4 SOLID DOSAGE FORMS: TABLETS

Pills are small spherical or ovoid products incorporating a medicinal agent in a doughy matrix. Pills were the dosage form that was used as a weapon to deliver "magic bullets." In the early days of the pill generation, the pills were very hard. Friable pills were first prepared by Upjohn in the 1950s. Later, pills were replaced by compressed tablets. Tablets are probably the most popular dosage form. The tablet dosage form accounts for approximately 50% of all dosage forms on the market. Tablets have many advantages over other dosage forms. Table 4.1 lists advantages as well as a few disadvantages of the tablet dosage form. The majority of tablets are used in the oral administration of drugs, which is the most convenient mode of drug administration.

I. TYPES OF TABLETS

A. COMPRESSED TABLETS

Compressed tablets are prepared by single compression using tablet machines. After a quantity of powdered or granulated tableting material flow into a die, the upper and lower punches of the tablet machine compress the material under a high pressure (~tons/in^2).

1. Multiple Compressed Tablets

Tablets may be subjected to compression more than once to prepare multiple-layered tablets or tablet-within-a-tablets (with cores and shells).

In preparing layered-tablets, a portion of fill material in a die is compressed initially, and then another portion of fill material is added to the same die. Each additional fill material is compressed to form multi-

Table 4.1 Advantages and Disadvantages of Tablets

Advantages
Ease of accurate dosing
Good physical and chemical stability
Competitive unit production costs
High level of patient acceptability
High convenience
Disadvantages
Irritant effects on the GI mucosa by some solids (e.g., aspirin)
Possibility of bioavailability problems resulting from slow disintegration and dissolution

layered tablets. In general, each portion of the fill material contains a different drug. This allows formulation of different drugs which are incompatible each other in one tablet. Each layer of the multiple-layered tablets can also provide different drug release profiles. This is in a sense a controlled release device. Each portion of the fill is usually colored differently for the unique appearance.

The preparation of tablets having another compressed tablet as the inner core requires special machines which can place the preformed tablet precisely within the die for the second compression.

2. Chewable Tablets

Chewable tablets are prepared mainly by wet granulation and compression. Chewable tablets disintegrate rapidly when chewed or allowed to dissolve in the mouth. Chewable tablets are especially useful in tablet formulations for children and are commonly employed in the preparation of multiple vitamin tablets. They are also used in the administration of antacids and antiflatulents (to remove excessive amount of gas in the stomach and intestines).

Mannitol, which is a white crystalline hexahydric alcohol, is widely used as an excipient in chewable tablets. The nonhygroscopicity of mannitol makes it an ideal excipient for the preparation of chewable tablets containing moisture-sensitive drugs. Mannitol may account for 50% or more of the weight of the formulation.

3. Tablet Triturates

Tablet triturates are small, usually cylindrical tablets containing small amounts of potent drugs. A combination of sucrose and lactose is usually used as diluents. They are prepared mainly by compression (rather than molding). Tablet triturates must be readily and completely soluble in water. Thus, any water-insoluble material is avoided in the formulation. In the preparation of these tablets by compression, only a minimal amount of pressure is applied.

Tablet triturates are used for oral administration or sublingual use (*e.g.*, nitroglycerin tablets). They may also be used in compounding procedures by pharmacists in the preparation of other solid or liquid dosage forms. They can be inserted into capsules, and this eliminates the problems of measuring the accurate amount of potent drugs in the powder form. They can also be dissolved in a small amount of water which can be subsequently mixed with the required volume of the liquid medication.

B. MOLDED TABLETS

While most commercially available tablets are primarily prepared by compression, tablets can also be prepared by molding. Molded tablets are prepared by tablet machinery or manually by forcing dampened tablet material into a mold of any shape. The formed tablet is then ejected from the mold and allowed to dry. Molding is generally reserved for laboratory and small-scale production. The commercial preparation of tablets by molding has been replaced by the tablet compression process.

Table 4.2 Miscellaneous Adjuncts

Anticaking agents
Colorants
Flavorants
Antioxidants
Preservatives

II. EXCIPIENTS FOR COMPRESSED TABLETS

Compressed tablets usually contain a number of pharmaceutical adjuncts, known as excipients, in addition to the medicinal substance(s). The use of appropriate excipients is important in the development of the optimum tablets. Excipients determine the bulk of the final product in dosage forms such as tablet, capsule, etc., the speed of disintegration, rate of dissolution/release of drug, protection against moisture, stability during storage, and compatibility (Banakar & Makoid, 1996). Excipients should have no bioactivity, no reaction with the drug substance, no effect on the functions of other excipients, and no support of microbiological growth in the product (Banakar & Makoid, 1996). Sections II.A–G describe many of the common adjuncts and excipients used in the pharmaceutical industry. Table 4.2 lists other adjuncts that are not described in the sections below.

A. DILUENTS (OR FILLERS)

Diluents increase the volume to a formulation to prepare tablets of the desired size. Widely used fillers are lactose, dextrin, microcrystalline cellulose (Avicel PH® from FMC Corp. and Emococel® from Mendell), starch, pregelatinized starch, powdered sucrose, and calcium phosphate.

