Encyclopedia of Pharmaceutical Technology

Second Edition

Volume 3
Ped–Z
Pages 2045–3032

edited by

James Swarbrick

President
PharmaceuTech, Inc., Pinehurst, North Carolina
and
Vice President for Scientific Affairs, aaiPharma, Inc.
Wilmington, North Carolina, U.S.A.

and

James C. Boylan

Pharmaceutical Consultant
Gurnee, Illinois, U.S.A.

MARCEL DEKKER, INC. NEW YORK • BASEL

Cover Art: Leigh A. Rondano, Boehringer angelheim Pharmaceuticals, Inc.

ISBN: Volume 1: 0-8247-2822-X
Volume 2: 0-8247-2823-8
Volume 3: 0-8247-2824-6
Prepack: 0-8247-2825-4

ISBN: Online: 0-8247-2820-3

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere distribution
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 41-61-261-8482; fax: 41-61-261-8896

World Wide Web
http://www.dekker.com

Current printing (last digit)

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

TABLET FORMULATION

Larry L. Augsburger
University of Maryland, Baltimore, Maryland

Mark J. Zellhofer
University Pharmaceuticals of Maryland, Inc., Baltimore, Maryland

INTRODUCTION OBJECTIVES OF TABLET FORMULATION

The best new therapeutic entity in the world is of little value without an appropriate delivery system. Tableted drug delivery systems can range from relatively simple immediate-release formulations to complex extended- or modified-release dosage forms. The most important role of a drug delivery system is to get the drug "delivered" to the site of action in sufficient amount and at the appropriate rate; however, it must also meet a number of other essential criteria. These include physical and chemical stability, ability to be economically mass produced in a manner that assures the proper amount of drug in each and every dosage unit and in each batch produced, and, as far as possible, patient acceptability (for example, reasonable size and shape, taste, color, etc. to encourage patients to take the drug and thus comply with the prescribed dosing regimen).

The discovery of new therapeutic entities always initiates excitement, but the contributions of the formulation specialist are either not well understood or are often taken for granted and thus remain "unsung." However, the drug and its delivery system cannot be separated. The general design criteria for tablets are given as follows

1. Optimal drug dissolution and, hence, availability from the dosage form for absorption consistent with intended use (i.e., immediate or extended release).
2. Accuracy and uniformity of drug content.
3. Stability, including the stability of the drug substance, the overall tablet formulation, disintegration, and the rate and extent of drug dissolution from the tablet for an extended period.
4. Patient acceptability. As much as possible, the finished product should have an attractive appearance, including color, size, taste, etc., as applicable, in order to maximize patent acceptability and encourage compliance with the prescribed dosing regimen.
5. Manufacturability. The formulation design should allow for the efficient, cost-effective, practical production of the required batches.

That tablets can be formulated to uniquely meet these criteria accounts for their emergence as the most prevalent oral solid dosage form. Although several different types of tablets may be distinguished, they are mostly made by compression, intended to be swallowed whole and designed for immediate release. This paper presents a systematic approach to the design and formulation of immediate-release compressed tablets.

MODERN TABLET FORMULATION DESIGN AND MANUFACTURE

Tablet dosage forms have to satisfy a unique design compromise. The desired properties of rapid or controlled disintegration and dissolution of the primary constituent particles must be balanced with the manufacturability and esthetics of a solid compact resistant to mechanical attrition.

Excipients are critical to the design of the delivery system and play a major role in determining its quality and performance (1). They may be selected to enhance stability (antioxidants, UV absorbers), optimize or modify drug release (disintegrants, hydrophilic polymers, wetting agents, biodegradable polymers), provide essential manufacturing technology functions (binders, glidants, lubricants), enhance patient acceptance (flavors), or aid in product identification (colorants). Thus a tablet formulation is not a random combination of ingredients, but rather a carefully thought out, rational formulation designed to satisfy the above criteria.

A long list of possible excipients is available to the formulation scientist, but certain external factors such as cost, functional reliability, availability, and international acceptance govern their selection. For example, although the official compendia provide standards for identity and purity of excipients, monographs may not provide tests to

assure their functionality. For instance, the NF monograph for Compressible Sugar provides no test for compressibility. The monograph for Lactose USP does not address the many particle size and tableting grades meeting monograph standards. The NF monograph for Pregelatinized Starch refers to grades that are "compressible and flowable in character," but provides no specifications or tests for these properties. Nor do the monograph tests for disintegrants and lubricants necessarily relate to their functionality. The need to provide functionality tests or tests for properties clearly related to functionality may be as important as controlling identity and purity (2). This point has been made even more apparent in recent years with the emergence of multiple sources of such modern excipients as direct-compression filler-binders and the various classes of "super" disintegrants.

A major problem currently being faced by multinational firms and others who market in the international arena, is the lack of universal acceptability of excipients in different countries. The selection of excipients for international markets is often a compromise between functional efficacy, local restrictions, and cost and availability in the countries where the product is to be made. In recent years, the globalization of the pharmaceutical industry has brought about an intense interest in developing harmonized pharmacopeial excipient standards, Good Manufacturing Practices (GMP) for excipient manufacture, and safety evaluation guidelines for new excipients to eliminate or avoid trade barriers between different countries (3). The International Pharmaceuticals Excipients Council (IPEC), which consists of producers, users, and pharmaceutical scientists, was launched in 1991 to assist regulatory authorities in the United States, Japan, and Europe with harmonization. The separate organizations later formed in the United States (IPEC-Americas), Europe (IPEC-Europe), and Japan (JPEC) are now known as TriPEC and include, as of 1993, more than 100 excipient and pharmaceutical firms (3).

