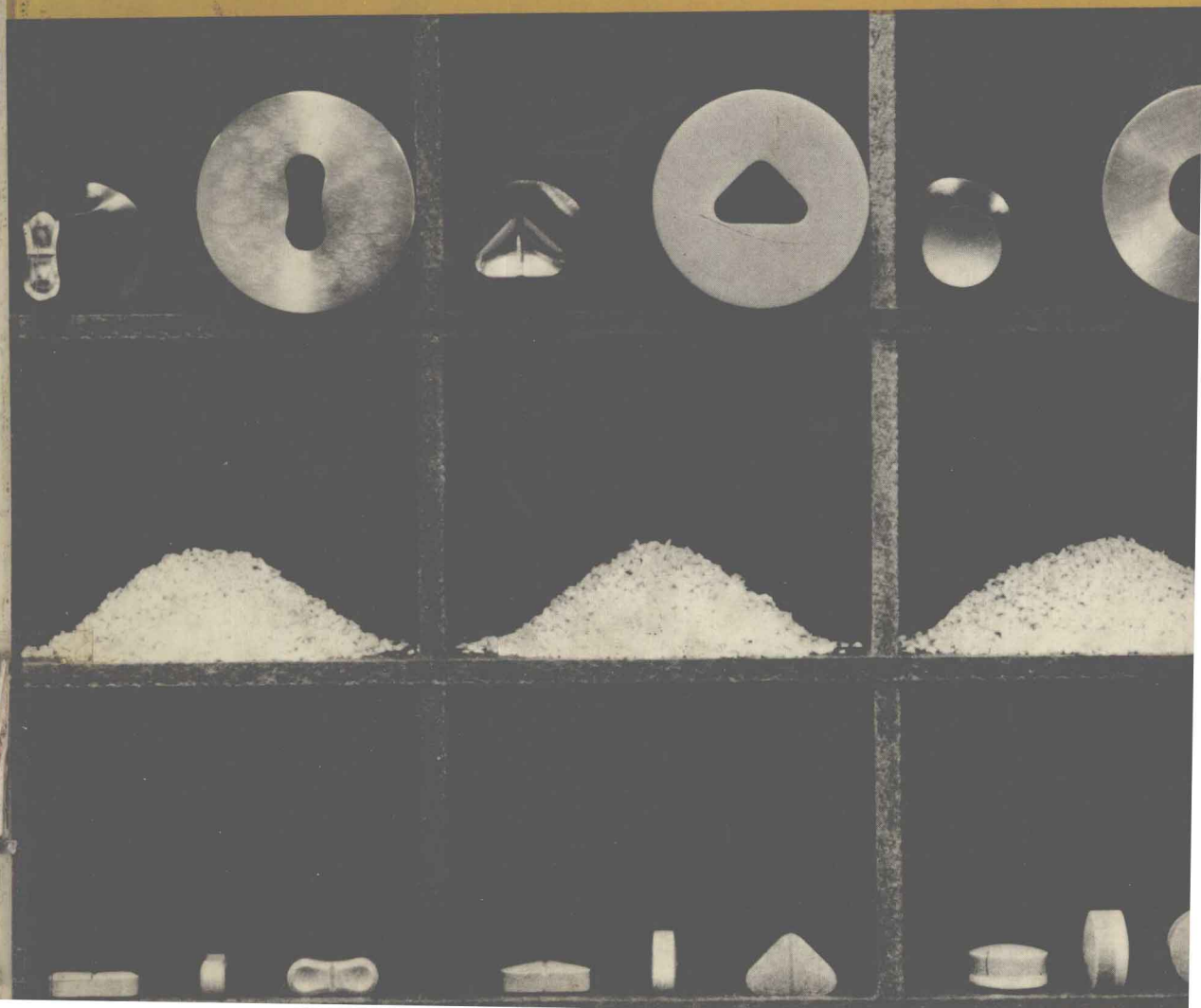
Pharmaceutical Dosage Forms: Tablets Volume 1

Edited by Herbert A. Lieberman and Leon Lachman



PHARMACEUTICAL DOSAGE FORMS

Tablets

In Three Volumes

VOLUME 1

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Preface

The most widely used dosage form in medicine today is the tablet. Yet despite this popularity, books describing the technology involved in developing, producing, and testing this dosage form are limited. Chapters concerned with tablets have appeared in various pharmaceutical texts. However, no comprehensive volume has been prepared that fully describes all facets of the technology related to the formulation of various tablet dosage forms.