The filler is selected based on various factors, such as the experience of the manufacturer in the preparation of other tablets, its cost, and compatibility with other formulation ingredients. For example, in the preparation of tablets or capsules of tetracycline antibiotics, a calcium salt should not be used as a filler since calcium interferes with absorption of the antibiotics from the GI tract.

B. BINDERS (OR ADHESIVES)

Binders promote the adhesion of particles of the formulation. Such adhesion enables preparation of granules and maintains the integrity of the final tablet. Commonly used binding agents are listed in Table 4.3. As described in Chapter 2, many of these are used as an aqueous solution in wet granulation.

Table 4.3 Examples of Binders

Carboxymethylcellulose, sodium	Karaya gum
Cellulose, microcrystalline (Avicel®)	Starch, pregelatinized
Ethylcellulose	Tragacanth gum
Hydroxypropyl methylcellulose	Poly(acrylic acid) (Carbopol®)

Methylcellulose	Polypvinylpyrrolidone (Povidone)
Acacia gum	Gelatin
Agar	Dextrin
Alginic acid	Glucose
Guar gum	Molasses (honey, sugar syrups)

C. LUBRICANTS AND GLIDANTS

Lubricant is a substance capable of reducing or preventing friction, heat, and wear when introduced as a film between solid surfaces. It works by coating on the surface of particles, and thus preventing adhesion of the tablet material to the dies and punches. Glyceryl monostearate (USP/NF $CH_2(OH)CH(OH)CH_2O_2CC_{17}H_{35}$) is one example of a lubricant. Lubricants play more than one role in the preparation of tablets as described below.

1. Lubricants improve the flow of granules in the hopper to the die cavity.
2. Lubricants prevent sticking of tablet formulation to the punches and dies during formulation.
3. Lubricants reduce the friction between the tablet and the die wall during the tablet's ejection from the tablet machine.
4. Lubricants give a sheen to the finished tablets.

A glidant is a substance that allows particles moving smoothly, continuously, and effortlessly. Both lubricants and glidants have the same effect, but the ways they work are different. Unlike lubricant, glidant works by removing moisture and as a result enhancing flow.

In tableting, a dry lubricant is generally added to the granules to cover each granule with lubricant. The most widely used lubricant is magnesium stearate. (Magnesium stearate is also the most widely used excipient.) Talc and glyceryl monostearate are also commonly used as lubricants. Fumed silicon dioxide is used as a glidant. Talc has both lubricant and glidant effects (Augsburger, 1990).

D. DISINTEGRATORS (OR DISINTEGRATING AGENTS)

The breakup of the tablets to smaller particles is important for dissolution of the drug and subsequent bioavailability. Disintegrators promote such breakup. To rupture or breakup of tablets, disintegrating agents must swell or expand on exposure to aqueous solution. Thus, the most effective disintegrating agents in most tablet systems are those with the highest water uptake property. In general, the more hydrophilic, the better disintegrating agents are therefore highly hydrophilic. A list of typical disintegrants is tabulated in Table 4.4.

Table 4.4 Examples of Commonly used Disintegrants

Starches (corn and potato)	Microcrystalline cellulose
Pregelatinized starch	Avicel PH® by FMC Corp.
Starch 1500® by Colorcon, Inc.	Polyvinylpyrrolidone (PVP)
Sodium starch glycolate	Crospovidone (cross-linked PVP)
Explotab® by Edward Mendell Co.	Polyplasdone XL® by GAF Corp.
Primojel® by Generichem Corp.	Kollidon CE 5050 by BASF Corp.
Sodium carboxymethylcellulose (CMC)	Cation-exchange resins
Croscarmellose	Clays
Ac-Di-Sol® by FMC Corp.	Magnesium aluminum silicate

(Kanig & Rudnic, 1984)

Croscarmellose (Type A) is made by crosslinking CMC. Sodium CMC is made to undergo an internal crosslinking reaction by lowering the pH of the solution, followed by heating. No chemical additives are used. The crosslinking reaction makes the soluble NaCMC insoluble but crosslinked CMC possesses swellable character owing to its highly hydrophilic nature. This is why crosslinked CMC, such as Ac-Di-Sol®, can be used as a super disintegrant for tablet dissolution. Croscarmellose is a super disintegrant for tablet dissolution which employs various mechanisms to cause rapid tablet breakdown. Water wicking (uptake) and disintegrant swelling represent two means commonly used in determining disintegrant performance. The fibrous nature of Ac-Di-Sol® gives it outstanding water wicking capabilities and it crosslinked chemical structure creates an insoluble hydrophilic, highly absorbant material with good swelling properties.

Please note that microcrystalline cellulose has various functions in direct compression. It can be used as a binder, disintegrant, lubricant, and filler. Microcrystalline cellulose was introduced as a tablet binder in the 1960s and since then provided a major advancement for the production of many solid dosage formulations. Microcrystalline cellulose allows direct compression of tablets and wet granulation processes. In wet granulation, it can be used as a binder and for rapid wicking action. It can be compressed to form various shapes and sizes that disintegrate rapidly in water. Furthermore, the binding capacity and absorptive power together with its anti-caking properties makes it very effective in formulating dry, free flowing mixtures for tablets and capsules. The limitations of MCC are low bulk density, poor flow characteristics, loss of compactability after wet granulation, and sensitivity to lubricants (Sherwood & Becker, 1998). To alleviate some of the known deficiencies of conventional MCC and to offer enhanced performance, silicified MCC (SMCC) was developed recently (Sherwood & Becker, 1998). SMCC is produced by combining MCC with colloidal silicon dioxide.

