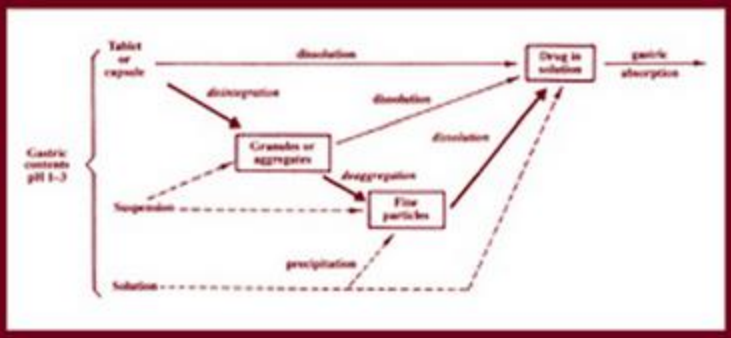
Modern Pharmaceutics

Fourth Edition, Revised and Expanded



edited by
Gilbert S. Banker
Christopher T. Rhodes

MYLAN EXHIBIT 1010

Modern Pharmaceutics

Fourth Edition, Revised and Expanded

edited by

Gilbert S.Banker
University of Iowa
Iowa City, Iowa

Christopher T.Rhodes
University of Rhode Island
Kingston, Rhode Island

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20130726

International Standard Book Number-13: 978-0-8247-4469-4 (eBook - PDF)

10

Tablet Dosage Forms

Edward M. Rudnic
Pharmavene, Inc., Rockville, Maryland

Mary Kathryn Kottke
AutoImmune, Inc., Lexington, Massachusetts

I. INTRODUCTION

During the past three and a half decades, the pharmaceutical industry has invested vast amounts of time and money in the study of tablet compaction. This expenditure is quite reasonable when one considers how valuable tablets, as a dosage form, are to the industry. As oral dosage forms can be self-administered by the patient, they are obviously more profitable to manufacture than parenteral dosage forms, which usually must be administered by trained personnel. This is reflected by the fact that well over 80% of the drugs in the United States that are formulated to produce systemic effects are marketed as oral dosage forms. Compared with other oral dosage forms, tablets are the manufacturers' dosage form of choice because of their relatively low cost of manufacturing, packaging, and shipping; increased stability, and virtual tamper resistance (i.e., most tampered tablets either become discolored or disintegrate).

II. DESIGN AND FORMULATION OF COMPRESSED TABLETS

A. General Considerations

The most common solid dosage forms in contemporary practice are *tablets*, which may be defined as unit forms of solid medicaments prepared by compaction. Most consist of a mixture of powders that are compacted in a die to produce a single, rigid body. The most common types of tablets are those intended to be swallowed whole and then disintegrate and release their medicaments in the gastrointestinal tract (GIT). A less common type of tablet is formulated to allow dissolution or dispersion in water before administration. Ideally, for this type of tablet, all ingredients should be soluble, but frequently, a fine suspension has to be accepted. Many tablets of this type are formulated to be effervescent, and their main advantages include rapid release of medicament and minimization of gastric irritation.

Some tablets are designed to be masticated (chewed). This type of tablet is often used when absorption from the buccal cavity is desired, or to enhance dispersion before swallowing.

Alternatively, a tablet may be intended to dissolve slowly in the mouth (e.g., lozenges) to provide local activity of the drug. A few tablets are designed to be placed under the tongue (sublingual) or between the teeth and gum (buccal) and rapidly release their medicament into the bloodstream. Buccal or sublingual absorption is often desirable for drugs subject to extensive hepatic metabolism by the first-pass effect (e.g., nitroglycerin, testosterone). Recently, a lozenge on a stick, or "lollipop," dosage form of fentanyl was developed for pediatric use.

There are now many types of tablet formulations that provide for the release of the medicament to be delayed or to control the rate of the drug's availability. Some of these preparations are highly sophisticated and are rightly referred to as complete "drug-delivery systems."

"Sustained-release" tablets can encompass a broad range of technologies. Since the concepts of prolonged drug delivery are the subjects of Chapter 15, the strategies of these systems will not be discussed here. However, solid dosage formulators must be aware of the various options available to them.

For example, some water-soluble drugs may need to be formulated so that their release and dissolution is controlled over a long period. For these, certain water-insoluble materials will have to be coformulated with the drug. If the dose of this drug is high, the drug will dictate the tableting properties of the formula. If the drug exhibits poor compactibility, hydrophobic agents, such as waxes, will surely make matters worse. To solve such a problem, the formulators would have to turn to other types of water-insoluble materials, such as polymers, to achieve drug release and tableting goals.

Some tablets combine sustained-release characteristics with a rapidly disintegrating tablet. Such products as K-Dur (Key Pharmaceuticals) combine coated potassium chloride (KCl) crystals in a rapidly releasing tablet. In this particular instance, the crystals are coated with ethylcellulose, a water-insoluble polymer and are then incorporated in a rapidly disintegrating microcrystalline cellulose matrix. The purpose of this tablet is to minimize GI ulceration, commonly seen with KCl therapy. This simple, but elegant, formulation is a masterpiece of solid dosage form strategy to achieve clinical goals.

Thus, the single greatest challenge to the tablet formulator is in the definition of the purpose of the formulation and the identification of suitable materials to achieve developmental objectives. To do this properly, the formulator must know the properties of the drug, the materials to be coformulated with the drug, and the important aspects of the granulation, tableting, and coating processes.

Pharmaceutical compressed tablets are prepared by placing an appropriate powder mix, or granulation, in a metal die on a tablet press. At the base of the die is a lower punch, and above the die is an upper punch. When the upper punch is forced down on the powder mix (single-punch press), or when the upper and lower punches squeeze together (rotary press), the powder is forced into a tablet. Despite that powder compaction has been observed for millennia, scientists still debate the exact mechanisms behind this phenomenon.

Perhaps the most significant factor in the tableting process arises from the need to produce tablets of uniform weight. This is achieved by feeding constant volumes of homogeneous material to the dies. Such an approach is necessary because direct weighing at rates commensurate with modern tablet press operation is impossible. This requirement immediately places demands on the physical characteristics of the feed and on the design of the tablet press itself. In the former, precompression treatment of the granulation is one of the most common ways of minimizing difficulties arising from this source.

The great paradox in pharmaceutical tableting is the need to manufacture a compact capable of reproducibly releasing the drug that is of sufficient mechanical strength to withstand the rigors of processing and packaging. Usually, the release of the drug is produced by the pene-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.