The United States Pharmacopia defines tablets as ". . . solid dosage forms containing medicinal substances with or without suitable diluents. They may be classed according to the method of manufacture, such as molded or compressed tablets."

The compacted solid dosage form exists in many shapes and forms stressing convenience for the patient, ease of identification, and drug availability. There are tablets which are chewable, sublingual, or buccal, or are meant to be sucked, such as certain compressed tablets or molded sugar tablets, referred to as troches, in the former case, and lozenges in the latter. Most tablets are meant to be swallowed with the aid of water, and others are meant to be palatable when dropped in water—effervescent tablets. Some tablets, when swallowed, readily dissolve in the stomach; others are formulated as enteric, coated tablets, to dissolve in the intestine, or to slowly release the medicament throughout the gastrointestinal tract—sustained-release tablets. Some tablets are layered to keep chemically reactive materials apart, and other tablets are coated to help cover the bad taste of the medicines, and also to keep medicines in the coating away from the chemically reactive materials in the tablets or atmosphere.

Each of these tablet forms requires special formulation techniques. Knowing how to make one type does not mean that one can make another. Expertise in each tablet form requires specialized experience. The editors have chosen the authors of chapters describing particular types of tablets on the basis of their experience and training and of their high degree of knowledge of their subject. Since considerable expertise is required for the myriad tablet dosage forms, a multiauthored text seemed to the editors to be the only way to accomplish their goal of a text which

provides a knowledgable coverage of subject matter in an applicable fashion. The purpose of this multivolume treatise is to fully describe the technology used today in formulating, producing, and controlling the many compacted and molded solid dosage forms that are part of modern medicine.

The authors chosen for the various chapters were charged with the task of covering their technology so that their material would teach and not be presented as a review of the literature. Each chapter begins by assuming the reader is not very familiar with the subject matter. Gradually, as each chapter develops, the discussion becomes more advanced and specific. By writing in this fashion, the text is intended as a teaching source for undergraduate and graduate students, as well as experienced and unexperienced industrial pharmaceutical scientists. The book can also act as a ready reference to all those interested in tablet technology, namely, students, product development pharmacists, hospital pharmacists, drug patent attorneys, governmental and regulatory scientists, quality control personnel, pharmaceutical production personnel, and those concerned with production equipment for making tablets.

Three volumes are the result of the in-depth treatment given this subject. The first discusses the various solid dosage forms; the second is concerned with the processes involved in producing tablets, bioavailability, and pharmacokinetics; and in the third and final volume additional processes in tablet production are discussed, as well as sustained drug release, stability-kinetics, automation, pilot plant, and quality assurance.

The authors are to be commended for the manner in which they covered their subject matter and their patience with the editors' continued comments concerning their manuscripts. The editors wish to express their special thanks to the contributors for the excellence of their works, as well as their continued forebearance with our attempts to achieve this level of accomplishment. In many instances no previous pharmaceutical literature existed to which the authors could refer to facilitate the writing of their chapters. Since this book is the first complete coverage of tablets, many technological descriptions appear for the first time. Although there has been a great deal written about various types of tablets, no particular type has been as completely described in one chapter as appears in this multivolume text. The acceptability and usefulness of these volumes will be attributable to the efforts and skills of each of the contributing authors.

The subject matter, format, and choice of authors are the responsibilities of the editors. Any multiauthor book has problems of coordination and minimizing repetition. Some repetition was purposely left in the text because in the editors' opinions it helped the authors in developing their theme, and because each treatment is sufficiently different to be a valuable teaching aid. It is our hope that the labors of the contributors and the judgments of the editors have resulted in a text on tablets that will facilitate the work of the many people who refer to it.