Avicel® RC/CL is a commercial product from FMC Corp. Microcrystals of Avicel® microcrystalline cellulose (< 0.2 μm) are leashed together with chains of soluble CMC to form a mesh-like powder particle by spray drying. Avicel® RC/CL is a water-dispersible organic hydrocolloid used in the preparation of pharmaceutical suspensions and emulsions. The colloidal MCC provides a structured dispersion vehicle while the CMC facili-

tates dispersion and serves as a protective colloid. Applications have been:

1. Oil/water emulsifier: pharmaceutical and cosmetic lotions and creams
2. Emulsion stabilizer: pharmaceutical and cosmetic creams
3. Foam stabilizer: aerosol foams
4. Suspending agent: pharmaceutical and cosmetic suspensions, reconstitutable pharmaceutical suspensions such as antibiotics
5. Bodying agent, thickener, opacifier: pharmaceutical and cosmetic creams, vaginal gels, cosmetic gels.

E. WETTING AGENTS

Water molecules attract each other equally in all directions. Water molecules on the surface, however, can only be pulled into the bulk water by water molecules underneath, since there are no water molecules to pull in the opposite direction. The surface tension of water is strong enough to support the weight of tiny insects such as water striders. The surface tension in action can be visualized by placing a small drop of alcohol on a thin layer of water. Alcohol with lower surface tension mixes with water causing reduction in the surface tension in the local region. Owing to the higher surface tension of water in the neighbor, water is pulled from the alcohol dropped region into the neighbor, and this leads to the formation of a dry spot in the middle of the water layer.

The first step toward dissolution of a tablet is wetting of the surface. If the surface of a tablet is not hydrophilic enough to allow water spread and absorb into the tablet, dissolution will not tale place or will take a long time and the bioavailability will be decreased. To increase the wetting, various wetting agents can be used. A wetting agent is a surfactant (*i.e.*, surface active agent) which allows easy spreading of water on the surface. It also makes water easy to displace air and spread over the surface inside the tablet.

The effect of a wetting agent can be realized by measuring the contact angle between the surface and the wetting liquid (*i.e.*, aqueous solution such as gastric juice in our case). A few examples of different contact angles are shown in Figure 4.1. As the wetting agent becomes more effective, the contact angle becomes smaller. If the surface is very hydrophilic, such as clean glass, the contact angle is almost zero. This means that water spread without forming any water droplets.

Surfactants have both polar and nonpolar groups. For this reason, they are also called amphiphiles. The amphiphilic property makes surfactants to possess a certain affinity to both polar and nonpolar solvents. The extent of the affinity to either polar or nonpolar solvent depends on the nature and the number of the polar and nonpolar groups present. Thus, a surfactant may be predominantly hydrophilic (water-loving), predominantly lipophilic (oil-loving), or well balanced between these two extremes. Since the balance between hydrophilic and lipophilic properties of a surfactant is important, an arbitrary scale of values is used for a quantitative

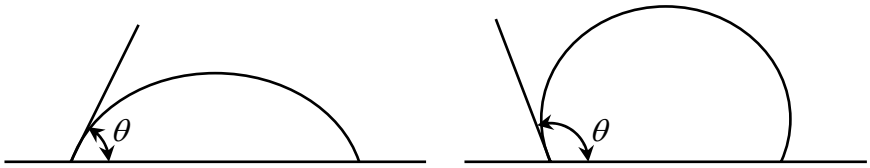


Figure 4.1 Two examples of contact angles. The contact angle of a drop on the left is smaller than 90° and that in the right is larger than 90°.

comparison of the hydrophilic-lipophilic balance (HLB) of different surfactants. The scale ranges from 0 to 20 and surfactants with the HLB value larger than 10 are more hydrophilic, while those with less than 10 are more lipophilic.

For the surfactants to be adsorbed to the tablet surface (or any solid surface), their HLB values must be in a certain range. Wetting agents are surfactants with the HLB values between 7 and 9. Examples are sorbitan monolaurate (Span® 20; HLB = 8.6), polyethylene lauryl ether (Brij® 30; HLB = 9.5), and gelatin (Pharmagel® B; HLB = 9.8).

Surfactants spread on water quite easily and this can be visualized using the powder of lycopodium (club moss spores), which are small and light enough to spread and do not aggregate at the air/water interface. If olive oil or oleic acid is dropped on water covered with lycopodium (*e.g.*, by using a clean toothpick), olive oil or oleic acid spreads quickly on the water surface, and this can be visualized by quick movement of lycopodium. The same result can be obtained by spraying other surfactants, such as WD-40® (polydimethyl siloxane). Another demonstration could be extinguishing hexane fire on water by touching the water surface with a tiny piece of soap mounted on a spatula. When agents which are not surface active such as mineral oil are applied to the water, they form a lens instead of spreading.

F. Release Rate Modifiers

The release of a drug from the tablets can be modified by including polymeric materials. The polymers are used mainly in the design of controlled release products, and these will be dealt with in depth in later chapters.

