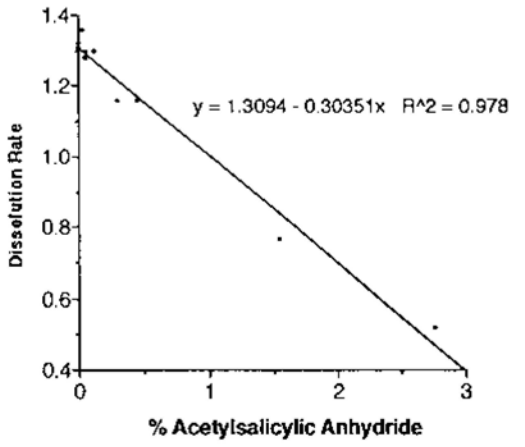


**Fig. 4** Effect of acetylsalicylic anhydride impurity on the dissolution rate of aspirin tablets. (From Ref. 34.)

## C. Tablet Components

Conventional solid dosage forms can be divided into two classes: those that disintegrate and those that do not. Disintegrating dosage forms release drug by breaking down the physical integrity of the dosage from, usually with the aid of solid disintegrating agents or gas-releasing effervescent agents. Nondisintegrating tablets are usually made of soluble drugs and excipients that will rapidly dissolve in the mouth or GIT upon ingestion.

With the advent of prolonged-release dosage forms, some pharmaceutical scientists have begun to regard conventional disintegrating dosage forms as "non–controlled-release." This term is a misnomer since, with the aid of "super-disintegrants" and other excipients, the disintegration of these dosage forms can be controlled, both quantitatively and qualitatively. Moreover, there are still many drugs in which rapid attainment of therapeutic levels, rather than controlled release, is required. Analgesics, antibiotics, and drugs for the acute treatment of angina pectoris are prime examples. These tablets need to be designed so that the drug is liberated from the dosage form in such a manner that dissolution of the drug is maximized. Very often, this means that disintegration of the tablet must be followed by granular disintegration (see Fig. 5) to promote rapid dissolution and, hence, absorption.

The ingredients, or excipients, used to make compressed tablets are numerous. They can be classified by their use, or function, as in Table 4. Keep in mind, however, that formulations need not contain all the types of ingredients listed in this table. Certain excipients, such as antioxidants and wetting agents, are used only in situations where they are expressly needed to assure the stability and solubility of the active ingredients. Other excipients, such as dissolution modifiers, are used primarily in controlled-release formulations. In fact, by reducing the number of ingredients in a formulation, one will generally be reducing the number of problems that can arise in the manufacturing process. Hence, many formulators adhere to the motto "Keep it simple."

Because of the nature of modern pharmaceutical systems, formulators have made more complete investigations of the materials they use. This interest has identified several materials that may have more than one use in tableted systems. The type of effect that an excipient will produce is often dependent upon the concentration in which it is used. For example, Table 5 lists some "multiuse" excipients and the corresponding concentration ranges required for their various applications.

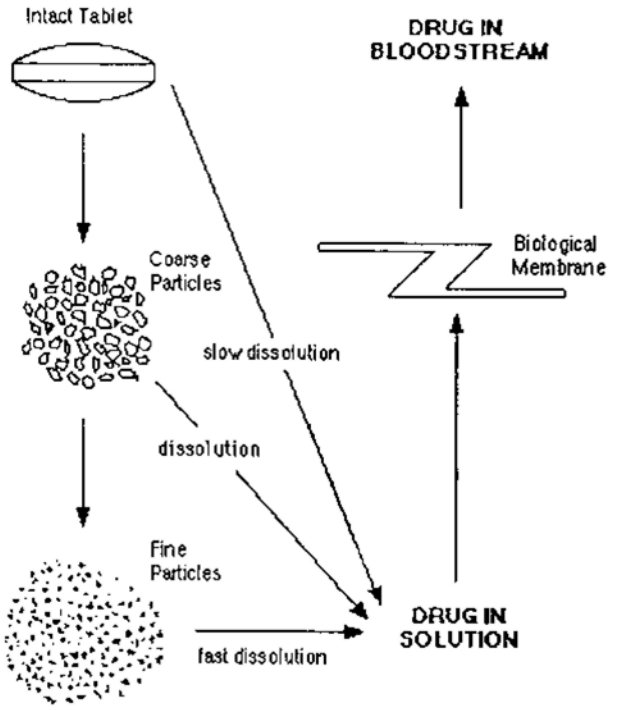


**Fig. 5** Absorption of a drug from an intact tablet.

A relatively new class of "co-processed" excipients now exists. These excipients are essentially a "preblend" of two or more excipients that are commonly used in conjunction with each other.

### *Active Ingredients*

The dose of the drug to be administered has a profound effect on the design and formulation of a dosage form. Content uniformity and drug stability become very important issues when dealing with highly potent compounds that are delivered in very small doses (e.g., oral contraceptives). However, the effect of the drug's properties on the tablet, in this case, is minimal. In general, as the dosage increases, so does the effect of the drug's attributes on the tablet.

**Table 4** Ingredients Used in Tablet Formulation

| | |
|---|---|
| Active ingredient (drug) | Dissolution modifiers |
| Fillers | Absorbents |
| Binders (dry and wet) | Flavoring agents |
| Disintegrants | Coloring agents |
| Antifrictional agents | Wetting agents |
| Lubricants | Antioxidants |
| Glidants | Preservatives |
| Antiadherants | |

**Table 5** Some Multiple-Use Excipients for Tablet Formulation

| Excipient/concentration in formula | Use |
|---|---|
| Ethylcellulose | |
| 1–3% | Wet or dry binder |
| 1–3% | Controlled-release coating |
| Glyceryl palmitostearate | |
| 0–5% | Lubricant |
| 10–50% | Controlled-release excipient |
| Hydroxypropylmethyl cellulose (HPMC), low viscosity | |
| 2–5% | Wet or dry binder |
| 2–10% | Film former |
| 5–25% | Controlled-release excipient |
| Magnesium aluminum silicate | |
| 2–10% | Binder |
| 2–10% | Disintegrant |
| Microcrystalline cellulose (MCC) | |
| 0–8% | Improve adhesion of film coat to core |
| 0.2–0.5% | Glidant |
| 5–20% | Antiadherant |
| 5–20% | Disintegrant |
| 5–95% | Binder/filler |
| Polyethylene glycol | |
| 0–10% | Lubricant |
| 0–15% | Thermoplastic filler/binder |
| 5–40% | Controlled-release excipient |
| Poly(methacrylates) | |
| 2–10% | Film former |
| 5–20% | Controlled-release excipient |
| 10–50% | Filler |
| 5–10% | Coating excipient |
| Poly(vinyl pyrrolidone) (Povidone, PVP) | |
| 5–15% | Wet binder |
| 5–10% | Coating excipient |
| 5–30% | Disintegrant |
| 10–35% | Controlled-release excipient |
| Starch | |
| 3–15% | Intragranular binder/disintegrant |
| 5–25% | Wet binder |
| 5–20% | Disintegrant |

Sometimes processing can affect the particle morphology of the active ingredient. This in turn may lead to adverse effects on mixing and tableting operations. In particular, micronization of a drug may cause crystals to change their shape even though polymorphism is not evidenced.

### *Fillers*

An increasing number of drugs are highly potent and are thus used in very low dosages. In order to produce tablets of a reasonable size (i.e., minimum diameter of 3 mm), it is necessary to dilute the drug with an inert material. Such diluents should meet important criteria, including low cost and good tableting qualities. It may be possible, in some instances, to combine the role of diluent with a different property, such as disintegrant or flavoring agent.

Commonly used fillers and binders and their comparative properties are listed in Table 6. As can be seen by this list, both organic and inorganic materials are used as fillers and binders. The organic materials used are primarily carbohydrates because of their general ability to enhance the product's mechanical strength as

**Table 6** Comparative Properties of Some Directly Compressible Fillers[a]

| Filler | Compactibility | Flowability | Solubility | Disintegration | Hygroscopicity | Lubricity | Stability |
|---|---|---|---|---|---|---|---|
| Dextrose | 3 | 2 | 4 | 2 | 1 | 2 | 3 |
| Spray-dried lactose | 3 | 5 | 4 | 3 | 1 | 2 | 4 |
| Fast-Flo lactose | 4 | 4 | 4 | 4 | 1 | 2 | 4 |
| Anhydrous lactose | 2 | 3 | 4 | 4 | 5 | 2 | 4 |
| Emdex (dextrates) | 5 | 4 | 5 | 3 | 1 | 2 | 3 |
| Sucrose | 4 | 3 | 5 | 4 | 4 | 1 | 4 |
| Starch | 2 | 1 | 0 | 4 | 3 | 3 | 3 |
| Starch 1500 | 3 | 2 | 2 | 4 | 3 | 2 | 4 |
| Dicalcium phosphate | 3 | 4 | 1 | 2 | 1 | 2 | 5 |
| Avicel (MCC) | 5 | 1 | 0 | 2 | 2 | 4 | 5 |

[a]Graded on a scale from 5 (good/high) down to 1 (poor/low); 0 means none.

well as their freedom from toxicity, acceptable taste, and reasonable solubility profiles.

One of the most commonly used carbohydrates in compressed tablets is lactose. Work by Bolhuis and Lerk [40] and Shangraw et al. [6] has demonstrated that all lactoses are not equivalent as determined by chemical, physiochemical, and functional measurements. In addition to the various particle-size grades of normal hydrous lactose, one can purchase spray-dried lactose, which is an agglomerate of α-lactose monohydrate crystals with up to 10% amorphous material. Spray-dried lactose has very good flow properties, but its poor compression characteristics require the addition of a binder such as MCC. However, one particular brand of spherical crystalline/amorphous agglomerate, Fast-Flo (NF hydrous), possesses superior compressibility and dissolution characteristics. The spherical nature of the crystals make them more compressible than spray-dried agglomerates of lactose [41]. Anhydrous lactose has also been used as a diluent, particularly in direct compression formulations where low moisture content is desirable, since it has very good stability and a reduced tendency to color upon aging. Another advantage in the use of anhydrous lactose is that its insensitivity to temperature changes allows it to be reworked with relative ease. Unfortunately, its flow properties are not particularly good and its compressibility is inferior to other forms of lactose. One must also give attention, though, to this component's stability, as aging may adversely affect these properties.

Some other sugars are now being produced in special grades to meet the needs of the pharmaceutical industry. Most of these products contain combinations of sucrose with invert sugar or modified dextrins and are of particular value in the formulation of chewable tablets. In addition, crystalline maltose and directly compressible grades of fructose are currently available and have gained a large degree of acceptance in the "nutraceutical" industry [41a].

Starch is often cited as a filler, but it is more commonly used in its dry state as a disintegrating agent. However, modified starches such as StaRx 1500 and National 1551 (partially hydrolyzed, or pregelatinized starch) are marketed for direct compression and appear to offer the advantage of substantial mechanical strength and rapid drug release.

Certain inorganic salts are also used as fillers. Some common examples are listed in Table 7 together with their comparative properties. Among the most popular

**Table 7** Comparative Properties of Some Inorganic Fillers[a]

| Filler | Availability | Mechanical | Solubility | Absorbency | Acid/base | Abrasiveness | Lubricity |
|---|---|---|---|---|---|---|---|
| Calcium carbonate | 2 | 4 | 0 | 3 | Base | 2 | 1 |
| Dicalcium phosphate | 2 | 2 | 0 | 4 | Base | 2 | 0 |
| Calcium triphosphate | 3 | 2 | 0 | 5 | Base | 2 | 0 |
| Magnesium carbonate | 2 | 2 | 0 | 4 | Base | 1 | 1 |
| Sodium chloride | 5 | 5 | 5 | 1 | Neutral | 3 | 2 |

[a]Graded on a scale from 5 (good/high) down to 1 (poor/low); 0 means none.

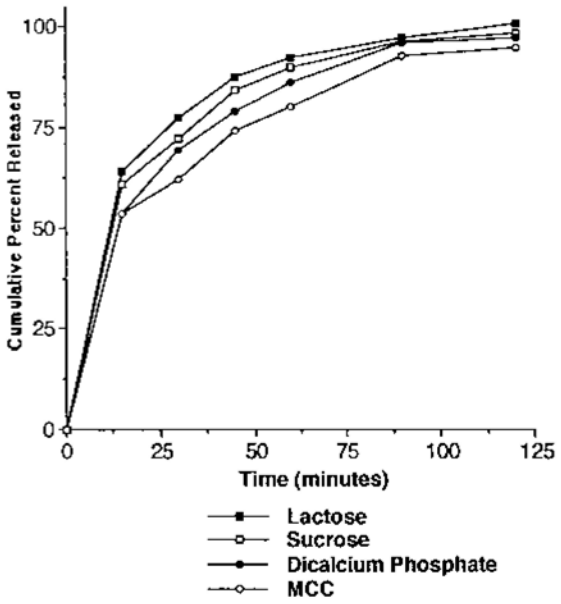


**Fig. 6** Dissolution of digoxin tablets containing different fillers (in simulated gastric fluid at 37°C). (From Ref. 45.)

is dicalcium phosphate dihydrate, a comparatively low-cost insoluble diluent with good powder flow potential but inherently poor compression characteristics [41]. It is important to note that this material is slightly alkaline and thus must not be used where the active ingredient is sensitive to pH values of 7.3 or above. Fuji has recently introduced an anhydrous grade of dibasic calcium phosphate (DCPA) as Fujicalin. Investigators have found that DCPA is highly compressible and promotes rapid dissolution, most likely due to its anhydrous nature [41b]. Special formulations in which unmilled dicalcium phosphate is the main ingredient are available under the trade name Emcompress® and contain 5–20% of other components designed to improve compaction and disintegration performance [6,40,42]. In accelerated stability studies, Shah and Arambulo [43] found Emcompress to be unsuitable for use with ascorbic acid and thiamine hydrochloride due to deteriorating hardness and disintegration characteristics evidenced, as well as the chemical degradation of ascorbic acid. In addition, calcium salts present in dibasic calcium phosphate may adversely affect the absorption profile of certain drugs [44].

The influence of the actual manufacturing process can also affect the contribution of the diluent to the final characteristics of the product. For instance, Shah et al. [45] demonstrated that the release of drug from tablets formulated with soluble excipients may be more prompt than those formulated with insoluble excipients (see Fig. 6). However, they also found that the method of preparing the triturates was also very significant. In this example, ball or Muller milling gave the best overall results.

Few tablets intended for oral administration are totally soluble in aqueous media, but if such a product is needed, then soluble excipients are employed. These include dextrose, lactose, mannitol, and sodium chloride, with the last of these sometimes acting as its own lubricant. Urea may also be used, but due to its known pharmacological effects, it is less desirable than the other soluble compounds cited.

### *Binders and Granulating Fluids*

Most binders used in wet granulation tend to be polymeric in nature. The binders most commonly used are natural in source, such as starch or cellulose derivatives. Typically, these agents are dispersed or dissolved in water or a hydro-alcoholic medium. The binders can be sprayed, poured, or admixed into the powders to be agglomerated. The methods of incorporating these materials can be classified into low-shear, high-shear, atomization, and extrusion methods. As illustrated in Fig. 7, one can see that the concentration of binder used and its method of addition (as a dry powder or as a granulating fluid) can affect significantly affect granule size [46]. Moreover, some researchers have found that increasing the amount of

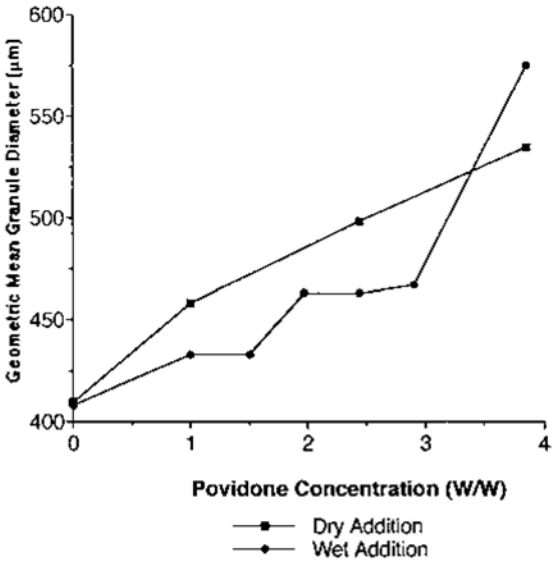


**Fig. 7** Effect of binder concentration and method of addition on granule size. (From Ref. 46.)

granulating fluid used can have profound effects on a tablet's mechanical strength and disintegration time [47]. Some commonly used binders are listed in Table 8.

Seager et al. [48] showed that a binder can be useful for a given process but may not be universally useful. They studied gelatin in granulations made by roller-compaction, conventional wet granulation, and spray-drying. These researchers found spray drying to be the preferred method of granulation for gelatin-granulated acetaminophen. They hypothesized that this was due to the improved distribution of the binder in this system. Studies evaluating the influence of PVP-based granulating methods on granules of lactose and MCC found that MCC granules (plastically deformable) were highly dependent on granulating method while brittle lactose granules were not (brittle) [48a]. Chowhan showed that considerable variability often occurs when scale-up of a granulation takes place. He demonstrated that a major factor in scale-up is the drug itself, which may require more or less granulating fluid and binder to make a suitable tablet. He also found that this may impact the drug release and thus bioavailability of the dosage form [49].

Iyer et al. [50] investigated the effects of roto-granulation on the performance of hydroxypropyl methylcellulose (HPMC), gelatin, and poly(-vinylpyrrolidone) (Povidone, PVP). In this process, all three binders produced similar results. However, HPMC was preferred due to prolonged drug release profiles, smaller particle size, and better content uniformity.

The use of hydroxypropyl cellulose (HPC), a binder, has increased in recent years [50a–50c]. This material has been shown to reduce the incidence of capping when compared with MCC, PVP, and starch [50a]. In addition, low substituted grades of HPC can also be used as a filler/ binder [50b].

York, reviewed the solid-state properties of solids and showed that both intrinsic and induced properties can have a profound effect on wettability and processing [51]. In addition, Lerk et al. [52,53] investigated the surface characteristics of a number of drugs and showed that the contact angles can vary greatly depending on the drug (see Table 9). Of interest is the difference in wettability of different crystalline forms of the same drug [52,53]. These properties will have a profound effect on the ability of various binders to function as well as change the processing parameters needed to effect proper granulation.

### *Disintegrants*

For most tablets, it is necessary to overcome the cohesive strength introduced into the mass by compression. It is therefore common practice to incorporate an excipient, called a disintegrant, which induces this process. Several types, acting by different mechanisms, may be distinguished: (a) those that enhance the action of capillary forces in producing a rapid uptake of aqueous liquids, (b) those that swell on contact with water, (c) those that release gases to disrupt the tablet

**Table 8** Some Commonly Used Wet Binders and Granulating Fluids

| Name | Strength (%) | Comments |
|---|---|---|
| Acacia mucilage[a] | 1–5 | Produces hard, friable granules |
| Cellulose derivates[a] | 5–10 | HPMC[b] is most common |
| Ethanol | | Applied to easily hydratable material |
| Gelatin solutions | 10–20 | Gels when cold, therefore use warm; strong adhesive; used in lozenges; less suitable in warm moist climates |
| Glucose syrups | 25–50 | Strong adhesive; tablets may soften in high humidity |
| Povidone | 5–15 | Different MW grades give varying results |
| Starch mucilage[a] | 5–10 | One of best general binders; better when used warm |
| Sucrose syrups[a] | 65–85 | Strongly adhesive; tablets may soften in high humidity |
| Tragacanth mucilage[a] | 10–20 | Produces hard, friable granules |
| Water | | Applied to easily hydratable material |

[a]May also be added as dry powder to the formulation, but this is less efficient than liquid preparation.
[b]Hydroxypropylmethylcellulose.

**Table 9** Contact Angles for Some Powders

| Material | Contact angle ($\phi$) |
|---|---|
| Acetylsalicylic acid | 74 |
| Aminophylline | 47 |
| Ampicillin, anhydrous | 35 |
| Ampicillin, trihydrate | 21 |
| Calcium stearate | 115 |
| Chloramphenicol | 59 |
| Chloramphenicol palmitate ($\alpha$-form) | 122 |
| Chloramphenicol palmitate ($\beta$-form) | 108 |
| Diazepam | 83 |
| Digoxin | 49 |
| Indomethacin | 90 |
| Lactose | 30 |
| Magnesium stearate | 121 |
| Phenylbutazone | 109 |
| Prednisolone | 43 |
| Prednisone | 63 |
| Stearic acid | 98 |
| Sulfacetamide | 57 |
| Theophylline | 48 |
| Tolbutamide | 72 |

*Source*: Refs. 52 and 53.

structure, and (d) those that destroy the binder by enzymatic action.

