PHARMACEUTICAL DOSAGE FORMS

Tablets

SECOND EDITION, REVISED AND EXPANDED

In Three Volumes
VOLUME 1

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observing the melting point, especially with a hot-stage microscope. More quantitative information can be obtained by using quantitative differential scanning calorimetry or by phase-rule solubility analysis.

As important to a compound's chemical characteristic are its physical ones. Crystalline form (including existence of solvates) is of fundamental importance, and for complete documentation of the compound X-ray powder diffraction patterns for each batch is desirable. This is simple to execute and provides useful information for later comparison and correlation to other properties.

IV. PARTICLE SIZE, SHAPE, AND SURFACE AREA

Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also, in some instances, on their biopharmaceutical behavior. For example, the bioavailability of griseofulvin and phenacetin is directly related to the particle size distributions of these drugs [3,4]. It is now generally recognized that poorly soluble drugs showing a dissolution rate-limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided state than as a coarse material. Very fine materials are difficult to handle [5]; but many difficulties can be overcome by creating solid solution of a material of interest in a carrier, such as a water-soluble polymer. This represents the ultimate in size reduction, since in a (solid) solution, the dispersed material of interest exists as discrete molecules or agglomerated molecular bundles of very small dimensions indeed.

Size also plays a role in the homogeneity of the final tablet. When large differences in size exist between the active components and excipients, mutual sieving (demixing) effects can occur making thorough mixing difficult or, if attained, difficult to maintain during the subsequent processing steps. This effect is greatest when the diluents and active raw materials are of significantly different sizes. Other things being equal, reasonably fine materials interdisperse more readily and randomly. However, if materials become too fine, then undersirable properties such as electrostatic effects and other surface active properties causing undue stickiness and lack of flowability manifest. Not only size but shape too influences the flow and mixing efficiency of powders and granules.

Size can also be a factor in stability; fine materials are relatively more open to attack from atmospheric oxygen, heat, light, humidity, and interacting exipients than coarse materials. Weng and Parrott [6] investigated influence of particle size of sulfacetamide on its reaction with phthalic anhydride in 1:2 molar compacts after 3 hr at 95°C. Their data, presented in Table 2, clarly demonstrate greater reactivity of sulfacetamide with decreasing particle size.

Because of these significant roles, it is important to decide on a desired size range, and thence to maintain and control it. It is probably safest to grind most new drugs having particles that are above approximately 100 μm in diameter. If the material consists of particles primarily 30 μm or less in diameter, then grinding is unnecessary, except if the material exists as needles—where grinding may improve flow and handling properties, or if the material is poorly water-soluble where grinding increases dissolution rate. Grinding should reduce coarse material to, preferably, the 10- to

Table 2 Influence of Particle Size on Conversion of Sulfacetamide

Particle size of sulfacetamide (μm)	% Conversion ± SD
128	21.54 ± 2.74
164	19.43 ± 3.25
214	17.25 ± 2.88
302	15.69 ± 7.90
387	9.34 ± 4.41

Source: Modified from Weng, H., and Parrott, E. L., *J. Pharm. Sci.*, *73*:1059 (1984). Reproduced with the permission of copyright owner.

40-μm range. Once this is accomplished, controlled testing can be performed both for subsequent in vivo studies and for in-depth preformulation studies. As the studies proceed, it may become apparent that grinding is not required and that coarser materials are acceptable. At that time, it is conceptually simpler to omit that step without jeopardizing the information already developed. The governing concept is to stage the material so that challenges are maximized.

There are several drawbacks to grinding that may make it inadvisable. Some are of lesser importance. For example, there are material losses when grinding is done. Sometimes a static electricity buildup occurs, making the material difficult to handle. Often, however, this problem, if it exists, may be circumvented by mixing with excipients such as lactose prior to grinding. Reduction of the particle size to too small a dimension often leads to aggregation and an apparent increase in hydrophobicity, possibly lowering the dissolution rate and making handling more troublesome. When materials are ground, they should be monitored not only for changes in the particle size and surface area, but also for any inadvertent polymorphic or chemical transformations. Undue grinding can destory solvates and thereby change some of the important characteristics of a substance. Some materials can also undergo a chemical reaction.

A. General Techniques for Determining Particle Size

Several tools are commonly employed to monitor the particle size. The most rapid technique allowing for a quick appraisal is microscopy. Microscopy, since it requires counting of a large number of particles when quantitative information is desired, is not suited for rapid, quantitative size determinations. However, it is very useful in estimating the range of sizes and the shapes. The preliminary data can then be used to determine if grinding is needed. A photomicrograph should be taken both before and after grinding. The range of sizes observable by microscopy is from about 1 μm upward.

For optical microscopy, the material is best observed by suspending it in a nondissolving fluid (often water or mineral oil) and using polarizing lenses to observe birefringence as an aid to detecting a change to an amorphous state after grinding.

For a quantitative particle size distribution analysis of materials that range upward from about 50 μm, sieving or screening is appropriate, although shape has a strong influence on the results. Most pharmaceutical powders, however, range in size from 1 to 120 μm. To encompass these ranges, a variety of instrumentation has been developed. There are instruments based on lasers (Malvern), light scattering (Royco), light blockage (HIAC), and blockage of an electrical conductivity path (Coulter Counter). The instrument based on light blockade has been adopted by the USP to monitor the level of foreign particulates in parenteral products. The instrument will measure particle size distribution of any powder properly dispersed in a suspending medium. The concentration of sample suspension should be such that only a single particle is presented to the sensor in unit time, thus avoiding coincidence counting.

Other techniques based on centrifugation and air suspension are also available. Most of these instruments measure the numbers of particles, but the distributions are readily converted to weight and size distributions. The latter way of expressing the data is more meaningful. A number of classical techniques based on sedimentation methods, utilizing devices such as the Andreasen pipet or recording balances that continuously collect a settling suspension, are also known. However, these methods are now in general disfavor because of their tedious nature. Table 3 lists some of the common techniques useful for measurement of different size ranges [7].

There are many mathematical expressions that can be used to characterize an average size. These refer to average volumes or weights, geometric mean diameters, and relationships reflecting shapes, such as the ratio of an area to a volume or weight factor [8].

Table 3 Common Techniques for Measuring Fine Particles of Various Sizes

Technique	Particle size (μm)
Microscopic	1–100
Sieve	>50
Sedimentation	>1
Elutriation	1–50
Centrifugal	<50
Permeability	>1
light scattering	0.5–50

Source: Parrott, E. L., *Pharm. Mfg.*, 4:31 (1985). Reproduced with the permission of copyright owner.

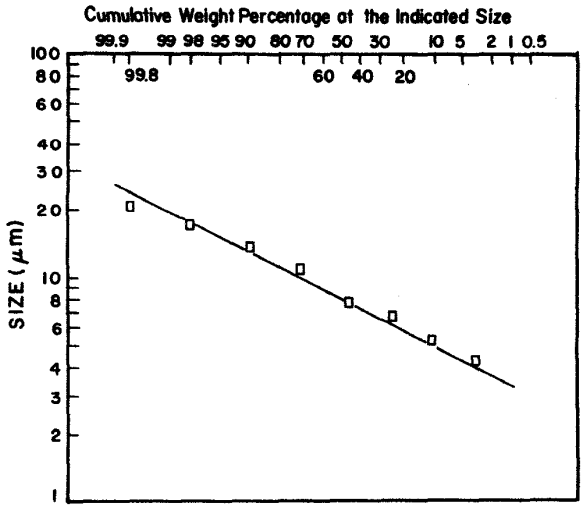

Figure 2 Log probability plot of the size distribution of a sample of triamcinolone acetonide.

A convenient way to characterize a particle size distribution is to construct a log probability plot. Log probability graph paper is commercially available, and particle size distributions resulting from a grinding operation with no cut being discarded will give a linear plot. An example is illustrated in Figure 2 for a powder sample of triamcinolone acetonide. The data used in the construction of Figure 2 are presented in Table 4.

The numbers of particles in Table 4 are converted into weight fractions by assuming them to be spheres and multiplying by the volume of a single sphere (particle) calculated from the geometric relationship:

$$V = \frac{\pi}{6} d^3$$

where V is the volume and d the particle diameter (using the average value of the range given in the first column of Table 4). The result is the total volume occupied by particles in each of the size ranges and is given in the third column of the table. The volume is directly related to a mass term by the reciprocal of the density. However, since the density is constant for all particles of a single species and is rarely known accurately, it is sufficient to use the volume terms to calculate the weight percentages in each size range by dividing the total volume of all the particles into the volumes in each range (column 4 of Table 4). If densities were used, it is obvious that they would cancel out in this calculation. The cumulative weight percentage in each size range is shown in the last column.

Statistical descriptions of distributions most often give a measure of central tendency. However, with powders the distributions are skewed in the direction of increasing size. This type of distribution can be described by the Hatch-Choate equation:

$$f = \frac{\Sigma n}{\sqrt{2\pi}\ \ln\ \sigma_g} \exp\left[-\frac{(\ln d - \ln M)^2}{2\ \ln^2\ \sigma_g}\right] \quad (1)$$

where f is the frequency with which a particle of diameter d occurs, and n is the total number of particles in a powder in which the geometric mean particle size is M and the geometric standard deviation is σ_g. Equation (1) is succinctly discussed by Orr and Dalla Valle [9].

The two measures M and σ_g uniquely characterize a distribution, and are readily obtained graphically from a log probability plot in which cumulative weight percentage is plotted against the particle size (Fig. 2). The geometric mean diameter corresponds to the 50% value of the abscissa, and the geometric standard deviation is given by the following ratios, the values for which are taken from the graph.

$$\sigma_g = \frac{84.13\%\ \text{size}}{50\%\ \text{size}} = \frac{50\%\ \text{size}}{15.87\%\ \text{size}}$$

For the example, the values are 8.2 and 1.5 μm for the geometric mean particle size and its standard deviation, respectively. The latter is also a slope term. For particle size distributions resulting from a crystallization, a linear plot can often be obtained using linear probability paper.

B. Determination of Surface Area

The determination of the surface areas of powders has been getting increasing attention in recent years. The techniques employed are relatively simple and convenient to use, and the data obtained reflect the particle

Table 4 Particle Size Distribution of a Ground Sample of Triamcinolone Acetonide

Size range (μm)	No. of particles	Volume of particles $\times 10^{-3}$ (μm^3)	Weight percent in range	Cumulative weight percent
22.5–26.5	5	38	0.2	100.0
18.6–22.0	54	237	1.7	99.8
14.9–18.6	488	1212	8.8	98.1
11.8–14.9	2072	2552	18.5	89.3
9.4–11.8	5376	3352	24.3	70.8
7.4–9.4	9632	2989	21.7	46.5
5.9–7.4	12,544	1888	13.7	24.8
4.7–5.9	12,928	1008	7.3	11.1
3.7–4.7	13,568	526	3.8	3.8

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Tablet Formulation and Design

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I. INTRODUCTION

The formulation of solid oral dosage forms, and tablets in particular, has undergone rapid change and development over the last several decades with the emergence of precompression, induced die feeding, high-speed and now ultrahigh-speed presses, automated weight-control systems, the availability of many new direct compression materials, and the microprocessor control of precompression, compression, ejection forces, as well as upper punch tightness on tablet presses. Some of the newer tablet presses have tablet rejection systems that are operated by a computer. Computer-controlled tablet presses only require an operator to set up the press at the proper tablet weight and thickness (or pressure). The computer can then assume complete control of the run. Still other tablet presses only require the operator to provide a product identification code to make tablets within specifications previously established and stored in the computer memory.

Most recently, new concepts and federal regulations bearing on bioavailability and bioequivalence, and on validation, are impacting on tablet formulation, design, and manufacture.

Once, lavish gold-plated pills were manufactured and marketed with little knowledge of their pharmacological activity. Appearance and later stability of the dosage form were the prime requirements of pharmaceutical preparations. The introduction of the *friable pill* denoted in part the realization that solid medicinals must—in some fashion—disintegrate within the body for the patient to benefit from the drug. We now realize that disintegration and dissolution alone do not insure therapeutic activity. As only one example of this point, Meyer et al [1] presented information on 14 nitrofurantoin products, which were evaluated both in vitro and in vivo. All products tested met USP XVIII specifications for drug content, disintegration time, and dissolution rate; however, statistically significant differences in bioavailability were observed.

The design of a tablet usually involves a series of compromises on the part of the formulator, since producing the desired properties (e.g., resistance to mechanical abrasion or friability, rapid disintegration and dissolution) frequently involves competing objectives. The correct selection and balance of excipient materials for each active ingredient or ingredient combination in a tablet formulation to achieve the desired response (i.e., production of a safe, effective, and highly reliable product) is not in practice a simple goal to achieve. Add to this fact the need today to develop tablet formulations and processing methods which may be (and must in the future be) validated, and the complexity of tablet product design is further increased in contemporary pharmaceutical development. Increased competition among manufacturers (brand versus generic, generic versus generic, and brand versus brand) has necessitated that products and processes be cost-efficient. Thus cost of a raw material or a particular processing step must be considered before a final tablet formulation or manufacturing process is selected.

Tablet formulation and design may be described as the process whereby the formulator insures that the correct *amount* of drug in the right *form* is delivered at or over the proper *time* at the proper *rate* and in the desired *location*, while having its chemical *integrity* protected to that point. Theoretically, a validated tablet formulation and production process is one in which the range in the variation of the component specifications and physical properties of the tablet product quality properties is known from a cause and effect basis. It is further known that raw materials specifications, at their limits, and when considered as interaction effects of the worst possible combinations, cannot produce a product that is out of specification from any standpoint. Likewise a validated tablet-manufacturing process is one which, when all the operating variables are considered, at any extremes which could ever be encountered in practice, and under the worst possible set of circumstances, will produce products that are within specifications. Total validation of a tablet product includes all combination effects involving formulation, raw materials variables, and processing variables, as well as their interaction effects, to assure that any system produced will be within total product specifications.

The amount or quantity of a drug which is sufficient to elicit the required or desired therapeutic response can be affected by several factors. In the case of compendial or official drugs, the dosage levels have been predetermined. With certain drugs (e.g., griseofulvin), the efficiency of absorption has been shown to depend on the particle size and specific surface area of the drug. By reducing the particle size of such drugs, the dosage level may be reduced by one-half or more and still produce the same biological response.

The form in which the drug is absorbed can affect its activity. Most drugs are normally absorbed in solution from the gut. Since the absorption process for most orally administered drugs is rapid, the rate of solution of the drug will be the rate-limiting step from the point of view of blood level and activity.

Thus, we must consider the contribution and influence of the active components and nonactive components—both separately and together—to measure their impact on the pharmacological response of any tablet system. The timing of administration may affect when and how a drug will act (and to a certain extent where it acts) as will be discussed further in Section

IV.A. Also, the timing of administration may be crucial in order to reduce gastric irritation (uncoated strong electrolytes are often given following food); to reduce drug interactions with food (formation of insoluble complexes between the calcium of milk and several antibiotics), reducing their bioavailability; or to enhance the solubility and bioavailability of certain drugs in foods (notably fats) by their administration with foods (e.g., griseofulvin). Depending on such timing factors plus the relationship and rationale of fast, intermediate, or slow drug release as well as other release considerations, a particular design and tablet formulation strategy is often indicated.

Many excellent review articles have been written on tablet technology, including various formulation aspects. Cooper [2] presented a review monograph on the contributions from 1964 to 1968 in the areas of tablet formulation, processing, quality standards, and biopharmaceutics. Later, Cooper and Rees [3] continued the review and included similar topics covering the period 1969 to 1971. Recent book chapters on tablets include those by Banker [4] and Sadik [5].

The present chapter will detail the general considerations of tablet product design; will describe a systematic approach to tablet design, including the practical use of preformulation data; will describe the commonly used tablet excipients with particular emphasis on their advantages and limitations or disadvantages; and will present some general tablet formulation approaches. Extensive references to the literature should provide the reader with directed reading on topics where additional information may be obtained. While it is impossible to exhaustively cover as broad a topic as tablet formulation and design in one chapter of a book, it is the goal of this chapter to cover the major concepts and approaches, including the most recent thought bearing on validation, optimization, and programmatic methods related to the formulation, design, and processing of compressed tablets.

II. PREFORMULATION STUDIES

The first step in any tablet design or formulation activity is careful consideration of the preformulation data. It is important that the formulator have a complete physicochemical profile of the active ingredients available, prior to initiating a formulation development activity. Compilation of this information is known as preformulation. It is usually the responsibility of the pharmaceutical chemistry research area to provide the data shown below on the drug substances.

1. *Stability (solid state)*: light, temperature, humidity
2. *Stability (solution)*: excipient-drug stability (differential thermal analysis or other accelerated methods)
3. *Physicomechanical properties*: particle size, bulk and tap density, crystalline form, compressibility, photomicrographs, melting point, taste, color, appearance, odor
4. Physicochemical properties: solubility and pH profile of solution/dispersion (water, other solvents)
5. *In vitro dissolution*: pure drug, pure drug pellet, dialysis of pure drug, absorbability, effect of excipients and surfactants

The basic purposes of the preformulation activity are to provide a rational basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product, and to ultimately provide a basis for optimizing drug product quality and performance. From a tablet formulator's perspective, the most important preformulation information is the drug-excipient stability study. The question then, for a new drug, or a drug with which the formulator lacks experience, is to select excipient materials that will be both chemically and physically compatible with the drug.

