

In Vitro Evaluation of Morphine Sulfate Extended-Release Formulation Sprinkled on Soft Foods – A Comparison of Two Dosage Strengths of T=0 M and T=6 M Drug Products

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Introduction

Dysphagia, or difficulty swallowing, mostly affects children and the elderly population [1, 2]. To help dysphagia-affected populations, some drug products have labeling that describes how the product can be sprinkled on soft foods. To better understand the effects of soft food selection, formulation, and storage on sprinkle administration, we tested different soft foods to evaluate how soft food properties could impact the drug release.

Objective

The purpose of the study is to investigate the dissolution performance, water content, and cracking point of morphine sulfate (MS) extended-release (ER) formulation of two dosage strengths after sprinkle administration on different soft foods.

Materials and Methods

MS ER pellets of 10 mg and 100 mg capsules were sprinkled over different soft foods such as applesauce, vanilla (Va.) yogurt, carrot puree, and chocolate (Ch.) pudding for 120 min contact time. The soft food pH values were measured by a pH meter (Orion Star A214 pH/ISE Meter, Thermo Scientific, MA, USA). Dissolution was performed with a 2-stage USP 1 dissolution test (1 h in 0.1 N HCl then 8.5 h in 7.5 Phosphate Buffer) with a dissolution tester (VISION® G2 ELITE 8TM, Teledyne Hanson, CA, USA). Pellet mechanical strengths were measured using a texture analyzer (n=40, TA.XTplusC Texture Analyzer, Stable Micro Systems, London, UK). Water content was analyzed on a thermogravimeter (TGA Q500, TA Instruments, New Castle, DE, USA). Both T=0 M capsules and capsules stressed at 40°C with 75% relative humidity for 6 months (T=6 M) were tested. Non-sprinkled pellets were used as controls.

Results and Discussion

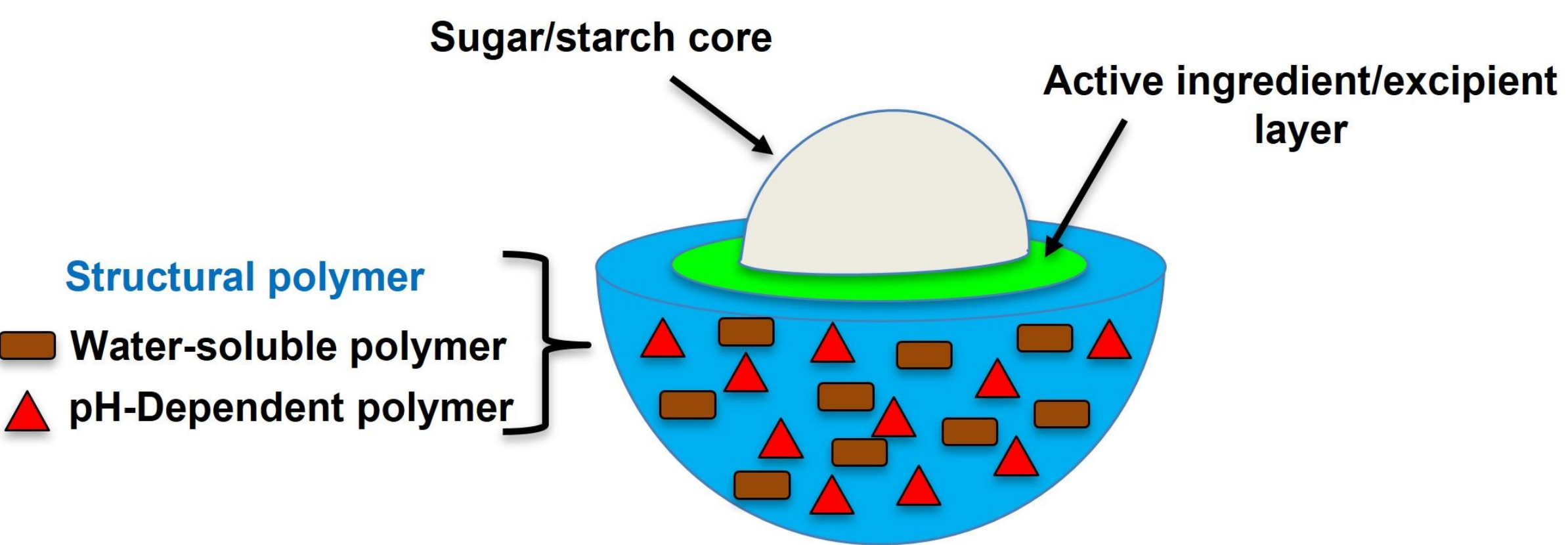


Figure 1. Overview of MS ER formulation

Table 1. Measured pH values of soft foods

Food	Measured pH	Literature Values
Applesauce	3.69±0.01	3.1 - 3.6
Vanilla Yogurt	4.28±0.01	4.4 - 5.0
Carrot Puree	5.05±0.01	5.9 - 6.4
Chocolate Pudding	6.19±0.01	5.5 - 6.0

