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Brief/Technical Note

Analysis of Bead Sizes for MR Capsules Labeled for Sprinkle

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Abstract. The bead sizes used in approved modified release capsules labeled for sprinkling on food was investigated to generate bead size guidelines for generic products labeled for sprinkling. The conclusions from a survey of FDA databases were corroborated with experimental data obtained by measuring the bead sizes of several reference-listed drugs on the market labeled for administration by sprinkling on food. The experimental data show that majority of the marketed products were found to have bead sizes of less than 1,500 μm (1.5 mm). Based on this information, a bead size of less than 1,500 μm should generally be considered acceptable for use in generic products labeled for sprinkling.

KEY WORDS: bead size; generic drugs; modified-release capsules; quality target product profile; sprinkle.

INTRODUCTION

It is estimated that 50% of the population have problems swallowing tablets (1). It may be difficult for aged persons to swallow tablets or capsules, or for children who may be difficult to medicate because they are unable or unwilling to swallow tablets or capsules. This leads to poor compliance or even non-compliance with treatment and thus has a negative impact on the effectiveness of the treatment. As a result, some drug products are formulated to be administered via sprinkling over soft food (commonly applesauce) to aid patients (such as children or the elderly) that have difficulty swallowing.

FDA's Office of Generic Drugs has recently faced a regulatory question regarding the acceptable bead size in modified release (MR) capsules that are labeled for administration by sprinkling. When an MR reference-listed drug (RLD) contains instructions for administration by sprinkling, FDA guidance generally recommends a bioequivalence (BE) study between the generic and RLD administered under the same conditions (sprinkling on food) (2,3). However, in several abbreviated new drug applications (ANDAs) submitted by generic firms, BE has been demonstrated for bead sizes that were significantly larger than those used in the RLDs. In other ANDAs, capsule containing mini-tablets have even been found to be bioequivalent to RLDs that are labeled for sprinkling. Because of the significant difference in bead size, a question is raised as to whether the bead size in the generic products needs to be controlled for patient acceptability.

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There may be biopharmaceutical constraints on the acceptable differences in bead size between generic and RLD products. However, the focus of this communication is on acceptability of bead sizes for sprinkling and not on the biopharmaceutical implications of a generic product that has a different bead size from its RLD. The biopharmaceutical impact of different bead sizes is directly evaluated through the fasting, fed, and sprinkle bioequivalence studies and is an important concern for ANDA sponsor as they develop a product.

MATERIALS AND METHODS

A search of FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) database found 436 approved modified release [extended release (ER) and delayed release] capsules as of January 2008. Refining of the above list for ER capsules with beads or pellets resulted in 60 products. The list was further narrowed based on label information as to whether the product was given sprinkled on applesauce or pudding for patient compliance for elderly or pediatric patients. There were 26 products identified for which the label mentions sprinkle administration of the drug product. Several labels clearly state that the capsules should not be crushed, chewed, divided, or dissolved. The formulation development and composition sections for the available Chemistry Manufacturing and Controls (CMC) and bio-pharmaceutics reviews were searched for bead/pellet size information. The information suggests that the products contain: (1) sugar spheres or microcrystalline cellulose as the core; (2) smallest core was 150 μm; (3) largest core was 1,400 μm (<1.4 mm); (4) average core was 700 μm; (5) coated particles were used as matrix in some cases; and (6) non-coated powder was used in some products. The highest approved bead size specification or in-process control for a product labeled for sprinkling was 2 mm.

The entire list was pared to products with label information indicating the product could be given by sprinkling on apple-

sauce or pudding to improve compliance for elderly or pediatric patients. Twenty-four of the RLD products were obtained for testing by FDA's Division of Pharmaceutical Analysis to confirm the size of the beads in these products and measure the sizes where no bead size information was available.

The diameter of the particles was determined using a Keyence Digital Microscope fitted with a VH-Z00R, ×0–50 lens. A photo was taken of the particles, and the area of the particle visible in the picture was determined. Any particles touching the edge of the photograph were not counted. If two separate particles were sized as one particle, the particle was not counted. The diameter of a circle containing the area of the particle was calculated. The diameter of the equivalent circle was reported. One hundred particles were measured for each sample, except for Drug Product 15 where only 91 particles were contained in the capsule (Table I).