The question is compounded by the fact that tablets are compacts; and while powder mixtures may be adequately stable, the closer physical contact of particles of potentially reactive materials may lead to instability. The typical preformulation profile of a new drug is usually of limited value to the formulator in assuring him or her that particular drug-excipient combinations will produce adequate stability in tablet form. An added problem is that the formulator would like to identify the most compatible excipient candidates within days of beginning work to develop a new drug into a tablet dosage form rather than to produce a series of compacts, place them on stability, and then wait weeks or months for this information.

Simon [6], in reporting on the development of preformulation systems, suggested an accelerated approach, utilizing thermal analysis, to identify possibly compatible or incompatible drug-excipient combinations. In his procedure, mixtures are made of the drug and respective excipient materials in a 1:1 ratio and subjected to differential thermal analysis. A 1:1 ratio is used, even though this is not the ratio anticipated for the final dosage form, in order to maximize the probability of detecting a physical or chemical reaction, should one occur. The analyses are made in visual cells, and physical observations accompany the thermal analysis. The thermograms obtained with the drug-excipient mixtures are compared to thermograms for the drug alone and the excipient alone. Changes in the termograms of the mixture, such as unexpected shifts, depressions, and additions to or losses from peaks are considered to be significant. Simon [6] has given an example of the type of information which may be obtained from such a study by the data shown in Figure 1. The thermal peak due to the drug alone was lost when the thermal analysis was run on the drug in combination with the commonly used lubricant, magnesium stearate. This was strong evidence for an interaction between these materials. It was subsequently confirmed by other elevated-temperature studies that the drug did decompose rapidly in the presence of magnesium stearate and other basic compounds. Simon has concluded the differential thermal analysis can aid immensely in the evaluation of new compounds and in their screening for compatibility with various solid dosage form excipients. The combination of visual and physical data resulting from differential thermal analysis of drugs with excipients is suggested as a programmatic approach to the very rapid screening of the drug-excipient combinations for compatibility.

Following receipt of the preformulation information, the formulator may prepare a general summary statement concerning the drug and its properties relative to tablet formulation. This statement must often also take into account general or special needs or concerns of the medical and marketing groups for that drug. A typical statement might be as follows.

Compound X is a white crystalline solid with a pyridine odor and bitter taste, which may require a protective coating (film or sugar). It displays excellent compressing properties and has not been observed to possess any

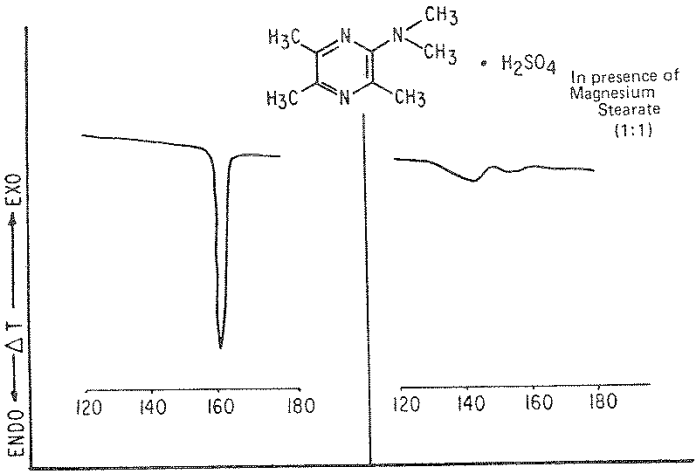

Figure 1 Thermograms showing the melting endotherm of triampyzine sulfate and loss of the endotherm in the presence of magnesium stearate.

polymorphs. It is nonhygroscopic, has low solubility in water, and in moderately volatile. It is an acidic moiety with a pK_a of 3.1 and a projected dose of 50 to 100 mg. The compound is soluble in organic solvents and aqueous media at pH 7.5. Below pH 5 it is sparingly soluble. In the dry state it is physically and chemically stable. This product, while requiring coating protection, must be designed for rapid drug dissolution release (the drug is an acidic moiety, presumably best absorbed high in the gut). No severe chemical stability problems are foreseen. The volatility of the tableted form must be checked, and special packaging may be required.

III. A SYSTEMATIC AND MODERN APPROACH TO TABLET PRODUCT DESIGN

Tablet product design requires two major activities. First, formulation activities begin by identifying the excipients most suited for a prototype formulation of the drug. Second, the levels of those excipients in the prototype formula must be optimally selected to satisfy all process/product quality constraints.

A. Factors Affecting the Type of Excipient Used in a Tablet Formula

The type of excipient used may vary depending on a number of preformulation, medical, marketing, economic, and process/product quality factors, as discussed in the following sections.

Preformulation

Only those excipients found to be physically and chemically compatible with the drug should be incorporated into a tablet formula. Preformulation

studies should also provide information on the flow and bonding properties of the bulk drug. Excipients that tend to improve on flow (glidants) and bond (binders) should be evaluated for use with poor-flowing and poor-bonding compounds, respectively.

At the conclusion of a preformulation study, it may be known which tableting process [direct-compression or granulation (wet/dry)] will be appropriate for the drug. If it is not known for certain which tableting process is most appropriate after preformulation, then initial formulation efforts should concentrate on a direct-compression method since it is most advantageous. Direct compression is the preferred method of tablet manufacture for the following four major reasons: (a) It is the cheapest approach since it is a basic two-step process (if components are of the proper particle size), involving only mixing and compressing, and it avoids the most costly process of unit operating, drying. (b) It is the fastest, most direct method of tablet production. (c) It has fewer steps in manufacture and fewer formulation variables (in simple formulations). (d) It has the potential to lead to the most bioavailable product (which may be critical if bioavailability is a problem).

Medical

The desired release profile for the tablet should be known early in tablet development. Immediate, controlled, and combinations of immediate and controlled release profiles require totally different approaches to formulation development. Immediate release tablets usually require high levels of disintegrants or the use of superdisintegrants. Controlled release are usually formulations of polymers or wax matrices.

In many instances, the rate-limiting factor to absorption of a drug is dissolution. It may be necessary for the formulator to select excipients which may increase drug dissolution and enhance absorption. Solvang and Finholt [7] studied the effect of binder and the particle size of the drug on the dissolution rate of several drugs in human gastric juice. Surface active agents such as sodium lauryl sulfate may be needed to promote wetting of the drug. Alternatively, the use of disintegrants or superdisintegrants may improve dissolution. Hydrophobic lubricants may be used only at low levels or not at all.

The targeting of drug delivery to various sites in the gastrointestinal tract is sometimes required to maximize drug stability, safety, or efficacy. This subject is discussed in detail in Section IV.A.2. Drugs that are acid-labile or cause stomach irritation should not be released in the stomach. The use of enteric coatings on tablets is the most common method of targeting the release of a drug in the small intestine. Tablets which are to be coated should be formulated to withstand the rigors of a coating process and to be compatible with the coating material. The use of alkaline excipients in the tablet may prove to weaken the integrity of the enteric coated tablet.

Marketing

The appearance of a tablet dosage form is usually not thought to have a large impact on the commercial success of a particular product. However, all tablets must meet a minimal elegance criteria. The appearance of a tablet can be evaluated by its color, texture, shape, size, and coating (when present), and any embossing information.

Tablet appearance can be affected by the color and texture each excipient brings to a tablet formulation. Lactose, starch, and microcrystalline cellulose appear white to off-white when compressed. The inorganic diluents such as calcium sulfate, calcium phosphate, and talc produce more of a gray color in the tablet. Drugs will impact on the overall color and appearance of the tablet. Drug–excipient interactions may change the appearance of the tablet with time. The use of dyes may be required to improve the appearance of certain tablets. Relatively large amounts of stearates and high molecular weight polyethylene glycols produce glossy tablets.

The tableting properties (flow and compressibility) of tablet formulations containing a low percentage of active (<100 mg) are primarily dictated by the tableting properties of the excipients in the formulation. The formulator will frequently have numerous excipients to choose from because the drug does not dominate the behavior of the formulation during processing. However, if the tablet formula contains a large percentage of active, the formulator may be somewhat restricted in the choice of excipients. In order to be easily swallowed and remain elegant, tablet size and weight is limited in these formulations. Tablet formulas with a higher percentage of active can contain only minimal quantities of excipients. These excipients must therefore perform their functions at relatively low levels. The use of a more effective binder such as microcrystalline cellulose may be required to produce these tablets. Tablets with a high percentage of actives frequently require granulation methods of manufacture simply because excipients will not perform their desired function at low levels in a direct-compression method.

Marketing may request a coated tablet product. The quality of a coating on a tablet can be greatly affected by the tablet formulation onto which it is applied. Tablets with low resistance to abrasion (high friability) will result in coatings that appear rough and irregular. Coating adhesion can be greatly affected by the tablet excipients. Hydrophilic excipients can promote greater contact with the coating and result in superior adhesion. Hygroscopic excipients or drugs will cause swelling of a coated tablet and result in rupture of the film with time.

Embossing of compressed tablets is becoming increasingly popular. Embossing permits the tablet to have identifying information without requiring coating and printing operations. Embossing does exacerbate any picking or sticking problems usually observed during compression. This may necessitate higher levels of lubricants and glidant to alleviate these problems. Extreme care should be taken in designing tooling for embossed and scored tablets. It may take several design attempts to select a tooling design that will consistently produce acceptable embossed or scored tablets. Embossed tablets that are to be film-coated present additional coating problems such as bridging of the coat across a depression in a tablet.

Economics

One factor often overlooked in the development of a tablet formula is the cost of the raw materials and the process of manufacture. Direct compression is usually the most economical method of tablet production as previously discussed. In spite of the more expensive excipients used in direct compression, the cost (labor, energy, and time) of granulating is usually greater. Franz et al. [8] showed that a thorough analysis of cost versus time relationships can be performed using simulations before selecting a tableting process. Some companies have preferred manufacturing processes and raw

materials. These general manufacturing processes and materials are considered the first choice when developing a new product. If it is demonstrated that the preferred manufacturing process or materials are not suitable for a new product, then alternative processes or materials are used. The use of preferred processes and materials helps keep the types of equipment needed to manufacture and materials in inventory at a minimum, thus reducing capital expenditures and material costs. Preferred manufacturing process and materials also makes it easier to automate a production facility for multiproduct use.

Process/Product Quality

Excipients should be selected that will enable the production of a tablet that will meet or exceed standard in-house quality tablet specifications. A formulator should be involved in the establishment of tablet specifications and be able to provide sound rationale for the critical specifications. Typical tests performed on tablets are as follows:

Weight variation
Hardness
Friability
Disintegration time
Dissolution
Water content
Potency
Content uniformity

Product quality is most often addressed at the tablet development stage. However, it is also important to monitor the processing quality of a formulation during development. Two reasons for monitoring processing quality during development are (a) to optimize the process as well as the product, and (b) to establish in-process quality control tests for routine production. It is more difficult to quantify the processing quality of a formulation than it is to meausre the product quality. Some measurements that could be performed on the process include

Ejection force
Capping
Sticking
Take-off force
Flow of lubricated mixture
Press speed (maximum)
Frequency of weight control adjustments
Sensitivity of formula to different presses
Tooling wear
Effect of consolidation load (batch size)
Hopper angle for acceptable flow
Hopper orifice diameter for acceptable flow
Compressional forces
Environmental conditions (temperature, humidity, and dust)

Each of the above processing parameters can become a source of trouble in scale-up or routine production. By monitoring these parameters in

development, it may be possible to adjust the formula or process early enough to alleviate the source of trouble.

The expected production output (numbers of tablets) per unit time will determine what speed tablet press will be required for a particular tablet product. If the anticipated unit output for a tablet product is expected to be large, a high-speed press will be required. Attempts should be made in formulation development to design a tablet formula that will perform well on a high-speed press. A formula to run on a high-speed press should have excellent flow to maintain uniform die fill during compressing. It should have good bonding characteristics so that it can compress with a minimal dwell time.

B. Experimental Approach to Developing a Prototype Tablet Formula

After conducting an excipient compatibility study, a formulator may still have a wide choice of excipients available to use in the final tablet formula. The formulator must select a few excipients from a list of chemically compatible excipients. The formulator may later eliminate many drug-compatible excipients by selecting only those excipients known to provide a much needed function in the tablet formula as dictated by medical, marketing, economic, or process/product quality concerns. The objective in screening excipients for a prototype tablet formula is to choose a combination of excipients that most completely achieves desirable tableting characteristics. Tablets made at this stage of experimentation can be made on a Carver, single-punch, or rotary press depending on the amount of drug available. Obviously, no evaluation of the flow properties of a mixture can be made on a Carver or single-punch press. The following is a list of several experimental techniques that may be used to assist the formulator to develop a prototype formula.

Analysis of variance (ANOVA)
Statistical screening designs (first-order designs)
- Plackett Burman
- Extreme vertices

Analysis of Variance (ANOVA)

The ANOVA approach involves making statistical comparisons of different tablet formulas. Each formula represents a different combination of excipients. The selection of a prototype formula is done by running an ANOVA on the results of all the tests performed. The formula that is significantly better than the others tested becomes the prototype formula.

Statistical Screening Designs (First-Order Designs)

Plackett Burman Designs

A statistical screening involves setting lower and upper limits on the levels of each excipient considered for use in a tablet formula. Usually no more than 10 excipients are being considered for use in the tablet at this point. An experimental design is chosen that will enable a statistical test for the effect of each excipient on each process/product quality

Table 1 Twelve-Run Plackett-Burman Design

Trial	× 1	× 2	× 3	× 4	× 5	× 6	× 7	× 8	× 9	× 10	× 11
1	+	+	−	+	+	+	−	−	−	+	−
2	+	−	+	+	+	−	−	−	+	−	+
3	−	+	+	+	−	−	−	+	−	+	+
4	+	+	+	−	−	−	+	−	+	+	−
5	+	+	−	−	−	+	−	+	+	−	+
6	+	−	−	−	+	−	+	+	−	+	+
7	−	−	−	+	−	+	+	−	+	+	+
8	−	−	+	−	+	+	−	+	+	+	−
9	−	+	−	+	+	−	+	+	+	−	−
10	+	−	+	+	−	+	+	+	−	−	−
11	−	+	+	−	+	+	+	−	−	−	+
12	−	−	−	−	−	−	−	−	−	−	−

characteristic (weight variation, hardness, friability, disintegration, dissolution, etc.).

This type of study requires at least n + 1 (n = number of excipients) trials to enable a statistical test. The type of statistical design employed in a screening study is referred to as a Plackett-Burman [9] design. Table 1 shows a 12-run Plackett–Burman design. Using this design, as many as 11 excipients could be screened for use in a tablet formula. Each column represents a different excipient. If seven excipients were to be screened, columns X1 to X7 would define the experimental design. Each row (tablet formula) in Table 1 represents combinations of high (+1) and low (−1) levels of each excipient (Xi) to be screened. The levels specified in each row are used to produce a tablet formula containing a fixed quantity of drug. Tablet formulas containing these mixtures of excipients are compressed and evaluated. A first-order regression model is fit to data collected during the tablet evaluation. Statistical tests can be performed to determine whether each excipient affected the tablet quality in a significantly positive or negative manner. Excipients that did not provide a significant "positive" effect on tablet quality may be either retested in a second screening study at different levels of eliminated from durtehr consideration for inclusion into the tablet formula. A second statistical screen may be performed on excipients to refine excipient ranges to more appropriate levels. Once acceptable excipients and excipient ranges have been established, formulation optimization can proceed.

Extreme Vertices

The extreme vertices design [10] is usually used as an optimization technique. However, it can be used as a screening study if at least n + 1 trials are run. The extreme vertices design is recommended when the

number of components (excipients) is six or more. A first-order model is fit to the data to test for significant excipients as was done in the Plackett-Burman design. The disadvantage of using the extreme vertices design in tablet development is that tablet weight must be kept constant throughout the screening process.

C. Experimental Approach to Optimizing a Prototype Tablet Formula

A tablet formulation optimization study should be performed using an appropriately statistically designed experiment. Numerous experimental design texts [11,12] are available that can assist a formulator in selecting the appropriate experimental design. The extreme vertices design is not recommended in most tablet optimization studies unless tablet weight is to be held constant. It can be beneficial to have a statistician experienced in experimental designs select an appropriate design based on the established excipients and excipient ranges. All excipients should be varied in the optimization study to truly optimize the formulation. Excipients levels are usually the only factors or variables in a formulation optimization study. To reduce the number of factors in a study, a ratio of two excipients can be used. However, the total quantity of those two excipients must be fixed in the formula. When using excipient ratios as factors, include a factor for tablet weight. Tablet weight can then be varied as a factor. If a formulator suspects an interaction between an excipient and a particular process variable, the process variable should be considered for inclusion in the formulation optimization study. For example, in a sustained release direct-compression tablet, compression force may impact on the release rate of the drug from the tablet. In this example, compression force should be included as a factor in a formulation optimization study. Usually, all other process variables are maintained constant. Process variables that cannot be held constant but are *not* expected to impact on the tablet characteristics should be "blocked" appropriately in the design. For instance, different lots of raw materials or bulk drug may be used in an optimization study. The different lots should be treated as blocks in the experimental design. This will allow for a statistical test for block (lot) effect at the data analysis stage of the experiment. In this example, blocks serve as a flag to signal the formulator that the quality of the raw materials is not well controlled. Since the use of blocks do not "cost" the formulator any additional trials, blocks should be used wherever possible. Statisticians experienced in experimental design frequently state that you cannot lose by blocking!