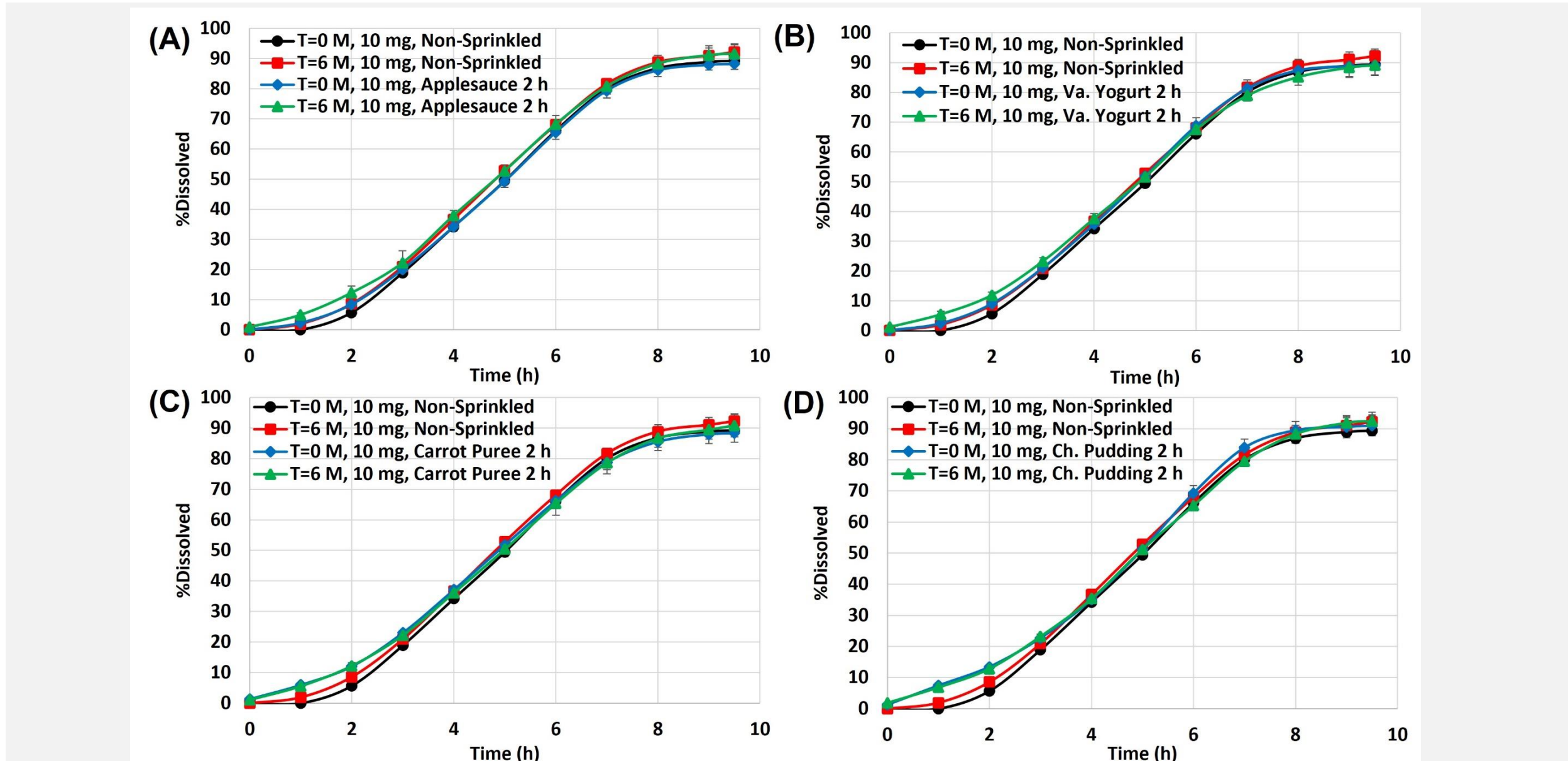


Figure 2. Dissolution profile summary of, mean±SD, n=6, T=0 M & T=6 M 10 mg, non-sprinkled pellets vs. pellets sprinkled on (A) applesauce, (B) Va. yogurt, (C) carrot puree, and (D) Ch. pudding for 2 h.

