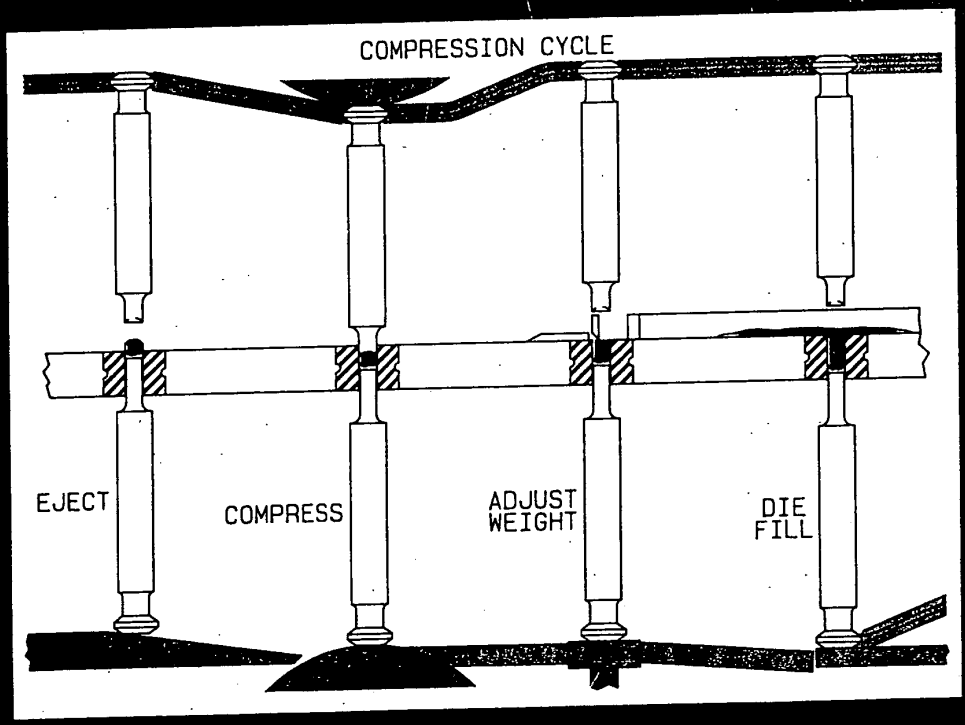
Pharmaceutical Dosage Forms: Tablets Volume 1

Second Edition, Revised and Expanded

Edited by Herbert A. Lieberman, Leon Lachman, and Joseph B. Schwartz



Pharmaceutical Dosage Forms: Tablets

Volume 1

Second Edition

Revised and Expanded

Lieberman • Lachman • Schwartz

Dekker

about the first edition . . .

" . . . represents the most comprehensive effort ever made in compiling technological, preformulation, and formulation concepts related to pharmaceutical tablets. . . . reviews the literature in a well-organized, highly cogent, and easily readable manner."
—*Pharmaceutical Technology*

" . . . the editors have provided valuable information which is difficult to find elsewhere. Usually these unique tablet forms are treated very superficially or not at all in pharmaceutics textbooks."
—*American Journal of Pharmaceutical Education*

about the second edition . . .

Focusing on recent innovations in the field, the ***Second Edition*** continues to provide in-depth, authoritative information on the science and technology of tablet formulation, manufacture, and testing.

Combining the work of 14 experts, ***Pharmaceutical Dosage Forms: Tablets, Second Edition*** contains *new material* on the formulation of sustained or prolonged release tablets by wet granulation, fluidized bed granulating, long-acting and controlled-release buccal tablets, vaginal and rectal tablets, and inclusion complexes and molecular complexes.

Expanding its scope, the ***Second Edition*** also offers *revised and updated coverage* on such topics as drug substance purity, dissolution, partition coefficient, the permeability concept, miscellaneous pharmaceutical properties of solids, the development of prototype formulas, direct compression excipients, effervescent technology, stability testing and shelf-life, testing for airtightness of sealed packets, microencapsulation and spray coating, and more.

about the editors . . .

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PHARMACEUTICAL DOSAGE FORMS

Tablets

SECOND EDITION, REVISED AND EXPANDED

In Three Volumes
VOLUME 1

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3
Compressed Tablets by Wet Granulation

Fred J. Bandelin

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Compressed tablets are the most widely used of all pharmaceutical dosage forms for a number of reasons. They are convenient, easy to use, portable, and less expensive than other oral dosage forms. They deliver a precise dose with a high degree of accuracy. Tablets can be made in a variety of shapes and sizes limited only by the ingenuity of the tool and die maker (i.e. round, oval, capsule-shaped, square, triangular, etc.).

Compressed tablets are defined as solid-unit dosage forms made by compaction of a formulation containing the drug and certain fillers or excipients selected to aid in the processing and properties of the drug product.

There are various types of tablets designed for specific uses or functions. These include tablets to be swallowed per se; chewable tablets formulated to be chewed rather than swallowed, such as some antacid and vitamin tablets; buccal tablets designed to dissolve slowly in the buccal pouch; and sublingual tablets for rapid dissolution under the tongue. Effervescent tablets are formulated to dissolve in water with effervescence caused by the reaction of citric acid with sodium bicarbonate or some other effervescent combination that produces effervescence in water. Suppositories can be made by compression of formulations using a specially designed die to produce the proper shape.

The function of tablets is determined by their design. Multilayer tablets are made by multiple compression. These are called layer tablets and usually consist of two and sometimes three layers. They serve several purposes: to separate incompatible ingredients by formulating them in separate layers, to make sustained or dual-release products, or merely for appearance where the layers are colored differently. Compression-coated tablets are made by compressing a tablet within a tablet so that the outer coat becomes the coating. As many as two coats can be compressed around a core tablet. As with layer tablets, this technique can also be used to separate incompatible ingredients and to make sustained or prolonged

release tablets. Sugar-coated tablets are compressed tablets with a sugar coating. The coating may vary in thickness and color by the addition of dyes to the sugar coating. Film-coated tablets are compressed tablets with a thin film of an inert polymer applied in a suitable solvent and dried. Film coating is today the preferred method of making coated tablets. It is the most economical and involves minimum time, labor, expense, and exposure of the tablet to heat and solvent. Enteric-coated tablets are compressed tablets coated with an inert substance which resists solution in gastric fluid, but disintegrates and releases the medication in the intestines. Sustained or prolonged release tablets are compressed tablets especially designed to release the drug over a period of time.

Most drugs cannot be compressed directly into tablets because they lack the bonding properties necessary to form a tablet. The powdered drugs, therefore, require additives and treatment to confer bonding and free-flowing properties on them to facilitate compression by a tablet press.

This chapter describes and illustrates how this is accomplished by the versatile wet granulation method.

I. PROPERTIES OF TABLETS

Whatever method of manufacture is used, the resulting tablets must meet a number of physical and biological standards. The attributes of an acceptable tablet are as follows:

1. The tablet must be sufficiently strong and resistant to shock and abrasion to withstand handling during manufacture, packaging, shipping, and use. This property is measured by two tests, the hardness and friability tests.
2. Tablets must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation test and the content uniformity test.
3. The drug content of the tablet must be bioavailable. This property is also measured by two tests, the disintegration test and the dissolution test. However, bioavailability of a drug from a tablet, or other dosage form, is a very complex problem and the results of these two tests do not of themselves provide an index of bioavailability. This must be done by blood levels of the drug.
4. Tablets must be elegant in appearance and must have the characteristic shape, color, and other markings necessary to identify the product. Markings are usually the monogram or logo of the manufacturer. Tablets often have the National Drug Code number printed or embossed on the face of the tablet corresponding to the official listing of the product in the National Drug Code Compendium of the Food and Drug Administration. Another marking that may appear on the tablet is a score or crease across the face, which is intended to permit breaking the tablet into equal parts for the administration of half a tablet. However, it has been shown that substantial variation in drug dose can occur in the manually broken tablets.
5. Tablets must retain all of their functional attributes, which include drug stability and efficacy.

II. FORMULATION OF TABLETS

The size and, to some extent, the shape of the tablet are determined by the active ingredient(s). Drugs having very small doses in the microgram range (e.g., folic acid, digitoxin, reserpine, dexamethasone, etc.) require the addition of fillers also called excipients to be added to produce a mass or or volume of material that can be made into tablets of a size that is convenient for patients. A common and convenient size for such low-dosage drugs is a 1/4-in. round tablet or equivalent in some other shape. It is difficult for some patients to count and handle tablets smaller than this. Tablets of this size ordinarily weigh 150 mg or more depending on the density of the excipients used to make up the tablet mass.

As the dose increases, so does the size of the tablet. Drugs with a dose of 100 to 200 mg may require tablet weights of 150 to 300 mg and round die diameters of 1/4 to 7/16 in. in diameter depending on the density and compressibility of the powders used. As the dose of the active ingredient(s) increases, the amount of the excipients and the size of the tablet may vary considerably depending on requirements of each to produce an acceptable tablet. While the diameter of the tablet may in some cases be fixed, the thickness is variable thus allowing the formulator considerable latitude and flexibility in adjusting formulations.

As the dose, and therefore the size, of the tablet increases, the formulator uses his expertise and knowledge of excipients to keep the size of the tablet as small as possible without sacrificing its necessary attributes. Formulation of a tablet, then, requires the following considerations:

1. Size of dose or quantity of active ingredients
2. Stability of active ingredient(s)
3. Solubility of active ingredient(s)
4. Density of active ingredient(s)
5. Compressibility of active ingredient(s)
6. Selection of excipients
7. Method of granulation (preparation for compression)
8. Character of granulation
9. Tablet press, type, size, capacity
10. Environmental conditions (ambient or humidity control)
11. Stability of the final product
12. Bioavailability of the active drug content of the tablet

The selection of excipients is critical in the formulation of tablets. Once the formulator has become familiar with the physical and chemical properties of the drug, the process of selecting excipients is begun. The stability of the drug should be determined with each proposed excipient. This can be accomplished as follows: In the laboratory, prepare an intimate mixture of the drug with an excess of each individual excipient and hold at 60°C for 72 hr in a glass container. At the end of this period, analyze for the drug using a stability-indicating assay. The methods of accelerated testing of pharmaceutical products have been extensively reviewed by Lachman et al in *The Theory and Practice of Industrial Pharmacy*, 3rd Ed., Lea and Febiger (1986).

Table 1 Suggested Excipient/Drug Ratio in Compatibility Studies

Excipient	Weight excipient per unit weight drug (anticipated drug dose, mg)				
	1	5–10	25–50	75–150	150
Alginic acid	24	24	9	9	9
Avicel	24	9	9	9	4
Cornstarch	24	9	4	2	2
Dicalcium phosphate dihydrate	34	34	9	9	9
Lactose	34	9	4	2	1
Magnesium carbonate	24	24	9	9	4
Magnesium stearate	1	1	1	1	1
Mannitol	24	9	4	2	1
Methocel	2	2	2	2	1
PEG 4000	9	9	4	4	2
PVP	4	4	2	1	1
Sta-Rx[a]	1	1	1	1	1
Stearic acid	1	1	1	1	1
Talc	1	1	1	1	1

[a]Now called starch 1500.
Source: Modified from Akers, M. J., *Can. J. Pharm. Sci.*, *11*:1 (1976). Reproduced with permission of the Canadian Pharmaceutical Association.

The suggested ratio of excipient to drug is given in Table 1. Excipients are specified according to the function they perform in the tablet. They are classified as follows:

Fillers (diluents)
Binders
Disintegrants
Lubricants
Glidants
Antiadherents

These additives are discussed in detail later in this chapter.

III. TABLET MANUFACTURE

A. Tablet Presses

The basic unit of any tablet press is a set of tooling consisting of two punches and a die (Fig. 1) which is called a station. The die determines the diameter or shape of the tablet; the punches, upper and lower, come together in the die that contains the tablet formulation to form a tablet. There are two types of presses: single-punch and rotary punch. The single-punch press has a single station of one die and two punches, and is capable of producing from 40 to 120 tablets per minute depending on the size of the tablet. It is largely used in the early stages of tablet formulation development. The rotary press has a multiplicity of stations arranged on a rotating table (Fig. 2) in which the dies are fed the formulation producing tablets at production rates of from a few to many thousands per minute. There are numerous models of presses, manufactured by a number of companies, ranging in size, speed, and capacity.

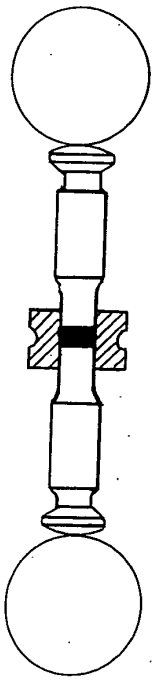


Figure 1 Two punches and die, comprises one station. (Courtesy of Pennsalt Chemical Corporation, Warminster, Pennsylvania.)

Tablet presses consist of:

1. Hoppers, usually one or two, for storing and feeding the formulation to be pressed
2. Feed frame(s) for distributing the formulation to the dies
3. Dies for controlling the size and shape of the tablet
4. Punches for compacting the formulation into tablets
5. Cams (on rotary presses) that act as tracks to guide the moving punches

All other parts of the press are designed to control the operation of the above parts.

B. Unit Operations

There are three methods of preparing tablet granulations. These are (a) wet granulation, (b) dry granulation (also called "slugging"), and direct compression (Table 2). Each of these methods has its advantages and disadvantages.

The first two steps of milling and mixing of the ingredients of the formulation are identical, but thereafter the processes differ. Each individual operation of the process is known as a unit operation. The progress or flow of materials through the process is shown in the schematic drawing (Fig. 3).

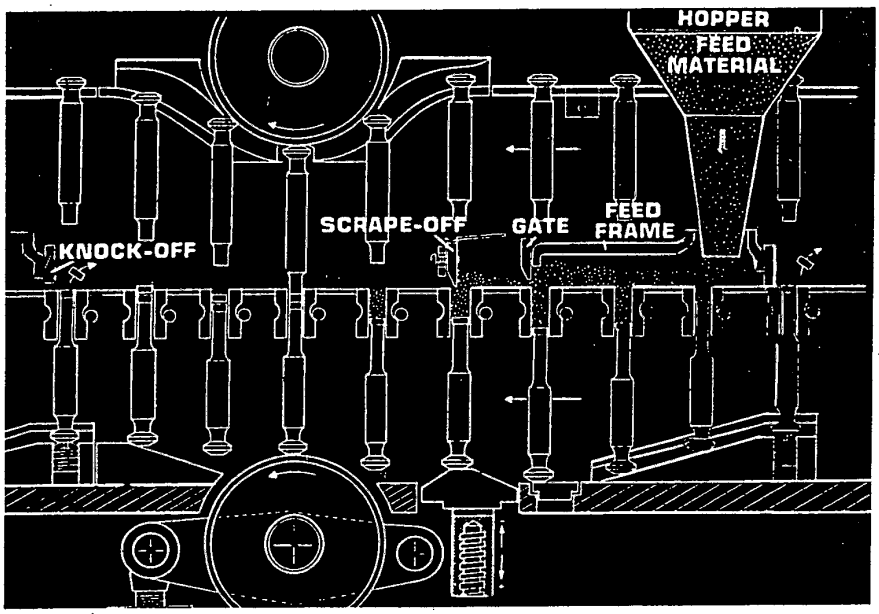
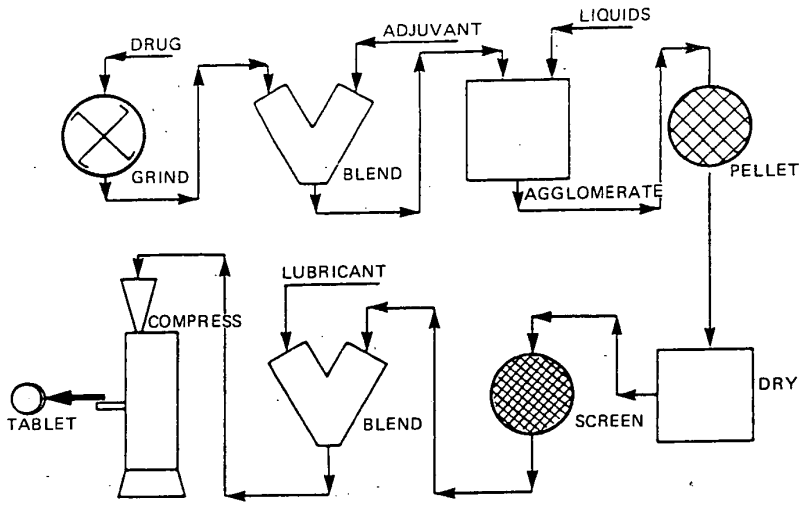


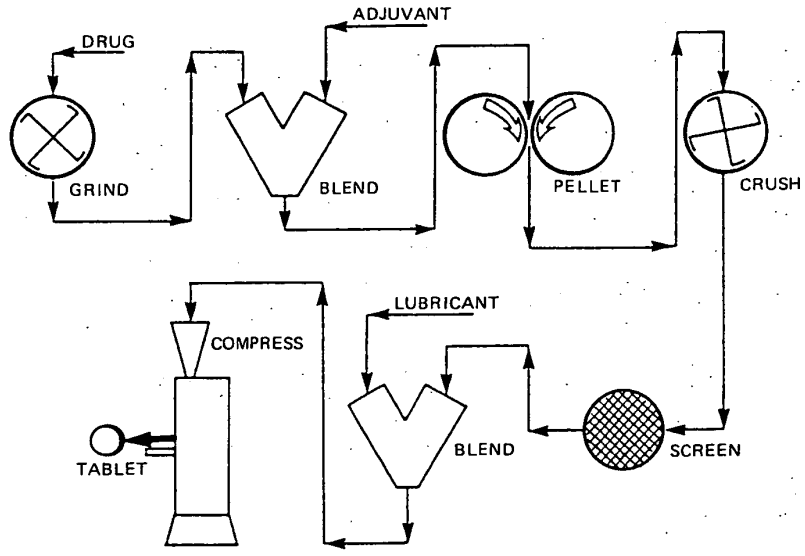
Figure 2 Punches and dies on rotary tablet press. (Courtesy of Pennwalt Chemical Corporation, Warminister, Pennsyovania.)

Table 2 Steps in Different Methods of Tablet Manufacture (Unit Operations)

Wet granulation	Dry granulation	Direct compression
1. Milling of drugs and excipients	1. Milling of drugs and excipients	1. Milling of drugs and excipients
2. Mixing of milled powders	2. Mixing of milled powders	2. Mixing of ingredients
3. Preparation of binder solution	3. Compression into large, hard tablets called slugs	3. Tablet compression
4. Mixing binder solution with powder mixture to form wet mass	4. Screening of slugs	
5. Coarse screening of wet mass using 6- to 12- mesh	5. Mixing with lubricant and disintegrating agent	
6. Drying moist granules	6. Tablet compression	
7. Screening dry granules with lubricant and disintegrant		
8. Mixing screened granules with lubricant and disintegrant		
9. Tablet compression		

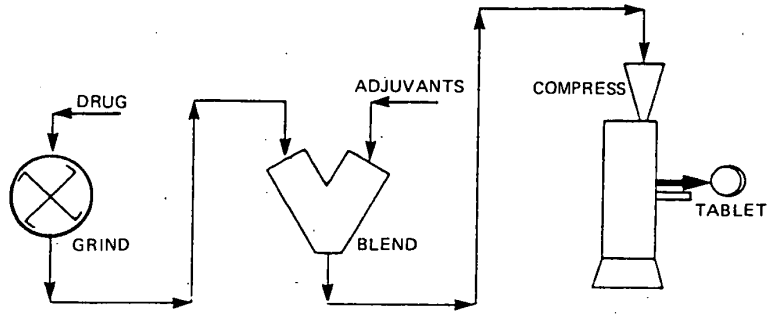


(a)



(b)

Figure 3 Unit operations in three methods of tablet manufacture: (a) wet granulation, (b) dry granulation, and (c) direct compression.



(c)

Figure 3 (Continued)

This chapter is devoted to the first of these processes—the wet granulation process.

The preliminary step of particle size reduction can be accomplished by a variety of mills or grinders such as shown in Figure 4. The next step is powder blending with a planetary mixer (Fig. 5) or a twin-shell blender (Fig. 6). The addition of the liquid binder to the powders to produce the wet mass requires equipment with a strong kneading action such as a sigma blade mixer (Fig. 7) or a planetary mixer mentioned above. The wet mass is formed into granules by forcing through a screen in an oscillating granulator (Fig. 8) or through a perforated steel plate in a Fitzmill (Fig. 9). The granules are then dried in an oven or a fluid bed dryer after which they are reduced in size for compressing by again screening in an oscillator or Fitzmill with a smaller orifice. The granulation is then transferred to a twin shell or other suitable mixer where the lubricant, disintegrant, and glidant are added and blended. The completed granulation is then ready for compression into tablets.

Fluid bed dryers have been adapted to function as wet granulators as depicted by the schematic drawings Figs. 10 and 11. In the latter, powders are agglomerated in the drying chamber by spraying the liquid binder onto the fluidized powder causing the formation of agglomerates while the hot-air flow simultaneously dries the agglomerates by vaporizing the liquid phase. This manner of wet granulation has the advantage of reducing handling and contamination by dust and offers savings in both process time and space [1–3]. It also lends itself to automation; however, by its nature it has the disadvantage of being limited to a batch-type operation. Unlike the wet-massing method, fluidized granulation is quite sensitive to small variations in binder and processing. Conversion of granule preparation from the wet massing to the fluid bed method is not feasible without extensive and time-consuming reformulation [4–8].

In one study it was noted that fluidized bed tablets were more friable than wet-massed tablets of the same tensile strength and attributes this to uneven distribution of the binder in the fluidized bed powders leading to drug-rich, friable areas on the surface and edges of the tablets causing breaking and chipping [9].

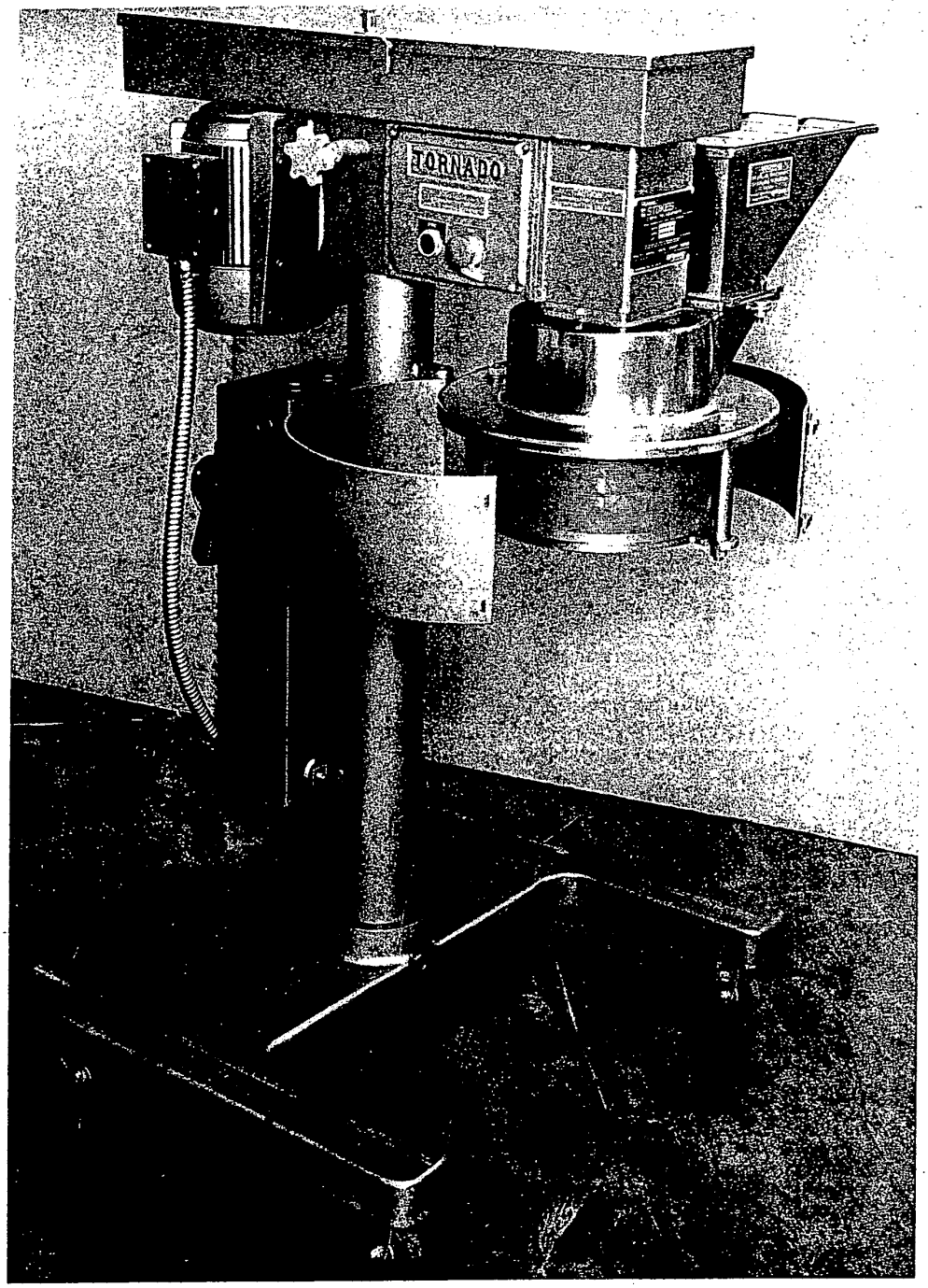


Figure 4 Tornado mill. (Courtesy of Pennwalt Chemical Corporation, Warminister, Pennsylvania.)

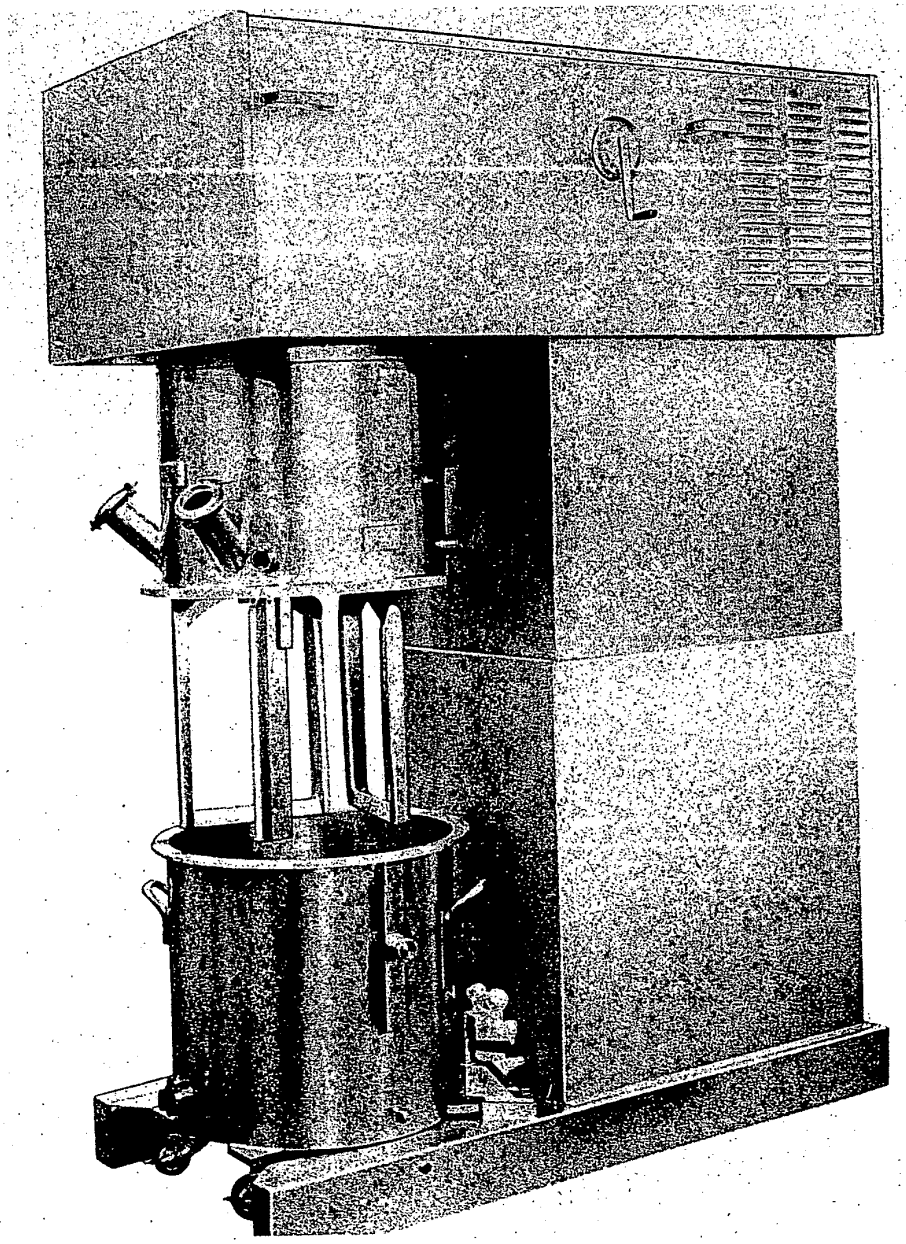


Figure 5 Ross HDM 40 sanitary double planetary mixer. (Courtesy of Charles Ross & Son Co., Happauge, New York.)