It is important that all trails are performed in a randomized manner. After all the tablets have been manufactured, data analysis begins. A standard quadratic model is most often used to fit second-order experimental design data. Commercially available software (XSTAT, STATGRAPHICS, PCSAS, ECHIP) may be used to generate the coefficients and statistical tests on the raw data collected. This software will also provide a statistical analysis of the regression models produced. The analysis of the regression model provides the scientist information on how well the model explained the data variation. If a particular regression model does not satisfactorily explain the data variation, transformations of the raw data can be tried to improve the fit of the model. For a regression model to be acceptable, the $R_2 > 0.75$ the lack of fit should not be significant, and the residuals should

have no more than a few outliers. Once acceptable models have been established for each tablet characteristic, the scientist should examine the models to determine which main effects, interactions, or quadratic terms are significant. The formulator should then generate response surface plots of significant interactions as a function of the tablet characteristic. Response surface plots of significant main effects and quadratic terms will also help the formulator to understand the critical relationships between tablet characteristics and the formulation factors.

Optimization of the final formulation can be performed using commercially available software (XSTAT, ECHIP, and PCSAS). Optimization invariably requires that constraints be placed on some or all of the critical response parameters. Constraints may also be placed on some or all of the factors as well. One critical tablet characteristic must be selected to optimize (minimize or maximize) while the other tablet characteristics and formulation factors are left constrained or unconstrained. For example, tablet friability could be constrained below 0.3% while dissolution rate is maximized. The mathematical algorithm used in specific optimization routines (software) varies. Optimization algorithms used in software routines are usually based on a simple method or a grid search method. The final formula determined to be optimal should be experimentally verified by manufacture and testing. Model predicted values for tablet characteristics should "agree" with actual experimental data collected on the optimal formula.

D. Establishment of Excipient and Preliminary Process Ranges

In light of the present interest in validating the product as well as the process of manufacture, it is to the formulator's advantage to establish excipient and process variable ranges. Having excipient and process ranges also allows production to make appropriate excipient or process changes without prior notification of the regulatory agencies.

If it can be demonstrated that the excipient ranges used for conducting the optimization study produced acceptable tablets (i.e., all tablets produced were acceptable, then the excipient ranges used in the study should be used as final product ranges. However, if the excipient ranges used in the optimization study were not always acceptable, the ranges should be narrowed to acceptable limits. This can be done by performing constrained optimization of the critical response variables using registration specifications on the response variables as the constraining limits.

E. Bioavailability Studies

In vivo test procedures appropriate for tablets and other solid dosage forms are also the subject of Chapter 6 in Volume II of this series. In some cases in vivo testing of tablet formulations involves studies in animals prior to studies in humans: in other cases the tablet formulations are studied directly in humans.

When in vivo studies in humans are undertaken, it may be desirable or even essential to conduct such studies with more than one formulation. This is particularly true if a goal of product design is product optimization, and a primary objective is to maximize bioavailability or response versus time profile. A bioavailability study should eventually be run comparing

the optimized formulation, a formulation (within the excipient ranges) predicted to have the slowest dissolution, and a formulation (within the excipient ranges) predicted to have the fastest dissolution. The bioavailability study results can be used to establish a correlation between the in vitro dissolution test and the in vivo bioavailability parameters. If the three formulations (optimal, slow, and fast-dissolving) turn out to be bioequivalent, the excipient ranges are valid from the in vivo performance viewpoint. If the three formulations are not bioequivalent, then the excipient ranges should be tightened using the in vitro/in vivo correlation. The specifications for the dissolution of the tablet should be set based on this correlation.

F. Development of Stability Data for Tablet Formulations

Stability data should be collected on the bulk drug as well as the final product stability. Stability on the bulk drug should be available in the preformulation data. Based on the results of the bulk drug stability testing, recommendations should be made about the storage conditions and the shelf life of the bulk drug.

The final tablet formulation should be placed up on stability as soon as possible after its invention. Also, formulas that "cover" the proposed excipient ranges may also be placed up on stability. Stability data should be generated with the tablet in all the expected packaging configurations (i.e., blisters, plastic and glass bottles, etc.). Ideally several lots of tablets should be put on stability using different lots of bulk drug. Having different lots of tablets containing different lots of bulk drug will give an indication of the lot-to-lot variability in product stability. Accelerated stability testing (high temperature, humidity, or intense lighting) can be helpful in judging the long-term stability of a tablet package system.

In addition to the stability data generated on the final formula, stability data generated on *similar* formulations can sometimes be used as supportive stability data. Usually there will be more supportive stability data available because the similar formulations were developed prior to the optimal formula.

Based on the product stability data, a formulator must recommend proper storage conditions, special labeling regarding storage, and an expiration date for each tablet package system.

G. Development of Validation Data for Tablet Formulations

As required under an NDA, process validation is the final step undertaken after the process has been scaled up to full production batch size. Under the concept of validation, an immense work load is placed on the pharmacy development group, the pilot plant group, and possibly the production department to achieve the goals of validation as previously defined. Because of the immense work load, some companies have created a group dedicated to assist formulators in validating their manufacturing processes. As a rule of thumb, the less complex the manufacturing process, the better defined the drug and excipient specifications, the easier the validation process. The need to validate tablet products provides a great impetus to the use of optimization techniques in tablet product design. The data base required for product validation will often be adequate when development has

proceeded using optimization techniques. The validation of a new or reformulated tablet product requires two phases. In phase I the development team formulates the product and general process of manufacture. In phase II, emphasis is placed on the process validation of production scale batches. Phase II is usually accomplished at the production startup of a new or reformulated product.

The objectives in phase I include:

1. Producing an optimal formula and process.
2. Identifying the most critical tablet characteristics and establishing specifications for the tablet.
3. Quantifying relationships between the critical tablet characteristics and process/formulation variables.
4. Establishing specifications for process/formulation variables to ensure that tablet specifications will be met.
5. Proposing in-process tests for critical process variables and raw materials specifications for critical formulation variables when appropriate.
6. Documenting above information.

The objectives in phase II include

1. Demonstrating that all manufacturing equipment and related systems (SOPs, equipment calibration, cleaning procedures, assays, packaging, and personnel training) have been qualified for use in the manufacture and testing of this product.
2. Drafting a process validation protocol before manufacture of first production lots that specifies the procedures to be validated. This protocol should be written to challenge the proposed limits on the critical process/formulation variables.
3. Running production/validation lots; collecting and analyzing data.
4. Demonstrating that all product specifications have been met in spite of the challenges presented to the process.
5. Documenting above information.

Usually several production lots are required to complete phase II validation. The more process/formulation variables, the more production lots will have to used. If the production scale validation lots pass all the required specifications for that tablet product, the lots may be used for commercial sale.

IV. TABLET COMPONENTS AND ADDITIVES

A. Active Ingredients

General Considerations

Broadly speaking, two classes of drugs are administered orally in tablet dosage form. These are (1) insoluble drugs intended to exert a local effect in the gastrointestinal tract (such as antacids and absorbents) and (2) soluble drugs intended to exert a systemic drug effect following their dissolution in the gut and subsequent absorption. With each class of drugs very careful attention must be given to product formulation and design as well as to manufacturing methods in order to produce an efficacious and

reliable product. The goal in designing tablet dosage forms for these two classes of drugs is different. When working with insoluble drugs whose action is usually strongly affected by surface phenomena (such as antacids and absorbents) it is critical that a product be designed that will readily redisperse the produce a fine particle size and large surface area. Accordingly the effect of formulation, granulation, and tableting on the surface properties of the material and the ability to regenerate a material in the gut with optimum surface properties are critical.

In the case of drug products intended to exert a systemic effect, the design of a dosage form which rapidly disintegrates and dissolves may or may not be critical, depending on whether the drug is absorbed in the upper gastrointestinal tract or more generally throughout the intestinal tract, and also based on the solubility properties of the drug at or above its absorption site. Dosage forms must, however, be designed which do disintegrate or dissolve to release the drug in an available form at or above the region of absorption in the gut.

The developmental pharmacist usually does not have a great deal of input into selecting the chemical form of an active ingredient. Drug-screening programs may not offer several salt or ester forms of the drug as candidates for a particular therapeutic claim. Instead the formulator, provided with small quantities of an active ingredient in a particular form to evaluate in the preformulation studies, is faced with the task of developing a tablet—which may be capable of handling only drugs of the same physical and chemical properties as the small sample. When large batches become available, often months later, they frequently differ in physical properties, making formulation and processing modification necessary. Given the opportunity, the preformulation scientist may suggest a particular salt or crystal form of the drug that is more stable, more suitable for tableting, or more bioavailable. As an example, ethanol-recrystallized (ethyl) ibuprofen is the form of drug initially developed to produce ibuprofen tablets. The ethyl drug is poorly compressible and usually must be tableted using wet granulation processing. Tablets made with the ethyl drug have a tendency to pick, stick, and laminate during compression. Methanol-recrystallized "methyl' ibuprofen [10] was subsequently developed. Methyl drug was capable of being tableted in a direct-compression formulation with no picking, sticking, or lamination problems. The difference between the crystal habits of the two drugs resulted in dramatically different tableting properties.

It is imperative that the physical properties of the active ingredient be thoroughly understood prior to the time of finalizing the formula. Indeed, these properties may provide a rational basis for a particular tablet design, such as rapid dissolution for a drug likely to be absorbed high in the upper gut, or the need for enteric or other forms of gastric protection for an acid-labile drug.

Although almost all tablets will require the addition of nonactive components or excipients—to produce satisfactory drug release, to achieve acceptable physical and mechanical properties, and to facilitate their manufacture—the formulator should not be anxious to begin adding excipients until the properties of the drug are thoroughly understood. If a substance possesses the proper crystalline structure, it can be compressed directly into a tablet without further treatment. Relatively few such materials (active or excipient) exist, and their number diminishes further if one considers only materials with therapeutic activity. Jaffe and Foss [13]

confirmed that generally drugs of cubic crystalline structure are compressible directly, since upon compression the crystals are fractured, and the fragments form a close-packed arrangement which readily consolidates on compression. In a cube, the structure is the same along each axis; thus, no alignment is necessary in order for ionic or van der Waals bonding to occur between the individual particles. Sodium choride has a cubic structure and is an example of a directly compressible material.

In crystals which are not cubic, some realignment is necessary, which results in a reduced probability of bonding. Employing potassium chloride as a model, Lazarus and Lachman [14] found that the compaction of these crystals depended on many factors, such as particle size distribution, crystal shape, bulk density, and moisture content. If the drug to be formulated happens to possess a crystalline structure allowing for direct compaction, the formulator's task will be lessened. Rankell and Higuchi [15] have presented a theoretical discussion on the physical process which may be responsible for interparticulate bonding during compression. While the tableting aspects will be straightforward, the other requirements, such as acceptable friability, hardness, appearance, disintegration, and dissolution, must be met.

It is extremely rare to find a drug system which does not involve the use of excipients. The contribution of excipients will be discussed in Section IV.B. The treatment of processing which the active ingredient receives (alone or in combination with the excipients) will depend upon the dosage level, the physical and chemical properties of the active drug substance and the excipients used, the nature of the drug, its use, any absorption or bioavailability problems, and the granulation and tableting method employed. When potent drugs of limited solubility are involved, their particle size and uniform distribution throughout the tablet can dramatically affect the rapidity of their dissolution and absorption as well as content uniformity. However, if large dosage regimens of a soluble drug are considered, the effect of particle size is important—more from a processing standpoint than because of dissolution or absorption considerations. The relationship of various particle size factors to therapeutic effectiveness of drugs was discussed by Rieckmann [16]. He pointed out that one must be cautious in equating micronization, dissolution, and adsorption, especially with drugs such as nitrofurantoin, chloramphenicol, and spironolactone.

The role of the active ingredient can then be considered in two broad systems: first, when the drug–excipient interactions are considered primarily from a pharmacological (dissolution and absorption) viewpoint; and second, where in addition to the concerns in the first area, significant processing questions must be answered.

Bioavailability Considerations

Before drugs can effectively pass through the gastrointestinal wall they must be in solution. Drugs which are only sparingly soluble in the gastrointestinal contents at or above the absorption site can have, as the controlling process affecting their absorption, the rate of drug solution in these fluids. In this type of system, the drug goes into solution at a slow rate; absorption occurs almost immediately and is not, therefore, the rate-limiting step. In one study, Nelson [17] correlated the blood level concentration of various theophylline salts with their dissolution rates.

As noted earlier in this chapter and throughout this volume, drugs which exert a systemic effect must dissolve as a prerequisite to effective

drug absorption. The various processes of tablet making, including the aggregation of drug into granular particles, the use of binders, and the compaction of the system into a dense compact, are all factors which mitigate against a rapid drug dissolution and absorption in the gastrointestinal tract. In considering in a general manner the availability of drugs from various classes of dosage forms, drugs administered in solution will usually produce the most available drug product—assuming the drug does not precipitate in the stomach or is not deactivated there.

The second most available form of a therapeutic agent would be drug dispersed in a fine suspension, followed by micronized drug in capsule form, followed by uncoated tablets, with coated tablets being the least bioavailable drug product in general. In formulating and designing drug products as well as in considering methods of manufacture, the fact that the tablet dosage form is one of the least bioavailable forms (all other factors being equal) should be kept in mind.

Many factors can affect drug dissolution rates from tablets, hence possibly drug bioavailability—including the crystal size of the drug; tablet disintegration mechanisms and rates; the method of granulation; type and amount of granulating agent employed; type, amount, and method of incorporation of disintegrants and lubricants; and other formulation and processing factors.

Levy et al. [18] showed the effects of granule size on the dissolution rate of salicylic acid. Salicylic acid of two mesh ranges, containing 300 mg of aspirin and 60 mg of starch, were compressed at 715 kg cm^{-2}. The data are shown in Figure 2.

Lachman et al. [19] studied the effect of crystal size and granule size on a delayed action matrix using tripelennamine hydrochloride. He noted that while granule and crystal size both affected release rate, in this instance the crystal size played a greater role than granule size in dissolution rate.

Paul et al. [20] showed that with nitrofurantoin there was an optimal average crystal size of about 150 mesh, which resulted in adequate drug excretion (hence absorption and efficacy) but minimized emesis. This exemplifies a situation in which too rapid drug dissolution in the stomach may produce nausea and emesis; an intermediate release rate reduces this effect while achieving adequate bioavailability.

Numerous accounts of the effect of particle size on the dissolution rate of steroids have been reported. In one study Campagna et al. [21] showed that, in spite of good disintegration, therapeutic inefficacy of prednisone tablets could occur.

B. Nonactive Ingredients

The selection and testing of nonactive ingredients or excipients in tablet formulas present to the formulator the challenge of predictive foresight. While the ability to solve problems when they occur is a valuable attribute, the ability to prevent the problem through adequate experimental design is a virtue, leads to more reliable and expeditious product development, and, when coupled with optimization methods, enables the formulator to tell how close a particular formula is to optimum conditions.

It will become obvious to the formulator, on reviewing the literature, that the total number of significant excipients currently in use is probably less than 25. These 25 materials fulfill the needs of the six major excipient

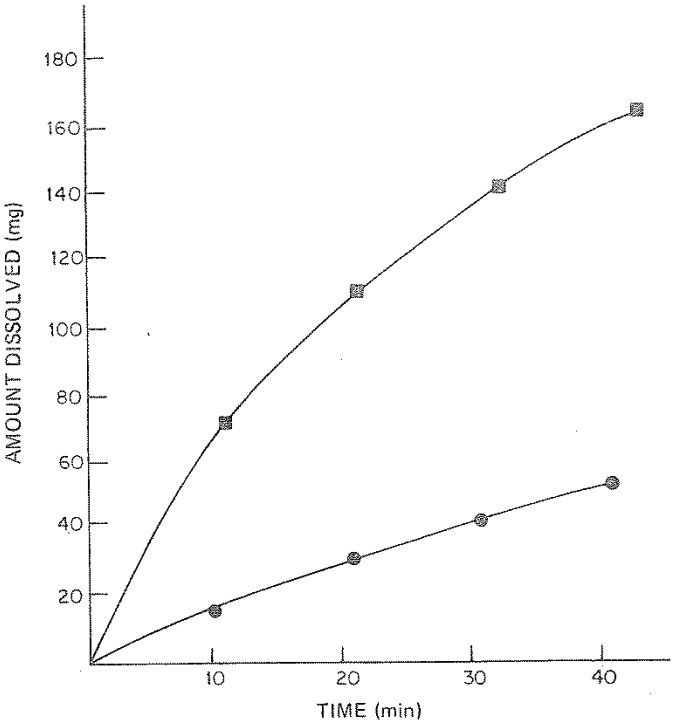

Figure 2 Effect of granule size on the dissolution rate of salicylic acid contained in compressed tablets. Key: ● 40- to 60-mesh granules; ■ 60- to 80-mesh granules.

categories: diluents, binders, lubricants, disintegrants, colors, and sweeteners (flavors excluded). The *United States Pharmacopeia* (USP XIX) recognized the important role excipients play in dosage form design by initiating a new section entitled "Pharmaceutic Ingredients." In time, official monographs may be developed for all the major or commonly used excipients. In 1974 the Swiss pharmaceutical companies, Ciba-Geigy, Hoffman-LaRoche, and Sandoz, joined together to publish in the German language an *excipient catalog (Katalog Pharmazeutischer Hilfsstoffe)*, covering almost 100 official and nonofficial excipients. The book contains general information, suppliers, tests, and specifications obtained from the literature or measured in the laboratories of the above companies. The development of an excipient codex was a major project of the Academy of Pharmaceutical Sciences of the American Pharmaceutical Association [22].