PREFORMULATION

The objective of preformulation studies is to develop a portfolio of information about the drug substance to serve as a set of parameters against which detailed formulation design can be carried out. Preformulation investigations are designed to identify those physicochemical properties of drug substances and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.

Following is a generalized preformulation protocol appropriate for tablet dosage forms. For certain tests, it is assumed that the drug substance is multisourced (a previously new chemical entity whose patent has expired and which is available to the generic market) for which a USP monograph exists.

Identity and Purity

The study of any drug substance must start with the determination of identity and purity. Such tests are necessary to identify degradents and contaminants and may include organoleptic tests for color, odor, and taste. Purity tests can be found in the USP for almost all marketed compounds. Alternative methods can be employed only if they are validated against the USP procedure. Tests other than potency, which can help to identify or determine the purity of compounds, are melting point, specific rotation, pH, heavy metals, residue on ignition, etc. Impurities can occasionally affect stability, and metal contamination can catalyze chemical reactions. Impurities can also alter the color of drug substances. Techniques can be utilized to give a quantitative estimate of impurities such as the impurity index (II) and the homogeneity index (HI). An ordinary impurity test can be found in the USP that estimates impurities by thin-layer chromatography (TLC).

Crystal Properties and Polymorphism

Many drug substances appear in more than one polymorphic form. The form is determined by certain conditions during the crystallization step. Occasionally drug substances are precipitated in such a way that molecules do not organize themselves in any set pattern, resulting in an amorphous powder. It is also possible for solids to entrap solvents stoichiometrically to form solvates.

Even though they are chemically identical, the different polymorphic forms of a compound are associated with different free energies, and, therefore, have different physical properties that can impact significantly on product performance (4). These include differences in solubility and dissolution rate (affecting bioavailability), solid-state stability (affecting potency), deformation characteristics (affecting compactibility), and particle size and shape (affecting powder density and flow properties). The form with the lowest energy is more stable than the others. Although the other polymorphs are thus energetically unfavored, if kept dry, they may persist indefinitely and are called "metastable." A metastable

form may be preferred, particularly for its ability to dissolve more rapidly.

Polymorphic transformation can take place during pharmaceutical processing, such as particle size reduction, wet granulation, drying, and even during the compaction process (5). Tests employed to determine crystal properties include differential thermal analysis (DTA), differential scanning calorimetry (DSC), and X-ray diffraction (4). See also the article Thermal Analysis of Drugs and Drug Products by D. Giron in this encyclopedia.

Particle Size, Shape, and Surface Area

Probably no characteristics of a drug substance are more important than particle characteristics in determining its performance in a formulation. This is particularly true in those cases where the drug is a poorly soluble nonelectrolyte or a free acid form with poor solubility at low pH values. Such drugs are likely to exhibit dissolution-rate-limited absorption, and if dissolution does not take place rapidly enough, a therapeutic concentration in the body fluids may never be achieved, the peak plasma concentration may be significantly delayed, or much of the drug may bypass that region of the gastrointestinal (GI) tract where absorption is best. Particle size reduction (e.g., micronization) is often utilized to enhance dissolution rate. Small particles present a larger surface area per unit weight to the dissolution media and hence dissolve more rapidly than large particles. Particle size and surface area are two of the most important properties determining the solubility rate of a drug and thus potentially its bioavailability. There are numerous examples of bioavailability problems and bioinequivalence due to the inappropriate particle size of the drug substance.

Particle size and shape also play an extremely important role in the homogeneity of powder blends and the unblending of powders in a mixer. Segregation in handling or during the compaction process has a significant effect on the content uniformity of the finished products. Particle size can also affect the stability of a drug substance in that it governs the surface area available for oxidation and hydrolysis. Surface area is critical for interaction with excipients in tablet dosage forms and can greatly affect stability. Methods to determine particle size and shape include light microscopy, scanning electron microscopy, sieve analysis, and various electronic sensing-zone particle counters. Methods available for surface area measurement include air permeability and various gas adsorption techniques.

Bulk Powder Properties

Bulk powder properties are extremely important in pharmaceutical processing (6). Knowledge of the true and bulk densities of the drug substance as well as of the excipients is extremely useful in

- Providing perspective as to the size of the final tablet and the size and type of processing equipment needed,
- Anticipating problems in the physical mixing of powders and the homogeneity of intermediate and final products because significant differences in true densities can result in segregation,
- Anticipating problems in flow properties, since that property is affected by density, and
- Identifying differences in different lots and raw materials from different suppliers because different polymorphic forms can be expected to exhibit different true densities.

A comparison of true particle density, apparent particle density, and bulk density can provide information on total porosity, interparticle porosity, and intraparticle porosity. Methods include true particle density measurements via helium pycnometry, mercury intrusion porosimetry, and poured and tapped bulk density.

The influence of sorbed moisture on chemical stability and the flow and compaction of powders and granulations is well established. The moisture content and hygroscopicity of excipients is particularly important as total product processing as well as finished product stability can be affected. Hygroscopicity, moisture-sorption isotherms, and equilibrium moisture content can be determined by thermogravimetric analysis and Karl Fisher titration methods.

The compactibility of relatively large-dose drug substances and formulations is another important property. Compactibility is of less concern for smaller-dose drugs for which direct compression fillers may be able to compensate for a lack of ability to form mechanically strong compacts. An instrumented tablet press (7) or compaction simulator (8) may be used to assess the relationship between the mechanical strength of the compact and the force (or pressure) employed to form the tablet. This relationship is the easiest of all compaction measurements to establish and provides important information on the ability of the material to form practical compacts. Measures of compact mechanical strength include hardness (or crushing force), tensile strength, and friability. Other more complex studies, more easily and perhaps best done using a compaction simulator, include measurement of the work or energy of compaction, pressure–density (Athy–Heckel) analysis, strain-rate sensitivity, and elastic recovery (9).

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