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Validation and applications of an expedited tablet friability method

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ABSTRACT

The harmonized monograph on tablet friability test in United States Pharmacopeia (USP), European Pharmacopeia (Pharm. Eur.), and Japanese Pharmacopeia (JP) is designed to assess adequacy of mechanical strength of a batch of tablets. Currently, its potential applications in formulation development have been limited due to the batch requirement that is both labor and material intensive. To this end, we have developed an expedited tablet friability test method, using the existing USP test apparatus. The validity of the expedited friability method is established by showing that the friability data from the expedited method is not statistically different from those from the standard pharmacopeia method using materials of very different mechanical properties, i.e., microcrystalline cellulose and dibasic calcium phosphate dihydrate. Using the expedited friability method, we have shown that the relationship between tablet friability and tablet mechanical strength follows a power law expression. Furthermore, potential applications of this expedited friability test in facilitating systematic and efficient tablet formulation and tooling design are demonstrated with examples.

1. Introduction

Tablet friability is the tendency of a tablet to lose component particles due to abrasion, friction, or mechanical shock (Shafer et al., 1956; Sinka et al., 2004). High friability leads to unacceptable loss of drug content during downstream processing (e.g., film coating), storage, and handling (Porter et al., 2009). Besides the potential loss in therapeutic effects due to sub-potency, damaged tablet appearance also creates doubts by patients on tablet quality. Although empirical in its origin (Burlinson and Pickering, 1950; Shafer et al., 1956), tablet friability has become an important tablet performance and quality attribute to assess during tablet product development (FDA, 2010; Yu, 2008). To put things in perspective, friability test may be compared to dissolution test as a tool for assessing critical performance of any tablet product.

The standard pharmacopeial method for measuring tablet friability requires a set of "identical" tablets from the same batch. A total of at least 6.5 g of tablets is required for a single test. Tablets are dropped 100 times from a fixed height, as the friabilator rotates. Tablets are then recovered, dedusted, and weighed to calculate weight loss of the set of tablets. Generally, ≤1% weight loss is acceptable for an existing compressed and uncoated tablet product. However, a more conservative weight loss of ≤0.8% is recommended for new formulations not yet having sufficient packaging data (USP, 2014; Pharm. Eur., 2013; JP, 2011). Lower limits may be set for specific products or for certain unit operations (Podczeck, 2012; Porter et al., 2009; Soh et al., 2013).

Ideally, friability test could have been used extensively to facilitate tablet product development. In reality, however, the standard friability test is routinely carried out "to supplement other physical strength measurements, such as crushing strength" (USP, 2014), tablet tensile strength (Fell and Newton, 1970), and indentation hardness (Aulton et al., 1974), to ascertain whether a batch of tablets will pass or fail the acceptance criterion. Failed friability test result triggers a change in formulation or compaction parameters, e.g., compaction pressure, speed, or tooling design. A new batch of tablets is then made and tested for friability. This process is repeated until a batch of tablet passes the acceptance criterion. Because the required test iterations demand the manufacture of batches of tablets, a significant amount of active pharmaceutical ingredient(s) and efforts are required in this kind of formulation development process. Friability test is most useful in guiding formulation development when it has been determined as a function of compaction force/pressure, from which the minimum compaction force/pressure required to make sufficiently strong tablets can be identified. This is much more effective than the trial and error approach described earlier. With such information, it is easy to determine the tablet mechanical strength that is necessary for adequate handling and shipping (Gunsel and Kanig, 1976). The traditional friability approach, however, does

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not provide the kind of quantitative information useful to guide formulation development unless multiple batches of tablets are prepared under different compaction conditions and tested. This is labor and material intensive, hence, unfit for adoption in early formulation development. Essentially, friability test has been mostly used as a tool for quality control (Chen et al., 2009; Pestieau et al., 2014). The use of friability testing as a formulation characterization tool or early formulation screening tool is rare, if any.

Tabletability (tablet tensile strength as a function of compaction pressure) of a formulation can be assessed using a relatively small amount of material (a few grams or less) for acceptability by applying an empirical acceptance criterion, e.g., >2 MPa tensile strength (Sun et al., 2009). Since the tensile strength of non-cylindrical tablet is more difficult to obtain (Sinka et al., 2004), a target tablet breaking force (frequently termed "tablet hardness" in the pharmaceutical industry) may be set for making a batch of tablets. However, even tablets meeting these criteria may still exhibit overly high friability because higher tablet breaking strength does not always lead to lower friability (Chowhan et al., 1992; Riippi et al., 1998) and density variation within a tablet can affect friability (Sinka et al., 2004). In addition, tablet tensile strength or breaking force is only one of the many factors that affect tablet friability, such as tablet size, tablet shape, or even tablet surface roughness (Chowhan et al., 1992; Riippi et al., 1998; Seitz and Flessland, 1965). Furthermore, in the development of certain products, such as orally disintegrating tablets, tablet tensile strength cannot be very high because of the requirement of a short disintegration time (Late et al., 2009). Consequently, acceptance criteria based on mechanical strength will not be suitable. Alternatively, tablet friability profile (friability as a function of compaction force/pressure) can be used to more reliably assess the manufacturability of a formulation than tabletability profile because friability is a direct test of tablet performance. The kind of stresses endured by tablets during friability test are relevant to those experienced during storage and handling (Shafer et al., 1956).

