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In Vitro Evaluation of Two Morphine Sulfate Extended-Release Products Sprinkled on Soft Foods

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PURPOSE

Per drug labeling, some drug products can be sprinkled on soft foods prior to administration to improve compliance in patients affected by dysphagia [1,2]. Currently, FDA recommends in vivo pharmacokinetics studies to evaluate generic formulation differences when sprinkled on soft foods described in the product labelling. However, generic drug product formulations for the same drug substance could perform differently when sprinkled on soft foods. Two FDA approved drug formulations of morphine sulfate (MS) extended-release (ER) capsules, ER1 and ER2, were studied to test the impact of two different formulation designs on dissolution performance after exposure to soft food. Both drug products were sprinkled on soft foods with different food properties expected to influence dissolution performance and the products were subsequently characterized for the resulting changes in dissolution, water content, and mechanical strengths.

OBJECTIVE

To develop in vitro methodology to discriminate the effect of soft food on the in vitro performance of different drug product formulations which could be used as a predictor of in vivo performance.

METHOD

Based on the pH sensitivity of the formulations, four soft foods, applesauce, vanilla yogurt, carrot puree, and chocolate pudding, with different pH values were selected to study the usefulness of the in vitro methods in detecting product performance changes. Applesauce is the only soft food described on the product labeling approved to administer the both MS ER products with. Vanilla yogurt, carrot puree, and chocolate pudding are not described on the product labeling for sprinkle administration. The pH of the soft foods was measured with a pH meter (n=3). The microcomputed tomography (micro CT) was done using Bruker SkyScan 1272 (Kontich, Belgium). Bruker software NRecon v1.7.4 was used for 3D reconstruction of the shadow projections, CTAnalyser (CTAn) v1.20.8 for quantification and CTVox v3.3.1 for volume rendering. MS ER pellets from either ER1–10 mg, ER1–100 mg, ER2–10 mg, or ER2–100 mg was sprinkled into the soft foods for 2 h to test effectiveness of the in vitro method. Dissolution was performed with a 2-stage United States Pharmacopeia (USP) dissolution Test 1 for MS ER capsules (n=6). Water content was analyzed on a thermogravimeter (n=3). Pellet diameter, cracking force and cracking distance were analyzed on a texture analyzer (n=40 pellets). Cracking distance was normalized to 1 mm to account for the diameter difference in ER1 and ER2. Non-sprinkled pellets were used as controls for all tests. An f2 similarity test compared to the individual non-sprinkled control pellets was employed for dissolution profile comparisons. Statistical analysis such as t-Test, and one-way ANOVA were performed on either Excel or SigmaPlot Version 11 (Systat Software, Inc., San Jose California USA).

RESULTS

Soft Foods	Label Use	Measured pH	Food Category
Applesauce	Yes	3.69±0.01	Low pH
Vanilla Yogurt	Off Label	4.28±0.01	
Carrot Puree		5.05±0.01	High pH
Chocolate (Ch.) Pudding		6.19±0.01	

Table 1. Measured pH of soft foods (n=3)

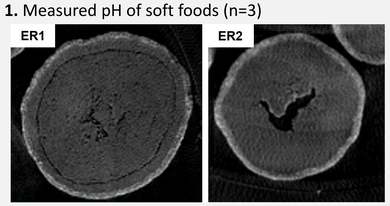

Figure 1. The micro CT image of ER1 and ER2 pellets.

A denser outer shell is observed in both formulations. ER1 shows a layered structure inside the shell. ER2 is a homogeneous matrix inside the shell.

Figure 2. Dissolution profiles of 10 mg ER1 and ER2 pellets sprinkled over different soft foods [mean ± standard deviation (SD), n=6]. NS = Non-Sprinkled, AS = Applesauce, CP = Chocolate pudding, CAP = Carrot Puree, VY = Vanilla Yogurt.

Dissolution profiles of 10 mg ER1 non-sprinkled pellets showed similarity to that of pellets sprinkled over all 4 soft foods studied. Dissolution profiles of 10 mg ER2 non-sprinkled pellets showed similarity to only that of pellets sprinkled over applesauce. Dissolution profiles of 10 mg ER1 pellets showed similarity to 10 mg ER2 pellets for non-sprinkled, applesauce and Va. yogurt sprinkled conditions.

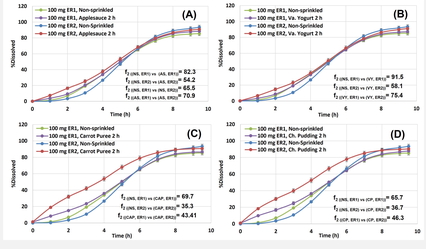

Figure 3. Dissolution profiles of 100 mg ER1 and ER2 pellets sprinkled over different soft foods (mean ± SD, n=6).

Dissolution profiles of 100 mg ER1 non-sprinkled pellets showed similarity to that of pellets sprinkled over all 4 soft foods studied. Dissolution profiles of 100 mg ER2 non-sprinkled pellets showed similarity to that of pellets sprinkled over applesauce and Va. Yogurt. Dissolution profiles of 100 mg ER1 pellets showed similarity to 100 mg ER2 pellets for non-sprinkled, applesauce and Va. yogurt sprinkled conditions.