G. Performance Characteristics of Excipients

Excipients can have profound effect on various aspects of the final dosage form. To make the final dosage forms with consistent quality, excipients should maintain the same performance specification. Currently, all the excipients are characterized in pharmacopoeia by their chemical specification, instead of performance specification, mainly because of the difficulty in standardizing the performance criteria. Unfortunately, the test of purity and identity described in pharmacopoeia are generally very limited to their relevance to characterizing materials relative to their formulation functionality (Banakar & Makoid, 1996). For example, excipients behave differently depending on the vendor (or even from lot-to-lot) to the extent that substitution from one source to the other is not possible. Since the

same excipient may have very different physical properties, it is necessary to establish the performance standards of the basic properties such as flowability, binding ability, lubricity, disintegration property, etc. Physical properties, such as particle size, roughness of the particle surface, density of the particles, compressibility, need to be standardized.

III. COATED TABLETS

A. SUGAR-COATED TABLETS

Compressed tablets can be coated with a sugar layer. Since the coating is water-soluble, it is quickly dissolved in aqueous environment (*e.g.*, in the gastric juice after oral administration).

The main purposes of having a sugar coating are: (1) to protect the drug from the air and humidity; (2) to provide a taste or a smell barrier to objectionable tasting or smelling drug; and (3) to enhance the appearance of compressed tablets.

Sugar coating of compressed tablets requires more time and expertise, and this may increase the cost of manufacturing.

Sugar coating also increases the size and weight of the compressed tablets. If the size of tablets is too small then the size is increased intentionally by sugar coating.

1. Process of Sugar Coating

a. **Waterproofing and Sealing** — If tablets contain components that may absorb moisture or be adversely affected on contact with moisture, a waterproofing layer of coating of a material such as shellac is placed on the compressed tablets first. The shellac or other waterproofing agent is applied in solution (usually alcohol).

b. **Subcoating** — Tablets with the waterproofing or sealing coat are given about 3 to 5 subcoats of sugar-based syrup. This is for rounding the tablet and bonding the sugar coating to the tablet. A subcoating is applied by adding a heavy syrup containing gelatin or PVP to the tablets as they roll in the coating pan.

c. **Smoothing and Final Rounding** — After subcoating, 5 to 10 additional coating of a very thick syrup are applied to complete the rounding of the tablet and smoothing the coating. The syrup used in this step may be a sucrose-based simple syrup, or may have additional components like starch and calcium carbonate.

d. **Finishing and Coloring** — Several coats of a thin syrup containing the desired colorant (if any) are applied to attain the final smoothness and the appropriate color to the tablets.

e. **Polishing** — Coated tablets may be polished in special drum-shaped pans made by stretching a cloth fabric over a metal frame or in ordinary coating pans lined with canvas. The fabric or canvas may be impregnated with a wax (such as carnauba wax) with or without the addition of beeswax. The tablets are polished as they roll about in the pan. Alternatively, the wax may be dissolved in a

nonaqueous solvent such as acetone or petroleum benzin and sprayed on the rolling tablets in small amounts.

B. FILM-COATED TABLETS

Compressed tablets can be coated with a thin layer of a polymer, which may be either water-soluble or water-insoluble. The polymer film has an advantage over sugar-coating in that the polymer film is more durable, less bulky, and less time-consuming to apply. Upon oral administration, the polymer film may remain intact or dissolve in the GI tract depending on the water-solubility.

Film-coating solutions may be nonaqueous or aqueous. The nonaqueous solutions generally contain various materials (as listed in Table 4.5) to provide the desired coating to the tablets. A film former should be able to produce smooth, thin films and be applicable to a variety of tablet shapes. An alloying substance provides water-solubility or permeability to the film to ensure penetration by body fluids and therapeutic availability. A plasticizer produces the flexibility and elasticity of the coating. This may enhance durability. Surfactants enhance spreadability of the film during application. Opaquants and colorants make the appearance of the coated tablets handsome and distinctive. Sweeteners, flavors, and aromas enhance the acceptability of the tablet to the patient. A glossant provides luster to the tablets without a separate polishing operation.

Volatile solvents allow spreading of the other components over the tablets while allowing rapid evaporation to permit an effective yet speedy operation. Owing to the high cost of using volatile solvents and the problem of releasing these potentially toxic agents into the atmosphere, organic solvents are not widely used anymore. Pharmaceutical manufacturers favor the use of aqueous-based film-coating solutions, although they evaporate much slowly than organic-based film-coating solutions. Table 4.6 lists components of a typical aqueous film-forming formulation.

Table 4.5 Components of Nonaqueous Film-Coating Solutions

Component	Example
Film former	Cellulose acetate phthalate
Alloying substance	Polyethylene glycol (less valuable material)
Plasticizer	Caster oil
Surfactant	Polyoxyethylene sorbitan derivatives
Opaquant	Titanium dioxide
Colorant	Dyes
Sweeteners	Saccharin
Flavors	Vanillin
Aromas	Vanillin
Glossant	Beeswax
Volatile solvent	Alcohol-acetone mixture

Table 4.6 Components of Aqueous Film-Coating Solutions

Component	Example
Film forming polymer	Cellulose ether polymers (methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose)
Plasticizer	Glycerin, glyceryl triacetate (triacetin), dimethyl (or ethyl or butyl) phthalate, di-(2-ethylhexyl) (or butyl) adipate, dibutyl cebacate, dibutyl subacetate, propylene glycol, polyethylene glycol, oleic acid
Opacifier	Iron oxide pigments
Colorant	Dyes
Vehicle	Water

