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In Vitro Evaluation of a Morphine Sulfate Extended-Release Formulation Sprinkled on Soft Foods

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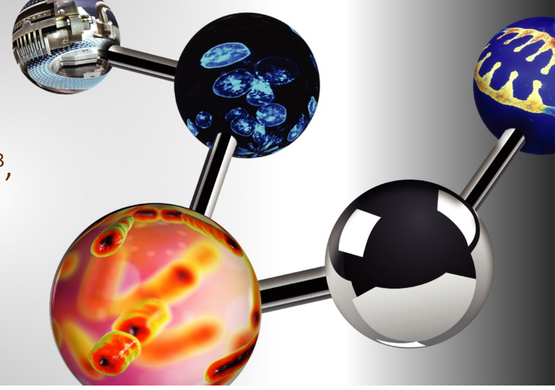


PURPOSE

Dysphagia affects ~15 million U.S. adults/year causing difficulty in swallowing tablets or capsules for therapeutic treatment. Some tablet or capsule products, such as morphine sulfate extended-release (ER) capsules, allow for co-administration via soft foods to improve compliance. Despite the benefits for dysphagic patients, the vast majority of tablet or capsule products are not formulated or assessed for co-administration via soft food. This study aims to evaluate how different soft food properties may impact product stability and integrity, which can inform development of reliable in vitro assessments to characterize co-administration of drug products with soft food. The morphine sulfate ER pellet formulation is approved for co-administration with applesauce (pH = 3.6) and relies on a pH-dependent polymer to specifically release in the gut (pH > 5.5). Due to this pH-dependent feature, soft foods with various viscosity and pH ranging from 3.6 – 6.3 were selected to evaluate whether soft food properties might influence product stability and integrity.

OBJECTIVE(S)

To characterize soft food pH and viscosity, and the effect of soft food contact time on hardness and dissolution of morphine sulfate ER drug pellets when sprinkled on soft foods.

METHOD(S)

Morphine sulfate ER capsules (100 mg), containing encapsulated ER pellets, were purchased from a commercial source. For each experiment, 1 capsule was sprinkled onto soft food (15 g) for contact times of 30 min, 60 min, or 120 min. Viscosity and pH of soft foods, including applesauce, apple juice, carrot puree, chocolate pudding (ch. pudding), and vanilla yogurt (va. yogurt) were measured at 25°C using a hybrid rheometer (TA Instruments, DE, USA) and standard pH meter, respectively. Phosphate buffer, pH 7.5 (pH 7.5 PB) was used as a positive control for higher pH soft food and non-sprinkled pellets were used as a negative control in each experiment. Pellet diameter and hardness were measured using a texture analyzer (TA.XTplusC Texture Analyzer, Stable Micro Systems, London, UK), while dissolution was performed with a 2-stage USP 1 dissolution test (0.1N HCl, then pH 7.5 PB) on a dissolution tester (VISION® G2 ELITE 8™, Teledyne Hanson, CA, USA). USP Level 1 criteria (%morphine-release ≤ 10% at 1 h, 25 – 50% at 4 h, 50 – 90% at 6 h, and ≥ 85% at 9 h) were used to evaluate dissolution profiles. One-way ANOVA followed by post hoc (SigmaPlot 12.5, SPSS Inc., Chicago, IL, USA) and an f2 similarity test were employed for statistical analysis of texture analyzer and dissolution data, respectively.

RESULT(S)

Measured viscosity of applesauce, apple juice, va. yogurt, carrot puree, and ch. pudding were 0.518, 0.001, 0.991, 0.758, and 1.854 Pa·s, respectively at shear rate 80 s^{-1}. Measured pH of applesauce, apple juice, va. yogurt, carrot puree, and ch. pudding were 3.63, 3.69, 4.34, 4.98, 6.29, respectively.