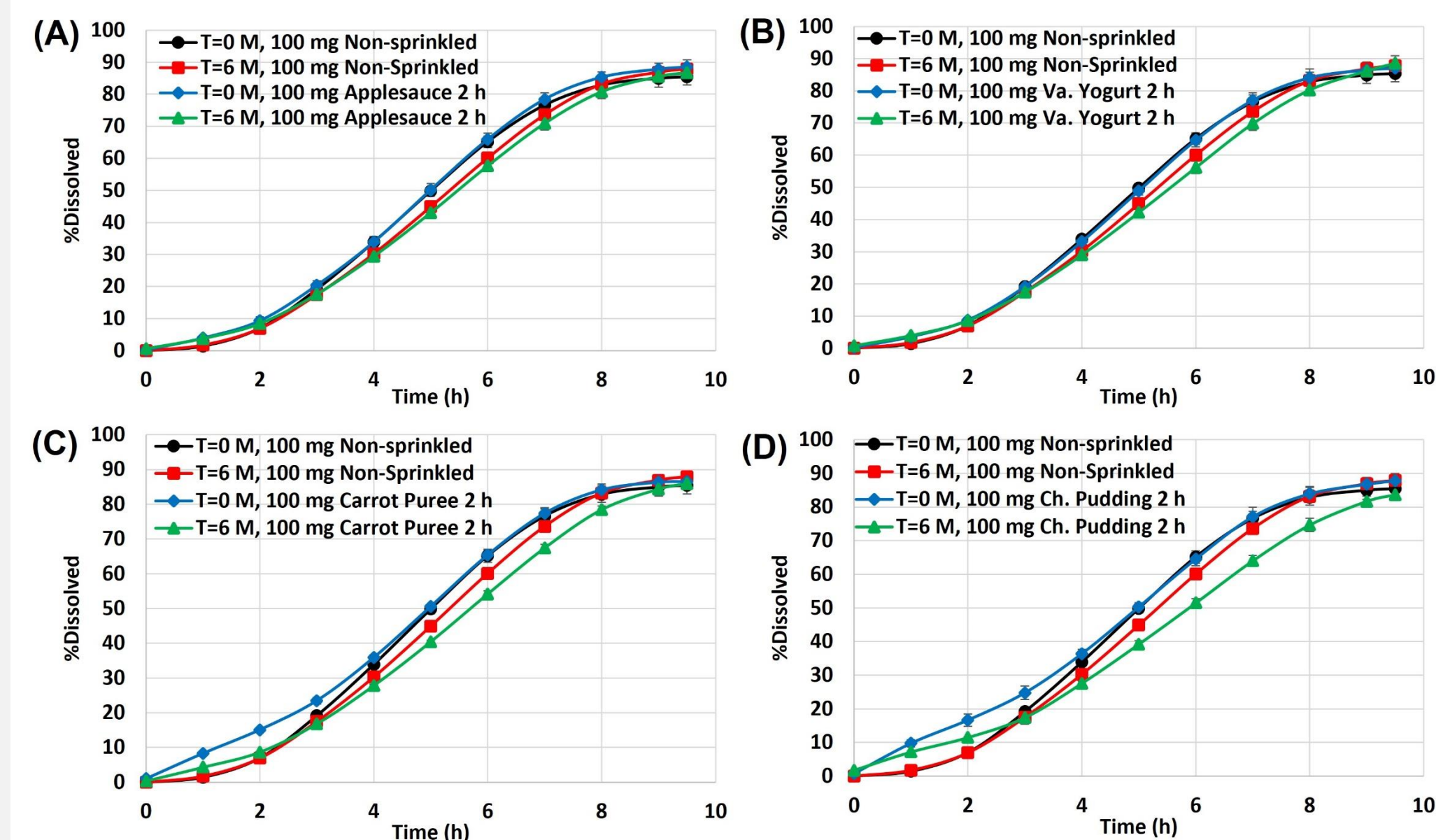


Figure 3. Dissolution profile summary of, mean±SD, n=6, T=0 M & T=6 M 100 mg, non-sprinkled pellets vs. pellets sprinkled on (A) applesauce, (B) Va. yogurt, (C) carrot puree, and (D) Ch. pudding for 2 h.