The method of addition has also received attention. In particular, during wet granulation, the addition of the disintegrant before (intragranular) or after (extragranular) the granulation process has been investigated (see Figs. 8 and 9) [54]. The extragranular portion

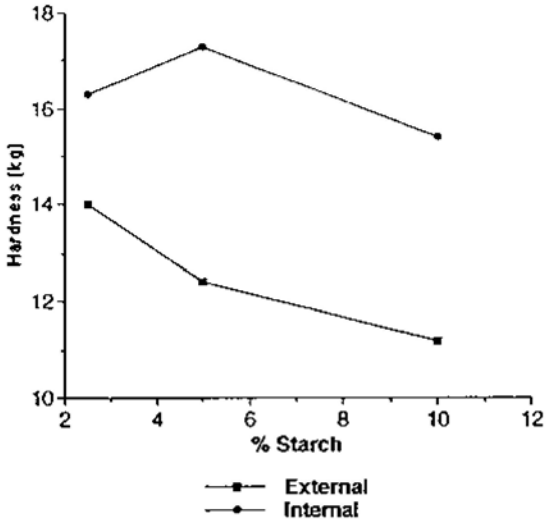


**Fig. 8** Effect of starch concentration and location on tablet hardness. (From Ref. 54.)

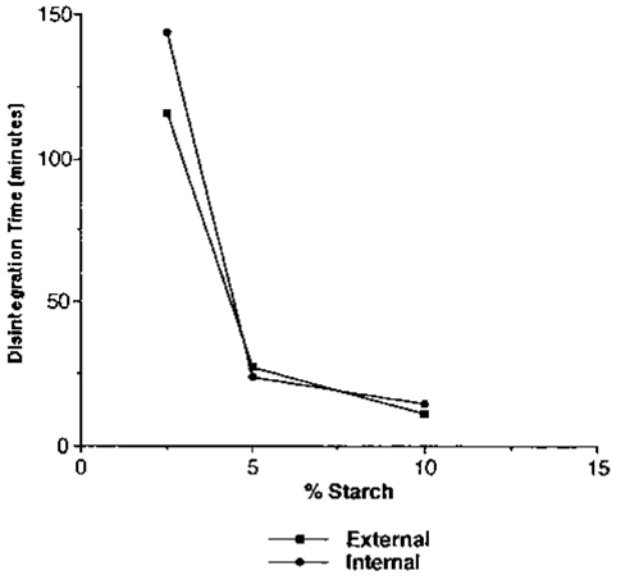


**Fig. 9** Effect of starch concentration and location on tablet disintegration time. (From Ref. 54.)

ensures rapid disintegration, while the intragranular fraction leads to harder tablets and a finer size distribution on dispersion. The consensus of the published papers on this topic appears to be that there are advantages to be gained in dividing the disintegrant into both extra- and intragranular portions, with between 20 and 50% being external. For example, 2.5% intragranular and 12.5% extragranular disintegrant produced the best overall performance in tablets of calcium orthophosphate [55].

*Water Uptake.* There is evidence to suggest that water uptake caused by capillary forces is the crucial factor in the disintegration process of many formulations. In such systems the pore structure of the tablet is of prime importance and any inherent hydrophobicity of the tablet mass will adversely affect it. Therefore, disintegrants in this group must be able to maintain a porous structure in the compressed tablet and show a low interfacial tension towards aqueous fluids. Rapid penetration by water throughout the entire tablet matrix to facilitate its breakup is thus achieved. Concentrations of disintegrant that ensure a continuous matrix of disintegrant are desirable and levels of between 5 and 20% are common.

Water uptake has been implicated as a mechanism of action for tablet disintegrants. Khan and Rhodes studied the adsorption and absorption properties of various disintegrants [56]. They concluded that the

ability of particles to draw water into the porous network of a tablet (wicking) was essential for efficient disintegration. Work conducted by Mitrevej and Hollenbeck substantiates these claims [57]. A sophisticated method of determining water uptake was developed by Nogami et al. [58]. Their study further supports the theory that the rate of wetting is responsible, at least in part, for the disintegrant action.

Starch was the first disintegrant used in tablet manufacture and still enjoys wide use today [59–66]. Its mode of action is probably through the induction of water uptake into the tablet rather than by the swelling action previously ascribed to it [57–63]. Other workers [67] still consider that the hydration of the hydroxyl groups causes them to move apart, yet it appears that starch swells little in water at body temperature. There is some evidence to suggest that the fat content of starch can also influence its performance as a disintegrant. In addition, since starch possesses poor binding characteristics, once the tablets containing it become thoroughly wetted they break up easily [62,63,65]. Varieties of starch containing large grains are preferred for other reasons, but in the present context a large particle size may provide the optimum pore size distribution within the tablet and thus promote capillary action (e.g., potato starch).

Some forms of MCC have been shown to be highly porous, with strong "wicking" tendencies, thereby making them good disintegrants. This is a fortuitous finding since they also serve as excellent binders and are able to improve significantly the mechanical strength of some weak formulations. One disadvantage of using MCC, however, is that dissolution performance may be adversely affected at higher compression forces. Another disintegrant group, the insoluble cationic exchange resins, typified by polyacrylin, exhibits better dissolution characteristics when subjected to higher pressures. Comparisons of disintegrant action, however, will only be valid if carried out under the same controlled conditions.

Some disintegrants propagate capillary effects but also swell and/or dissolve to enhance disintegration behavior. Sodium starch glycolate and insoluble cationic exchange resins are two examples that have been extensively studied by Khan and Rhodes [56,68], who demonstrated their superiority to sodium carboxymethylcellulose and corn starch. Their results correlated will with the comparative release patterns of a dye from tablets containing these materials. In addition, they were able to show the long-term deterioration in hardness and disintegration time when the tablets containing the more effective disintegrants were subjected to high humidities. A comparative evaluation of sodium starch glycolate against cross-linked carboxymethylcellulose and sodium glycine carbonate has been carried out by Bavitz et al. [69], who determined that cross-linked carboxymethylcellulose compared very favorably with sodium starch glycolate in formulations of four different actives over long test periods. Colloidal silicon dioxide has been investigated as a disintegrant, and, although capable of absorbing approximately nine times more water than starch, the process is several times slower; the hindered action offsets much of the advantage of its greater absorbency.

*Swelling*. Perhaps the more widely accepted general mechanism of action for tablet disintegrants is swelling. Almost all disintegrants swell to some extent, and swelling has been reported quite universally in the literature [6,70,71]. Historically, sedimentation volumes of the disintegrant in a slurry have been used as measures of swelling. This test is a fair appraisal of swelling capacity but does not provide for the dynamic measurement of the swelling itself. As a result, many disintegrants studied by this method do not show a correlation between sedimentation volumes and disintegrant efficiency. Nogami et al. developed a reliable test to measure swelling and water uptake simultaneously with the aid of two graduated columns connected by a rubber tube [58]. This apparatus was later refined by several research groups [72–74]. Figure 10 illustrates the essential features of this apparatus, which is very useful for the quantification of swelling and hydration rates for many excipients and polymers.

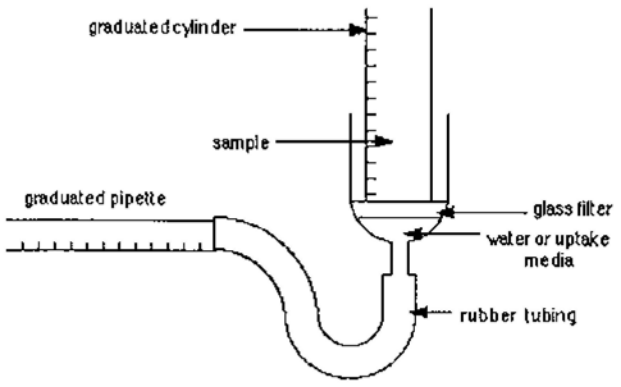


**Fig. 10** Bulk swelling and water uptake apparatus.

Both sedimentation volumes and swelling rates were evaluated by Rudnic et al., who found a poor correlation between the static test (sedimentation) and disintegrant efficiency [74]. In addition, they found that swelling tests, such as those reported above, are dependent upon a number of variables including water transport through a gel layer and rates of hydration. These investigators developed methods to evaluate intrinsic swelling through the use of high-speed cinemicroscopy in conjunction with computerized image analysis. Although their method allowed for more accurate and precise measure of swelling, they concluded that both bulk swelling and intrinsic swelling produced similar rank order disintegrant swelling rates.

All of the investigations described above have placed importance not only on the extent of swelling, but also on the rate at which swelling develops. In addition, it is important to understand that, as particles swell, there must be little or no accommodations by the tablet matrix to that swelling. If the matrix yields elasticity to the swelling, little or no force will be expended on the system and disintegration will not take place. If the matrix is rigid and does not accommodate swelling, however, deaggregation or disintegration will occur.

One general problem with this group of disintegrants is that upon swelling, many disintegrants produce a sticky or gelatinous mass that resists breakup of the tablet, making it particularly important to optimize the concentration present within the granulation. For example, some powdered gums, such as agar, karaya, or tragacanth, swell considerably when wet, but their pronounced adhesiveness limits their value as disintegrants and restricts the maximum concentration to which they can be effectively used to approximately 5% of tablet weight. Because these substances are nonsynthetic, they also exhibit considerable lot-to-lot variability, are liable to microbiological contamination, and can be quite expensive. However, alginic acid and its sodium salt have sufficient swelling with minimum stickiness, and concentrations as low as 4 or 5% are often adequate. The small levels of alginates required compensate for the somewhat high cost of these materials.

Although untreated starches do not swell sufficiently, certain modified forms, such as sodium starch glycolate, do swell in cold water and are better as disintegrants. Various cellulose derivatives, including methylcellulose and carboxymethylcellulose, have been used in this role, but with limited success due to the marked increase in viscosity they produce around the dispersing tablet mass.

*Gas Production.* Gas-producing disintegrants are used when especially rapid disintegration or a readily soluble formulation is required [70]. They have also been found to be of value when poor disintegration characteristics have resisted other methods of improvement. Their main drawback is the need for more stringent control over environmental conditions during the manufacture of tablets made with these materials. In particular, gas-producing disintegrants are quite sensitive to small changes in humidity levels. For this reason, these disintegrants are often incorporated immediately prior to compression, when the moisture content can be controlled more easily and/or they can be added to two separate fractions of the formulation. Composition is based upon the same principles as those used for effervescent tablets, the most common being mixtures of citric and tartaric acids plus carbonates or bicarbonates.

In many instances, lower concentrations of gas-producing disintegrants can be used than are required by other disintegrating agents. This is a distinct point in their favor. Certain peroxides that release oxygen have been used for this purpose, but they do not perform as well as those releasing carbon dioxide.

*Enzymes.* Where tablets are not naturally very cohesive and have thus been manufactured by a wet granulation process involving one of the binders listed in Table 8, addition of small quantities of appropriate enzyme may be sufficient to produce rapid disintegration. It has also been proposed that disintegration action might result from expansion of the entrapped air due to generation of "heat of wetting" when the tablet is placed in a fluid. This concept has received little attention.

### *Other Factors*

DEFORMATION. The existence of plastic deformation under the stress of tableting has been reported for many years. Hess determined that disintegrant particles deform when compressed during the tableting process with the aid of scanning electron micrographs [64]. He found that the deformed particles returned to their normal shapes when exposed to water. Work completed by Fuhrer yielded similar results [75]. In some cases, the swelling capacity of starch granules was improved when the granules were extensively deformed during compression. Obviously, the role of deformation and rebound under actual production conditions need to be studied in more detail before the full effect of this phenomenon can be understood.

PARTICLE REPULSION THEORY. Another theory of tablet disintegration attempts to explain the swelling of tablets made with "nonswellable" starch. Guyot-Hermann and Ringard have proposed a particle repulsion theory based upon the observation that particles that do not seem to swell may still disintegrate tablets [66]. In their study they altered the dielectric constant of the disintegrating media in an effort to identify electric repulsive forces as the mechanism of disintegration and concluded that water is required for tablet disintegration. These investigators espoused repulsion, secondary to wicking, as the primary mechanism of action for all tablet disintegrants.

HEAT OF WETTING. Matsumaru was the first to propose that the heat of wetting of disintegrant particles could be a mechanism of action [76]. He observed that starch granules exhibit slight exothermic properties when wetted and reported that this was the cause of localized stress resulting from capillary air expansion. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents. List and Muazzam [77] studied this phenomenon and also found disintegrants where significant heat of wetting is generated. However, in these cases there is not always a corresponding decrease in disintegration time.

PARTICLE SIZE. Physical characteristics of disintegrants, such as particle size, also have some bearing on the mechanisms of disintegration (e.g., swelling and water uptake). Several authors have attempted to relate the particle size of disintegrants to their relative efficiency. Smallenbroek et al. [78] evaluated the effect of particle size of starch grains on their ability to disintegrate tablets. They concluded that starch grains with relatively large particle sizes were more efficient disintegrants than the finer grades. These authors theorized that this behavior resulted from increased swelling pressure. Investigations made by Rudnic et al. [74,79] confirm these results. They also found a correlation between the rate of swelling and the amount of water uptake of sodium starch glycolate and have thus postulated that particle size plays a key role in the overall efficiency of commercial sources of this material.

MOLECULAR STRUCTURE. In their attempts to identify the mechanism(s) of action of tablet disintegrants, researchers recently have turned their attention to the molecular structure of disintegrants. Schwartz and Zelinskie [65] published one of the first such reports in which they examined the two corn starch fractions amylose and amylopectin. They concluded that the linear polymer amylose was responsible for the disintegrant properties of starch while the amylopectin fraction was primarily responsible for the binding properties associated with starches (see Fig. 11). Because of the work by Schwartz and Zelinskie, tablet formulators can now select from a range of specialty starches that represent different ratios of amylose and amylopectin content to solve disintegrant/dissolution problems encountered in tablet formulation.

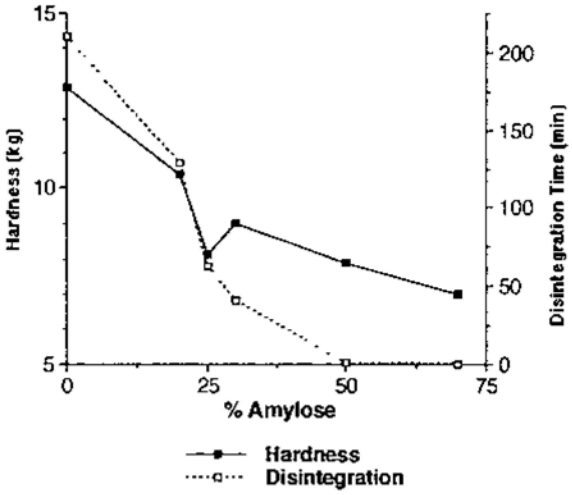


**Fig. 11** Effect of amylose on the hardness and disintegration of dicalcium phosphate tablets. (From Ref. 62.)

*Super Disintegrants.* Shangraw et al. identified three major groups of compounds that have been termed superdisintegrants [6]. Many of these so-called superdisintegrants are substituted and cross-linked polymers. One group—the sodium starch glycolates—has enjoyed widespread popularity due to its exceptional ability to disintegrate tablets as well as the relative ease with which this type of compound can be processed into tablet formulations.

Sodium starch glycolate is manufactured by cross-linking and carboxymethylating potato starch. It provides an excellent opportunity to measure the relationship between molecular structure and disintegrant efficiency by altering the degree of substitution and the extent of cross-linking. Optimization of one sodium starch glycolate was performed using both direct compression and wet granulation methods.

These studies showed that the swelling to the disintegrant particles was inversely proportional to the level of substitution [80].

A number of published studies have described the use of various substances as tablet disintegrants. Reviews by Lowenthal and Kanig and Rudnic have been published on the various agents used to bring about tablet disintegration [70,71]. Shangraw et al. reviewed the modern so-called superdisintegrants and compared their relative morphological properties [6]. Most published studies have attempted to explain mechanisms that relate to observed efficiency of the disintegrating agent, and some have explored secondary attributes within the disintegrants themselves. None have succeeded, however, in advancing an explanation of disintegration that approaches a universal understanding applicable to all disintegrants. It now seems obvious that no single mechanism is applicable to all tablet disintegrants. In fact, a combination of mechanism may be operative.

### *Antifrictional Agents*

*Insoluble Lubricants.* Lubricants act by interposing an intermediate layer between the tablet constituents and the die wall. The smaller the amount of stress needed to shear the material, the better its lubricant properties will be. Since they are primarily required to act at the tooling/material interface, lubricants should be incorporated in the final mixing step after all granulation and preblending is complete. In this way, overmixing is less likely to occur.

A common mistake in the design of tablet operations is adding both the disintegrant and lubricant together in one mixing step. This causes the disintegrant to become coated with lubricant and often results in both a decrease in the disintegrant's porosity and a decrease in the efficiency of the disintegrant. Rather than add the disintegrant and lubricant simultaneously, a better approach is to add these excipients sequentially, with a disintegrant being first.

The surface area of the lubricant may be the most important parameter to monitor, in terms of lubricant efficiency. Substantial decreases in both ejection forces and tablet hardness are noted when using brands of magnesium with larger surface areas. Lubricants with high surface areas may also be more sensitive to changes in mixing time than lubricants with low surface areas. Thus, if a particular drug or formulation is deleteriously affected by prolonged mixing of lubricants, adequate characterization of monitoring of a lubricant surface area should be an integral part of product development and quality control.

Some of the more common antifrictional agents are listed in Table 10. Many of these are hydrophobic and may consequently affect the release of medicament. Therefore, lubricant concentration and mixing time should be kept to the absolute minimum. Lubricants may also reduce significantly the mechanical strength of the tablet (see Fig. 12) [29,81]. Stearic acid and its magnesium and calcium salts are widely used, but the

**Table 10** Some Commonly Used Antifrictional Agents

| | |
|---|---|
| Soluble lubricants | Insoluble lubricants |
| Adipic acid | Calcium, magnesium, and zinc salts of stearic acid |
| *d*, *l*-Leucine | Glyceryl monostearate |
| Glyceryl triacetate | Glyceryl palmitostearate |
| Magnesium lauryl sulfate | Hydrogenated vegetable oils |
| PEG 400, 6000, and 8000 | Hydrogenated castor oil |
| Polyoxyethylene monostearates | Light mineral oil |
| Sodium benzoate | Paraffins |
| Sodium lauryl sulfate | Polytetrafluoroethylene |
| Sucrose monolaurate | Sodium stearyl fumarate |
| Glidants | Stearic acid |
| Calcium silicate | Talc |
| Colloidal silicon dioxide | Waxes |
| Magnesium carbonate | Antiadherants |
| Magnesium trisilicate | Most lubricants |
| Starch | Starch |
| Talc | Talc |

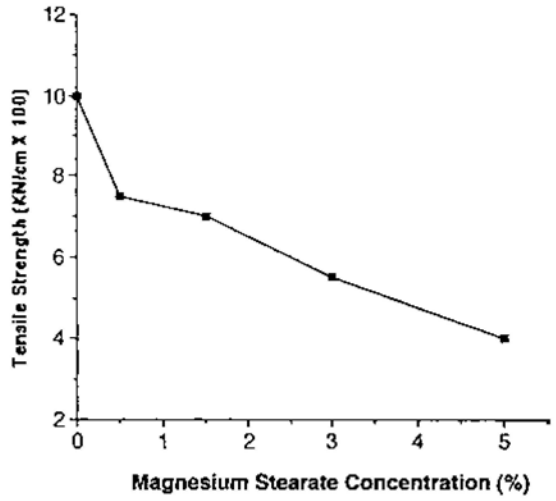


**Fig. 12** Tensile strength of calcium sulfate tablets as a function of magnesium stearate concentration (solid fraction = 0.57). (From Ref. 29.)

latter can be sufficiently alkaline to react with certain amine salts such as aminophylline, resulting in the release of free base and discoloration of the tablet. Published formulas show levels of these lubricants between 1 and 4%, but there is evidence to show that, in many cases, they can be reduced to as little as 0.25% without significantly affecting the lubrication of the system.