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1

Preformulation Testing

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Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance—alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass-produced. Obviously, the type of information needed will depend on the dosage form to be developed. This chapter will describe a preformulation program needed to support the development of tablets and granulations as dosage forms.

During the early development of a new drug substance, the synthetic chemist, alone or in cooperation with specialists in other disciplines (including preformulation), may record some data which can be appropriately considered as preformulation data. This early data collection may include such information as gross particle size, melting point, infrared analysis, thin-layer chromatographic purity, and other such characterizations of different laboratory-scale batches. These data are useful in guiding, and becoming part of, the main body of preformulation work.

The formal preformulation study should start at the point after biological screening, when a decision is made for further development of the compound in clinical trials. Before embarking upon a formal program, the preformulation scientist must consider the following:

The available physicochemical data (including chemical structure, different salts available)
The therapeutic class of the compound and anticipated dose
The supply situation and the development schedule (i.e., the time available)
The availability of a stability-indicating assay
The nature of the information the formulator should have or would like to have

The considerations above will offer the preformulation scientist some guidance in deciding the types and the urgency of studies that need attention. Selectivity

is very critical to the success of a preformulation program. Not all the preformulation parameters are determined for every new compound. Data, as they are generated, must be reviewed to decide what additional studies must be undertaken. For example, a detailed investigation of dissolution is not warranted for a very soluble compound. On the other hand, particle size, surface area, dissolution, and the means of enhancing solubility are important considerations in the preformulation evaluation of a sparingly soluble drug.

I. Organoleptic Properties

A typical preformulation program should begin with the description of the drug substance. The color, odor, and taste of the new drug must be recorded using descriptive terminology. It is important to establish a standard terminology to describe these properties in order to avoid confusion among scientists using different terms to describe the same property. A list of some descriptive terms to describe the most commonly encountered colors, tastes, and odors of pharmaceutical powders is provided in Table 1.

The color of all the early batches of the new drug must be recorded using the descriptive terminology. When color is considered unappealing to the eye or is variable from batch to batch, the development of instrumental methods to monitor this property is suggested. A record of color of the early batches is very useful in establishing appropriate specifications for later production. When the color attributes are undesirable or variable, incorporation of a dye in the body or coating of the final product could be recommended.

All drug substances have characteristic odors and tastes. In tasting the new drug, due caution must be exerted. If taste is considered as unpalatable, consideration ought to be given to the use of a less soluble chemical form of the drug, if one is available—provided, of course, the bioavailability is not unacceptably compromised. The odor and taste may be suppressed by using appropriate flavors and excipients or by coating the final product. The flavors, dyes, and other excipients selected to alleviate the problems of unsightly or variable color and unpleasant odor and taste must be screened for their influence on the stability and bioavailability of the active drug.

Table 1

Suggested Terminology to Describe Organoleptic Properties of Pharmaceutical Powders

Color	Odor	Taste
Off white	Pungent	Acidic
Cream yellow	Sulfurous	Bitter
Tan	Fruity	Bland
Shiny	Aromatic	Intense
	Odorless	Sweet
		Tasteless

II. Purity

The preformulation scientist must have some perception of the purity of a drug substance. It is not this individual's primary responsibility to rigorously establish and investigate the purity (notwithstanding that this is an important subject). Such studies are most often performed in an analytical research and development group. But some early knowledge is necessary so that subsequent preformulation studies are not compromised as to their validity. This is not to mean necessarily that relatively inhomogeneous material or material showing some impurity be rejected for preformulation studies. It does mean that such properties be recognized and be acceptable. It is another control parameter which allows for comparison with subsequent batches.