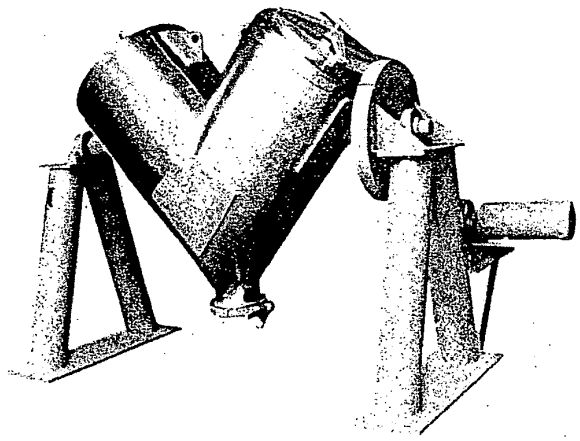


Figure 6 Twin-shell blender. (Courtesy of Patterson-Kelley Company, East Strousberg, Pennsylvania.)

In the past few years considerable improvements have been made in equipment available for fluidized bed drying. These have reduced the risk of channeling by better design of the fluid bed, improved design from a Good Manufacturing Practices viewpoint, and by means of in-place washing together with automatic controls.

Several other methods of granulating not extensively used in the pharmaceutical industry but worthy of investigation are the following.

Pan granulating is achieved by spraying a liquid binder onto powders in a rotating pan such as that used in tablet coating. The tumbling action of the powders in the pan produces a fluidizing effect as the binder is impinged on the powder particles. The liquid (water or solvent) is evaporated in the heated pan by a current of hot air and the vapors are carried off by a vacuum hood over the upper edge of the pan opening.

Although pan granulation has found extensive application in other industries (e.g., agricultural chemicals), it has not found favor in the pharmaceutical industry. One reason may be the lack of acceptable design.

Spray drying can serve as a granulating process. The drying process changes the size, shape, and bulk density of the dried product and lends itself to large-scale production [10]. The spherical particles produced usually flow better than the same product dried by other means because the particles are more uniform in size and shape. Spray drying can also be used to dry materials sensitive to heat or oxidation without degrading them. The liquid feed is dispersed into droplets, which are dried in seconds, and the product is kept cool by the vaporization of the liquid. Seager and others describe a process for producing a variety of drug formulations by spray drying [11–13].

Extrusion, in which the wet mass is forced through holes in a steel plate by a spiral screw (similar to a meat grinder), is an excellent method of granulating and densifying powders. It lends itself to efficient,

Figure 7 Sigma blade mixer. (Courtesy of J. H. Day Company, Cincinnati, Ohio.)

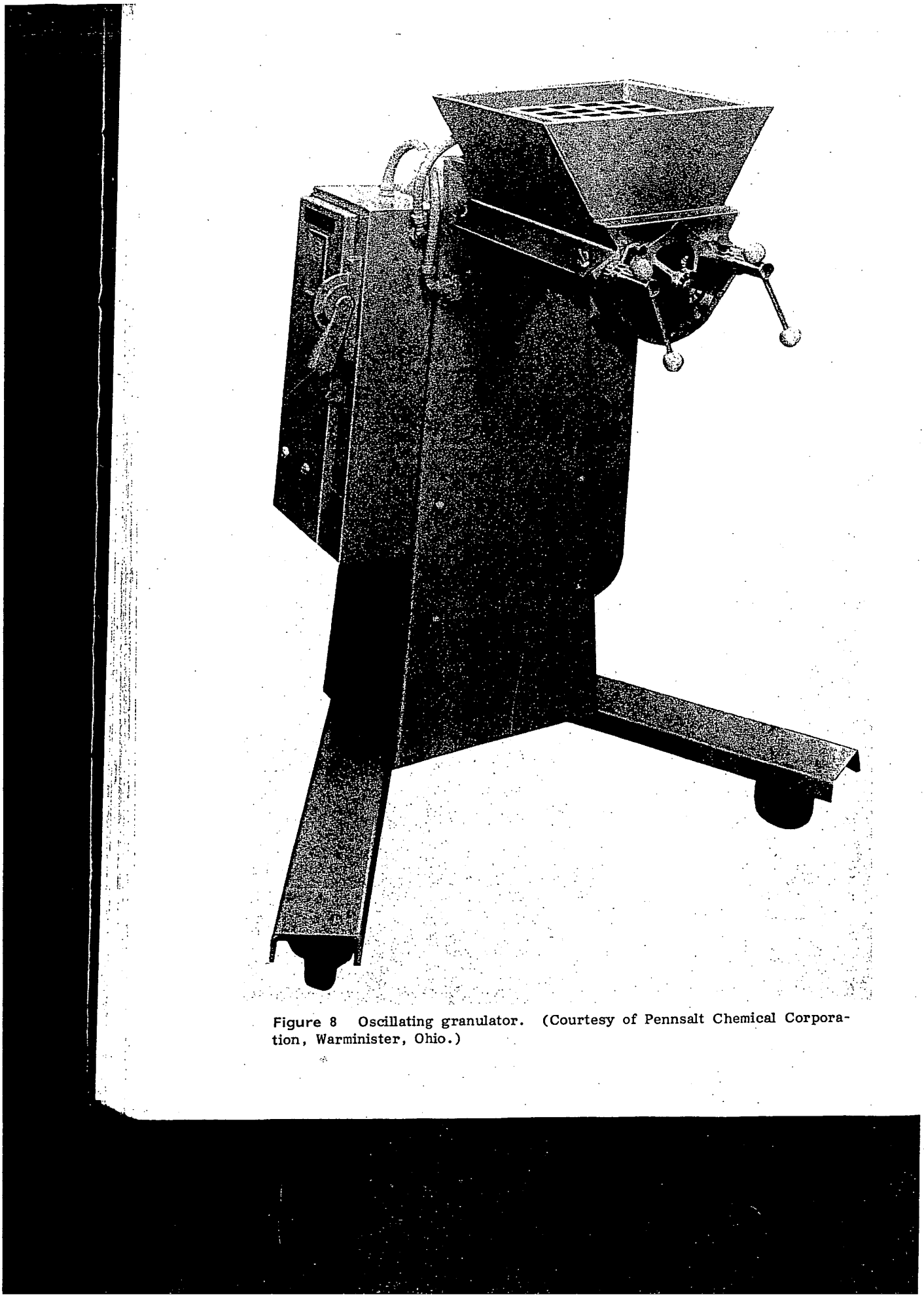


Figure 8 Oscillating granulator. (Courtesy of Pennsalt Chemical Corporation, Warminister, Ohio.)

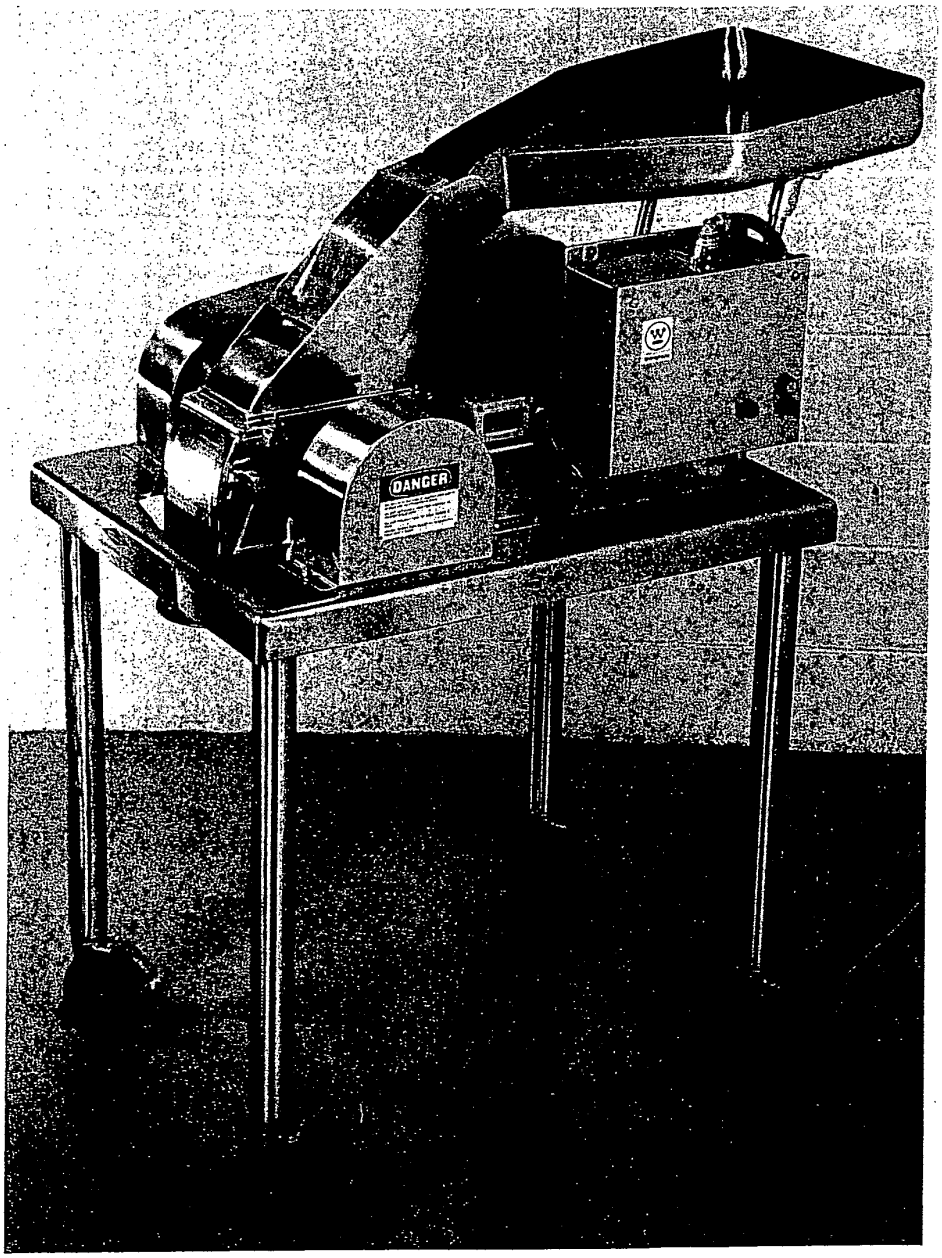


Figure 9 Fitzmill. (Courtesy of The Fitzpatrick Company, Elmhurst, Illinois.)

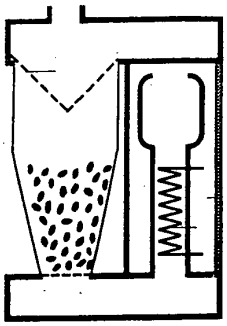


Figure 10 Fluid bed dryer. (Courtesy of Aeromatic, Inc., South Somerville, New Jersey.)

large-scale production as part of an enclosed continuous wet-granulating system protected from airborne contamination.

The extruder can also act as a wet-massing mixer by providing a continuous flow of the binder into the screw chamber, allowing the spiral screw to act as the massing instrument as it moves the powder, infusing it with the liquid to form a wet mass that is then extruded to form granules. The extruder has the added advantage of being a small unit as compared with other mixers, and has a high production capacity for its size. It is easily cleaned and is versatile in its ability to produce granules of various size depending on the size of the plate openings used.

Pellets can be prepared by spheroidization of the wet mass after extrusion [14–16].

The transfer of wet granulation technology from lab batches to production equipment, generally known as "scale-up," is a critical step because

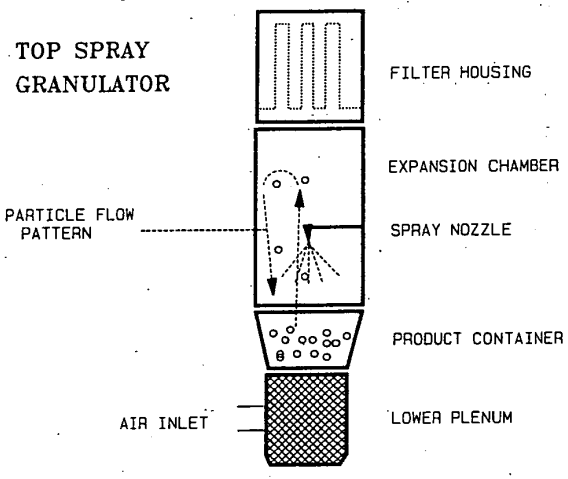


Figure 11 Spray granulator. (Courtesy of Glatt Air Techniques, Inc., Ramsey, New Jersey.)

of the increased mass of the larger batches and different conditions in larger equipment. To attempt to anticipate granulation variation due to scale-up, intermediate pilot equipment facilitates the step-up to production quantities. This permits the use of various types of equipment or unit operations to determine which produces the best end result of the granulation process. Often, however, scale-up is limited to the available equipment, which limits, or locks in, the process. In this situation, it is incumbent on the formulator to utilize his or her expertise and experience in selecting excipients and binder which yield the best granulation and tablets with the equipment available [17–19].

Attempts to apply experimental design to scaling up the wet granulation process has not been rewarding so that, in practice, trial and error remains the most widely used procedure.

Wet granulation research has greatly increased and expanded in the last decade because of the advent of new types of granulating equipment. Notable among these are the Lodige, Diosna, Fielder, and Baker–Perkins mixers. These are equipped with high-speed impellers or blades that rotate at speeds of 100 to 500 rpm. In addition to merely mixing the powders, they produce rapid and efficient wetting and densification of the powders. Most of these mixers are also equipped with a rotating chopper that operates at speeds of 1000 to 3000 rpm. This facilitates uniform wetting of the powders in a matter of minutes. Granule formation can be achieved by the controlled spraying or atomization of the binder solution onto the powders while mixing [20]. While these highly efficient mixers serve to optimize the wet granulation process, they also demand greater understanding of their effects on the individual fillers and binders as processed by the mixers [21].

Another mixer, blender, and granulator that has found application in the pharmaceutical industry is the Patterson–Kelley twin-shell liquid-solids Blender (Fig. 12). These twin-shell units are equipped with a jacket for

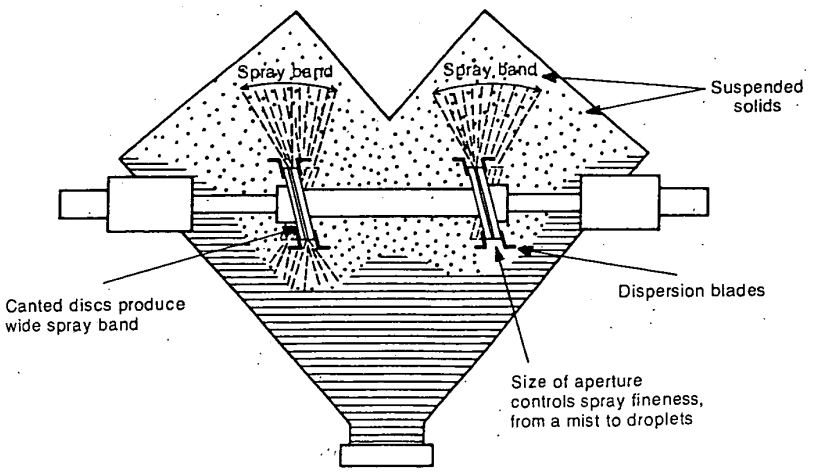


Figure 12 Twin-shell liquid-solid blender. (Courtesy of Patterson-Kelley Company, East Stroudsburg, Pennsylvania.)

heating and cooling, a vacuum take-off, and a liquid dispersion bar through which a liquid binder can be added. As the blender rotates, liquid is sprayed into the powder charge through the rotating liquid dispersion bar, located concentric to the trunnion axis. The bar's dog-eared blades, rotating at 3300 rpm, aerates the powder to increase the speed and thoroughness of the blend. Granulation can be controlled by the rate of binder addition through the dispersion bar. After heating, the liquid of the binder is removed under reduced pressure. Mixing, granulating, heating, cooling, and removal of excess liquid are carried out in a continuous operation in an enclosed system, thereby protecting the contents from contamination and the adjacent area from contamination by the contents. Once the granulation process is completed, the remaining excipients can be added and blended by the simple rotating action of the blender. This unit is also known as a liquid-solids processor.

IV. GRANULATION

Most powders cannot be compressed directly into tablets because (a) they lack the proper characteristics of binding or bonding together into a compact entity and (b) they do not ordinarily possess the lubricating and disintegrating properties required for tableting. For these reasons, drugs must first be pretreated, either alone or in combination with a filler, to form granules that lend themselves to tableting. This process is known as granulation.

Granulation is any process of size enlargement whereby small particles are gathered together into larger, permanent aggregates [22] to render them into a free-flowing state similar to that of dry sand.

Size enlargement, also called agglomeration, is accomplished by some method of agitation in mixing equipment or by compaction, extrusions or globulation as described in the previous section on unit operations [4,23, 24].

The reasons for granulation as listed by Record [23] are to:

1. Render the material free flowing
2. Densify materials
3. Prepare uniform mixtures that do not separate
4. Improve the compression characteristics of the drug
5. Control the rate of drug release
6. Facilitate metering or volume dispensing
7. Reduce dust
8. Improve the appearance of the tablet

Because of the many possible approaches to granulation, selection of a method is of prime importance to the formulator.

A. Wet Granulation

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. This process has been extensively reviewed by Record [23], Kristensen and Schaefer [26], and Capes [27].

It is the oldest and most conventional method of making tablets. Although it is the most labor-intensive and most expensive of the available methods, it persists because of its versatility. The possibility of moistening powders with a variety of liquids, which can also act as carriers for certain ingredients, thereby enhancing the granulation characteristics, has many advantages. Granulation by dry compaction has many limitations. It does not lend itself to all tablet formulations because it depends on the bonding properties of dry powders added as a carrier to the drug thereby increasing the size of the tablet. In wet granulation, the bonding properties of the liquid binders available is usually sufficient to produce bonding with a minimum of additives.

The phenomena of adhesion and cohesion may be defined as follows: adhesion is the bonding of unlike materials, while cohesion is that of like materials. Rumpf [28] identified mechanisms by which mechanical links are formed between particles. The following are involved in the bonding process:

1. Formation of crystalline bridges by binders during drying
2. Structures formed by the hardening of binders in drying
3. Crushing and bonding of particles during compaction

Wet granulation is a versatile process and its application in tablet formulation is unlimited.

B. Advantages of Wet Granulation

1. The cohesiveness and compressibility of powders is improved due to the added binder that coats the individual powder particles, causing them to adhere to each other so they can be formed into agglomerates called granules. By this method, properties of the formulation components are modified to overcome their tableting deficiencies. During the compaction process, granules are fractured exposing fresh powder surfaces, which also improves their compressibility. Lower pressures are therefore needed to compress tablets resulting in improvements in tooling life and decreased machine wear.
2. Drugs having a high dosage and poor flow and/or compressibility must be granulated by the wet method to obtain suitable flow and cohesion for compression. In this case, the proportion of the binder required to impart adequate compressibility and flow is much less than that of the dry binder needed to produce a tablet-by-direct compression.
3. Good distribution and uniform content for soluble, low-dosage drugs and color additives are obtained if these are dissolved in the binder solution. This represents a distinct advantage over direct compression where the content uniformity of drugs and uniform color dispersion can be a problem.
4. A wide variety of powders can be processed together in a single batch and in so doing, their individual physical characteristics are altered to facilitate tableting.
5. Bulky and dusty powders can be handled without producing a great deal of dust and airborne contamination.

6. Wet granulation prevents segregation of components of a homogeneous powder mixture during processing, transfering, and handling. In effect, the composition of each granule becomes fixed and remains the same as that of the powder mixture at the time of the wetting.
7. The dissolution rate of an insoluble drug may be improved by wet granulation with the proper choice of solvent and binder.
8. Controlled release dosage forms can be accomplished by the selection of a suitable binder and solvent.

C. Limitations of Wet Granulation

The greatest disadvantage of wet granulation is its cost because of the space, time, and equipment involved. The process is labor-intensive as indicated by the following.

1. Because of the large number of processing steps, it requires a large area with temperature and humidity control.
2. It requires a number of pieces of expensive equipment.
3. It is time consuming, especially the wetting and drying steps.
4. There is a possibility of material loss during processing due to the transfer of material from one unit operation to another.
5. There is a greater possibility of cross-contamination than with the direct-compression method.
6. It presents material transfer problems involving the processing of sticky masses.
7. It can slow the dissolution of drugs from inside granules after tablet disintegration if not properly formulated and processed.

A recent innovation in wet granulating, which reduces the time and energy requirements by eliminating the drying step, is the melt process. This method relies on the use of solids having a low softening or melting point which, when mixed with a powder formulation and heated, liquefy to act as binders [29,30]. Upon cooling, the mixture forms a solid mass in which the powders are bound together by the binder returning to the solid state. The mass is then broken and reduced to granules and compressed into tablets. Materials used as binders are polyethylene glycol 4000 and polyethylene glycol 6000 [31–33], stearic acid [30], and various waxes [34,35].

The amount of binder required is greater than for conventional liquid binders (i.e., 20 to 30% of the starting material).

Another advantage of the method is that the waxy materials also act as lubricants, although in some cases additional lubricant is required.

A new variation of the granulating process known as "moisture-activated dry granulation" [36] combines the efficiency of dry blending with the advantages of wet granulation. As little as 3% water produces agglomeration. The process requires no drying step because any free water is absorbed by the excipients used. After granulation, disintegrant and lubricant are added and the granulation is ready for compression.

The complex nature of wet granulation is still not well understood, which accounts for the continuing interest in research on the process. One significant problem is the degree of wetting or massing of the powders. Wetting plays an exceedingly important roll in the compression characteristics

of the granules, and also in the rate of drug release from the final tablet. Some attempts at standardizing the wetting process have been made, particularly in the matter of overwetting [37–39]. Factors that affect wetting are

1. Solubility of the powders
2. Relative size and shape of the powder particles
3. Degree of fineness
4. Viscosity of the liquid binder
5. Type of agitation

Although the wet granulation method is labor-intensive and time consuming, requiring a number of steps, it continues to find extensive application for a number of reasons. One reason is because of its universal use in the past, the method persists with established products where, for one reason or another, it cannot be replaced by direct compression. Although a number of these products might lend themselves to the direct-compression method, to do so would require a change in ingredients to other excipients. A change of this nature would be considered a major modification requiring a careful review to evaluate the need to carry out additional studies or product stability, safety, efficacy, and bioavailability as well as the impact of pertinent practical and regulatory considerations. Since extensive data are likely to have been accumulated on the existing product(s), there is understandable reluctance on the part of the drug industry to undertake such changes unless dictated by compelling reasons. Another reason is that formulators prefer to use the wet granulation method to assure content uniformity of tablets where small doses of drug(s) and/or color additives are being dispersed by dissolving in the liquid binder. This procedure affords better and more uniform distribution of the dissolved material. The method is also singular for use in the granulation of drugs having a high dosage where direct compression, because of the necessity to add a considerable amount of filler to facilitate compaction, becomes unfeasible because of the resulting increase in tablet size.

V. EXCIPIENTS AND FORMULATION

Excipients are inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch-all term which includes various subgroups comprising diluents or fillers, binders or adhesives, disintegrants, lubricants, glidants or flow promoters, colors, flavors, fragrances, and sweeteners. All of these must meet certain criteria as follows:

1. They must be physiologically inert.
2. They must be acceptable to regulatory agencies.
3. They must be physically and chemically stable.
4. They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
5. They must not interfere with the bioavailability of the drug.
6. They must be commercially available in form and purity commensurate to pharmaceutical standards.
7. For drug products that are classified as food, such as vitamins, other dietary aids, and so on, the excipients must be approved as food additives.

8. Cost must be relatively inexpensive.
9. They must conform to all current regulatory requirements.

Certain chemical incompatibilities have been reported in which the filler interfered with the bioavailability of the drug as in the case of calcium phosphate and tetracycline [40] and the reaction of certain amine bases with lactose in the presence of magnesium stearate [41,42].

To assure that no excipient interferes with the utilization of the drug, the formulator must carefully and critically evaluate combinations of the drug with each of the contemplated excipients and must ascertain compliance of each ingredient with existing standards and regulations.

Two comprehensive publications cataloging the various excipients used in the pharmaceutical industry are available. The first of these, published in German in 1974 by the combined Swiss Pharmaceutical firms of Ciba Geigy, Hoffman LaRoche, and Sandoz, and entitled *Katalog Pharmaceutischer Hillstoff* contains specifications, tests, and a listing of suppliers. More recently, the listing by the Academy of Pharmaceutical Science of the American Pharmaceutical Association entitled *Handbook of Pharmaceutical Excipients* was published.

The screening of drug–excipient and excipient–excipient interactions should be carried out routinely in preformulation studies. Determination of the optimum drug–excipient compatibility has been adequately presented in the literature [43–45].

A. Fillers (Diluents)

Tablet fillers or diluents comprise a heterogeneous group of substances that are listed in Table 3. Since they often comprise the bulk of the tablet, selection of a candidate from this group as a carrier for a drug is of prime importance. Since combinations are also a possibility, consideration should be given to possible mixtures.

Calcium sulfate, dihydrate, also known as terra alba or as snow-white filler, is an insoluble, nonhygroscopic, mildly abrasive powder. Better grades are white, others may be greyish white or yellowish white. It is the least expensive tablet filler and can be used for a wide variety of

Table 3 Tablet Fillers

Insoluble	Soluble
Calcium sulfate, dihydrate	Lactose
Calcium phosphate, dibasic	Sucrose
Calcium phosphate, tribasic	Dextrose
Calcium carbonate	Mannitol
Starch	Sorbitol
Modified starches (carboxymethyl starch, etc.)	
Microcrystalline cellulose	

acidic, neutral, and basic drugs. It has a high degree of absorptive capacity for oils and has few incompatibilities. Suggested binders are polymers such as PVP and methylcellulose, and also starch paste. See Example 1 for a typical formulation.

Determination of final tablet weight: Since the amount of starch added as starch paste in the massing procedure was not known, it is necessary to determine the amount added to find the tablet weight for pressing. One method of doing this is to weigh the completed granulation before pressing and determine the tablet weight as follows:

$$\frac{\text{Weight of completed granulation}}{\text{Theoretical number of tablets}} = \text{tablet weight}$$

Calcium phosphate, dibasic is insoluble in water, slightly soluble in dilute acids, and is a nonhygroscopic, neutral, mildly abrasive, fine white powder. It produces a hard tablet requiring a good disintegrant and an effective lubricant. Its properties are similar to those of calcium sulfate, but it is more expensive than calcium sulfate and is used to a limited extent in wet granulation. If inorganic acetate salts are present in the formulation, the tablets are likely to develop an acetic odor on aging. It can be used with salts of most organic bases, such as antihistamines, and with both water- and oil-soluble vitamines. Best binders are starch paste, PVP, methylcellulose, or microcrystalline cellulose. See Example 2.

Tricalcium phosphate Is an insoluble, slightly alkaline, nonhygroscopic, abrasive, fine white powder. It is used to a limited extent in wet granulation. It should not be used with strong acidic salts of weak organic bases or in the presence of acetate salts. It should not be used with the water-soluble B vitamines or with certain esters such as vitamin E or vitamin A acetate or palmitate.

Calcium carbonate is a dense, fine, white, insoluble powder. It is available in degrees of fineness. Precipitated calcium carbonate of a very fine particle size is used as a tablet filler. It is inexpensive, very white, nonhygroscopic, and inert. It cannot be used with acid salts or with acidic compounds. Its main drawback, when used as a filler, is that when granulated with aqueous solutions, care must be taken not to overwet by adding too much granulating liquid or overmixing because this produces a sticky, adhesive mass that is difficult to granulate, and tends to form hard granules that do not disintegrate readily. For this reason, it is best used in combination with another diluent such as starch or microcrystalline cellulose.

Calcium carbonate, in common with calcium phosphates, can serve as a dietary source of calcium. It also serves as an antacid in many products. A tablet with unique mouth-feel and a sweet, cooling sensation. See Example 3.

Microcrystalline cellulose (*Avicel*) is a white, insoluble, nonreactive, free-flowing, versatile filler. It produces hard tablets with low-pressure compression on the tablet press. It produces rapid, even wetting by its wicking action, thereby distributing the granulating fluid throughout the powder bed. It acts as an auxiliary wet binder promoting hard granules with less fines. It lessens screen blocking and promotes rapid, uniform drying. It promotes dye and drug distribution thus promoting uniform color dispersion without mottling. Microcrystalline cellulose also serves as a disintegrant, lubricant, and glidant. It has an extremely low coefficient

Example 1: Phenylpropanolamine Hydrochloride Tablets

Ingredients	Quantity per tablet (mg)	Quantity per 10,000 tablets (g)
Phenylpropanolamine hydrochloride	60	600
Calcium sulfate, dihydrate	180	1800
10% Starch paste*	q.s.	q.s.
Starch 1500 (StaRx) (disintegrant)	12	120
Magnesium stearate (lubricant)	6	60

*Starch paste is made by mixing 10% starch with cold water and heating to boiling with constant stirring and until a thick, translucent white paste is formed.

Mix the phenylpropanolamine hydrochloride with the calcium sulfate in a sigma blade mixer for 15 min, then add sufficient starch paste to form a wet mass of suitable consistency. Allow to mix for 30 min. Pass the wet mass through a no. 14 screen and distribute on drying trays. Dry in a forced-air oven at 120 to 130°F or in a fluid bed dryer. When dry, screen through a no. 18 mesh screen, place in a twin-shell blender, add the starch 1500 starch and the magnesium stearate, blend for 6 to 8 min, and compress the completed granulation on a tablet press using 3/8-in. standard cup punches.

Example 2: Diphenylhydramine (Benadryl) Tablets

Ingredients	Quantity per tablet (mg)	Quantity per 10,000 tablets (g)
Diphenhydramine hydrochloride	25	250
Calcium phosphate, dibasic	150	1500
Starch 1500 (StaRx)	20	200
10% PVP in 50% alcohol	q.s.	q.s.
Stearic acid, fine powder	75	75
Microcrystalline cellulose	25	250

Mix the diphenylhydramine hydrochloride, calcium phosphate, dibasic, and the starch in a planetary mixer. Moisten the mixture with the polyvinylpyrrolidone solution and granulate by passing through a 14-mesh screen. Dry the resulting granules in an oven or fluid bed dryer at 120 to 130°F. Reduce the size of the granules by passing through a

no. 20 mesh screen and dry. Add the stearic acid after passing through a 30-mesh screen and the microcrystalline cellulose in a twin-shell blender for 5 to 7 min. Compress to weight using 5/16-in. standard concave punches.
Important: In all formulations where an indeterminate amount of granulating agent is added, weigh the dried granulation *after* all other ingredients (e.g., lubricant, disintegrant, etc.), which were not part of the wet granulation, and calculate the weight for compression of the tablet as illustrated in Example 1.

