

Stability of Pantoprazole Sodium Delayed Release Granules When Sprinkled on Soft Foods

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360

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PURPOSE

Oral delivery is the most widely used route of drug administration. However, due to the large size of solid dosage forms (e.g., capsules, tablets), it is 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. This project aims to evaluate the effect of soft food properties (e.g., viscosity, pH) and contact time of the drug product with soft food on the in vitro performance of pantoprazole sodium drug product.

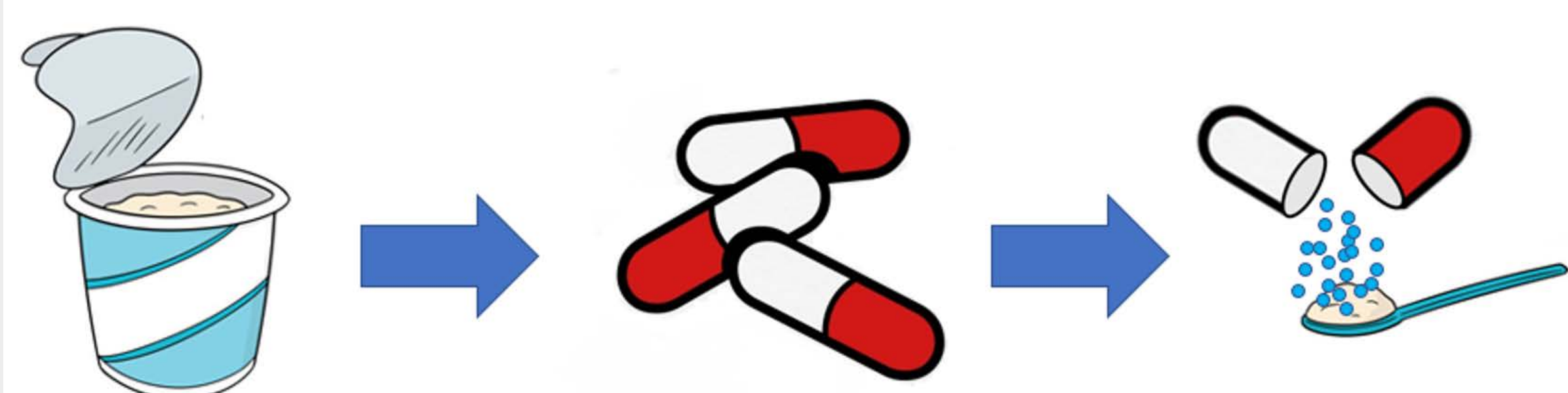


Figure 1. Schematic of general sprinkle administration method

Pantoprazole sodium drug product is formulated with three coating layers. The enteric coating layer is coated with methacrylic acid-acrylate copolymer (Eudragit® L30 D-55) which suppresses the pantoprazole degradation in an acidic medium. This enteric coating layer hydrates and swells when exposed to pH >5.5 conditions. Therefore, it is a good drug candidate to investigate soft foods pH and viscosity effects.

MATERIALS AND METHODS

Materials

Pantoprazole sodium delayed release (DR) granules, EQ 40 mg Base, (Protonix, 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.

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

- Approximately 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 30, 60, and 120 minutes before the dissolution testing. Granules without soft food were used as the control group.
- Dissolution testing was conducted after drug product was sprinkled on soft foods for a predetermined contact 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 2-hour acid stage in 0.1 N HCl and a 1-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.

RESULTS

pH and viscosity of soft foods

As shown in Table 1, the pH of applesauce, apple juice, strawberry yogurt, and milk was 3.55, 3.56, 4.06, and 6.76, respectively. The liquid soft foods (apple juice and milk) exhibited low viscosity, whereas the semi-solid soft foods (applesauce and strawberry yogurt) showed higher viscosity.

Particle deformation after sprinkle process

The granules may have absorbed water from soft food and 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 (Figure 2).

Scanning electron microscopy images of pantoprazole sodium DR granules before and after sprinkle process

The average equivalent circle diameter of the product granules is 1080 μm (n=40). Granule coating layer remained intact after sprinkled into applesauce, apple juice and strawberry yogurt for 2 hours. On the other hand, granule coating layer became thinner and eroded after sprinkled into milk for 2 hours (Figure 3).

Effect of soft food contact time on the dissolution of Protonix via USP 4

The contact time of DR granules in soft food had no effect on dissolution behaviors of pantoprazole when soft food pH is lower than 5.5 (Figure 4). When sprinkled into 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 (Figure 5).