Liquid paraffins, particularly those of low viscosity, have been used and are said to be of value for colored tablets, and even the use of modified vegetables has been attempted. However, they appear, in general, to offer little advantage over solid lubricants, and their incorporation into the precompression mixture is more difficult, requiring solution in a volatile liquid that is then sprayed onto the unlubricated material. Due to handling and EPA requirements, these materials are often rejected in the preformulation stage.

Isolated references in the literature describe the use to talc as a lubricant, but this material is better regarded as a glidant [82–85]. It has several disadvantages, including its insolubility in body fluids and the abrasiveness found when using all but the finest grades of this material. Finally, it loses some of its effectiveness after compression so that tablets containing talc cannot be readily reworked without extra quantities of it being added to the formulation.

*Soluble Lubricants.* Because of the association of lubricant properties with lipophilic materials (and hence poor aqueous solubility), alternative, more hydrophilic materials have been investigated. Soluble lubricants do not appear to be as efficient in lubricating tablet systems as their insoluble counterparts [82]. Receiving increasing attention in this context is a group of soluble, if less effective, lubricants that also possess surfactant qualities and are typified by the lauryl sulfates. For example, when tablets lubricated with sodium lauryl sulfate were compared to those lubricated with magnesium stearate, the tablets containing sodium lauryl sulfate exhibited a significantly higher rate of dissolution. Physical mixtures of the lubricant with stearates can lead to the best compromise in terms or lubricity, tablet strength, and disintegration. Recently, magnesium lauryl sulfate has been found to have an attractive balance of these properties, although requiring a concentration of 5% to provide the same lubricating efficiency as 2% magnesium stearate.

Some of the synthetic, soluble, wax-like polymers, typified by the high molecular weight polyethylene glycols (PEGs), have also been used as soluble lubricants. PEG 4000 and 6000 have been investigated, but their lubricant efficiency is less than that of magnesium stearate. In attempts to find the optimum lubricant from all standpoints, combinations of polymers such as polyoxyethylene monostearates and polyoxethylene lauryl sulfates have undergone limited trials, with some encouraging results, but more information is required.

*Glidants.* Glidants are added to the formulation in order to improve the flow properties of the material to be fed into the die and sometimes aid in particle rearrangement within the die during the early stages of compression [6,85]. They may act by interposing their particles between those of the other components and so, by virtue of their reduced adhesive tendencies, lower the overall interparticulate friction of the system. In addition, there may be adsorption of glidant into the irregularities of the other materials. It follows that, like lubricants, they are required at the surface of feed particles and that they should be in a fine state of division and appropriately incorporated in the mix.

Starches remain a popular glidant, in particular those with the larger grain sizes such as potato starch, possibly because of their additional value as a disintegrant in the formulation. Concentrations up to 10% are common, but it should be appreciated that excess may result in exactly the opposite effect of that desired (i.e., flow properties may worsen). Talc is also widely used and has the advantage that it is superior to starches in minimizing any tendency for material to stick

to the punch faces, a property sometimes classified as antiadherent. Because of its totally insoluble nature, and hence potential retardant effect of dissolution, concentration must be strictly limited and should rarely exceed 5%. In fact, the best overall compromise may be realized by using a mixture of starch and talc.

Several silaceous materials have been used successfully to induce flow. Among those quoted in the literature are pyrogenic silica in concentrations as low as 0.25% and hydrated sodium silioaluminate in concentrations of around 0.75%. The former has the additional property of being able to scavenge moisture, which might otherwise contribute to restricted flow characteristics.

Phyllosilicates, in addition to talc and silica, have recently been evaluated for their use as tableting excipients. These compounds include the smectites, palygorskites, and sepiolites [85a]. Although they show some promise, current levels of metallic impurities are currently too high for use in pharmaceutical preparations.

*Antiadherents.* Some materials strongly adhere to the metal of the punches and dies. Although not a frictional effect, this results in material preferentially sticking to the punch faces and gives rise to tablets with rough surfaces. This effect, called picking, can also arise in formulations containing excess moisture.

Normally, the lubricants present in the tableting mass also act as antiadherents, but in the worst cases it may be necessary to add more starch or even talc to overcome the defect. So by judicious choice of a combination of excipients, all of these undesirable effects of the tableting process can be minimized.

### *Dissolution Modifiers*

This topic is the subject of Chapter 15, but some of the materials that are used in these systems have other uses as well (Table 5). Materials used to modify dissolution can be incorporated in the formulation on either a dry or wet basis. Table 11 lists some of the more commonly used controlled release excipients.

**Table 11** Some Commonly Used Controlled-Release Excipients

| |
|---|
| Hydrophilic |
| Acrylic acid |
| Acrylic acid derivatives/esters |
| Carboxymethyl cellulose (CMC) |
| Ethylcellulose (EC) |
| Hydroxypropylcellulose (HPC) |
| Hydroxypropylmethylcellulose (HPMC) |
| Methylcellulose (MC) |
| Poly(acrylic acid) (PAA) |
| Poly(aminobutyl glycolic acid) (PAGA) |
| Poly(caprolactone) (PCL) |
| Poly(lactic acid) (PLA) |
| Poly(lactic co-glycolic acid) (PLGA) |
| Poly(vinyl acetate) (PVAc) |
| Poly(vinyl alcohol) (PVA) |
| Poly(vinyl pryrrolidone) (Povidone, PVP) |
| Polyethylene glycol (PEG) |
| Hydrophobic |
| Carnauba wax |
| Glyceryl monostearate |
| Glyceryl palmitostearate |
| Hydrogenated vegetable oil |
| Paraffin |
| White wax |
| pH-dependent |
| Cellulose acetate phthalate (CAP) |
| Hydroxypropylmethyl cellulose phthalate (HPMCP) |
| Poly(methacrylates) |
| Poly(vinyl acetate phthalate) (PVAP) |
| Shellac |
| Zein |
| Surface-active |
| Pluronics |

### *Absorbents*

Some tablet formulations call for the inclusion of a small amount of semisolid, or even semiliquid, ingredient. It is highly desirable that any such component should be adsorbed onto, or absorbed into, one of the powders. In cases where none of the other excipients in the formulation is able to act as a carrier, an absorbent may have to be included. When oily substances, such as volatile-favoring agents, are involved, magnesium oxide and magnesium carbonate have been found to be suitable for this purpose. Natural earths, such as kaolin, bentonite, and Fuller's earth, have also been used and possess pronounced absorbent qualities. In general, they tend to reduce tablet hardness and may be abrasive. Therefore, fine, grit-free grade must be specified.

An absorbent may also be necessary when the formulation contains a hygroscopic ingredient, especially when absorption of moisture produces a cohesive powder that will not feed properly to the tablet press. In such instances, silicon dioxide has been found to be of particular value.

One special problem in the tableting of volatile medicaments, like nitroglycerin, is the loss of activity

through evaporation. This effect can be reduced by fixing agents such as PEG 400 or 4000 in concentrations of 85%. Alternatively, cross-linked povidone can also be used to enhance the stability of this particular drug.

### *Flavoring Agents*

Making a formulation palatable enough to be chewed may result in enhanced availability of the drug. In addition, for patients who are unable to swallow a tablet whole (e.g., children), such a tablet may be the only reasonable alternative. Sweetening agents such as dextrose, mannitol, saccharin, and sucrose are widely used as flavoring agents (see Table 12). When choosing a flavoring agent, however, one must carefully assess potential incompatibilities that may exist between the agent and the active ingredient. Perhaps the most extensively documented examples concern nitroglycerin tablets, which at one time were formulated in a chocolate base containing nonalkalized cocoa. Unfortunately, the cocoa affected the product's stability and has since been replaced by mannitol.

Flavoring agents proper are commonly volatile oils that have been dissolved in alcohol and sprayed onto the dried granules or have simply been adsorbed onto another excipient (e.g., talc). They are added immediately prior to compression to avoid loss through volatilization. In some cases they may even have some lubricating activity. If the oil normally contains terpenes, a low terpene grade is better so as to avoid possible deterioration in taste due to terpene oxidation products. When an oil flavoring is prone to oxidation, it may be protected by a special type of encapsulation involving spray drying or an aqueous emulsion containing the flavor. The emulgent used in spray-dried products may be starch or acacia gum giving rise to the so-called dry flavors.

**Table 12** Some Commonly Used Sweetening Agents

| |
|---|
| Bulk |
| Compressible sugar |
| Confectioner's sugar |
| Dextrose |
| Glycerin |
| Lactose |
| Liquid glucose |
| Maltitol solution |
| Mannitol |
| Sorbitol |
| Sucrose |
| Xylitol |
| Intense |
| Acesulfame potassium |
| Aspartame |
| Saccharin |
| Saccharin sodium |
| Sodium cyclamate |

### *Pharmaceutical Colors*

Colorants do not contribute to therapeutic activity, nor do they improve product bioavailability or stability. Indeed, they increase the cost and complication of the manufacturing process. Their main role is to facilitate identification and to enhance the esthetic appearance of the product. In common with all material to be ingested by humans, solid dosage forms are severely restricted in the coloring agents that are allowable. This situation is complicated by the lack in international agreement on an approved list of colorants suitable for ingestion.

Colorants are available as either soluble dyes (i.e., giving a clear solution) or insoluble pigments that must be dispersed in the product (see Table 13). There is an increasing tendency to use dyes in the form of special pigments termed "lakes." The pigment in this case is adsorbed onto some inert substrate, usually aluminum hydroxide. These pigments can be directly incorporated into tablets. In such cases it is often preferable to mix the lake with an extendor prior to incorporation into the tablet blend to minimize any mottling. Ordinary starch or modified starches, such as StaRx 1500, or sugars can be used for this purpose. In addition, mottling is less evident in pastel shades and colors in the center of the visible spectrum.

For tablet coating there are distinct advantages to using pigments rather than dyes. Color development is more rapid and hence processing time is shorter. Since the final color is a function of the quantity of dye in the coating suspension, rather than the number of coats applied, there will be less operator influence and a better chance of achieving uniformity within and between batches. There may also be a reduced risk of interaction between the drug and other ingredients.

All dyes, and to a lesser extent lakes, are sensitive to light to varying degrees, and their color may be affected by other ingredients in the formulation. For example, since many colorants are sodium salts of organic acid, they may react in solution with cationic drugs (e.g., antihistamines). In addition, nonionic surfactants may adversely effect color stability. This is more prevalent when using natural colorants, which also tend to have a higher degree of batch-to-batch

**Table 13** Differences Between Lakes and Dyes

| Characteristics | Lakes | Dyes |
|---|---|---|
| Solubility | Insoluble in most solvents | Soluble in water, propylene glycol, and glycerin |
| Method of coloring | By dispersion | By solution |
| Pure dye content | 10–40% | Primary colors: 90–93% |
| Rate of use | 0.1–0.3% | 0.01–0.03% |
| Particle size | $< 0.5$ μm | 12–200 mesh |
| Stability | | |
| Light | Better | Good |
| Heat | Better | Good |
| Coloring strength | Not proportional to dye content | Directly proportional to pure dye content |
| Shades | Varies with pure dye content | Constant |

*Source*: Warner Jenkinson Pamphlet on Lake Pigments, September 1990.

variability. However, unlike artificial dyes, natural colors do not require FDA certification prior to use in drug products. Some of the more common synthetic colorants are listed in Table 14 together with their important properties.

### *Wetting Agents*

Wetting agents have been used in tablets containing very poorly soluble drugs in order to enhance their rate of dissolution [86–89]. Surfactants are often chosen for this purpose, with sodium lauryl sulfate being the most common. Paradoxically, some ionic surfactants have recently been formulated with oppositely charged drugs to produce a sustained release complex [90–92]. Thus, one might want to consider using an uncharged surfactant, such as polysorbate 80 (Tween 80), which has less likelihood of interacting with charged molecules.

### *Co-processed Excipients*

It is now possible to commercially obtain co-processed excipients (see Table 15). These excipients are essentially a "preblend" of two or more excipients that are commonly used in conjunction with each other [92a–92d]. Advantages to using co-processed excipients include a reduction in the number of raw materials and processing time required for a given formulation and a potential for improved batch-to-batch consistency. In addition, investigators found that tablets prepared from silified MCC (co-processed MCC and colloidal silicon dioxide) exhibited improved tablet strength, improved retention of compressibility after granulation, and superior flow properties when compared to tablets made from these MCC and colloidal silicon dioxide added as individual components [92d].

## III. TABLET MANUFACTURE

Thus far in this chapter, the emphasis has been on the material rather than on the processes involved in tablet manufacture, but the latter are of equal importance. The pharmaceutical industry is highly regulated and must comply with current Good Manufacturing Practices (cGMPs). In terms of equipment, this translates into preparing products in totally enclosed systems by processes that minimize the handling and transfer of materials. Irrespective of the particular production route—wet granulation or direct compression—the first stage is likely to involve the intimate mixing together of several powdered ingredients.

### A. Powder Mixing

The successful mixing together of fine powder is acknowledged to be one of the more difficult unit operations because, unlike the situation with liquid, perfect homogeneity is practically unattainable. All that is possible is to realize a maximum degree of randomness in the arrangement of the individual components of the mix. In practice, problems also arise because of the inherent cohesiveness and resistance to movement between the individual particles. The process is further complicated in many systems by the presence of significant segregative influences in the powder mix. These arise due to difference in particle size, shape, and density of the component particles.

**Table 14** Some Commonly Used Pharmaceutical Colorants (Synthetic)

| | | Solubility (g/100 mL at 25°C) | | | | Stability to | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| FD&C color | Common name | Water | Glycerin | Propylene glycol | 25% Ethanol | Light | Oxidation | pH 3 | pH 5 | pH 7 | pH 8 |
| Red[a] | Erythrosine | 9.0 | 20.0 | 20.0 | 8.0 | Poor | Fair | Insol | Insol | NNC | NNC |
| Red 40 | Allura red AC | 22.0 | 3.0 | 1.5 | 9.5 | Good | Fair | NNC[b] | NNC | NNC | NNC |
| Yellow 5 | Tartrazine | 20.0 | 18.0 | 7.0 | 12.0 | V. Good | Fair | NNC | NNC | NNC | NNC |
| Yellow 6 | Sunset Yellow | 19.0 | 20.0 | 2.2 | 10.0 | Mod | Fair | NNC | NNC | NNC | NNC |
| Blue 1 | Brilliant blue | 20.0 | 20.0 | 20.0 | 20.0 | Fair | Poor | S. fade[c] | V.S. fade[d] | V.S. fade | V.S. fade |
| Blue 2 | Indigotine | 1.6 | 1.0 | 0.1 | 1.0 | V. poor | Poor | A. fade[c] | A. fade | A. fade | C. fade[f] |
| Green 3 | Fast green | 20.0 | 14.0 | 20.0 | 20.0 | Fair | Poor | S. fade | V.S. fade | V.S. fade | S. fade |

[a]Note: FD&C Red 3 lake has been delisted by FDA as of January 29, 1990.
[b]No noticeable change.
[c]Slight fade.
[d]Very slight fade.
[e]Appreciable fade.
[f]Completely fades.
*Source*: Warner-Jenkinson Pamphlet of Certified Colors, September 1990.

**Table 15** Several Co-Processed Excipients

| Excipient | Components | Manufacturer |
|---|---|---|
| Advantose FS | Fructose, pregelatinized starch | DMV |
| Avicel CE-15 | MCC, guar gum | FMC |
| Cellactose | MCC, α-lactose monohydrate | Meggle GmbH |
| Ludipress | α-Lactose monohydrate, povidone, crospovidone | BASF |
| LustreClear | MCC, carrageenan | FMC |
| Microcelac | MCC, α-lactose monohydrate | Meggle GmbH |
| Pharmatose DCL | Anhydrous lactose, lactitol | DMV |
| ProSolv SMCC | MCC, colloidal silicon dioxide | Penwest |

MCC, Microcrystalline cellulose.

It is not possible here to present a full account of the interactions between these effects, so the reader is referred to standard texts dealing with this important topic [93]. However, there may be an optimum mixing time and in such cases, prolonged mixing may result in an undesired product. In the special case of mixing in a lubricant, which is required at the granule surface, overmixing can be particularly detrimental.

Powder mixers vary widely in their ability to produce adequately mixed powders and the time needed to accomplish it. For intimate mixing of powders, energy must be supplied at a high enough rate to overcome the inherent resistance to differential movement between particles. Older mixers attempt to supply sufficient energy to mix the entire batch at once, but modern designs tend to be based on mechanisms for sequentially feeding a proportion of the total mix to a region of high-energy mixing potential. Typical examples of the general design of such mixers are shown diagrammatically in Fig. 13. Mixing is achieved by means of a main impeller, which feeds material to a high-speed "chopper," producing an intense shear mixing zone.

With all mixers, however, it is necessary to establish that an acceptable degree of homogeneity has been reached. Quantitative methodologies for establishing an "index of mixing" or "efficiency of mixing" are reported in the literature [94].

### *Direct Compression*

For obvious reasons, the possibility of compressing mixed powders into tablets without an intermediate granulating step is an attractive one. For many years,

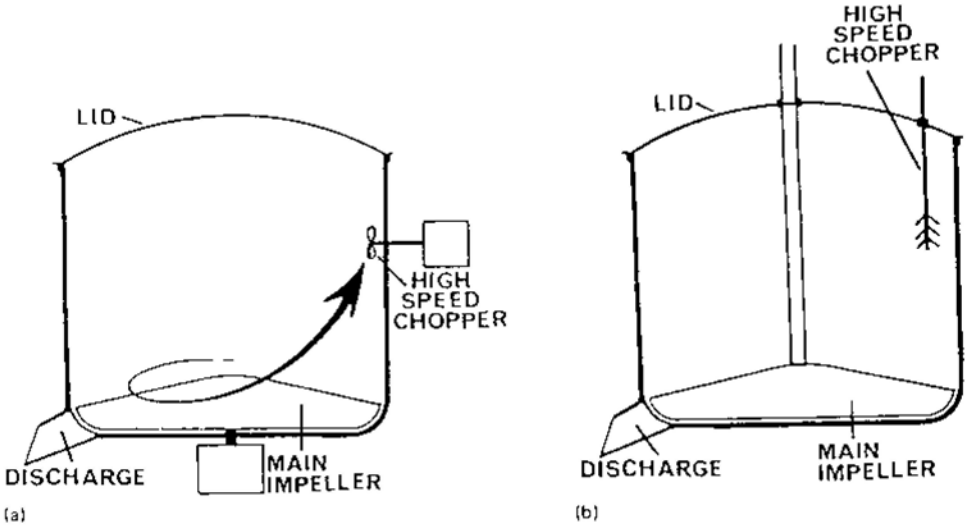


**Fig. 13** High-shear mixers: (a) underdriven; (b) overdriven.

several widely used drugs, notably aspirin, have been available in forms that can be tableted without further treatment. Recently, there has been a growing impetus to develop so-called direct compression (DC) formulations, and the range of excipients, especially diluents, designed for this specific role has expanded dramatically.

It is possible to distinguish two types of DC formulations: (a) those where a major proportion is an active ingredient, and (b) those where the active ingredient is a minor component (i.e., <10% of the compression weight). In the former case, the inherent characteristics of the drug molecule, in particular the ability to prepare a physical form that will tablet directly, will have profound effects on the tablet's characteristics.

It may sometimes by necessary to supplement the properties of the drug so that it compresses more easily, and these needs have been realized by several manufacturers of excipients. Materials described as "compression aids" are now commercially available. Ideally, such adjuvants should develop mechanical strength while improving, or at least not adversely affecting, release characteristics. Among the most successful at meeting both these needs have been the microcrystalline celluloses (partially acid-hydrolyzed forms of cellulose). A number of grades are available based upon particle size and distribution.