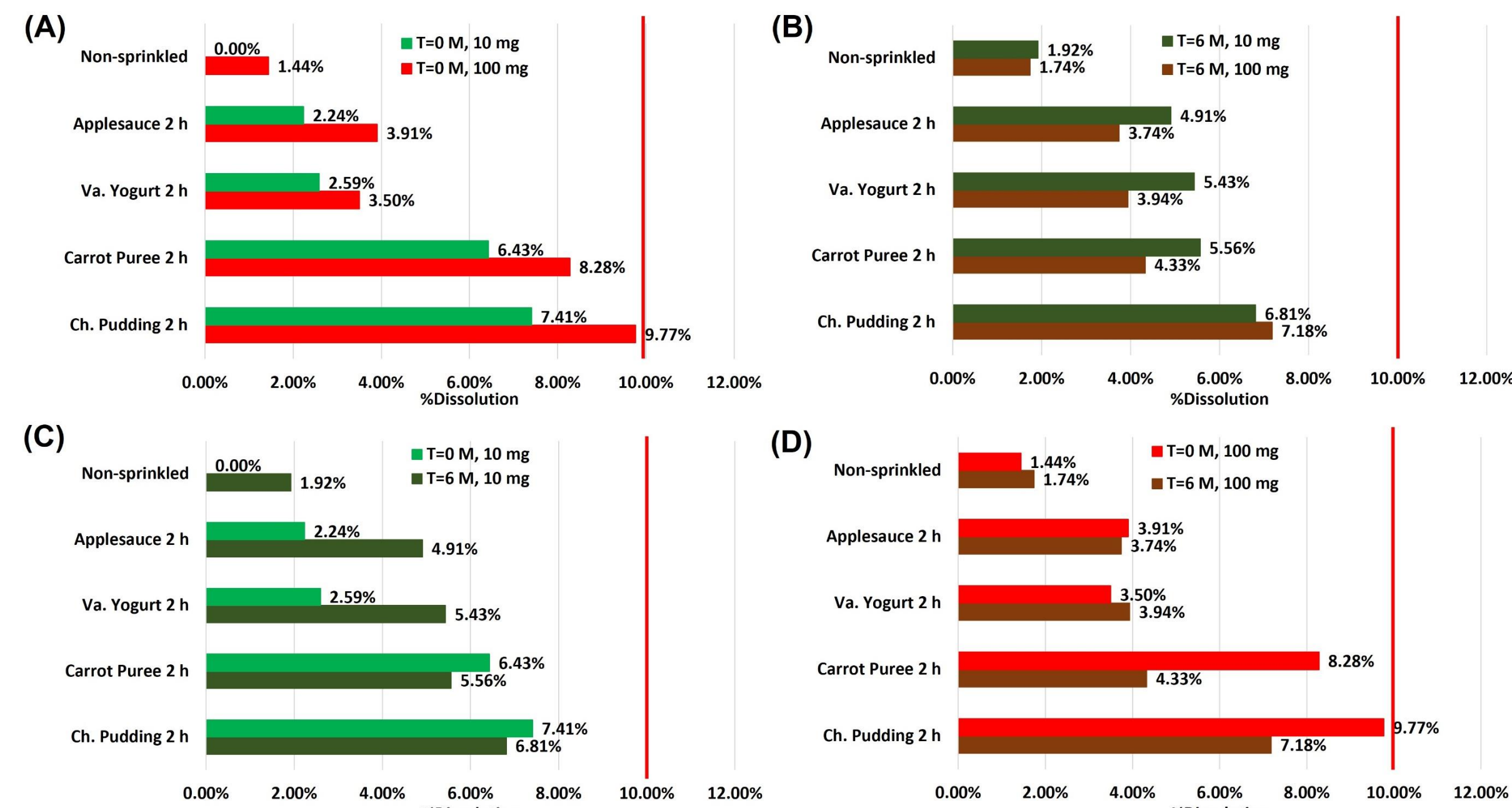


Figure 4. Comparison of mean % dissolved at the end of the acid stage (1 h, n = 6) of all test groups with contact times of 2 h for (A) T=0 M, 10 mg vs. 100 mg, (B) T=6 M 10 mg vs. 100 mg, (C) 10 mg, T=0 M vs. T=6 M, and (D) 100 mg, T=0 M vs. T=6 M.