Water-insoluble polymers can also be coated by aqueous coating techniques. In this case, intead of using polymer solution dissolved in water, a latex is used. Latex is a polymer emulsion (*i.e.*, a dispersion of small (≤1 μm) spherical polymer particles in water). One commercially available water-based, colloidal coating dispersion is called Aquacoat® (FMC Corp.), which contains a 30% ethylcellulose pseudolatex. (Pseudolatex is different from "true" latex in that the pseudolatex is manufactured starting with polymer itself and not the monomer (Hogan, 1995). Pseudolatex dispersions have an advantage of high solid content and this allows greater coating ability with relatively low viscosity. The low viscosity allows less water to be used in the coating dispersion, and this results in a lesser requirement for water-evaporation and a reduced likelihood of water interference with the tablet formulation. Furthermore, the low viscosity permits greater coat penetration into the crevices of monogrammed or scored tablets. Another commercial aqueous coating system based on ethylcellulose is Surelease® from Colocon. ethylcellulose product is Surelease®.

1. Enteric-Coated Tablets

a. Structures of Enteric-Coating Materials

Of the many water-soluble polymers, some polymers show the property of pH-dependent water-solubility. Some polymers do not dissolve at low pH (*e.g.*, pH in the stomach) but readily dissolve at neutral pH (*e.g.*, pH in the intestine). If such a polymer film is coated on compressed tablets, the tablets will resist dissolution or disruption in the stomach but not in the intestine. Such tablets are known as enteric-coated tablets.

Since enteric-coated tablets do not dissolve in the stomach, they are useful for the drugs which are not stable in gastric juice (*i.e.*, at low pH) or are irritating to the gastric mucosa. By-passing the stomach and release of acid-labile drugs in the intestine will enhance the drug absorption significantly.

Table 4.7 Examples of enteric coating materials

Polymers	Dissolution pH
Shellac (esters of aleurtic acid)	7.0
Cellulose acetate phthalate (CAP)	6.2
Poly(methacrylic acid-co-methyl methacrylate)	5.5–7.0

Cellulose acetate trimellitate (CAT)	5.0
Poly(vinyl acetate phthalate) (PVAP)	5.0
Hydroxypropyl methylcellulose phthalate (HPMCP)	4.5–5.5

Cellulose acetate phthalate was patented as an enteric coating in 1940 by Dr. G.D. Hiatt, a researcher at Eastman Kodak. The dissolution of the enteric coating materials is generally triggered by a systemic change of pH values. It does not dissolve in the stomach, where pH is 1~4, but begins to disintegrate at higher pH in duedenum or jejunum. Sureteric®, commercially available aqueous enteric coating system from Colocon, is a blended combination of poly(vinyl acetate phthalate), plasticizers, and other ingredients. The dissolution pH values of enteric coating materials are listed in Table 4.7.

The chemical structures of a few enteric coating materials are shown in Figure 4.2. As shown in the structures, all of them possess carboxyl

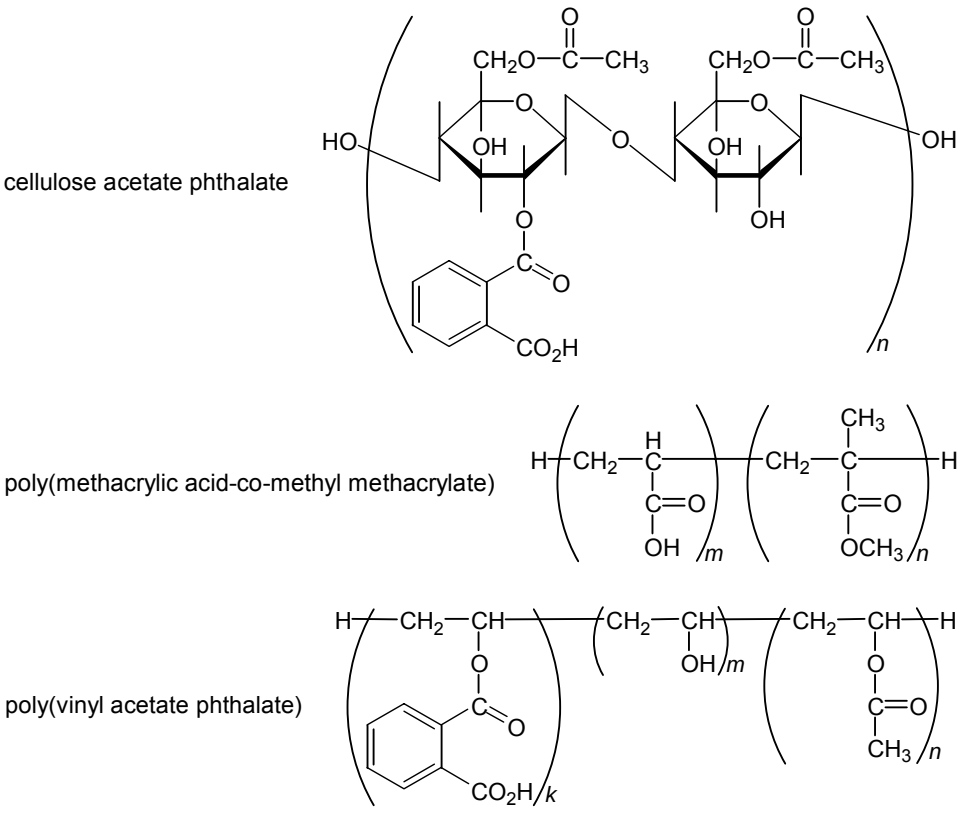


Figure 4.2 Chemical structures of cellulose acetate phthalate, poly(methacrylic acid-co-methyl methacrylate), and poly(vinyl acetate phthalate).