Most other DC excipients really belong in the second category, where the drug is present in low concentration. In such cases, the use of an inexpensive DC diluent is warranted. Before considering some of these, certain generalizations are worth noting since there seems to have arisen an erroneous belief that DC is always a simpler formulation route. For instance, many DC fillers, such as spray-dried lactose, should not be reworked because this affects their compressibility. In addition, those diluents with a large particle size may give rise to mixing problems due to segregation unless an optimum proportion of fine material is present. More often, one is faced with the problem of an excessively narrow particle size distribution so that flow, in general, and uniform feeding to the dies, in particular, are difficult. Sometimes batch-to-batch variation is more prevalent in soluble DC fillers, such as sugars. Unlike wet granulation, DC has little ability to mask inherent tableting deficiencies in an ingredient. In addition, there will be little possibility for prior wetting of a hydrophobic drug and subsequent dissolution enhancement, which is a proven effect of wet granulation. On the other hand, DC formulations are likely to be more stable, show fewer aging effects, and, in specific cases, offer the only workable production method.

### *Wet Granulation*

Although many existing products continue to be processed by a lengthy wet granulation that includes blending of dry ingredients, wet massing, screening, and then tray or fluidized bed drying, there is a trend toward using machines that can carry out the entire granulation sequence in a single piece of equipment or single-pot processor [95]. Formulators must be aware, however, that the type of granulation procedure used can have a profound impact on the granules produced. Thus, a formulation that produces adequate granules by conventional planetary mixing may produce suboptimal product if transferred to a single-pot processor.

It is generally agreed that there will exist an optimum range of granule sizes for a particular formulation, and therefore, certain generalizations are worthy to note here. Within limits, smaller granules will lead to higher and more uniform tablet weight and higher tablet crushing strength, with subsequent longer disintegration time and reduced friability. The strength of granules has also been shown to influence the tensile strength of the tablets prepared from them, with stronger granules leading, in general, to harder tablets [96].

One important finding with widespread implications arises from work by Chaudry and King [97], who demonstrated that migration of a soluble drug during moist granulation was responsible for uneven content uniformity of tablets of warfarin. A modified base (containing dibasic calcium phosphate, alginic acid, and acacia), developed from experiments to assess migration-retarding ability, enhanced tablet performance.

## B. Powder Compaction

For simplicity, the physics of tablet compaction discussed here will deal with the single punch press, where the lower punch remains stationary. Initially, the powder is filled into the die with the excess being swept off. When the upper punch first presses down upon the powder bed, the particles rearrange themselves to achieve closer packing. As the upper punch continues to advance upon the powder bed, the rearrangement becomes more difficult and deformation of particles at points of contact begins. At first the particle will undergo elastic deformation, which is a reversible process, but as continual pressure is applied, the particle begins to deform irreversibly. Irreversible deformation

can be due either to plastic deformation, which is a major factor attributing to the tablet's mechanical strength, or to brittle fracture, which produces poor quality compacts that crumble as the tablets are ejected [25,98]. In general, as increasing pressure is applied to a compact, its porosity will be reduced.

The surface area of the individual particles themselves changes during the compaction process. Initially, an increase in surface area is noted due to the fracture as compression force increases. Eventually, the surface area decreases due to bonding and consolidation of particles at higher compression forces [25,98]. Higuchi et al. [98] postulated that an additional increase in surface area occurs after this point and that this effect may cause lamination of the tablet due to extensive rebound at decompression. In other words, at the tablet punch powder interface, there may be zones of high density during compression, but upon decompression these zones have elastic rebound and are pulled apart from the rest of the tablet that did not contain this high density.

The major forces involved in the formation of a tablet compact are illustrated in Fig. 14 (a single-ended model) and are notated as follows: $F_A$ represents the axial pressure, which is the force applied to the compact by the upper punch, $F_L$ is the force translated to the lower punch, and $F_D$ is the force lost to the die wall. If one remembers that for every force there must be an equal and opposite force, the following relationship is obvious:

$$F_A = F_L + F_D$$

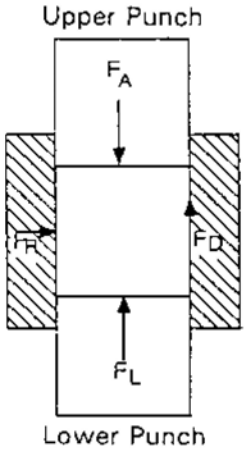


**Fig. 14** Forces developed in the formation of a tablet compact. , die wall; $F_A$, axial pressure applied by upper punch; $F_D$, force lost to die wall; $F_R$, radial die wall; □, tablet compact.

$F_R$ is the radial die wall force that develops because the powder is in a confined environment (i.e., not able to spread outward as pressure is applied down upon it because it is residing within the die). The coefficient of friction at the die wall, $\mu_W$, is due to the shearing adhesion that occurs along the die a as the powder is made more dense and compressed. The following relationship between and $F_D$, $\mu_W$, and $F_R$ is found to exist:

$$F_D = \mu_W F_R$$

The force of tablet ejection from the die, $F_E$, is a function of both and the residual die wall force, *RDWF*, that exists after decompression. As the friction decreases, one will obviously see a corresponding drop in $F_E$. It is important to remember here that it is desirable for $F_E$ to be as low as possible so that minimal damage is imparted to both the tablet and the tooling.

The first applications of this technique [99] were directed to developing a more sensitive assessment of lubricant efficiency than that offered by the traditional "coefficient of lubrication", or R-value (i.e., $F_L : F_A$ ratio). Since then, its use has been extended to provide predictive information on formulation performance [100,101]. Lammens et al. [102] have stressed the importance of ensuring precision and accuracy in such measurements for correct interpretation of the data so produced.

Although the choice of precise tablet geometry may be more the prerogative of the marketing department than of the pharmaceutical formulation or production department, certain general technical observations must be taken into account. Bearing in mind that most tablets are cylindrical in shape, diameters between 3 and 12 mm are preferred, with either beveled edges or biconvex profile. Low height-to-diameter ratios, consistent with adequate tablet strength, are desirable so as to minimize die-wall fractional effects, which can consume a significant amount of the total energy required in tableting. In addition, the internal stress differences will be minimized if a biconvex profile is selected, although the tablet's shape may affect the release of the drugs in matrix tablets [103]. The effect of punch face geometry and lubricant compression on tablet properties has been reported by Mechtersheimer and Zucker [104].

As a generalization, increasing compressional force will retard dispersion on administration, and therefore, levels should be kept as low as possible, consistent with achieving acceptable mechanical properties. With some excipients there is a critical compressional force range required to achieve minimum disintegration times.

This has been demonstrated for starch-containing formulations and was thought to be linked to production of an optimum pore size distribution that allowed rapid uptake of water without providing large internal air spaces to accommodate the swelling starch grains [105]. The importance of press speed must also be taken into account, particularly where plastic deformation is thought to play a major role in tablet formation. The effect of this rate of compaction has been demonstrated quantitatively in a report by Roberts and Rowe [106].

## IV. TABLETING EQUIPMENT

### A. Granulators

Originally, wet granulation involved the hand process of preparing a wet mass and forcing it through a screen onto trays that was placed into a convection oven where the granules were dried. With increasing batch sizes, the need for bulk granulation procedures became necessary. Many of these procedures involved mixing the powdered ingredients in a special ribbon blender, which could also accomplish the wet massing process. The moistened materials were then usually granulated by forcing them through a screen, using oscillating blades of a modified comminuting mill, onto trays that were then transferred to an oven for drying. Current granulating methods can be classified into the following categories: (a) traditional methods as detailed above; (b) high-shear mixing; (c) fluid-bed granulation; and (d) single-pot processing.

High shear mixers, which make use of both a high-speed mixing blade and chopper, have largely replaced traditional planetary mixing. This process can reduce granulation time and produces dense granules. Material processed in a high-shear mixer is discharged from the unit and transferred to a drying unit, with or without an intermediate screening step.

Fluidized beds have been expanded from their original use as dryers to encompass granulation as well. Granulation in a fluidized bed is achieved by suspending the powder in the air of the fluidized bed and then spraying a liquid binder from nozzles that are positioned above or below the powder bed. In general, top-spray operation produces porous granules while bottom-spray granules are dense and highly spherical. When using fluidized beds in the granulation/drying mode, the process conditions, such as drying temperature and length of the drying cycle, must be optimized, and it may be necessary to adopt a different approach to formulation than would have been used with the more traditional equipment. For example, granulating fluid is sprayed into the bed of mixed powder at a given temperature; its volatility and viscosity under these conditions will influence the characteristics of the final product. The important parameters governing the performance of fluidized beds used as MGDs has been studied by Worts and Schoefer [107]. They concluded that in addition to the inlet air temperature, the type of binder solution and its flow rate and droplet size were critical variables that had to be controlled. These investigators also found that the residual moisture levels of granulations are a major factor contributing to the *in vitro* dissolution and friability of tablets made from them.

Single-pot processors that can are capable of mixing, granulation, drying, and even pelletization and coating are now commercially available from a number of sources. The first of these processors were simply granulation units that had been retrofitted for drying and did not provide significant advantages over traditional granulation and drying methods. With the advent of microwave- and gas-assisted vacuum-drying techniques, drying times were drastically reduced, thereby making these units more viable as commercial equipment [95]. In addition to time savings that can be realized when using single-pot processors, these systems offer the following advantages over conventional methods: (a) improved yield due to minimization of product loss during transfer; (b) closed unit operation, minimizing product contamination and environmental exposure to high potent substances; and (c) reduced risk of explosion due to near absence of oxygen in the closed unit [95].

Granulation by preliminary compression, originally performed in heavy-duty tablet machines, when it was called "slugging," has been used for a small number of products for many years. This approach has been further developed in machines that are essentially roll compactors, squeezing the material to produce agglomerates. In addition, most high-output tablet presses are now equipped with precompression rollers that perform the "slugging" of the granulation prior to its "true" compaction (see Fig. 15).

Another method of producing materials to be tableted is pelletization. Pellets are typically larger and more spherical in nature than granules and possess high bulk density and excellent flow properties. Pellets can be prepared by several methods, including (a) layering active material onto an inert core (nonpariel), (b) extruding a wet mass through a large number of small orifices and then rotating the "strands" in a special bowl capable of spheronizing the granules, or

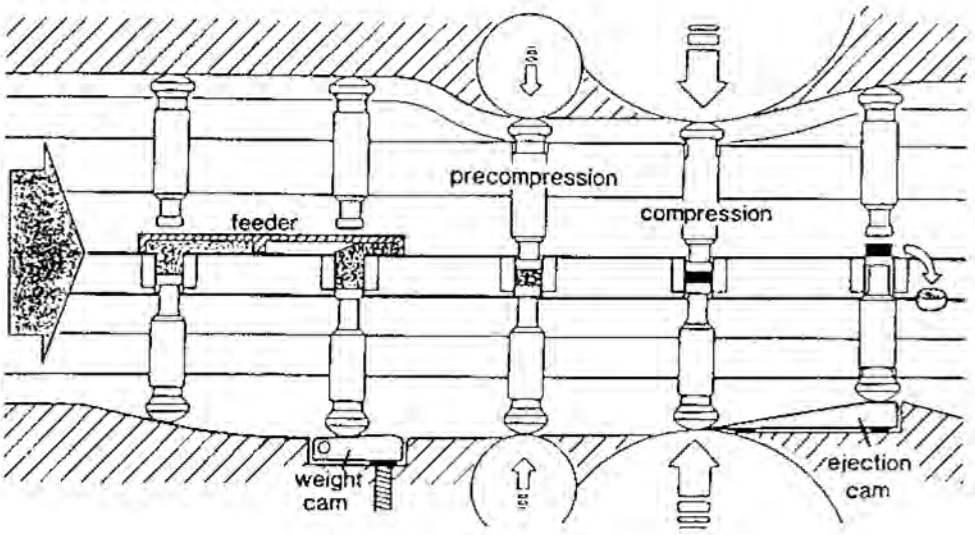


**Fig. 15** Multistation press cycle.

(c) mixing the active substance and binder powders together and then heating to a temperature above the melting point of the binder. Pelletization by extrusion and spheronization, or marumerization, is the most common of these methods. The parameters controlling this process have been studied by Malinowski [108] and the effect on the tablet produced from it evaluated.

## B. Tablet Presses

With the exception of presses designed to produce coated or layered tablets, the development of tableting equipment has been one largely of continuing evolution. In many areas, the incentives have come from the pharmaceutical industry, rather than the tablet press manufacturers, as a result of certain trends in tableting operations. These include (a) increased rate of production, (b) direct compression of powders, (c) stringent standards for cleanliness to comply with cGMPs, and (d) automation, or at least continuous monitoring of the process. However, there is now evidence to suggest that we may be approaching inherent limits to further development of some press variables on existing lines.

At present, and in the immediate future, one can anticipate the continual vying of one manufacturer with another over relatively minor improvements, with possibly significant advances in instrumentation, automation, and hygiene. However, several easy-to-clean high-output presses are currently manufactured. Most Kikisui models are "self-cleaning" and allow for the entire turret area to be filled with solvents and cleaned by running the press.

All tableting presses employ the same basic principle—they compress the granular or powdered mixture of ingredients in a die between two punches with the die and its associated punches being called a "station of tooling." Tablet machines can be divided into two distinct categories:

1. Those with a single set of tooling—"single station" (or "single-punch") or "eccentric" presses
2. Those with several stations of tooling—"multistation" (or "rotary") presses

Figures 15 and 16 provide a summary of the compression cycles for rotary and single-punch tablet presses. The formation of the tablet compact in these two types of presses mainly differs in the compaction mechanism itself, as well as the much greater speeds achieved with rotary type presses. The single punch basically uses a hammering type of motion (i.e., the upper punch moves down while the lower punch remains stationary), while rotary presses make use of an accordion-type compression (i.e., both punches move toward each other). The former find their primary use as an R&D tool, whereas the latter, having higher outputs, are used in most production operations.

### *Single Station Presses*

All commercial types of single station presses have essentially the same basic operating cycle (see Fig. 16), where filling, compression, and ejection of tablets from the die is accomplished by punch movement utilizing cam actions. Material is fed to the die from the hopper

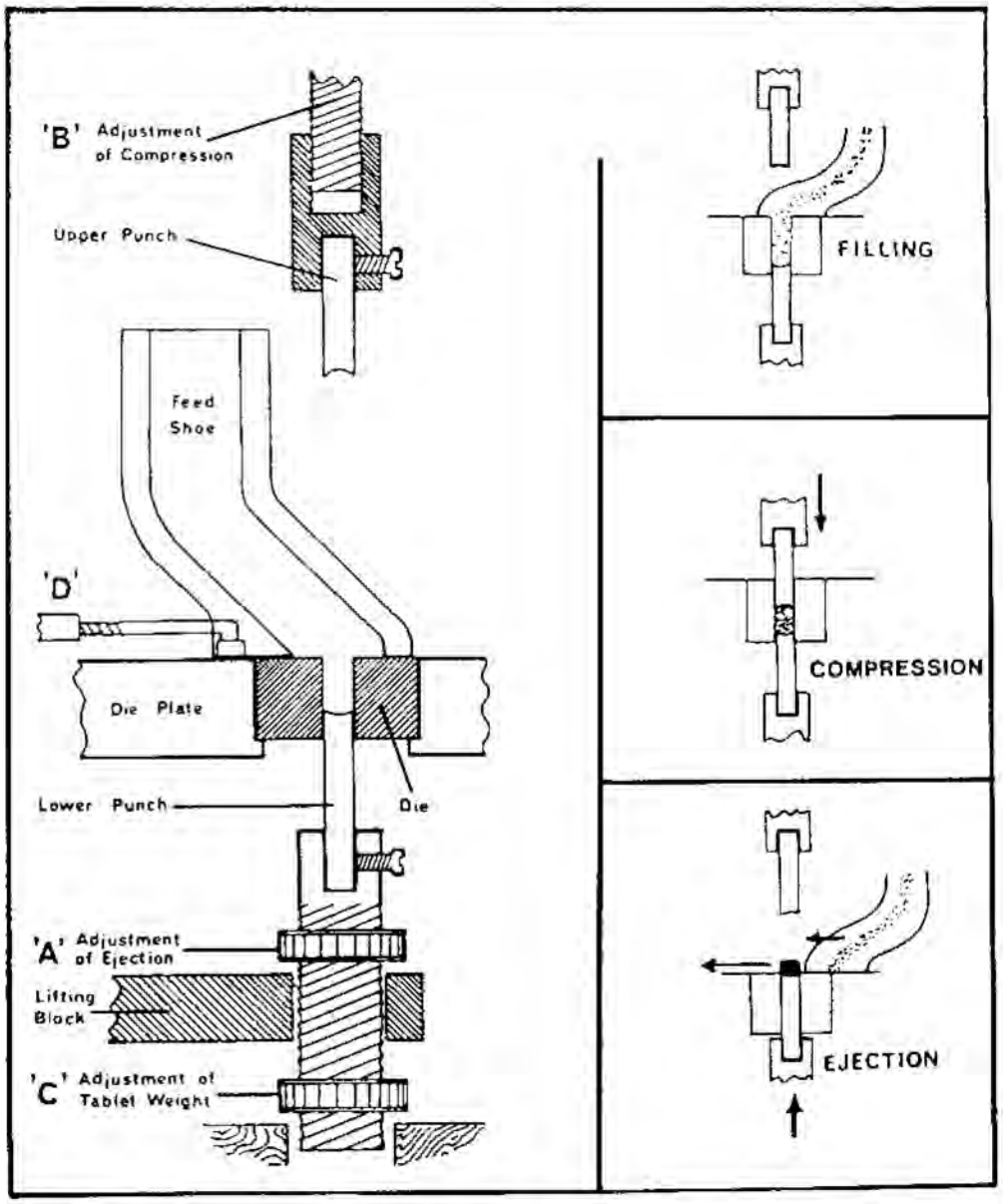


**Fig. 16** Single station press cycle.

via an oscillating feed shoe; the position of the lower punch at this point determines the tablet weight. The feed shoe then moves away and the upper punch descends into the die to compress the tablet, with the extent of this movement controlling the level of compression force. As the upper punch moves upward, the lower punch rises and in so doing ejects the tablet from the die. At this point, the feed shoe moves in and knocks the tablet out of the machine as the lower punch moves to its bottom position ready for the next press cycle.

The largest single-punch machines are capable of making tablets up to 22 mm in diameter at rates of about 80 tablets per minute (TPM) and exerting maximum forces on the order of 40 kN (see Table 16). In isolated cases tablets can only be made on this type of machine, probably because their mode of operation gives the material a longer "dwell time" under compression. Although the table output rate from single station presses can be increased by use of multitip tooling, the rotary machine remains the method of choice for production purposes.

**Table 16** Approximate Specifications of Some Small Single-Station Laboratory Presses

| Manufacturer: / Model Number: | Fette Exacta 1 | Kilian SP300 | Korsch EK-O/DMS | Manesty F3 |
|---|---|---|---|---|
| Maximum output (tabs/min) | 75 | 80 | 60 | 85 |
| Maximum tablet diameter (mm) | 15 | 18 | 20 | 22 |
| Maximum fill (mm) | 16 | 16 | 20 | 17 |
| Maximum applied force (kN) | 15 | 25 | 30 | 40 |
| Motor (HP) | 0.75 | 1.1 | 0.5 | 2.0 |
| Weight (kg) | 250 | 300 | 200 | 476 |
| Approximate dwell time (ms) | 133 | 125 | 100 | 118 |

*Multistation Presses*

In this type of machine the operating cycle and methods of filling, compression, and ejection are different from those of single-station presses and are summarized in Fig. 15. More specifically, the dies and punches are mounted on a rotating turret.

All operations take place simultaneously in different stations. Sixteen stations were commonly used in earlier machines with outputs between 500 and 1000 TPM and tablet diameters up to 15 mm. Presses with outputs orders of magnitude greater than the above are now widely available. The dies are filled as they pass beneath a stationary feed frame, which may be fitted with paddles to aid material transfer. The die cavities are completely filled and excess ejected prior to compression. Compression involves the movement of both punches between compression rolls, in contrast to single station operations where only the upper punch effects compression. Ejection occurs as both punches are moved away from the die on cam tracks until the tablet is completely clear of the die, at which point it hits the edge of the feed frame and is knocked off the press. Tooling pressure may be exerted hydraulically, rather than through the use of mechanical camming actions, as is the case with machines produced by Courtoy.

The ways in which individual manufacturers of tableting equipment have sought to achieve higher output fall into four groups:

1. Increasing the effective number of punches (i.e., multitipped)
2. Increasing the number of stations
3. Increasing the number of points of compression
4. Increasing the rate of compression (i.e., turret speed)

Each of these approaches has its own particular set of advantages and disadvantages. In addition, all make demands on other aspects of press design and certain general inherent characteristics of die compaction have to be taken into account.