In general, pellets sprinkled on high pH soft foods, such as chocolate pudding, showed higher MS release at 1 h than low pH soft foods.

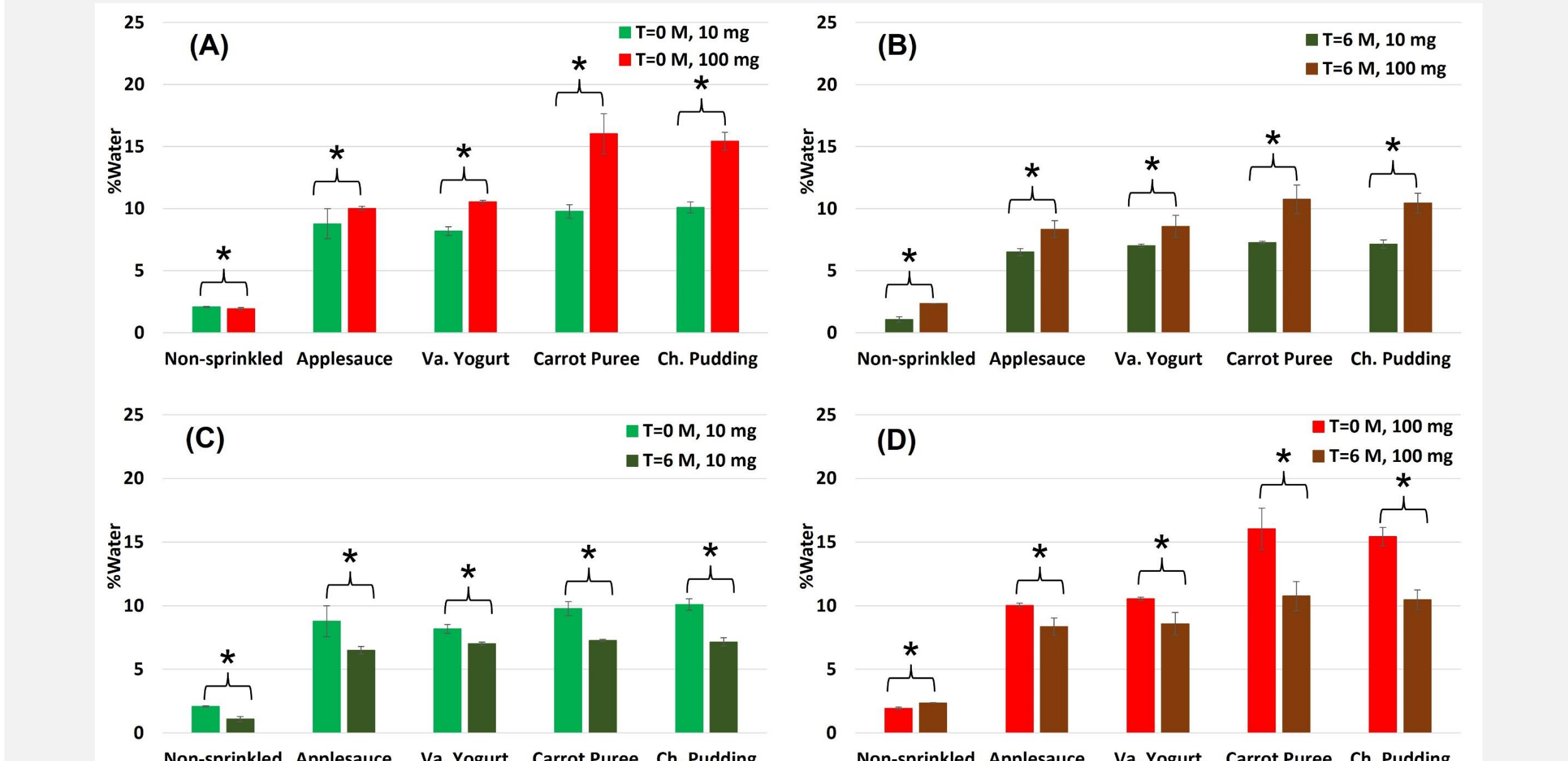


Figure 5. Comparison of percent water content for all test groups with contact times of 2 h for (A) T=0 M, 10 mg vs. 100 mg, (B) T=6 M 10 mg vs. 100 mg, (C) 10 mg, T=0 M vs. T=6 M, and (D) 100 mg, T=0 M vs. T=6 M. *t-Test, $P < 0.05$.