It will become apparent later in this section that many times the 25 or so excipients have been repeatedly evaluated over the past 50 years, and yet these same materials continue to stand the test of time. Rather than belabor the point we must simply be reminded that the tried and tested materials, by their longevity, deserve careful consideration. The formulator should not, however, be fearful of change or of evaluating new

ingredients. Some formulators tend to "lock-in" on particular formulation types of approaches which have been successful in the past; the danger here is that one becomes dated. At the other extreme is the formulator who takes a quick look at a new disintegrant or binder, which then ends up in the formula months before sufficient data are available to make possible a sound judgment of total acceptability. Thus the best formulator is an individual who is constantly searching for new and better methods and systems, who avoids becoming sterotyped, and who is cautious and thoroughly analyzes new approaches without developing an undue proprietary or vested interest in them.

Additives are usually classified according to some primary function they perform in the tablet. Many additives will also often have secondary functions, which may or may not be of a beneficial nature in good, solid design of oral dosage forms. Some fillers or diluents may facilitate tablet dissolution, which is beneficial, while others may impair dissolution. The most effective lubricants are water repellent by their nature, which may retard both disintegration and dissolution.

Bavitz and Schwartz [23] concluded, in a paper evaluating common tablet diluents, that their proper choice becomes more critical when formulating water-insoluble drugs as opposed to water-soluble drugs. They showed that "inert ingredients" can profoundly affect the properties of the final dosage form. A knowledge of the properties of additives and how they affect the properties of the total formulation is necessary to provide guidelines in their selection. This is particularly true when the drug concentration is small. The drug plays a more significant role in determining the physical characteristics of the tablet as the drug concentration increases.

Two major classifications of additives by function include those which affect the compressional characteristics of the tablet:

Diluents
Binders and adhesives
Lubricants, antiadherents, and glidants

and those which affect the biopharmaceutics, chemical and physical stability, and marketing considerations of the tablet:

Disintegrants
Colors
Flavors and sweeteners
Miscellaneous components (e.g., buffers and adsorbents)

Diluents

Although diluents are normally thought of as inert ingredients, they can significantly affect the biopharmaceutic, chemical, and physical properties of the final tablet. The classic example of calcium salts interfering with the absorption of tetracycline from the gastrointestinal tract was presented by Bolger and Gavin [24]. The interaction of amine bases or salts with lactose in the presence of alkaline lubricants, and subsequent discoloration (as discussed by Costello and Mattocks [25] and Duvall et al. [26]), emphasized that excipient "inertness" may often not exist in the design of drug dosage form.

Keller [27] reviewed the properties of various excipients while Kornblum [28,29] proposed preformulation methods of screening materials for use as

diluents. Simon [6] described rapid thermal analytical methods of screening for possible drug–excipient interactions. In another study Ehrhardt and Sucker [30] discussed rapid methods to identify a number of excipients used in tablet formulations.

Usually tablets are designed so that the smallest tablet size which can be conveniently compressed is formed. Thus, where small dosage level drugs are involved, a high level of diluent or filler is necessary. If, however, the dosage level is large, little or no diluent will be required, and the addition of other excipients may need to be kept to a minimum to avoid producing a tablet that is larger than is acceptable. In such large drug dosage situations, nevertheless, excipient materials must often be added to produce a granulation or direct-compression mixture which may be compressed into acceptable tablets.

Where moisture is a problem affecting drug stability, the initial moisture level, as well as the tendency of the material to retain or pick up moisture, must be considered. The hygroscopic nature of excipients, as described by Daoust and Lynch [31], is an important consideration in formulation studies for the following reasons:

1. Water sorption or desorption by drugs and excipients is not always reversible. Absorbed moisture may not be easily removed during drying.
2. Moisture can affect the way in which a system accepts aqueous granulating solutions.
3. The moisture content and rate of moisture uptake are functions of temperature and humidity and should be considered.
4. Moisture content in a granulation affects the tableting characteristics of the granulation.
5. Hygroscopicity data can aid in the design of tablet-manufacturing areas.
6. Moisture-sensitive drugs should not be combined with hygroscopic excipients.
7. Packaging materials should be chosen to suit the product.

Sangekar et al. [32] reported on the percent moisture uptake of tablets prepared from various direct compression excipients. Figure 3 indicates that a range of 1.7 to 5.6% uptake is possible, depending on the excipient used. Dicalcium phosphate, lactose anhydrous DTG, and lactose beadlets absorbed the minimum amount of moisture, while sorbitol and sucrose absorbed the maximum. Mannitol, dextrose, and monocalcium phosphate were shown to be intermediate.

In selecting diluents, the materials will be found to contain two types of moisture, bound and unbound. The manner in which a diluent holds its moisture may be more important than the affinity of the material for moisture or the amount of moisture present. Calcium sulfate dihydrate, for example, contains 12% moisture on a mole-for-mole basis. The water is present, however, as bound moisture (as water of crystallization). Furthermore the tightly bound water is not liberated until a temperature of about 80°C is reached (well above normal product exposure temperatures). Since calcium sulfate dihydrate is thermodynamically satisfied as to water content and moisture demand, it is not hygroscopic and absorbs little moisture. Since the bound water is generally unavailable for chemical reaction, $CaSO_4 \cdot 2H_2O$ has been widely used in vitamin tablets and other systems

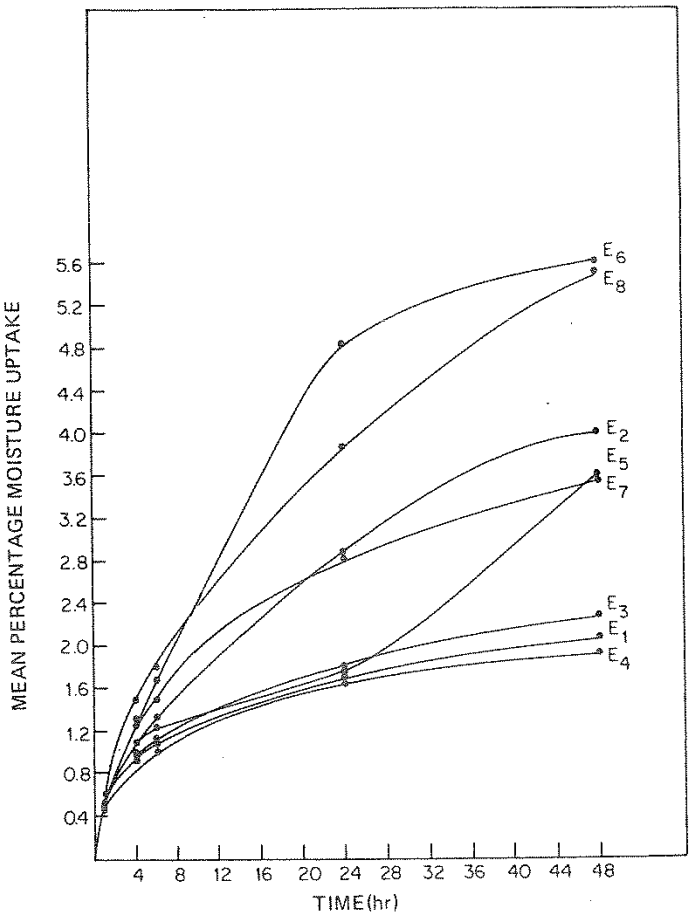

Figure 3 Direct-compression tablets with different excipients (E_1 to E_8), common binder (microcrystalline cellulose), and common disintegrant (alginic acid). Mean percent moisture uptake across humidity levels of 43, 65, 75, and 100% relative humidity at 25°C. Key: E_1, dibasic calcium phosphate dihydrate (unmilled); E_2, monobasic calcium phosphate monohydrate; E_3, lactose anhydrous DTG; E_4, lactose hydrous beadlets; E_5, mannitol granular; E_6, sorbitol crystalline, tablet type; E_7, dextrose; E_8, sucrose.

which are moisture-sensitive. Such a system, containing tightly bound water but with a low remaining moisture demand, may be vastly superior to an anhydrous diluent (or other excipient) which has a high moisture demand. When using a hydrate or excipient containing water of crystallization or other bound water, careful attention must be paid to the conditions under which this water is released.

The degree of cohesiveness which a diluent imparts to various drug substances when compacted into tablets becomes increasingly important when tablet size is a factor. Where size is not a factor, the ratio of the cohesiveness imparted by a diluent to its cost per kilogram should be considered. For example, if size is not a factor, a diluent that costs $3.08 per kilogram and is effective at a 10% concentration might be replaced by a diluent that must be present at a 25% concentration, that costs $0.66 per kilogram. Kanig [33] reviewed the ideal properties of a direct compaction diluent material, many of which hold true of any diluent.

In special tablets, such as chewable tablets, taste and mouth-feel become paramount in diluent selection. In these specialized tablets a consideration of unique aging effects, such as increased hardness and reduced "chewability," must be carefully examined.

The sensitivity of diluents to physicochemical changes caused by processing or manufacturing, both of which influence final tablet quality, should be considered in diluent selection. This is illustrated in Figures 4 and 5 [34] by a comparative evaluation of excipients for direct-compression formulas. These figures indicate the variety of disintegration and hardness

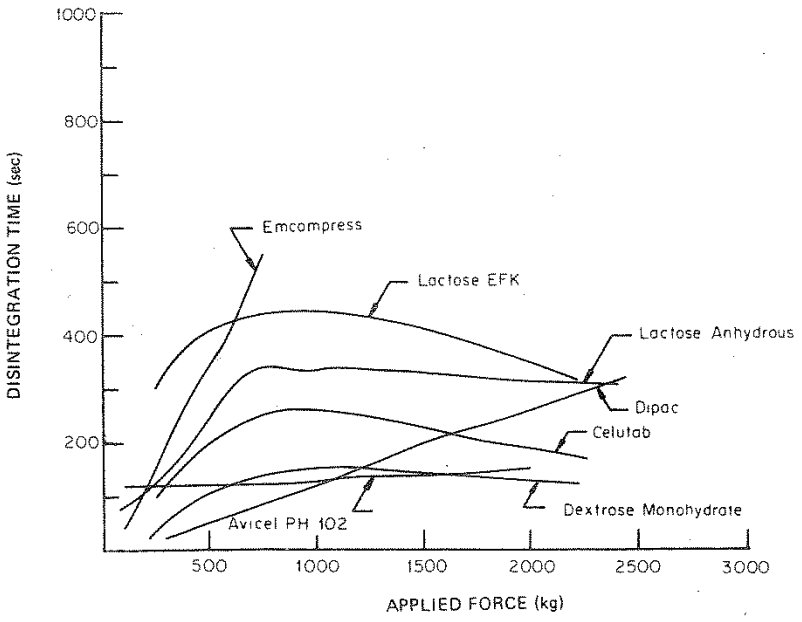

Figure 4 Disintegration time versus applied force for compacts of various materials.

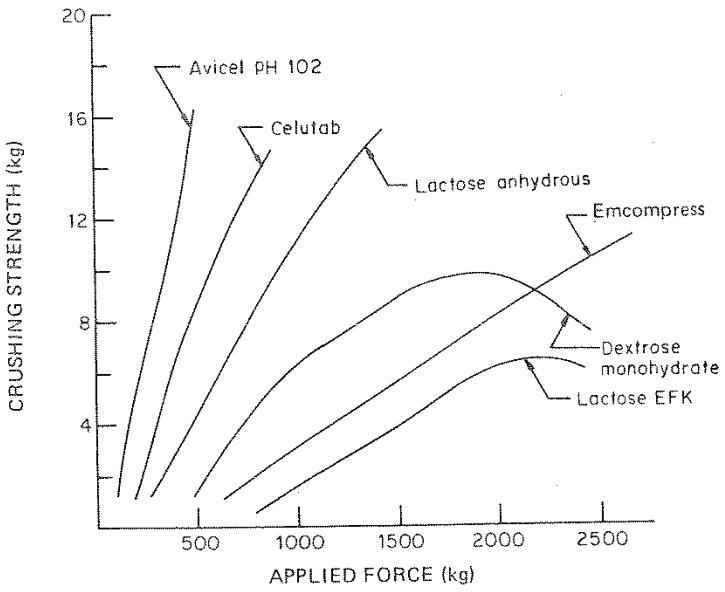

Figure 5 Crushing strength versus applied force for compacts of various materials.

profiles possible. Combinations of two or more excipients generally provide a final disintegration-hardness spectrum which lies between the values for each material when used separately. The figures also show the sensitivity of various agents to alterations in properties (disintegration time and crushing strength) with changes in compressive load. Emcompress, for example, was very sensitive to a change in compressive load in this study whereas Celutab and dextrose monohydrate are almost totally insensitive. Ideally, the diluent selected will not be sensitive to processing variables, such that the quality of the final tablet features can degrade appreciably under the processing variables encountered in production. This is an important consideration in the validation of a product and its method of manufacturing: identifying the range of product quality features produced by the expected limits of the processing variables encountered in production, and designing product formulation and processes so as to minimize such variability.

Lactose USP is the most widely used diluent in tablet formulation. It displays good stability in combination with most drugs whether used in the hydrous or the anhydrous form. Hydrous lactose contains approximately 5% water of crystallization. The hydrous form is commonly used in systems that are granulated and dried. Several suppliers offer various grades of hydrous and anhydrous lactose. The various grades have been produced by different crystallization and drying processes. It is most important not to assume that one form of lactose will perform in a similar manner as another form. Lactose is available in a wide range of particle size distributions. Nyqvist and Nicklasson [35] studied the flow properties of directly compressible lactose in the presence of drugs. While lactose is freely

(but slowly) soluble in water, the particle size of the lactose employed can affect the release rate of the medicinal. Recent studies indicate the $T_{50\%}$ (time required for 50% of the drug to dissolve) was decreased by a factor of 8 when micronized lactose (2 to 5 $mg^2\ g^{-1}$) was used rather than unmicronized lactose (0.5 $m^2\ g^{-1}$ surface area).

Lactose formulations usually show good drug release rates, are easy to dry (both in thrays and fluidized bed dryers), and are not sensitive to moderate variation in tablet hardness upon compression. They find exceptional application in tablets employing small levels of active ingredients (e.g., steroids). The cost of lactose is low relative to many other diluents. As noted previously, lactose may discolor in the presence of amine drug bases or salts and alkaline lubricants.

Lactose USP, anhydrous offers most of the advantages of lactose USP, hydrous, without the reactivity of the Maillard reaction, which leads to browning. Tablets generally show fast disintegration, good friability, and low weight variation, with an absence of sticking, binding, and capping. The applications of the anhydrous form have recently been evaluated by a number of investigators [36–39]. Mendell [40] has reported on the relative sensitivity of lactose to moisture pickup at elevated humidities. Blister packages should be tested at elevated temperatures and humidity to establish their acceptability with lactose-based formulas.

Lactose USP, spray-dried has improved flow and bond properties over the regular lactose due to the general spherical form of the aggiomerates. This shape can be affected by high-shear milling. The effect of particle diameter on particle and powder density, and angle of friction and repose, and the effect of orifice diameter on the flow rate have been studied by Alpar et al. [41] and Mendell [40]. Even when granulated, spray-dried lactose displays its flow and bond properties. It is commonly combined with microcrystalline cellulose and used as a direct-compaction vehicle. Alone, it usually must be used at a minimum concentration of 40 to 50% of the tablet weight for its direct-compaction properties to be of value. It has the capacity of holding 20 to 25% of active ingredients. Care must be exercised upon storage since loss of the usual 3% moisture content can adversely affect compressional properties.

Brownley and Lachman [42] reported that, as with lactose USP, care must be taken in using spray-dried lactose since it tends to become brown due to the presence of 5-(hydroxymethyl)-2-furaldehyde, when combined with moisture, amines, phosphates, lactates, and acetates. Similar findings were reported by Duvall et al. [26] even in systems not containing amines. The employment of neutral or acid lubricants such as stearic acid appears to retard the discoloration, while alkaline lubricants (e.g., magnesium stearate) accelerate the darkening. Bases as well as drugs which release radicals (e.g., amino salts) can bring about this browning, known as the Maillard reaction. Richman [43] reviewed the lubrication of spray-dried lactose in direct-compaction formulas and reported that this lactose form may affect the mechanism of action of lubricants.

The cost of spray-dried lactose is moderate; however, the fact that it is not available from a large number of suppliers could limit its widespread use. Tablets made with spray-dried lactose generally show better physical stability (hardness and friability) than regular lactose, but tend to darken more rapidly.

It was reported by Henderson and Bruno [39] that the tableting characteristics of spray-dried lactose were inferior to those of lactose beadlets. However, the physical stability of the resulting products was similar.

Starch USP may come from corn, wheat, or potatoes and finds application as a diluent, binder, and disintegrant. Tablets containing high concentrations of starch are often soft and may be difficult to dry, especially when a fluidized bed dryer is used. Commercially available starch USP may vary in moisture content between 11 and 14%. Certain specially dried types of starch are available at moisture levels of 2 to 4% at a premium price. Where the starch is used in a wet (aqueous) granulated system, the use of specially dried starch is wasteful since normal drying techniques will result in a moisture level of 6 to 8%. Recent studies indicate that, in some drug systems, starch—initially at a moisture level of 10% or greater—may perform differently with respect to dissolution than starch at a 5 to 7% level, even though the final equilibrium moisture levels of the tablet are the same.