Effect of soft food viscosity on the dissolution of Protonix via USP 2

Strawberry yogurt reduced the dissolution rate of granules compared to pantoprazole sodium DR granules not sprinkled onto soft food in the first 10 minutes in buffer stage (Figure 6).

Effect of soft food pH on the dissolution of Protonix via USP 4

For pH adjusted apple juice, degradation pantoprazole peaks were observed when granules were sprinkled into apple juice with pH value of 5.5 and 6.5 for 2 hours. Contact time (up to 2 hours) of granules in soft food had no significant effect on dissolution behaviors of pantoprazole when adjusted apple juice pH was lower than 5.5 (Figure 6).

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

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

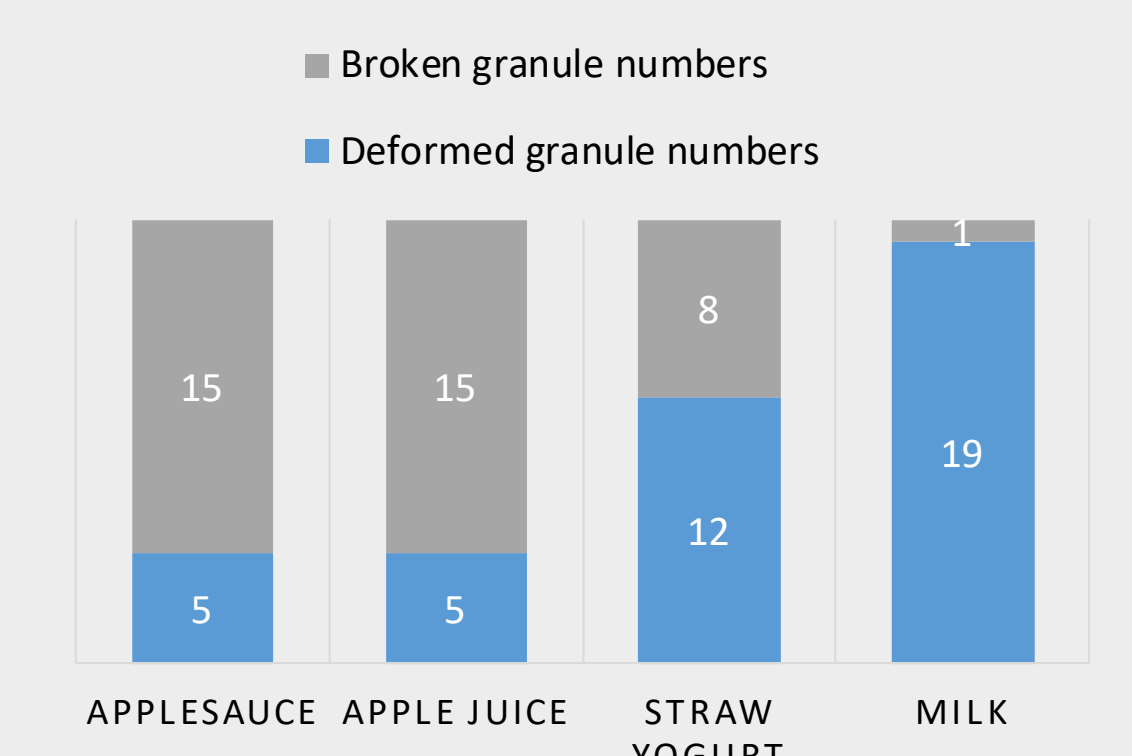


Figure 2. Number of deformed pantoprazole sodium DR granules when sprinkled on soft foods for 30 minutes