To successfully integrate friability measurement into tablet development for fully realizing its potential benefits, the availability of a material-sparing and expedited friability method is critical. Therefore, the goals of this research are twofold: (1) to develop and validate a time and material sparing friability test method, and (2) to demonstrate some of the potential applications of this method in product development, especially in the areas of tooling design and formulation optimization. We hypothesize that the replacement of the batch of "identical" tablets in the USP friability test by tablets varying in mechanical strength does not significantly alter the stress state experienced by individual tablets and friability of individual tablets is an acceptable approximation of corresponding batch friability determined using the standard pharmacopeial method. The availability of such an "expedited method" makes it possible to readily determine tablet friability as a function of compression conditions in a material- and time-sparing manner.

2. Materials and methods

2.1. Materials

Materials used in this study were: microcrystalline cellulose (MCC, Avicel PH102, Lot. P208819889, FMC Biopolymer, Philadelphia, PA), croscarmellose sodium (Ac-Di-Sol-Lot. TN08819630, FMC Biopolymer, Philadelphia, PA), dibasic calcium phosphate dihydrate (DCPD, Emcompress, Lot. 7100X, JRS Pharma, Chicago Heights, IL), acetaminophen (APAP, Lot. 124K0165, Johnson & Johnson Company, New Brunswick, NJ), celecoxib (Lot. CBX/1010121, Aarti Drugs Ltd., Maharashtra, India), and magnesium stearate (Lot. J03970, Mallinckrodt, St. Louis, MO). All materials were used as received.

2.2. Methods

2.2.1. Blending and compaction

Powder mixtures of MCC and DCPD were prepared at various ratios (20–80% w/w, 100 g batch size) by hand-mixing in a pan, followed by blending for 10 min in a 2 quart (1.89 L) twin shell blender (Patterson-Kelley, East Stroudsburg, PA) operated at 25 rpm. Two formulations containing 40% of APAP or celecoxib in an excipient matrix consisting of MCC (34.5% w/w), DCPD (20% w/w), Ac-Di-Sol (5% w/w), and magnesium stearate (0.5% w/w) were prepared using the same blending procedure. Tablets were compressed using a variety of toolings on a universal material testing machine (model 1485, Zwick, Germany) at ambient laboratory conditions (37 ± 9% RH and 24 ± 1 °C, Table 1S). The tableting speed used in this study was 100 mm/min unless indicated otherwise. Except for the two formulations that contain 0.5% magnesium stearate, compaction of other powders was carried out using tablet toolings coated with 5% (w/v) suspension of magnesium stearate in ethanol and air dried. Mean compaction pressure was calculated from the force and cross-sectional area of the punch tip.

2.2.2. Tensile strength and porosity determination

To obtain tablet tensile strength – porosity relationship, cylindrical tablets (10 mm diameter) were made under different pressures. Tablet dimensions were measured using a digital caliper immediately after ejection and tablet density was calculated from tablet weight and volume. Tablet diametrical breaking force was determined using a texture analyzer (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK), at a speed of 0.01 mm/s with a 5 g trigger force. True density of each mixture powder was calculated from the true densities of pure powders (ρ_{true}), which were obtained by fitting their tablet density (ρ_{tablet}) – compaction pressure (P) data using Eq. (1) (Sun, 2004, 2006).

$$P = \frac{1}{C}\left[(1-\varepsilon_c) - \frac{\rho_{tablet}}{\rho_{true}} - \varepsilon_c \ln\left(\frac{1-\frac{\rho_{tablet}}{\rho_{true}}}{\varepsilon_c}\right)\right] \quad (1)$$

where C (MPa^{-1}) and ε_c are constants related to powder consolidation properties under pressure. Helium pycnometry is unable to yield accurate true density values for water-containing powders, such as MCC (Sun, 2004).

Tablet porosity was calculated from tablet density and true density. The function that describes the relationship between tablet tensile strength (σ) – porosity (ε) for each powder was obtained by fitting data to Eq. (2) (Ryshkewitch, 1953; Osei-Yeboah and Sun, 2013), which was then used to calculate tensile strengths of tablets used in friability test from their porosity (Fig. 1S).

$$\sigma = \sigma_o e^{-b\varepsilon} \quad (2)$$

where b and σ_o are empirical constants.

2.2.3. Conventional USP friability test

USP friability tests were conducted using batches of compressed tablets that were coded and weighed individually (Mettler Toledo, AG245, Columbus, OH). The number of tablets used in a batch was chosen to afford a total weight of at least 6.5 g. The friability test was conducted using a dual drum, automatic tablet friabilator (Pharma Alliance Group Inc., Model F2, Santa Clarita, CA) at 25 rpm for 4 min. After the friability test and dedusting as per the USP procedure, weight loss of both each tablet and the batch was determined. The friability, expressed as a percentage of the initial weight, of individual tablets and the whole batch was calculated.