There are also indications that, although starch reaches a moisture plateau of 11 to 14%, it often serves as a local desiccant to help stabilize moisture-sensitive drugs. This attribute can act in a negative fashion, however, as in steroid tablets, where the localization of moisture may result in reduced dissolution rates.

In a study on the effect of granule size, compression force, and starch concentration on the dissolution rate of salicylic acid, Levy [44] showed an increase in dissolution rate with decreasing granule size, increasing precompression force, and increasing starch content.

The effect of starch on the disintegration time of tolbutamide tablets was studied by Commons et al. [45]. They showed a critical starch concentration for different granule sizes of tolbutamide; however, disintegration times did not decrease with increasing starch levels.

Schwartz et al. [46] evaluated the incorporation of starch USP versus a modified cornstarch in various formulations. The modified starch generally exhibited improved processing characteristics and improved tablet properties, compared to starch USP.

Directly compressible starch, marketed commercially as Starch 1500, is physically cornstarch. Chemically, compressible starch does not differ from starch USP. It is a free-flowing, directly compressible excipient, which may be used as a diluent, binder, and disintegrating agent. When compressed alone, it is self-lubricating and self-disintegrating, but when combined with as little as 5 to 10% of an ingredient that is not self-lubricating, it requires additional lubricant and usually a glidant, such as colloidal silicone dioxide, at 0.25%.

Starch 1500 contains about 10% moisture and is susceptible to softening when combined with excessive amounts (greater than 0.5%) of magnesium stearate. Direct compaction starches have been reported [47] to not affect the stability of aspirin where moisture may be a concern. Most of the formulas evaluated also contained microcrystalline cellulose.

Underwood and Cadwallader [48] studied the effect of various starches on the dissolution rate of salicylic acid from tablets. They showed that the dissolution of the drug was most rapid from tablets containing a compressible starch (Fig. 6).

Mannitol USP finds increasing application in the formulation of chewable tablets where mouth-feel and palatability are important considerations. Its mouth-feel is related to its negative heat of solution and its slow solubility, which is experienced by the user as a cool sensation during dissolution of the sugar. It has been reported to be about 72% as sweet as sucrose. One gram dissolves in 5.5 ml of water. Chewable vitamins and antacids are the primary application for this material, although certain regular chewable

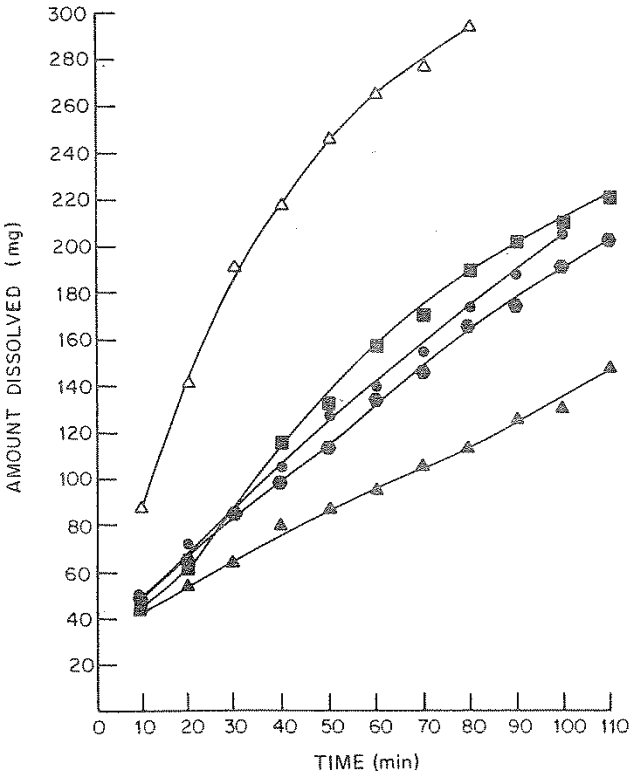

Figure 6 Dissolution rates of salicylic acid from tablets containing various starches, using the USP-NF method type 1 (basket, 100 rpm) at 37°C. Key: ● cornstarch; ■ potato starch; ▲ rice starch; ◍ arrowroot starch; △ compressible starch.

tablets intended for swallowing do incorporate mannitol because of its non-hygroscopicity.

Mannitol formulations, because of their poor flow properties, usually require higher lubricant levels (3 to 6 times as great) and higher glidant levels for satisfactory compression than other diluents. Kanig [49] has reported on studies to overcome these shortcomings by spray-congealing fused mannitol alone with sucrose or lactose. A wide range of tablet hardness can be obtained with mannitol-based tablets. Staniforth et al. [50] crystallized mannitol to produce an excipient with an optimal particle size and surface coarseness for a direct-compression excipient. Mannitol is a relatively expensive diluent, and attempts are usually made to reduce its quantity per tablet. A granular form of mannitol is now available as a direct-compression excipient. Mannitol has been shown to be chemically compatible with moisture-sensitive compounds. It picks up less than 1.0% moisture at relative humidities as high as 90%.

Sorbitol is an optical isomer of *mannitol* but differs dramatically from it in that sorbitol is hygroscopic at humidities above 65% and is more water-soluble than mannitol. It may be combined with an equal weight of dicalcium phosphate to form a direct compaction carrier. Mannitol and sorbitol are noncariogenic sugars and are of low nutritional and caloric content.

Microcrystalline cellulose N.F., often referred to as Avicel, has found wide application in the formulation of direct-compaction products. Tablets prepared from the more widely used tablet grades PH 101 (powder) and 102 (granular) show good hardness and friability. The flow properties of microcrystalline cellulose have been described by Mendell [40] as poor, by Fox et al. [51] as good, and by Livingstone [52] as very good, once again indicating that each additive must be evaluated in the formulator's own system.

Numerous other investigators [53–58] have reviewed the applications of microcrystalline cellulose in tablet formulations. The capillarity of Avicel explains the penetration of water into a tablet, thereby destroying the cohesive bonds between particles. The hardness of the compressed tablet can significantly affect the disintegration time by breaking down the structure of the intermolecular spaces and destroying the capillary properties.

Avicel is a relatively expensive diluent when compared with lactose USP or starch USP. Usually it is not used in tablets alone as the primary diluent unless the formulation has a specific need for the bonding properties of Avicel. It is capable of holding in excess of 50% active ingredients and has certain unique advantages in direct compression which may more than offset its higher cost. As a diluent, Avicel offers many interesting possibilities to control drug release rates when combined with lactose, starch, and dibasic calcium phosphate. Bavitz and Schwartz [23,37] have reported on various combinations for use with water-soluble and water-insoluble drugs. Avicel possesses the ability to function both as a binder and disintegrant in some tablet formulas, which may make it very useful in tablets which require improvement in cohesive strength, but which cannot tolerate lengthened disintegration times.

Tablets containing high Avicel levels may be senstive to exposure to elevated humidities and may tend to soften when so exposed.

Dibasic calcium phosphate dihydrate NF, unmilled, is commonly used as a tablet diluent. A commercially available free-flowing form is marketed as Emcompress and has been described for use in tablet making by Mendell [40]. It is used primarily as a diluent and binder in direct-compaction formulas where the active ingredient occupies less than 40 to 50% of the final tablet weight. Emcompress is composed of 40- to 200-mesh material, is nonhygroscopic, and contains about 0.5% moisture. In direct-compaction formulas, 0.5 to 0.75% magnesium stearate is required as a lubricant. It shows no apparent hygroscopicity with increasing relative humidities (40 to 80%).

Bavitz and Schwartz [23] showed the negative effect on dissolution of increasing the ratio of dibasic calcium phosphate to microcrystalline cellulose in a system containing an "insoluble" drug, indomethacin USP (Fig. 7). Formula IV (50:50) released 66% of the drug in 30 min. The amount released decreased to 18% and 10% in 30 min as the ratio of dibasic calcium phosphate to microcrystalline cellulose increased to 70:30 (formula V) and 84:16 (formula VI), respectively. The study highlights the importance of carriers when insoluble drugs are employed.

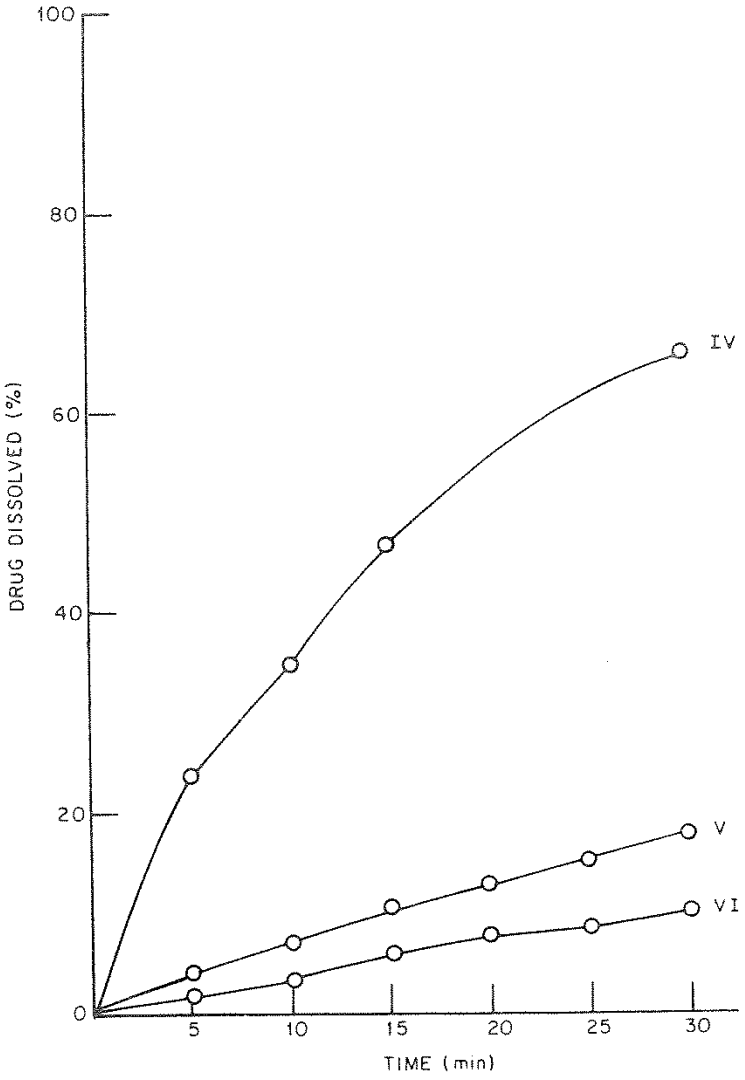

Figure 7 Drug release of an insoluble drug from direct-compression diluents diluents (see text). IV = microcrystalline cellulose N.F./dibasic calcium phosphate N.F., 50:50. V = microcrystalline cellulose N.F./dibasic calcium phosphate N.F., 30:70. VI = microcrystalline cellulose N.F./dibasic calcium phosphate N.F., 16:84.

Khan and Rhodes [59] reviewed the disintegration properties of dibasic calcium phosphate dihydrate tablets employing insoluble and soluble disintegrating agents. The insoluble disintegrants showed a greater effect when compressional forces were varied than did the soluble disintegrants.

The use of a medium coarse dicalcium phosphate dihydrate has been reported [60,61]. It has interesting applications in vitamin-mineral formulations as both a direct-compaction vehicle and as a source of calcium and phosphorus.

Sucrose-based tablet diluent-binders are available under a number of trade names which include Sugartab (90 to 93% sucrose plus 7 to 10% invert sugar), Di-Pac (97% sucrose plus 3% modified dextrins), NuTab (95% sucrose, 4% invert sugar, and 0.1 to 0.2% each of cornstarch and magnesium stearate).

All of the above sucrose-based diluent-binders find application in direct compaction tablet formulas for chewable as well as conventional tablets. All three demonstrate good palatability and mouth-feel when used in chewable tablets and can minimize or negate the need for artificial sweeteners. Due to their high sucrose level, they may exhibit a tendency to undergo moisture uptake. The initial moisture content is usually less than 1% on an "as-received" basis.

NuTab is available to two grades, medium (40 to 60 mesh) and coarse (20 to 40 mesh), in white only. Mendes et al. [62] reported on the use of NuTab as a chewable direct compression carrier for a variety of products. The medium grade of NuTab, in moisture uptake studies, initially took on moisture more rapidly than the coarse; however, both reached the same equilibrium uptake of 3.3 to 3.5% after 2 weeks at 80% relative humidity.

Di-Pac is available in one grade (40 to 100 mesh), the white and six colors, while Sugartab comes in one grade (20 to 80 mesh), the white only.

Tablets made with these sucrose-based diluents at high levels do not disintegrate in the classical sense but rather dissolve.

Confectioner's sugar N.F. may serve as a diluent in both chewable and nonchewable tablets, but does require granulation to impart bonding if present at significant levels. Powdered sugar is not pure sucrose; it contains starch.

Calcium sulfate dihydrate N.F. has been suggested as a diluent for granulated tablet systems where up to 20 to 30% of active ingredients are added to a stock calcium sulfate granulation. It is inexpensive, and has been reported to show good stability with many drugs. The recent lack of availability of an N.F. grade of material makes its choice as a diluent questionable. Two N.F. grades are marketed in the United States.

Bavitz and Schwartz [23] showed the effect on dissolution rate of a calcium sulfate and microcrystalline cellulose based vehicle (product no. 2834-125) when used with a water-soluble versus a water-insoluble drug. The water-soluble drugs showed a rapid release pattern while the water-insoluble drug was released slowly (Fig. 8).

Calcium lactate trihydrate granular N.F. has been used as diluent and binder in direct-compaction formulas with reasonable success. Its long-term availability should be reviewed before extensive studies are undertaken.

Emdex and Celutab are hydrolyzed starches containing 90 to 92% dextrose, 3 to 5% maltose, and the remainder higher glucose saccharides. They are free-flowing powders composed of spray-crystallized maltose-dextrose spheres. Hydrolyzed starches are often used as mannitol substitutes in chewable tablets because of their sweet taste and smooth

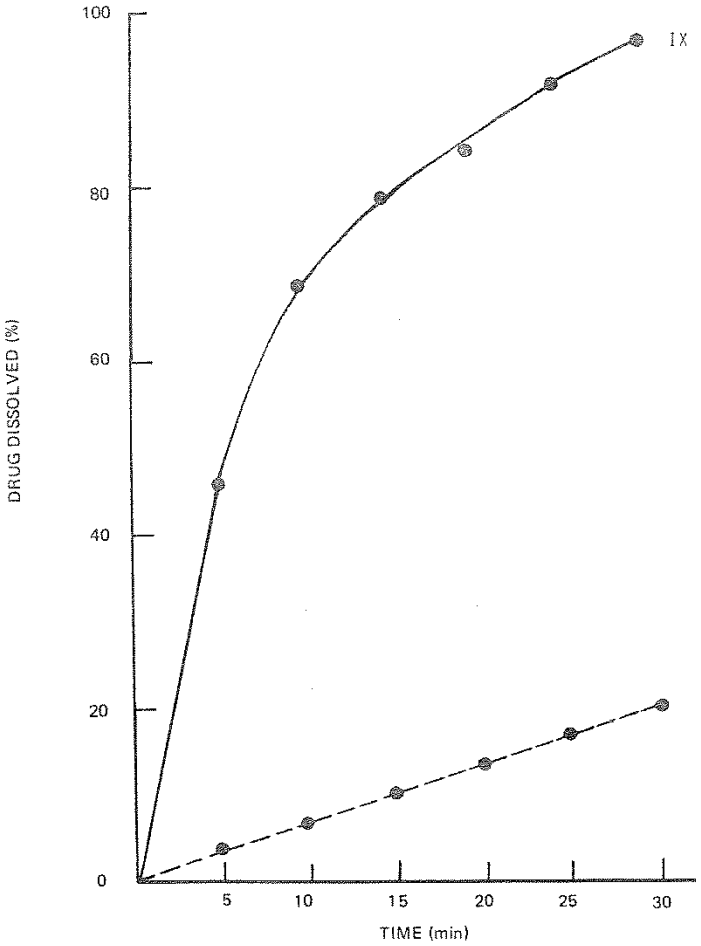

Figure 8 Release of a soluble (——, amitriptyline hydrochloride USP) compared to an insoluble (– – –, hydrochlorothiazide USP) drug from direct compression diluents (see text).

mouth-feel. They show good stability with most drugs, but may react with drugs having active primary amino groups, when stored at high temperature and humidity. Tablets compressed using Emdex show an increase in hardness from 2 to 10 kg during the first few hours after compression. These materials contain 8.5 to 10.5% moisture, which must be considered when combining them with hydrolytically unstable drugs.

Dextrose, commercially available as *Cerelose*, can be used as filler, carrier, and extender where a sweet material is desired, as in chewable tablets. It is available as a hydrate (Cerelose 2001) and in an anhydrous form (Cerelose 2401) where low moisture is needed. It can be used to partly replace spray-dried lactose in direct-compaction formulas. It requires higher lubricant levels than spray-dried lactose and has been shown to have a lesser tendency to turn brown than spray-dried lactose. A comparison of dextrose and spray-dried lactose has been presented by Duvall et al. [26].

Inositol has been used as a replacement diluent for chewable tablets employing mannitol, lactose, and a sucrose-lactose mixture.

Hydrolyzed cereal solids such as the *Maltrons* and *Mor-Rex* have been suggested as lactose replacements. Except for economic considerations, their advantages are limited.

