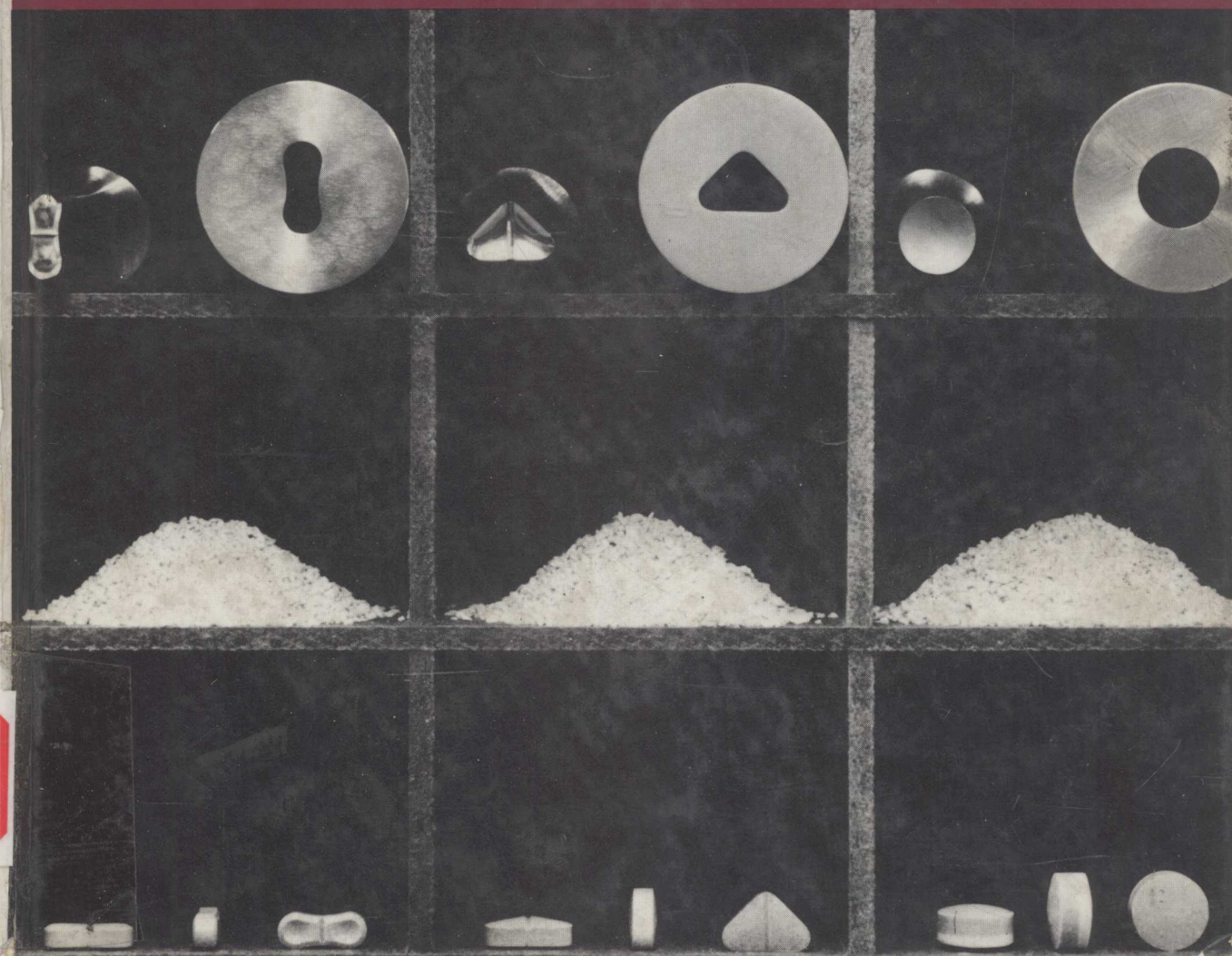
Pharmaceutical Dosage Forms: Tablets Volume 3

Edited by Herbert A. Lieberman and Leon Lachman



PHARMACEUTICAL DOSAGE FORMS

Tablets

In Three Volumes

VOLUME 3

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PHARMACEUTICAL DOSAGE FORMS

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 Pharmacopeia 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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Principles of Improved Tablet Production System Design