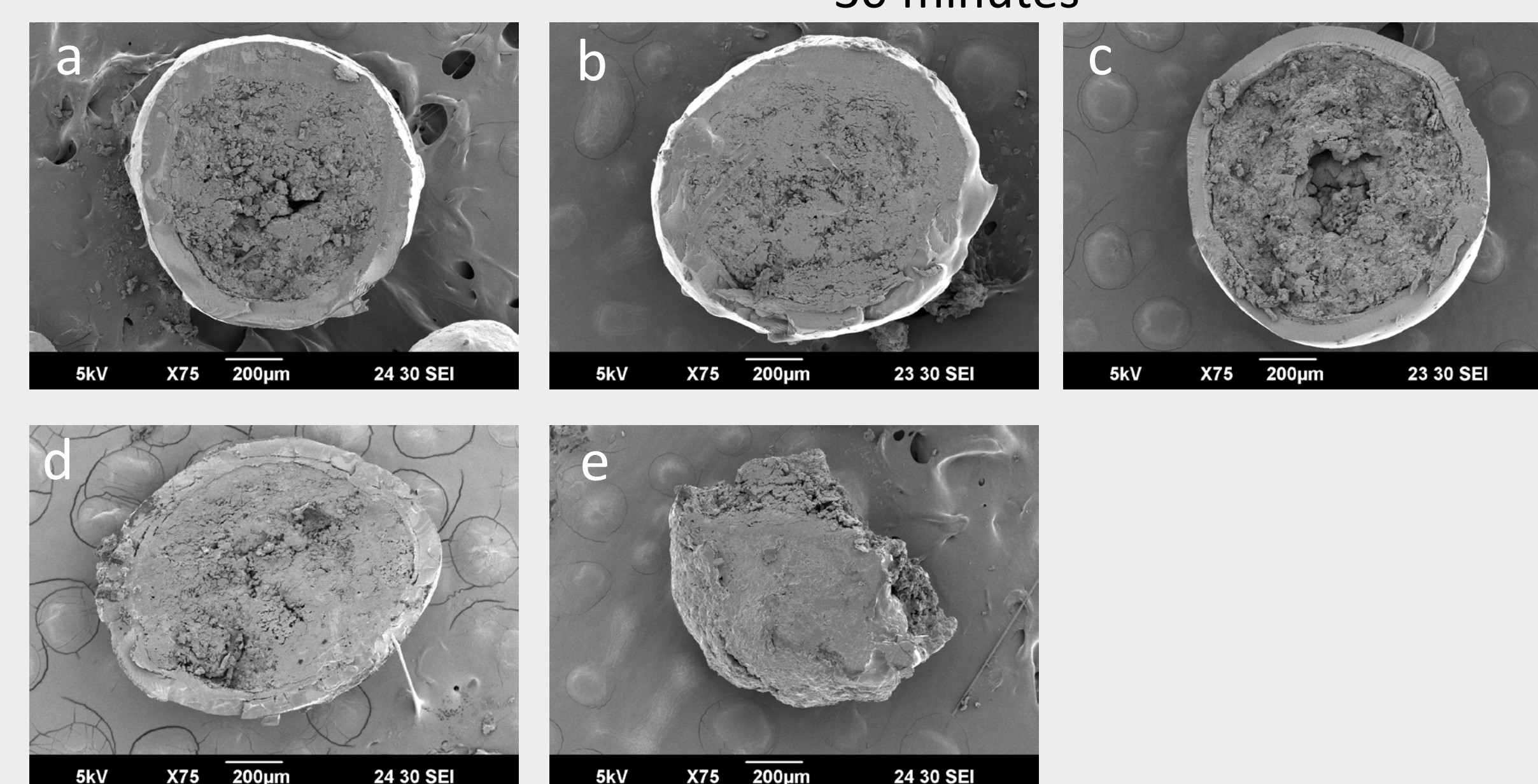


Figure 3. SEM images pantoprazole sodium DR granule cross section (a) without soft food, sprinkled for 2 hours on (b) applesauce, (c) apple juice, (d) strawberry yogurt and (e) milk