There are also more direct concerns. Occasionally, an impurity can affect stability. Metal contamination at the level of a few parts per million is a relatively common example in which certain classes of compounds are deleteriously affected. The appearance is another instance where a slight impurity can have a large effect. Off-color materials, upon recrystallization, can become white in many instances. Finally, some impurities require circumspection because they are potentially toxic. The presence of aromatic amines, suspected of being carcinogenic, is an example. In these instances, discussions must be initiated with the chemist preparing the material so that remedial action can be taken. Very often a problem batch can be made satisfactory by a simple recrystallization.

Fortunately, the techniques used for characterizing the purity of a drug are the same as those used for other purposes in a preformulation study. Most of the techniques, to be mentioned below, are described in more detail elsewhere in this chapter and are used to characterize the solid state, or as an analytical tool in stability or solubility studies.

Thin-layer chromatography is of very wide-ranging applicability and is an excellent tool for characterizing the chemical homogeneity of very many types of materials. High-pressure liquid chromatography (HPLC), paper chromatography, and gas chromatography are also useful in the determination of chemical homogeneity.

Differential and gravimetric thermal analysis often indicate, qualitatively, the homogeneity or purity of a substance. Since these methods are simple, and are used in characterizing the material, their use for purity information is incidental. The appearance of several peaks or the acuteness of an endotherm can often be indicative of the purity. Similar information may sometimes also be generated by 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.

III. 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 [1,2]. 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 rather than as a coarse material.

Size also plays a role in the homogeneity of the final tablet; fine materials, on a statistical basis, can be expected to be distributed more uniformly. Size and shape influence the flow and the 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, the humidity, and interacting excipients than are coarse materials.

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 improves flow and handling properties. Grinding should reduce coarse material to, preferably, the 10 to 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. 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. As those challenges are found to be unimportant, then they can be relaxed.

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 hydrophobicity—lowering, possibly, 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 transformations.

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 determination. 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 0.3 μm upwards.

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 upwards from about 40 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 light scattering (Royco), light blockage (Hiac), and blockage of an electrical conductivity path (Coulter Counter). Other techniques based on centrifugation, air suspension, and such principles 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. One 50-μm spherical particle weighs as much as 1000 spherical particles of the same substance 5 μm in diameter.

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 known. However, these methods are now in general disfavor because of their tedious nature.

There are a variety of 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 [3].

A convenient tool for characterizing 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 1 for a powder sample of triamcinolone acetonide. The data used in the construction of Figure 1 are presented in Table 2.

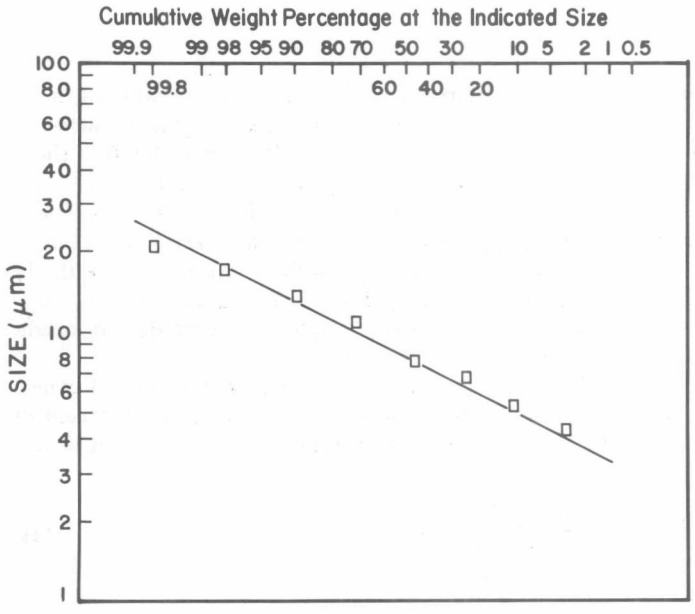

Figure 1. Log-probability plot of the size distribution of a sample of triamcinolone acetonide.

Table 2

The 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

The numbers of particles in Table 2 are converted into weight fractions by assuming them to be spheres, and multiplying by the volume of a single sphere (particle) calculated from the geometrical 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 2). 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 a 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 2). If densities were used, it is obvious 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 give, most often, 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:

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

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