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I. INTRODUCTION

The old saying that "all progress is change but not all change is progress" is considered a truism by product manufacturers. Changes that are made in the production process of an established product are thoroughly evaluated from every point of view before implementation is allowed. The very existence of the company depends on its ability to produce products for sale. Therefore, any suggested change in the manufacture of an existing product must be viewed with suspicion until it can be shown that the change will indeed be advantageous to the company and not simply represent change for the sake of change. A company's prestige, profitability, and compliance with legal requirements are at stake when production changes are considered. Therefore, changes in the pharmaceutical industry must clearly be warranted before they are implemented. The object of this chapter is to introduce to the pharmaceutical scientist how changes can be accomplished in a pharmaceutical tablet production facility that will constitute progress for the company.

A. Unit Operations and Pharmaceutical Processing

A unit operation can be defined as a process designed to achieve one or more changes in the physical and/or chemical properties of the raw material(s) being processed.

Two or more unit operations that are designed to convert the basic raw materials into the final product or at least to have significantly improved the quality or value of the original raw material(s) describes a manufacturing system. In a tablet-manufacturing system, some of the unit operations may include (1) particle size reduction, (2) sieving or classification, (3) mixing, (4) particle size enlargement, (5) drying, (6) compression, (7) sorting, and (8) packaging.

The literature is well documented with various unit operations involved in the manufacture of tableted products which may impact on a number of final dosage

form quality features. The features include, but are not limited to, such items as content uniformity, hardness, friability, drug dissolution properties, and bioavailability. The traditional responsibility of the development pharmacist has been to identify and control such impacts. This includes the establishment of specific operating limits for each unit operation to ensure that the production system is under sufficient control for the production of safe, effective, and reliable tablets. The scope and purpose of this chapter is to examine system design considerations, and as a result, the individual unit operations and their potential impact on product quality will not be covered. The authors assume that each unit operation has been thoroughly investigated and is under sufficient control to do what it is purported to do. Specific effects of processing variables on product quality are dealt with in the pertinent chapters in this book series.

B. Batch Versus Continuous Processing

Most pharmaceutical production operations are batch operations, whereby a series of manufacturing steps are used to prepare a single batch or lot of a particular product. The same quantity or batch of material, if processed "en mass" through the various production steps to produce the final product, will then typically be treated by the manufacturer and the FDA as one lot. A relatively few pharmaceutical products are prepared by true continuous-processing procedures whereby raw materials are continuously fed into and through the production sequence, and the finished product is continuously discharged from the final processing step(s). In continuous processing, one day's production, the production from one work shift, the quantity of a critical raw material from a given lot, or a combination thereof may define a single lot of manufactured product. Development of continuous-processing procedures requires specially designed and interfaced equipment, special plant layouts, and dedicated plant space, which reduces plant flexibility. The equipment, special plant design requirements, and dedicated space are all factors leading to the high costs of setting up and maintaining a continuous-manufacturing operation for a product. Unless the volume of product being produced is very high, the cost of setting up a product-dedicated, continuous-production operation will not usually be justified. Since pharmaceutical products, even within a dosage form class such as compressed tablets, differ materially in many important aspects, such as drug dosage, excipients used, critical factors, affecting product quality, manufacturing problems, and the like, it is usually not feasible or possible to set up a continuous-processing operation for one product and then apply it to several others. Thus true continuous-processing operations are largely limited in the drug industry to large-volume products, which often also have large doses (or high weights per tablet), such as Tums, Gelusil, Aldomet, or Alka Seltzer, for which tons of material must be processed each day, on an ongoing basis.