Example 3: Calcium Carbonate-Glycine Tablets

Ingredients	Quantity per tablet (mg)	Quanity per 10,000 tablets (g)
Calcium carbonate, precipitated	400	4000
Glycine (aminoacetic acid)	200	2000
10% starch paste	q.s.	q.s.
Light mineral oil (50 to 60 SUS)	6.5	65

Mix the calcium carbonate and the glycine in a sigma blade or planetary mixer for 10 min. Add the starch paste with constant mixing until sufficiently moistened to granulate.
Important: Powders are considered to be sufficiently moistened to granulate when a handful of the wet mass can be squeezed into a solid, hand-formed mass that can be broken in half with a clean fracture while the two halves retain their shape. (This method of determining when powders are adequately moistened to granulate holds true for most wet granulations.) Then force the wet mass through a no. 12 screen and dry the resulting granulation in a forced-air oven at 130 to 140°F or in a fluid bed dryer. Size the granules by passing thorugh a no. 12 mesh screen. Reduce the particle size by forcing through a no. 18 mesh screen. Using a 30-mesh screen, separate out all particles passing through the screen. Finally, add the light mineral oil in a tumble mixer. Mix for 8 min and compress to weight with 7/16-in. punches and dies.

of friction, both static and dynamic, so that it has little lubricant requirement itself. However, when more than 20% of drug or other excipient is added, lubrication is necessary. It can be advantageously combined with other fillers such as lactose, mannitol, starch, or calcium sulfate. In granulating, it makes the consistency of the wet mass less sensitive to variations in water content and overworking. This is particularly useful with materials which, when overwet or overmixed, become claylike, forming a mass that clogs the screens during the granulating process. When dried, these granules become hard and resistent to disintegration. Materials that

Example 4: Calcium Carbonate and Water Only

Ingredient	Quantity
Calcium carbonate	1000 g
Water	300 ml

Example 5: Calcium Carbonate Plus Microcrystalline Cellulose and Water

Ingredient	Quantity
Calcium carbonate	1000 g
Avicel PH-101	100 g
Water	300 ml

cause this problem are clays such as kaolin and certain other materials such as calcium carbonate. This is illustrated by Examples 4 and 5.

The material of Example 4 produces a sticky mass, which is difficult to granulate, whereas that of Example 5 produces a nonsticky mass, which can be granulated through a no. 12 screen.

Microcrystalline cellulose added to a wet granulation improves bonding on compression and reduces capping and friability of the tablet.

For drugs having a relatively small dose, microcrystalline cellulose used as a filler acts also as an auxiliary binder, controls water-soluble drug content uniformly, prevents migration of water-soluble dyes, and promotes rapid and uniform evaporation of liquid from the wet granulation.

Although the usual method of making wet granulations is a two-step procedure, Avicel granulations can be prepared by a one-step procedure. In the two-step procedure, the drug and fillers are formed into granules by wetting in the presence of a binder, drying the resulting moist mass, and passing through a screen or mill to produce the desired granule size. These granules are then blended with a disintegrant and lubricant, and, if necessary, a glidant as in the following formulation (Example 6).

In the one-step method, the lubricant is included in the wet granulation contrary to what is usually taught concerning the necessity for small particle size of these substances in order to coat the granules to obtain easy die release. Apparently, in the comminution of the granulation, sufficient lubricant becomes exposed to perform its intended function (Example 7).

The quantities used in the one-step formulations are the same as those used in the two-step formulations. This method eliminates the usual mixing step for incorporating lubricants. It is also a good idea to incorporate a disintegrant in the wet granulation so that the granules will also disintegrate readily when the tablet breaks up. The practice is valid and can be widely used with modifications in one-step formulations. The materials and

Example 6: Two-Step Avicel Granulation

Ingredients	Percent
Drug	q.s.
Avicel PH-101	q.s.
Confectioners sugar	2.5
Starch 1500	5.0
Starch paste, 10%	q.s.
Talc	3.0
Magnesium stearate	0.5
Sodium lauryl sulfate	1.0

Note: The amount of Avicel is replaced by the amount of the drug.
Blend the first four ingredients and pass through a no. 1 perforated plate (round hole) in a Fitzmill, hammers foreward. Add the starch paste to the powder to form a uniform wet mass. Dry at 140°F. Reduce the granule size by passing through a 20-mesh wire screen in a Fitzmill with knives foreward, medium speed. Transfer the dry granules to a twin-shell blender, add the last three ingredients, blend, and compress into tablets at the predetermined weight.

quantities used in the one-step method are essentially the same as those in the two-step method.

Example 7 illustrates the one-step method.

In the above formulation, if the amount of the drug is less than 10% of the total tablet weight, up to 30% of the Avicel may be replaced with calcium sulfate dihydrate.

Avicel PH-101 mixed with starch and cooked until the starch forms a thick paste makes an excellent wet granulating mixture. Using 60% Avicel and 40% starch as a 10% paste makes the wet mass easier to push through a screen, forms finer granulations and harder granules on drying with fewer fines than with starch paste alone.

Lactose, also known as milk sugar, is the oldest and traditionally the most widely used filler in the history of tablet making. In recent years, however, with new technology and new candidates, other materials have largely replaced it. Its solubility and sweetening power is somewhat less than that obtained with other sugars. It is obtained by crystallization from whey, a milk byproduct of cheese manufacture. Chemically, lactose exists in two isomeric forms, α and β. In solution, it tends to exist in equilibrium between the two forms. If it is crystallized at a temperature

Example 7: One-Step Avicel Granulation

Ingredients	Percent
Drug	q.s
Avicel PH-101	q.s
Confectioners sugar	5.0
Starch 1500	6.0
Polyethylene glycol 6000	3.0
Talc	5.0
Magnesium lauryl sulfate	0.5
50% alcohol	q.s.

In a planetary mixer, blend all of the ingredients except the polyethylene glycol 6000 and the hydroalcoholic solution. Dissolve 1 part of polyethylene glycol 6000 in 1 part (w/v) of the 50% alcohol by heating to 50°C. Add this solution to the blended powders with constant mixing in a sigma blade mixer until uniformly moist. Spread the wet mass on trays and dry in an oven at 50°C. Pass the dry mass through a no. 2 perforated plate in a Fitzmill, knives foreward. Compress to predetermined size and weight. The use of alcohol is not essential, but it gives better control of wetting the powders and promotes more rapid drying.

over 93°C., β-lactose is produced that contains no water of crystallization (it is anhydrous). At lower temperatures, α-lactose monohydrate (hydrous) is obtained.

α-Lactose monohydrate is commercially available in a range of particle sizes from 200- to 450-mesh impalpable powder. The spray-dried form is used for the direct-compression method of producing tablets. Lactose is a reducing sugar and will react with amines to produce the typical Maillard browning reaction. It will also turn brown in the presence of highly alkaline compounds. Lactose is also incompatible with ascorbic acid, salicylamide, pyrilamine maleate, and phenylephrine hydrochloride [46]. Nevertheless, it has a place in tableting by the wet granulation method in the sense that on wetting some goes into solution thereby coating the drug and offering an amount of protection and slow release where rapid dissolution is not required.

Sucrose can be used as both a filler and as a binder in solution. It is commercially available in several forms: granular (table sugar), fine

Example 8: Vitamin B_{12} Tablets

Ingredient	Quantity per tablet	Quantity 10,000 per tablets
(1) Vitamin B_{12} (Cyanocobalamin, USP)	55 µg*	0.55 g
(2) Lactose, anhydrous, fine powder	150 mg	1500 g
(3) 10% Gelatin solution	q.s.	q.s.
(4) Hydrogenated vegetable oil (Sterotex)	5 mg	50 g

*Includes 10% manufacturing overage.

Dissolve the vitamin B_{12} in a portion of the gelatin solution. Slowly add this to the lactose in a sigma blade mixer with constant mixing. Add sufficient additional gelatin solution to form a wet mass suitable to granulate. Pass through a no. 14 mesh screen and dry in a suitable dryer. Reduce the granule size by passing through a no. 20 mesh screen. Add the Sterotex to the granules in a twin-shell blender and blend for 5 min. Compress using 1/2-in. punches and dies. This procedure forms hard tablets that do not disintegrate readily but dissolve rather slowly.

granular, fine, superfine, and confectioners sugar. The latter is the most commonly used in wet granulation formulations and contains 3% cornstarch to prevent caking. It is very fine, 80% passing through a 325-mesh screen. When used alone as a filler, sucrose forms hard granulations and tablets tend to dissolve rather than disintegrate. For this reason, it is often used in combination with various other insoluble fillers. It is used in chewable tablets to impart sweetness and as a binder to impart hardness. In this role it may be used dry or in solution. When used as a dry filler, it is usually granulated with water only or with a hydroalcoholic binder. Various tablet hardnesses can be obtained depending on the amount of binder used to granulate. The more binder, the harder the granulation and the tablet. If a mixture of water and alcohol is used, softer granules are produced.

Sucrose has several disadvantages as a filler. Tablets made with a major portion of it in the formulation tend to harden with time. It is not a reducing sugar but with alkaline materials, it turns brown with time. It is somewhat hygroscopic and tends to cake on standing.

Dextrose has found some limited use in wet granulation as a filler and binder. It can be used essentially in the same way as sucrose. Like sucrose, it tends to form hard tablets, especially if anhydrous dextrose is used. It has the same disadvantages of both lactose and sucrose in that it turns brown with alkaline materials and reacts with amines to discolor.

Mannitol is a desirable filler in tablets when taste is a factor as in chewable tablets. It is a white, odorless, pleasant-tasting crystalline powder that is essentially inert and nonhygroscopic. It is preferred as a diluent in chewable tablets because of its pleasant, slightly sweet taste and its smooth, cool, melt-down mouth-feel. Its negative heat of solution is

responsible for its cool taste sensation. Mannitol may be granulated with a variety of granulating agents but requires more of the solution than either sucrose or lactose and approximately the same as dextrose. The moisture content of these granulations after overnight drying at 140 to 150°F for sucrose, dextrose, and mannitol was less than 0.2%, except for dextrose granulations made with 10% gelation and 50% glucose, in which case the moisture content was 1.15 and 0.2%, respectively. In all lactose granulations, the moisture content was between 4 and 5%. Mannitol and sucrose were the lowest, having about the same moisture content. It was found, however, that mannitol, although requiring more granulating solution, generally gave a softer granulation than either sucrose or dextrose.

B. Binders

Binders are the "glue" that holds powders together to form granules. They are the adhesives that are added to tablet formulations to provide the cohesiveness required for the bonding together of the granules under compaction to form a tablet. The quantity used and the method of application must be carefully regulated, since the tablet must remain intact until swallowed and must then release its medicament.

The appearance, elegance, and ease of compression of tablets are directly related to the granulation from which the tablets are compressed. Granulations, in turn, are dependent on the materials used, processing techniques, and equipment for the quality of the granulation produced. Of these variables, none is more critical than the binder used to form the granulation, for it is largely the binder that is fundamental to the granulation particle size uniformity, adequate hardness, ease of compression, and general quality of the tablet [47–50].

Binders are either sugars or polymeric materials. The latter fall into two classes: (a) natural polymers such as starches or gums including acacia, tragacanth, and gelatin, and (b) synthetic polymers such as polyvinylpyrrolidone, methyl- and ethylcellulose and hydroxypropylcellulose. Binders of both types may be added to the powder mix and the mixture wetted with water, alcohol-water mixtures, or a solvent, or the binder may be put into solution in the water or solvent and added to the powder. The latter method, using a solution of the binder, requires much less binding material to achieve the same hardness than if added dry. In come cases, it is not possible to get granules of sufficient hardness using the dry method. In practice, solutions of binders are usually used in tablet production. Reviews of binders and their effects are available [23,26,51,52]. A guide to the amount of binder solution required by 3000 g of filler is presented in Table 4.

A study on the addition of a plasticizer to the binder solution on the tableting properties of dicalcium phosphate, lactose, and paracetamol (acetaminophen) indicated that it improved the wet-massing properties of the granulation. Including a placticizer in the binder increased the tensile strength, raised the capping pressure, and reduced the friability of all the tablets. The plasticizers used in this study were propylene glycol, polyethylene glycol 400, glycerine, and hexylene glycol [53].

A list of commonly used binders is given in Table 5. These are treated in detail as discussed in the following paragraphs.

Table 4 Granulating Solution Required by 3000 g of Filler

Volume of granulating solution required (ml)	Filler			
	Sucrose	Lactose	Dextrose	Mannitol
10% Gelatin	200	290	500	560
50% Glucose	300	325	500	585
2% Methylcellulose (400 cps)	290	400	835	570
Water	300	400	660	750
10% Acacia	220	400	685	675
10% Starch paste	285	460	660	810
50% Alcohol	460	700	1000	1000
10% PVP[a] in water	260[b]	340[b]	470[b]	525[b]
10% PVP[a] in alcohol	780[b]	650[b]	825[b]	900[b]
10% Sorbitol in water	280[b]	440[b]	750[b]	655[b]

[a]Polyvinylpyrrolidone.

[b]Derived by the author, not from source noted below.

Source: Taken in part from the *Technical Bulletin*, Atlas Mannitol, ICI Americas, Wilmington, Delaware, 1969.

Starch in the form of starch paste has historically been, and remains, one of the most used binders. Aqueous pastes usually employed range from 5 to 10% in concentration. Starch paste is made by suspending starch in 1 to 1-1/2 parts cold water, then adding 2 to 4 times as much boiling water with constant stirring. The starch swells to make a translucent paste that can then be diluted with cold water to the desired concentration. Starch paste may also be prepared by suspending the starch in cold water and heating to boiling in a steam-jacketed kettle with constant stirring. Starch paste is a versatile binder yielding tablets that disintegrate rapidly (see Example 9) and in which the granulation is made using starch as an internal binder and granulated with water only.

An example of granulation made by massing with starch paste as an internal binder rather than an external binder when wetted with water only as in Example 9 is given in Example 10.

Pregelatinized starch is starch that has been cooked and dried. It can be used in place of starch paste and offers the advantage of being soluble in warm water without boiling. It can also be used as a binder by adding it dry to the powder mix and wetting with water to granulate as indicated in Example 9.

Starch 1500 is a versatile, multipurpose starch that is used as a dry binder, a wet binder, and a disintegrant. It contains a 20% maximum cold water-soluble fraction which makes it useful for wet granulation. It can be

Table 5 Binders Commonly Used in Wet Granulation

Binder	Usual concentration
Cornstarch, USP	5–10% Aqueous paste
Pregelatinized cornstarch	5–10% Aqueous solution
Starch 1500	5–10% Aqueous paste
Gelatin (various types)	2–10% Aqueous solution
Sucrose	10–85% Aqueous solution
Acacia	5–20% Aqueous solution
Polyvinylpyrrolidone	5–20% Aqueous, alcoholic, or hydroalcoholic solution
Methylcellulose (various viscosity grades)	2–10% Aqueous solution
Sodium carboxymethylcellulose (low-viscosity grade)	2–10% Aqueous solution
Ethylcellulose (various viscosity grades)	2–15% Alcoholic solution
Polyvinyl alcohol (various viscosity grades)	2–10% Aqueous or hydroalcoholic solution
Polyethylenene glycol 6000	10–30% Aqueous, alcoholic, or hydroalcoholic solution

Example 9: Aminophylline Tablets

Ingredients	Quantity per tablet (mg)	Quantity per 10,000 tablets (g)
Aminophylline	100	1.0
Tricalcium phosphate	50	0.5
Pregelatinized starch	15	0.15
Water	q.s.	q.s.
Talc	30	0.3
Mineral oil, light	2	0.02

Mix the aminophylline, tricalcium phosphate, and starch and moisten with water with constant mixing. Pass through a 12-mesh screen and dry at 110°F. Size the dry granulation through a 20-mesh screen; add the talc and mix in a suitable mixer for 8 min. Add the mineral oil, mix for 5 min, and compress with 5/16-in. standard concave punches.

Example 10: Pseudoephedrine Tablets

Ingredients	Quantity per tablet (mg)	Quantity per 10,000 tablets (kg)
Pseudoephedrine hydrochloride	60	0.6
Calcium sulfate, dihydrate	200	2.0
Citric acid, fine powder	5	0.05
Starch (as starch paste)	8	0.08
Sterotex (hydrogenated vegetable oil)	10	0.10
Alginic acid (disintegrant)	7	0.07
FD&C Yellow No. 6	0.005	(5 mg)

Mix the pseudoephedrine hydrochloride, citric acid, and calcium sulfate in an appropriate mixer for 15 min. Dissolve the FD&C Yellow No. 6 in the water used to make the starch paste, or dissolve the dye in a small quantity of water and add to the prepared paste. Add the starch paste sufficient to form a suitable wet mass and granulate through a 14-mesh screen. Dry at 120 to 130°F. Reduce the granules by passing through an 18-mesh screen, add the alginic acid, mix, and compress with 5/16-in. standard cup punches.

dry-blended with powder ingredients and granulated with ambient temperature water. The water-soluble fraction acts as an efficient binder, while the remaining fraction aids in the disintegration of the tablet. It also will not present overwetting problems as commonly experienced with pregelatinized starch.

Approximately 3 to 4 times as much starch is required to achieve the same tablet hardness as with starch paste.

Gelatin. If a still stronger binder is needed, a 2 to 10% gelatin solution may be used. Gelatin solutions should be made by first allowing the gelatin to hydrate in cold water for several hous or overnight, then heating the mixture to boiling. Gelatin solutions must be kept hot until they are used for they will gel on cooling. Although gelatin solutions have been extensively used in the past as a binder, they have been replaced to a large extent by various synthetic polymers, such as polyvinylpyrrolidone, methylcellulose, etc.

Gelatin solutions tend to produce hard tablets that require active disintegrants. The solutions are generally used for compounds that are difficult to bind. These solutions have another disadvantage in that they serve as culture media for bacteria and molds and, unless a preservative is added, they are quickly unfit to use.

Sucrose solutions are capable of forming hard granules. Some gradation of tablet hardness can be achieved by varying the concentration of sucrose from 20 to 85% depending on the strength of binding required.

In ferrous sulfate tablets, sucrose acts both as a binder and to protect the ferrous sulfate from oxidizing.

Example 11: Ferrous Sulfate Tablets

Ingredients	Quantity per tablet (mg)
Ferrous sulfate, dried	300
Corn starch	60
Sucrose as a 70% w/w syrup	q.s.
Explotab (sodium carboxymethyl starch)	45
Talc	30
Magnesium stearate	6

Mix the ferrous sulfate and the starch; moisten with the sugar solution to granulate through a 14-mesh screen. Dry in a tray oven overnight at 130 to 140°F. Size through an 18-mesh screen, add the Explotab, talc, and magnesium stearate, and compress to weight using 3/8-in. deep-cup punches. The reason for the deep-cup punches is that ferrous sulfate tablets need to be coated and tablets prepared with deep-cup punches lend themselves better to the coating process in that the edges at the perimeter are less obtuse than the standard punch tablets.

Sugar solutions are good carriers for soluble dyes, producing granulations and tablets of uniform color. Sugar syrups are used to granulate tribasic phosphate excipient, which usually requires a binder with greater cohesive properties than starch paste. Some other compounds for which sugar is indicated include aminophylline, acetophenetidin, acetaminophen, and meprobamate.

Acacia solutions have long been used in wet granulation, but now they have been largely replaced by more recently developed polymers such as polyvinylpyrrolidone and certain cellulose derivates. However, for drugs with a high dose and difficult to granulate, such as mephenesin, acacia is a suitable binder. It produces hard granules without an increase in hardness with time as is the case with gelatin. One disadvantage of acacia is that it is a natural product and is often highly contaminated with bacteria, making it objectionable for use in tablets. Tragacanth is another natural gum which, like acacia, has been used in 5 to 10% solutions as a binder. It does not produce granulations as hard as acacia solutions. Like acacia, it often has a high bacterial count. In the following formula, a soluble lubricant, polyethylene glycol 6000, is added to the acacia solution to assist both in tableting and in disintegration of the tablet (Example 12).

Polyvinylpyrrolidone has become a versatile polymeric binder. This compound, first developed as a plasma substitute in World War II, is inert and has the advantage of being soluble both in water and in alcohol. Although it is slightly hygroscopic, tablets prepared with it do not, as a rule, harden with age, which makes it a valuable binder for chewable tablets (Example

Example 12: Mephenesin Tablets

Ingredients	Quantity per tablet (mg)
Mephenesin	400
Acacia, 10% aqueous solution with 1% polyethylene glycol 6000	q.s.
Talc	8
Starch	20

Add sufficient acacia-polyethylene glycol 6000 solution to the mephenesin in a planetary or other suitable mixer to granulate; pass the wet mass through a 12-mesh screen and dry in an oven or other suitable dryer at 130 to 140°F. Force the dry granules through a 16-mesh screen, add the talc and the starch in a tumble mixer, mix for 10 to 15 min. and compress using 1/2-in flat-face, bevel edge punches.

13). Generally, it is better to granulate insoluble powders with aqueous or hydroalcoholic solutions of PVP and to granulate soluble powders with PVP in alcoholic solution. Effervescent tablets comprising a mixture of sodium bicarbonate and citric acid can be made by wet granulation using solutions of PVP in anhydrous ethanol since no acid-base reaction occurs in this anhydrous medium. Anhydrous ethanol should always be used in this granulation and not anhyrous isopropanol, since the latter leaves a trace of its odor in the tablets no matter how, or how long, the granulation has been dried. A concentration of 5% PVP in anhydrous ethanol produces a granulation of good compressibility of fine powders of sodium bicarbonate and citric acid, and makes the vigorous effervescence and rapid dissolution of the resulting tablets. Polyvinylpyrrolidone is also an excellent binder for chewable tablets, especially of the aluminum hydroxide–magnesium hydroxide type (Example 12). The inclusion of 2 to 3% of glycerine (based on the final weight of the tablet) tends to reduce hardening of these tablets with age. It is a versatile and excellent all-purpose binder used in approximately the same concentration as starch, but considerably more expensive.

Methylcellulose in aqueous solutions of 1 to 5%, depending on the viscosity grade, may be used to granulate both soluble and insoluble powders. A 5% solution produces granulations similar in hardness to 10% starch paste. It has the advantage of producing granulations that compress readily, producing tablets that generally do not harden with age. Methylcellulose is a better binder for soluble excipients such as lactose, mannitol, and other sugars. It offers considerable latitude in binding strength because of the range of viscosity grades available. Low-viscosity grades, 10 to 50 cps, allow for higher working concentrations of granulating agent than higher viscosity grades, such as the 1000 to 10,000 cps grades.

Example 13: Chewable Antacid Tablets

Ingredients	Quantity per tablet (mg)
Aluminum hydroxide, dried gel	200
Magnesium hydroxide, fine powder	200
Sugar, confectioners 10X	20
Mannitol, fine powder	180
Polyvinylpyrrolidone, 10% solution in 50% alcohol solution	q.s.*
Magnesium stearate	12
Cab-O-Sil M-5	4
Glycerine	8
Oil of peppermint	0.2

Mix the first four ingredients in a suitable mixer. Add the glycerine to the PVP solution and use to moisten the powder mix. Granulate by passing through a 14-mesh screen and dry at 140 to 150°F. Mix the oil of peppermint with the Cab-O-Sil and the magnesium stearate, mix, and size through a 20-mesh screen. Mix well and compress using 1/2-in. flat-face, bevel edge punches.
*10 milligrams of dry PVP may be added to the powder mix and granulated with 50% hydroalcoholic solution instead of the PVP solution. This, however, is about 3 times as much as is required when used in solution.

Sodium carboxymethylcellulose (sodium CMC) in concentrations of 5 to 15% may be used to granulate both soluble and insoluble powders. It produces softer granulations than PVP, and tablets have a greater tendency to harden. It is incompatible with magnesium, calcium, and aluminum salts, and this tends to limit its utility to some extent. Although producing softer granulations, these generally compress well. However, tablets have a relatively long disintegration time.

Ethylcellulose is insoluble in water and is used in alcohol solutions. Like methylcellulose, it is available in a range of viscosities, depending on the degree of substitution of the polymer. Low-viscosity grades are usually used in concentrations of 2 to 10% in ethanol. It may be used to granulate powders which do not readily form compressible granules, such as acetaminophen, caffeine, meprobamate, and ferrous fumarate (Example 14), and it offers a nonaqueous binder for medicaments that do not tolerate water (Example 15).

Polyvinyl alcohols are water-soluble polymers available in a range of viscosities. As granulating agents they resemble acacia but have the advantage of not being heavily laden with bacteria. They are film-formers and their granulations are softer than those made with acacia, yielding tablets that

Example 14: Ferrous Fumarate Tablets

Ingredients	Quantity per tablet (mg)
Ferrous fumarate, fine powder	300
Ethylcellulose 50 cps, 5% in ethanol	q.s. (approx. 10 mg)
Avicel	30
Stearowet*	10
Cab-O-Sil	5

Slowly add the ethylcellulose solution to the ferrous fumarate in a double-S arm mixer with constant mixing until sufficiently moist to granulate. Force through a 16-mesh screen and dry in a suitable dryer. Transfer the dry granulation to a tumble mixer, add the Stearowet and the Cab-O-Sil, mix, and compress using 3/8-in. standard cup punches.
*Stearowet is a mixture of calcium stearate and sodium lauryl sulfate. This combination of hydrophobic and a hydrophilic lubricant tends to decrease the disintegration time of the tablets.

disintegrate more readily and generally do not harden with age. Viscosities lending themselves to tablet granulation range from 10 to 100 cps.

Polyethylene glycol 6000 may serve as an anhdrous granulating agent where water or alcohol cannot be used. Polyethylene glycol 6000 is a white to light yellow unctuous solid melting at 70 to 75°C and solidifying at 56 to 63°C.

Example 15: Ascorbic Acid Tablets

Ingredient	Quantity per tablet (mg)
Ascorbic acid, 20-mesh granules	250
Ethylcellulose 50 cps, 10% in ethanol	q.s. (approx. 4 mg)
Explotab (sodium carboxymethyl starch)	15
Calcium silicate	10

In a rotating drum or coating pan add the ethylcellulose solution slowly to the ascorbic acid with rapid rotation of the drum. Dry with warm air directed into the rotating drum or pan equipped with an exhaust system to remove alcohol vapor. When dry, transfer to a tumble mixer, add the Explotab and the calcium silicate, mix, and compress with 13/32-in. punches.

Example 16: Polyethylene 6000 granulation

Ingredients	Quantity per tablet
Drug	q.s.
Filler, calcium sulfate dihydrate, or dicalcium phosphate, or lactose, or any other suitable filler	q.s.
Polyethylene glycol 6000 up to 30% of the above mixture*	
Explotab	q.s.
Magnesium stearate	q.s.
Aerosil 200	q.s.

Uniformly mix the drug with the filler and the polyethylene glycol 6000 and pass through a pulverizer using a no. 20 screen. Spread on trays and place in an oven at 75 to 80°C for 3 hr. Cool the heated mass to room temperature and screen through an 18-mesh screen, blend with the balance of the ingredients, and compress into tablets of proper weight.
*Because of variation of drug and filler, the amount of polyethylene glycol 6000 needs to be determined on an experimental basis for each formula.

A procedure for making tablets by this method has been given by Shah et al. [29] in which polyethylene glycol 6000 acts as the binding agent (Example 16).

Another method described by Rubenstein [32] carries out the granulation in a coating pan modified so that the pan contents can be heated to 60°C. The disintegrant is charged into the pan followed by 4% of polyethylene glycol 6000 in powder form. The heated pan is then rotated to melt the polyethylene glycol. The drug is then added and the whole mass is tumbled and heated for 5 min. The molten PEG 6000 acts as a binder covering the surface of the powders. After thoroughly mixing, the heat is discontinued and the mass allowed to cool to room temperature. During the cooling period, the PEG 6000 solidifies coating the powders to produce granules. The resulting granules are free flowing but require the addition of a glidant (0.2% Aerosil 200) for tableting. The granules are not self-lubricating and require the addition of a lubricant to permit tableting.

Sustained Release Applications

Binders as waterproofing agents having been used to obtain sustained or prolonged release dosage forms. By granulating or coating powders with relatively insoluble or slowly soluble binders (i.e. shellac, waxes, fatty acids and alcohols, esters and various synthetic polymers), tablets having delayed or prolonged release properties have been formulated. This application is discussed later in this chapter.

C. Lubricants

Lubricants are used in tablet formulations to ease the ejection of the tablet from the die, to prevent sticking of tablets to the punches, and to prevent excessive wear on punches and dies. They function by interposing a film of low shear strength at the interface between the tablet and the die wall and the punch face. Lubricants should be carefully selected for efficiency and for the properties of the tablet formulation.

Metal stearates because of their unctuouse nature and available small particle size, are probably the most efficient and commonly used lubricants. They are generally unreactive but are slightly alkaline (except zinc), and have the disadvantage of retarding tablet disintegration and dissolution because of their hydrophobic nature [59,63,64]. Of the metal stearates, magnesium is the most widely used. It also serves as a glidant and antiadherent. Butcher and Jones [59] showed that particle size, packing density, and frictional shear tests are necessary to evaluate the quality and suitability of commercially available stearates as lubricants.

Stearowet C, because of its surfactant component, is less likely to interfere with disintegration and dissolution. Sodium lauryl sulfate is an auxiliary lubricant as well as a surfactant.

