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In Vitro Evaluation of an Extended-Release Methylphenidate Hydrochloride Product Sprinkled on Food Vehicles

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PURPOSE

Crushing tablets or opening capsules improves swallowability and facilitates oral administration [1, 2]. However, manipulation of drug by crushing tablets or opening capsules prior to oral administration or taking the medications with food vehicles may alter the potency and stability of the drug product, as well as possibly increase potential side-effects.

Methylphenidate hydrochloride (MPH) is a central nervous system stimulant that is often used for the treatment of attention-deficit hyperactivity disorder (ADHD), especially in children. To help pediatric patients who can not swallow the whole MPH medication, oral dosage forms (e.g., capsules or tablets) can be opened up or crushed and sprinkled on a small amount of food vehicle prior to administration.

An extended-release (ER) MPH drug product was selected as the model drug to investigate the effect of using food vehicles on the integrity and in vitro dissolution of enteric-coated granules . The drug product is taken once-daily in the evening and is formulated with two functional coatings surrounding the MPH core (**Figure 1**). The outer delayed-release (DR) layer limits the overnight release of MPH so it works when patients wake up in the morning. The inner ER layer keeps control on the release of MPH throughout the day.

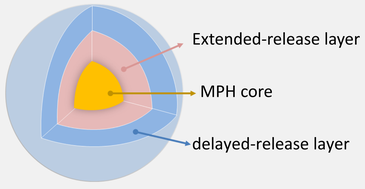

Figure 1. Schematic of the ER MPH drug product

OBJECTIVE

The objective of this study was to develop in vitro analytical and characterization methods for an ER MPH drug product sprinkled onto different types and amount of food vehicles, and to assess the integrity and in vitro dissolution of enteric-coated granules exposed to food vehicles.

METHODS

Food pH and viscosity testing

An electronic pH meter (Mettler-Toledo, OH, USA) was used to measure the pH of two food vehicles: applesauce (Mott's LLP, TX, USA) and apple juice (Mott's LLP, TX, USA).

A Discovery Hybrid Rheometer (TA Instruments Inc. DE, USA) was used to measure the viscosity of apple juice and applesauce.

Granule size and shape analysis

The ER MPH capsules were opened, and drug contents were sprinkled onto 15 mL of apple juice or 15 g of applesauce for 2 hours. The granules (n=20) were dispersed on a glass slide to measure granule diameter, length, width, and shape using a static auto imaging system (Morphologi 4-ID, Malvern, UK).

Scanning electron microscopy and energy dispersive X-ray spectroscopy

The surface features, internal structure, and elemental analysis of drug product were examined using a scanning electron microscope (SEM) coupled with energy-dispersive X-ray spectroscopy (EDS) (TESCAN Mira3, PA, USA).

Raman Spectroscopy

A HORIBA LabRam HR Evolution Raman Microscope (Horiba Jobin Yvon, Japan) with the excitation wavelength of 532 nm was used to extract Raman vibration information on the MPH drug product for qualitative analysis.

Drug content and in vitro sprinkle dissolution testing

An Ultra Performance Liquid Chromatography (UPLC) method was developed and validated using Acquity UPLC (Waters, MA, USA) for the analysis of drug content and drug dissolution. For the dissolution study, the weight of six capsules were individually weighed and recorded. Capsules were opened and mixed with apple juice (15 mL) or applesauce (5 or 15 g) and kept at room temperature for 2 hours before conducting the dissolution studies (n=6). The food-drug mixtures were placed into baskets (40 mesh) and operated as per USP 1 apparatus method at 75 rpm, 37˚C. Dissolution testing was conducted at 3 stages: Stage 1 (0-2 hours) in 700 mL of pH 1.2 hydrochloric acid; Stage 2 (2-6 hours) in 900 mL of pH 6.0 phosphate buffer; and Stage 3 (6-24 hours) in 910 mL of pH 7.2 phosphate buffer. Samples were withdrawn at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 22, and 24 hours.

RESULTS

Food vehicles characterization

Mean pH of applesauce and apple juice were 3.61 ± 0.02 and 3.63 ± 0.01, respectively. The pH values of tested food vehicles were less than pH 7.0, which is the dissolution and ionization threshold of enteric methacrylic acid copolymer. Apple juice exhibited low viscosity (0.001±0.00 Pa.s), while applesauce showed higher viscosity (0.643±0.136 Pa.s).