In general, pellets sprinkled in high pH soft foods showed high water content. For pellets of the same storage condition (Fig. 5A and 5B), water content of 100 mg dosage strength was higher compared to 10 mg for all soft foods treatment groups. For pellets of the same dose strength (Fig 5C and 5D), water content of T=0 pellets were higher compared to T=6 M pellets for all soft foods groups.

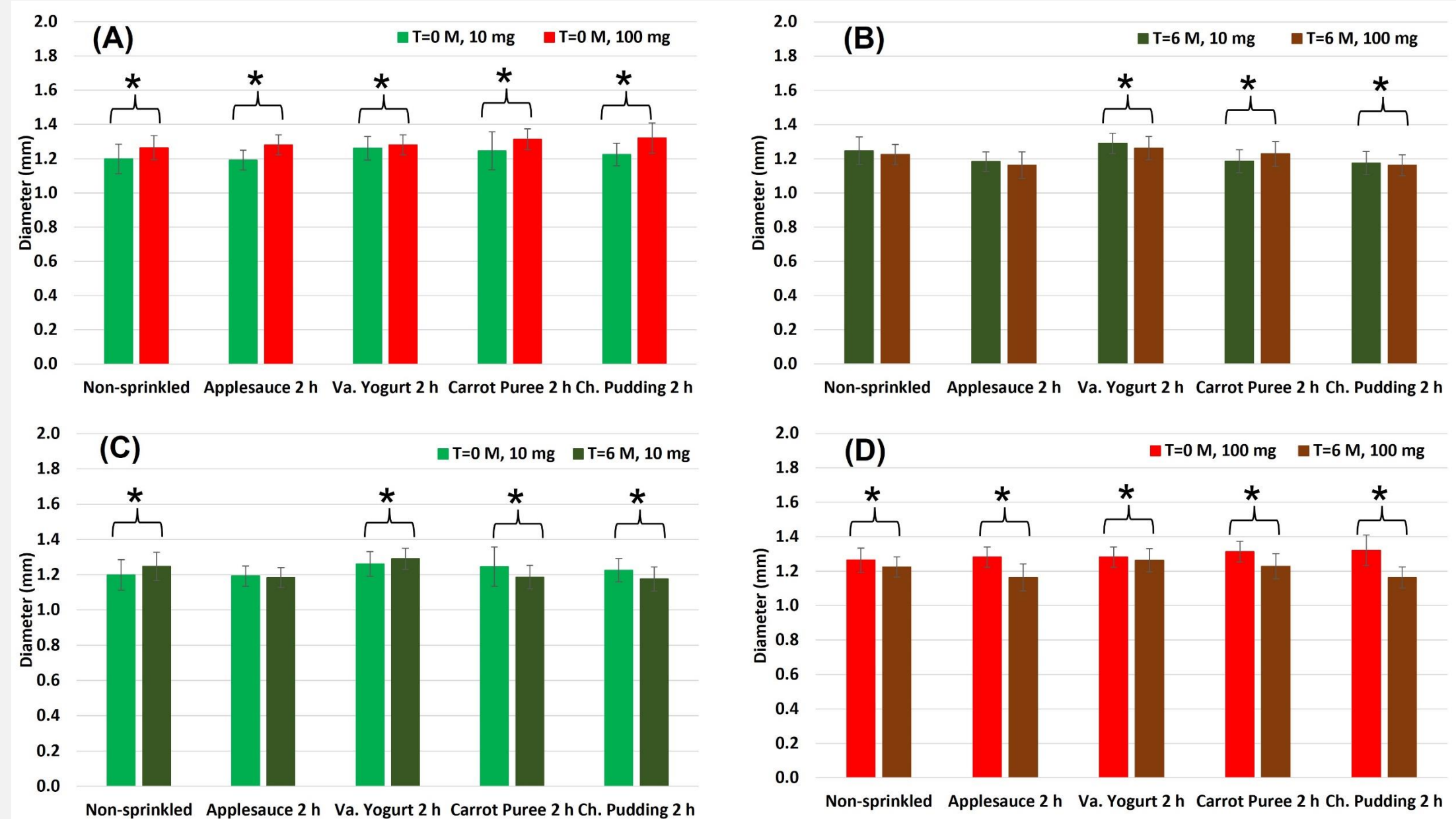


Figure 6. Comparison of mean pellet diameter for all test groups with contact times of 2 h for (A) T=0 M, 10 mg vs. 100 mg, (B) T=6 