In instances where lubrication is a problem, an internal and an external lubricant can be used in conjunction with each other as given in Example 17.

Allow the gelatin to soak in 70% of the water for several hous or overnight. Heat to 80°F, add the polyethylene glycol 6000, stir until dissolved, and cool slowly to 110 to 120°F. Add water, maintaining the temperature in the above range. The solution must be used at this temperature because it will gel on cooling.

Stearic acid is a less efficient lubricant than the metal stearates. It melts at 69 to 70°C, so that it does not melt under usual conditions of storage. It should not be used with alkaline salts of organic compounds such as sodium barbiturates, sodium saccharin, or sodium bicarbonate. With these compounds it has a tendency to form a gummy, sticky mass that causes sticking to the punches.

Numerous studies of lubricants indicate that there is no universal lubricant and that the formula, method of manufacture, and the formulators knowledge and experience determine the choice and amount used [56–60].

In selecting a lubricant, the following should be considered:

1. Lubricants markedly reduce the bonding properties of many excipients.
2. Overblending is one of the main causes of lubrication problems. Lubricants should be added last to the granulation and tumble-blended for not more than 10 min.
3. The optimum amount of lubricant must be determined for each formulation. Excess lubricant is no more effective but rather interferes with both disintegration and bioavailability by waterproofing the granules and tablet.
4. Lubricant efficiency is a function of particle size; therefore, the finest grade available should be used and screened through a 100 to 300-mesh screen before use.

Ragnarssen et al. [61] found that a short mixing time for magnesium stearate in excipient blends resulted in poor distribution of the lubricant but did not impair the lubricating efficiency in tablet compression.

Example 17: Analgesic-Decongestant Tablets

Ingredients	mg per tablet
Acetaminophen	325
Pseudoephedrine hydrochloride	30
Chlorpheniramine maleate	2
Sucrose	20
10% gelatin—5% polyethylene glycol 6000 aqueous solution*	q.s.
Microcrystalline cellulose	30
Starch 1500	15
Stearowet C	15
Cab-O-Sil (silica aerogel)	0.2

Mix the acetaminophen, pseudoephedrine hydrochloride, chlorpheniramine maleate, and sucrose, and granulate with the gelatin—polyethylene 6000 solution, passing the wet mass through a 12-mesh screen. Dry at 130 to 140°F and size through an 18-mesh screen. Add the Cab-O-Sil, Starch 1500, and microcrystalline cellulose in order and blend for 15 min. Finally, add the Sterowet C and blend for 3 min. Compress using 7/16-in. standard cup punches.

*Preparation of gelatin-polyethylene glycol 6000 solution.

Another study [62] found that prolonged mixing time tends to limit or reduce lubricant effectiveness and that glidants should be added first and intimately blended after which the lubricant is added and blended for a relatively short time.

Insufficient lubrication causes straining of the tablet press as it labors to eject the tablet from the die. This may cause a characteristic screeching sound and straining of the press parts involved. Another indication of insufficient lubrication is the presence of striations or scratch marks on the edges of the tablets.

Lubricants fall into two classes: water-insoluble and water-soluble. A listing of the hydrophobic and the soluble lubricants is given in Table 6.

Hydrogenated vegetable oils, commercially available as Sterotex and Duratex, are bleached, refined, and deodorized hydrogenated vegatable oils of food grade. They are usually available in spray-congealed form. While the particle size is not as small as may be desirable, the establishment of appropriate blending times with specific granulations can aid in the distribution on the granules through attrition of the lubricant powder. These have special application where alkaline metal stearates cannot be used, or where their metallic taste may be objectional as in tablets or lozenges to be dissolved in the mouth. Example 18 illustrates this use.

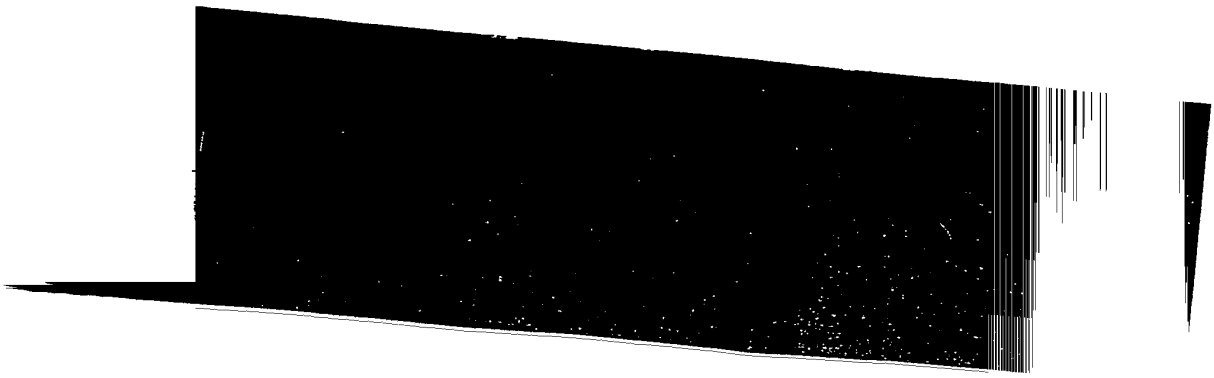


Table 6 Lubricants: Typical Amounts Used

Lubricants	Amount used in granulations (% w/w)
Hydrophobic	
Metal stearates, calcium, magnesium, zinc	0.5–2
Stearowet C: a water-wettable mixture of calcium stearate and sodium lauryl sulfate	0.5–2
Stearic acid, fine powder	1.0–3.0
Hydrogenated vegetable oils (Sterotex, Duratex)	1–3
Talc	5–10
Starch	5–10
Light mineral oil	1–3
Water-Soluble	
Sodium benzoate	2–5
Sodium chloride	5–20
Sodium and magnesium lauryl sulfate	1–3
Polyethylene glycol 4000 and 6000 (Carbowax 4000 and 6000), fine powder	2–5

High-Melting Waxes. Numerous food grade waxes are available, and while these are not generally used as lubricants, they offer possibilities for investigation. Waxes of both mineral sources (ceresin) and vegetable sources (carauba) offer possibilities as lubricants.

Talc acts as both lubricant and glidant. It is less efficient than the previously mentioned products and larger quantities are required for adequate lubrication. It has the disadvantage of retarding disintegration. Smaller quantities can be used in conjunction with other lubricants. It is essential that talc used in tableting be asbestos-free and, to this end, each lot should be accompanied by a certification from the supplier to this effect.

Starch is derived from a number of sources: corn, potatoe, rice, and tapioca. It may exist as dry granules, powder, swollen granules, in solution, and may be used as a filler, binder, disintegrant and film-former. It is available both as hydrophilic and hydrophobic corn starch.

Pharmaceutically cornstarch is the item of commerce most commonly used. Although there are much more efficient lubricants, starch because of its multiple properties is often included in formulations as an auxiliary lubricant because of its many applications in tablet making by the wet granulation method.

Mineral oil. Light mineral oil having a Saybolt viscosity of 50 to 60 SUS (approximately 8 centistokes) is a liquid lubricant with universal application because it is unreactive, odorless, tasteless, and can be easily sprayed onto

Example 18: Medicated Throat Lozenges

Ingredients	per tablet
Sucrose, fine powder (10X confectioners sugar	8.00
Acacia, fine powder	0.50
Citric acid, fine powder	15 mg
10% Gelatin solution	q.s.
Menthol	12 mg
Benzocaine	10 mg
Hexylresorcinol	2.4 mg
Hydrogenated vegetable oil (Sterotex, Duratex)	160 mg
Ethanol 95%	0.04 ml

Mix the sucrose, acacia, and citric acid and mass with the gelation solution. Granulate through an 8-mesh screen and dry at 130 to 140°F. Dissolve the methol, benzocaine, and the hexylresorcinol in the ethanol and distribute on the granulation in a twin-shell blender. Spread on trays in an oven and remove alcohol with forced air at ambient temperature. Transfer the granulation to a tumbel blender, add the hydrogenated vegetable oil, blend for 5 min, and compress with 3/4-in. flat-face, bevel edge punches.

granulations. It should be sprayed onto the formulation in a closed container, preferably in a twin-shell or double-cone blender equipped with a spray head or an intensifier bar. On compression, tablets lubricated with mineral oil often show mottling with oil spots on the surface of the tablet. This is more noticeable with colored tablets, especially dark colors. This mottling disappears after a day or two as the oil disperses in the tablet. One disadvantage of mineral oil as a lubricant is that the granulation, after the addition of the oil, must be compressed within 24 to 48 hr because the oil has a tendency to penetrate into the granules and thereby lose its effectiveness as a lubricant. Mineral oil is a largely neglected but excellent lubricant that greately reduces die wall friction and sticking to punches.

Sodium benzoate and sodium chloride have limited application in pharmaceuticals but find some use in household products. Sodium benzoate is essentially tasteless and can be used in tablets intended to be chewed or allowed to dissolve in the mouth.

Sodium and magnesium lauryl sulfate are water-soluble surfactants that can be used instead of the metal stearates to counteract their waterproofing properties as tablet lubricants. Studies indicate that granulations run on a rotary tablet press using both magnesium stearate and magnesium lauryl sulfate as lubricants, produced tablets having less variation in physical properties with the latter than with the former. It appears that magnesium lauryl sulfate is at least as efficient as magnesium stearate and has the advantage of reduced interference with dissolution [65,66].

Magnesium lauryl sulfate also has less taste than the sodium salt and is therefore better for chewable tablets.

Polyethylene glycol 4000 and 6000, also known as Carbowax 4000 and 5000, are water-soluble lubricants that find considerable use in tablet manufacture and in the formulation of chewable tablets. They are generally unreactive and can be used with sensitive ingredients such as aspirin, ascorbic acid, and other vitamins.

As with other lubricants, the smaller the particle size, the greater the distribution on granules, which makes for more efficient lubrication. Solid polyethylene glycols in very fine powder are not commercially available; however, they may be micronized if cooled to $-10°$ to $-20°C$.

Polyethylene glycol 6000 can be used in aqueous, alcoholic, or hydroalcoholic solution with various binders thereby obtaining a binder-lubricant combination that can be used in wet massing. Solutions may also be sprayed or atomized onto powders in a fluidized bed granulator or in a twin-shell or double-cone blender equipped with a vacuum takeoff to remove solvent thus applying both binder and lubricant.

Recently, two new additions to the field of lubricants have been proposed. These are sodium stearyl fumarate and glyceryl behenate [67]. Using magnesium stearate for comparison, these were added to granulations of lactose and salicylic acid and compressed with equivalent force on an instrumented tablet press. The new lubricants showed less effect on tablet strength and had a lesser effect on dissolution rate of the active ingredients than did magnesium stearate. Magnesium stearate and sodium stearyl fumarate were effective at 1 to 3% levels whereas glyceryl behenate required 3% for effective lubrication.

In tablet formulation, a lubricant often permits the resolution of several production problems that are related to compression. Lubrication facilitates glidancy of granules during material flow, eliminates binding in the die, and minimizes picking and sticking to punch-face surfaces on compression. Mixing time in the scale-up of tablet production is greatly influenced by the type of mixing equipment and by the batch size. Vigorous mixing shortens the time required for the distribution of the disintegrant and the batch size, due to the shear weight on the charge, influences the mixing time because of the increased flow of particles in tumble-, twin-shell, and double-cone-type mixers. The release characteristics and performance criteria of the final tablet (such as physical integrity and stability) depend on lubricant–excipient interaction and the manner in which these materials are affected by mixing.

D. Disintegrants

Disintegrant is the term applied to various agents added to tablet granulation for the purpose of causing the compressed tablet to break apart (disintegrate) when placed in an aqueous environment. Basically, the disintegrant's major function is to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet. The stronger the binder, the more effective must be the disintegrating agent in order for the tablet to release its medication. Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into the powder particles from which the granulation was prepared [68–71].

There are two methods used for incorporating disintegrating agents into tablets. These methods are called *external addition* and *internal addition*. In this, the disintegrant is added to the sized granulation with mixing just prior to compression. In the internal addition method, the disintegrant is mixed with other powders before wetting the powder mixture with the granulating solution. Thus, the disintegrant is incorporated within the granule. When this method is used, part of the disintegrant can be added internally and part externally. This provides immediate disruption of the tablet into the previously compressed granules while the disintegrating agent within the granules produces further erosion of the granules to the original powder particles. Although this latter is an attractive theory, it is only partially effective in practice because any disintegrating agent bound within the granules loses some of its disruptive force due to its encasement by the binder. Nevertheless, the two-step method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.

Disintegrants constitute a group of materials that, on contact with water, swell, hydrate, change in volume or form, or react chemically to produce a disruptive change in the tablet. This group includes various forms of starch, cellulose, algins, vegetable gums, clays, ion exchange reins, and acid-base combinations. A list of commonly used tablet disintegrants and the amounts usually used are given in Table 7.

Starch is the oldest and probably the most widely used disintegrant used by the pharmaceutical industry. Regular cornstarch USP, however, has certain limitations and has been replaced to some extent by modified starches with specialized characteristics to serve specific functions. Starch 1500 is a physically modified cornstarch that meets all the specifications of pregelatinized starch NF. It is somewhat unique in that it lends itself well

Table 7 Disintegrants: Typical Amounts Used

Disintegrant	Concentration in granulation (% w/w)
Starch USP	5–20
Starch 1500	5–15
Avicel PH 101, PH 102 (microcrystalline cellulose	5–15
Solka floc (purified wood cellulose)	5–10
Alginic acid	2–8
Explotab (sodium starch glycolate)	2–8
Guar gum	0.5–5
Polyclar AT (polyvinylpyrrolidone, crosslinked PVP)	0.5–5
Amberlite IPR 88 (ion exchange resin)	5–10
Methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose	

to conventional manufacturing techniques, especially to wet granulation. There are many classical theories that attempt to explain the mode of action of disintegrants, especially starches. One theory is that the disintegrant forms pathways throughout the tablet matrix that enable water to be drawn into the structure by capillary action, thus leading to disruption of the tablet. An equally popular concept relates to the swelling of starch grains on exposure to water, a phenomenon that physically ruptures the particle–particle bonding in the tablet matrix. Neither of these mechanisms explains the dramatic explosion that often takes place when tablets containing starch are exposed to water. Unique work carried out by Hess [72] would seem to suggest that on compression there is a significant distortion of the starch grains. On exposure to water, these grains attempt to recover their original shape, and in so doing release a certain amount of stress which, in effect, is responsible for the destruction of interparticulate hydrogen bonds and causes the tablet to be literally blown apart. Starch thus functions as the classical disintegrant. Starch 1500, by virtue of its manufacturing process, retains the disintegrant qualities of the parent cornstarch. These qualities make it a versatile disintegrating agent as both an internal and external disintegrant in tablet formulations (Example 19).

Avicel (microcrystalline cellulose) is a highly effective disintegrant. It has a fast wicking rate for water, hence, it and starch make an excellent combination for effective and rapid disintegration in tablet formulations. One drawback to its use is its tendency to develop static charges with increased moisture content, sometimes causing striation or separation in the granulation. This can be partially overcome by drying the cellulose to remove the moisture. When wet-granulated, dried, and compressed, it does not disintegrate as readily as when unwetted. It can be used with almost all drugs except those that are moisture-sensitive (such as aspirin, penicillin, and vitamins) unless it is dried to a moisture content of less than 1% and then handled in a dehumidified area.

Solka floc (purified wood cellulose) is a white, fibrous, inert, neutral material that can be used alone or in combination with starch as a disintegrating agent for aspirin, penicillin, and other drugs that are pH- and moisture-sensitive. Its fibrous nature endows it with good wicking properties and is more effective when used in combination with clays such as kaolin, bentonite, or Veegum. This combination is especially effective in tablet formulations possibly having a high moisture content (such as ammonium chloride, sodium salicylate, and vitamins).

Alginic acid is a polymer derived from seaweed comprising D-mannuronic and L-glucuronic units. Its affinity for water and high sorption capacity make it an excellent disintegrant. It is insoluble in water, slightly acid in reaction, and should be used only in acidic or neutral granulations. It can be used with aspirin and other analgesic drugs. If used with alkaline salts or salts of organic acids, it tends to form soluble or insoluble alginates that have gelling properties and delay disintegration. It can be successfully used with ascorbic acid, multivitamin formulations, and acid salts of organic bases.

Explotab (sodium starch glycolate) is a partially substituted carboxymethyl starch consisting of granules that absorb water rapidly and swell. The machanism by which this action takes place involves accelerated absorption of water leading to an enormous increase in volume of granules. This results in rapid and uniform tablet disintegration. Explotab is official in the N.F. XVI.

Example 19: Multivitamin Tablets

Ingredients	Per tablet
Vitamin A (coated)	5000 USP units
Vitamin D (coated)	400 USP units
Vitamin C (ascorbic acid, coated)	60 mg
Vitamin B_1 (thiamine mononitrate)	2 mg
Vitamin B_2 (riboflavin)	1.5 mg
Vitamin B_6 (pyridoxine hydrochloride)	1 mg
Vitamin B_{12} (cyanocobalamin)	2 μg
Calcium pantothenate	3 mg
Niacinamide	10 mg
Sodium saccharin	0.3 mg
Mannitol NF (fine powder)	350 mg
Starch 1500 (internal disintegrant)	65 mg
Magnesium stearate	10 mg
Talc	12 mg
Starch 1500 (external disintegrant)	40 mg
Flavor	q.s.

Blend the mannitol, saccharin, and internal Starch 1500 with 10% of the riboflavin and all the other vitamins except A, D, and C. Granulate this blend with water. Dry at 120°F, pass through a 16-mesh screen, and add the flavor. Mix the ascorbic acid with the magnesium stearate; mix the vitamins A and D with the remainder of the riboflavin. Add these and the talc and the external Starch 1500 to the previous mixture and mix well. Compress using 7/16-in., flat-face, bevel edge punches.

Guar gum is a naturally occurring gum that is marketed under the trade name Jaguar. It is a free-flowing, completely soluble, neutral polymer composed of sugar units and is approved for food use. It is available in various particle sizes and finds general use as a tablet disintegrant. It is not sensitive to pH, moisture content, or solubility of the tablet matrix. Although an excellent disintegrant, it has several drawbacks. It is not always pure white, and it sometimes varies in color from off-white to tan. It also tends to discolor with time in alkaline tablet.

Polyclar AT (Polyplasdone XL and Polyplasdone XL10) are crosslinked, insoluble homopolymers of vinylpyrrolidone. Polyplasdone XL ranges in particle size from 0 to 400 + μm, and Polyplasdone XL10 has a narrower range and smaller particle size (0 to 74 μm), which makes for better distribution and reduced mottling in tablet formulations. Tablet hardness

and abrasion resistance are less affected by the addition of Polyplasdone XL as compared to starches, cellulose, and pectin compounds [73]. A tendency toward tablet capping is reduced [74]. Polyplasdone XL disintegrants do not reduce tablet hardness and provide rapid disintegration and improved dissolution [75–77]. Polyplasdone, due to its high capillary activity, rapidly draws water into the tablet causing swelling which exceeds the tablet strength, reuslting in spontaneous tablet disintegration.

Amberlite IPR 88 (ion exchange resin) has the ability to swell in the presence of water thereby acting as a disintegrant. Care must be taken in the selection of a resin as a disintegrant since many resins have the ability to adsorb drugs upon them. Anionic and cationic resins have been used to absorb substances and release them when the charge changes.

Methyl cellulose, sodium carboxymethylcellulose, and hydroxypropylcellulose are disintegrants to some extent depending on their ability to swell on contact with water. Generally, these do not offer any advantage over more efficient products such as the starches and microcrystalline cellulose. However, in certain cases they may be of benefit when used in conjunction with the above.

E. Glidants

Glidants are materials that improve the flow characteristics of granulations by reducing interparticulate friction. They increase the flow of materials from larger to smaller apertures, from the hopper into the die cavities of the tablet press.

The effects produced by different glidants depend on (a) their chemical nature in relation to that of the powder or granule (i.e., the presence of unsaturated valences, ionic or hydrogen bonds on the respective surfaces that could interact chemically) and (b) the physical factors including particle size, shape, and distribution of the glidant and various other formulation components, moisture content, and temperature. In general, hydrophilic glidants tend to be more effective on hydrophilic powders, and the opposite is true for hydrophobic glidants. For any particular system there is usually an optimum concentration above which the glidant may start to act as a antiglidant [78]. This optimum depends, among other factors, on the moisture level in the granulation [79].

When fine particles of less than the optimum for flowability are added to a bulk powder of similar chemical constitution, there is often an improvement in the rate of flow through an orifice [80]. The improvement is dependent on the size and concentration of the fine particles; the smaller the particles, the lower the concentration required to produce an increased flow.

Some glidants commonly used and suggested concentrations for optimum glidant effect are shown in Table 8.

The silica-type glidants are the most efficient probably because of their small particle size. In one study [81], it was found that all silica-type glidants improved the flow properties of granulations as reflected in increased tablet weight and in decreased weight variation in the tablets. Chemically, the silica glidants are silicon dioxide. They are available as two types, both insoluble: (a) the pyrogenic silicas prepared by burning silicon tetrachloride in an atmosphere of oxygen and (b) the hydrogels, which are prepared by the precipitation of soluble silicates. The pyrogenic

Table 8 Commonly Used Glidants and Usual Concentration Range

Glidant	Percent
Silica aerogels	
Cab-O-Sil M-5	0.1–0.5
Aerosil 200	0.1–0.5
QUSO F-22	0.1–0.5
Calcium stearate	0.5–2.0
Magnesium stearate	0.2–2.0
Stearowet C*	0.2–2.0
Zinc stearate	0.2–1.0
Calcium silicate	0.5–2.0
Starch, dry flow	1.0–10.0
Starch 1500	1.0–10.0
Magnesium lauryl sulfate	0.2–2.0
Magnesium carbonate, heavy	1.0–3.0
Magnesium oxide, heavy	1.0–3.0
Talc	1.0–5.0

silicas are generally composed of smaller particles that tend to be more spherical in shape. Pyrogenic silicas are available in both hydrophilic and hydrophobic form [82]. The particle size of most commercially available silicas used as glidants range in size from 2 to 20 nm and have an enormous surface area averaging 200 to 300 $m^2 g^{-1}$.

There are no specific rules dictating the amount of any glidant required for a particular granulation. Glidants differ not only in chemical properties but also in physical characteristics such as size, frictional properties, structure, and density. For these reasons the amount of glidant varies with the material to which it is added. Since it is the purpose of the glidant to confer fluidity on the granulation, this property may be measured by one of several methods [83]. One method is the determination of the angle of repose [84,85]. When powdered material is allowed to fall freely from an orifice onto a flat surface, the material deposited forms a cone. The base angle of the cone is referred to as the angle of repose. By this method it has been found, for example, that the repose angle of a sulfathiazole granulation increases with decreasing particle size. Talc added in small quantities reduces the angle of repose, indicating greater flow, but tends to increase the repose angle at higher concentrations, thus becoming an antiglidant. The addition of fines causes a marked increase in the repose angle.

Another method of determining the effect of glidants on the flow properties of a granulation is that of allowing a given amount of granulation, with and without glidant, to flow through an orifice ranging in size from

3/8 to 1 in. in diameter depending on the size of the granules, and observing the efflux time. The glidant efficiency factor may then be determined as follows:

$$f = \frac{\text{rate of flow in presence of glidant}}{\text{rate of flow in absence of glidant}}$$

Since many materials used as glidants are also efficient lubricants, a reduction in interparticulate friction may also be encountered. This reduction can occur in two ways: (a) The fine material may adhere to the surface rugosity, minimizing the mechanical interlocking of the particles. (Rugosity refers to surface roughness or deviation of shape from spherical. The coefficient of rugosity is defined as the ratio of actual surface area, as determined by a suitable method, to the geometric surface area found by microscopy.) (b) Certain glidants, such as talc and silica aerogels, roll under shear stresses to produce a "ball bearing" effect or type of action, causing the granules to roll over one another.

Many powders acquire a static charge during handling, in mixing, or in an induced die feed. The addition of 1% or more of magnesium stearate or polyethylene glycol 4000 or 2% or more of talc effectively lowers the accumulated charge.

Magnesium oxide should be considered an auxiliary glidant to be used in combination with silica-type glidants, especially for granulations that tend to be hygroscopic or somewhat high in moisture content. Magnesium oxide binds water and keeps the granulation dry and free flowing.

That anomalies exist in the action of glidants has been pointed out [86] in some cases of the physical and mechanical properties of mixtures of lactose, paracetamol, and oxytetracycline when small amounts of silica glidants are added to them. Owing to the differing propensities to coat the particles of the host powders, the silica aerogels act as a glidant for lactose and paracetamol but as an antiglidant for oxytetracycline.

Selection of glidants must be determined by the formulator by trial and error since there is no way of predicting which will be effective in a specific granulation.

VI. MULTILAYER TABLETS

Multilayer tablets are tablets made by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

A. Advantages of Multilayer Tablets

1. Incompatible substances can be separated by formulating them in separate layers as a two-layer tablet or separating the two layers by a third layer of an inert substance as a barrier between the two.

2. Two layer tablets may be designed for sustained release—one layer for immediate release of the drug and the second layer for extended release, thus maintaining a prolonged blood level.
3. Layers may be colored differently to identify the product.

B. Layer Thickness

Layer thickness can be varied within reasonable proportions within the limitations of the tablet press. Thinness is dependent on the fineness of the granulation.

C. Sizes and Shapes

Size is limited by the capacity of the machine with the total thickness being the same as for a single-layer tablet. Many shapes other than round are possible and are limited only by the ingenuity of the die maker. However, deep concavities can cause distorition of the layers. Therefore, standard concave and flat-face beveled edge tooling make for the best appearance, especially when layers are of different colors.

D. Granulations

For good-quality tablets with sharp definition between the layers, special care must be taken as follows:

1. Dusty fines must be limited. Fines smaller than 100 mesh should be kept at a minimum.
2. Maximum granule size should be less than 16 mesh for a smooth, uniform scrape-off at the die.
3. Materials that smear, chalk, or coat on the die table must be avoided to obtain clean scrape-off and uncontaminated layers.
4. Low moisture is essential if incompatibles are used.
5. Weak granules that break down easily must be avoided. Excessive amounts of lubrication, especially metallic stearates, should be avoided for better adhesion of the layers.
6. Formulation of multilayer tablets is more demanding than that of single-layer tablets. For this reason, selection of additives is critical.

E. Tablet Layer Press

A tablet multilayer press is simply a tablet press that has been modified so that it has two die-filling and compression cycles for each revolution of the press. In short, each punch compresses twice, once for the first layer of a two-layer tablet and a second time for the second layer. Three-layer presses are equipped with three such compression cycles.

There are two types of layer presses presently in use—one in which each layer can be ejected from the press separately for the purpose of weight checking, and the second in which the first layer is compressed so hard that the second layer will not bond to it, or will bond so poorly that upon ejection the layers are easily separated for weighing. Once the

proper weight adjustments have been made by adjusting the die fill, the pressure is adjusted to the proper tablet hardness and bonding of the layers.

One hazard of layer tablet production is the lack of proper bonding of the layers. This can result in a lot of 100,000 tablets ending up as 200,000 layers after several days if the layers are not sufficiently bonded.

In a two-layer tablet press, two hoppers above the rotary die table feed granulated material to two separate feed frames without intermixing. Continuous, gentle circulation of the materials through the hoppers and feed frames assures uniform filling without segregation of particle sizes that would otherwise carry over to the second layer and affect layer weight, tablet hardness, and, in the case of differently colored granulations, the appearance of the tablet. The same procedure is followed in the three-layer press with three hoppers for the three granulations instead of two.

Certain single-layer or unit tablet presses are equipped with two precompression stations prior to the final compaction. This provides high-speed production by increasing dwell time of the material under pressure making for harder, denser tablets.

VIII. PROLONGED RELEASE TABLETS

Prolonged or sustained release tablets can be made by the wet granulation method using slightly soluble or insoluble substances in solution as binding agents or low-melting solids in molten form in which the drug may be incorporated. These include certain natural and synthetic polymers, wax matrices, hydrogenated oils, fatty acids and alcohols, esters of fatty acids, metallic soaps, and other acceptable materials that can be used to granulate, coat, entrap, or otherwise limit the solubility of a drug to achieve a prolonged or sustained release product.

Freely soluble drugs are more difficult to sustain than slightly soluble drugs because the sustaining principle is largely a waterproofing effect.

Ideally, the ultimate criterion for a sustained release tablet is to achieve a blood level of the drug comparable to that of a liquid product administered every 4 hr. To this end, prolonged release dosage forms are designed to release the drug so as to provide a drug level within the therapeutic range for 8 to 12 hr with a single dose rather than a dose every 4 hr (Fig. 13). They are intended as a convenience so that the patient needs to take only one dose morning and evening and need not get up in the night.

Prolonged drug forms are not without disadvantages. Since gastrointestinal tracts are not all uniform, certain individuals may release too much drug too soon and experience toxic or exaggerated response to the drug, whereas others may liberate the drug more slowly and not receive the proper benefit or response anticipated. This is especially true of older people whose gastrointestinal tract is less active than that of the younger. Also, where liberation is slow, there is danger of accumulation of the drug after several days resulting in high blood levels and a delayed exaggerated response.