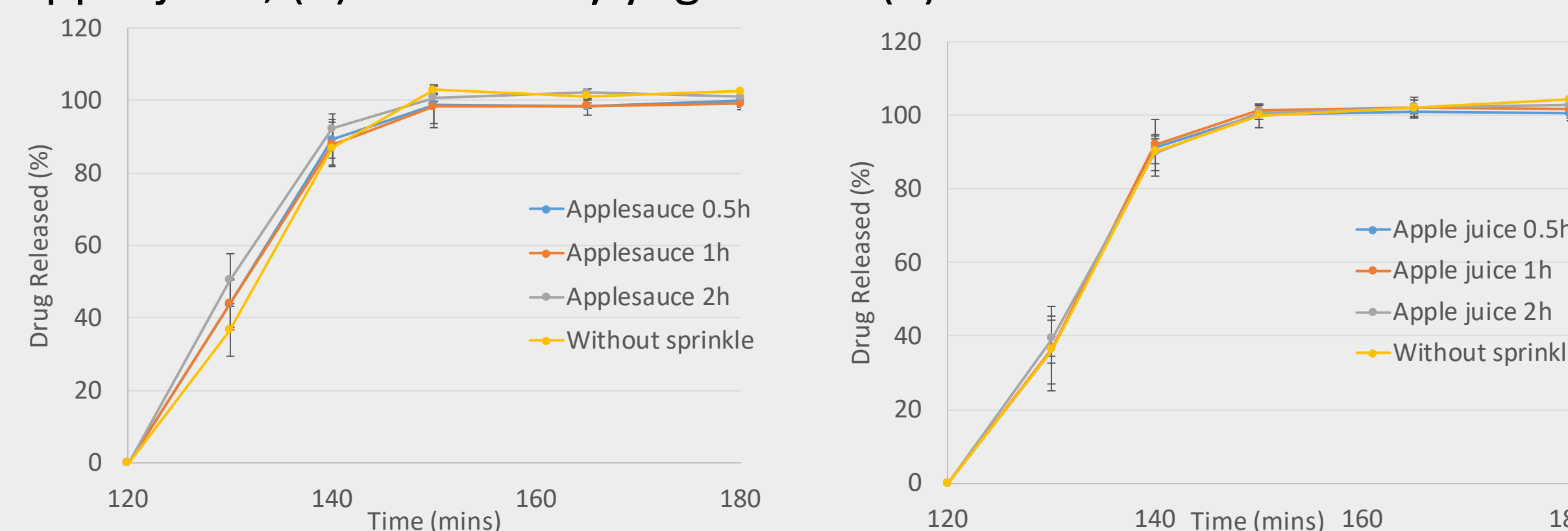


Figure 4. Impact of contact time on dissolution of pantoprazole sodium DR granules using USP 4 when sprinkled on applesauce (left) and apple juice (right) (mean ± SD, n=6)

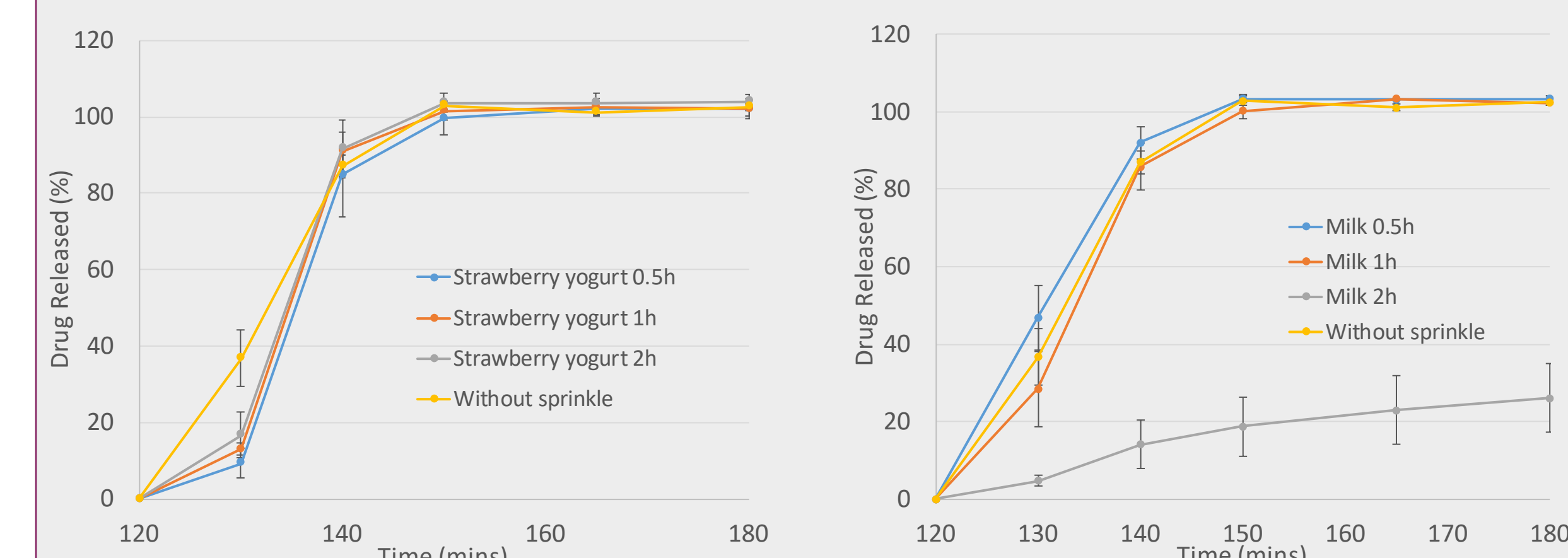


Figure 5. Impact of contact time on dissolution of pantoprazole sodium DR granules using USP 4 when sprinkled on strawberry yogurt (left) and milk (right) (mean ± SD, n=6)

