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Dissolution Rate Increases for Morphine Sulfate Extended-Release Drug Product when Mixed with High pH Soft Food for Long Contact Times

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PURPOSE

Dysphagia is prevalent across sex and age groups in the U.S. population [1, 2]. To ease administration of solid oral dosage form medications amongst populations affected by dysphagia, many drug products have labelling that describes how the product can be sprinkled over soft foods. A morphine sulfate extended-release (ER) formulation was selected as a model drug product to study the impact of soft food viscosity, pH and contact time with drug product on dissolution performance.

OBJECTIVE

To study the effect of soft food viscosity, pH, and contact time on the dissolution performance of morphine sulfate ER capsules.

METHOD

Viscosity and pH of the soft foods were measured at 25°C by a rheometer scanned from shear rate 0 to 100 s^{-1} and a pH meter, respectively. The viscosity from non-Newtonian soft foods was reported from the shear rate of 80 s^{-1}. Morphine sulfate ER pellets from capsules were sprinkled over soft foods (15 g), including applesauce, apple juice, carrot puree, chocolate (Ch.) pudding, and vanilla yogurt, for contact times of 30 and 120 min. Pellets sprinkled in 0.1 N hydrochloric acid (pH 1.2 HCl), phosphate buffer (pH 7.5 PB), and modified Ch. puddings were used for acidic and basic controls of pH 1.2 and 7.5, respectively, while non-sprinkled pellets were used as a negative control in each experiment. Dissolution was performed with a 2-stage USP 1 test apparatus. Using a texture analyzer (TA) the pellet mechanical strength was evaluated from the cracking point, i.e., force required to crack the pellet (cracking force) vs pellet deformation distance till cracking (cracking distance). Water content was analyzed with a thermogravimeter using five pellets per measurement and average of three measurements was performed for each sprinkle condition. A screening design of experiments (DOE) was performed using JMP® Pro 15. Soft food pH, contact time, and viscosity were used as the primary factors on a screening DOE, and their interactions were also evaluated. The mean percent drug dissolved at 1 h in the acid stage was chosen as the outcome to represent the dissolution profile.

RESULTS

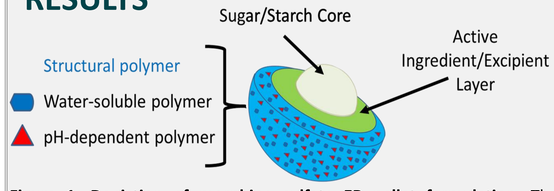

Figure 1. Depiction of morphine sulfate ER pellet formulation. The structural polymer is water-insoluble and maintains the structure of the pellet shell. The water-soluble polymer is designed to begin to dissolve in the upper gastrointestinal tract. The pH-dependent polymer is designed to start to dissolve in the intestine.

Soft Food	Viscosity (Pa.s)	pH
Applesauce	0.52	3.63
Apple Juice	0.001	3.69
Vanilla Yogurt	0.99	4.34
Carrot Puree	0.76	4.98
Ch. Pudding	1.85	6.29
pH 1.2 Ch. Pudding	2.39	1.20
pH 7.5 Ch. Pudding	2.18	7.50

Table 1. Viscosity and pH of soft foods
Apple juice exhibits Newtonian fluid behavior and other food items exhibit non-Newtonian behavior.

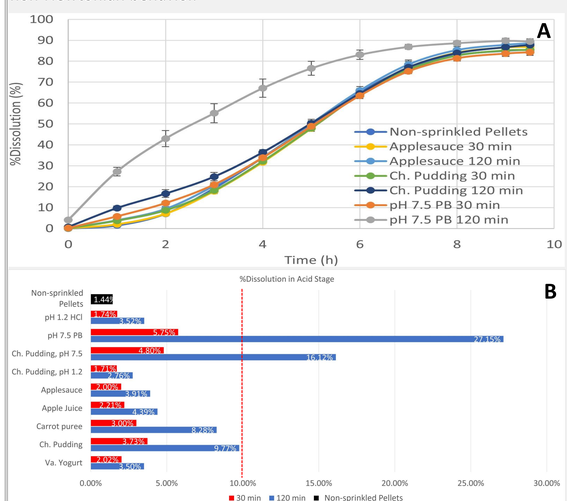

Figure 2. Dissolution profile of pellets sprinkled on pH 1.2 and 7.5 Ch. pudding for contact times of 30 and 120 min (A) and summary of mean percent morphine dissolved at 1 h of all sprinkle groups (B). Red dash line represents USP acceptance criteria NMT 10% at 1 h. Higher pH of the soft food and longer contact time are associated with higher mean percent morphine dissolved.

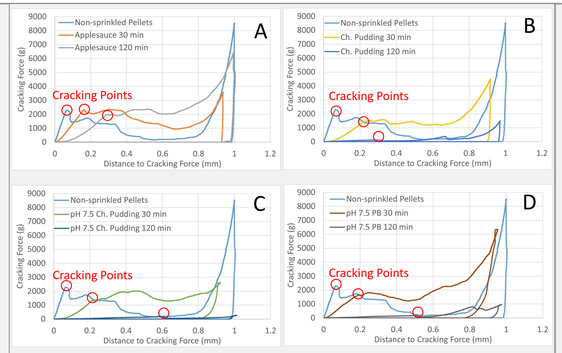

Figure 3. Representative TA curves of non-sprinkled pellets and pellets sprinkled on (A) applesauce, (B) Ch. pudding, (C) pH 7.5 Ch. pudding, and (D) pH 7.5 PB for 30 min and 120 min contact time showing cracking force (g) vs. distance to cracking force (mm).