Prolonged release products may be divided into two classes:

1. Prolonged release
2. Repeat action

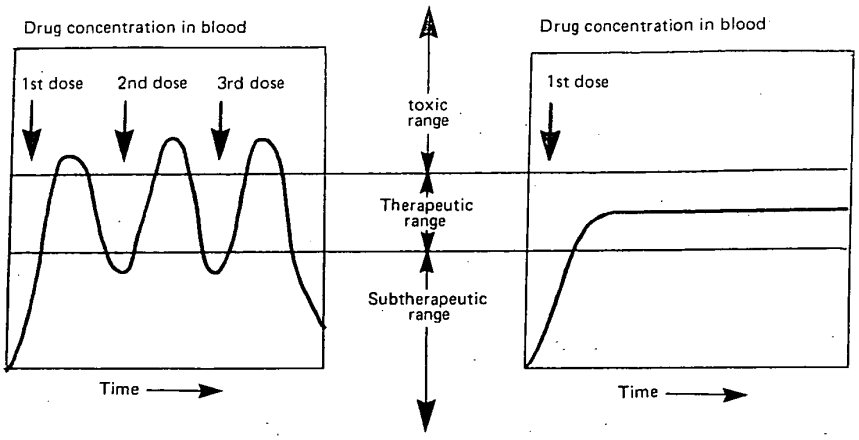


Figure 13 Conventional versus prolonged release dosage forms. (Left) repeated doses of conventional drug, and (right) single dose of ideal controlled release drug.

A prolonged (or sustained) release product is one in which the drug is initially made available to the body in an amount sufficient to produce the desired pharmacological response as rapidly as is consistent with the properties of the drug and which provides for the maintenance of activity at the initial level for a desired number of hours.

A repeat action preparation provides for a single usual dose of the drug and is so formulated to provide another single dose at some later time after administration. Repeat action, as defined here, is difficult to achieve and most products on the market today are of the sustained release type.

Many varied materials have been used in practice to achieve prolonged release dosage forms. The following example illustrates the ubiquitous nature shown in Example 20.

Prolonged release tablets must be tested for the rate of drug release by the prescribed in vitro laboratory method. Each product has an inherent release rate based on properly designed clinical trials of blood concentration and excretion in humans which is compared to the concentration and pharmacological activity resulting from the usual single-dose schedule of the drug administered in solution.

Once established, the in vitro testing based on the above is valuable for manufacturing control purposes to assure batch-to-batch uniformity of drug release.

Typical examples of release rates by laboratory tests are illustrated in Example 21.

Different drugs require different time release patterns depending on the half-life of the drug in the blood.

A prolonged release tablet containing two drugs in a single granulation has been patented in Example 22.

Some formulations are so constructed as to separate the ingredients into two formulations, one for immediate release and one for prolonged

Example 20: Ferrous Sulfate Prolonged Release Tablets

Ingredients	mg per tablet
Ferrous sulfate, anhydrous, fine powder	325
Lactose, fine powder	70
Methocel E 15LV	100
Ethylcellulose, 50 cps, 15% in 95% ethanol	35
Magnesium stearate, fine powder	15
Cab-O-Sil	2

Mix the ferrous sulfate and the lactose and granulate with the ethylcellulose solution and dry at 120 to 130°F. (It will be necessary to granulate several times to achieve 25 mg per tablet of ethylcellulose. The batch must be weighed after each addition until the proper weight is attained.)

In a twin-shell blender, add the Cab-O-Sil and blend for 5 min, next add the magnesium stearate and blend for 2 min. Compress with 13/32-in.-deep cup punches. Coat the tablets with cellulose acetate phthalate solution in alcohol and ethyl acetate.

release. The following formulation illustrates this by employing a two-layer tablet for the formulations.

Still another type is a tablet containing the prolonged release drug(s) in the core tablet and the immediate release dose in the coating as is illustrated by Example 24.

Prolonged release tablets have also been prepared by incorporating the drug in a granulation for immediate release and in another granulation for prolonged release, then mixing the two granulations and compressing as given in Example 24.

Example 21: Typical In Vitro Drug Release Rates

Time increment (hr)	Percent cumulative release	
	Product A	Product B
1	28	36
2	26	44
4	54	58
6	71	74
8	82	86

Example 22: Prolonged Release Hydrochlorothiazide with Probenecid Tablets [87]

Ingredients	mg per tablet
Hydrochlorothiazide	12.5
Probenecid	250.0
Lactose	100.0
Starch	20.0
Cellulose acetate phthalate (5% solution in acetone)	7.5
Starch	30.0
Magnesium stearate	5.0

Mix the hydrochlorothiazide, probenecid with the lactose and 20 mg of starch, granulate with the cellulose acetate phthalate solution; pass the wet mass through a 10-mesh screen. Dry at 120 to 130°F. Screen through a 20-mesh screen, incorporate the magnesium stearate and the remaining starch, and compress into tablets.

Example 23: Prolonged and Immediate Release Tablet Containing Pentaerythritol Tetranitrate Two-Layer Tablets

Ingredients	mg per layer
Immediate Release Layer	
Pentaerythritol tetranitrate	20
Phenobarbital	10
Calcium sulfate, dihydrate	140
Starch	50
Starch paste, 10%	q.s.
Magnesium stearate	12
Prolonged Release Layer	
Penterythritol tetranitrate	60
Phenobarbital	35
Lactose	30
Beeswax	180

Example 23 (Continued)

Ingredients	mg per layer
Prolonged Release Layer	
Acacia, powdered	30
Cab-O-Sil M-5	15

Procedure for immediate release layer: Mix the first four ingredients and granulate with the starch paste through a 12-mesh screen. Dry at 130 to 140°F and size the dry granulation through a 20-mesh screen, add the magnesium stearate, and blend for 3 min. Hold for compressing on the following layer.
Procedure for prolonged release layer: Melt the beeswax and add all of the ingredients except the Cab-O-Sil with constant stirring and heating to maintain the molten state. Allow to cool and granulate by passing the mass through an 18-mesh screen; blend in the Cab-O-Sil.
Compression: On a two-layer tablet press, first compress the immediate release layer with 7/16-in. flat-face, bevel edge punches; then compress the prolonged release layer on top of it. Check the tablets for layer bonding.

Example 24: Antihistamine Decongestant Prolonged Release Tablet

Ingredients	mg in core tablet	mg in coating
Brompheniramine maleate	8	4
Phenylpropanolamine hydrochloride	10	5
Calcium sulfate, dihydrate	160	–
Kaolin	30	–
Zein granulating solution*	q.s.	–
Zinc stearate	10	–

*Zein granulating solution is prepared as follows:

Zein G-200[a]	100 g
Propylene glycol	10 g

Example 24 (Continued)

Stearic acid	10 g
Ethyl alcohol, 90%	200 ml

Dissolve the stearic acid in the alcohol at 35 to 40°F, next add the propylene glycol and then the zein with constant agitation until all is in solution.

[a]Zein G-200 is a protein derived from corn. It is resinlike and is acceptable for food use. Zein resists microbial decomposition.
Granulating procedure for core tablet: Mix the three drugs with the calcium sulfate and the kaolin, and moisten with the zein granulating solution until evenly wetted. Granulate by passing through a 12-mesh screen and dry at 120 to 130°F. Pass the dry granulation through an 18-mesh screen, add the zinc stearate, and compress with 5/16-in.-deep cup punches.
Sugar coating: Dissolve the three drugs for immediate release in a solution of 810 g of sucrose, 80 g of acacia in 400 ml water, and apply as a sugar coating in a coating pan.

Example 25: Chloroprophenpyridamine Tablets [88]

Ingredients	Pounds
Prolonged release granulation—A	
Chloroprophenpyridamine maleate, 50 mesh	5.0
Terra alba, 60 mesh	45.0
Sucrose, 75% w/v aqueous solution	15.0
Cetyl alcohol	10.0
Stearic acid	5.0
Glyceryl trilaurate	20.0

The cetyl alcohol, stearic acid, and glyceryl trilaurate are melted together. The chloroprophenpyridamine maleate and terra alba are added to the melted mixture with stirring. After mixing, the mixture is cooled until congealed to a hard mass. The mass is ground and sieved through a 30-mesh screen. The sucrose syrup is added to the powder obtained and thoroughly mixed to mass the powder. The resulting product is ground through a 14-mesh screen. The granules thus formed are dried at 37°C and sieved through aa 18-mesh screen.

Example 25 (Continued)

Ingredients	Pounds
Immediate release granulation—B	
Chloroprophenpyridamine maleate, 60 mesh	5.0
Terra alba, 60 mesh	65.0
Dextrose, 40 mesh	20.0
Lactose, 60 mesh	4.0
Starch, 80 mesh	5.0
Gelatin, 13% aqueous solution	1.0

Mix the chloroprophenpyridamine maleate, terra alba, lactose, dextrose, and starch and mass with the gelatin solution. Granulate through a 14-mesh screen and dry at 40°C. Sieve the dried granules through an 18-mesh screen.

Mix equal quantities of the prolonged release granulation—A and immediate release granulation—B and compress into 200-mg tablets.

Example 26: Prednisolone Tablets [89]

Ingredients	mg per tablet
Prednisolone	5.0
Dicalcium phosphate	117.0
Aluminum hydroxide, dried gel	25.0
Sugar, as syrup	25.0
Magnesium stearate	3.4

Blend the first three ingredients and wet with 15 ml of syrup having a sugar concentration of 850 g/L. Screen through a 20-mesh screen to form granules and dry at 60°C for 12 hr. The dried material is then passed through a 20-mesh screen to form final granules. These granules are blended with the magnesium stearate and compressed into tablets. This formulation is claimed to have a disintegration time of 12 hr.

Drugs may also be prepared in prolonged release form by adsorbing on acceptable materials such as ionic synthetic resins, aluminum hydroxide, and various clays. The following example presents the use of aluminum hydroxide and an aqueous granulating liquid (Example 26).

Prolonged action drug tablets have also been prepared with drugs bound to ion exchange resins that permit slow displacement of the drug from the drug-resin complex when it comes into contact with the gastrointestinal fluids. The displacement reaction of drug-resin complex may be described by the following equation:

$$(R{-}SO_3{-}H_3N{-}R') - (X{-}Y) \longrightarrow (R{-}SO_3{-}Z) - (H_3N{-}R'Y)$$

where X is H or some other cation and Y is Cl or some other anion. The opposite of this would occur if an acidic drug were bound to an anion exchange resin with Cl or other anion causing drug displacement.

Preparation of drug–ion exchange complexes are described in several patents [89–93]. Drug in solution in excess or less than the amount required by stoichiometric considerations is exposed to a suitable resin displacing the cation or anion, as the case may be, for the resin. After washing with water, the resin is dried and is then incorporated into a tablet granulation.

VIII. MANUFACTURING PROBLEMS

Although tablet presses have become more complex over the years as a result of numerous modifications, the compaction of material in a die between upper and lower punches remains essentially the same. The main differences that have been made are increase in speed, mechanical feeding of the material from the hopper into the die, and electronic monitoring of the press. Precompression stations allow for the elimination of air from the granulation by partially compressing the tablet material prior to final pressing of the tablet. This makes for harder, firmer tablets with less tendency toward capping and lower friability. The number of tablets a press can produce is determined by the number of tooling stations and the rotational speed of the press. Large presses can produce as many as 10,000 tablets per minute. All these advancements and innovations, however, have not decreased the problems often encountered in production, and in fact have increased the problems because of the complexities of the presses and the greater demands of quality.

The production of faulty or imperfect tablets creates problems that range from annoying to serious. These are time consuming and costly. Imperfections may arise from causes inherent in the granulation to improper machine adjustment and/or tooling.

A. Binding

Binding in the die or difficult ejection is usually due to insufficient lubrication. It is the resistance of the tablet to ejection from the die. This can cause the tablet press to labor and squeak producing tablets with rough edges and vertical score marks on the edges. This may be overcome by,

1. Increasing lubrication
2. Using a more efficient lubricant
3. Improving the distribution of the lubricant by screening through an 30-mesh screen and mixing with a portion of fines screened from the granulation
4. Reducing the size of the granules
5. Increasing the moisture content of the granulation
6. Using tapered dies
7. Compressing at a lower temperature and/or humidity.

B. Sticking, Picking, and Filming

Sticking is usually due to improperly dried or lubricated granulation causing the tablet surface to stick to the punch faces. Contributing to this are tablet faces that are dull, scratched, or pitted. This condition usually becomes progressively worse.

Picking is a form of sticking in which a small portion of granulation sticks to the punch face and grows with each revolution of the press, picking out a cavity on the tablet face.

Filming is a slow form of picking and is largely due to excess moisture in the granulation, high humidity, high temperature, or loss of highly polished punch faces due to wear. These may be overcome by

1. Decreasing the moisture content of the granulation
2. Changing or decreasing the lubricant
3. Adding an adsorbent (i.e., silica aerogel, aluminum hydroxide, microcrystalline cellulose)
4. Polishing the punch faces
5. Cleaning and coating the punch faces with light mineral oil, low-viscosity dimethylpolysiloxane

C. Capping and Laminating

Capping occurs when the upper segment of the tablet separates from the main portion of the tablet and comes off as a cap. It is usually due to air entrapped in the granulation that is compressed in the die during the compression stroke and then expands when the pressure is released. This may be due to a large amount of fines in the granulation and/or the lack of sufficient clearance between the punch and the die wall. It is often due to new punches and dies that are tight fitting. Other causes may be too much or too little lubricant or excessive moisture.

Lamination is due to the same causes as capping except that the tablet splits and comes apart at the sides and is ejected in two parts. If tablets laminate only at certain stations, the tooling is usually the cause. The following should be tried to overcome capping and laminating:

1. Changing the granulation procedure
2. Increasing the binder
3. Adding dry binder such as pregelatinized starch, gum acacia, powdered sorbitol, PVP, hydrophilic silica, or powdered sugar
4. Increasing or changeing lubrication

5. Decreasing or changing lubrication
6. Using tapered dies
7. Decreasing the upper punch diameter by 0.0005 in. to 0.002 in. depending on the size

D. Chipping and Cracking

Chipping refers to tablets having pieces broken out or chipped, usually around the edges. This may be due to damaged tooling or an improperly set takeoff station. These problems are similar to those of capping and laminating, and are annoying and time consuming. Cracked tablets are usually cracked in the center of the top due to expansion of the tablet, which is different from capping. It may occur along with chipping and laminating and/or it may be due to binding and sticking. It often occurs where deep concave punches are used. These problems may be overcome by one or more of the following:

1. Polishing punch faces
2. Reducing fines
3. Reducing granule size
4. Replacing nicked or chipped punches
5. Adding dry binder such as pregelatinized starch, gum acacia, PVP, spray-dried corn syrup, powdered sugar, or finely powdered gelatin

Solving many of the manufacturing problems requires an intimate knowledge of granulation processing and tablet presses, and is acquired only through long study and experience.

The foregoing are just a few of the problems of tablet manufacture that are encountered in production by the pharmaceutical scientist, and as new technologies develop, new problems arise.

For decades wet granulations have been processed on a purely empirical basis, often on a small scale. If tablet compression ran smoothly, reproducibility of the granulation was unimportant. Today, however, high-speed presses, demanding specifications, GMP regulations, and validation requirements have given rise to the need for more and greater effort to assure uniformity and reproducibility of the granulation. Experience indicates that formulation and process variables greatly influence the performance characteristics of the final product. Recent developments in techniques utilizing various high-shear mixers, granulating by extrusion, spray drying, pan granulating, and fluid bed agglomeration have presented new areas of investigation. Fast-running, automated processes demand greater control through instrumental and computer monitoring for satisfactory scale-up from laboratory to production scale. It is to this end that more research needs to be directed.

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4

Compressed Tablets by Direct Compression

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I. INTRODUCTION AND HISTORY

Until the late 1950s the vast majority of tablets produced in the world were manufactured by a process requiring granulation of the powdered constituents prior to tableting. The primary purpose of the granulation step is to produce a free-flowing and compressible mixture of active ingredients and excipients. The availability of new excipients or new forms of old excipients, particularly fillers and binders, and the invention of new (or the modification of old) tablet machinery have allowed the production of tablets by the much simpler procedure of direct compression. However, in spite of its many obvious advantages, tableting by direct compression has not been universally adopted even in those cases where it would seem to be technically feasible and advantageous. The reasons for this can be understood only by reviewing the development of direct-compression technology and the decision-making steps involved in selecting one manufacturing process over another.

The term *direct compression* was long used to identify the compression of a single crystalline compound (usually inorganic salts with cubic crystal structures such as sodium chloride, sodium bromide, or potassium bromide) into a compact without the addition of other substances. Few chemicals possess the flow, cohesion, and lubricating properties under pressure to make such compacts possible. If and when compacts are formed, disintegration usually must take place by means of dissolution—which can take a considerable length of time, delaying drug release and possibly causing physiological problems such as have occurred in potassium chloride tablets.

Note: A glossary of direct-compression excipients, trade names, and supplies can be found on page 243.

Furthermore, the effective dose of most drugs is so small that this type of direct compression is not practical for most drug substances.

Pellets of potassium bromide are directly compressed for use in infrared spectrophotometry, and disks of pure drug have been directly compressed for the study of intrinsic dissolution rates of solids. However, there are few examples today of direct compression as classically defined in the literature.

The term direct compression is now used to define the process by which tablets are compressed directly from powder blends of the active ingredient and suitable excipients (including fillers, disintegrants, and lubricants), which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation procedures is necessary. Occasionally, potent drugs will be sprayed out of solution onto one of the excipients. However, if no granulation or agglomeration is involved, the final tableting process can still be correctly called direct compression. The first significant discussion of the concept of direct compression was presented by Milosovitch in 1962 [1].

Increasingly, there has been a trend toward integrating traditional wet granulation and direct-compression processes wherein triturations of potent drugs or preliminary minigranulations are added to direct-compression filler binders and then compressed. These techniques will be described later in the chapter.

The advent of direct compression was made possible by the commercial availability of directly compressible tablet vehicles that possess both fluidity and compressibility. The first such vehicle was spray-dried lactose, which, although it was subsequently shown to have shortcomings in terms of compressibility and color stability, initiated the "direct-compression revolution" [2]. Other direct-compression fillers were introduced commercially in the 1060s, including: Avicel (microcrystalline cellulose), the first effective dry binder/filler [2]; Starch 1500, a partially pregelatinized starch that possesses a higher degree of flowability and compressibility than plain starch while maintaining its disintegrant properties; Emcompress, a free-flowing compressible dicalcium phosphate; a number of direct-compression sugars such as Nutab, Di-Pac, and Emdex; and a variety of sorbitol and mannitol products. The relatively minimal compression properties of spray-dried lactose were improved by enhanced agglomeration of smaller crystals and the problems of browning due to impurities in the mother liquid were corrected. At the same time major advances were made in tablet compression machinery, such as improved positive die feeding and precompression stages that facilitate direct-compression tableting. By the beginning of the 1980s, the excipients and machinery had become available to make possible the direct compression of the vast majority of tablets being manufactured. It is important to understand why this has not occurred.

The simplicity of the direct-compression process is obvious. However, it is this apparent simplicity that has caused so many initial failures in changing formulations from wet granulation to direct compression. *Direct compression should not be conceived as a simplified modification of the granulation process for making tablets.* It requires a new and critical approach to the selection of raw materials, flow properties of powder blends, and effects of formulation variables on compressibility. During the wet granulation process the original properties of the raw materials are, to a great

extent, completely modified. As a result, a new raw material, the granulation, is what is finally subjected to compression. Many inadequacies in the raw materials are covered up during the granulation step. This is not true in direct compression and therefore the properties of each and every raw material and the process by which these materials are blended become extremely critical to the compression stage of tableting. If direct compression is approached as a unique manufacturing process requiring new approaches to excipient selection, blending, and compressibility, then there are few drugs that cannot be directly compressed. If this is not done, failures are very likely to be encountered.

II. ADVANTAGES AND DISADVANTAGES OF THE WET GRANULATION PROCESS

The process of wet granulation is historically embedded in the pharmaceutical industry. It produces in a single process (although many steps may be involved) the two primary requisites for making a reproducible tablet compact (i.e., fluidity and compressibility). The various methods of granulation as well as the steps involved in the process of granulation and the materials used are reviewed in an article by Record [4] and described extensively in Chapter 3 of this book.

The advantages of the wet granulation process are well established and the advent of high-shear mixers and fluidized bed granulation and drying equipment has made wet granulation a more efficient process today than it was a quarter of a century ago. The advantages include the fact that it (a) permits mechanical handling of powders without loss of mix quality; (b) improves the flow of powders by increasing particle size and sphericity; (c) increases and improves the uniformity of powder density; (d) improves cohesion during and after compaction; (e) reduces air entrapment; (f) reduces the level of dust and cross-contamination; (g) allows for the addition of a liquid phase to powders (wet process only); and (h) makes hydrophobic surfaces hydrophilic.

On the other hand, the granulation process is subject to a great many problems. Each unit process gives rise to its own specific complications. The more unit processes, the more chance for problems to occur. Granulation essentially involves the production of a new physical entity, the granule. It is therefore necessary to control and validate all the steps involved in making a new material (the granulation) and to assure that this final material is in fact reproducible.

In addition to blending, problems include (a) type, concentration, rate of addition, distribution, and massing time of the binder solution; (b) effects of temperature, time, and rate of drying on drug stability and distribution during the drying process; and (c) granule size and segregation during the dry screening and subsequent final granulation blending. Each of these factors often involves a considerable effort in regard to both process and equipment validation.

When taken as an aggregate, these problems can be imposing, and it is easy to see why direct compression has both a scientific and economic appeal. However, it certainly offers no panacea for the unwary or unthinking formulator.

III. THE DIRECT-COMPRESSION PROCESS

A. Advantages

The direct-compression process assumes that all materials can be purchased or manufactured to specifications that allow for simple blending and tableting.

The most obvious advantage of direct compression is economy. It is safe to say that there would be a relatively minor interest in the process of direct-compression tableting if economic savings were not possible. Savings can occur in a number of areas, including reduced processing time and thus reduced labor costs, fewer manufacturing steps and pieces of equipment, less process validation, and a lower consumption of power. Two unit processes are common to both wet granulation and direct-compression tableting: blending and compression. Prior micronization of the drug may be necessary in either process. Although a number of pieces of equipment, such as granulators and dryers, are not needed in preparing tablets by direct compression, there may be a need for greater sophistication in the blending and compression equipment. However, this is not always the case.

The most significant advantage in terms of tablet quality is that of processing without the need for moisture and heat which is inherent in most wet granulation procedures, and the avoidance of high compaction pressures involved in producing tablets by slugging or roll compaction. The unnecessary exposure of any drug to moisture and heat can never be justified; it cannot be beneficial and may certainly be detrimental. In addition to the primary problem of stability of the active ingredient, the variabilities encountered in the processing of a granulation can lead to innumerable tableting problems. The viscosity of the granulating solution—which is dependent on its temperature, and sometimes on how long it has been prepared—can affect the properties of the granules formed, as can the rate of addition. The granulating solution, the type and length of mixing, and the method and rate of wet and dry screening can change the density and particle size of the resulting granules, which can have a major effect on fill weight and compaction qualities. The drying cycles can lead not only to critical changes in equilibrium moisture content but also to unblending as soluble active ingredients migrate to the surfaces of the drying granules. There is no question that, when more unit processes are incorporated in production, the chances of batch-to-batch variation are compounded.

Probably one of the least recognized advantages of direct compression is the optimization of tablet disintegration, in which each primary drug particle is liberated from the tablet mass and is available for dissolution. The granulation process, wherein small drug particles with a large surface area are "glued" into larger agglomerates, is in direct opposition to the principle of increased surface area for rapid drug dissolution.

Disintegrating agents, such as starch, added prior to wet granulation are known to be less effective than those added just prior to compression. In direct compression all of the disintegrant is able to perform optimally, and when properly formulated, tablets made by direct compression should disintegrate rapidly to the primary particle state. However, it is important that sufficient disintegrant be used to separate each drug particle if ideal dissolution is to occur. One bioavailability advantage of making tablets by wet granulation has never been fully appreciated. The wetting of hydrophobic drug surfaces during the granulation step and the resulting film of

hydrophilic colloid that surrounds each drug particle can certainly speed up the dissolution process providing that each one of the primary drug particles can be liberated from the granule. Although this is not as likely to occur in a tablet made by direct compression as in one made by granulation, it is possible to add a wetting agent in the dry blend of powders to enhance dissolution rates. Prime particle disintegration in direct-compression tablets depends on the presence of sufficient disintegrating agent and its uniform distribution throughout the tablet matrix. High drug concentrations can lead to cohesive particle bonding during compression with no interjecting layer of binder or disintegrating agent.

Although it is not well documented in the literature, it would seem obvious that fewer chemical stability problems would be encountered in tablets prepared by direct compression as compared to those made by the wet granulation process. The primary cause of instability in tablets is moisture. Moisture plays a significant role not only in drug stability but in the compressibility characteristics of granulations. While some direct-compression excipients do contain apparently high levels of moisture, this moisture in most cases is tightly bound either as water of hydration (e.g., lactose monohydrate) or by hydrogen bonding (e.g., starch, microcrystalline cellulose) and is not available for chemical degradation. The role of moisture is discussed further under the description of individual excipients.

One other aspect of stability that warrants increasing attention is the effect of tablet aging on dissolution rates. Changes in dissolution profiles are less likely to occur in tablets made by direct compression than in those made from granulations. This is extremely important as the official compendium now requires dissolution specifications in most solid dosage form monographs.

B. Concerns

On the basis of the distinct advantages listed above, it is difficult to understand why more tablets are not made by the direct-compression process. To understand this fully, one must have an appreciation of not only the technology, but the economics and regulation of the pharmaceutical industry.

The technological limitations revolve mainly about the flow and bonding of particles to form a strong compact, and the speed at which this must be accomplished in an era of ever-increasing production rates.

With an increased emphasis on dissolution and bioavailability, many drugs are commonly micronized. Micronization invariably leads to increased interparticulate friction and decreased powder fluidity, and may also result in poor compressibility. Very often a decision has to be made as to whether to granulate a micronized powder—which may result in a longer dissolution time—or to directly compress a slightly larger particle size of the drug. In either case the decision should be based on in vivo blood studies as well as in vitro dissolution tests.

The choice of excipients is extremely critical in formulating direct-compression tablets. This is most true of the filler-binder, which often serves as the matrix around which revolves the success or failure of the formulation. Direct-compression filler-binders must possess both compressibility and fluidity. In most cases they are specialty items available from only one supplier and often cost more than comparable fillers used

in granulations. In addition, there is a need to set functionality specifications on properties such as compressibility and fluidity, as well as on the more traditional physical and chemical properties. These specifications must be rigidly adhered to in order to avoid lot-to-lot variations in raw materials, which can seriously interfere with tableting qualities. This is as true of the drug substance as it is of the excipients. The costs of raw materials and raw material testing are thus higher in direct compression. However, this increased cost is often more than offset by the economies described earlier.

Many active ingredients are not compressible in either their crystalline or their amorphous forms. Thus, in choosing a vehicle it is necessary to consider the dilution potential of the major filler-binder (i.e., the proportion of active ingredient that can be compressed into an acceptable compact utilizing that filler). Fillers-binders range from highly compressible materials such as microcrystalline cellulose to substances that have very low dilution capacity such as spray-dried lactose. It is not possible to give specific values for each filler because the dilution capacity depends on the properties of the drug itself. In some cases it is necessary to employ tablet presses with precompression capabilities in order to achieve an acceptable compact at a reasonable dilution ratio.

Outside of compressibility failures, the area of concern most often mentioned by formulators of direct-compression tablets is content uniformity. The granulation process does lock active ingredients into place and, provided the powders are intimately dispersed before granulation and no drying-initiated unblending occurs after wetting, this can be advantageous. Direct-compression blends are subject to unblending in postblending handling steps. The lack of moisture in the blends may give rise to static charges that can lead to unblending. Differences in particle size or density between drug and excipient particles may also lead to unblending in the hopper or feed frame of the tablet press.

The problems of unblending can be approached in either of two ways. The traditional approach involves trying to keep particle sizes or densities uniform. Ideally the vehicle itself (drug and/or filler binder) should incorporate a range of particle sizes corresponding as closely as possible to the particle size of the active ingredients. This range should be relatively narrow and should include a small percentage of both coarse and fine particles to ensure that voids between larger particles of drugs or filler excipients are filled by smaller sized particles. In such an approach, Avicel or Starch 1500 could be used to fill voids between larger excipient particles such as Emdex or Emcompress. The problem can also be solved by ordered blending which is discussed in detail later in the chapter.

One other technical disadvantage of direct compression related to blending is the limitation in coloring tablets prepared in this manner. There is no satisfactory method for obtaining tablets of a uniformly deep color. However, it is possible through the use of highly micropulverized lakes preblended or milled with fillers such as Starch 1500 or microcrystalline cellulose to obtain a wide variety of pastel shade tablets.

Lubrication of direct-compression powder blends is, if anything, more complicated than that of classical granulations. In general the problems associated with lubricating direct-compression blends revolve around both the type and amount needed to produce adequate lubrication and the softening effects that result from lubrication. It may be necessary to avoid

the alkaline stearate lubricants completely in some direct-compression formulations.

The most common approach to overcome the softening as well as hydrophobic effects of alkaline stearate lubricants is to substantially limit the length of time of lubricant blending often to as little as 2 to 5 min. In fact, it is probably advisable in all direct-compression blending not to include the lubricant during the majority of the blending period. Lubricants should never be added to direct-compression powder blends in a high-shear mixer. In addition, the initial particle size of the lubricant should be carefully controlled. Another approach is to abandon the alkaline stearate lubricant and use hydrogenated vegetable oils such as Sterotex, Lubritab, and Compritol. In such cases, higher concentrations are necessary than would be used to lubricate granulations of similar filler/drug mixtures with magnesium stearate.

Outside of the limitations imposed by vehicle and formulation, there are economic and regulatory considerations necessary in making a decision to convert present products or to develop new products utilizing direct-compression technology.

It is interesting to note that, except for spray-dried lactose, all direct-compression excipients were developed after the 1962 Kefauver–Harris amendmant to the Food, Drug and Cosmetic Act, which placed very strigent restrictions on dosage form as well as drug development. There is no question that this has led to a much more conservative approach to product development and formulation. Because of a 3- or 5-year or longer interval between formulation and marketing, many product development pharmacists hesitate to develop direct-compression formulations with unproven excipients. Of even greater uncertainty today is the physical specifications of the drug substance after its production has been scaled up to commercial proportions. In addition, there are increasing pressures to develop formulations that will be accepted internationally. In this respect, direct compression is much more widely used in the States than in Europe, although this situation is rapidly changing. Direct compression is more likely to be used by noninnovator companies because by the time patents have expired, the physical properties of the drug substance are more clearly defined.

