In Vitro Performance of Pantoprazole Sodium Delayed Release Granules when Sprinkled on Soft Foods

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Abstract

Sprinkling medications on soft foods is a promising route to improve patient compliance. However, the characterization and evaluation of drug product performance after contact with soft foods is limited. This study aims to evaluate the effect of soft food viscosity and pH on the in vitro performance of pantoprazole sodium delayed release (DR) granules.

Introduction

Oral delivery is a widely used route of drug administration. However, solid dosage forms (e.g., capsules, tablets), may be difficult for people with dysphagia, especially children and the elderly, to swallow them. For capsule products, sprinkling the enclosed granules on soft foods could improve patient compliance. However, the knowledge of the stability of the drug products after they are sprinkled on soft foods is limited. It is important to evaluate the effect of soft food properties (e.g., viscosity, pH) and contact time of the drug product with soft food on in vitro performance.

Figure 1. Schematic of general sprinkle administration method.

Pantoprazole sodium is a proton pump inhibitor (PPI) drug that inhibits the secretion of gastric acid and is considered an agent in the management of peptic acid disorders. It is unstable when exposed to acidic conditions. Pantoprazole sodium DR granules are formulated with an enteric coating layer. This enteric coating layer erodes when exposed to pH > 5.5 condition. Therefore, it is an ideal candidate to investigate the effects of soft foods pH and viscosity effects on drug product stability.

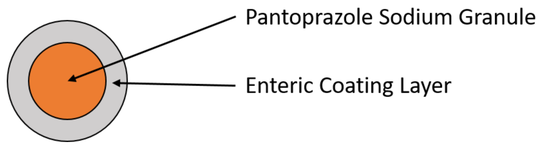

Figure 2. Pantoprazole sodium delayed release granule coating layers.

Materials

Materials: Pantoprazole sodium DR granules, EQ 40 mg Base, (Pfizer Inc, NY), was used as a model drug in this study. Applesauce (Mott's LLP, TX), apple juice (Mott's LLP, TX), strawberry yogurt (Great Value, Walmart, MD) and milk (Horizon Organic, CO) were used as model soft foods. All chemicals and solvents used for chromatography were of analytical grade.

Methods

Methods:

Characterization of Soft Foods:

- pH testing (SevenExcellent Multiparameter, Mettler-Toledo, LLC, OH)
- Viscosity testing (Discovery HR3, TA Instruments Inc. DE): The viscosity was tested at 25°C with 80 1/s shear rate (n=3).

Characterization of Pantoprazole Sodium DR Granules:

- Particle size testing (BX51, Olympus Corporation, Tokyo, Japan Scanning electron microscope (SEM) (JEM-6390-LV, JEOL, Ltd, Tokyo, Japan)
- Mechanical properties (TA.XT plus, Stable Micro Systems Ltd, Godalming, UK)

In Vitro Dissolution Testing:

- Approx. 5 g of soft food was placed in the 20 mL polypropylene weighing dish. The granules were sprinkled into the selected soft food and kept at room temperature for 0, 30, 60 and 120 minutes before the dissolution testing.
- Dissolution testing was conducted after drug product was sprinkled on soft foods for predetermined retention time using USP Apparatus 4 (Sotax, Horsham, PA) with 16 mL/min flow rate (n=6).
- The two-stage dissolution method was used with a two-hour acid stage in 0.1 N HCl and a one-hour buffer stage in pH 6.8 phosphate buffer (PBS) at 37°C. The sampling time points were 60, 90, 120, 130, 140, 150, 165 and 180 minutes. Samples were analyzed by High Performance Liquid Chromatography (HPLC) with UV detection at 290 nm.
- Dissolution testing was conducted with FDA-recommended dissolution method using USP Apparatus 2 for comparison.

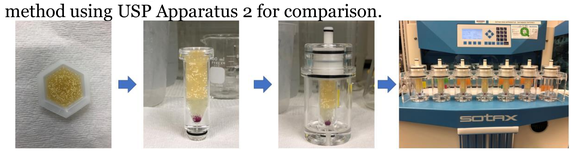

Figure 3. USP 4 dissolution testing process for pantoprazole sodium granules sprinkle study.

Results and Discussion

Table 1. pH and viscosity of soft foods (mean ± SD, n=3)

Soft Food	pH	Viscosity (Pa.s)
Apple juice	3.55 ± 0.01	0.001 ± 0.00
Applesauce	3.56 ± 0.02	0.643 ± 0.136
Strawberry yogurt	4.06 ± 0.01	0.558 ± 0.053
Milk	6.76 ± 0.01	0.002 ± 0.00

Applesauce and apple juice exhibited similar pH values around 3.5, while milk showed the highest pH (6.76) among the foods studied. The liquid soft foods, apple juice and milk exhibited low viscosity. The semi-solid soft foods, applesauce and yogurt showed higher viscosity.

The average equivalent circle diameter of the product granules is 1080 µm (n=40).