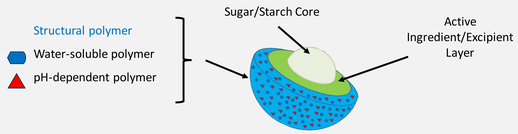


Figure 1. Depiction of morphine sulfate ER pellet formulation. Structural polymer shown in blue, active ingredient/excipient layer shown in green, and sugar/starch core shown in beige.

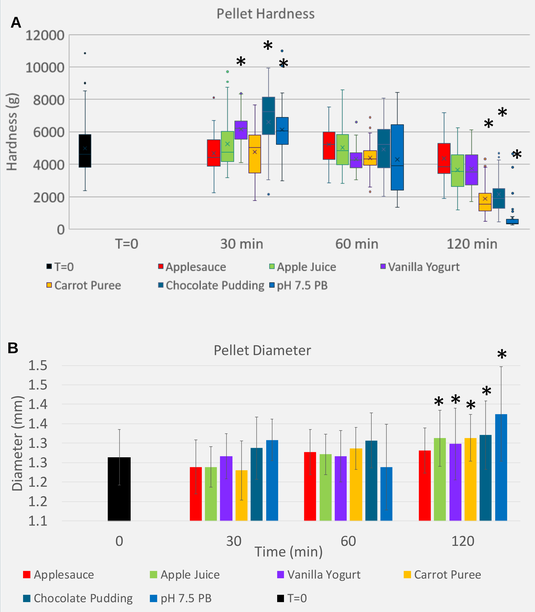
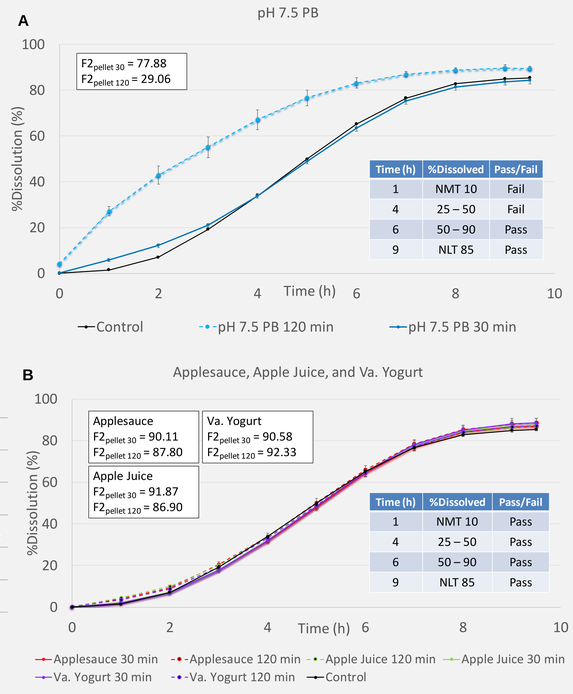


Figure 2. Pellet hardness and pellet diameter at 30, 60, and 120 min. (A) Box and whisker plot comparing median pellet hardness. Compared to negative control (median = 4,613.5 g, n = 40), pellet hardness increased for 30 min va. yogurt and ch. pudding samples, while 120 min carrot puree and ch. pudding samples decreased. (B) Histogram comparing mean ± SD. Compared to negative control (mean = 1.26 mm ± 0.07, n = 40), there was no difference in pellet diameter for 30 min or 60 min samples. However, at 120 min, pellet diameter increased for apple juice, va. yogurt, carrot puree, and ch. pudding. Statistical significance (P < 0.05) indicated by asterisk (*).



Time (h)	%Dissolved	Pass/Fail
1	NMT 10	Fail
4	25 – 50	Fail
6	50 – 90	Pass
9	NLT 85	Pass

