Modern Pharmaceutics

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Chapter 10

Tablet Dosage Forms

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I. INTRODUCTION

During the past four 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. Because oral dosage forms can be self-administered by the patient, they are obviously more profitable to manufacture than parenteral dosage forms that must be administered, in most cases, 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 to other oral dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package, and shipment; increased stability and virtual tamper resistance (most tampered-with tablets either become discolored or disintegrate).

II. DESIGN AND FORMULATION OF COMPRESSED TABLETS

A. General Considerations

The most common solid dosage forms in contemporary use 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 that is rapidly gaining popularity in the United States is formulated to allow dissolution or dispersion in water prior to 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 drug and minimization of gastric irritation.

Some tablets are designed to be masticated (i.e., chewed). This type of tablet is often used when absorption from the buccal cavity is desired or to enhance dispersion prior to swallowing. Alternatively, a tablet may be intended to dissolve slowly in the mouth (e.g., lozenges) so as to provide local activity of the drug. A few tablets are designed to be placed under the tongue (i.e., sublingual) or between the teeth and gum (i.e., buccal) and rapidly release drug into the bloodstream. Buccal or sublingual absorption is often desirable for drugs liable 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 preoperative sedation in pediatric patients (Oralet®) and breakthrough cancer pain in adults (Actiq®). Active ingredient is released from the lozenge into the bloodstream from the oral mucosa.

There are now many types of tablet formulations that provide for the release of drug to be delayed or 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." Since the concepts of controlled 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, when prolonged release of a water-soluble drug is required, water-insoluble materials must be co-formulated with the drug. If the dose of the drug is high and it exhibits poor compactibility, purely hydrophobic agents, such as waxes, will exacerbate the inability of the material to form a compact. In such cases, formulators need to turn to other types of water-insoluble materials, such as polymers, to achieve both drug release and tableting goals.

Some tablets combine sustained-release and rapid disintegration characteristics. Products such as K-Dur® (Key Pharmaceuticals) combine coated potassium chloride crystals in a rapidly releasing tablet. In this particular instance, the crystals are coated with ethylcellulose, a water-insoluble polymer, and are then incorporated into a rapidly disintegrating microcrystalline cellulose (MCC) matrix. The purpose of this tablet is to minimize GI ulceration, commonly encountered by patients treated with potassium chloride. This simple but elegant formulation is an example of a solid dosage form strategy used 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 meet development objectives. In order to do this properly, the formulator must know the properties of the drug, the materials to be co-formulated 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 station press) or when the upper and lower punches squeeze together (rotary or multiple station press), the powder is forced into a tablet. Despite the fact that powder compaction has been observed for hundreds of years, scientists still debate the exact mechanisms behind this phenomenon.

Perhaps the most significant factor in the tableting of materials for use as drug products is 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 case of 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 of sufficient mechanical strength to withstand the rigors of processing and packaging that is also capable of reproducibly releasing the drug. In most cases, the release of the drug is produced by the penetration of aqueous fluids into the fine residual pore structure of the tablet and the contact of these fluids with components that either swell or release gases.

The selected precompression treatment, if any, markedly affects the manufacture of tablets. In particular, one must determine whether a mixture of powdered ingredients is to be tableted directly or if an intervening wet granulation step is to be introduced. This decision is influenced by many factors, including the stability of the drug to heat and moisture; the flow properties of the granulation; and the tendency of the granulation to segregate. At the present time there are also two conflicting considerations that tend to play a major role in this choice. These are the reluctance to change methods employed traditionally by the company versus the economic advantages of omitting complete stages in the production sequence.

In wet granulation, the components of the formulations are mixed with a granulating liquid, such as water or ethanol, to produce granules that will readily compress to give tablets. Wet granulation methods predominate in the manufacture of existing products, while the trend for new products is to use direct compression procedures. Although many steps are eliminated when using direct compression, some formulators have found that wet granulated products are more robust and able to accommodate variability in raw materials and tableting equipment. Thus, for some

companies, the trend is reverting to the formulation of tablets by wet granulation.