Generally, the high-speed machines consist of "double-rotary" presses where the cycle of operation is repeated twice in one revolution of the turret carrying the tooling, although one press (Magna, Vector Corp.) has four cycles per revolution (the Magna is no longer manufactured due to the small demand required for these very high-output machines). Most high-output tablet presses have odd numbers of stations, with up to 101 in the largest presses (see Table 17). Double-rotary presses have also been modified to produce layered tablets, whereas other machines have been adapted to produce coated tablets by a "dry" compression technique.

## C. Tablet Machine Instrumentation

In order to produce an adequate tablet formulation, certain requirements, such as sufficient mechanical strength and desired drug release profile, must be met. At times this may be a difficult task for the formulator to achieve, due to poor flow and compactibility characteristics of the powdered drug. This is of particular importance when one only has a small amount of active material to work with and cannot afford to make use of trial-and-error methods. The study of the physics of tablet compaction through the use of instrumented tableting machines (ITMs) enables the formulator to systematically evaluate his formula and make any necessary changes.

ITMs provide a valuable service to all phases of tablet manufacture, from research to production and quality control [109–111]. As a research tool, ITMs allow in-depth study of the mechanism of tablet compaction by measuring the forces that develop during formation, ejection, and detachment of tablets. ITMs can also provide clues about how materials bond,

**Table 17** Comparative Specifications of Some High-Output Tablet Presses

| Manufacturer: Model: | Fette PT3090 | Kikusi Gemini | Korsch PH 800 | Manesty Rotapress |
|---|---|---|---|---|
| Maximum output (tabs/min) | 16,750 | 10,720 | 18,360 | 13,360 |
| Number of stations | 79 | 67 | 85 | 75 |
| Maximum turret speed (rpm) | 106 | 80 | 108 | 89 |
| Maximum tablet diameter (mm) | 34 | 25 | 34 | 25 |
| Maximum fill depth (mm) | 18 | 16 | 22 | 20.6 |
| Maximum compression force (kN) | 100 | 80 | 80 | 100 |
| Precompression (kN) | 100 | 80 | 80 | 10 |
| Net weight (kg) | 4500 | 3900 | 4000 | 3700 |

deform, and react to frictional effects. The formulator himself is able to monitor the effects of additives in the overall tableting process, as well as the effects of operation variables in the manufacture and performance of the dosage form. As stated above, this markedly reduces the formulator's reliance on empiricism in formulation design. In the area of product and quality control, ITMs are able to monitor tablet weight and punch and machine wear and damage. More recently, ITMs have been used to characterize unique "typical batches" of materials so that one has a baseline for troubleshooting formulations or a basis for quality control [109–111].

### *ITMs in Research and Development*

The tableting process involves two phenomena: (a) a reduction in the bulk volume of the tablet mass by elimination of air, referred to as "compression," and (b) an increase in the mechanical strength of the mass due to particle-particle interactions, which is termed "consolidation." This latter process results from utilization of the free surface energies of the particles in bond formation, referred to as "cold welding," plus intermolecular interactions via van der Waals forces, for example. The process is enhanced by generation of large areas of clean surface, which are then pressed together; such a mechanism is feasible if appreciable brittle fracture and plastic deformation can be introduced into the system. Therefore, the manner in which the various components compress will be significant.

It is also important to appreciate that the behavior on decompression can markedly affect the characteristics of the finished tablets, because the structure must be strong enough to accommodate the recovery- and ejection-induced stresses. Indeed, tablet strength is a direct function of the number of "surviving bonds" in the finished tablet. In addition, ability to monitor ejection forces leads to valuable information on lubricant efficiency.

### *Analysis of Data Obtained from ITMs*

Measurement of the punch and die forces plus the relative displacement of the punches can provide raw data which, when suitably processed and interpreted, facilitate the evaluation of many tableting parameters. Many of the workers first involved in instrumenting tablet presses concentrated on deriving relationships between the applied force ($F_A$) and the porosity ($E$) of the consolidating mass.

Heckel proposed that a correlation exists between yield strength and an empirically determined constant, $K$, which is a measure of the ability of the compact to deform [28,112]. He discovered that, indeed, $K$ is inversely proportional to yield strength. Further, he derived an equation expressing the relationship between the density of a compact and the compressional force applied. This relationship is based on the assumption that decreasing void space (i.e., decreasing porosity) of a compact follows a first order rate process:

$$\frac{dD}{dP} = K(1 - D)$$

where

$D$ = relative density
$P$ = pressure
$(1 - D)$ = pore fraction
$K$ = proportionality constant

By integrating and rearrange this equation, one obtains the following linear relationship:

$$\ln\left(\frac{1}{1 - D}\right) = KP + A$$

where

$$A = \ln\left(\frac{1}{1 - D_0}\right) + B$$

and $B$ is a measure of particle rearrangement.

It has been claimed [113] that the presentation of data in the form of Athy-Heckel plots [112,114], as illustrated in Figure 17, facilitates assessment of the relative proportions of brittle fracture and plastic deformation present. Each set of curves within a plot represents the same formulation, with decreasing particle size fractions. If the curves remain discrete, as in Fig. 17a, one can assume that plastic deformation is the predominant mechanism because all formulations have sufficient time to rearrange (n.b., plastic deformation is a time-dependent process). In contrast, Fig. 17b illustrates the behavior of a material that primarily deforms by brittle fracture. Here, the original particle size distribution is rapidly destroyed and the curves become superimposed. Additionally, the slope of the lines, which represents $K$, is approximately unity. Higher slopes (i.e., low yield pressure) are found when evaluating plastically deforming materials. Subsequent studies [115,116] have cast doubts on the universality of this claim, and conflicting data have been reported. In addition, several adaptations have been made to correct for inconsistencies present in Heckel's model [116a,116b].

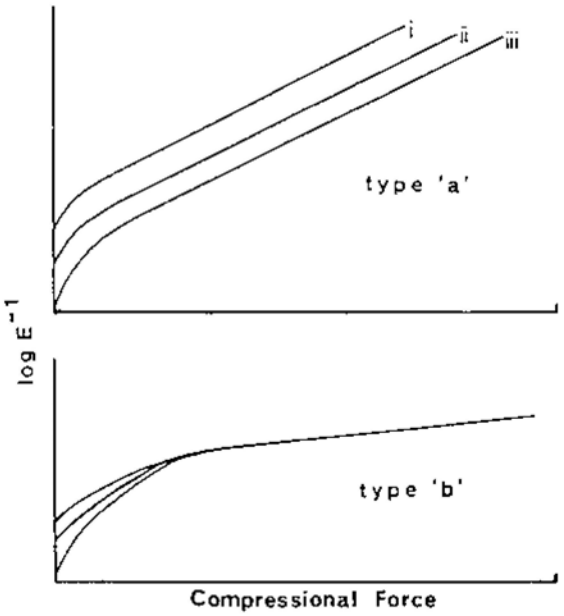


**Fig. 17** Athy-Heckel plots: (a) material undergoing plastic deformation; (b) material undergoing brittle fracture.

Applied force and displacement measurements have also been used to generate force versus displacement curves ($F$-$D$ plots) [99]. Such information can be used to estimate the energy necessary to form a compact in the following manner:

$$W = F \int dD$$

where

$W$ = work
$F$ = force
$D$ = distance

When one plots force vs. displacement, the area under the curve thus represents work. In practice, the compression/decompression data take the form shown in Fig. 18. The area under the upward line represents the work done on the tableting mass during compaction, while that under the downward line arise from the fact work is done on the punch by the tablet as a result of the latter's elastic recovery on decompression.

In single-station presses a further subdivision of work can be made by considering the force transmitted to the lower punch during the compression. This will be less than that registered by the upper punch due to frictional effects at the die wall. Three components to the total work can therefore be distinguished; $W_F$, the work done in overcoming die wall friction, $W_D$, the work of elastic recovery, and $W_N$, the net work involved in forming the tablet. Interpretation of $F$-$D$ curves, on single-station presses, has proved to be particularly attractive, as demonstrated by the work of Travers and Cox [117].

Some researchers have extended the monitoring of work to the determination of the rate of doing work, or power [116], as illustrated in the following equation:

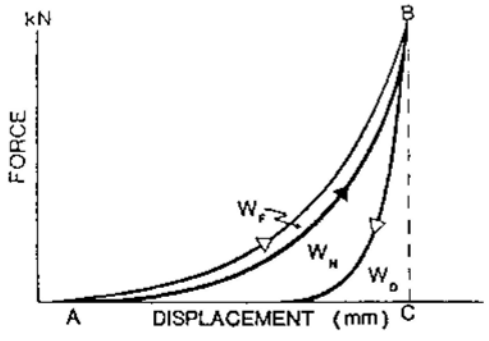


**Fig. 18** A typical force-displacement curve. $W_F$ = work done overcoming die wall friction; $W_D$, work of elastic recovery; $W_N$, net work involved in tablet compact formation.

$$\frac{dW}{dt} = power$$

The rationale behind this approach is that due to the varying degrees of bond formation, different materials require a greater, or lesser, amount of energy to compress them to a given degree. In a tablet press running at a given speed, the rate of doing work must therefore be different and may be related to tablet strength. In addition, since plastic deformation is a time-dependent phenomenon, power, which takes time into account, may be indicative of the contribution of this mechanism.

The compressive behavior of the material is also reflected in that proportion of the axial force ($F_A$) that is transmitted radially to the die wall ($F_R$) during compression and decompression. Therefore, monitoring the ratio of these two forces during the entire machine operation can provide valuable data referred to as the "compaction profile." As shown in Fig. 19, this normally takes the form of a hysteresis loop, the area of which is a function of the departure of the material from purely elastic behavior. Other features of the profile provide valuable guidelines as to tablet strength, likely levels of lubrication required, and predominant type of deformation. The line OA is represented as a dotted line because this region is due to repacking, which can be quite variable. At point A, elastic deformation becomes dominant and continues until the yield stress, at point B, is reach. At this point, the deformation of the compact is due to plastic deformation and brittle fracture. This process continues to point C, at which time force is removed and decompression begins. From point C to D, the material is elastically recovering. If a second yield point, D, is reached, the material has become plastically deformed of brittley fractured. To sum up all of these processes:

Slope AB = function of elastic deformation
Slopes BC and DE = function of plastic deformation and brittle fracture
Slopes BC′and CD = function of elastic recovery
Lines OC′and OE = function of (residual die wall force) RDWF

One should note that BC′ represents a highly elastic material as little plastic deformation or brittle fracture has occurred. Also, sharp differences between the slope CD and DE are indicative of weak, or failed, tablet structures. The *RDWF* estimated from these plots can provide a good indication of the ejection force. More detailed treatments of such studies are now in the open literature, to which the interested reader is referred [118–120].

Another approach to determining the contribution being made by each of the possible compression/decompression mechanisms involves monitoring the degree and rate of relaxation in tablets immediately after the point of maximum applied force has been reached. Once a powder bed exceeds a certain yield stress, it behaves as a fluid and exhibits "plastic flow" [121,122]. Certain investigators [122] have studied plastic flow in terms of viscous and elastic elements and have derived the following equation:

$$\ln F_1 = \ln F_0 - kt$$

where

$F$ = compressional force in viscoelastic region
$t$ = time
$k$ = degree of plastic flow

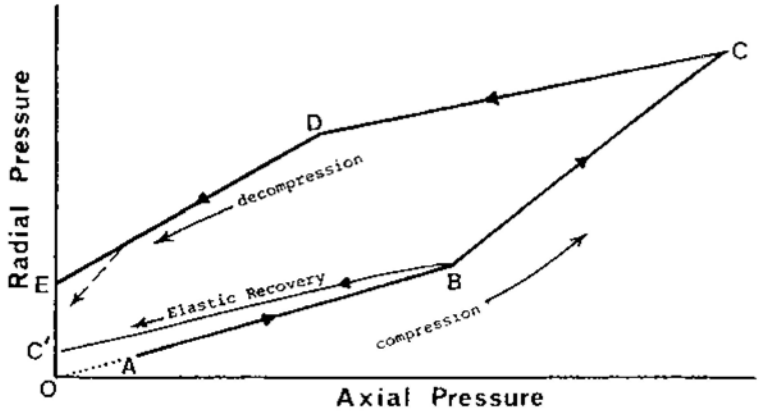


**Fig. 19** Compaction profile.

which can be integrated and rearranged to yield the linear equation:

$$\ln F_1 = \ln F_0 - kt$$

Thus, if one plots log($F$) vs. time, one only needs to calculate the slope of the line so plotted to determine the plastic flow, $k$. Materials with higher values of $k$ (i.e., more plastic flow) tend to form stronger tablets than those with low $k$ values.

### *Compaction Simulators*

In 1972, Rees et al. [123] developed the compaction simulator that, in oversimplified terms, is a hydraulic press capable of accurately mimicking the action of any high-speed rotary press. This is an overwhelming achievement in the study of compaction physics when one reflects upon the various disadvantages associated with single punch and rotary presses that this system can overcome. For instance, single punch measurements, while providing a baseline for formulation development, do not accurately reflect the forces incurred at the production level; the lower punch remains stationary rather than moving in single punch systems, and the dwell time, which influences the extent of plastic deformation, is significantly increased due to the low speed of manufacture. On the other hand, rotary presses require relatively large amounts of granulation and therefore are inappropriate for the initial phases of formulation when only small amounts of material are available. Also, the rate of applying and removing forces varies appreciably from machine to machine depending on the way the machine is operated, the punches used, etc. The compaction simulator is able to compensate for all of these disadvantages so that production level conditions can exist for small amounts of material. Additionally, the compaction simulator is capable of reproducing the variables associated with each machine and thereby providing adequate means for transferring a formulation from one machine to another. Until the 1990s, there were only two compaction simulators in use in the United States: one at SmithKline Beecham and the other, used by a consortium of companies in the U.S., at Rutgers College of Pharmacy. Several commercial "simulators" are now available, including the PCS-1 from AC Computing, the Presster from Metropolitan Computing Corp. and the P1200 G/TSC Galenic Version from Fette International.

Several reviews of the mechanisms involved in the compaction process and interpretation of the large amount of data generated from such studies have been published [124,125]. The solution to this complex process is still incomplete and provides continuing research opportunities for the pharmaceutical scientist. The actual mechanics of instrumenting presses has also been reviewed [111], and a recently published book [126] is devoted entirely to this subject. Instrumentation typically involves the use of piezoelectric transducers or strain gauges and requires that modifications be made to either the tablet punches or the die table. However, Yeh et al. have described the use of finite element analysis (FEA) that does not require die table modification [126a]. Guo et al. have also developed a noninvasive technique that relies on the use of confocal laser scanning microscopy [126b]. Another new development is the use of calorimeters to directly evaluate the thermodynamic properties of compression [126c].

There has also been significant growth in the number of press manufacturers offering instrumentation packages for use with high-speed multistation machines to control tablet weight variation and, in some cases, divert out-of-tolerance tablets to a reject container. The more sophisticated systems result in a fully automated press operation with minimal operator intervention required (see Fig. 20).

## V. COATED TABLETS

The coating of pharmaceutical tablets may be divided conveniently into the traditional sugar, or pan-coating procedures, and contemporary techniques that include film coating and compression coating. Coating methods were developed for a variety of reasons, including the need to mask an unpleasant taste or unsightly appearance of the uncoated tablet, as well as to increase patient acceptability. Protection of an ingredient from degradation effects due to exposure to moisture, air, and light were further incentives. The newer techniques have extended the usefulness of coating to include the facilitation of controlled-release characteristics and the ability to co-formulate inherently incompatible materials.

### A. Sugar Coating

The sugar coating process involves building up layers of coating material on the tablet cores as they are tumbled in a revolving pan by repetitively applying a coating solution or suspension and drying off the solvent. Traditionally, the cores were made using tooling with deep concave geometry so as to reduce the problems associated with producing a sufficiently thin coat around the tablet's edge, as illustrated in Fig. 21.

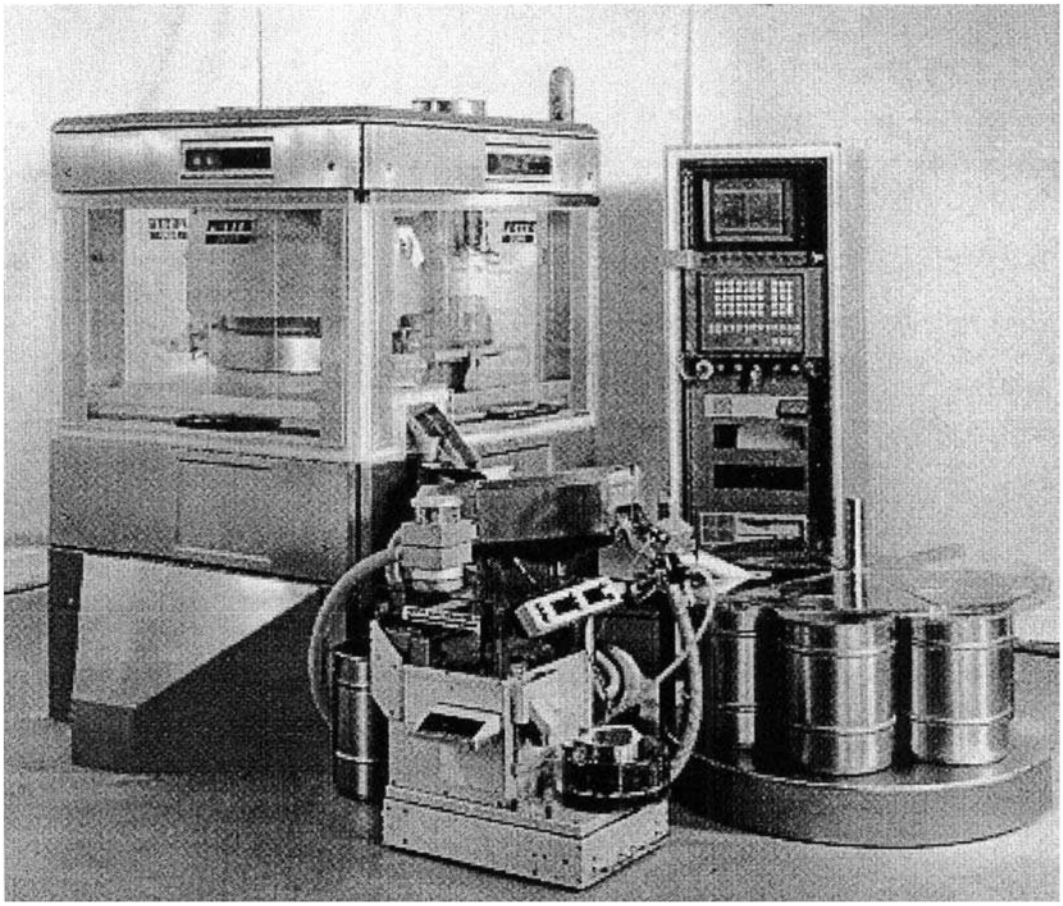

**Fig. 20** Automated high-output rotary tablet press. (Courtesy of Fette America.)

However, it has been shown that this shape may not be ideal for all products due to the inherent softer crown region exhibited in tablets manufactured from such tooling. In addition, deep concave tooling often produces tablets of poor mechanical strength [127]. Core mechanical strength, in particular friability, must be adequate enough to withstand the abrasive effects of the tumbling action while retaining the dissolution characteristics of an uncoated tablet. Large tablets, in particular, sometimes require higher compressional forces than are necessary for uncoated tablets of the same size. Care must also be exercised to minimize penetration of coating solutions into the core itself, although the coat should, of course, adhere well to the tablet surface. It will also be important to maintain a smooth, uniform surface and to provide careful control of the environment within the coating pan. Because of these requirements, the process may best be described by means of a generalized example.

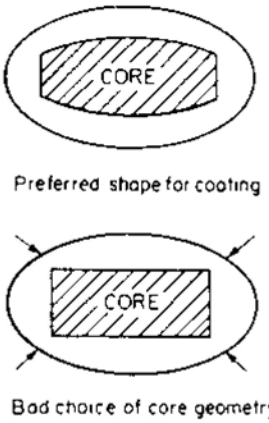


**Fig. 21** Tablet-coating geometry.

In the past, the initial layers of coating (the sealing coat) were achieved by applying one or two coats of shellac. However, due to the variability between batches of this material, PVP-stabilized types of shellac or other polymeric materials, such as cellulose acetate phthalate (CAP) and poly(vinyl acetate phthalate) (PVAP), are now more popular. It should be appreciated that a fine balance must exist between minimizing the thickness of the sealing coat and providing an adequate moisture barrier.