Amylose, a derivative of glucose, possesses interesting direct-compaction properties and has been described for use in tablets [63]. Since amylose contains 10 to 12% water, its use with drugs subject to hydrolytic decomposition should be avoided.

A list of *miscellaneous tablet diluents* would be extensive. Some additional materials used include *Rexcel* (food-grade natural source of α- and amorphous cellulose); *Elcema* (microfine cellulose, principally an α-cellulose) available in powder, fibrous, and granular forms; calcium carbonate; glycine; bentonite; and polyvinylpyrrolidone.

Binders and Adhesives

Binders or adhesives are added to tablet formulations to add cohesiveness to powders, thereby providing the necessary bonding to form granules, which under compaction form a cohesive mass or compact referred to as a tablet. The location of the binder within the granule can affect the quality of the granulation produced [64]. Granule strength is maximized when granulations are prepared by roller compaction followed by wet massing and spray drying [65]. The formation of granules aids in the conversion of powders of widely varying particle sizes to granules, which may more uniformly flow from the hopper to the feed system, and uniformly fill the die cavity.

Granules also tend to entrap less air than powders used in a direct-compression formulation. Table 2 summarizes some common granulating systems.

The primary criterion when choosing a binder is its compatibility with the other tablet components. Secondarily, it must impart sufficient cohesion to the powders to allow for normal processing (sizing, lubrication, compression, and packaging), yet allow the tablet to disintegrate and the drug to dissolve upon ingestion, releasing the active ingredients for absorption. Binder strength as a function of moisture has been reported by Healey et al. [66].

In a study [67] of a comparision of common tablet binder ingredients, the materials compressed were, in descending order of adhesive strength:

Table 2 Examples of Typical Granulating Systems

Material	System normally used (% of granulating)	Concentration used (% of formula)
Acacia	10–25	2–5
Cellulose derivatives	5–10	1–5
Gelatin	10–20	1–5
Gelatin-acacia	10–20	2–5
Glucose	25–50	2–25
Polymethacrylates	5–15	5–20
Polyvinylpyrrolidone	3–15	2–5
Starch paste	5–10	1–5
Sucrose	50–75	2–25
Sorbitol	10–25	2–10
Pregelatinized starch	2–5	1–10
Tragacanth	3–10	1–4
Sodium alginate	3–5	2–5

glucose, acacia, gelatin, simple syrup, and starch. Although starch has the least adhesive strength of the materials in the list, it also has the least deleterious effect on general tablet disintegration rates of the materials listed. Different binders can significantly affect the drying rate and required drying time of a granulation mass, and the equilibrium moisture level of the granulation.

Acacia, a natural gum, has been used for many years as a granulating solution for tablets. In solutions ranging from 10 to 25%, it forms tablets of moderate hardness. The availability of acacia has been uncertain over the past few years, and it should be avoided for that reason in new formulations. In addition to shortages, contamination by extraneous material and bacteria makes its use questionable.

Tragacanth, like acacia, is a natural gum which presents similar problems to those of acacia. Mucilage is difficult to prepare and use. Thus, adding it dry and activating it through the addition of water works best. Such wet granulation masses should be quickly dried to reduce the opportunity for microbial proliferation.

Sucrose, used as a syrup in concentration between 50 and 75%, demonstrates good bonding properties. Tablets prepared using syrup alone as a binder are moderately strong, but may be brittle and hard. The quantity of syrup used and its rate of addition must be carefully followed, especially in systems where overwetting occurs quickly.

Gelatin is a good binder. It forms tablets as hard as acacia or tragacanth, but is easier to prepare and handle. Solutions of gelatin must be used warm to prevent gelling. Alcoholic solutions of gelatin have been used but without great success. Jacob and Plein [68] and Sakr et al. [69]

have shown that increasing the gelatin content of tablets causes increases in their hardness, disintegration, and dissolution times.

Glucose as a 50% solution can be used in many of the same applications as sucrose.

Starch as a paste forms tablets which are generally soft and brittle. It requires heat to facilitate manufacture. Depending on the amount of heat employed, starch undergoes hydrolysis to dextrin and then to glucose. Thus, care in preparation of starch paste is necessary to produce a correct and consistent ratio of starch and its hydrolysis products, as well as to prevent charring.

Cellulose materials such as methylcellulose and sodium carboxymethylcellulose (CMC) form tough tablets of moderate hardness. They may be used as viscous solutions or added dry and activated with water, which results in less effective granule formation. They are available in a wide variety of molecular weights which affect the viscosity of the solution as well as their swelling properties.

Miscellaneous water-soluble or dispersible binders include alginic acid and salts of alginic acid, magnesium aluminum silicate, Tylose, polyethylene glycol, guar gum, polysaccharide acids, bentonites, and others.

Combinations of the previously discussed binding agents often impart the desirable properties of each. Some typical combinations include:

Gelatin + acacia
Starch paste + sucrose (as a syrup)
Starch + sucrose (as a syrup) + sorbitol
Starch + sorbitol

Some binders are soluble in nonaqueous systems, which may offer advantages with moisture-sensitive drugs. Most nonaqueous vehicle binders have as their main disadvantages the possible need for explosion-proof drying facilities and solvent recovery systems. A number of oven explosions have occurred in the pharmaceutical industry—related to the use of alcohol in wet granulation. Some manufacturers have used the approach of partially air-drying such granulations and then employing high air flow rates in their dryers to stay below the explosive limit of alcohol in air. While this approach may work for many years without incident, if a power failure occurs at the wrong time, alcohol vapor can build to the explosive limit, triggering an explosion when the power is turned back on. Great care should be taken in drying any granulation employing flammable solvents or in designing an oven system for such use.

Polyvinylpyrrolidone (PVP) is an alcohol-soluble material which is used in concentrations between 3 and 15%. Granulations using a PVP–alcohol system process (granulate) well, dry rapidly, and compress extremely well. PVP finds particular application in multivitamin chewable formulations where moisture sensitivity can be a problem.

Polymethacrylates (Eugragit NE30D, RS30D) can be used as binders in wet granulations. It is supplied as a 30% aqueous dispersion. Dilution with water prior to use is recommended.

Hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (Klucel) are soluble in various organic solvents or cosolvent systems, as well as water. L-HPC is a low molecular weight, crosslinked form of Klucel. It functions not only as a tablet binder but also a tablet disintegrant. Unlike Klucel, it is not soluble in water. It has tremendous swelling capability

which accounts for its disintegration property. L-HPC may be used in both direct-compression as well as wet granulation tablet formulas. Various grades of L-HPC may be used depending on whether the tablet is to be wet-granulated or directly compressed.

Ethylcellulose (Ethocel) is used as alcohol solutions of 0.5 to 2.0% and affords moisture-sensitive components a protective coating. Vitamin A and D mixtures, which are usually sensitive to moisture, may be coated with ethylcellulose solution, dried, and granulated with conventional aqueous systems. Ethylcellulose may have a serious retardant effect on tablet disintegration and drug dissolution release.

Pregelatinized starch (National 1551 and Starch 1500) can be blended dry with the various components of a tablet formula and activated with water at the desired time of granulation. In a direct-compression formulation, no more than 0.5% magnesium stearate should be used to prevent softening of the tablets.

Disintegrants

The purpose of a disintegrant is to facilitate the breakup of a tablet after admisinistration. Disintegrating agents may be added prior to granulation or during the lubrication step prior to compression or at both processing steps. The effectiveness of many disintegrants is affected by their position within the tablet. Six basic categories of disintegrants have been described: starches, clays, celluloses, algins, gums, and miscellaneous. It should be noted that many disintegrants have also been shown to possess binder or adhesive properties. Since disintegration is the opposite operation to granulation (agglomeration) and the subsequent formation of strong compacts, one must carefully weigh these two phenomena when designing a tablet. Khan and Rhodes [70] reviewed the water sorption properties of four tablet disintegrants: starch, sodium CMC, sodium starch glycolate, and a cation exchange resin. The different disintegration properties were related to the differing mechanisms by which the disintegrants affect tablet rupture. Intergranular and extragranular disintegrating agents were reviewed by Shotton and Leonard [71]. The extragranular formulations disintegrated more rapidly than the intragranular ones, but the latter resulted in a much finer dispersion of particles. A combination of the two types of agents was suggested. Since the most effective lubricants are hydrophobic, water-repellent, and function by granule coating, it is not surprising that such materials may impede tablet wetting, disintegration, and dissolution. To overcome this problem, disintegrants such as starch are often combined with the lubricant to provide extragranular disintegration and to facilitate tablet wetting. Such combinations of lubricant and disintegrant which are added to tablet granulations prior to compression are termed *running powders*.

Starches are the most common disintegrating agents (Table 3) in use today. Ingram and Lowenthal [72] have attributed their activity as disintegrants to intermolecular hydrogen bonding which is formed during compression and is suddenly released in the presence of excess moisture. In a later study, Lowenthal [73] evaluated the effects of pressure on starch granules and showed that they do not regain their original shape when moistened with water.

Lowenthal and Wood [74] showed that the rupture of the surface of a tablet employing starch as a disintegrant occurred where starch agglomerates were found. The conditions best suited for rapid tablet disintegration are

Table 3 Starch Disintegrants

Material	Usual range (%)
Natural starch (corn, potato)	1–20
Sodium starch glycollate (Primogel, Explotab)	1–20 (4% optimum)
Pregelatinized starch (National 1551)	5–10
Pregelatinized starch (Amijel)	5–10
Modified cornstarch (Starch 1500)	3–8

a sufficient number of starch agglomerates, low compressive pressure, and the presence of water.

Starches show a great affinity for water through capillary action, resulting in the expansion and subsequent disintegration of the compressed tablet. Formerly accepted swelling theories of the mechanism of action of starches as disintegrants have been generally discounted. In general, higher levels of starch result in more rapid disintegration times. However, high starch levels often result in a loss of bonding, cohesion, and hardness in tablets. It has been suggested [45] that an optimum starch level exists for many drugs such as tolutamide.

It is important to dry starch at 80 to 90°C to remove absorbed water. Equally important is starch storage while awaiting use, since starches will quickly equilibrate to 11 to 13% moisture by picking up atmospheric moisture.

Sodium starch glycolate modified starches with dramatic disintegrating properties are available as Primogel and Explotab, which are low-substituted carboxymethyl starches. While natural predried starches swell in water to the extent of 10 to 25%, these modified starches increase in volume by 200 to 300% in water. One benefit of using this modified starch is that disintegration time may be independent of compression force. However, high-temperature and humidity conditions can increase disintegration time, slowing dissolution of tablets containing this starch.

Clays such as Veegum HV (magnesium aluminum silicate) have been used as disintegrants at levels ranging from 2 to 10%. The use of clays in white tablets is limited because of the tendency for the tablets to be slightly discolored. In general clays, like the gums, offer few advantages over the other more common, often more effective, and no more expensive disintegrants such as the starches (including derivatives), celluloses, and alginates.

Celluloses, such as purified cellulose, methylcellulose, sodium carboxymethylcellulose, and carboxymethylcellulose, have been evaluated as disintegrants but have not found widespread acceptance. A crosslinked form of sodium carboxymethylcellulose (Ac-Di-Sol) has been well accepted as a tablet disintegrant. Unlike sodium carboxymethylcellulose, Ac-Di-Sol is essentially water-insoluble. It has a high affinity for water which results in rapid tablet disintegration. Ac-Di-Sol has been classifed as a "super-disintegrant."

Microcrystalline cellulose (Avicel) exhibits very good disintegrant properties when present at a level as low as 10%. It functions by allowing water

water to enter the tablet matrix by means of capillary pores, which breaks the hydrogen bonding between adjacent bundles of cellulose microcrystals. Excessively high levels of microcrystalline cellulose can result in tablets which have a tendency to stick to the tongue, due to the rapid capillary absorption, dehydrating the moist surface and causing adhesion.

Alginates are hydrophilic colloidal substances extracted from certain species of kelp. Chemically they are available as alginic acid or salts of alginic acid (with the sodium salt being the most common). They demonstrate a great affinity for water, which may even exceed that of cornstarch. Alginic acid is commonly used at levels of 1 to 5% while sodium alginate is used between 2.5 and 10%. Unlike starch, microcrystalline cellulose, and alginic acid, sodium alginates do not retard flow.*

National 1551 and Starch 1500 are *pregelatinized corn starches* with cold water swelling properties. They swell rapidly in water and display good disintegrant properties when added dry at the lubrication step. When incorporated into the wet granulation process, pregelatinized starch loses some of its disintegrating power.

Gums have been used as disintegrants because of their tendency to swell in water. Similar to the pregelatinized starches in function, they can display good binding characteristics (1 to 10% of tablet weight) when wet. This property can oppose the desired property of assisting disintegration, and the amount of gum must be carefully titrated to determine the optimum level for the tablet. Common gums used as disintegrants include agar, guar, locust bean, Karaya, pectin, and tragacanth. Available as natural and synthetic gums, this category has not found wide acceptance because of its inherent binding capabilities.

Miscellaneous disintegrants include surfactants, natural sponge, resins, effervescent mixtures, and hydrous aluminum silicate. Kornblum and Stoopak [75] evaluated cross-linked PVP (Povidone-XL) as a tablet disintegrant in comparison with starch USP and alginic acid. The new material demonstrated superiority over the other two disintegrants tested in most of the experimental tablet formulations made as direct compaction or wet granulation systems. Povidone-XL also falls under the classification of superdisintegrant.

Lubricants, Antiadherents, and Glidants

The primary function of tablet lubricants is to reduce the friction arising at the interface of tablet and die wall during compression and ejection. The lubricants may also possess antiadherent or glidant properties. Strickland [76] has described:

Lubricants:	Reduce friction between the granulation and die wall during compression and ejection
Antiadherents:	Prevent sticking to the punch and, to a lesser extent, the die wall
Glidants:	Improve flow characteristics of the granulation

*A wide variety of grades are available from the Algin Corporation of America.

Lubricants

Lubrication is considered to occur by two mechanisms. The first is termed fluid (or hydrodynamic) lubrication because the two moving surfaces are viewed as being separated by a finite and continuous layer of fluid lubricant. A hydrocarbon such as mineral oil, although a poor lubricant, is an example of a fluid-type lubricant. Hydrocarbon oils do not readily lend themselves to application to tablet granulations and, unless atomized or applied as a fine dispersion, will produce tablets with oil spots. The second mechanism, that of boundary lubrication, results from the adherence of the polar portions of molecules with long carbon chains to the metal surfaces of the die wall. Magnesium stearate is an example of a boundary lubricant. Boundary-type lubricants are better than fluid-type lubricants since the adherence of a boundary lubricant to the die wall is greater than that of the fluid type. This is expected since the polar end of the boundary lubricant should adhere more tenaciously to the oxide metal surface than the nonpolar fluid type.

The type and level of lubricant used in a tablet formulation is greatly affected by the tooling used to compress the tablets. Mohn [77] reviewed the design and manufacture of tablet tooling. Proper inspection of tablet tooling is critical to ensure that tooling continues to perform up to expectations. Capping of tablet is more often formulation-related; however, it can be caused by improper tooling. Compressing tablets at pressures greater than what the tooling was designed to handle can result in damage to punch heads. The use of cryogenic material treatments can increase tooling life. Vemuri [78] discussed the selection of the proper tooling for high speed tablet presses.

Recommendations have been made to standardize tablet-tooling specifications by the IPT Section of the Academy of Pharmaceutical Sciences [79].

Mechtersheimer and Sucker [80] determined that die wall pressure is considerably greater when curve-faced punches are used to compress tablets instead of fat-faced punches. Additional lubricant is often needed in tablet formulations that are to be compressed with curved-face punches.

Lubricants tend to equalize the pressure distribution in a compressed tablet and also increase the density of the particle bed prior to compression. When lubricants are added to a granulation, they form a coat around the individual particles (granules) which remains more or less intact during compression. This coating effect may also extend to the tablet surface. Since the best lubricants are hydrophobic, the presence of the lubricant coating may cause an increase in the disintegration time and a decrease in the drug dissolution rate. Since the strength of a tablet depends on the area of contact between the particles, the presence of a lubricant may also interfere with the particle-to-particle bond and result in a less cohesive and mechanically weaker tablet. Matsuda et al. [81] reviewed the effect on hardness and ejection force of two methods of applying the lubricant (stearic acid, magnesium stearate, calcium stearate, and talc) to statically compressed tablets prepared from a lactose granulation. In one method of addition the lubricant was incorporated into the granulation during preparation, while in the other it was added to (mixed with) the final granules. The mixing method gave better results for ease of ejection and tablet hardness than the incorporation method.

As the particle size of the granulation decreases, formulas generally require a greater percent of lubricant. Danish and Parrott [82] examined

the effect of concentration and particle size of various lubricants on the flow rate of granules. For each lubricant there was an optimum concentration, not exceeding 1%, which produced a maximum flow rate. For a constant concentration of lubricant, the flow rate increased to a maximum rate as the size of the lubricant particles was decreased to 0.0213 cm. A further reduction hindered the flow rate. Usually as the concentration of lubricant increases, the disintegration time increases and the dissolution rate decreases, as the ability of water to penetrate the tablet is reduced.