II. BENEFITS OF IMPROVED TABLET PRODUCTION SYSTEMS

In either the batch or the continuous mode of operation, the objective of the production function is to produce pharmaceutical tablets for sale. Consequently, a production process should always be viewed as a candidate for progressive change

in an effort to maintain the company's products in the marketplace. When looking at a process for possible changes, one must be aware of the potential benefits for the company. The major benefits that can be obtained, and which constitute the major valid reasons for changing or redesigning a pharmaceutical tablet manufacturing process, are the following [1-5]:

Regulatory compliance
  Current Good Manufacturing Practices (CGMP)
  Occupational Safety and Health Administration (OSHA)
  Environmental Protection Agency (EPA)
Increased production capacity
Decreased product throughput time
Reduced labor costs
Increased energy savings
Broadened process control or automation
Enhanced product quality
Enhanced process reliability

The benefits that can be derived from the redesign of a process are dependent to a large extent on how "good" or "bad" the old process is. With perhaps the exception of some CGMP, OSHA, or even EPA requirements, the expected benefits to be derived from proposed process design changes are generally reduced to a dollar figure in order to compare the cost of implementing the change with the expected savings to be generated by the change. Proposed changes on a "good" facility may not be cost-justifiable while the same proposal on a "bad" facility can easily be cost-justified. What can be justified and what cannot is a function of what can be referred to as the "corporate policy" or "corporate personality" at the time the proposal is made. A pharmaceutical company, like any company, is a part of the community in which it resides and as such has responsibilities to many other societal groups. These include governments, stockholders, employees, the community, the competition, and customers. The interaction of all these groups with the company results in a "corporate personality." Therefore, companies have different standards for evaluating different financial situations, different production philosophies, varying time constraints for design and implementation, and varying technical support available for design changes. All of these items will be given consideration and will influence the decision-making process when a redesign proposal is made.

III. PRODUCTION PROCESS DESIGN CONSIDERATIONS

A fact that should be well understood is that the production unit is not an independent organization within the company. Any changes made in the production unit impact on many other units that come in contact with the production unit. However, with the rising costs of materials, labor, inflation, and regulations being constantly added to the manufacture of pharmaceuticals, the pharmaceutical industry cannot afford to neglect change or the modification of existing processes simply because there are "established standards" that may be difficult to change. Increased productivity matched with a reduction in direct labor cost will probably be the way of the future. This can only be accomplished by a conscious effort on the part of

those in process development. The development pharmacist should therefore be familiar with ways in which the manufacture of pharmaceutical products can be increased and labor reduced. Even though the development pharmacist will not be thoroughly knowledgeable in all areas of process design considerations, he or she should at least be aware that those considerations exist and be able to interact with experts in those fields to accomplish cost savings.

Major advances in efficiency have been made in tablet production over the last 20 to 30 years. These advances have come about by the development of methods, pieces of equipment, and instrumentation with which tablet production systems have been able to (1) improve materials handling, (2) improve specific unit operations, (3) eliminate or combine processing steps, and (4) incorporate automated process control of unit operations and processes.

A. Materials Handling

1. Materials-Handling Risks

Possibly the single largest contribution to the effectiveness of a manufacturing facility is made by the facility's materials-handling capabilities. In addition to a lack of efficiency, there are certain risks involved with improper or inefficient materials handling. These risks include increased product costs, customer dissatisfaction, and employee safety liabilities. Materials that are not handled efficiently can increase the cost of raw materials. For example, penalty charges are assessed (demurrage) when railroad cars are not loaded or unloaded according to schedule. If raw materials are not moved as required by production schedules, delays are incurred which can lead to situations in which machine time is wasted, personnel time is wasted, in-process inventories are increased, and the entire manufacturing process is slowed down. In addition, the improper handling and storage of materials can lead to damaged, outdated, and lost materials. Improper materials handling can place employees in physical danger. An increase in employee frustration generated by constant production delays due to poor materials handling can result in reduced morale.

2. Materials-Handling Objectives

A well-designed and efficiently operated materials-handling system should impart to the manufacturing facility reduced handling costs, increased manufacturing capacity, improved working conditions, and improved raw material distribution to the appropriate manufacturing areas. To achieve an efficient materials-handling system, as many of the basic general principles of efficient materials handling need to be implemented as practical.

3. Basic Principles of Materials Handling

Short Distances

Raw materials used in the production process should only be moved over the shortest possible distances. Moving materials over excessive distances increases production time, wastes energy, creates inefficiency, increases the possibilities of delays, and adds to the labor costs if the material is moved by hand.