The next stage is to build up a subcoat that will provide a good bridge between the main coating and the sealed core, as well as rounding off any sharp corners. This is normally a two-step procedure. The first step involves the application of a warm subcoat syrup (containing acacia and/or gelatin) that rapidly distributes uniformly over the tablets and eventually becomes partially dry and tacky. At this point, a subcoat powder (containing material such as calcium carbonate, talc, kaolin, starch, and acacia) is dusted evenly over the tablets, after which the pan is allowed to rotate until the coat is hard and dry. This subcoat cycle is usually repeated three or four times, taking care to avoid the production of rough surfaces, which would be difficult to eradicate later on, and ensuring that each coat is absolutely dry before the next is applied.

The step that follows is known as "smoothing" or "grossing." It produces the bulk of the total coating weight and involves the application of a suspension of starch, calcium carbonate, or even some of the subcoat powder, in syrup. Each application is dried and the process repeated until the desired build-up has been realized. The last few applications may be made with a syrup free from suspended powders, so as to produce a smooth surface. If the tablets are to be colored, colorants are normally added in these clear syrup layers. It is important that the tablet surfaces be smooth before this is attempted, otherwise uneven coloring may result. The final finishing stage is accomplished by again applying one or two layers of clear syrup, taking care not to overdry between coats and stopping while the final coat is still slightly damp. Jogging (i.e., pan stationary apart from intermittent rotation through a small angle) is then carried out until the tablets appear dry.

The tablets are then left for several hours and are transferred to the polishing pan, which is usually of cylindrical design with canvas side walls. The polish is a dilute wax solution (e.g., carnauba or beeswax in petroleum spirit) applied sparingly, following which the tablets are left to roll until a high luster is produced. They are the normally "racked" to allow any traces of solvent to evaporate before being sent to the inspection and packing operations.

There are as many variations in coating procedures as there are tablet coaters, and so the account given here is only a guide. Nevertheless, it illustrates the complexity and time-consuming nature of the process, and the reader will realize why efforts have been made to develop alternate coatings, equipment, and methods that permit at least some degree of automation.

### B. Film Coating

Film coating has increased in popularity for a number of reasons. The film process is simpler, and therefore easier to automate. It is also more rapid than sugar coating, since weight gains of only 2–6% are involved, as opposed to more than 50% with sugar coating. In addition, moisture involvement can be avoided, if necessary, through the use of nonaqueous solvents. Moreover, distinctive identification tablet markings are not obscured by film coats.

There are now many synthetic polymeric materials available for film coating, many of which meet all the requirements of a good film former. These include lack of toxicity and a suitable solubility profile for film application and upon ingestion, together with the ability to produce a tough, yet elastic film even in the presence of powdered additives such as pigments. The film must, of course, be stable to heat, light, and moisture and be free from undesirable taste or odor.

Some of the more commonly used materials meeting these criteria are listed in Table 18 together with some important properties. Two major groups may be distinguished: (a) materials that are nonenteric and for the most part cellulose derivatives and (b) materials that can provide an enteric effect and are commonly esters of phthalic acid. Within both groups it is general practice to use a mixture of materials to give a film with the optimum range of properties. They may contain a plasticizer that, as the name implies, prevents the film from becoming brittle with consequent risk of chipping [128]. Some popular choices are shown in Table 19. Because they essentially function by modifying polymer-to-polymer molecular bonding, the choice of plasticizer is dependent upon the particular film polymer. Like so many other facets of tablet coating, there is no substitute for properly designed experimental trials in developing a robust procedure.

The nature of the solvent system may markedly influence the quality of the film [129], and, to optimize the various factors, mixed solvents are usually necessary. More specifically, the rate of evaporation, and hence the time for the film to dry, has to be con-

**Table 18** Some Commonly Used Film-Coating Materials

| Full name | Abbreviation | Soluble in | Comments |
|---|---|---|---|
| Nonenteric | | | |
| Methylcellulose | MC | Cold water, GI fluids, organic solvents | Useful polymer for aqueous films; low-viscosity grade best |
| Ethylcellulose | EC | Ethanol, other organic solvents | Cannot be used alone as is totally insoluble in water and GI fluids; employed as a film toughner |
| Hydroxyethylcellulose | HEC | Water and GI fluids | Properties similar to MC, but gives clear solutions |
| Methylhydroxyethylcellulose | MHEC | GI fluids | Similar properties to HPMC, but less soluble in organic systems |
| Hydroxypropylcellulose | HPC | Cold water, GI fluids, polar organics such as anhydrous lower alcohols | Difficulty in handling due to tackiness while drying |
| Hydroxypropylmethylcellulose | HPMC | Cold water, GI fluids, methanol/methylene chloride, alcohol/fluorohydrocarbons | Excellent film former and readily soluble throughout GIT; low-viscosity grades to be preferred, e.g., Methocel HG (Dow) |
| Sodium carboxymethylcellulose | Na-CMC | Water and polar organic solvents | Main use where presence of moisture in solvent not a problem |
| Povidone | PVP | Water, GI fluids, alcohol, and IPA | Care needed in use due to tackiness during drying; best used in mixtures to increase adhesion; is hydroscopic if used alone |
| Polyethylene | PEGs | Water, GI fluids, some organic solvents | Low molecular weight grades used mainly as film modifiers, particularly plasticizers[a] |
| Enteric | | | |
| Shellac | | Aqueous if pH 7.0 | May delay release too long; high batch-to-batch variability |
| Cellulose acetate | CAP | Acetone, ethyl acetate/IPA, alkalies, if pH 6.0 | Dissolves in distal end of duodenum; requires presence of plasticizer such as triacetin or castor oil; is somewhat hygroscopic |
| Polyvinyl acetate phthalate | PVAP | As above, if pH > 5.0 | Dissolves along whole length of duodenum |
| Hydroxypropylmethylcellulose phthalate | HPMCP | As above, if pH > 4.5 | Dissolves in proximal end of duodenum |
| Poly(methacrylates) | | Eudragit L[b] pH > 6<br>Eudragit S[b] pH > 7 | Solubilized in alkaline media; mixtures of "L" and "S" can provide enteric coating plus sustained release |

[a]High molecular weight grades are less hygroscopic and give tough coating.
[b]Rohm Pharma.

**Table 19** Some Commonly Used Film Plasticizers

| | |
|---|---|
| Phthalate esters | Propylene glycol |
| Citrate esters | Polyethylene glycol |
| Triacetin | Glycerin |

trolled within fine limits if a uniform smooth coat is to be produced. The solvent mixture must be capable of dissolving the required amount of coating material, yet give rise to a solution within a workable range of viscosity. Until relatively recently, alcohols, esters, chlorinated hydrocarbons, and ketones were among the most frequently used types of solvents.

However, as a result of increasing regulatory pressures against undesirable solvents, there has been a pronounced trend towards aqueous film coating. Many of the same polymers can be used, but it may be necessary to employ lower molecular weight grades due to their high viscosity in aqueous systems. Alternatively, water-insoluble polymers may be dispersed as a latex (emulsion) or pseudo-latex (suspension) in an aqueous media. This approach permits a high solids content without attendant high viscosity problems. However, acceptable film forming in these systems is dependent upon coalescence or agglomeration. In the case of pseudo-latices, this agglomeration requires a soft particle, and thus a high concentration of plasticizer in the system, to ensure formation of a continuous film.

In a four-part article, Porter [130] provided a comprehensive review of tablet coating technology, with emphasis on contemporary practice. More specifically, a recent review [131] discusses characterization techniques for the aqueous film coating process and provides a useful "influence matrix" between process variables and final product attributes.

Due to the need to develop a uniform color, with minimum application, the colorants used in film coating are more likely to be lakes than dyes. In "lakes" the colorant has been adsorbed onto the surface of an insoluble substrate. This gives both opacity and brightness to the pigments that are formulated with other materials so as to be easily dispersed while retaining the desired film-forming capabilities of the polymeric film former. Complete, matched coloring systems are now available as fine powders that can be readily suspended in organic solvents or aqueous systems and, as such, provide a very convenient colorant source.

## C. Modified Release Coatings

A coating may be applied to a tablet to modify the release pattern of the active ingredient from it. There are two general types of modified release coatings: enteric and controlled-release. The former are insoluble in the low pH environment of the stomach but dissolve readily on passage into the small intestine with its elevated pH. They are used to minimize irritation of the gastric mucosa by certain drugs and to protect others that are degraded by gastric juices. Controlled-release coatings are reviewed in Chapter 15.

The most common mode of action of enteric coating is pH-related solubility (i.e., insoluble at gastric pH but soluble at some pH above $\sim$4.5). A list of the most widely used enteric coatings is given in Table 18. A less popular alternative has been the use of materials that are affected by the changing enzymatic activity on passage from the stomach to the small intestine. Since their performance is dependent upon the digestion of the coating, the intrinsic in vivo variability of this action makes this type of enteric coating less predictable.

## D. Coating Equipment

Conventional coating pans are subglobular, pear-shaped, or even hexagonal (see Fig. 22) with a single front opening through which materials and processing air enter and leave. Their axis is normally inclined at approximately 45° to the horizontal plane, and they are rotated between 25 and 40 rotations per minute (rpm), the precise speed depending, most often, on the product involved. One modification of the normal pan has been the substitution of a cylindrical shape, rotated horizontally with regions of the walls perforated by small holes or slots. This design permits a one-way air flow through the pan as shown in Fig. 23. This figure also illustrates the ways in which vendors have chosen to modify the basic concept. In the Accela-Cota (Manesty) and Hi-Coater (Vector Corp.) (Fig. 24), the flow of air is through the tablet bed and out through the perforated wall of the pan. In the Driacoater (Driam) the air flows from the perforated pan wall through the tablet and into the central region (i.e., countercurrent to the direction of the coating spray). The Glatt-Coater (Glatt Air Techniques) permits either co- or countercurrent air flow to suit particular products.

The traditional method of ladling the coating solutions into the rotating bed of tablets has given way to systems capable of spraying material, with or without the assistance of an air jet. More specifically, two general types are available: those that rely entirely on hydraulic pressure to produce a spray when material is forced through a nozzle (airless spraying) and those in which atomization of the spray is assisted by turbulent

**Fig. 22** Conventional coating pan.

jets of air introduced into it. The latter type tends to produce a more easily controlled spray pattern and is therefore better for small-scale operations, although both are capable of giving the flat jet profile preferred for pan operation. Other important parameters include the distance from nozzle to bed surface and whether continuous or intermittent spraying is utilized. One interesting development in this area has been the introduction of a special plough-shaped head, which is immersed in the tumbling bed of tablets and through which both coating solutions and air can be delivered into the bed.

The film-coating process can be carried out in conventional pans, although operation variables such as speed of pan rotation, angle of pan axis, and temperature and humidity control may be more critical. Newer pans with one-way air flow through the tablet bed offer an even better alternative, because the pan environment can be controlled within finer limits.

### *Coating in Fluidized Beds*

Fluidized beds, in general, and the air-suspension technique patented by Wurster, in particular, now offer an attractive alternative to pan coating. The basic principle underlying their operation is to suspend the tablets in an upward moving stream of air so that they are no longer in contact with one another.

An atomizer introduces spray solution into the stream and onto the tablets, which are then carried away from the spraying region where the coating is dried by the fluidized air. In the Wurster process, the design is such that the tablets are sprayed at the bottom of the coating column and move upwards centrally, being dried as they do so. They then leave the top of the central region and return down the periphery of the column to be recycled into the coating zone, as shown in Fig. 25. The process can be controlled by careful adjustment of the air and rate of coating solution delivery and monitoring of the exiting air temperatures.

### *Compression Coating*

A method has been described [132] for compressing a coating around a tablet "core" using specially designed presses. The process involves preliminary compression of the core formulation to give a relatively soft tablet, which is then transferred to a large die already containing some of the coating material. After centralizing the core, further coating granulation is added and the whole compressed to form the final product. From a formulation point of view, this requires a core material that develops reasonable strength at low compressional loads and a coating material in the form of fine free-flowing granules with good binding qualities.

Perhaps the best known commercial presses developed for this work are the Drycota (Manesty) and the Prescoter (Killian). Due to the small number of applications in which it can be used, Manesty no longer manufactures the Drycota. The Prescoter, however, is in the process of being updated (Model S250M) for the first time since its introduction 15 years ago. The Prescoter uses cores produced on another machine and, for this reason, requires somewhat harder cores capable of withstanding the additional handling that may result in weaker bonding between core and coating.

Incompatible drugs may be co-formulated by this method by incorporating one drug in the core and the other in the coating formulation. The possibility of having a dual-release pattern of the same drug (e.g., a rapidly released fraction in the coat and an extended release component in the core) is perfectly feasible. Compression of an enteric coating around a tablet, and even a second layer of coating, have been attempted, but not widely adopted. A machine developed for this purpose, the Bicota (Manesty), is no longer commercially available.

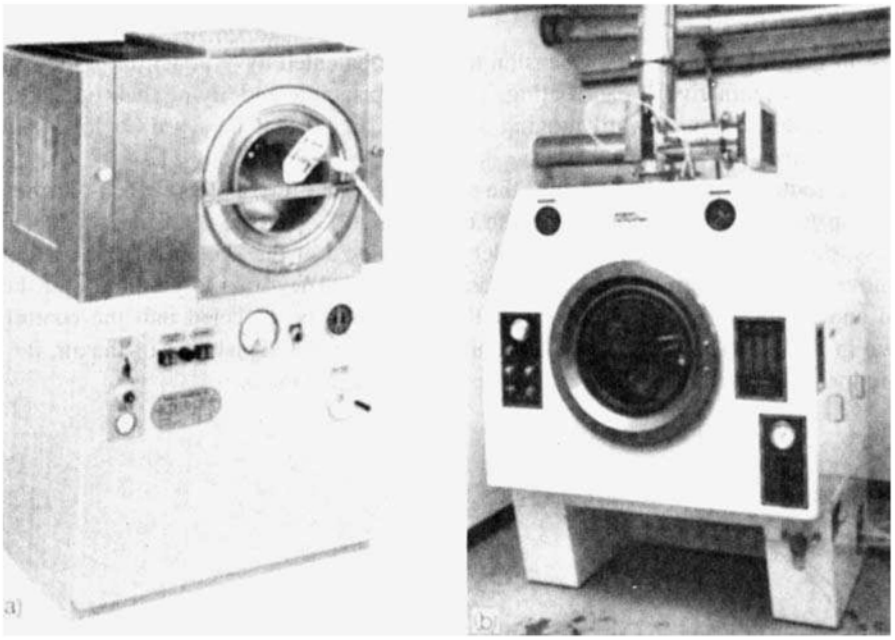

**Fig. 23** Typical side-vented pan.

*Layered Tablets*

In a search for novelty as much as functionality, tablets have been produced on presses capable of compressing a second (or even third) layer on top of the original material. Indeed, the standard double-rotary machines require little modification in order to achieve this goal. Such tableting procedures facilitate the co-formulation of incompatible materials and design of complex release patterns, as well as adding a new dimension to ease of identification. A considerable amount of expertise is needed to formulate and consistently manufacture these tablets to meet the strict regulatory requirements now demanded. Several high-output tablet presses designed to produce two- or three-layered tablets are commercially available.

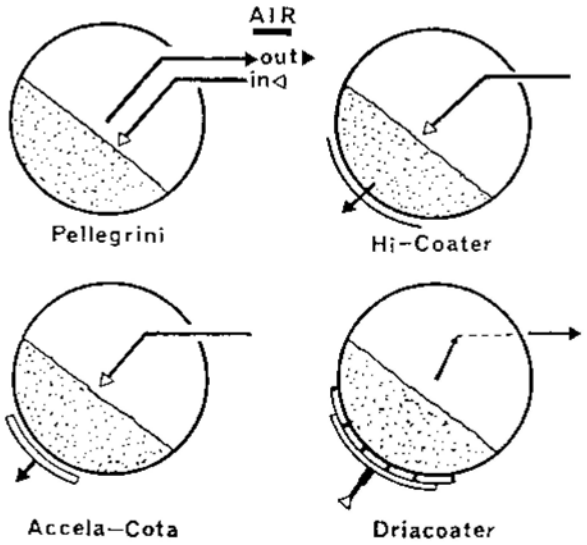


**Fig. 24** Coating pan air configurations.

## VI. EVALUATION OF TABLETS

Under this heading it will be convenient to divide the types of test procedures into two major categories: those that are requirements in an official compendium and those that, though unofficial, are widely used in commerce. In certain cases it will also be of value to consider specialized evaluative procedures that have perhaps a more academic background.

Several "all-in-one" tablet testers are currently available that measure weight, thickness, diameter, and hardness of tablets. In addition these instruments provide digital storage and calculation of statistical parameters and allow for rapid feedback during the tableting process so that the tableting equipment can be adjusted accordingly with minimal "downtime."

### A. Official Standards

The discussion will be restricted to those tests that are mandatory in The United States Pharmacopoeia (USP)

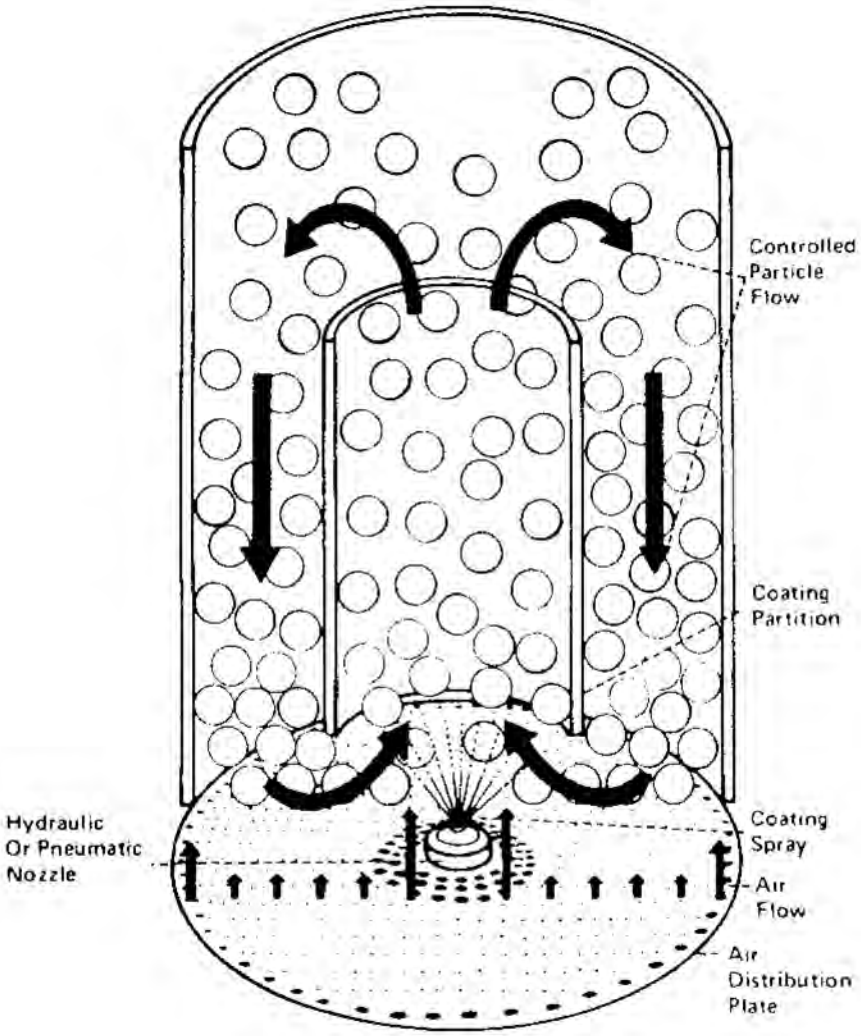


**Fig. 25** Diagram of Wurster coating chamber.

and The National Formulary (NF), although reference to the monographs of other compendia is included where appropriate. Tests concerned with dissolution rate determinations are discussed in Chapter 20, and assay procedures are omitted as they are essentially analytical methods pertaining to a particular drug.