M 10 mg vs. 100 mg, (C) 10 mg, T=0 M vs. T=6 M, and (D) 100 mg, T=0 M vs. T=6 M. * t-Test, $P < 0.05$. Despite of the statistical significance, the difference in absolute values of pellet diameters are small (maximum difference of 0.16 mm observed between T=0 M and T= 6 M Ch. pudding, 100 mg).

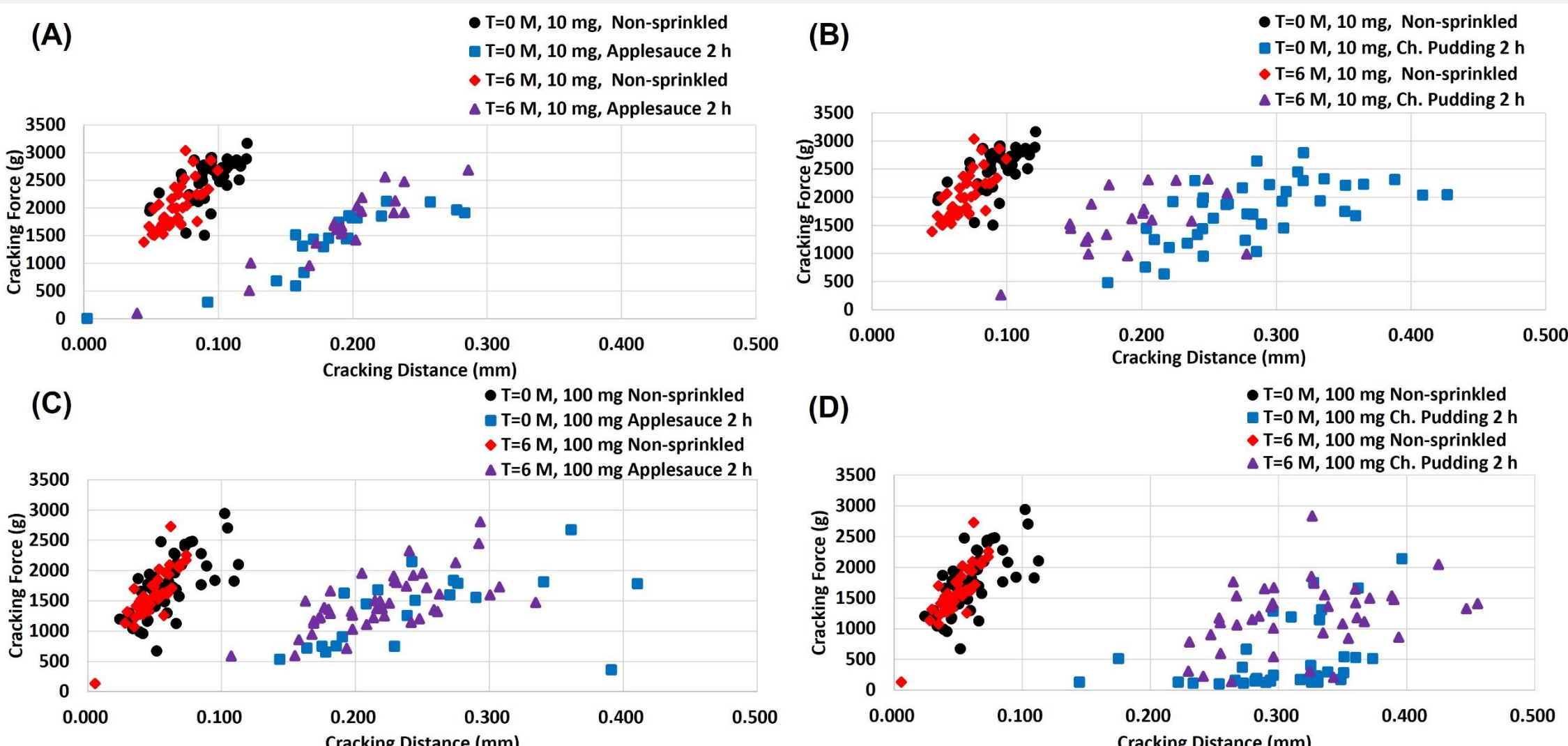


Figure 7. Scatter plots showing cracking force vs. cracking distance (n=40). (A) and (B) T=0 M and T=6 M 10 mg, and (C) and (D) T=0 M and T=6 M 100 mg; non-sprinkled pellets and pellets sprinkled on applesauce and Ch. pudding.