Results and Discussion

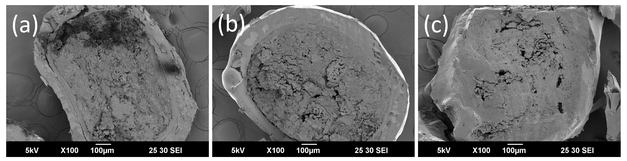

Figure 4. SEM images of pantoprazole sodium DR granule cross section (a) without soft food, sprinkled for 2 hours in (b) applesauce and (c) milk.

Granule coating layer remained intact after sprinkled in applesauce for 2 hours. On the other hand, granule coating layer became thinner and eroded after sprinkled in milk for 2 hours.

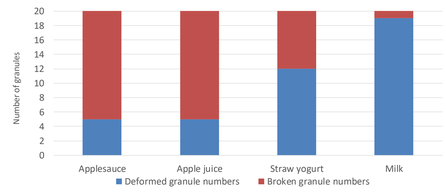

Figure 5. Number of deformed pantoprazole sodium DR granules when sprinkled in soft foods for 30 minutes.

The granules may have absorbed water from soft foods which explains why they became softened. The softened granules underwent deformation rather than breaking in mechanical testing. The number of deformed granules increased with increasing soft food pH value (apple juice: n=5 and milk: n=19).

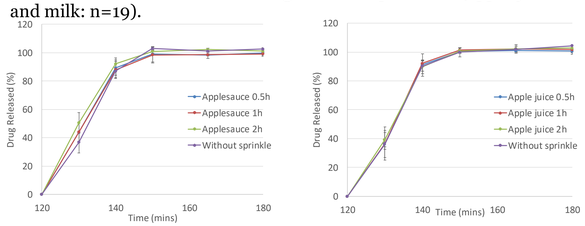

Figure 6. Impact of retention time on dissolution of pantoprazole sodium DR granules using USP 4 when sprinkled on applesauce (left) and apple juice (right) (mean ± SD, n=6).

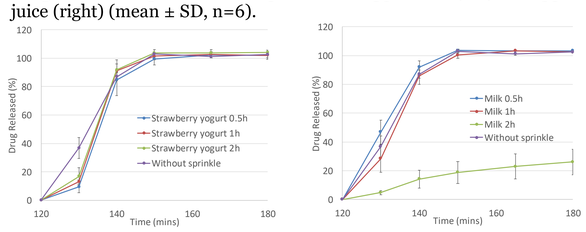

Figure 7. Impact of retention time on dissolution of pantoprazole sodium DR granules using USP 4 when sprinkled on strawberry yogurt (left) and milk (right) (mean ± SD, n=6).

When sprinkled in applesauce, apple juice and yogurt, pantoprazole was not released in acid stage and no pantoprazole peak was observed in HPLC chromatographs. Complete pantoprazole release was reached after 30 minutes in buffer stage. When sprinkled in milk for 2 hours, pantoprazole peak absorbance at 290 nm was not observed, however, degradation product peaks were observed and only 26% of pantoprazole was released within 60 min in the buffer stage. F2 test results showed significant difference when compared with other sprinkle conditions. Strawberry yogurt reduced the dissolution rate of granules compared to pantoprazole sodium DR granules not sprinkled on soft food in the first 10 minutes in buffer stage. Retention time of DR granules in soft foods had no effect on dissolution behaviors of pantoprazole sodium when soft food pH is lower then 5.5. The dissolution rate and pantoprazole release percentage reduced with increased retention time in milk, which may be related to its high pH value (6.7).

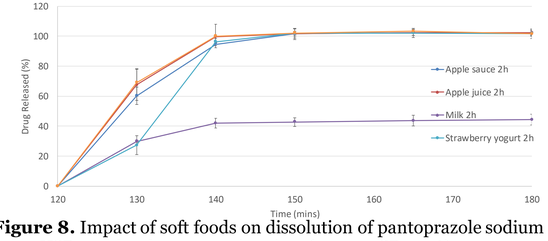

Figure 8. Impact of soft foods on dissolution of pantoprazole sodium using USP 2 with 2-hour retention time (mean ± SD, n=6).

Compared to the dissolution behaviors using USP 4, a similar trend was observed using UPS 2. Milk reduced the pantoprazole dissolution rate as well as release percentage compared to the other soft foods. This was due to the high pH of milk breaking the enteric coating layer of pantoprazole sodium DR granules. High viscosity food vehicles (strawberry yogurt) reduced the dissolution rate of pantoprazole sodium, especially in the first 10 minutes in PBS stage.

Conclusion

The pH and viscosity of the soft foods commonly used for sprinkle administration could significantly impact the in vitro performance of pantoprazole sodium DR granules. Soft food with high pH (e.g., milk) could cause enteric coating layer erosion when retention time was 2 hours. The high pH of milk could result in premature pantoprazole release in the acid stage, degradation and incomplete release compared to the other soft foods (i.e., apple juice, applesauce and yogurt). When sprinkled in soft foods with high viscosity (e.g., strawberry yogurt), the drug dissolution rate could be reduced, especially in the first 10 minutes in buffer stage regardless of retention time.

When sprinkled in apple juice or applesauce, the in vitro performances of pantoprazole sodium DR granules remained the same for retention time up to 2 hours.

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