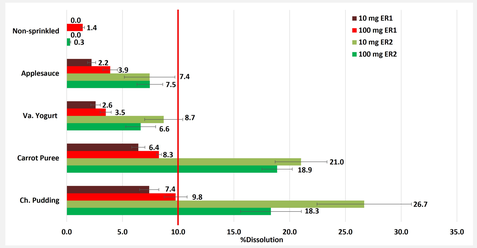

Figure 4. % Dissolved at the end of the acid stage (1 h) of 10 and 100 mg ER1 and ER2 pellets sprinkled over different soft foods (mean ± SD, n=6). The red vertical bars represent the USP specification at 1 h, which is %MS release ≤ 10%.

All products tested passed USP dissolution testing (%MS release ≤ 10% at 1 h) when sprinkled over applesauce and Va. yogurt. In addition, 10 mg and 100 mg ER1 meet the specification in carrot puree and Ch. Puddling. The average %MS released at 1 h for pellets sprinkled over soft foods are higher than that of non-sprinkled pellets. The average %MS released at 1 h for 10 mg and 100 mg ER2 pellets sprinkled over soft foods are higher than that of ER1 pellets. The average %MS released at 1 h for 100 mg ER1 pellets sprinkled over soft foods are higher than that of 10 mg ER1 pellets. The average %MS released at 1 h for 10 mg ER2 pellets sprinkled over soft foods are higher than that of 100 mg ER2 pellets. For all four products, the average %MS released at 1 h increased in high pH compared to low pH soft foods.

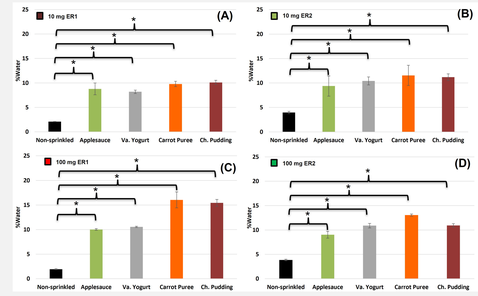

Figure 5. Water content of 10 and 100 mg ER1 and ER2 non-sprinkled pellets and pellets sprinkled on different soft foods (% water content expressed as mean ± SD, n=3). *t-Test, $P<0.05$.

Pellets sprinkled on soft foods showed significantly higher water content compared to non-sprinkled pellets for all four products.

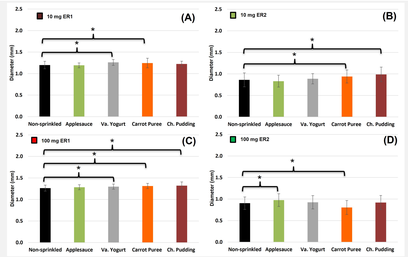

Figure 6. Pellet diameters of 10 and 100 mg ER1 and ER2 non-sprinkled pellets and pellets sprinkled over different soft foods (mean ± SD, n=40). *t-Test between non-sprinkled and individual soft food groups, $P<0.05$.

Despite the statistical differences observed, due to the small change in the absolute value and measurement method, it is not conclusive that the diameter change is dependent on the type of soft food pellets are administered in.

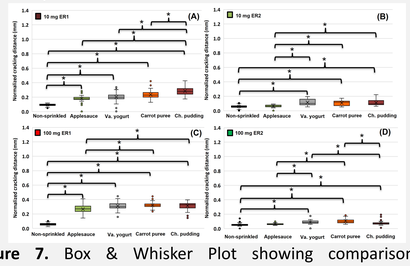

Figure 7. Box & Whisker Plot showing comparison of normalized cracking distance of 10 and 100 mg ER1 and ER2 non-sprinkled pellets against pellets sprinkled over different soft foods, ANOVA on rank, $P<0.05$, n=40. Data are presented as Q1 – Q3, median.

Significant increase in normalized cracking distance was observed for sprinkled pellets from both formulations for vanilla yogurt, carrot puree and chocolate pudding.

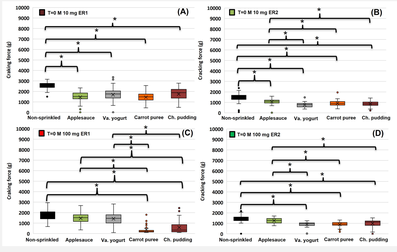

Figure 8. Box & Whisker Plot showing comparison of cracking force of 10 and 100 mg ER1 and ER2 non-sprinkled pellets against pellets sprinkled over different soft foods, ANOVA on rank, $P<0.05$, n=40. Data are presented as Q1 – Q3, median.

Significant decrease in cracking force was observed for sprinkled pellets for most soft foods for both formulations.

The pellets from ER1 and ER2 cracked under lower forces and longer cracking distances when sprinkled on high pH soft foods, carrot puree and chocolate pudding. Non-sprinkled pellets for each strength had lower cracking distance and higher cracking force compared to sprinkled pellets.

CONCLUSION

Both products passed USP dissolution testing for labelled sprinkle condition. Higher percent MS release was observed for sprinkled ER2 pellets compared to ER1 pellets when sprinkled on the listed soft foods. The *in vitro* methods developed for MS ER drug products sprinkled on different soft foods were able to detect changes in product performance after sprinkle on soft foods described in the product labelling as well as outside the labelling. These results can be useful to develop in vitro-in vivo relationship models for generic version of MS ER drug products sprinkled on soft foods with different properties.

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REFERENCE

[1] Cho, S. Y., Choung, R. S., Saito, Y. A., Schleck, C.D., Zinsmeister, A. R., Locke III, G. R. & Talley, N. J., *Prevalence and risk factors for dysphagia: a USA community study*. Neurogastroenterol. & Motil., 2015. 27(2): 212-219.

[2] Prasse, J.E. and Kikano, G. E., *An Overview of Pediatric Dysphagia*. Clin. Pediatr., 2008. 48(3): 247-251.

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