groups, and the presence of the carboxyl groups makes dissolution of such materials to be pH-dependent. At low pH solution, the carboxyl group remain protonated (*i.e.*, in acid form) and thus the mateial is not not water-soluble. At high pH, however, the carboxyl group is ionized and the material becomes water-soluble.

Enteric coating materials are readily soluble in organic solvents, and for this reason enteric coating has been done using organic solvent. For ex-

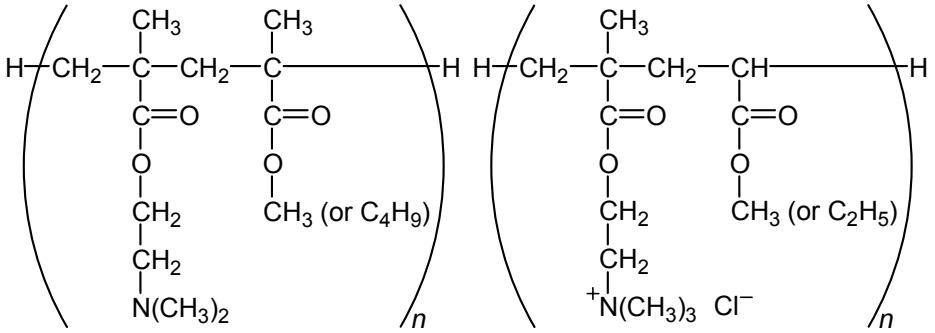
ample, cellulose acetate phthalate is soluble in acetone, methyl ethyl ketone, diacetone alcohol, or methyl acetate. Since the use of organic solvents is not desirable for safety as well as environmental reasons, aqueous film coating techniques have been developed.

Enteric coating materials, such as CAP and CAT, can be dissolved in water using 30% ammonium hydroxide as a neutralizing agent. Ammonia ionizes the free acid moiety on the polymer, forming a water-soluble salt of the polymer. After addition of plasticizer and appropriate coloring agent, the solution may be sprayed onto tablets or granules. Alternatively, latex (*i.e.*, aqueous polymeric dispersion) system can be used. Latex can be dried and then redispersed before use (Gumowski, Doelker, & Gurny, 1987). Commercially available aqueous enteric coating materials are Aquateric® (a redispersible latex made of CAP with a particle size of less than 1 μm by FMC), Coateric® (a latex made of PVAP by Colorcon Ltd., England), and Eudragit® L 100-55 (a latex made of poly(ethyl acrylate-methacrylic acid) by Röhm Pharma).

Figure 4.3 shows examples of Eudragits® (pronounced oy´·dra·gits), basically methacrylic acid copolymers with different available properties.

Eudragit® E is a terpolymer (ternary copolymer) containing three different repeat units. It contains 2-dimethylaminoethyl methacrylate, methyl methacrylate, and butyl methacrylate in the ratio of 2:1:1. Eudragit® E is soluble at pH below 5 (*i.e.*, in gastric fluid). It is used as a plain insulating film former.

Eudragit® S is a copolymer of methyl methacylate and methacrylic acid in the ratio of 2:1. Eudragit® L is a copolymer of ethyl acylate and



Eudragit® E | Eudragit® RL & RS

Eudragit® S | Eudragit® NE 30 D

Figure 4.3 Strutctures of selected Eudragits®.

methacrylic acid in the ratio of 1:1. Eudragit® L and S types are resistant to gastric fluid and become water soluble in neutral to weakly alkaline conditions (pH 6–7). Thus, they are used as enteric coating agents.

Eudragit® RL is a terpolymer containing methyl methacrylate, ethyl acrylate, and trimethylammonioethyl methacrylate chloride in the ratio of 2:1:0.2. Eudragit® RS is in the ratio of 2:1:0.1. Owing to the low concentration of the charged group, Eudragits® RL and RS are not water soluble, and thus are used to form water-insoluble film coats for making controlled release dosage forms.

Eudragit® NE 30 D is poly(ethyl acrylate-co-methyl methacrylate). It is also water-insoluble.

2. Tablets Coated with Water-Insoluble Polymers

When a drug is loaded inside a layer of water-insoluble polymers, the drug release profile from such a tablet is often different from other compressed tablets. They are widely used in the design of controlled release dosage forms. This topic will be discussed in more detail in the later chapters dealing with controlled release technology.

IV. CHARACTERISTICS AND QUALITY OF COMPRESSED TABLETS

A. PHYSICAL SPECIFICATIONS OF COMPRESSED TABLETS

When compressed tablets are prepared, various physical specifications are examined (for quality control). They should be controlled to assure not only the outward appearance of the product but also its therapeutic efficacy. The factors to be examined are listed in Table 4.8.