The cracking point of each group is highlighted in the red circle. Within the same soft food, the cracking force decreased as the contact time with soft food increased; while the cracking distance increased as the contact time with soft food increased. Among the different soft food groups, the general trend was the cracking force decreased and the cracking distance increased as the soft food pH increased. This change was more drastic for the 120 min contact time compared to 30 min contact time groups. The longer distance to cracking force suggested the pellets sprinkled on soft foods were more malleable.

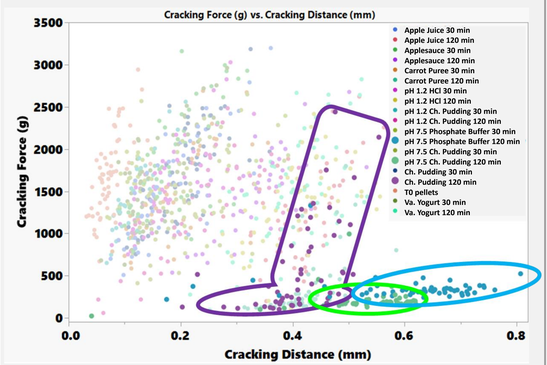

Figure 4. Summary of cracking points from TA curves plotted as cracking force vs. cracking distance of pellets in different sprinkle groups.

Cracking points occurred under lower forces and with longer deformation distances when the pellets were sprinkled into higher pH soft food and were in contact with the soft food for 120 min. The blue, green and purple circles contain pellets sprinkled on pH 7.5 PB 120 mins, pH 7.5 Ch. pudding 120 min, and Ch. pudding 120 min, respectively.

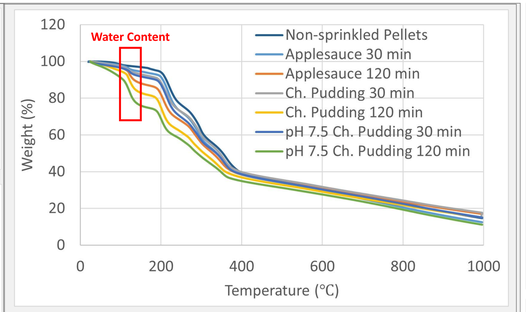

Figure 5. Representative thermogravimetric analysis curves of the pellets sprinkled over different soft foods showing weight change over temperature. Water content was calculated from the weight drop indicated within the red box.

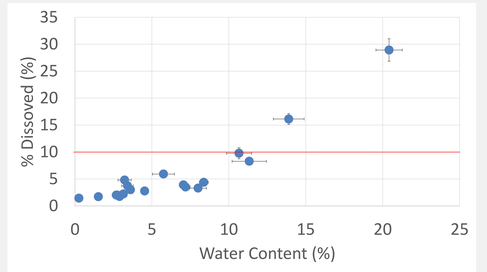

Figure 6. Mean percent morphine dissolved vs mean water content from thermogravimetric analysis. Error bars were obtained from the average of three measurements for water content and six measurements for %dissolved. Higher water content appeared to be associated with higher % dissolved of morphine sulfate at 1 h.

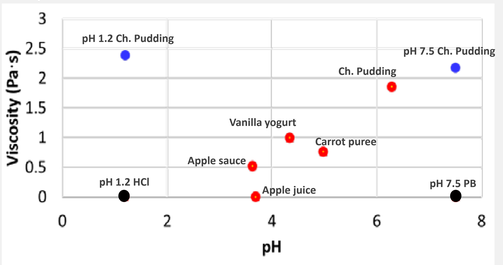

Figure 7. Screening DOE design panel showing all soft foods and media for sprinkle administration.
The five red dots represent commercial soft foods. The two black dots represent pH 1.2 HCl and pH 7.5 PB buffers. The two blue dots represent modified Ch. puddings adjusted to pH 1.2 and pH 7.5. Thus, the effects from extreme pH and viscosities can be differentiated.

Source	LogWorth	PValue
pH	24.077	0.00000
Time	15.315	0.00000
Time*pH	13.402	0.00000
pH*Viscosity	4.074	0.00008
Viscosity	1.910	0.01232 ^
Time*Viscosity	1.468	0.03401

('^' denotes effects with containing effects above them)

Figure 8. Screening DOE results from completed pH-viscosity design panel. Top three factors to influence morphine release were identified as pH of soft food, followed by contact time with soft food and the interaction between pH and the contact time.

CONCLUSION

Pellets sprinkled over soft foods with pH above 4.5 and at 120 min contact time exhibited higher percent morphine sulfate dissolved at 1 h, lower mechanical strength and higher water content.

Screening DOE suggest that soft food pH, contact time with soft food and the interaction between the pH and contact time were the top three significant factors affecting the dissolution of the sprinkled pellets of morphine ER.

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