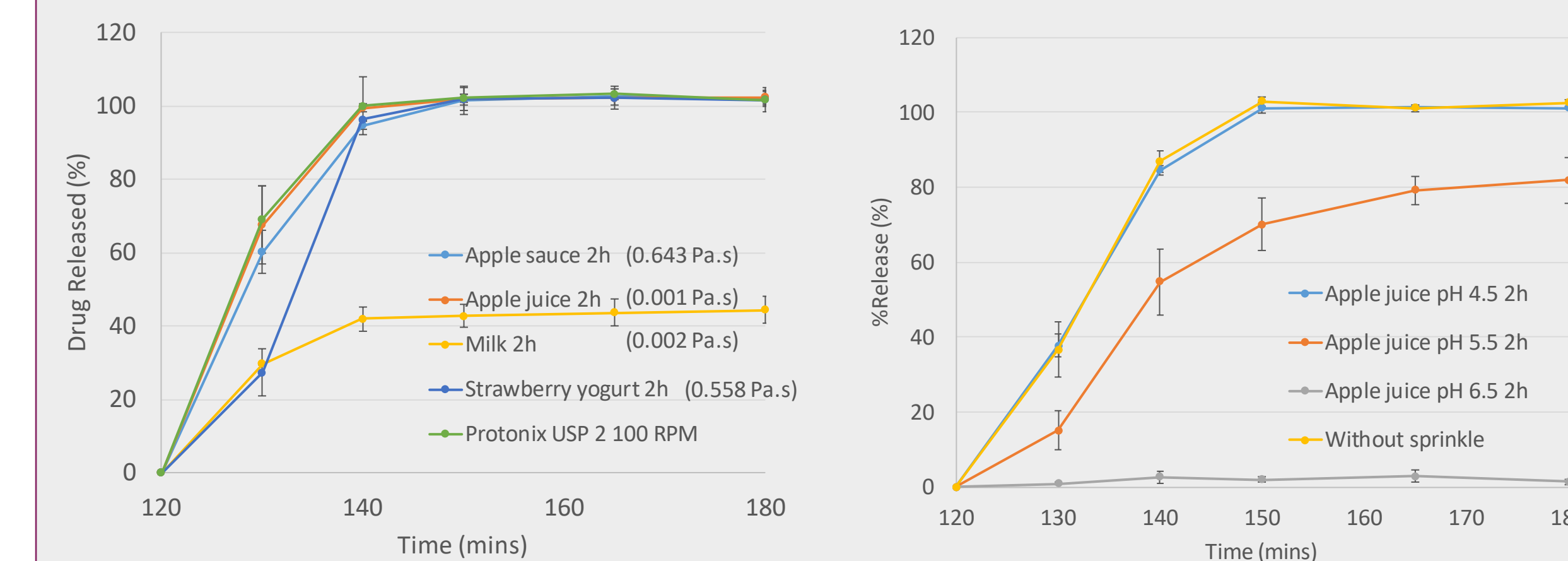


Figure 6. Impact of soft food viscosity on dissolution of pantoprazole sodium using USP 2 with 2-hour contact time (left) and impact of soft food pH on dissolution of pantoprazole sodium DR granules using USP 4 (right) (mean ± SD, n=6)

CONCLUSIONS

The pH and viscosity of the soft foods used for sprinkle administration could impact the in vitro performances of pantoprazole sodium DR granules. High pH of soft foods (e.g., milk) could result in premature pantoprazole release in the acid stage, drug degradation and incomplete pantoprazole release. When sprinkled onto low pH soft foods, the in vitro performances (e.g., particle morphology and drug dissolution) of pantoprazole granules remained unchanged even when in contact with soft food for up to 2 hours. When sprinkled onto soft foods with high viscosity (strawberry yogurt), the drug dissolution rate could be reduced, especially in the first 10 minutes in the buffer stage regardless of contact time.

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