B. Desirable Properties of Raw Materials

Most formulations are composed of one or more medicaments plus a variety of excipients. Irrespective of the type of tablet, general criteria for these raw materials are necessary. In order to produce accurate, reproducible dosage forms, it is essential that each component be uniformly dispersed within the mixture and that any tendency for component segregation be minimized. In addition, the processing operations demand that the mixture be both free-flowing and cohesive when compressed.

Particle Size

In general, the tendencies for a powder mix to segregate can be reduced by maintaining similar particle size distribution, shape, and, theoretically, density of all the ingredients. Flow properties are enhanced by using regular-shaped, smooth particles with a narrow size distribution together with an optimum proportion of "fines" (particles 50 μm). If such conditions cannot be met, then some form of granulation should be considered.

Particle size distribution, and hence surface area of the drug itself, is an important property that has received considerable attention in the literature. For many drugs, particularly those whose absorption is limited by the rate of dissolution, attainment of therapeutic levels may depend upon achieving a small particle size [1]. In fact, it has been suggested that for such drugs, standards for specific surface areas and the number of particles per unit weight should be developed. However, the difficulty in handling very fine powders, as well as the possibility of altering the material in other ways, has shifted the emphasis towards producing an optimum, rather than a minimum, particle size. For instance, several researchers have found that decreasing particle size produces tablets of increased strength that also have a reduced tendency for lamination [2–5]. This is probably due to the minimization of any adverse influences that a particular crystal structure may have on the bonding mechanism. On the other hand, samples of milled digoxin crystals prepared by a number of size-reduction techniques have been reported to elicit different equilibrium solubilities [1]. This suggests that the method of grinding may well affect the dissolution behavior of certain drugs.

The effect of particle size on the compaction characteristics of two model sulfonamide drugs, one exhibiting brittle fracture and the other being compressed chiefly by plastic deformation, has been reported [3]. In particular, it was shown that the tensile strength of tablets made from the brittle material were more sensitive to the drug's particle size than that of tablets made from the plastically deforming material. In addition, larger granules possess better flow, while small aggregates deform during compaction (e.g., spray-dried lactose) [6].

An alternative approach aimed at reducing the segregation tendencies of medicaments and excipients involves milling the former to a small particle size and then physically absorbing it uniformly onto the surface of the larger particles of an excipient substrate. By these means "ordered," as opposed to "random," mixing is realized and dissolution is enhanced as a result of the fine dispersion [7].

Moisture Content

One of the most significant parameters contributing to the behavior of many tablet formulations is the level of moisture present during manufacture as well as that residual in the product. In addition to its role as a granulation fluid and its potentially adverse effects on stability, water has some subtle effects that should not be overlooked. For example, there is increasing evidence to suggest that moisture levels may be very critical in minimizing certain faults, such as lamination, that can occur during compression. Moisture levels can also affect the mechanical strength of tablets and may act as an internal lubricant. For example, Fig. 1 illus-

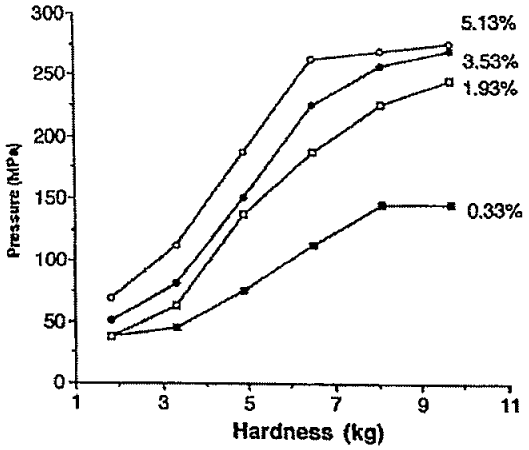

Fig. 1 The effect of moisture content on the compactibility of anhydrous beta lactose tablets. (From Ref. 8.)

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