RESULTS AND DISCUSSION

The particle sizes for the 24 products ranged from 277 to 1,485 μm, all less than the 2,000 μm value that is reported for masticated food. Studies of human mastication suggest that food is chewed to 2 mm (2,000 μm) in mean particle size before swallowing (4,5). From the food literature, it is noted that particulates can be detected in food when they are greater than 25 μm in size (6). From this information, it is clear that the usual bead sizes in pharmaceutical products can be perceived by patients; thus, bead size may affect the product acceptability and cause potential difficulty in swallowing. Sixteen of the samples contain particles with a mean particle size less than the 1,000 μm value that is purported to empty continuously from the stomach (7). The experimentally measured particle sizes for these products (Table I) are generally in agreement with the available particle size information found in the CMC sections of the applications. The percent standard deviations for Products 2, 3, and 4 were found to be higher, and this may be due to wide range in the selection of bead sizes during the manufacturing process of the products.

Coated particles/beads currently used in both extended release and delayed release dosage forms offer advantages over larger, non-disintegrating delivery systems. These delivery systems can (1) disperse throughout the GI tract, (2) have multiple types of coatings to achieve a variety of release profiles, and (3) in most cases, show dose proportionality. Gastric emptying of coated particles differs from the large non-disintegrating dosage forms in that they will empty from the stomach at a constant rate, provided the diameter and density are of the appropriate size. For example, Teflon beads that have a diameter of 1.6 mm and a density of 1 g/cm^3 empty from the stomach, in the fed state, at a rate of approximately 30%/h (8). Depending on the design of the delivery system, dissolution tests for bead formulations may consist of 2 to 3 h in simulated gastric fluid at pH 1.2, followed by 15–30 min in simulated intestinal fluid at pH 5.5, and then simulated intestinal fluid at pH 6.8 or pH 8.0. Beads smaller than 1 mm are generally considered to empty from the stomach continuously and have less food effect than larger beads. Therefore, the bead sizes will have significant impact on the effect of food on bioavailability.

An important part of the development of generic products using a quality by design approach is to fully assess the impact of quality target product profile (QTPP) on the drug product quality as described in ICH Q8 (R1) (9). QTPP

Table I. Measured Particle Size Results for MR Capsules Labeled for Sprinkle

Capsule product name	Average (μm)	std dev (μm)	% RSD	CMC particle size (μm)
Drug Product 1	622	62	9.9	500–600 (core)
Drug Product 2	292	244	83.5	190–1,190
Drug Product 3	430	215	50	n/a
Drug Product 4	277	107	38.5	150–300 (core)
Drug Product 5	1,074	72	6.7	710–1,400
Drug Product 6	795	76	9.6	500–710 (core)
Drug Product 7	1,241	191	15.4	n/a
Drug Product 8	626	100	16	n/a
Drug Product 9	559	62	11.1	250–355 (core)
Drug Product 10	1,050	66	6.3	n/a
Drug Product 11	803	84	10.5	600–710 (core)
Drug Product 12	944	75	7.9	700–1,000 (core)
Drug Product 13	1,368	56	4.1	1,000–1,180 (core)
Drug Product 14	1,096	118	10.7	1,000
Drug Product 15	1,485	190	12.8	<2,000
Drug Product 16	1,033	62	6	n/a
Drug Product 17	494	104	21.1	n/a
Drug Product 18	951	131	13.8	n/a
Drug Product 19	993	188	19	n/a
Drug Product 20	984	65	6.6	n/a
Drug Product 21	957	196	20.5	n/a
Drug Product 22	1,088	218	20.1	n/a
Drug Product 23	994	123	12.4	n/a
Drug Product 24	982	167	17	n/a

nla not available, *MR* modified release, *CMC* Chemistry Manufacturing and Controls

is a prospective summary of the quality characteristics of a drug product that should be achieved to ensure the desired quality, and hence the safety and efficacy, of a drug product. Therefore, the QTPP must take into consideration the physical characteristics of the reference product where applicable to meet the patient compliance. In case of capsule dosage forms labeled for administration via sprinkling, the generic sponsor should include a target bead size as part of their drug product profile. The proposed bead size for sprinkling must take into consideration the bead size of the reference product and its impact on patient acceptance.

CONCLUSIONS

The experimental data suggest that bead sizes up to 1,500 μm (1.5 mm) may be a cutoff for MR capsules labeled for sprinkle. A generic product with a proposed bead size of 2,000 μm may require additional justification if the RLD has a significantly smaller bead size (e.g., <500 μm).

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