The primary function of a lubricant is to reduce the friction between the die wall and the tablet edge as the tablet is being ejected. Lack of adequate lubrication produces *binding*, which results in tablet machine strain and can lead to damage of lower punch heads, the lower cam track, and even the die seats and the tooling itself. Such binding on ejection is usually due to a lack of lubrication. Such tablets will have vertically scratched edges, will lack smoothness or gloss, and are often fractured at the top edges. With excessive binding the tablets may be cracked and fragmented by ejection. Ejection force can be monitored as an indicator of adhesion problems during compressing studies [83]. A film forms on the die wall, and ejection of the tablet is difficult.

Sticking is indicated by tablet faces which are dull. Earlier stages of sticking are often referred to as *filming* of the punch faces and may result when punches are improperly cleaned or polished or when tablets are compressed in a high humidity, as well as when lubrication is inadequate. Advanced states of sticking are called *picking*, which occurs when portions of the tablet faces are lifted or picked out and adhere to the punch face. Picking usually results from improperly dried granulations, from punches with incorrectly designed logos, and from inadequate glidant use, especially when oily or sticky ingredients are compressed.

Capping and *laminating*, while normally associated with poor bonding, may also occur in systems which are overlubricated with a lubricant such as a stearate. Attempts have been made to measure the tendency of a powder to cap and stick when compressed based on theoretical calculations [83]. Rue et al. [84] correlated acoustic emissions during tableting of acetaminophen with lamination and capping events. Acoustic emission analysis demonstrated that capping occurs within the die wall during the decompression phase and not during ejection. Capping or lamination observed with curve-face punches can often be eliminated by switching to flat-faced punches.

Lubricants may be further classified according to their water solubility (a (as water-soluble or water-insoluble). The choice of a lubricant may depend in part on the mode of administration and the type of tablet being produced, the disintegration and dissolution properties desired, the lubrication and flow problems and requirements of the formulation, various physical properties of the granulation or powder system being compressed, drug compatibility considerations, and cost.

Water-insoluble lubricants in general are more effective than water-soluble lubricants and are used at a lower concentration level. Table 4 summarizes some typical insoluble lubricants and their usual use levels.

In general lubricants, whether water-soluble or insoluble, should be 200 mesh or finer and are passed (bolted) through a 100-mesh screen (nylon cloth) before addition to the granulation. Since lubricants function by coating (as noted), their effectiveness is related to their surface area

Table 4 Water-Insoluble Lubricants

Material	Usual range (%)
Stearates (magnesium, calcium, sodium)	1/4–2
Stearic acid	1/4–2
Sterotex	1/4–2
Talc	1–5
Waxes	1–5
Stearowet	1–5

and the extent of particle size reduction. The specific lubricant, its surface area, the time (point) and procedure of addition, and the length of mixing can dramatically affect its effectiveness as a lubricant and the disintegration-dissolution characteristics of the final tablet.

Glyceryl behapate (*Compritol 888*) is a new addition to the list of tablet lubricants. It has the unique classification of being both a lubricant and a binder. Therefore, it should alleviate both sticking and capping problems. When used with magnesium stearate in a tablet formula, its level should be reduced. The stability of aspirin has been extensively studied in conjunction with various lubricants. In combination with talc, the rate of decomposition has been related to the calcium content and loss on ignition of the talc source. Alkaline materials such as alkaline stearate lubricants may be expected to have a deleterious effect on the stability of aspirin-containing products. For those formulations that are not sufficiently lubricated with stearates, the addition of talc may be beneficial. Mechtersheimer and Sucker [80] also found that talc should be added prior to the lubrication step to optimize the tableting properties. When added together, talc and magnesium stearate provided acceptable lubrication. Magnesium lauryl sulfate has been compared to magnesium stearate as a tablet lubricant [83]. Higher levels of magnesium lauryl sulfate were required to provide an equivalent lubricantion as measured by tablet ejection force. However, harder and more compressible blends can be prepared with magnesium lauryl sulfate than with magnesium stearate at the same ejection force.

Boron-coated tablet tooling has permitted the use of a lower lubricant level in some tablet formulations [85].

Water-soluble lubricants are in general used only when a tablet must be completely water-soluble (e.g., effervescent tablets) or when unique disintegration or, more commonly, dissolution characteristics are desired. Possible choices of water-soluble lubricants are shown in Table 5. Boric acid is a questionable member of the list due to the recognized toxicity of boron. A review of some newer water-soluble lubricants combined with talc and calcium stearate has been reported [86]. Polyethylene glycols and 20 low melting point surfactants have been suggested as water-soluble lubricants [87].

Table 5 Water-Soluble Lubricants

Material	Usual range (%)
Boric acid	1
Sodium benzoate + sodium acetate	1–5
Sodium chloride	5
DL-Leucine	1–5
Carbowax 4000	1–5
Carbowax 6000	1–5
Sodium oleate	5
Sodium benzoate	5
Sodium acetate	5
Sodium lauryl sulfate	1–5
Magnesium lauryl sulfate	1–2

Methods of Addition. Lubricants are generally added dry at a point where the other components are in a homogeneous state. Thus, the lubricant is added and mixed for a period of only 2 to 5 minutes rather than the 10 to 30 minutes necessary for thorough mixing of a granulation. Overmixing may lead to diminished disintegration-dissolution characteristics and loss of bonding in the tablet matrix.

Lubricants have also been added to granulations as alcoholic solutions (e.g., Carbowaxes) and as suspensions and emulsions of the lubricant material. In one study [88] various lubricants were added, without significant loss of lubricating properties, to the initial powder mixture prior to wet granulation. However, as a rule, powdered lubricants should not be added prior to wet granulation since they will then be distributed throughout the granulation particles rather than concentrated on the granule surface where they operate. In addition, powder lubricants added in this manner will reduce granulating agent and binder efficiency.

Antiadherents

Antiadherents are useful in formulas which have a tendency to pick easily. Multivitamin products containing high vitamin E levels often display extensive picking, which can be minimized through the use of a colloidal silica such as Syloid. Studies have indicated that Cab-O-Sil, although similar chemically, does not perform satisfactorily, probably because of its lesser surface area.

Talc, magnesium stearate, and cornstarch display excellent punch-face or antiadherent properties. An extremely efficient yet water-soluble punch-face lubricant is DL-leucine. The use of silicone oil as an antiadherent has been suggested [89]. Table 6 summarizes the more common antiadherents.

Table 6 Antiadherents

Material	Usual range (%)
Talc	1–5
Cornstarch	3–10
Cab-O-Sil	0.1–0.5
Syloid	0.1–0.5
DL-Leucine	3–10
Sodium lauryl sulfate	<1
Metallic stearates	<1

Glidants

In general materials that are good glidants are poor lubricants. Table 7 lists a few of the common glidants. Glidants can improve the flow of granulations from hoppers into feed mechanisms and ultimately into the die cavity. Glidants can minimize the degree of surging and "starvation" often exhibited by direct-compaction formulas. They act to minimize the tendency of a granulation to separate or segregate due to excessive vibration. High-speed tablet presses require a smooth, even flow of material to the die cavities. When flow properties are extremely poor, and glidants are ineffective, consideration of forced-feed mechanisms may be necessary. The uniformity of tablet weights directly depends on how uniformly the die cavity is filled.

Tablet Formulation and Design

A review by Augsburger and Shangraw [90] of a series of silica-type glidants used decreased weight variation as a criterion of evaluation. The use of starch as a glidant has been widely practiced in tablet and capsule formulation. In general many materials commonly referred to as lubricants possess only a minimal lubricating activity, and are better glidants or

Table 7 Glidants

Material	Usual range (%)
Talc	5
Cornstarch	5–10
Cab-O-Sil	0.1–0.5
Syloid	0.1–0.5
Aerosil	1–3

antiadherents. Thus, a blend of two or more materials may be necessary to obtain the three properties.

York [91] presented data indicating the relative efficiency of glidants for two powder systems and reported that the order of effectiveness was

Fine silica > magnesium stearate > purified talc

The mechanisms of action of glidants have been hypothesized by various investigators and include:

1. Dispersion of electrostatic charges on the surface of granulations [92, 93]
2. Distribution of glidant in the granulation [94]
3. Preferential adsorption of gases onto the glidant versus the granulation [94]
4. Minimization of van der Waals forces by separation of the granules [92]
5. Reduction of the friction between particles and surface roughness by the glidant's adhering to the surface of the granulation [92,93]

The most efficient means of measuring the effectiveness of a glidant in a powder blend is to compress the blend and determine weight variation. The use of shear cell and flowmeter data also gives some indication of the flow properties of a particular blend. A complete shear cell analysis of a powder blend can be performed to determine the appropriate hopper design (i.e. angle from vertical, orifice diameter, hopper diameter, and material of construction). Shear-cell analysis also provides information on the tendency of a blend to consolidate with time and under a load. Excessive consolidation can result in a good-flowing formulation turning into a poor-flowing formulation. Nyqvist [95] correlated the frequency of tablet machine adjustments with shear cell and flowmeter data. The moisture content of dried granulations was found to impact on the flowability of the granules.

The Running Powder. Since the best lubricants are not only water-insoluble but also water-repellent, and since lubricants function by coating the granulation to be compressed, it is not surprising that the lubricants used and the process of lubrication may have a deleterious effect on tablet disintegration and drug dissolution release. To overcome the tendency a second agent is often added to the lubricant powder to produce a less hydrophobic powder to be added as the lubricant system. The mixture of lubricant and a second, hydrophilic agent is called the *running powder*, since it is added to permit compression or running of the granulation on a tablet machine. The most common hydrophilic agent added to the lubricant is starch. The starch/lubricant ratio is typically in the range 1:1 to 1:4.

Colorants

Colors are incorporated into tablets generally for one or more of three purposes. First, colors may be used for identifying similar-looking products within a product line, or in cases where products of similar appearance exist in the lines of different manufacturers. This may be of particular importance when product identification (because of overdosing or poisoning and drug abuse) is a problem. Second, colors can help minimize the possiblity of mix-ups during manufacture. Third, and perhaps least important, is the addition of colorants to tablets for their aesthetic value or their marketing value.

The difficulties associated with the banning of FD&C Red No. 2 (amaranth), FD&C Red No. 4, and carbon black in 1976 should be a prime example of what may be the trend of the future. Other colors such as FD&C No. 40 and FD&C Yellow No. 5 have been questioned recently and will continue to be suspect for one reason or another. The pharmaceutical manufacturer can maximize the identification of his products through product shape and size, NDC number, and use of logos. One should not rely on color as a major means of eliminating in-house errors but should instead develop adequate general manufacturing practices to insure that mix-ups do not occur.

Today the formulator may choose a colorant from a decreasing list of colors designated as D&C and FD&C dyes and lakes, and a small number of acceptable natural and derived materials approved for use by the U.S. Food and Drug Administration. Historically, drug manufacturers have, for the most part, restricted their choice of dyes to the FD&C list. Table 8 summarizes the colors available at this time.

Dyes are water-soluble materials, whereas lakes are formed by the absorption of a water-soluble dye on a hydrous oxide (usually aluminum hydroxide), which results in an insoluble form of the dye.

The photosensitivity of lakes and dyes will be affected by the drug, excipients, and methods of manufacture and storage of each product. Ultraviolet-absorbing chemicals have been added to tablets to minimize their photosensitivity. Pastel shades generally show the least amount of mottling, especially in systems utilizing water-soluble dyes. Colors near the mid-range of the visible spectrum (yellow, green) will show less mottling than those at either extreme (blue, red).

Methods of Incorporation

Water-soluble dyes are usually dissolved in the granulating system for incorporation during the granulating process. This method assures uniform distribution through the granulation but can lead to mottling during the drying process. Colors may also be adsorbed onto carriers (starch, lactose, calcium sulfate, sugar) from aqueous or alcoholic solutions. The resultant color mixtures are dried and used as *stock* systems for many lots of a particular product. Water-soluble dyes may also be dry-blended with an excipient prior to the final mix.

Lakes are almost always blended with other dry excipients because of their insoluble nature. In general, direct-compression tablets are colored with lakes because no granulation step is used.

Flavors and Sweeteners

Flavors and sweeteners are commonly used to improve the taste of chewable tablets. Cook [96] reviewed the area of natural and synthetic sweeteners.

Flavors are incorporated as solids in the form of spray-dried beadlets and oils, usually at the lubrication step, because of the sensitivity of these materials to moisture and their tendency to volatilize when heated (e.g., during granulation drying). Aqueous (water-soluble) flavors have found little acceptance due to their lesser stability upon aging.

Since oxidation destroys the quality of a flavor, oils are usually emulsified with acacia and spray-dried. Dry flavors are easier to handle and are generally more stable than oils. Oils are usually diluted in alcohol and sprayed onto the granulation as it tumbles in a lubrication tub. Use of a P-K V-blender with an intensifier bar has also been used. Oils may also be adsorbed onto an excipient and added during the lubrication process. Usually, the maximum

Table 8 Status of Color Additives: Code of Federal Regulations (4-1-87)

FD&C Blue No. 1	May be used for coloring drugs in amounts consistent with current good manufacturing practice.
FD&C Blue No. 2	May be used for coloring drugs in amounts consistent with current good manufacturing practice.
D&C Blue No. 4	May be used in externally applied drugs in amounts consistent with current good manufacturing practice.
D&C Blue No. 9	May be used for coloring cotton and silk surgical sutures including sutures for ophthalmic use in amounts not to exceed 2.5% by weight of the suture.
FD&C Green No. 3	May be used for coloring drugs in amounts consistent with current good manufacturing practice.
D&C Green No. 5	May be used for coloring drugs in amounts consistent with current good manufacturing practice.
D&C Green No. 8	May be used in externally applied drugs in amounts not exceeding 0.01% by weight of the finished product.
D&C Orange No. 4	May be used for coloring externally applied drugs in amounts consistent with current good manufacturing practice.
D&C Orange No. 5	May be used for coloring mouthwashes and dentifrices and for externally applied drugs in amounts not to exceed 5 mg per daily dose of the drug.
D&C Orange No. 10	May be used for coloring externally applied drugs in amounts consistent with current good manufacturing practice.
D&C Orange No. 11	May be used for coloring externally applied drugs in amounts consistent with current good manufacturing practice.
D&C Orange No. 17	May be used for coloring externally applied drugs in amounts consistent with current good manufacturing practice.
FD&C Red No. 3	May be used for coloring ingested drugs in amounts consistent with current good manufacturing practice.
FD&C Red No. 4	May be used for externally applied drugs in amounts consistent with current good manufacturing practice.
D&C Red No. 6	May be used for coloring drugs such that the combined total of D&C Red No. 6 and D&C Red No. 7 does not exceed 5 mg per daily dose of the drug.
D&C Red No. 7	May be used for coloring drugs such that the combined total of D&C Red No. 6 and D&C Red No. 7 does not exceed 5 mg per daily dose of the drug.
D&C Red No. 8	May be used for coloring ingested drugs in amounts not exceeding 0.1% by weight of the finished product

Table 8 (Continued)

	and for externally applied drugs in amounts consistent with current good manufacturing practice.
D&C Red No. 9	May be used for externally applied drugs in amounts consistent with current good manufacturing practice.
D&C Red No. 17	May be used for externally applied products in amounts consistent with current good manufacturing practice.
D&C Red No. 19	May be used for externally applied products in amounts consistent with current good manufacturing practice.
D&C Red No. 21	May be used for coloring drug product in amounts consistent with current good manufacturing practice.
D&C Red No. 22	May be used for coloring drug product in amounts consistent with current good manufacturing practice.
D&C Red No. 27	May be used for coloring drug product in amounts consistent with current good manufacturing practice.
D&C Red No. 28	May be used for coloring drug product in amounts consistent with current good manufacturing practice.
D&C Red No. 30	May be used for coloring drug product in amounts consistent with current good manufacturing practice.
D&C Red No. 31	May be used for externally applied drugs in amounts consistent with current good manufacturing practice.
D&C Red No. 34	May be used for coloring externally applied in amounts consistent with current good manufacturing practice.
D&C Red No. 39	May be used for external germicidal solutions not to exceed 0.1% by weight of the finished drug product.
FD&C Red No. 40	May be used in coloring drugs subject to restrictions and in amounts consistent with current good manufacturing practice.
D&C Violet No. 2	May be used for coloring externally applied drugs in amounts consistent with current good manufacturing practice.
FD&C Yellow No. 5	In general products containing FD&C Yellow No. 5 (tartrazine) must be so labeled. The Code of Federal Regulations should be consulted for use restrictions that may be added.
FD&C Yellow No. 6	May be used for coloring drugs in amounts consistent with current good manufacturing practice.
D&C Yellow No. 7	May be used for externally applied drugs in amounts consistent with current good manufacturing practice.
D&C Yellow No. 10	May be used for coloring drugs in amounts consistent with current good manufacturing practice.

Table 8 (Continued)

D&C Yellow No. 11	May be used for externally applied drugs in amounts consistent with current good manufacturing practice.
D&C Lakes, Ext. D&C Lakes, FD&C Lakes	Consult the current regulations for status.

amount of oil that can be added to granulation without affecting the bond or flow properties is 0.75% (w/w).

Sweeteners are added primarily to chewable tablets when the commonly used carriers such as mannitol, lactose, sucrose, and dextrose do not sufficiently mask the taste of the components.

Saccharin, which is FDA-approved, is about 400 times sweeter than sucrose. The major disadvantage of saccharin is its bitter aftertaste, which can sometimes be minimized by incorporating a small quantity (1%) of sodium chloride. The saccharin aftertaste is highly discernible to about 20% of the population.