### *Uniformity of Dosage Units*

The dose uniformity of tablets can be determined by two different general approaches: the weight variation between a specified number of tablets or the extent of drug content uniformity. The USP permits the latter approach in all cases. Moreover, drug content uniformity must be measured for coated tablets because the tablet coat, which does not usually contain the active ingredient(s), may vary significantly from tablet to tablet. The use of weight uniformity as a singular means of quantifying uniformity of dosage units is only permitted in cases where the tablet is uncoated and contains 50 mg or more of a single active ingredient that comprises 50% or more of the total tablet weight.

Most pharmacopoeias include a simple weight test on a specified number of tablets that are weighed individually. The arithmetic mean weight and relative standard deviation (i.e., mean divided by standard deviation) of these tablets is then calculated. Only a specified number of test tablets may lie outside the prescribed limits. These specifications vary depending upon the type of tablet and amount of active present.

Content uniformity is a USP test is designed to establish the homogeneity of a batch. Ten tablets are assayed individually after which the arithmetic mean and relative standard deviation (RSD) are calculated. USP criteria are met if the content uniformity lies within 85–115% of the label claim and the RSD is not greater than 6%. Provision is included in the compendium for additional testing if one or more units fail to meet the standards.

*Disintegration Testing*

Determination of the time for a tablet to disintegrate when immersed in some test fluid has been a requirement in most compendia for many years. For many years, it was the only test available to evaluate the release of medicaments from a dosage unit. We now recognize the severe limitations of such tests in assessing this property—hence, the introduction of dissolution rate requirements.

The USP disintegration test is typical of most and is described in detail in a monograph of that volume. Briefly, it consists of an apparatus in which a tablet can be introduced into each of six cylindrical tubes, the lower end of which is covered by a 0.025 $in.^2$ wire mesh. The tubes are then raised and lowered through a distance of 5.3–5.7 cm at a rate of 29–32 strokes per minute in a test fluid maintained at $37 \pm 2°C$. Continuous agitation of the tablets is ensured by this stroking mechanism and by the presence of a specially designed plastic disk, which is free to move up and down in the tubes.

The tablets are said to have disintegrated when the particles remaining on the mesh (other than fragments of coatings) are soft and without palpable core. A maximum time for disintegration to occur is specified for each tablet, and at the end of this time the aforementioned criteria must be met. The disintegration media required varies depending on the type of tablet to be tested. Apparatus meeting the official specification is available from several sources. Several modifications of the official method have been suggested in the literature, including a basket insert as an alternative to the disks [133].

The disintegration time may be markedly affected by the amount of disintegrant used as well as the tablet process conditions. In particular, a log/linear relationship between disintegration time and compressional force has been suggested by several authors [134–136]. Mufrod and Parrot concluded that although disintegration is affected by changes in compression pressure, these changes do not significantly alter the product's dissolution profile [137].

## B. Unofficial Tests

*Mechanical Strength*

The mechanical strength of tablets is an important property of this form of drug presentation and plays a significant role in both product development and control. It has been described by various terms, including friability [138], hardness [139], fracture resistance [140], crushing strength [141], and flexure, or breaking strength [142].

Even in tablets of the simplest geometry, interpretation of this property is less straightforward than it first might appear. Some degree of anisotropy is almost certain to be present, and the ideal test conditions, employing closely defined uniform stresses, are rarely met. The mechanical strength of the tablet is primarily due to two events that occur during compression: the formation of interparticulate bonds and a reduction in porosity resulting in an increased density.

*Crushing Strength*

Many crushing strength testers are described in the literature [133,138–141]. In industry, mechanical strength is most often referred to as the tablet's hardness or, more precisely, its crushing strength. Brook and Marshall described crushing strength as "the compressional force that, when applied diametrically to a tablet, just fractures it" [141]. In most cases, the tablet is placed upon a fixed anvil and the force is transmitted to it by means of a moving plunger. Many testers of this type are commercially available, including the Stokes (or Monsanto), Strong-Cobb, Pfizer, and Erweka and Schleuniger (or Heberlein). Based upon the particular tester's design, the plunger is moved either manually or electronically. Comparisons between the different types of testers has proved that the electronic testers produce results that are much more reproducible than those obtained from the manual testers [130,141,143–145]. This is due, in large part, to the constant rate of loading achieved with electronic testers [123] (see Fig. 26).

In general, the load is applied at 90° to the longest axis (i.e., across the tablet's diameter) (see Fig. 27). In such cases, the load required to break the tablet is referred to as the diametrical strength. The load can also be applied across the tablet's thickness, in which case it is referred to as flexure or breaking strength [140,142]. The tensile strength, $\sigma$, can be calculated once the load required to fracture the tablet has been determined. The precise calculation of tensile strength depends upon the method used to break the tablet. When using a diametrical, or diametral, test the calculation is as follows:

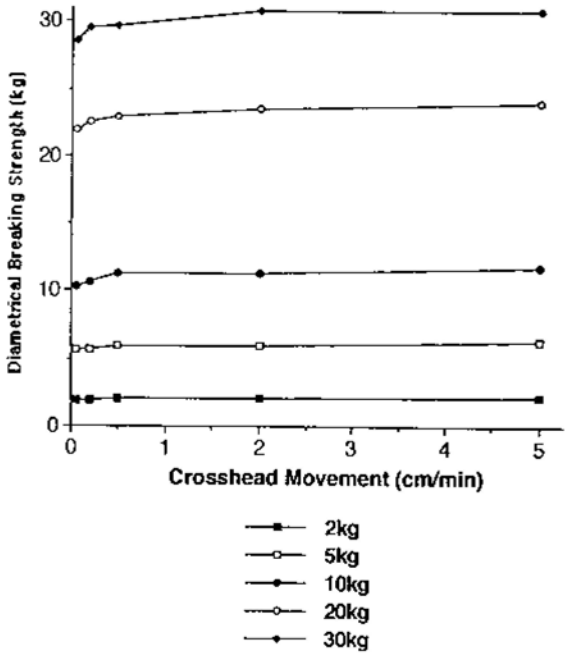


**Fig. 26** Effect of loading rate on the diametrical breaking strength of tablets compressed at different levels. (From Ref. 123.)

$$\sigma_d = \frac{2F_d}{\pi DH}$$

where

$\sigma_d$ = tensile strength
$F_d$ = load required to fracture tablet
$D$ = tablet diameter
$H$ = tablet height

From a test of the tablet's flexure, tensile strength ($\sigma_f$) is calculated from the following equation:

$$\sigma_f = \frac{3F_f D'}{4DH^2}$$

where

$\sigma_f$ = tensile strength
$F_f$ = load required to fracture tablet
$D$ = tablet diameter
$D$ = distance from fulcrum to fulcrum
$H$ = tablet height

In their evaluation of flexure and diametral testing, David and Augsburger found the tensile strength to be the same regardless of the method used as long as the appropriate calculation was employed [142].

Two types of inherent error may be present: that associated with an incorrect zero and a scale that does not accurately indicate the actual load being applied. In some models there is the additional problem of a variable rate of loading. Moreover, when using unpadded flat anvils the failure may involve some compression. Thus, it is essential to realize what is being measured in a particular instrument.

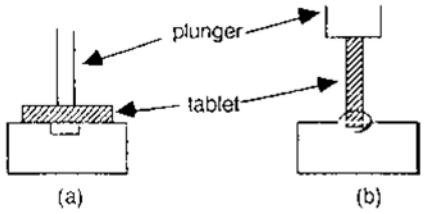


**Fig. 27** Methods of evaluating tablet crushing strength: (a) bending or flexure strength; (b) diametrical compression. (From Ref. 145.)

The Stokes and Pfizer testers apply force through a coil spring, which after long periods of use shows signs of fatigue and may also show some loss of load due to frictional effects [141,145]. The rate of loading is not controlled in these types or in the Strong-Cobb tester, which applies force through hydraulic pressure. The scale of this machine registers air pressure, and comparison of results with other instruments is therefore only possible if these readings are converted to compressional load.

The Erweka and Schleuniger testers operate on a counterweight principle that eliminates fatigue, if not frictional, losses. The latter of these two devices is supplied calibrated and a "mechanical tablet" is available for periodic recalibration. More recently, testers have been introduced that measure the load being applied to the tablet by means of load cells and therefore facilitate direct electronic digital readout. This eliminates the two major sources of error referred to above and permits recording of production of hard copies of the test results.

Comparative reports in the literature confirm the necessity of employing some calibration procedure if results from testers are to be compared or reduced to actual units of force. This is particularly true where the information is being used to determine relationships between crushing strength to other tablet properties.

It can be argued that the crushing strength of a tablet is more closely related to the compressional process, and the results may not give the best indication of how the tablet will behave during handling. If information in this respect is required, then the groups of instruments in the following paragraphs are more relevant.

One might anticipate that the crushing strength ($F$) of a tablet is a function of the pressure ($P$) employed during its compaction [134]. For example the following relationship may hold true:

$$F = k \log P + k_1$$

where $k$ and $k_1$ are constants. However, deviation from this logarithmic relationship at compressional pressure values, above 150 MPa has been reported [81,135]. In addition, the crushing strength has been related to certain physical properties of the compact. For example:

$$F = kE^{-1} + k_1$$

where $E$, the porosity, has values between 5 and 20%. The most obvious use of crushing strength measurements has been to give indications of possible disintegration times ($t_p$), i.e.,

$$F = kt_p + k_1$$

### *Abrasion*

While the crushing strength of a tablet gives some indication of its mechanical robustness, it does not truly measure the ability of the tablet to withstand the handling it will encounter during processing and shipping. Tests designed to assess the resistance of the surface regions to abrasion or other forms of general "wear and tear" may be more appropriate in this regard.

Many tests to assess abrasion are quoted in the literature [138,146,147]. Most measure the weight loss on subjecting tablets to a standard level of agitation for a specified time. The choice of agitation should be based on knowledge of the likely level during use or manufacture.

More specifically a certain weight of tablets, $W_0$, is subjected to a well-defined level of agitation in a fixed-geometry, closed container for a specific time. They are then reweighed, $W$. The measure of abrasion resistance or friability, $B$, is usually expressed as a percentage loss in weight:

$$B = 100 \cdot \left[1 - \frac{W}{W_0}\right]$$

It might be advantageous to relate friability to unit time or number of falls.

The Roche Friabilator is one of the most common methods used to test for resistance to abrasion [147]. In this case, a minimum of 6 g (often 20 tablets) of dedusted and weighed tablets are placed in a 12 in. high drum, which is then rotated for 100 revolutions. A shaped arm lifts the tablets and drops them half the height of the drum during each revolution. At the end of this operation, the tablets are removed, dedusted, and reweighed. Should any tablet break up, the test is rejected. Values of $B$ from 0.8 to 1.0% are frequently quoted as the upper level of acceptability for pharmaceutical products [147].

Indentation hardness using modified tests based on "Brinell" hardness measurements have been used by some researchers [148] to provide information on the surface hardness of tablets. In addition, these tests are capable of providing a measure of a tablet's plasticity or elasticity. For the most part, such tests have been confined to basic research applications in a few laboratories, but their value is beginning to be more widely recognized.

### *Porosity*

The bioavailability of drugs from tablets can be markedly influenced by the rate and efficiency of the initial disintegration and dissolution process. Unfortunately, one is faced with a compromise situation — a structure that has both a durable structure prior to administration and the ability to readily break down when placed in the in vivo environment. One of the major factors affecting both these properties is the structure of the tablet, in particular its density (or porosity) and the pore structure. Study of the significance of such measurements and interpretation of the results is a relatively recent field of interest.

Determination of the porosity of a tablet presents the classic problem of defining the appropriate volume to be measured. The displacement medium may be able to penetrate the most minute crevices, as is the case for helium. Other displacement media, such as mercury, are unable to enter the smallest tablet crevices and thus produce different porosity values. Standardization of displacement media is therefore necessary for comparative evaluations.

### *Pore Structure and Size*

The relationship between applied pressure ($P$) and the diameter of the smallest circular pore penetrated ($d$) by a liquid gas is given by the equation:

$$d = \frac{4\pi\gamma \cos\beta}{P}$$

where $\gamma$ is the surface tension of the liquid and $\beta$ is the contact angle solid and liquid.

Originally, the method of porosimetry was only of interest to those involved with the high-pressure

techniques associated with pore analysis. However, with the increasing availability of sophisticated porosimeters, the technique of porosimetry is being used on a frequent basis to investigate tablet structure. High-pressure mercury intrusion porosimeters are capable of assessing a wide range of pore radii. A typical example of the application of such an instrument to evaluate wet and dry techniques of precompression treatment is reported by Ganderton and Selkirk [149]. These authors found that lactose granulations resulted in a wider pore size distribution than ungranulated lactose.

This technique has also been used in combination with nitrogen absorption to study the pore structure of some excipients, particularly MCC in both the powdered and compacted state. The intraparticulate porosity of MCC has been shown to be unaffected by tableting; the interparticular pores, however, are gradually reduced in size [38]. Recently this method has been used to evaluate the internal structure of tablets prepared from microcapsules [150].

### *Liquid Penetration*

The rate at which selected liquids penetrate into tablets can be used to study their pore structure. A knowledge of the rate of liquid penetration should also provide information on the disintegration/dissolution behavior of a tablet on administration. Such investigations are capable of forming a valuable link between physicomechanical characteristics and in vivo performance.

### *Evaluation of Bioadhesive Tablets*

With the advent of increasingly sophisticated tableted delivery systems comes the task of assessing these systems. Bioadhesive tablets, in particular, present an interesting problem to the formulator. Although such tablets are not currently marketed in the U.S., they are currently being evaluated in many laboratories as an alternative means for providing sustained release of drug. The sustained-release characteristic of bioadhesive tablets is afforded through their ability to adhere to the intestinal mucosa. Thus, an estimation of their adhesiveness is a key factor in their in vitro evaluation.

Ishida et al. were some of the first investigators to propose a method for investigating the adhesive properties of tablets [151]. Their method involved placing a tablet onto a membrane under constant pressure for one minute and then measuring the force required to remove it. Most methods published since that time involve essentially the same principle, with variations in the type of membrane used and the manner in which the adhesive force is measured [152,153]. An excellent review of these methods has been published by Duchene et al. for those interested in the precise details of such tests [154].

Jimenez-Castellanos et al. developed a method to measure both the adhesional and frictional forces involved in the attachment of such tablets to mucosa. These researchers found that a good correlation existed between the maximal adhesion strength and polymer content of the tablets tested [155].

### *Near-Infrared Spectroscopy*

In the late 1990s researchers began to evaluate the use of near-infrared (NIR) spectroscopy in pharmaceutical analyses [156–158]. NIR analyses are particularly useful because they are both rapid and nondestructive to the sample. Morisseau and Rhodes reviewed the application of NIR in the pharmaceutial industry and determined that it has been used to measure sample composition and identification, moisture content, content uniformity, homogeneity of mixing, degradation products, and particle size [156]. Recently its potential to differentiate between compression force used during tableting and to assess moisture profile during the granulation process has been evaluated [157,158]. As researchers become more familiar with this method, its applications will undoubtedly grow.

## VII. RECENT DEVELOPMENTS IN TABLETING

### A. Rapidly Disintegrating Tablets

The trend toward formulation of dispersible tablets is evident in Europe [159–162] and is becoming more commonplace in the United States with over-the-counter preparations available in the form of the following technologies: Zydis® (Scherer DDS), Lyoc® (Farmalyoc), WOW® Tab (Yamanouchi), FlashDose® (Fuisz Technologies), OraSolv® (CIMA), and DuraSolv® (CIMA). These tablets are either placed in the mouth where they quickly dissolve or are placed in a glass of water prior to ingestion and provide consumers with a dosage form that is both potable and easy to swallow.

A challenge faced by formulators designing dispersible tablets is the ability to develop a formulation that rapidly disintegrates and is able to withstand shipping processes. In addition, this type of tablet should form a uniform and somewhat stable suspension when dispersed in water. An interesting answer to

this challenge is the design of a "porous table" [163–165], in which a volatizable solid (e.g., urethane or ammonium bicarbonate) is added to a standard, directly compressible formulation. After the tablets have been compressed, the volatilizable solid is removed by a freeze-drying or heating process. Water easily penetrates through the pores and promotes rapid disintegration of the tablets produced in this manner. Thus, these tablets are able both to maintain their mechanical strength and to provide rapid disintegration or dispersion of product. Lyoc and Zydis tablets both use freeze-drying technologies.

### B. Three-Dimensional Printing Tablets

For years, formulators have been searching for a means to accurately and consistently deliver a specified level of coating onto a tablet. The answer may have been found in the three-dimensional printing (3DP) of tablets. The process involves the computer-controlled preparation of tablets by building layer upon layer of powder that are joined by a binder solution dispersed by a printing head [166,167]. Several modes of release have successfully been implemented in 3DP tablets, including (a) immediate- and extended-release tablets with two drug-containing components whose release with pH-dependent release, (b) breakaway tablets composed an interior fast-eroding section that separates two drug-containing components, (c) enteric dual pulsatory tablets comprised of a continuous enteric excipient with two drug-containing sections, and (d) immediate- and extended-release tablets with two drug-containing components with erosion-dependent release [166].

### C. Web System

A system was developed at Roche Laboratories whereby a sheet (or "web") was coated with a drug/binder mixture. The solid dosage units were then punched from the web [168]. This system was very flexible and amenable to immediate release and sustained-release technologies. However, due to the impracticality of the system, it was abandonned in the mid-1980s and is only of historical significance.

## VIII. FUTURE DIRECTIONS

Tablets were a viable dosage form well before William Brockendon's patent for a tablet machine in 1843. His invention only made them easier to produce. As tablet presses and production-monitoring systems developed, these dosage forms have become the most economical of any ever developed. It will be hard to improve on their efficiency, but several attempts, like three-dimensional printing, have been made recently.

Newer technologies may become available, but it is unlikely that any new tableting technology will render the old technology obsolete any time soon. Processing technologies such as high-shear mixing and microwave drying seem to be having the most impact on processing times and efficiency. Coating technologies are becoming more controllable, and they offer the most hope for efficiency improvements.

Another new development has been the application of oral absorption promoters. These materials are designed to enhance the oral bioavailability of many compounds and improve variable absorption. However, many of these compounds are hydrophobic in nature and cause difficulty during tableting itself. The challenge for formulators is to arrive at clever solutions to the process problems while retaining material performance.

The ultimate challenge for tablet formulators in the twenty-first century is to achieve a true understanding of material properties and material science. Those who can quickly conceive a compatible, functional formulation will be irreplaceable as large companies shrink their R&D resources and the public sector demands better efficiency.

## REFERENCES


1. A. T. Florence, E. G. Salole, and J. B. Stenlake, J. Pharm Pharmacol., 26, 479 (1974).
2. P. Timmins, I. Browning, A. M. Delargy, J. W. Forrester, and H. Sen, Drug Dev. Ind. Pharm., 12, 1293 (1986).
3. N. Kaneniwa, K. Imagawa, and J.-I. Ichikawa, Chem. Pharm. Bull., 36, 2531 (1988).
4. B. M. Hunter, J. Pharm. Pharmacol., 26, 58P (1974).
5. S. Vesslers, R. Boistelle, A. Delacourte, J. C. Guyot, and A. M. Guyot-Hermann, Drug Dev. Ind. Pharm., 18, 539 (1992).
6. R. F. Shangraw, J. W. Wallace, and F. M. Bowers, Pharm. Tech., 11, 136 (1987).
7. J. W. McGinity, C.-T. Ku, R. Bodmeier, and M. R. Harris, Drug Dev. Ind. Pharm., 11, 891 (1985).
8. A. J. Shukla, and J. C. Price, Drug Dev. Ind. Pharm., 17, 2067 (1991).
9. H. Ando, M. Ishii, M. Kayano, and H. Ozawa, Drug Dev. Ind. Pharm., 18, 453 (1992).
10. P. W. S. Heng, and J. N. Staniforth, J. Pharm. Pharmacol., 40, 360 (1988).