Complicating this picture in the past was the sampling of experimental direct-compression excipients that were never marketed commercially or were subsequently withdrawn, leading to instability in the specialty excipient marketplace. Lot-to-lot variation in common direct-compression fillers commercially available today is rare. Of equal importance is the number of companies that have tried direct-compression formulations that failed when placed in full-scale production. In many cases this could be attributed to a failure to appreciate the complexities of the direct-compression technology, failure to set adequate specifications on raw materials, and failure of lot-to-lot reproducibility in the drug substances, particularly high-dose active ingredients.

In order to reduce the likelihood of raw material failure, it is advisable to set quality specifications on particle size, bulk density fluidity, and even compressibility. The latter can be easily done using a Carver press or single-punch machine under carefully prescribed conditions and determining the breaking strengths of resulting compacts.

The major advantages and concerns for the wet granulation and direct-compression processes are contrasted in Table 1.

Table 1 Comparison of Direct-Compression and Wet Granulation Processes for Making Tablets

Wet granulation	Direct Compression
Compressibility	
Harder tablets for poorly compressible substances	Potential problem for high-dose drugs
Fluidity	
Excellent in most cases	Many formulations may require a glidant Cannot micronize high-dose drugs
Particle Size	
Larger with greater range	Lower with narrower range
Content Uniformity	
Massing and drying induced	Segregation may occur in mass transport, hopper, and feed frame
Mixing	
High or low shear	Low shear with ordered blending
Lubricant	
Less sensitive to lubricant softening and overblending	Minimal blending with magnesium stearate
Disintegration	
Often problems with granules	Lower levels usually necessary
Dissolution	
1. Drug wetted during processing	1. No wetting, may need surface active agent
2. Drug dissolution from granules may be a problem	2. Dissolution may be slower if larger size drug crystals used
3. Generally slower than direct compression	3. Generally faster than wet granulation
Costs	
Increase in equipment, labor, time, process validation, energy	Increase in raw materials and their quality control

Table 1 (Continued)

Wet granulation	Direct compression
Flexibility of Formulation	
Granulation covers raw material flaws	Properties of raw materials must be carefully defined
Stability	
1. Problems with heat or moisture	1. No heat or moisture added
2. Dissolution rate may decrease with time	2. Dissolution rate rarely changes
Attitude of Equipment Suppliers	
Positive	Very negative
Tableting Speed	
May be faster	May require lower speed
Dust	
Less dusty	More dusty
Color	
Deep or pastel (dyes or lakes)	Pastel only (lakes only)

IV. DIRECT-COMPRESSION FILLER BINDERS

A. General Considerations

Direct-compression excipients, particularly filler-binders, are specialty excipients. In most cases they are common materials that have been modified in the chemical manufacturing process to impart to them greater fluidity and compressibility. The physical and chemical properties of these specialty products are extremely important if they are to perform optimally. It is most important for the direct-compression formulator to understand that there is no chance to cover up flaws in raw materials in direct compression as there is in the wet granulation process.

Many factors influence the choice of the optimum direct-compression filler to be used in a tablet formulation. These factors vary from primary properties of powders (particle size, shape, bulk density, solubility) to characteristics needed for making compacts (flowability and compressibility) to factors affecting stability (moisture), to cost, availability, and governmental acceptability. It is extremely important that raw material specifications be set up that reflect many of these properties if batch-to-batch

Table 2 Factors Influencing Choice of Direct-Compression Fillers

1. Compressibility[a]
   a. Alone
   b. Dilution factor or capacity
   c. Effect of lubricants, glidants, disintegrants
   d. Effect of reworking
2. Flowability[a]
   a. Alone
   b. In the finished formulation
   c. Need for glidant
3. Particle Size[a] and Distribution
   a. Effect on flowability
   b. Effect on compressibility
   c. Effect on blending
   d. Dust problems
4. Moisture Content and Type[a]
   a. Water of hydration (lactose, dextrose, dicalphosphate)
   b. Bound and free moisture
   c. Availability for chemical degradation
   d. Effect on compressibility
   e. Hydroscopicity
5. Bulk Density[a]
   a. Compression ratio = $\frac{\text{volume of tablet}}{\text{bulk volume of powder}}$
   b. Effect of handling and blending
6. Compatibility with Active Ingredient
   a. Moisture
   b. pH
   c. Effect on assay
7. Solubility (in GI Tract)
   a. Rate of dissolution
   b. Effect of pH
8. Stability of Finished Tablets
   a. Color
   b. Volume
   c. Hardness
9. Physiological Inertness
   a. Toxicity
   b. Reducing sugar
   c. Osmotic effect
   d. Taste and mouth-feel (if appropriate)
10. Cost and Availability
11. Governmental Acceptability
    a. United States and foreign countries
    b. Master File
    C. GRAS status
    d. Compendial standards (N.F.)

[a]Need to set purchase specifications for each lot of raw material.

manufacturing uniformity is to be assured. This is particularly true in the case of the filler-binders because they often make up the majority of the tablet weight and volume. However, this fact is still not fully appreciated by pharmaceutical formulators and production personnel. A list of factors involved in the choice of a filter-binder can be found in Table 2.

Most all of the classic tablet fillers have been modified in one way or another to provide fluidity and compressibility. In viewing the scanning electron photomicrographs of the various direct-compression filler-binders, one is taken with the fact that none of the products consist of individual crystals. Instead, all of them are actually minigranulations or agglomerations that have been formed in the manufacturing process by means of co-crystallization, spray drying, etc. The resulting material thus is able to deform plastically in much the same manner as the larger particle size granules formed during the traditional wet granulation process. The key to making any excipient or drug directly compressible thus becomes obvious and the possibility of making all tablets by direct compression appears to be within the scope of present technology.

B. Soluble Filler-Binders

Lactose

Spray-dried lactose is the earliest and still one of the most widely used direct-compression fillers. It is one of the few such excipients available from more than a single supplier. In spite of many early problems, this material revolutionized tableting technology.

Coarse and regular grade sieved crystalline fractions of α-lactose monohydrate have very good flow properties but lack compressibility. However spray drying produces an agglomerated product that is more fluid and compressible than regular lactose [1].

In the production of spray-dried lactose, lactose is first placed in an aqueous solution which is treated to remove impurities. Partial crystallization is then allowed to occur before spray-drying the slurry. As a result the final product contains a mixture of large α-monohydrate crystals and spherical aggregates of smaller crystals held together by glass or amorphous material. The fluidity of spray-dried lactose results from the large particle size and intermixing of spherical aggregates. The compressibility is due to the nature of the aggregates and the percentage of amorphous material present and the resulting plastic flow, which occurs under compaction pressure.

The problem of compressibility of spray-dried lactose is still real and troublesome. The compressibility of spray-dried lactose is borderline, and furthermore, it has relatively poor dilution potential. Spray-dried lactose is an effective direct-compression filler when it makes up the major portion of the tablet (more than 80%), but it is not effective in diluting high-dose drugs whose crystalline nature is, in and of itself, not compressible. Furthermore, spray-dried lactose does not lend itself to reworking because it loses compressibility upon initial compaction.

Spray-dried lactose has excellent fluidity, among the best for all direct-compression fillers. It contains approximately 5% moisture, but most of this consists of water of hydration. The free surface moisture is less than

0.5% and does not cause significant formulation problems. It is relatively nonhygroscopic.

Spray-dried lactose is available from a number of commercial sources in a number of forms [5]. Because the processing conditions used by different manufacturers may vary, all spray-dried lactoses do not necessarily have the same properties particularly in terms of degree of agglomeration, which influences both fluidity and compressibility. Alternative sources of supply should be validated, as is true of all direct-compression fillers.

When spray-dried lactose was first introduced, two major problems existed. The one that received the most attention was that of browning [2]. This browning was due to contaminants in the mother liquid, mainly 5-hydroxyfurfural, which was not removed before spraying. This browning reaction was accelerated in the presence of basic amine drugs and catalyzed by tartrate, citrate, and acetate ions [6]. Although the contaminants are now removed during the manufacturing process in most commercial products, the specter of browning still remains. However, at the present time, there appears to be no more danger of browning in spray-dried lactose than in any other form of lactose.

After many abortive attempts to improve on spray-dried lactose, a much more highly compressible product was introduced in the early 1970s [7]. This product, called Fast-Flo lactose, consists mainly of spherical aggregates of microcrystals. These microcrystals are lactose monohydrate, and they are held together by a higher concentration of glass than is present in regular spray-dried lactose. During the manufacturing process the microcrystals are never allowed to grow but are agglomerated into spheres by spray drying. Because it is much more compressible, it has replaced regular spray-direct lactose in many new direct-compression formulations.

Because of the spherical nature of the spray-dried aggregates, Fast-Flo lactose is highly fluid. It is nonhygroscopic and, as is the case with most spray-dried lactose, contaminants that could lead to browning are removed in the manufacturing process. Tablets made from Fast-Flo lactose are three to four times harder than those made from regular spray-dried lactose when compressed at the same compression force. An agglomerated form of lactose that is more compressible than spray-dried but less compressible than Fast-Flo lactose is marketed under the name Tabletose.

Anhydrous lactose is a free-flowing crystalline lactose with no water of hydration, first described in the literature in 1966 [8]. The most common form of anhydrous lactose is produced by crystallization above 93°C which produces the β form. This is carried out on steam-heated rollers, the resultant cake being dried, ground, and sieved to produce the desired size. It is available in a white crystalline form that has good flow properties and is directly compressible. Its compressibility profile (compression force versus hardness) is similar to that of Fast-Flo lactose. Anhydrous lactose can be reworked or milled with less loss of compactability than occurs with other forms of lactose. However, anhydrous lactose contains a relatively high amount of fines (15 to 50% passes through a 200-mesh screen), so that its fluidity is less than optimal. The use of a glidant such as Cab-O-Sil or Syloid is recommended if high concentrations are included in a formulation.

At high relative humidities anhydrous lactose will pick up moisture, forming the hydrated compound. This is often accompanied by an increase in the size of the tablets if the excipient makes up a large portion of the total tablet weight. At a temperature of 45°C and a relative humidity of 70%, plain anhydrous lactose tablets will increase in size by as much as 15% of

their original volume. Much has been made of the fact that anhydrous lactose contains less moisture than regular lactose and thus is a better filler for moisture-sensitive drugs. In fact, the surface moisture of the anhydrous and hydrous forms is about the same (0.5%) and the water of hydration does not play a significant role in the decomposition of active ingredients. Anhydrous lactose possesses excellent dissolution properties, certainly as good as, if not better than, α-lactose monohydrate.

Anhydrous lactose possesses excellent dissolution properties which is due in part to the fact that it is predominantly β-lactose. The intrinsic dissolution rate is considerably faster than α-lactose monohydrate. Lactose N.F., anhydrous, direct tableting, is available in the United States from Sheffield products while both high-β- and high-α-content anhydrous lactose are produced by DMV in Europe. Dehydration of the hydrous form must occur above 130°C in order to obtain stable anhydrous crystals needed for pharmaceutical use. A number of excellent articles on the various types of lactose and their tableting properties have been published by Lerk, Bolhuis, and coworkers [9–14].

Sucrose

Sucrose has been extensively used in tablets both as a filler, usually in the form of confectioners sugar, and in the form of a solution (syrup), as a binder in wet granulations. Attempts to directly compress sucrose crystals have never been successful, but various modified sucroses have been introduced into the direct-compression marketplace. One of the first such products was Di-Pac, which is a cocrystallization of 97% sucrose and 3% highly modified dextrins [15]. Each Di-Pac granule consists of hundreds of small sucrose crystals "glued" together by the dextrin. Di-Pac has good flow properties and needs a glidant only when atmospheric moisture levels are high (greater than 50% relative humidity). It has excellent color stability on aging, probably the best of all the sugars.

Di-Pac is a product that points out the need for setting meaningful specifications in purchasing raw materials for direct compression. The concentration of moisture is extremely critical in terms of product compressibility. Compressibility increases rapidly in a moisture range of 0.3 to 0.4%, plateaus at a level of 0.4 to 0.5%, and rises again rapidly up to 0.8% when the product begins to cake and lose fluidity [16]. The moisture-compressibility profile of Di-Pac is closely related to the development of monomolecular and multimolecular layers of moisture on both the internal and external surfaces of the sucrose granules—a process that increases hydrogen bonding on compression. The dilution potential of Di-Pac and most other sucroses is only average, ranging from 20 to 35% active ingredients.

While a moisture concentration of 0.4% is probably optimal for most pharmaceuticals, material of high moisture content is extremely advantageous when making troches or candy tablets. Interestingly, as moisture levels increase, lubricant requirements decrease. Tablets containing high concentrations of Di-Pac tend to harden slightly (1- to 2-kg units) during the first hours after compression, or when aged at high humidities and then dried. This is typical of most direct-compression sucroses or dextroses. Like all direct-compression sucroses, the primary target products are chewable tablets, particularly where artificial sweeteners are to be avoided. Both the process for making cocrystallized sucrose products and their properties are described in an article by Rizzuto et al. [17].

Nutab is a directly compressible sugar consisting of processed sucrose, 4% invert sugar (equimolecular mixture of levulose and dextrose), and 0.1 to 0.2% each of cornstarch and magnesium stearate [18]. The latter ingredients are production adjuncts in the granulation process by which the product is made and are not intended to interject any disintegrant or lubricant activity in a final tablet formulation. NuTab has a relatively large particle size distribution which makes for good fluidity but could cause blending problems if cofillers and drugs are not carefully controlled relative to particle size and amounts. In formulations NuTab has poor color stability relative to other direct-compression sucroses and lactoses.

Dextrose

One of the most dramatic modifications of natural raw materials for improving tableting characteristics is directly compressible dextrose marketed under the name Emdex [19]. This product is spray-crystallized and consists of 90 to 92% dextrose, 3 to 5% maltose, and the remainder higher glucose polysaccharides. It is available as both an anhydrous and a hydrous product (9% moisture). Reports indicate that the anhydrous form is slightly more compressible than the monohydrate; but the compressibility of both is excellent, being second only to microcrystalline cellulose when not diluted with drugs or other excipients. The most widely used product is the monhydrate and the water of hydration does not appear to affect drug stability. At approximately 75% relative humidity both forms of Emdex become quite hygroscopic, particularly if they have been milled or sheared on the surface of a die table. Above 80% relative humidity both products liquefy. Tablets produced from Emdex show an increase in hardness of approximately 2 kg at all levels of initial hardness up to 10 kg. The increase occurs in the first few hours after compression with no further significant hardening on long-term storage under ambient conditions. However, hardness increases do not result in significant changes in rates of dissolution.

Emdex possesses the largest particle size of all the common direct-compression excipients. Blending problems can occur if blends of other smaller particle size excipients are not used to fill in voids. This filler lends itself to ordered blending, where the micronized drug is first blended with the large particle size Emdex, before other excipients are added to the blender. The micronized drug becomes lodged in the pores on the surfaces of the large spheres and are apparently held in place with sufficient attractive force to prevent dislodging during subsequent blending operations.

Sorbitol

Sorbitol is one of the most complex of all direct-compression fillers. It is available from a number of suppliers in various direct-compression forms. However, sorbitol exists in a number of polymorphic crystalline forms as well as an amorphous form. Failure of many suppliers to fully appreciate the ramifications of these crystalline forms on both compressibility and stability has caused major problems among users. The less stable (α and β) polymorphic forms of sorbitol will convert to the more stable form (γ), which often results in dendritic growth (small, hairlike crystals). This causes a caking of particles and is accentuated by the presence of moisture. More stable products such as Sorbitol 834 and NeoSorb 60, consisting almost solely of the γ form, are now available and overcome most of the stability

problems. However, all γ-sorbitols are not crystallized in the same way and thus still have different compressibilities and lubricant requirements. At the present time interchange of one directly compressible form for another is not recommended without some validation of processing characteristics. The complexities of sorbitol and the modification of its crystalline structure to influence tableting properties are described by DuRoss [20], while an evaluation of ascorbic acid and gamma sorbitol tablets is presented by Guyot-Hermann and Leblanc [21].

Sorbitol is widely used as the sole ingredient in "sugar-free" mints and as a vehicle in chewable tablets. It forms a relatively hard compact, has a cool taste and good mouth-feel. However, it is hygroscopic and will clump in the feed frame and stick to the surfaces of the die table when tableted at humidities greater than 50%.

Lubricant requirements increase when the moisture content of the sorbitol drops below 0.5% or exceeds 2%.

Mannitol

Recently, there has been an increased interest in direct-compression mannitol. Mannitol does not make as hard a tablet as sorbitol but is less sensitive to humidity. Mannitol is widely used in the direct compression of reagent tablets in clinical test kits where rapid and complete solubility is required and can be lubricated sufficiently for this purpose using micronized polyethylene glycol 6000. One company has developed a highly specialized technique to produce beads of sensitive biological materials and mannitol or sorbitol for direct compression [22,23]. Its use as a filler in chewable tablets is limited by its cost, although its cool mouth feel is highly attractive. Mannitol also exists in a number of polymorphic forms and this phenomenon should be explored if a lot of mannitol behaves in a peculiar fashion. Debord et al. [24] tested four polymorphic forms of mannitol, two of which they obtained in pure state. Different forms were shown to have different compression characteristics.

Maltodextrin

A free-flowing agglomerated maltodextrin is available for direct-compression tableting under the name Maltrin. The product is highly compressible, completely soluble, and has very low hygroscopic characteristics.

C. Insoluble Filler-Binders

Starch

One of the most widely used tablet excipients starch, does not in its natural state possess the two properties necessary for making good compacts: compressibility and fluidity. There have been many attempts to modify starch to improve its binding and flow properties. The only modification of starch that has received widespread acceptance in direct compression is Starch 1500. Starch 1500 is more fluid than regular starch and meets the specifications for pregelatinized starch, N.F. Starch 1500 consists of intact starch grains and ruptured starch grains that have been partially hydrolyzed and subsequently agglomerated [25]. It has an extremely high moisture content (12 to 13%), but there is little indication that this moisture is readily available to accelerate the decomposition of moisture-sensitive drugs [26].

Although Starch 1500 will readily compress by itself, it does not form hard compacts. Its dilution potential is minimal, and it is not generally used as the filler-binder in direct compression, but as a direct-compression filler disintegrant. The major advantage of Starch 1500 is that it retains the disintegrant properties of starch without increasing the fluidity and compressibility of the total formulation, which is not the case with plain starch. Because Starch 1500, like all starches, deforms elastically when a compression force is applied, it imparts little strength to compacts. As few clean surfaces are formed during compaction, lubricants, particularly the alkaline stearate lubricants, tend to dramatically soften tablets containing high concentrations of Starch 1500, Lubricants such as stearic acid or hydrogenated vegetable oils are preferred in such formulations.

Cellulose

The first widespread use of cellulose in tableting occurred in the 1950s when a floc cellulose product, Solka-Floc, was introduced as a filler disintegrant. Solka-Floc consists of cellulose that has been separated from wood by digestion and formed into sheets that are mechanically processed to separate and break up individual fibers into small pieces. This converts the cellulose into a free-flowing powder. However, this material has poor fluidity and compressibility, and is not used as a direct-compression excipient.

The most important modification of cellulose for tableting was the isolation of the crystalline portions of the cellulose fiber chain. This product, microcrystalline cellulose (Avicel), was introduced as a direct-compression tableting agent in the early 1960s and stands today as the single most important tablet excipient developed in modern times [3]. Although it was developed with no though of tableting in mind, its properties are close to optimal. Microcrystalline cellulose is derived from a special grade of purified alpha wood cellulose by severe acid hydrolysis to remove the amorphous cellulose portions, yielding particles consisting of bundles of needlelike microcrystals. Microcrystalline cellulose for direct-compression tableting comes in a number of grades, the most widely used of which is PH 101, which was the original product, and PH 102, which is more agglomerated and possesses a larger particle size, resulting in slightly better fluidity but with no significant decrease in compressibility.

Microcrystalline cellulose is the most compressible of all the direct-compression fillers and has the highest dilution potential. This can be explained by the nature of the microcrystalline particles themselves, which are held together by hydrogen bonds in the same way that a paper sheet or an ice cube is bonded [27]. Hydrogen bonds between hydrogen groups on adjacent cellulose molecules account almost exclusively for the strength and cohesiveness of compacts. When compressed, the microcrystalline cellulose particles are deformed plastically due to the presence of slip planes and dislocations on a microscale, and the deformation of the spray-dried agglomerates on a macroscale. A strong compact is formed due to the extremely large number of clean surfaces brought in contact during the plastic deformation and the strength of the hydrogen bonds formed.

Other factors are important in the ability of a comparatively small amount of microcrystalline cellulose to bind other materials during compaction, the low bulk density of the microcrystalline cellulose, and the broad range of particle sizes. An excipient with a low bulk density will exhibit a high dilution potential on a weight basis, and the broad particle size

range provides optimum packing density and coverage of other excipient materials.

Microcrystalline cellulose has an extremely low coefficient of friction (both static and dynamic) and therefore has no lubricant requirements itself. However, when more than 20% of drugs or other excipients are added, lubrication is necessary. Because it is so compressible, microcrystalline cellulose generally withstands lubricant addition without significant softening effects. However, when high concentrations (greater than 0.75%) of the alkaline stearate lubricants are used, and blending time is long, the hardness of tablets compressed at equivalent compression forces is lower.

Because of cost and density considerations, microcrystalline cellulose is generally not used as the only filler in a direct-compression tablet but is more often found in concentrations of 10 to 25% as a filler-binder-disintegrant. Although it is not as effective a disintegrant as starch in equivalent concentrations, it can be used as the only disintegrant at levels of 20% or higher and has an additive effect with starch at lower levels. Hard compacts of microcrystalline cellulose disintegrate rapidly due to the rapid passage of water into the compact and the instantaneous rupture of hydrogen bonds. The fluidity of microcrystalline cellulose is poor compared to that of most other direct-compression fillers because of its relatively small particle size. However, comparisons with other direct-compression fillers *based on a weight per unit time flow through an orifice are misleading due to its inherently low-bulk density* [28]. A comparison of the relative volumetric and gravimetric flow rates of typical direct-compression fillers can be seen in Table 3. Small amounts of glidant are recommended in many formulations containing high concentrations of microcrystalline cellulose.

Tablets made from higher concentrations of microcrystalline cellulose soften on exposure to high humidities due to moisture pickup and loosening of interparticulate hydrogen bonds. This softening is often reversible when tablets are removed from the humid environment. Cycling of temperature and moisture over a period of time can cause both increases or decreases of equilibrium hardness, depending on the total formulation.

Because microcrystalline cellulose is highly compressible, self-lubricating, and a disintegrant, attempts have been made to use it as the only filler-binder in tablets containing drugs with low doses. It has been found that formulations containing more than 80% microcrystalline cellulose may slow the dissolution rates of active ingredients having low water solubility. Apparently, the small particles get physically trapped between the deformed microcrystalline cellulose particles, which delays wetting and dissolution. This phenomenon can be easily overcome by adding portions of water-soluble direct-compression excipients such as Fast-Flo lactose.

During the middle 1980s, a number of cellulose products were introduced into the marketplace to compete with Avicel. These products represent a continuum from floc to crystalline celluloses, some of which meet N.F. specifications for microcrystalline cellulose (i.e., Emcocel). Personen and Paronen [29] compared the crystallinity, particle size, densities, flow, and binding properties of Emcocel and Avicel PH 101.

However, the most complete comparative evaluation of microcrystalline cellulose products was conducted by Doelker et al. [30]. They studied the tableting characteristics of N.F. grade microcrystalline celluloses produced by seven manufacturers. The powders were examined for moisture content, particle size, densities, flow, and tableting properties (on an instrumented press) by measuring diametral crushing force of the compacts.

Table 3 Volumetric and Gravimetric Comparative Flow Rates of Selected Direct-Compression Fillers

Filler-binder	Poured bulk density ($g\ cm^{-3}$)	Gravimetric flow rate ($kg\ min^{-1}$)	Volumetric flow rate based on poured bulk density ($L\ in.^{-1}$)
Microcrystalline cellulose[a]	0.314	1.300	4.140
Powdered cellulose[b]	0.531	1.499	2.823
Pregelatinized starch[c]	0.589	1.200	2.037
Hydrous lactose[d]	0.650	2.200	3.385
Compressible sugar[e]	0.694	3.747	5.399
Dibasic calcium phosphate[f]	0.933	4.300	4.609

[a]Avicel PH-102, FMC Corp., Philadelphia, Pennsylvania.

[b]Elcema G-250, Degussa Corp., Teterboro, New Jersey.

[c]Starch 1500, Colorcon, Inc., West Point, Pennsylvania.

[d]Fast-Flo, Foremost Whey Products, Barzboo, Wisconsin.

[e]Di-Pac, Amstar Corp., New York, New York.

[f]Di-Tab, Stauffer Chemical Co., Westport, Connecticut.

Source: From *Pharm. Tech.*, *7*(9), 94 (1983).

Great differences in packing and tableting properties and in sensitivity to the addition of a lubricant were generally observed between products from various manufacturers. In contrast, lot-to-lot variability was quite acceptable. Using an empirical scale, the authors rated the various products and found Avicel and Emcocel to overall outperform other products. However, the functionality of microcrystalline cellulose depends as much on physical form as it does on crystalline content. Equivalence of microcrystalline products varies with desired functionality and substitutions of one product for another must be validated. Often less compressible microcrystalline cellulose can be substituted for Avicel with acceptable results because products may have been overly formulated with microcrystalline cellulose to begin with.

It should be remembered that the effectiveness of microcrystalline cellulose as a binder decreases as moisture is added to it in processing. Thus microcrystalline cellulose is effective as a binder in direct compression, slugging, roller compaction, or when added to a granulation in the free-flowing mix directly before compression. Its binding advantages in granulation decrease with an increase in water addition.

Another form of cellulose advocated for direct compression is microfine cellulose, (Elcema). This material is a mechanically produced cellulose powder which also comes in a granular grade (G-250), which is the only form that possesses sufficient fluidity to be used in direct compression. Microfine cellulose is a compressible, self-disintegrating, antiadherent form of cellulose that can be made into hard compacts. However, unlike microcrystalline cellulose, it possesses poor dilution potential, losing its compressibility rapidly in the presence of noncompressible drugs. It is not a particularly effective dry binder due to the large particle size of the G-250 granules and the resistance to fracture under compression. Microfine cellulose forms few fresh or clean surfaces during compression because of the lack of slip planes and dislocations in the cellulose granules. Thus little interparticulate binding occurs, and sufaces "contaminated" by lubricant during mixing show little inclination to form firm compacts.

Inorganic Calcium Salts

The most widely used inorganic direct-compression filler is unmilled dicalcium phosphate, which consists of free-flowing aggregates of small microcrystals that shatter upon compaction. This material is available in a tableting grade under the names Emcompress or DiTab. Dicalcium phosphate is relatively inexpensive and possesses a high degree of physical and chemical stability. It is nonhygroscopic at a relative humidity of up to 80%. Dicalcium phosphate in its directly compressible form exists as a dihydrate. Although this hydrate is stable at room and body temperature, it will begin to lose small amounts of moisture when exposed to temperatures of 40 to 60°C [31]. This loss is more likely to occur in a humid environment than a dry environment. This anomaly is theorized to occur because at low humidities and high temperatures, the outer surfaces of the particles lose water of hydration and become case-hardened, preventing further loss. In a humid environment the loss continues to occur. When combined with a highly hygroscopic filler like microcrystalline cellulose, the loss of moisture may be sufficient to cause a softening of the tablet matrix due to weakening of the interparticulate bonds and to accelerate decomposition of moisture-sensitive drugs like vitamin A.

The fluidity of dicalcium phosphate is good, and glidants are generally not necessary. While it is not as compressible as microcrystalline cellulose and some sugars (Fast-Flo lactose, Emdex), it is more compressible than spray-dried lactose and compressible starch. It apparently deforms by brittle fracture when compressed, forming clean bonding surfaces. Lubricants exert little softening effect on compacts.

Because it is relatively water-insoluble, tablets containing 50% or more of dicalcium phosphate disintegrate rapidly. Dicalcium phosphate does dissolve in an acidic medium, but it is practically insoluble in a neutral or alkaline medium. Therefore, it is not recommended for use in high concentrations in combination with drugs of low water solubility. This is of particular concern in formulating tablets that may be used in geriatric patients where the incidence of achlorhydria is significant.

Dicalcium phosphate dihydrate is slightly alkaline with a pH of 7.0 to 7.3, which precludes its use with active ingredients that are sensitive to even minimal amounts of alkalinity. Tricalcium phosphate (TriTab) is less compressible and less soluble than dicalcium phosphate but contains a higher ratio of calcium ions [32]. Calcium sulfate, dihydrate N.F., is also available in direct-compression forms [Delaflo, Compactrol].

Cel-O-Cal is the first significant direct-compression tablet filler specifically designed to combine the advantages of dissimilar materials by the method of coprocessing. It consists of 30 parts of microcrystalline cellulose and 70 parts of anhydrous calcium sulfate coprocessed in a spray dryer. It combines the compressibility and disintegrant advantages of microcrystalline cellulose with the cost advantages of calcium sulfate. The product is significantly more compressible than a physical mixture of its component parts and produces tablets of much lower friability. It is also less subject to lubricant softening effects due to its larger particle size. Because Cel-O-Cal is composed of two substances that are not water-soluble, care should be taken in using it in formulation of drugs with low water solubility particularly if the product is to be wet-granulated.