The shapes of the compressed tablets differ widely. It can be round, oblong, or triangular. Tablets may be flat or have varying degree of convexity depending on the contours of the punches, such as flat face, shallow cup, standard cup, deep cup, or modified ball.

Table 4.8 Physical Specifications of Compressed Tablets

Shape
Size (diameter and thickness)
Weight (size and weight determines the density)
Score (or groove)
Imprinting
Color
Hardness (or breaking strength)
Disintegration
Dissolution
Content uniformity

Some tablets are scored or grooved in halves, thirds, or quadrants. This allows fairly accurate breaking of the tablet for the administration of a partial amount. In general scored tablets are grooved on a single side. Tablet shapes and size are determined by the die and punches used for the compression of the tablet.

Tablets may be imprinted with a symbol of the manufacturer to denote the company, the product, or both. To make imprinted tablets punches having impressions are used. Punches with raised impressions will produce recessed (embossed) impressions on the tablets, and vice versa. By FDA regulation effective in 1995, all solid dosage forms for human consumption must be imprinted with product-specific identification codes. Code imprints, in conjunction with a product's size, shape, and color, permit the unique identification of a drug product and its manufacturer or distributor. Code imprints may contain any combination of letters and numbers, or the product's National Drug Code number, and any marks, symbols, logos, or monograms assigned by the drug company to the product. Each product's imprint must be registered with the FDA.

Tablets should be made sufficiently hard to resist breaking during packaging, shipment, and normal handling. At the time tablets should be soft enough to disintegrate and dissolve properly after administered.

It is a common practice in hospitals and extended care facilities to crush tablets to mix with food or drink for easy swallowing. Some tablets, such as enteric coated tablets, controlled release tablets, and sublingual or buccal tablets, should not be crushed, since the release characteristics of the drug from the dosage form and subsequently the drug absorption could adversely affect the patient's welfare.

B. Disintegration and Dissolution Tests

Tablet disintegration is the first step for a drug to become bioavailable. The tablet must first disintegrate and discharge the drug to the body fluids. The drug in the disintegrated tablets (*i.e.*, drug in particulates) must be dissolved in the fluid to be absorbed into the blood stream. Some drugs, such as antacids or antidiarrheals, are intended to be used locally in the GI tract. In these instances, tablet disintegration provides drug particles with a greater surface area for increased localized activity.

Since the disintegration and dissolution of tablets are so important that each batch of tablets must meet the specified disintegration and dissolution standards.

1. Disintegration Test

The disintegration test apparatus consists of a basket-rack assembly containing six open-ended glass tubes held vertically on a 10-mesh (sieve opening of 2 mm) stainless-steel wire screen. Tablets are placed in each of the six tubes of the basket. The basket is mechanically raised and lowered in the immersion fluid at a frequency of 29–32 cycles/min. During this testing, the wire screen is always maintained below the level of the immersion fluid. The temperature is maintained at 37 °C unless specified otherwise in the individual monograph.

Complete disintegration of tablets (or capsules) is defined as "the state in which any residue of the unit, except fragments of insoluble coating (or capsule shell), remaining on the screen of the test apparatus is a soft mass having no palpably firm core." The disintegration time of uncoated tablets vary from about 2 min (for nitroglycerin tablets) up to 4 h (for buccal tab-

lets). The disintegration time of sublingual and other tablets is usually around 30 min.

For testing of plain coated tablets, any water-soluble external coating can be removed by initial soaking in water at room temperature for 5 min. Then the tablets are immersed in simulated gastric fluid at 37 °C for 30 min. If the tablets fail to disintegrate, they are subjected to the test using simulated intestinal fluid at 37 °C for the period specified in the individual monograph (of USP). For the testing of enteric-coated tablets, the tablets are permitted to be tested in the simulated gastric fluid for 1 h. There should be no sign of disintegration or dissolution after 1 h. The enteric-coated tablets are then actively immersed in the simulated intestinal fluid for 2 h or for the period specified in the individual monograph.

In each testing, if one or two of the six tablets fail to disintegrate completely, tests should be repeated on twelve additional tablets, and not less than sixteen of the total of eighteen tablets tested must disintegrate completely to meet the standard.

2. Dissolution Test

Since drug absorption depends on the drug in the dissolved state, the dissolution property is highly important for bioavailability. If the rate of dissolution is lower than the rate of absorption (*i.e.*, if the rate of dissolution is the rate-limiting step), then the dissolution rate determines the bioavailability. The therapeutic effect of different formulations of the same drug depends on the rates at which the drug is released (Banakar & Makoid, 1996).

In the dissolution test, a volume of the dissolution medium (typically 900 mL) is placed in the 1-L vessel (made of glass or other inert, transparent material) and the temperature maintained at 37 °C. Then a single tablet (or capsule) to be tested is immersed in the vessel and stirred using a variable-speed stirrer motor at the speed specified in the individual monograph. At timed intervals, aliquots of the medium are withdrawn for analysis of the dissolved drug.

Dissolution testing of pharmaceutical solid dosage forms has become the single most important test which will ensure the quality of the product (Banakar & Makoid, 1996). Dissolution of a drug is prerequisite for absorption of the drug into the body and the dissolution rate is directly related to the bioavailability. For this reason, dissolution testing is commonly used as a tool to compare the bioavailability of the same drugs manufactured by different companies. Different drug products that contain the same active ingredients frequently result in different therapeutic effects. This is most likely due to the differences in the rate at which the active ingredients are released from the given dosage form (Banakar & Makoid, 1996).