Aspartame, a nondrug approved artificial sweetener, is about 180 times sweeter than sucrose and is approved for use in beverages, desserts, and instant coffee and tea. It exhibits discoloration in the presence of ascorbic acid and tartaric acid, thus greatly limiting its use. Becuase of the possible carcinogenicity of the artificial sweeteners (cyclamates and saccharin), pharmaceutical formulators are increasingly attempting to design their tablet products without such agents. The following formulation represents such a system for a chewable antacid tablet.

Example 1: Chewable Antacid Tablet, Aluminum Hydroxide, and Magnesium Carbonate Codried Gel (Direct Compression)

Ingredient	Quanity per tablet
Aluminum hydroxide and magnesium carbonate codried gel (Reheis F-MA 11)	325.0 mg
Mannitol, USP (granular)	675.0 mg
Microcrystalline cellulose	75.0 mg
Starch	30.0 mg
Calcium stearate	22.0 mg
Flavor	q.s.

Blend all ingredients and compress using a 5/9-in. flat-faced level edge punch to a hardness of 8 to 11 kg (Strong-Cobb-Arner tester).

Adsorbents

Adsorbents such as silicon dioxide (Syloid, Cab-O-Sil, Aerosil) are capable of retaining large quantities of liquids without becoming wet. This allows many oils, fluid extracts, and eutectic melts to be incorporated into tablets. Capable of holding up to 50% of its weight of water, silicon dioxide adsorbed systems often appear as free-flowing powders. This adsorbent characteristic explains why these materials function well in tablet formulations to alleviate picking, especially with high-level vitamin E tablets. Silicon dioxide also exhibits glidant properties and can play both a glidant and an adsorbent role in the formula.

Other potential adsorbents include clays like bentonite and kaolin, magnesium silicate, tricalcium phosphate, magnesium carbonate, and magnesium oxide. Usually the liquid to be adsorbed is first mixed with the adsorbent prior to incorporation into the formula. Starch also displays adsorbent properties.

V. REGULATORY REQUIREMENTS FOR EXCIPIENTS IN THE UNITED STATES

In 1974 the U.S. Congress received a report on *Drug Bioequivalence* from the Office of Technology Assessment which noted as a major conclusion the potential influence of excipients on the bioavailability of many drug products. A further major comment made in the report, which has been largely overlooked as readers focused on the bioavailability issue, was a strong criticism regarding the current standards for excipients in the compendia. Obviously, if test methods for excipients are nonspecific and incomplete, especially as these properties may relate to bioavailability of drug products, compendial and other government standards cannot provide good assurance of the bioequivalence of marketed drug products. The report went on to note that many commonly used excipients (including those used in tablets and other solid dosage forms) were not even included in the compendia.

The general notices of USP XX and NF XV contain broad, restrictive statements that require all excipients to be harmless in the amounts used, not to exceed the minimum amounts needed to produce the intended effect, not to impair the bioavailability or therapeutic effect of the drug(s) in the dosage form, and not to produce interference with any of the assays or tests required to determine adherence to compendial standards. Cooper [97] tabulated the various types of tests and standards applied to the 223 excipients listed in USP XIX and NF XIV. Each excipient has either a specific assay or an identity test, or both, together with various limit tests, which may include water content or loss on drying (for less than 80 excipients), tests for chloride, sulfate, arsenic, heavy metals, ash, residue on ignition, various specific or nonspecific impurities, tests for solubility or insolubility (23 excipients), and tests for other specified physicochemical properties (24 excipients).

A. Physicochemical Test Methods for Excipients

While it has been known for some time that many (if not most) pharmaceutical excipients were lacking in characterizing physicochemical tests, the Swiss drug companies were the first to take corrective steps, when they specified certain standard physical tests for excipients in their *Katalog Pharmazeutischer*

Hilfsstoffe (Catalog of Pharmaceutical Excipients). John Rees of the Department of Pharmacy, University of Aston, Birmingham, England, has translated these tests for German to English, as they are given in the Swiss catalog. Five of the standard tests are given there, since they relate to excipients for tablets, and since detailed tests for these properties are not given in the current compendia. Other tests in the catalog will not be detailed (for vapor density, flash point, fire point, ignition temperature, explosive limits, or maximum working conditions concentration).

The development of the *Handbook of Pharmaceutical Excipients* by the Academy of Pharmaceutical Sciences of the American Pharmaceutical Association in collaboration with the Pharmaceutical Society of Great Britain has produced a reference text with a comprehensive list of pharmaceutical excipients and suitable standards for each. This reference should prove to be invaluable to the formulator [22].

In selecting excipients for pharmaceutical dosage forms and drug products, the development pharmacist should be certain that standards exist and are available to assure the consistent quality and functioning of the excipient from lot to lot.

A major task of the committee that worked on the *Handbook of Pharmaceutical Excipients* was the development of standard test methods for important excipient properties. Standard methods to evaluate over 30 physical properties were developed.

The reader is urged to become familiar with the test methods, published in the *Handbook*, that allow comprehensive characterization of tablet excipient materials, especially the following:

Flow rate	Particle hardness	Shear rate
Gel strength (binders)	Particle size distribution:	Tensile strength
Lubricity (frictional)	(1) sieve analysis	Volume, bulk
Microbiological status	(2) air permeability	Water absorption
Moisture sorption isotherm	Porosity	Water adsorption

B. Tablet Formulation for International Markets

Many drug companies must consider regulatory requirements in many parts of the world when they undertake the formulation of new tablet products or reformulation of existing products. This is true not only for the largest drug companies with major international divisions, but is also the case for much smaller companies who market abroad through a separate foreign manufacturing or distributing company, or who hope (in the future) to license their product for foreign sale. Such formulations must take into account not only the acceptability of various excipients in the other countries and areas of the world of interest, but also the environmental restrictions of these countries which may impact on proposed manufacturing methods (e.g., the proposed solvents used, if any) and the worldwide availability of all excipient components in the required purity and specifications. While little information may be found in any literature compilation on this subject, Hess [98] presented a symposium paper in 1976 on the choice of excipients for international use; much of the following information has been drawn from this presentation.

Excipients that are in use in the pharmaceutical industry for tablets or other oral dosage forms generally fall into one of the following categories: (1) excipients permitted in foodstuffs; (2) excipients described in

pharmacopoeias; (3) newer excipients with no official status, but registered with health authorities in various countries of the world, and approved for use in some of these countries.

Excipients permitted in foodstuffs are generally regarded as acceptable for like uses in drug products. Materials approved for excipient uses (e.g., fillers, surfactants, preservatives, binding agents) have usually been extensively tested in food and will be used in relatively low amounts as a tablet or pharmaceutical component compared to use as a food component. In general, an excipient listed in a major pharmacopoeia such as the United States, British, or European Pharmacopoeia can be used worldwide.

An exception to this rule should be noted for Japan, where only excipients named in one of the official Japanese compendia may be used. These compendia currently include: *Japan Pharmacopoeia VIII*, the *Japanese Standards of Food Additives III*, or the *Special Koseisho Regulations*. These compendia list some excipients not regularly used in the United States or Europe (e.g., calcium carboxymethylcellulose), while not listing such common ones as the free acid of saccharin (the sodium salt is listed) or diethyl phthalate (the dibutyl phthalate is listed). Polyvinylpyrrolidone, which was formerly acceptable, has now become restricted. Of the iron oxides only the red variety (Fe_2O_3) is permitted, while the use of the yellow (Fe_2O_3 monohydrate) and especially the black oxide ($FeO \cdot Fe_2O_3$) seems doubtful. Koseisho, the Japanese health authority, also restricts the use of excipients with a pharmacological effect (e.g., citric and ascorbic acid) to one-fifth of the minimum daily dose.

Pharmaceutical manufacturers must be careful to assure that excipients listed in pharmacopoeias, and made available by various suppliers around the world, do in fact comply with all the relevant pharmacopoeial specifications. In certain instances this may restrict the use of very similar, but not identical, compounds (e.g., cellulose ethers with different degrees of substitution).

The development of new materials for use as pharmaceutical excipients requires the demonstration of the absence of toxicity and freedom from adverse reactions. In most countries today it is very difficult to obtain approval by regulatory agencies for the use of new excipient agents. Reportedly, the only clear recommendations for the type of toxicological data currently required on a new excipient are provided in the German regulations (1971) and the European Economic Community Directives (EEC 75/318, dated May 20, 1975). These regulations and directives call for acute toxicity studies in three animal species, observed over 14 days. If possible, the LD_{50} by the parenteral route should also be established in one species. The combined acute and long-term studies may be summarized as follows:

Toxicological data on a new excipient: long-term oral administration
Acute toxicity: to standard international protocols
Repetitive administration: 6 months, 2 species (one nonrodent)
Carcinogenicity: 1 species (18 months, mouse or 2 years, rat)
Reproduction studies, segments 1, 11, and 111 (fertility, teratogenicity, effects on lactation): 1, 11, and 111 (rat); 11 (at least one other species nonrodent, e.g., rabbit)

In the FDA-oriented countries (Australia and Canada in addition to the United States), 2-year repetitive-dose studies in rats and 1-year studies in

dogs may be expected to be required rather than the 6-month studies described above. It may also be necessary to conduct mutagenicity studies. For excipients with any potential for complexation or drug binding, drug bioavailability studies will be required for products in which the excipient is incorporated. If the excipient is absorbed its ADME and pharmacokinetic profile may need to be established. In the event that the agent can be clearly demonstrated to not be absorbed from the gut, these later studies may be simplified, shortened, or omitted. This would assume the excipient is also a well-characterized high-purity agent. Excipients that are clearly known to be components of the normal human diet, such as, for example, a form of pure cellulose, are much easier to clear with regulatory agencies than a compound not normal to the diet, or for which no prior knowledge of human exposure or exposure effects exists. The very high cost of obtaining the necessary toxicological data for a unique new excipient agent makes it obvious that few totally new excipient agents will make their appearance in the future.

Another consideration bearing on excipient use in international markets (that is expected to become increasingly important) is the subject of disclosure. Paragraph 10 of the 1976 Drug Law of the Federal Republic of Germany states that all active ingredients must be publicly declared. This requirement includes preservatives because of their antimicrobial activity. Whether dyestuffs with a weak allergenic potential should be included in this category is still debated. However, in countries such as Sweden, lists of drug preparations containing tartrazine and other azo dyestuffs have already been published. This obviously leads to a certain marketing disadvantage for these products. According to new regulations issued in November 1976, the azo dyestuffs tartrazine Sunset Yellow FCF, ponceau 4R, and amaranth were not to be permitted in foodstuffs in Sweden after 1979. Prohibitions or major restrictions against these, if not all, azo dyes may follow in the years ahead in other countries. Amaranth or FD&C Red No. 2 is currently prohibited in the United States, Taiwan, and Venezuela.

The choice of the excipients to be used in any drug product is usually a compromise. This is even more the case in selecting excipients for international use, since technical performance must be balanced against local restrictions in some countries as well as cost and availability in all countries where the product is to be produced.

Hess [98] has tabulated priorities of use for some common tablet and capsule excipients for international use. A number 1 indicates the highest priority for use based on all considerations (e.g., compatibility, availability, cost). His tabulations of priority of use for fillers and disintegrants and for binders, glidants, and lubricants are shown in Tables 9 and 10.

In the last few years some powerful new disintegrants for tablets have appeared. They are of great assistance where long disintegration times or slow dissolution rates are a problem. The compounds have been grouped below according to their acceptability; it appears that sodium carboxymethyl starch creates the least problem worldwide, even though it is not listed yet in any pharmacopoeia. The new disintegrants are:

Primogel, Scholten (NL): sodium carboxymethyl starch
Nymcel, ZSB-10 mod., Nyma (NL): sodium carboxymethylcellulose, low degree of substitution
Plasdone XL, GAF (USA): cross-linked polyvinylpyrrolidone
LHPC, Shinetsu (J): hydroxypropyl cellulose, low substitution

Table 9 Priority for Use: Fillers, Disintegrants

Substance	Comment	Rating
Cornstarch	OK (formaldehyde)	1
Lactose	OK (except primary amines)	1
Mannitol	OK (technical problems)	11
Sucrose	OK (hygroscopic point at 77.4% relative humidity)	11
Avicel	Somewhat less satisfactory than starch	1
Primogel		11
Emcompress	May lose water	11
Tricalcium phosphate	May accelerate hydrolytic degradations	11

Source: Adapted from Hess [98].

Ac-Di-Sol, FMC Corp: internally crosslinked form of sodium carboxymethylcellulose of USP purity

Starch is ranked as the most inert filler and disintegrant. It is also generally available worldwide in satisfactory quality at relatively low cost. Lactose, though not completely inert, is given a priority of 1, based on its

Table 10 Priority for Use: Binders, Glidants, Lubricants

Substance	Comment	Rating
Starch paste	OK	1
PVP	Frequently accelerates degradation	11
HPMC	Better than PVP	11
Gelatin	Rather worse than HPMC or starch	11
Colloidal silica	Quite reactive	1
Talc	Mostly OK	11
Magnesium stearate	Individual incompatibilities, no general rules	1
Calcium stearate		11
Stearic acid		
Neutral fats	Usually nonreactive	11

Source: Adapted from Hess [98].

Table 11 Legal Status of Carotenoid Food Colors (April 1987)

Country	β-Carotene	β-Apocarotenal	Canthaxanthin
European Economic Community Countries	X	X	X
South American Countries	X	X	X
Switzerland	X	X	X
United States	X	X	X
Philippines	X	X	
Japan	X	–	–
New Zealand	X	–	–
South Korea	X	–	–
Turkey	X	–	–
USSR and Eastern European Countries	X	–	–

Source: Adapted from Hess [98].

worldwide availability and good technical properties. Mannitol, though inert, is ranked as second choice because of its less satisfactory technical properties. Sucorse is also quite inert and has compression properties similar to those of lactose, but has a relatively low hygroscopicity point, is cariogenic, and is not a desired intake material in some patients.

The preferred binder, for reasons cited previously, is starch paste. Hydroxypropylmethylcellulose (HPMC) and gelatin are less inert; gelatin promotes microbial growth, and polyvinylpyrrolidone is not acceptable worldwide. Colloidal silica, while being potentially reactive, has unique technical properties of combined binding, disintegrating, and lubricant action. Talc, though not reactive, is difficult to obtain in good and constant quality. Magnesium stearate is rated priority 1, based on availability, while it is recognized that different lubricants must be evaluated individually for compatibility in any particular application. See Table 10.

The use of coloring agents to increase the elegance of coated and uncoated tablets, or for purposes of product identification, has changed rapidly since 1975. The trend in international product development appears to be to use iron oxides and titanium dioxide as tablet colorants and carotenoid food colors in tablet coatings in place of FD&C dyes. The legal status of the carotenoid food colors is expected to expand in worldwide markets in the future. The status of these colors given in Table 11.

Defined chemical composition and physical properties and defined chemical and microbiological properties are essential prerequisites for excipients in general, and for excipients for international use in particular. Excipients should conform to the same stringent requirements in all these properties as must active ingredients. The most common problems with excipients used in international pharmaceutical manufacture are the presence of undesired impurities and unacceptable variations in technological performance. The

Table 12 Microcrystalline Cellulose: Differences in Commercial Grades

Type	Molecular weight	Degree of polymerization	Crystallinity (%)
Native cellulose (cotton)	300,000–500,000	2000–3000	90–94
Microcrystalline cellulose	30,000–50,000	200–300	–
Avicel	–	–	81–37
Elcema (Rehocel)	–	–	12–24

Source: Huttenrauch and Keiner, *Pharmazie*, *31*:183 (1976).

careful choice and continual monitoring of suppliers of excipients in international markets is essential. Suppliers who concentrate on the pharmaceutical and food industries are usually more reliable and better qualified to provide the high-quality products required by the drug industry.

Drug companies engaged in international manufacture must be assured of reliable availability of the excipients they use. The quality and performance of excipients used at every manufacturing site must be consistent and reliable. Some of the most commonly employed newer classes of tablet excipients used internationally include microcrystalline cellulose, most of the new disintegrants, directly compressible excipients composed of lactose, various sugars, dicalcium phosphate, and special types of starches. In most cases when working with these specialized but very useful materials, one product cannot easily be replaced by another. For example, there are several brands of so-called microcrystalline cellulose available internationally. One type, known by the trade name of Avicel, is obtained by mechanical as well as acid treatment; another type (Elcema) is produced by mechanical treatment only. This leads to different degrees of crystallinity, which may be expected to have an influence on the effectiveness of each agent and on the properties of the dosage forms in which they are contained. The much higher level in the crystallinity of the Avicel product (Table 12) compared to the other microcrystalline forms accounts for its being a superior product as a disintegrant and directly compressible material.

According to Hess [98] companies operating in international markets will usually employ brand name or specialty excipients only if they lead to a better product, usually one with better controlled bioavailability or one with superior mechanical or analytical properties. This will justify their use, their possibly higher price, and problems which may be encountered in importing these substances (including high import duties). In some countries, such as Mexico and India, such imports may not be possible at all or may be possible only with great difficulty. There are many difficult decisions, potential problems, and pitfalls in choosing excipients in a company which operates worldwide. Additional research and development and closer cooperation among the industries, the universities, and the regulatory agencies—to define the properties, the scope, and the use of pharmaceutical excipients—will be needed during the immediate future. In addition, the development of a catalog with standards for all the major excipients used in tablet making—which are accepted by regulatory agencies around the world—will provide a giant step forward for the quality assurance and standardization of products made in international markets.

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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. Co-processing 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 (l = 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. C 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