Calcium Carbonate

Calcium carbonate has been used in the past as a tablet filler even though it does have a significant pharmacological effect (antacid). It is available from a number of suppliers in directly compressible forms. There has been a renewed interest in calcium carbonate in the United States because of its use as a nutritional supplement in the prophylaxis of osteoporosis. Although its effectiveness for this condition has been questioned, numerous calcium supplements, including combinations with vitamin D and multivitamins are being marketed. Calcium carbonate is available in a number of forms including precipitated, ground oyster shells and mined limestone. There is no evidence that any one of these sources provides a nutritionally superior product and all have similar dissolution profiles. They do differ in terms of degree of whiteness, particle size, and impurities. Calcium carbonate has been coprocessed with various binders to make it directly compressible. The solubility of calcium carbonate does depend on pH. The effectiveness of calcium carbonate as a source of calcium in achlorhydric patients has been questioned.

On the other hand, calcium carbonate is much more soluble than either dicalcium phosphate, tricalcium phosphate, or calcium sulfate. The use of these other substances even in normal patients would appear to be even less justified.

A glossary of direct compression excipients, trade names, and suppliers can be found at the end of the chapter.

V. FACTORS IN FORMULATION DEVELOPMENT

More than in any other type of tablets, successful formulations of direct-compression tablets depend on careful consideration of excipient properties and optimization of the compressibility, fluidity, and lubricability of powder blends. The importance of standardizing the functional properties of the component raw materials and the blending parameters cannot be overstressed. Preformulation studies are essential in direct-compression tableting even for what would appear to be a simple formulation.

A. Compressibility

Formulation should be directed at optimizing tablet hardness without applying excessive compression force while at the same time assuring rapid tablet

disintegration and drug dissolution. In those cases where the drug makes up a relatively minor proportion of the tablet, this is usually no problem, and concern revolves around homogeneous drug distribution and content uniformity. Often much simpler excipient systems can be utilized, and factors such as relative excipient costs become more important. In those cases where the drug makes up the greater part of the final tablet weight, the functional properties of the active ingredient and the type and concentration of the excipient dominate the problem. Often the decision resolves about the question of what is the least amount of excipient necessary to form an acceptable and physically stable compact. In regard to the active ingredient it is important to determine the effect of particle size on compressibility as well as the effect of crystalline form (crystalline or amorphous) on compressibility. It may be necessary to granulate the active ingredient by slugging to improve compressibility and increase density.

The most effective dry binder is microcrystalline cellulose. It can add significant hardness to compacts at levels as low as 3 to 5%. It should always be considered first if the major problem in the formulation is tablet hardness or friability. It has been used at levels as high as 65% to bind active ingredients with extremely poor compressibility characteristics. No other direct-compression excipient acts as well as a dry binder in low concentrations. The compressibilities of varying fillers have been discussed as they relate to individual substances. Most disintegrating agents (such as starch) or glidants have negative effects on compressibility, although compressible starch is better than plain cornstarch.

A comparison of the relative compressibilities of various direct-compression fillers using magnesium stearate and stearic acid as lubricants is presented in Figures 1 and 2. As can be seen, microcrystalline cellulose is by far the most compressible of the substances tested. Magnesium stearate causes a softening of compacts to the point that Starch 1500 cannot be tableted. However, the relative compressibility of the fillers remains constant.

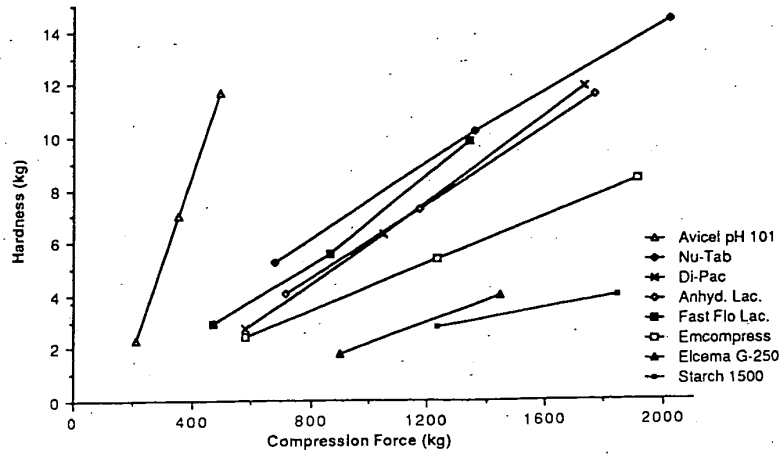

Figure 1 Excipient compressibility with 2% stearic acid as lubricant.

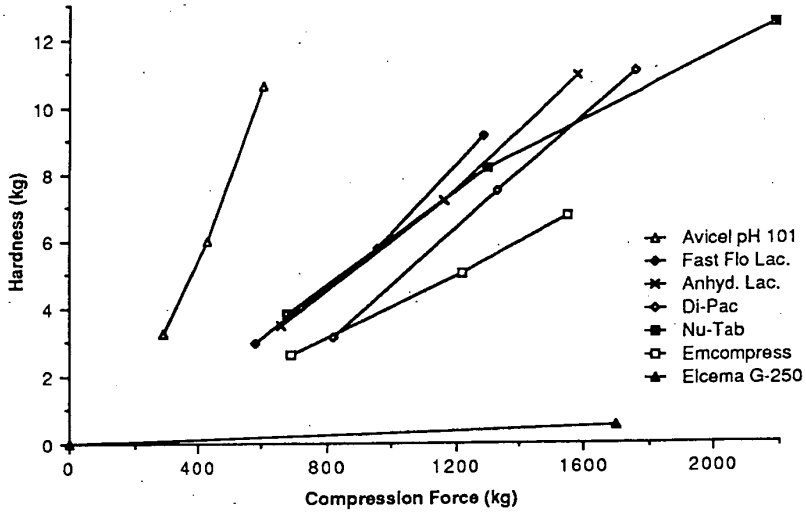

Figure 2 Excipient compressibility with 0.75% magnesium stearate as lubricant.

It is possible to compare the relative compressibility of a variety of direct-compression lactoses in a similar manner (Fig. 3). As can be seen, there can be as great as a twofold difference in the compressibility of two different forms at equivalent compression forces.

It might be expected that compressibility properties would be additive (i.e., that a mixture of microcrystalline cellulose and spray-dried lactose would have a compressibility profile of some proportionate value between those of the individual ingredients). For instance, Lerk et al. [33] showed an additive effect between most lactose fillers when they were combined with other lactoses or microcrystalline cellulose. However, an antagonistic behavior was demonstrated by blends of fast-dissolving vehicles such as dextrose or sucrose with cellulose or starch products. For instance, almost all combinations of microcrystalline cellulose and compressible dextrose gave poorer compressibility profiles and longer disintegration times than either ingredient alone. Bavitz and Schwartz [34] showed essentially additive effects in hardness when blending fillers, but their work did not include either sucrose or dextrose.

Almost all disintegrating agents retard compressibility as well as fluidity due to particle size. In order to have optimal disintegration into primary particles, it is desirable to have the particle size of the disintegrating agent as small as possible, preferably smaller than that of the active ingredient. This is not always possible.

One of the major advances in the development of direct-compression technology and its adoption by industry has been the introduction of the "superdisintegrants." These agents, which include Croscarmellose N.F. (AcDiSol), Crospovidone N.F. (Polyplasdone XL), and sodium starch glycolate N.F. (Explotab and Primogel), allow for faster disintegration of tablets, and lower use levels, therefore minimizing the softening effect

and fluidity problems encountered when high levels of starch are used. Fortunately, direct-compression formulations generally do not require as high a disintegrant concentration as wet granulation because the problem of intragranular disintegration does not exist.

As direct-compression blends may not possess ideal compressibility, operational problems may be reduced by the use of one or two precompression stages or use of large compression rolls.

It is generally concluded that direct-compression formulations are less compressible than wet granulation formulations. Obviously, this depends to a great extent on the materials used. However, when direct-compression and wet-granulated formulations of norfloxacin were compared in a recent publication, it was found that the direct-compression formulation was superior not only in terms of disintegration and dissolution, but was also more compressible [35].

B. Fluidity

The fluidity of tablet blends is important not only from the direct effect on uniformity of die fill and thus uniformity of tablet weight, but also from the role it plays in blending and powder homogeneity. Because of the overall smaller particle size encountered in direct-compression blends, fluidity is a much more serious problem than in the case of granulations. A comparison of the bulk densities and particle size of some of the most common direct-compression fillers can be found in Table 4.

It is important that fludity specifications be placed on all active ingredients and fillers that make up more than 5% of a final tablet formulation. Fluidity of active ingredients becomes a factor when the drug has been micronized to improve dissolution rate or provide more key particles of

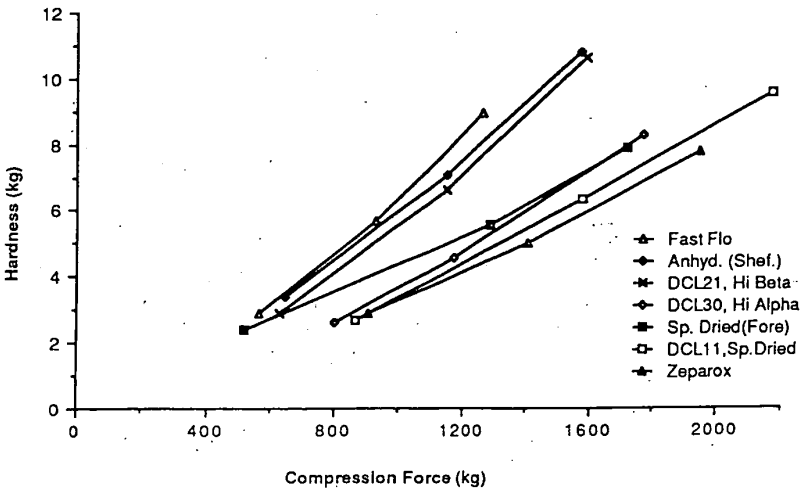

Figure 3 Compressibility profiles of different directly compressible lactoses.

Table 4 Physical Specifications of Direct-Compression Fillers

Filler	Moisture (%)	Bulk density (loose) (g ml^{-1})	Particle size[b]
Spray-dried lactose Foremost	5.0[a]	0.68	100% through 30 30–60% on 140 15–50% through 200
Fast-Flo lactose	5.0[a]	0.70	0.5–1.5% on 60 25–65% on 140 15–45% through 200
Anhydrous lactose	0.25–0.5	–	16% on 60 65% between 60–200 20% through 200
Emdex	7.8–9.2	0.64	1% on 20 20% max. through 100
Di-Pac	0.4–0.75	0.58	3% max. on 40 75% min. on 100 5% max. through 100
Nu-Tab	<1	0.70	50% min. on 60 10% max. through 120
Microcrystalline cellulose			
Avicel pH 101	<5	0.32	1% max. on 60 7% through 200
Avicel pH 102	<5	0.34	8% max. on 60 45% on 200
Starch 1500	12	0.62	0% on 8 0.5% max. on 40 90% through 100
Emcompress	0.5	0.91	5% max on 40 15 max through 200

[a]Contains 4.5% water of hydration.

[b]Mesh size of screen.

drug per tablet. If the amount of drug is small, this problem can be overcome by a proper choice of excipient fillers. However, when the drug makes up higher proportions of the tablet weight, the use of glidants in addition to careful selection of tablet fillers is necessary. The most effective glidants are the micronized silicas such as Cab-O-Sil and Syloid. They are generally used in concentrations of 0.1 to 0.25%. At higher levels the weight variation of tablets will often increase, and tablet hardness per specific die volume fill becomes less [36]. However, higher concentrations may be helpful as antiadherents, and may reduce filming and picking problems on punch faces.

Most direct-compression fillers are purposely designed to give good flow properties. In most cases, fluidity in terms of *volume* (not weight) flow per unit time is directly related to particle size (Table 3). The two fillers with poorest flow appear to be microcrystalline cellulose and compressible starch. However, flow of these materials is not as poor as is often recorded when gravimetric flow and not volumetric flow data are presented [28].

The trend toward higher tablet machine output has necessitated the development of more sophisticated feeders because in older designs the dwell time of the die cavity in contact with the feeder was not adequate to allow uniform filling. This problem can become even more critical in direct compression because of the smaller mean particle size of direct-compression powder. There are two basic approaches to increasing die-feeding efficiency: (a) to force material into the die cavity; (b) to improve flow properties of material directly above the die cavity so that the material will naturally flow downward. The latter approach appears to be the more realistic and serves as the basis for most tablet machine modifications for improvement of die fill. One such system, designed by the Manesty Corporation, employs a rotary feeder with two horizontal paddles, which rotate in opposite directions. The paddle speeds can be synchronized with the main drive. It is possible that the use of such positive die-feeding equipment may be necessary if optimum fluidity cannot be obtained through careful selection of ingredients and choice of their concentrations.

C. Content Uniformity

Highly fluid powder blends facilitate unblending. The narrower the particle size range of all components and the more alike the particle densities, the less chance for unblending or segregation. It is important to note that it is the particle density and not the bulk density that is important in segregation. Cellulose and starch products tend to have lower true densities than sugars or inorganic chemicals. However, the small and angular particle shape of microcrystalline cellulose makes it difficult for higher density particles to sift down through the spaces between the blend of materials. Major problems with segregation can occur in spherically shaped fillers, particularly if the particle is large and spherical, such as is the case with compressible dextrose (Emdex). In such cases it is necessary to select other excipients to fill the empty spaces or to purposely preblend a micronized active ingredient with the large-particle filler. This approach is recommended by Ho and Crooks [37], who blended sulfaphenazole (mean particle diameter of 2 μm) with coarse direct-compression tablet fillers, and then studied the blends, using a sampling method and electron microscopy. After mixing with a 180- to 250 μm fraction of direct-compression

sucrose (DiPac) for 100 min, the standard deviation of 200-mg samples containing 4 mg of sulfaphenazole was equivalent to that predicted for a random mix. The mix did not appear to segregate during mixing or vibration. It is theorized that blending of the filler particles first (with lubricant, etc.) or simply blending all materials at once would have interfered with the surface attraction of drug particles to filler and resulted in decreased homogeneity. There are a number of other excellent articles on ordered blending that point out its importance to direct compression [38–40].

D. Lubrication

Lubrication has always been one of the most complicated and frustrating aspects of tablet formulation. The lubrication of direct-compression powder blends is, if anything, more complicated than that of classical granulations. In general, the problems associated with lubricating direct-compression blends can be divided into two categories: (a) type and amount needed to produce adequate lubrication; (b) the softening effects of lubrication.

Because the overall mean particle size of direct-compression blends is less than that for granulations, higher concentrations of lubricants are often needed. The recognized need for small particle size of lubricants in granulations is of even greater importance in direct compression.

Because there are already many more surfaces covered with lubricant in direct-compression blends, the softening effect upon compression is magnified. This is particularly true in direct-compression fillers that exhibit almost no fracture or plastic flow on compression. Even when all surfaces of a granulation are covered by a layer of lubricant, significant clean surfaces are formed during compression. In most instances standard blending times will result in complete coverage of these surfaces. The same blending times in direct-compression blends may or may not cover all primary surfaces. Thus length of blending becomes much more critical in direct compression than in lubrication of tablet granulations. If blended long enough, alkaline stearate lubricants will shear off and completely cover all exposed particle surfaces. It may be necessary to avoid the alkaline stearate lubricants completely in some direct-compression formulations. The influence of the duration of lubricant and excipient mixing on the processing characteristics of powders and on the properties of compacts prepared by direct compression was studied by Shah and Mlodozeniec [41]. They found that ejection force, hardness, disintegration, and dissolution of directly compressed tablets of lactose and microcrystalline cellulose were all significantly affected by blending times. The properties of directly compressed tablets can also be dramatically affected by the type of blender, which can be a major problem when scaling up from laboratory to production equipment [42]. When operated at the same rotation speed, the decrease in crushing strength of tablets was much faster for the large industrial mixers than for the laboratory blenders. Lubrication of direct-compression formulations is one of the more complex and difficult problems faced by a pharmaceutical formulator.

VI. MORPHOLOGY OF DIRECT-COMPRESSION FILLERS

The compressibility of direct-compression filler-binders can be more easily understood by viewing the morphology of individual particles. As was

mentioned previously, most direct-compression fillers are minigranulations in which the raw material itself has in some way been agglomerated or granulated after being chemically or physically modified.

The scanning electron microscope has provided a unique tool to visualize such modifications while at the same time allowing for a qualitative assessment of product quality. The scanning electron microscope was dramatically used by Hess to depict the nature of pharmaceutical compacts and the effects of compression force and disintegrating agents on tablet morphology [43]. The use of scanning electron photomicrographs for the characterization of direct-compression excipients was first reported by Shangraw et al. [44,45] and updated in a later article that further reviewed the usefulness of scanning electron microscopy in studying excipient properties [46].

As can be seen in Figures 4 and 5, the spnay drying of lactose can result in agglomerates consisting of small α-monohydrate crystals held together by amorphous glass. These agglomerates now have the prerequisite flow and deformation properties to make them compressible. The cocrystallization of sucrose with modified dextrins changes the poorly compressible sucrose crystals into a highly deformable dense aggregate of crystallites (Figs. 6 and 7).

It was not possible to utilize fibrous cellulose as a tableting agent until it was mechanically formed into a large-particle floc that improved flow characteristics but with little improvement in compressibility (Fig. 8). However, it was the acid hydrolysis of cellulose and the subsequent spray drying of the more crystalline portions of the fibers into a free-flowing powder that revolutionized direct-compression tableting. This product, microcrystalline cellulose (Fig. 9), not only forms extremely hard compacts, but has the ability to improve the compressibility of other substances when it is added in concentrations of 10 to 30%.

A scanning electron photomicrograph of unmilled dicalcium phosphate provides evidence of the aggregates of crystallites that shatter upon compaction to give tablet strength (Fig. 10). The agglomeration of starch

Figure 4 Crystalline lactose, N.F. (non-spray-dried).

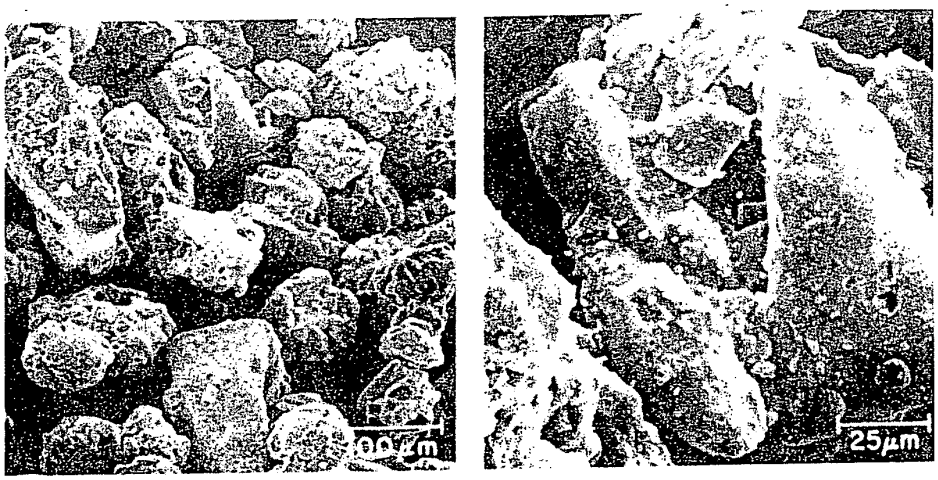

Figure 5 Lactose, N.F. Spray-dried. (Fast-Flo).

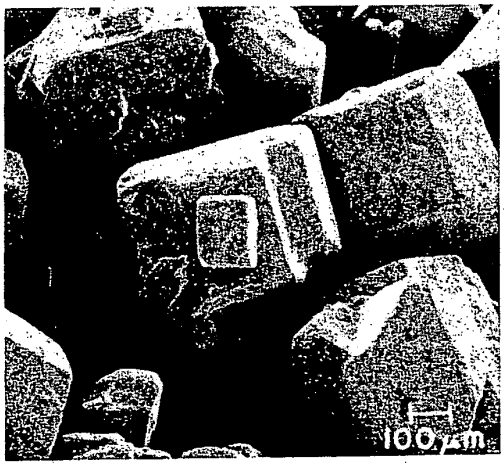

Figure 6 Sucrose, N.F. (crystalline).

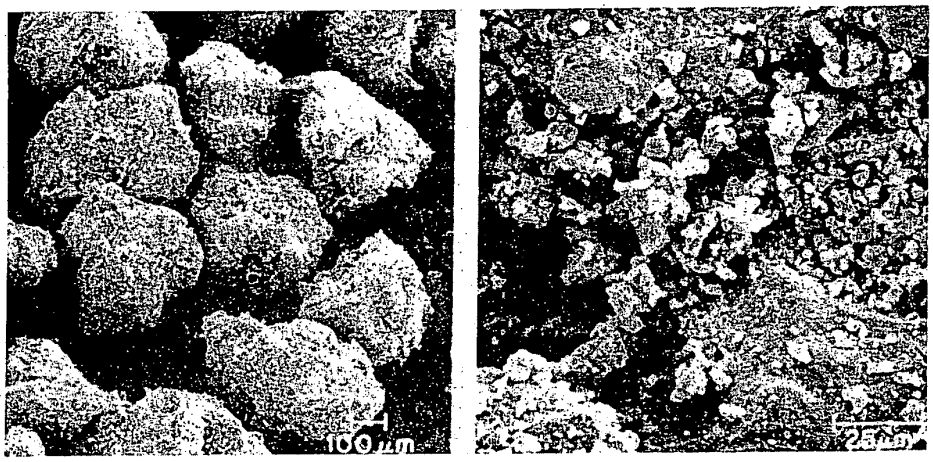

Figure 7 Compressible sugar, N.F. (Dipac).

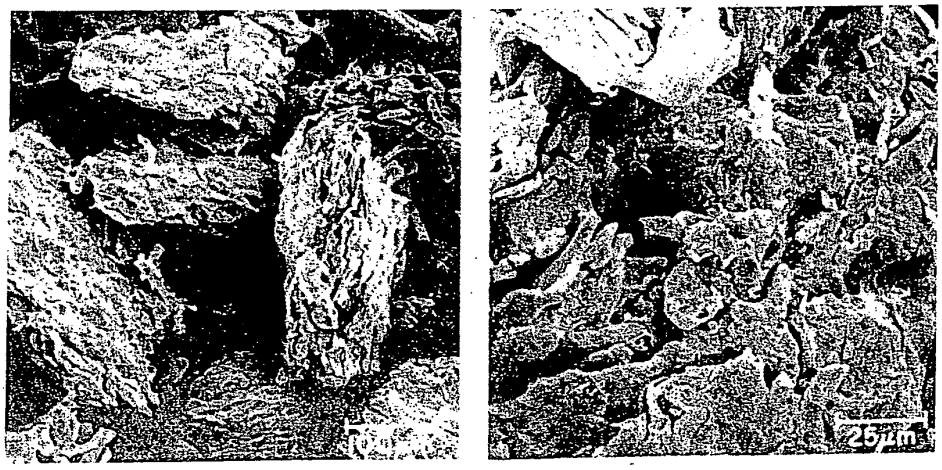

Figure 8 Powdered cellulose, N.F. (Elcema 250).

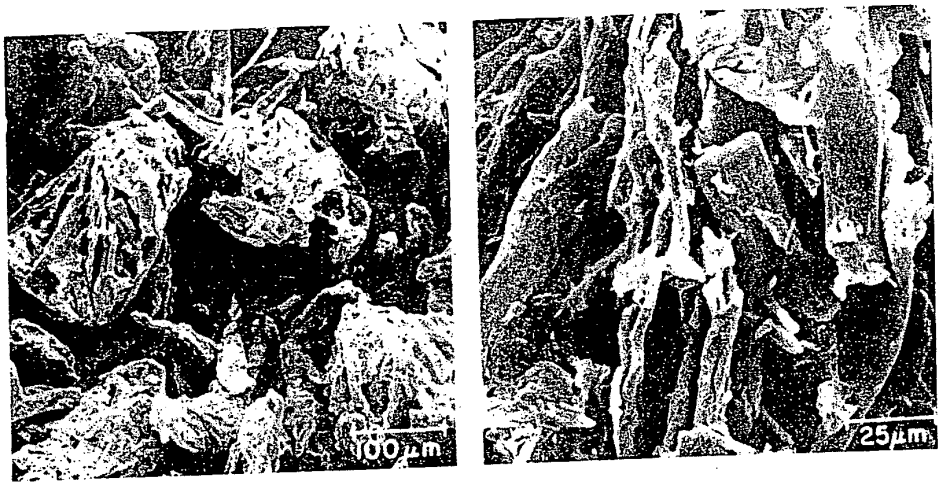

Figure 9 Microcystalline cellulose, N.F. (Avicel pH 102)

with partially hydrolyzed starch to form a free-flowing compressible granulation can be seen in Figure 11.

One of the most significant contributions to the literature of pharmaceutical excipients is *The Handbook of Pharmaceutical Excipients* [47]. Of particular interest to those concerned with morphology and functionality are the book's scanning electron photomicrographs of almost all tablet fillers and disintegrating agents. A wide range of data is also presented for products that have the same chemical composition yet different morphologies. Such data include information about particle size, compressibility, and moisture sorption.

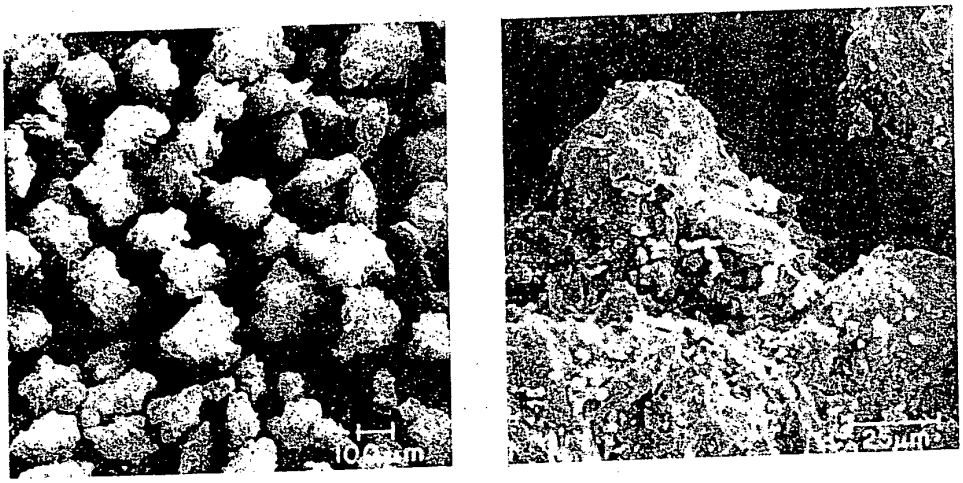

Figure 10 Dibasic calcium phosphate, USP unmilled (Di-Tab, Emcompress).

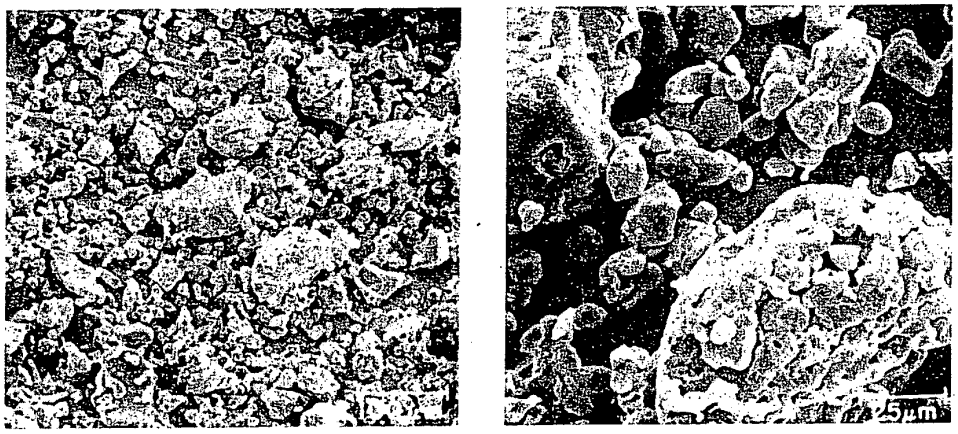

Figure 11 Pregelatinized starch N.F. compressible (Starch 1500).

VII. COPROCESSED ACTIVE INGREDIENTS

As it has become more and more apparent what makes chemical substances compressible and also what enhances their dissolution rates, it has become increasingly obvious that emphasis in tablet formulation has been misplaced. There is nothing less compressible or less rapidly soluble than a perfectly pure crystalline material. Yet for a century there has been an emphasis on producing the purest possible drug crystals. It is then up to the pharmaceutical formulator to take those crystals and mask the inadequacies of compressibility and dissolution inherent in them by means of external excipients. A more logical approach would be to supply the drug in an impure form (with known quantities of known impurities) so that the crystals are actually flawed or in fact do not exist as large crystals but as aggregates of microfine crystals. Although this has not yet been done for drug substances, pregranulations of some common drugs are available commercially.

Ascorbic acid has long been available in a number of powder or granular forms. Ascorbic acid is commonly crystallized in monoclinic, platelike crystals. The term granular simply means large crystals (similar to granular sugar), not a granulation in terms of aggregated powders.

In the mid 1970s Roche marketed ascorbic acid C-90 in which micronized ascorbic acid particles are granulated with starch paste. The product appears to be extruded through a compactor and then ground. Each large particle is actually a granule of ascorbic acid and pasted starch, and is much more compressible than the pure crystalline material. However, the product does have an extremely wide variation in particle size, and addition of some filler-binder, such as microcrystalline cellulose, is recommended to optimize compressibility. More recently, Roch marketed a C-95 ascorbic acid that contains only 5% excipients and utilizes methylcellulose rather than starch as the binder. Takeda Chemical Industries markets both a C-97 direct-compression ascorbic acid and SA-99, a direct-compression sodium ascorbate.