11. J. C. Callahan, G. W. Cleary, M. Elefant, G. Kaplan, T. Tensler, and R. A. Nash, Drug Dev. Ind. Pharm., 8, 355 (1982).
12. A. Wade and P. J. Weller (eds.), Handbook of Pharmaceutical Excipients, 2nd ed., The Pharmaceutical Press, Washington, DC, 1994.
13. C. M. Anderson, Aust. J. Pharm., 47, S44 (1966).
14. J. W. Poole and C. K. Bahal, J. Pharm. Sci., 57, 1945 (1968).
15. O. Weis-Fogh and T. Dansk, Farm. Suppl., 11, 276 (1956).
16. H. K. Chan and E. Doelker, Drug Dev. Ind. Pharm., 11, 315 (1985).
17. S. Kopp, C. Beyer, E. Graf, F. Kubel, and E. Doelker, J. Pharm. Pharmacol., 41, 79 (1989).
18. M. Otsuka, T. Matsumoto, and N. Kaneniwa, J. Pharm. Pharmacol., 41, 667 (1989).
19. T. Matsumoto, N. Kaneniwa, S. Higuchi, and M. Otsuka, J. Pharm. Pharmacol., 43, 74 (1991).
20. C. R. Lerk and H. Vromans, Acta Pharm. Suec., 24, 60 (1987).
21. P. York, Drug Dev. Ind. Pharm., 18, 677 (1992).
22. W. I. Higuchi, P. D. Bernardo, and S. C. Mehta, J. Pharm. Sci., 56, 200 (1967).
23. E. N. Hiestand, J. Bane, and E. Strzelinski, J. Pharm. Sci., 60, 758 (1971).
24. E. N. Hiestand and C. B. Peot, J. Pharm. Sci., 63, 605 (1974).
25. E. N. Hiestand, J. E. Wells, C. B. Peot, and J. F. Ochs, J. Pharm. Sci., 66, 510 (1977).
26. E. N. Hiestand and D. Smith, Powder Technol., 38, 145 (1984).
27. E. N. Hiestand, J. Pharm. Sci., 74, 768 (1985).
28. E. N. Hiestand, Pharm. Tech., 10, 52 (1986).
29. R. O. Williams, and J. W. McGinnity, Drug Dev. Ind. Pharm., 14, 1823 (1988).
30. A. J. Romero, G. Lukas, and C. T. Rhodes, Pharm. Acta Helv., 66, 34 (1991).
31. D. Q. M. Craig, C. T. Davies, J. C. Boyd, and L. B. Hakess, J. Pharm. Pharmacol., 43, 444 (1991).
32. H. G. Brittain, Drug Dev. Ind. Pharm., 15, 2083 (1989).
33. D. S. Phadke, and J. L. Eichorst, Drug Dev. Ind. Pharm., 17, 901 (1991).
34. H. Bundgaard, J. Pharm. Pharmacol., 26, 535 (1974).
35. Y. K. E. Ibrahim and P. R. Olurinaola, Pharm. Acta Helv., 66, 298 (1991).
36. H. L. Avallone, Pharm. Tech., 16, 48 (1992).
37. D. C. Monkhouse, and A. Maderich, Drug Dev. Ind. Pharm., 15, 2115 (1989).
38. H. Nyquist, Drug Dev. Ind. Pharm., 12, 953 (1986).
39. Z. T. Chowhan and L.-H. Chi, J. Pharm. Sci., 75, 534 (1986).
40. G. K. Bolhuis and C. F. Lerk, Pharm. Weekblad., 108, 469 (1973).
41. J. W. Wallace, J. T. Capozzi, and R. F. Shangraw, Pharm. Tech., 7, 95 (1983).
41a. K. B. Mulderrig, Pharm. Tech., 24(5), 34 (2000).
41b. Y.-E. Zhang and J. B. Schwartz, Drug Dev. Ind. Pharm., 26(7), 761 (2000).
42. J. T. Carstensen and C. Ertell, Drug Dev. Ind. Pharm., 16, 1121 (1990).
43. D. H. Shah and A. S. Arambulo, Drug Dev. Ind. Pharm., 1, 495 (1974–1975).
44. K. A. Khan and C. T. Rhodes, Chemist Druggist, 159, 158 (1973).
45. N. Shah, R. Pytelewski, H. Eisen, and C. I. Jarowski, J. Pharm. Sci., 63, 339 (1974).
46. G. D. D'Alonzo and R. E. O'Connor, Drug Dev. Ind. Pharm., 16, 1931 (1990).
47. O. Shirakura, M. Yamada, M. Hashimoto, S. Ishimaru, K. Takayama, and T. Nagai, Drug Dev. Ind. Pharm., 18, 1099 (1992).
48. H. Seager, P. J. Rue, I. Burt, J. Ryder, and J.K. Warrack, Int. J. Pharm. Tech Prod. Mfr., 2(2), 41 (1981).
48a. E. Horisawa, K. Danjo, and H. Sunada,
49. Z. Chowhan, Pharm. Tech., 12(2), 26 (1988).
50. R. M. Iyer, L. L. Augsburger, and D. M. Parikh, Drug, Dev. Ind. Pharm., 19(9), 981 (1993).
50a. S. K. Joneja, W. W. Harcum, G. W. Skinner, P. E. Barnum, and J.-H. Guo, Drug Dev. Ind. Pharm., 25(10), 1129 (1999).
50b. C. Alvarez-Lorenzo, J. L. Gomez-Amoza, P. Martinez-Pacheco, C. Souto, and A. Concheiro, Int. J. Pharm., 197(1–2), 107 (2000).
51. P. York, Int. J. Pharm., 14, 1 (1983).
52. C. F. Lerk, M. Lagas, J. P. Boelstra,, and P. Broersma, J. Pharm. Sci., 66, 1480 (1977).
53. C. F. Lerk, M. Lagas, J. T. Fell, and P. Nauta. J. Pharm. Sci., 67, 935 (1978).
54. E. Shotton and G. S. Leonard, J. Pharm. Pharmacol., 24, 798 (1972).
55. M. H. Rubinstein and D. M. Bodey, J. Pharm. Pharmacol., 26, 104P (1974).
56. K. A. Khan and C. T. Rhodes, J. Pharm. Sci., 64, 166 (1975).
57. A. Mitrevej and R. G. Hollenbeck, Pharm. Tech., 6, 48 (1982).
58. H. Nogami, T. Nagai, E. Fukuoka, and T. Sonobe, Chem. Pharm. Bull., 17, 1450 (1969).
59. R. F. Shangraw, Manuf. Chem., 57, 22 (1986).
60. H. Burlinson and C. Pickering, J. Pharm. Pharmacol., 2, 630 (1950).
61. L. C. Curlin, J. Am. Pharm. Assn., Sci. Ed., 44, 16 (1955).
62. N. R. Patel and R. E. Hopponen, J. Pharm. Sci., 55, 1065 (1966).
63. K. S. Manudhane et. al., J. Pharm. Sci., 58, 616 (1969).
64. H. Hess, Pharm. Tech., 11, 54 (1987).

65. J. B. Schwartz and J. A. Zelinskie, Drug Dev. Ind. Pharm., 4, 463 (1978).
66. A. M. Guyot-Hermann and J. Ringard, Drug Dev. Ind. Pharm., 7, 155 (1981).
67. W. Lowenthal and J. H. Wood, J. Pharm. Sci., 62, 287 (1973).
68. K. A. Khan and C. T. Rhodes, J. Pharm. Pharmacol., 23, 261A (1971).
69. J. F. Bavitz, N. R. Bohidar, and F. A. Restaino, Drug Dev. Comm., 1, 331 (1974–1975).
70. W. Lowenthal, J. Pharm. Sci., 61, 1695 (1972).
71. J. L. Kanig and E. M. Rudnic, Pharm. Tech., 8, 50 (1984).
72. D. Gissinger and A. Stamm, Drug Dev. Ind. Pharm., 6, 511 (1980).
73. P. V. Marshall, D. G. Pope, and J. T. Carstensen, J. Pharm. Sci., 80(19), 899 (1991).
74. E. M. Rudnic, C. T. Rhodes, S. Welch, and P. Bernardo, Drug Dev. Ind. Pharm., 8, 87 (1982).
75. C. Fuhrer, Informationsdienst APV, 20, 58 (1964).
76. H. Matsumaru, Yakugaku Zashi, 79, 63 (1959).
77. P. H. List and V. A. Muazzam, Drugs Made in Germany, 22, 161 (1979).
78. A. J. Smallenbroek, G. K. Bolhuis, and C. F. Lerk, Pharm. Weekblad Sci. Ed., 3, 172 (1981).
79. E. M. Rudnic, J. M. Lausier, R. N. Chilamkurti, and C. T. Rhodes, Drug Dev. Ind. Pharm., 6, 291 (1980).
80. E. M. Rudnic, J. L. Kanig, and C. T. Rhodes, J. Pharm. Sci., 74, 647 (1985).
81. E. Shotton and C. Lewis, J. Pharm. Pharmacol., 16, 111T (1964).
82. H. C. Caldwell and W. J. Westlake, J. Pharm. Sci., 61, 984 (1972).
83. Y. Matsuda, Y. Minamida, and S.-I. Hayashi, J. Pharm. Sci., 65, 1155 (1976).
84. J. Kikuta and N. Kitamori, Durg Dev. Ind. Pharm., 11, 845 (1985).
85. S. Dawoodbhai and C. T. Rhodes, Drug Dev. Ind. Pharm., 16, 2409 (1990).
85a. C. Viseras, A. Yebra, and A. Lopez-Galindo, Pharm. Dev. Technol., 5(1), 53 (2000).
86. P. W. S. Heng, L. S. C. Wan, and T. S. H Ang, Drug Dev. Ind. Pharm., 16, 951 (1990).
87. L. S. C. Wan and P. W. S. Heng, Pharm. Acta Helv., 62, 169 (1987).
88. L. S. C. Wan and P. W. S. Heng, Pharm. Acta Helv., 61, 157 (1986).
89. H. Schott, L. C. Kwan, and S. Feldman, J. Pharm. Sci., 71, 1038 (1982).
90. M. L. Wells and E. L. Parrott, Drug Dev. Ind. Pharm., 18, 175 (1992).
91. M. L. Wells and E. L. Parrott, Drug Dev. Ind. Pharm., 18, 265 (1992).
92. M. L. Wells and E. L. Parrott, J. Pharm. Sci., 81, 453 (1992).
92a. L. Flores, R. Arellano, and J. Esquivel, Drug Dev. Ind. Pharm., 26(3), 297 (2000).
92b. L. Flores, R. Arellano, and J. Esquivel, Drug Dev. Ind. Pharm., 26(4), 465 (2000).
92c. R. Heinz, H. Wolf, H. Schuchmann, L. End, and K. Kolter, Drug Dev. Ind. Pharm., 26(5), 513 (2000).
92d. G. Buckton and E. Yonemochi, Eur. J. Pharm. Sci., 10(1), 77 (2000).
93. J. T. Carstensen, *Theory of Pharmaceutical Systems*, Vol. 2, Academic Press, New York, 1973.
94. J. A. Hersey, J. Pharm. Pharmacol., 63, 1685 (1967).
95. H. Stahl, Pharm. Tech. Yearbook 2000, 32–40 (2000).
96. P. J. Jarosz and E. L. Parrott, J. Pharm. Sci., 72, 530 (1983).
97. I. A. Chaudry and R. E. King, J. Pharm. Sci., 61, 1121 (1972).
98. T. Higuchi, E. Nelson, and L. W. Busse, J. Am. Pharm. Assn. Sci. Ed., 43, 344 (1954).
99. J. Polderman and C. J. DeBlaey, Farm. Aikak., 80, 111 (1971).
100. C. J. DeBlaey and J. Polderman, Pharm. Weekblad, 105, 241 (1970).
101. C. J. DeBlaey, A. B. Weekers-Anderson, and J. Polderman, Pharm. Weekblad, 106, 893 (1971).
102. R. F. Lammens, J. Polderman, and C. J. DeBlaey, Int. J. Pharm. Tech. Prod. Mfr., 1, 26 (1979).
103. J. Cobby, M. Mayersohn, and G. C. Walker, J. Pharm. Sci., 63, 725,732 (1974).
104. B. Mechtersheimer and H. Zucker, Pharm. Tech., 38 (1986).
105. T. Higuchi, L. N. Elow, and L. W. Busse, J. Am. Pharm. Assn. Sci. Ed., 43, 688 (1954).
106. R. J. Roberts and R. C. Rowe, J. Pharm. Pharmacol., 38, 567 (1986).
107. O. Worts and T. Schoefer, Arch. Pharm. Chem. Sci. Ed., 6, 1 (1978).
108. H. J. Malinowski, Ph.D. dissertation, Philadelphia College of Pharmacy, 1973.
109. J. J. Williams and D. M. Stiel, Pharm. Tech., 8, 26 (1984).
110. J. B. Schwartz, Pharm. Tech., 5, 102 (1981).
111. K. Marshall, Pharm. Tech., 7, 63 (1983).
112. R. W. Heckel, Trans. Met. Soc. AIME, 221, 671,1001 (1961).
113. J. A. Hersey and J. E. Rees, Nature, 230, 96 (1971).
114. L. F. Athy, Bull. Am. Assn. Petrol. Geologist, 14, 1 (1930).
115. R. J. Rue and J. E. Rees, J. Pharm. Pharmacol., 30, 642 (1978).
116. M. Celik and K. Marshall, Drug Dev. Ind. Pharm., 15, 759 (1989).
116a. F. Nicklasson and G. Alderborn, Pharm. Res., 17(8), 949 (2000).
116b. M. Krumme, L. Schwabe, and K. Fromming, Eur. J. Pharm. Biopharm., 49(3), 275 (2000).

117. D. N. Travers and M. Cox, Drug Dev. Ind. Pharm., 4, 157 (1978).
118. S. Leigh, J. E. Carless, and B. W. Burt, J. Pharm. Sci., 56, 888 (1967).
119. E. Shotton and B. A. Obiorah, J. Pharm. Pharmacol., 25, 37P (1973).
120. J. T. Carstensen, J.-P. Marty, F. Puisieux, and H. Fessi, J. Pharm. Sci., 70, 222 (1981).
121. E. G. Rippie and D. W. Danielson, J. Pharm. Sci., 7, 476 (1981)
122. S. T. David and L. L. Augsburger, J. Pharm. Sci., 66, 155 (1977).
123. J. E. Rees, J. A. Hersey, and E. T. Cole, J. Pharm. Pharmacol., 22, 64S (1970).
124. I. Krycer and D. G. Pope, Drug Dev. Ind. Pharm., 8, 307 (1982).
125. I. Krycer, D. G. Pope, and J. A. Hersey, Int. J. Pharm., 12, 113 (1982).
126. P. Ridgeway-Watt, *Tablet Machine Instrumentation in Pharmaceutics*, J. Wiley & Sons, New York, 1988.
126a. C. Yeh, S. A. Altaf, and S. W. Hoag, Pharm. Res., 14(9), 1161 (1997).
126b. H. X. Guo, J. Heinamaki, and J. Yliruusi, Int. J. Pharm., 186(2), 99 (1999).
126c. M. T. DeCrosta, J. B. Schwartz, R. J. Wigent, and K. Marshall, Int. J. Pharm., 198(1), 113 (2000).
127. H. Seager, P. J. Rue, I. Burt, J. Ryder, J. K. Warrack, and M. Gamlen, Int. J. Pharm. Tech. Prod. Mfr., 6, 1 (1985).
128. S. M. Blaug and M. R. Gross, Drug Standards, 27, 100 (1959).
129. G. S. Banker, J. Pharm. Sci., 55, 81 (1966).
130. S. C. Porter, Drug Cosmet. Ind., 130, 46 (May); 131, 44 (June) (1981).
131. L. K. Mathur and S. J. Forbes, Pharm. Tech., 42 (1984).
132. R. C. Whitehouse, Pharm. J., 172, 85 (1954).
133. L. L. Kaplan and J. A. Kish, J. Pharm. Sci., 51, 708 (1962).
134. T. Higuchi, A. N. Rao, L. W. Busse, and J. V. Swintosky, J. Am Pharm. Assn. Sci. Ed., 42, 194 (1953).
135. T. Higuchi, L. N. Elowe, and L. W. Busse, J. Am. Pharm. Assn. Sci. Ed., 43, 685 (1954).
136. K. C. Kwan, F. O. Swart, and A. M. Mattocks, J. Am. Pharm. Assn., 46, 236 (1957).
137. Mufrod and E. L. Parrot, Drug Dev. Ind. Pharm., 16, 1081 (1990).
138. A. Nutter-Smith, Pharm. J., 163, 194 (1949).
139. A. McCallum, J. Buchter, and R. Albrecht, J. Am. Pharm. Assn. Sci. Ed., 44, 83 (1955).
140. C. J. Endicott, W. Lowenthal, and H. M. Gross, J. Pharm. Sci., 50, 343 (1961).
141. D. B. Brook and K. Marshall, J. Pharm. Sci., 57, 481 (1968).
142. S. T. David and L. L. Augsburger, J. Pharm. Sci., 63, 933 (1974).
143. H. J. Fairchild and F. Michel, J. Pharm. Sci., 50, 966 (1961).
144. J. F. Bavitz, N. R. Bohidar, J. I. Karr, and F. A. Restaino, J. Pharm. Sci., 62, 1520 (1973).
145. F. W. Goodhardt, J. R. Draper, D. Dancz, and F. C. Ninger, J. Pharm. Sci., 62, 297 (1973).
146. H. Burlinson and C. Pickering, J. Pharm. Pharmacol., 2, 630 (1950).
147. E. G. E. Shafer, E. G. Wollish, and C. E. Engel, J. Am. Pharm. Assn. Sci. Ed., 45, 114 (1956).
148. K. Ridgway, M. E. Aulton, and P. H. Rosser, J. Pharm. Pharmacol., 22, 70S (1970).
149. D. Ganderton and A. B. Selkirk, J. Pharm. Pharmacol., 22, 345 (1970).
150. H. Yuasa, Y. Kanaya, and K. Omata, Chem. Pharm. Bull., 38, 752 (1990).
151. M. Ishida, Y. Machida, N. Nambu, and T. Nagai, Chem. Pharm. Bull., 29, 810 (1981).
152. G. Ponchel, F. Touchard, D. Duchene, and N. A. Peppas, J. Controll. Rel., 5, 129 (1987).
153. V. S. Chitnis, V. S. Malshe, and J. K. Lalla, Drug Dev. Ind. Pharm., 17, 879 (1991).
154. D. Duchene, F. Touchard, and N. A. Peppas, Drug Dev. Ind. Pharm., 14, 283 (1988).
155. M. R. Jimenez-Castellanos, H. Zia, and C. T. Rhodes, Int. J. Pharm., 89, 223 (1993).
156. K. M. Morisseau and C. T. Rhodes, Pharm. Technol. Yearbook. 1997, 6 (1997).
157. J. Rantanen, O. Antikainen, J.-P. Mannermaa, and J. Yliruusi, Pharm. Dev. Tech., 5(2), 209 (2000).
158. J.-H. Guo, G. W. Skinner, W. W. Harcum, J. P. Malone, and L. G. Weyer, Drug Dev. Ind. Pharm., 25(12), 1267 (1999).
159. E. Norris and M. Guttadauria, Eur. J. Rheumatol. Inflamm., 8(1), 94 (1987).
160. T. Ishikawa, Y. Watanabe, N. Utoguchi, and M. Matsumoto, Chem. Pharm. Bull. (Tokyo), 47(10), 1451 (1999).
161. Y. Bi, Y. Yonezawa, and H. Sunada, J. Pharm. Sci., 88(10), 1004 (1999).
162. Y. X. Bi, H. Sunada, Y. Yonezawa, and K. Danjo, Drug Dev. Ind. Pharm., 25(5), 571 (1999).
163. S. Corveleyn and J. P. Remon, Drug Dev. Ind. Pharm., 25(9), 1005 (1999).
164. S. Corvelyn and J. P. Remon, Int. J. Pharm., 166, 65 (1997).
165. S. Corvelyn and J. P. Remon, Int. J. Pharm., 173, 149 (1998).
166. C. W. Rowe, W. E. Katstra, R. D. Palazzolo, B. Giritlioglu, P. Teung, and M. J. Cima, J. Control. Release, 66(1), 11 (2000).
167. W. E. Katstra, R. D. Palazzolo, C. W. Rowe, B. Giritlioglu, P. Teung, and M. J. Cima, J. Control. Release, 66(1), 1 (2000).
168. A. Sturzeneggar, A. R. Mlodozeniec, and E. S. Lipinsky, United States Patent 4,197,289 (8 April 1980).