It has been recognized that the dissolution rate of a drug from its dosage form can often become the rate-limiting process in the physiologic availability of the drug. Thus, the development of a reliable *in vitro* dissolution test method which can positively characterize the *in vivo* dissolution rate-controlled absorption of drugs become very important. Although *in vitro* dissolution test alone can not make it possible to predict the *in vivo* bioavailability of a drug, it provides a good indicator on the *in vivo* drug release profiles. Since excipients play a key role in controlling the dissolution of solid dosage forms, selection of appropriate excipients is critical in the performance of the pharmaceutical products. Table 4.9 lists various factors affecting the dissolution rate (and thus the bioavailability).

C. APPROACHES TO INCREASING POORLY-SOLUBLE DRUG DISSOLUTION RATES

If a drug is not highly water soluble, so that the dissolution of the drug is the rate-limiting step for drug absorption (*i.e.*, the drug dissolution is the slowest step), then a number of approaches can be used to increase the dissolution rate as listed in Table 4.10. For compounds with limited solubility (0.1 mg/mL or less), decreasing the particle size increases the absorption. If the solubility of a drug is 1 mg/mL or less, then changing the size of the drug particles may be considered for increasing the absorption (Ba-

Table 4.9 Factors Affecting the Dissolution Rate

Physicochemical Factors of the Active Ingredient
Amorphous vs crystal state
Polymorphism of crystals
Solvation
Chemical structure (acid, base, salt)
Complex formation
Particle size
Presence of surface active agents
Manufacturing Factors
Type and quantity of excipients
Size and size distribution of granules and powder particles
Tableting pressure and rate (for tablets)
Properties of the Dosage Form
Moisture content
Storage content
Age of the drug product
Test Factors
Intensity, rate, and type of stirring
Fluid dynamics and geometrical factors
Dissolution fluid composition
Temperature of the dissolution fluid

(Banakar & Makoid, 1996; Banakar, 1992)

nakar & Makoid, 1996). Oral absorption of griseofulvin was increased following micronization of the compound. The bioavailability of sulfadi-

Table 4.10 Approaches to Increasing Poorly-Soluble Drug Dissolution Rates

Increase in surface area
Formation of salt forms from the acid or base form of the drug
Choice of anhydrous or hydrate form
Change in crystal form of polymorphs
Increase in surface wettability
Use of hydrotropic agents
Formation of solid dispersion

(Banakar & Makoid, 1996)

methoxine was increased as the tablet formulation was made into a suspension form.

When a salt form is used to increase the dissolution rate, it may change the pH value in the boundary layer since the salt form acts as a buffer. A salt of the acid or base form of the drug increases the dissolution rate, but the different salts of the same drug have different stability in the GI tract (*i.e.*, their solubilities are different). As the stability of the salt increases, the salt is less ionized and thus is less water soluble. The more stable salt form (*i.e.*, the less ionized form) is more lipid soluble, and thus results in higher bioavailability. Table 4.11 shows an example of penicillin salts.

Dissolution of carbamazpine anhydrate is much slower than that of dihydrate in 0.1 *N* HCl, but this difference disappears in the presence of 0.01% polysorbate 80 (Kahela *et al*., 1983).

Altering the crystal form of polymorphic drugs is another way of increasing the dissolution rate. Phenylbutazone crystals showed different dissolution profiles depending on their crystal forms A–E (Tuladhar, Carless, & Summers, 1983).

Treatment of hydrophobic drugs with wettable materials increases the total amount of drugs released. Treatment of hexobarbital (Lerk & Lagas, 1977) and griseofulvin (Fell, Calvert, & Rileybentham, 1978) with hydrophilic materials (*e.g.*, methylcellulose) increased the amount of the drug released. Hydrotropy is a solubilization process whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute (Coffman & Kildsig, 1996). The increase in the solubility of sparingly soluble organic substances owing to hydrotropes has been found to be an exponential function of the hydrotrope concentration over a wide range (Pandit & Sharma, 1987). Examples of hydrotropic materials are sodium salicylate, sodium gentisate, sodium glycinate, nicotinamide,

Table 4.11 Stability and Bioavailability of Various Salts of Penicillin

Type of salt	Stability	Ionization	Water Solubility	Bioavailability
Sodium	Low	High	More soluble	Low
Acid				
Calcium				
Potassium	High	Low	Less soluble	High

sodium benzoate, sodium toluate, sodium ibuprofen, pheniramine, lysine, tryptophan, and isoniazid.

The solid dispersion method requires making of eutectic mixtures. A eutectic mixture is composed of microscopically fine crystals of each component, mixed very intimately (Sekiguchi, & Obi, 1961). The solid dispersion can be prepared by melting poorly-soluble drugs in the presence of the other component of the mixture, and rapidly cooling in an ice bath under vigorous stirring until solidification. The obtained mass, which may be very hard, can be crushed into small particles. Alternatively, the solid dispersions can be prepared in the presence of PEG, and this method allows direct capsule filling of the melt (Ford, 1986; Chiou & Riegelman, 1971; Serajuddin, 1999). This breakthrough technology resulted in easier processing for making solid dispersions.

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