MPH drug product characterization

ER MPH capsules were filled with round, white functional film coated granules with an average capsule fill weight of 305±5 mg (n=24). Mean size of MPH ER granules was 861±47 µm. The average drug recovery was 99.8±0.7%. Granules were also examined under SEM-EDS and Raman microscope. SEM-EDS images confirmed that ER MPH granules were spherical in shape and were fully covered by two functional coating layers (**Figure 2**). The functional coating layers consisted mainly of silicone and magnesium, which were presumably from the inactive ingredients: magnesium stearate and talc. Raman microscopy was used to characterize the chemical composition of MPH and excipients. The Raman spectrum of identified MPH and functional coating materials can be seen in **Figure 3**.

Figure 2 . SEM (left) and SEM-EDS (right) images of the ER MPH product

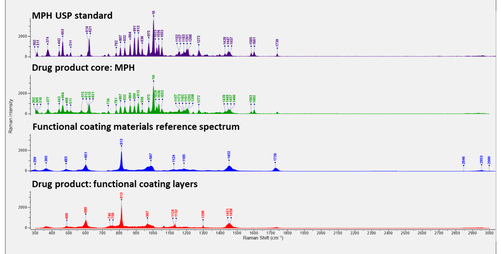

Figure 3 . Raman spectrum of the ER MPH product

Evaluating the impact of food vehicles on in vitro ER MPH drug product performance

Granule morphology was not impacted by the sprinkle process

The particle size of granules exhibited minimal change (p>0.05) after being sprinkled on applesauce (815±70 µm) and apple juice (825±74 µm) for 2 hours. The circularity, aspect ratio, and convexity of the particles were greater than 0.9, and the elongation ratio is near 0.1, indicating particles remain round and smooth in shape after being sprinkled on food vehicles (**Table 1**). In addition, the structure of the functional coatings was not affected by both tested food vehicles (applesauce and apple juice) (**Figure 4**).

Table 1. Granule size and shape analysis of control group (intact granules) and granules sprinkled on food vehicles for 2 hours. The results were presented as mean ± SD.

	Control	Apple juice	Applesauce
Circular equivalent diameter (um)	861.03±47.27	825.15±74.34	815.06±70.66
Aspect ratio	0.92±0.05	0.89±0.06	0.91±0.07
Circularity	0.98±0.01	0.97±0.02	0.97±0.02
Convexity	0.99±0.00	0.98±0.02	0.98±0.01
Elongation	0.10±0.06	0.09±0.07	0.09±0.07

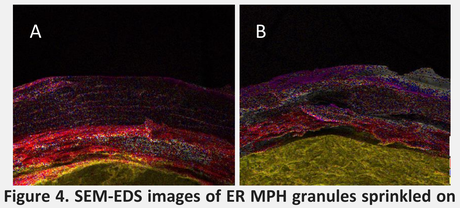

Figure 4. SEM-EDS images of ER MPH granules sprinkled on (a) apple juice and (b) applesauce for 2 hours

Types and volume of food vehicles change drug dissolution rates

The in vitro dissolution studies of drug-food mixtures revealed that drug dissolution rate in stage 3 differed when different food vehicles were used for sprinkle administration (**Figure 5**). For sprinkle administration with apple juice (15 mL) and applesauce (15 g), less than 0.5% drug dissolution was observed during stage 1 (pH 1.2) and stage 2 (pH 6.0). After transition to stage 3 media (pH 7.2), approximately 100% drug dissolution was achieved in 24 hours. However, the dissolution time for 50% release of the label content for drug-apple juice (15 mL) mixture and drug-applesauce (15 g) mixture was 14 and 16 hours, respectively. The similarity factor for these profiles (apple juice 15 mL vs. applesauce 15 g) was 46. When the amount of applesauce used for sprinkle administration changed from 15 g to 5 g, the dissolution rate at stage 3 was increased and the similarity factor (applesauce 5 g vs. apple juice 15 mL) was 76.

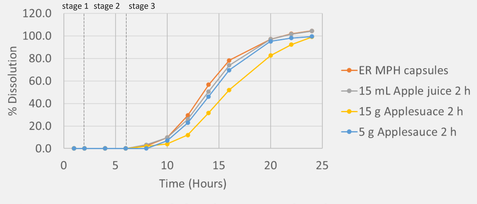

Figure 5 . Impact of food type and volume on ER MPH dissolution

CONCLUSIONS

The in vitro analytical and characterization methods for an ER MPH drug product were successfully developed. The characterization results (e.g., analysis of granule morphology) showed that the integrity of the ER MPH drug product remained unaltered after being sprinkled on applesauce and apple juice for 2 hours. However, dissolution of ER MPH slowed down when tested with a large amount of high viscosity food vehicle (e.g., 15 g applesauce). Further studies would be needed to properly assess the impact of the soft food volume used in the dissolution studies on in vitro drug performance.

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