Because of the increasing popularity of acetaminophen as an analgesic, it was only natural that a modification of this substance to improve compressibility would be attempted. Acetaminophen generally occurs as large monoclinic crystals, a crystal form which is not easily deformed and resists compaction. A direct-compression form of acetaminophen is available commercially from Mallinckrodt containing 90% acetaminophen and 10% of partially pregelatinized starch under the name COMPAP [48]. The spherical nature of the particles indicates that the material is prepared by spray drying; each particle is almost a perfect minigranule. Deformation can occur along any plane and multiple clean surfaces are formed during the compaction process. Moreover, each granule consists of hundreds of small crystals with wetted surfaces which optimize dissolution. Tablets with rapid dissolution can be easily formed by the addition of small concentrations of AcDiSol (2%) and lubricant (0.5% magnesium stearate). A self-lubricating version of this material is also available (COMPAP-L) as well as a combination of acetaminophen and codeine (Codacet-60).

Another direct-compression acetaminophen product is marketed by Monsanto under the name DC-90 [49]. This product is prepared by fluidized bed granulation instead of spray drying. It has a compressibility profile similar to that of COMPAP but is only available in the self-lubricating form. Both products exhibit rapid dissolution profiles when formulated with effective disintegrant systems. The compressibility of both materials can be enhanced by the addition of 10 to 20% microcrystalline cellulose. The different morphologies or these products is debicted in Figure 12a and b.

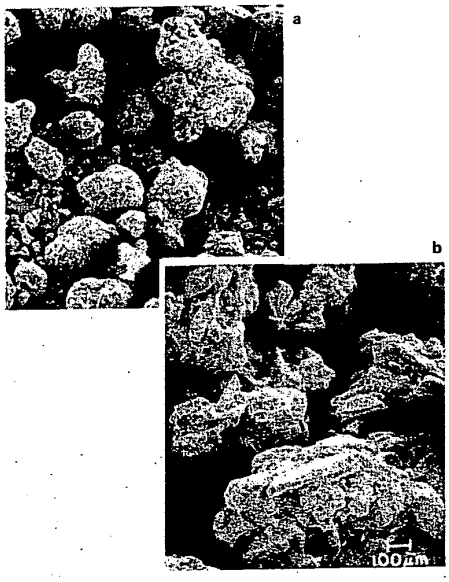

Figure 12 Direct-compression acetaminophen: (a) Compap (Mallinckrodt); (b) DC 90 (Monsanto).

In 1982, Mallinckrodt introduced a directly compressible ibuprofen product under the name DCI. However, this product contains only 63% active ingredient and appears to be a classic granulation with little innovation.

In some respects the term direct-compression is a misnomer when applied to any of these products. However, it is apparent that these products will continue to multiply and provide convenient intermediate materials for manufacturing companies with limited processing equipment. In many ways, they resemble the slugged aspirin/starch (90/10) granulations that became popular in the post-World War II period and are still commercially available.

There is no reason to believe that it would not be possible to convert any active ingredient into a compressible form by crystal modification. The question remains as to whether or not this technique will be applied to drug substances or if pharmaceutical formulators will be forced to continue working with noncompressible, poorly soluble pure crystals.

VIII. MODIFICATION AND INTEGRATION OF DIRECT-COMPRESSION AND GRANULATION PROCESSES

It is in the area of dry granulation and mixed processing systems where the most recent impact of direct-compression technology has taken place.

When initially developed, direct compression was thought of as an all-or-nothing system. Gradually the integration of direct compression with various granulation processes has occurred. These include:

1. Use of direct-compression excipients in postgranulation running powders
2. Optimization of granulations prepared by roll compaction and Chilsonation
3. Semi- or pseudogranulations, mini- or microgranulations, preblending of triturations
4. Matrix for controlled relase granules or beads

The use of microcrystalline cellulose, which was originally thought of as a direct-compression binder-filler, in the postgranulation running powder for increasing tablet hardness has been a common practice almost since its introduction. Subsequently, microcrystalline cellulose has gained acceptability in mini- or microgranulations in which small quantities of wet binders are used but are more thoroughly distributed in loosely agglomerated powders [50]. This allows for the maximization of the effect of both the wet binder and the dry binder. However, care in the granulation step has to be taken because the overwetting of the granules tends to reduce the binding effectiveness of the microcrystalline cellulose.

A unique modification of this process was proposed by Ullah using a process called "moisture-activated dry granulation" (MADG) [51]. In this procedure, the binder (polyvinylpyrrolidone) is blended with the drug plus filler, a small amount of water is added, and the combination is then mixed thoroughly. Microcrystalline cellulose is subsequently added to sorb the small amount of moisture present. No traditional drying step is involved. The granulation tends to be nondense, with a relatively small particle size.

Direct compression has had a significant impact on the particle size originally thought necessary for tablet manufacture. Formulators have come to realize that with the use of glidants, much smaller mesh materials can be used as granulations and the particle size of granules can in fact approach the particle size of direct-compression fillers. In fact, as was stated earlier, most direct-compression fillers are nothing more than micro- or minigranulations.

The innovative use of compressible excipients for increasing the compressibility of a difficult material to tablets is illustrated by one approach to manufacturing 800-mg ibuprofen tablets [52]. Ibuprofen has a very low bulk density, low melting point, poor compaction properties, and tablets produced by wet granulations may age due to scintering. The patent for a stable high-dose high-bulk-density ibuprofen granulation describes the preparation of a dry granulation of croscarmellose and ibuprofen by roll compaction or chilsonation, and the subsequent blending of the granulation with additional croscarmellose and microcrystalline cellulose to produce a tablet. One might argue that this process is not direct compression, but the fact of the matter is that without the unique sorbent and disintegrating properties of croscarmellose and the unusual dry-binding properties of microcrystalline cellulose in the post blend powder, this product would not be possible.

A further modification of the direct-compression process is the use of premixed triturations of potent drug substances with one or more fillers and the subsequent addition of other fillers and binders before the final blend is directly compressed. This process is now being used successfully for making tablets of such potent drugs as clonidine with tablet strengths of 0.1, 0.2, and 0.3 mg. Preparation of tablets of this strength by direct compression would have been thought impossible 10 years ago.

More recently, two potassium supplements have been introduced into the marketplace that involve the compression of coated potassium chloride crystals into directly compressed tablet matrices. One product is made by coating KCl crystals with a solution/suspension of paraffin, acetyl tributyl citrate, ethylcellulose, and silicon dioxide in isopropanol. The coated crystals are then blended with microcrystalline cellulose, rice starch, magnesium stearate, and talc, and then compressed. The tablets are easily crushed and can be administered as a powder without changing the release characteristics of the KCl.

A similar potassium chloride tablet with a strength of 20 meq has also been marketed. The tablet is extremely hard but disintegrates into the primary coated KCl crystals very rapidly. Microcrystalline cellulose and crospovidone act both as compressible cushioning agents during compaction and disintegrating agents during the very rapid breakup that occurs on exposure to fluids, which allows the tablet contents to be administered as a suspension if so desired.

IX. FUTURE OF DIRECT-COMPRESSION TABLETING

In spite of the slow adoption of direct-compression tableting by the pharmaceutical industry, there is every indication that its acceptance will continue to grow. Its use in the manufacture of generic drug and

nonprescription drug products, where innovation is easier to apply and justify economically, is now widespread. As was mentioned in the last section, there is an increasing inclination to integrate aspects of direct compression, dry granulation, and wet granulation in product manufacture. Coprocessing of excipients and active ingredients to provide drum-to-hopper tableting of raw materials will no doubt also increase in volume. It is difficult to envision significant new filler-binders because the basic building materials that are both chemically and physiologically acceptable have already been modified. However, there will be a continuing search for dry binders that can mimic or exceed the properties of microcrystalline cellulose and to discover a lubricant with the functionality of magnesium stearate but without its hydrophobic properties.

X. FORMULATIONS FOR DIRECT COMPRESSION

As indicated above, the development of formulations for direct compression is both an art and a science. All formulations are highly dependent on the properties of the raw materials including the drug substance. It is not desirable to change sources of supply or grades of raw materials without validating effects on fluidity, compressibility, and solubility. This applies to the active ingredient also, particularly in a high-dose drug. Following is a collection of formulations taken from the literature (Examples 1 to 25) illustrating many of the points discussed in the chapter. These are guide formulations only and results may vary depending on the properties of the drug substance and the type of blender or tablet press used. A number of them have been taken or adapted from formularies available from FMC, Food and Pharmaceutical Products Division and Edward Mendell Co., Inc.

Example 1: Aspirin Tablets USP (325 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Aspirin, USP (40-mesh)	80.0	325.0
2. Avicel PH 102	12.0	48.0
3. Cornstarch, N.F.	8.0	32.0
	100.0	405.0

Note: Hardness of finished tablets can be improved by replacing corn starch with Starch 1500 with no resultant decrease in disintegration. Use of stearic acid is optional depending on aspirin type and concentration of Avicel. Blend all the ingredients for 20 min. Compress into tablets using 7/16-in. standard concave tooling.

Example 2: Aspirin-Caffeine Tablets

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Aspirin, USP (40-mesh crystal)	80.0	384.00
2. Caffeine, USP	3.30	15.84
3. Avicel PH 102	10.00	48.00
4. Cornstarch, N.F.	5.95	28.56
5. Stearic acid, N.F.	0.75	3.60
	100.0	480.00

Blend all ingredients in a P-K blender or equivalent for 20 min. Compress into tablets using 7/16-in. standard concave tooling.

Example 3: Acetaminophen Tablets USP (325 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Acetaminophen, USP, granular	56.5	325.0
2. Solka Floc-BW 100	20.9	120.0
3. Emcocel	18.8	108.3
4. Cab-O-Sil M-5	0.5	3.0
5. Explotab	2.5	14.40
6. Magnesium stearate, N.F.	0.7	4.30
	100.0	575.0

Mix 1, 2, and 3 together for 10 min. Add 4 and 5 and blend for 10 min. Add 6 and blend for 5 min. and compress at maximum compression force.
Note: Harder tablets can be made by replacing additional portions of Solka Floc with Emcocel.

Example 4: Acetaminophen Tablets USP (325 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Acetaminophen USP	70.00	325.00
2. Avicel PH 101	29.65	138.35
3. Stearic acid, N.F. (fine powder)	0.35	1.65
	100.00	465.00

Note: If smaller crystalline size acetaminophen is desired to improve dissolution, it would be necessary to use a higher proportion of Avicel and to use PH 102 in place of PH 101, and to use a glidant. All lubricants should be screened before adding to blender.
Blend 1 and 2 for 20 min. Screen in 3 and blend for an additional 5 min. Compress tablets using 7/16-in. standard concave or flat bevel tooling.

Example 5: Analgesic Tablets

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Asprin, USP	33.44	194.00
2. Salicylamide, USP	16.72	97.00
3. Acetaminophen, USP (large crystals or granular)	16.72	97.00
4. Caffeine, USP (granular)	5.60	32.50
5. Avicel PH 101	25.00	145.00
6. Stearic acid (powder), N.F.	2.00	11.50
7. Cab-O-Sil	0.52	3.00
	100.00	580.00

Blend all the ingredients except 5 for 20 min. Screen in 5 and blend for an additional 5 min. Compress into tablets using 7/16-in. standard concave tooling.

Example 6: Propoxyphene Napsylate-Acetaminophen (APAP) Tablets (100/650 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. 90% Pregranulated APAP	93.01	722.19
2. Propyoxyphene napsylate, USP	11.49	100.00
3. Avicel PH 102	4.00	34.77
4. Ac-Di-Sol	1.00	8.70
5. Cab-O-Sil	0.15	1.30
6. Magnesium stearate, N.F.	0.35	3.04
	100.00	870.00

Note: Pregranulated APAP is available from both Mallinckrodt and Monsanto in directly compressible forms containing 90% active ingredient.
Screen 2 and 6 through a 40-mesh sieve. Screen 5 through a 20-mesh sieve. Blend 1, 2, 3, 4, and 5 in a twin-shell blender for 15 min. Add 6 and blend for 5 min. Compress using precompression force equal to one-third the final compression force.

Example 7: Chewable Ascorbic Acid Tablets (100 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Ascorbic acid, USP (fine crystal)	12.26	27.60
2. Sodium ascorbate, USP	36.26	81.60
3. Avicel PH 101	17.12	38.50
4. Sodium saccharin (powder), N.F.	0.56	1.25
5. DiPac	29.30	66.00
6. Stearic acid, N.F.	2.50	5.60
7. Imitation orange juice flavor	1.00	2.25

Example 7: (Continued)

Ingredient	Composition (%)	Quantity per tablet (mg)
8. FD&C Yellow No. 6 dye	0.50	1.10
9. Cab-O-Sil	0.50	1.10
	100.00	225.00

Note: It is not possible to make chewable ascorbic acid tablets with over 50% active ingredient. Other direct-compression sugars such as Emdex could be used to replace DiPac. Magnesium stearate should be avoided in ascorbic acid formulations. Addition of a higher concentration of Avicel will not usually increase tablet hardness. Blend all ingredients, except 6, for 20 min. Screen in the stearic acid and blend for an additional 5 min. Compress into tablets using 7/16-in. standard concabe tooling.

Example 8: Ascorbic Acid Tablets, USP (250 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Ascorbic acid, USP (fine crystal or granular)	60.0	250.0
2. Avicel PH 101	20.0	84.0
3. Starch 1500	17.5	75.5
4. Stearic acid, N.F. (powder) or Sterotex	2.0	8.5
5. Cab-O-Sil	0.5	2.0
	100.0	418.0

Note: It is important to use free-flowing types of ascorbic acid due to the high concentration in the formulation. Ascorbic acid concentration could be increased slightly by using more Avicel and less Starch 1500.
Stearic acid, Sterotex, Compritol 888, and Lubritab are interchangeable in most formulations.
Blend all the ingredients, except 4, for 25 min. Screen in 4 and blend for an additional 5 min. Compress into tablets using 7/16-in. standard concave tooling.

Example 9: Thiamine Hydrochloride Tablets, USP (100 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Thiamine hydrochloride, USP	30.0	100.00
2. Avicel PH 102	25.0	83.35
3. Lactose, N.F. anhydrous	42.5	141.65
4. Magnesium stearate, N.F.	2.0	6.65
5. Cab-O-Sil	0.5	1.65
	100.0	333.30

Note: Anhydrous lactose could be replaced with Fast-Flo lactose with no loss in tablet quality. This would reduce (the need for a glidant (which is probably present in too high a concentration in many formulations). (Usually only 0.25% is necessary to optimize fluidity.) Blend all ingredients, except 4, for 25 min. Screen in 4 and blend for an additional 5 min. Compress using 13/32-in. standard concave tooling.

Example 10: "Maintenance" Multivitamin Tablets

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Vitamin A acetate (dry form 500 IU and 500 D_2 per mg)	5.5	11.0
2. Thiamine monoitrate, USP	0.8	1.65
3. Riboflavin, USP	1.1	2.20
4. Pyridoxine HCl, USP	1.0	2.10
5. 1% Cyanocobalamin (in gelatin)	0.1	0.22
6. D-Calcium pantothenate, USP	3.75	7.50
7. Ascorbic acid, USP (fine crystals)	33.25	66.50
8. Niacinamide	11.0	22.00

Example 10: (Continued)

Ingredient	Composition (%)	Quantity per tablet (mg)
9. Emcompress or DiTab	13.1	26.23
10. Microcrystalline cellulose, N.F.	25.0	50.00
11. Talc USP	3.0	6.00
12. Stearic acid, N.F. (powder)	1.5	3.00
13. Magnesium stearate, N.F. (powder)	1.0	2.00
	100.00	200.00

Note: This formulation could be converted into a chewable tablet by adding 40 to 50% sugar filler (i.e., Di-Pac and a small quantity of saccharine or aspartame). Blend all ingredients in a suitable blender. Compress at a tablet weight of 200 mg using 3/8-in. standard concave tooling.

Example 11: Geriatric Formula Vitamin Tablets

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Ferrous sulfate, USP 95% Ethecal granulation	30.00	156.00
2. Thiamine mononitrate, USP	1.09	6.00
3. Riboflavin, USP	1.00	5.50
4. Niacinamide, USP	6.00	33.00
5. Ascorbic acid, C-90	17.45	96.00
6. Calcium pantothenate, USP	0.73	4.00
7. Pyridoxine HCl, USP	0.14	0.75
8. Cyanocobalamin, 0.1% spray-dried	0.82	4.50
9. AcDisol	2.00	11.00
10. Stearic acid N.F. (powder)	2.00	11.00

Example 11: (Continued)

Ingredient	Composition (%)	Quantity per tablet (mg)
11. Magnesium stearate N.F.	0.25	1.38
12. CeloCal	38.52	211.87
	100.00	550.00

Prepare a premix of items 2, 3, 6, 7. Mix in other ingredients except 10 and 11 and blend for 15 min. Add 10 and mix for 5 min. Add 11 and blend for an additional 5 min. Compress using oval punches (1 = 0.480-in., w = 0.220 × cup = 0.040-in.). Sugar or film coat.

Example 12: Pyridoxine HCl Tablets (10 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Pyridoxine HCl, USP	5.0	10.00
2. Emcompress	92.5	185.00
3. Emcosoy	2.0	4.00
4. Magnesium stearate, N.F.	0.5	1.00
	100.0	200.00

Blend 1 and 2 together for 10 min in a twin-shell blender. Add 3 and blend for an additional 10 min. Add 4 and blend for 5 more min and compress.

Example 13: Sodium Fluoride Chewable Tablets (2.2 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Sodium fluoride	2.0	2.200
2. Emdex	96.75	106.425
3. Artificial grape flavor S.S. (Crompton and Knowles)	0.25	0.275
4. Color, grape S3186 (Crompton and Knowles)	0.25	0.275
5. Magnesium stearate, N.F.	0.75	0.825
	100.00	110.000

Mix ingredient 1 and one-third of 2 for 10 min. Add remaining amount of 2 and 4 and mix thoroughly for 20 min. Add 3 and blend for 10 min. Add 5 and blend 5 additional min and compress.

Example 14: Chewable Antacid Tablets

Ingredient	Composition (%)	Quantity per tablet (mg)
1. FMA-11* (Reheis Chemical Co.)	25.2	400.00
2. Syloid 244	3.2	50.00
3. Emdex	69.3	1100.00
4. Pharmasweet powder (Crompton and Knowles)	1.3	20.00
5. Magnesium stearate, N.F.	1.0	16.00
	100.0	1586.00

Note: An appropriate flavor may be added.
*Aluminum hydroxide/magnesium carbonate co-dried gel.
Mix 1 and 2 together for 5 min. Screen through 30-mesh screen (if ingredients no already prescreened) and mix for 10 to 15 min. Add 3 and 4 and blend thouroughly for 10 to 15 min. Add 5, blend 5 min, and compress.

Example 15: Calcium Lactate Tablets (10 gr)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Calcium lactate,* USP	71.25	470
2. AcDiSol	1.25	10
3. Avicel PH 101	10.00	80
4. Stearic acid, N.F. (powder)	2.50	20
5. Magnesium stearate, N.F.	0.50	4
6. CeloCal	14.50	116
	100.00	800

*Equivalent to calcium lactate pentahydrate 650 mg.
Mix ingredients 1, 2, 3, and 6 for 10 min. Add 5 and blend for an additional 5 min. Compress on Stokes 551 using 1/2-in. standard concave upper bisect punches.

Example 16: Pyrilamine Meleate Tablets, USP (25 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Pyrilamine maleate, USP	12.50	25.00
2. Avicel PH 101	17.00	34.00
3. Lactose, N.F. anhydrous	68.40	136.80
4. AcDiSol	1.00	2.00
5. Cab-O-Sil	0.35	0.70
6. Stearic acid, N.F. (powder)	0.25	0.50
7. Magnesium stearate, N.F.	0.50	1.00
	100.00	200.00

Screen 1, 6, and 7 through 40-mesh sieve. Belnd 1 and 3 for 3 min in V blender. Add 2, 4, and 5 to step-2 and blend for 17 min. Add 6 to step 3 and blend for 3 min. Add 7 to step 4 and blend for 5 min. Tablet using 5/16-in standard concave punches to a hardness of 5.5 kg.

Example 17: Doxylamine Succinate Tablets USP

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Doxylamine succinate, USP	6.4	25.13
2. Syloid 244	0.85	3.35
3. Solka Floc, BW100	4.05	16.70
4. Emcompress	83.95	331.82
5. Explotab	5.0	20.0
6. Magnesium stearate, N.F.	0.75	3.0
	100.00	400.0

Screen 6 through 30 mesh screen and blend with 2 for 10 to 15 min. Add 3 and one-third of 4 and mix for 10 min. Add remaining 4 and blend for 10 min. Add 5 and blend for 5 to 7 min. Add 6 and blend for 3 to 5 min.

Example 18: Amitriptyline HCl Tablets USP (25 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Amitriptyline HCl, U.S.P.	22.73	25.0
2. Fast-Flo lactose	59.52	05.47
3. Avicel PH 102	15.00	16.50
4. Ac-Di-Sol	2.00	2.20
5. Cab-O-Sil	0.25	0.28
6. Magnesium stearate, N.F.	0.50	0.55
	100.00	110.0

Screen 1, 2, and 6 through a 40-mesh screen. Blend 1, 2, 3, 4, and 5 in a suitable twin-shell blender for 5 min using intensifier bar. Blend above mixture for an additional 5 min without the intensifier bar. Add 6 and blend for another 5 min. Compress.

Example 19: Furosemide Tablets USP (40 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Furosemide, USP	25.00	40.00
2. Avicel, PH-102	12.00	19.20
3. AcDiSol	1.50	2.40
4. Fast-Flo lactose	59.50	95.20
5. Cab-O-Sil	0.50	0.80
6. Stearic acid, N.F.	1.00	1.60
7. Magnesium stearate, N.F.	0.50	0.80
	100.00	160.00

Screen 5 through a 20-mesh sieve. Screen 6 and 7 through a 40-mesh sieve. Blend 1, 2, and 4 in twin-shell blender without intensifier bar for 1 min and then blend with aid of intensifier bar for 0.5 min and without intensifier bar for 1.5 min. Add 3 and 5 and blend for 3 min. Add 6 and blend for 3 min. Add 7 and blend for 5 min. Discharge blender and pass blend through 40-mesh sieve using oscillating granulator. Charge blender with sieved blend and blend for 5 min. Compress using 6/16-in. flat-faced, beveled edge punches. Compression force as needed to give a tablet of 6-kg hardness.

Example 20: Allopurinol Tablets (300 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Allopurinol, USP	55.74	300.00
2. Emcompress	37.2	200.00
3. Explotab	3.8	20.50
4. Talc	1.8	10.00
5. Cab-O-Sil	0.5	2.50
6. Magnesium stearate, N.F.	1.0	5.00
	100.0	538.00

Blend 1 and 2 for 10 min. Add 3 and blend for 10 more min. Add 4 and 5 and blend 3 to 5 min. Add 6 and blend 5 more min.

Example 21: Chlorpheniramine Maleate and Pseudoephedrine HCl Tablets (4/60 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Chlorpheniramine maleate, USP	1.82	4.0
2. Pseudoephedrine HCl, USP	27.27	60.0
3. Avicel PH-101	16.95	37.3
4. Fast-Flo lactose	51.36	113.0
5. AcDiSol	1.00	2.2
6. Cab-O-Sil	0.50	1.1
7. Stearic acid, N.F.	0.59	1.3
8. Magnesium stearate, N.F.	0.50	1.1
	100.00	220.00

Screen 2, 7, and 8 through 40-mesh sieve. Blend 1, 2, and 3 in V blender for 3 min. Add 4, 5, and 6 to step 2 and blend for 17 min. Add 7 to step 3 and blend for 3 min. Add 8 to step 4 and blend for 5 min. Tablet to a hardness of 5.3 kg using 5/16-in standard concave punches.

Example 22: Penicillin V Potassium Tablets USP (250 mg; 400 IU)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Penicillin V potassium, USP	50.00	250.00
2. Avicel PH 102	24.25	121.25
3. Ditab or Emcompress (unmilled dicalcium phosphate)	22.00	110.00
4. Magnesium stearate, N.F.	3.75	18.75
	100.00	500.00

Blend 1, 2, and 3 for 25 min. Screen in 4 and blend for an additional 5 min. Compress using 7/16-in. standard concave tooling.

Example 23: Quinidine Sulfate Tablets USP (200 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Quinidine sulfate, USP	55.85	200.0
2. Avicel PH 102	40.25	144.0
3. Cab-O-Sil	0.50	1.8
4. Stearic acid, N.F. (powder)	2.50	9.0
5. Magnesium stearate, N.F.	0.90	3.2
	100.10	358.0

Blend 1, 2, and 3 for 25 min. Screen in 4 and 5 and blend for 5 min more. Compress using 3/8-in. standard concave tooling.

Example 24: Chlorpromazine Tablets USP (100 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Chorpromazine hydrochloride, USP	28.0	100.00
2. Avicel PH 102	35.0	125.00
3. Ditab or Emcompress	35.0	125.00
4. Cab-O-Sil	0.5	1.74
5. Magnesium stearate, N.F.	1.5	5.25
	100.0	357.00

Blend all the ingredients, except 5, for 25 min. Screen in 5 and blend for an additional 5 min. Compress into tablets using 11/32-in. tooling.

Example 25: Isosorbide Dinitrate Tablets (10 mg, oral)

Ingredient	Composition (%)	Quantity per tablet (mg)
1. Isosorbide dinitrate (25% in lactose)	20.00	40.00
2. Avicel PH 102	19.80	39.60
3. Fast-Flo lactose	59.45	118.90
4. Magnesium stearate, N.F.	0.75	1.50
	100.00	200.00

Blend 1, 2, and 3 in a P-K blender for 25 min. Blend in 4 for 5 min. Compress into tablets using 5/16-in. standard concave tooling.

Glossary of Trade Names and Manufacturers

Trade name	Chemical/description	Manufacturer
Ac-Di-Sol	Croscarmellose, N.F.	FMC Corporation, Philadelphia, PA 19103
Anhydrous lactose	Lactose N.F. (anhydrous direct tableting)	Sheffield Chemical, Union, NJ 07083
		DMV Corp., Veghel, The Netherlands
Avicel 101, 102	Microcrystalline cellulose, N.F	FMC Corp., Philadelphia, PA 19103
Compritol 88	Glyceryl behenate, N.F.	Gattefose Corp., Elansford, NY 10523
DCL-Lactose	Lactose, N.F. (various types)	DMV Corp., Veghel, Holland
Delaflo	Direct-compression calcium sulfate	J.W.S. Delavau Co., Philadelphia, PA 19122
Des-Tab	Compressible sugar, N.F.	Desmo Chemical Corp., St. Louis, MO 63144
Di-Pac	Compressible sugar, N.F.	American Sugar Co., New York, NY 10020
Di-Tab	Dibasic calcium phosphate, USP (unmilled)	Stauffer Chemical Co., Westport, CT 06880
Elcema G-250	Powdered cellulose, N.F.	Degussa, D-6000 Frankfurt (Main) Germany

Glossary of Trade Names and Manufacturers (Continued)

Trade name	Chemical/description	Manufacturer
Emcocel	Microcrystalline cellulose, N.F.	Edward Mendell Co., Carmel, NY 10512
Emcompress	Dibasic calcium phosphate, USP special size fraction	Edward Mendell Co., Carmel, NY 10512
Emdex	Dextrates, N.F. (dextr	Edward Mendell Co., Carmel, NY 10512
Explotab	Sodium starch glycolate, N.F.	Edward Mendell Co., Carmel, NY 10512
Fast-Flo Lactose	Lactose, N.F. (spray dried)	Foremost Whey Products Banaboo, Wi. 53913
Lubritab	Hydrogenated vegetable oil, N.F.	Edward Mendell Co., Carmel, NY 10512
Maltrin	Agglomerated maltrodextrin	Grain Processing Corp., Muscatine, IA 52761
Neosorb 60	Sorbitol, N.F. (direct-compression)	Roquette Corp., 645 5th Avenue New York, NY 10022
Nu-Tab	Compressible sugar, N.F.	Ingredient Technology, Inc., Pennsauken, NJ 08110
Polyplasdone XL	Crospovidone, N.F. (cross-linked polyvinylpyrrolidone)	GAF Corp., New York, NY 10020
Primojel	Sodium starch glycolate, N.F. (carboxymethyl starch)	Generichem Corp., Little Falls, NJ 07424
Solka Floc	Cellulose floc	Edward Mendell Co., Carmel, NY 10512
Sorbitol 834	Sorbitol, N.F. (crystalline for direct compression)	ICI United States, Wilmington, DE 19897
Spray-dried lactose	Lactose N.F. (spray-dried)	Foremost Whey Products, Baraboo, Wi. 53913
		DMV Corp., Vehgel, Holland
Sta-Rx 1500 (Starch 1500)	Pregelatinized starch, N.F. (compressible)	Colorcon, Inc., West Point, PA 19486
Sterotex	Hydrogenated Vegetable oil, N.F.	Capital City Products Co., Columbus, OH 43216

Glossary of Trade Names and Manufacturers (Continued)

Trade name	Chemical/description	Manufacturer
Tab-Fine	Trade name identifying a number of direct-compression sugars including sucrose, fructose, dextrose	Edward Mendell Co., Carmel, NY 10512
Tablettose	Lactose, N.F. hydrous (for direct compression)	Fallek Chemical Co., New York, NY 10022 (Product of Meggle Milchindustrie—GMBM & Co., KG
TriTab	Tricalcium phosphate anhydrous direct compression	Stauffer Chemical Co., Westport, CT 06881
Vitacel	Coprocessed product containing 30% calcium carbonate and 70% microcrystalline cellulose	FMC Corp., Philadelphia, PA 19103

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