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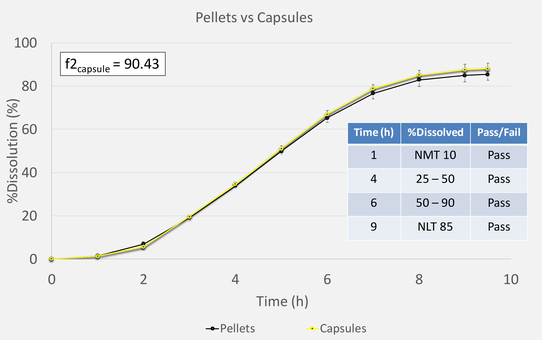
Figure 3. Dissolution profiles for morphine sulfate 100 mg ER pellets at 30 min and 120 min. (A) Dissolution profile of pellets in pH 7.5 PB condition compared to negative control (n=6). (B) Dissolution profiles of applesauce, apple juice, and va. yogurt conditions compared to negative control (n=6) after soft food contact at 30 min or 120 min compared to negative control. (C) Dissolution profiles of carrot puree and ch. pudding compared to negative control (n=6). All curves presented as mean ± SD.



Time (h)	%Dissolved	Pass/Fail
1	NMT 10	Pass
4	25 – 50	Pass
6	50 – 90	Pass
9	NLT 85	Pass

Figure 4. Dissolution profiles of morphine sulfate ER capsules versus pellets. Dissolution similarity between encapsulated pellets and non-encapsulated pellets (negative control) was established. All curves presented as mean ± SD, n = 6.

Similarity (F2) in Various Soft Food Conditions, 120 min

	Applesauce	Apple Juice	Va. Yogurt	Carrot Puree	Ch. Pudding	pH 7.5 PB
Applesauce	---	---	---	---	---	---
Apple Juice	96.14	---	---	---	---	---
Va. Yogurt	92.74	95.05	---	---	---	---
Carrot Puree	75.52	76.97	72.29	---	---	---
Ch. Pudding	70.03	71.35	67.71	92.66	---	---
pH 7.5 PB	29.95	29.87	29.25	31.99	32.52	---

Table 1. Similarity (F2) in various soft food conditions at 120 min. Table showing similarity of dissolution profiles for morphine sulfate ER pellets in each soft food.

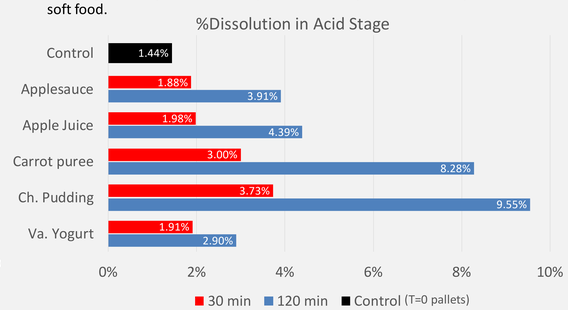


Figure 5. %Dissolution in Acid Stage. The mean percent morphine-release (n = 6) during acid stage dissolution for either 30 min or 120 min. Comparison shows a greater difference from the negative control (T=0 pallets) for carrot puree and ch. pudding at 1 h dissolution, whereas dissolution at 4, 6, and 9 h time points deviated from control to a lesser extent (See Figure 4 C). Red dotted line indicates criteria for percent morphine-release to pass USP Level 1 at 1 h (%morphine-release ≤ 10% at 1 h, 25 – 50% at 4 h, 50 – 90% at 6 h, and ≥ 85% at 9 h). Though the morphine sulfate ER pellets are more likely to be administered within a 30 min timeframe, the data suggest longer residence times in soft foods may adversely impact drug dissolution.

CONCLUSION(S)

Viscosity and pH were measured for each soft food. Carrot puree, ch. pudding and pH 7.5 PB reduced pellet hardness after 120 min contact time. Dissolution profiles for carrot puree, ch. pudding, and pH 7.5 PB conditions show that differences in soft food play a significant role in the pass or fail acceptance criteria of pellet dissolution according to USP Level 1 (%morphine-release ≤ 10% at 1 h, 25 – 50% at 4 h, 50 – 90% at 6 h, and ≥ 85% at 9 h). Further study is needed to understand the individual effects of pH and viscosity; however, percent morphine-release at 1 h timepoint per USP Level 1, appears to increase with soft food contact time.

ACKNOWLEDGEMENTS

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REFERENCES

[1] FDA Guidance for Industry: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments (2018)

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