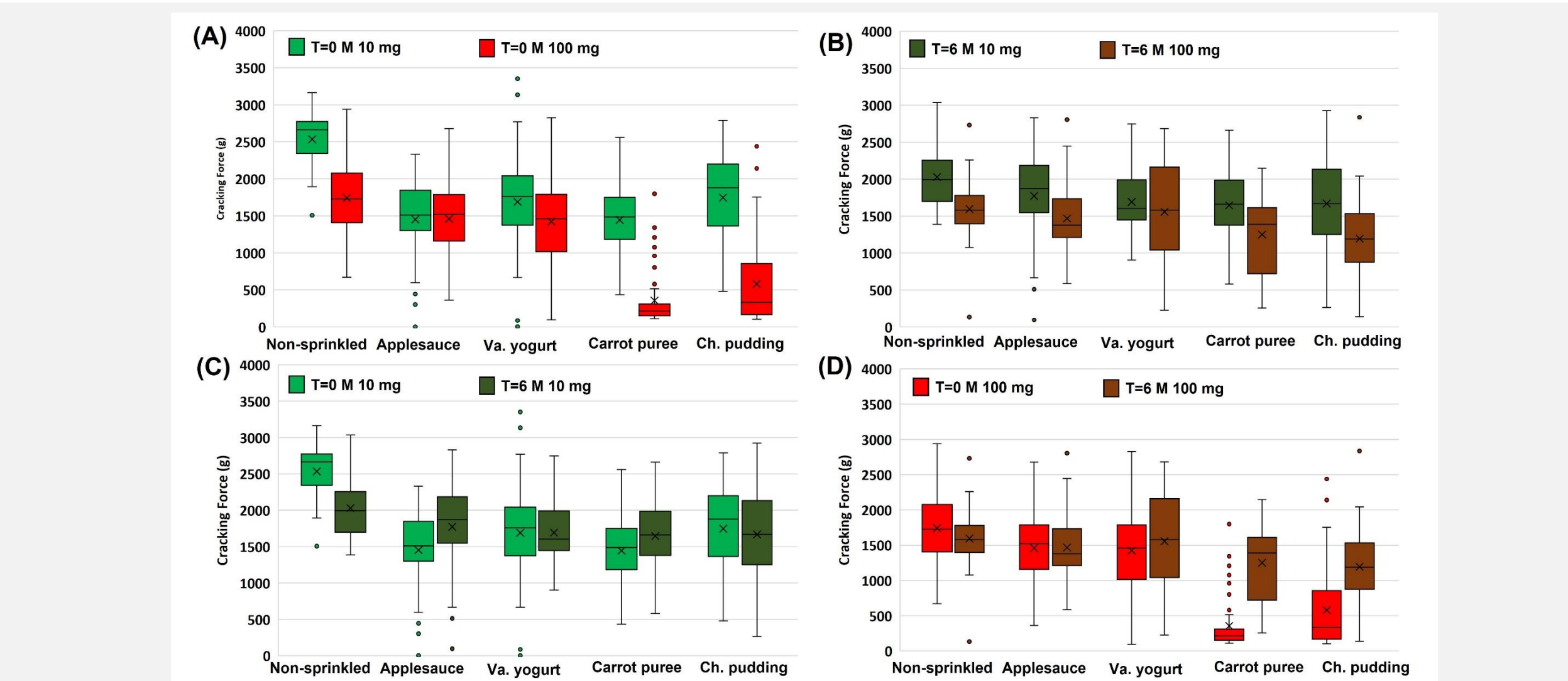


Figure 8. Box & Whisker Plot showing cracking force (n=40) for all test groups with contact times of 2 h for (A) T=0 M, 10 mg vs. 100 mg, (B) T=6 M 10 mg vs. 100 mg, (C) 10 mg, T=0 M vs. T=6 M, and (D) 100 mg, T=0 M vs. T=6 M.

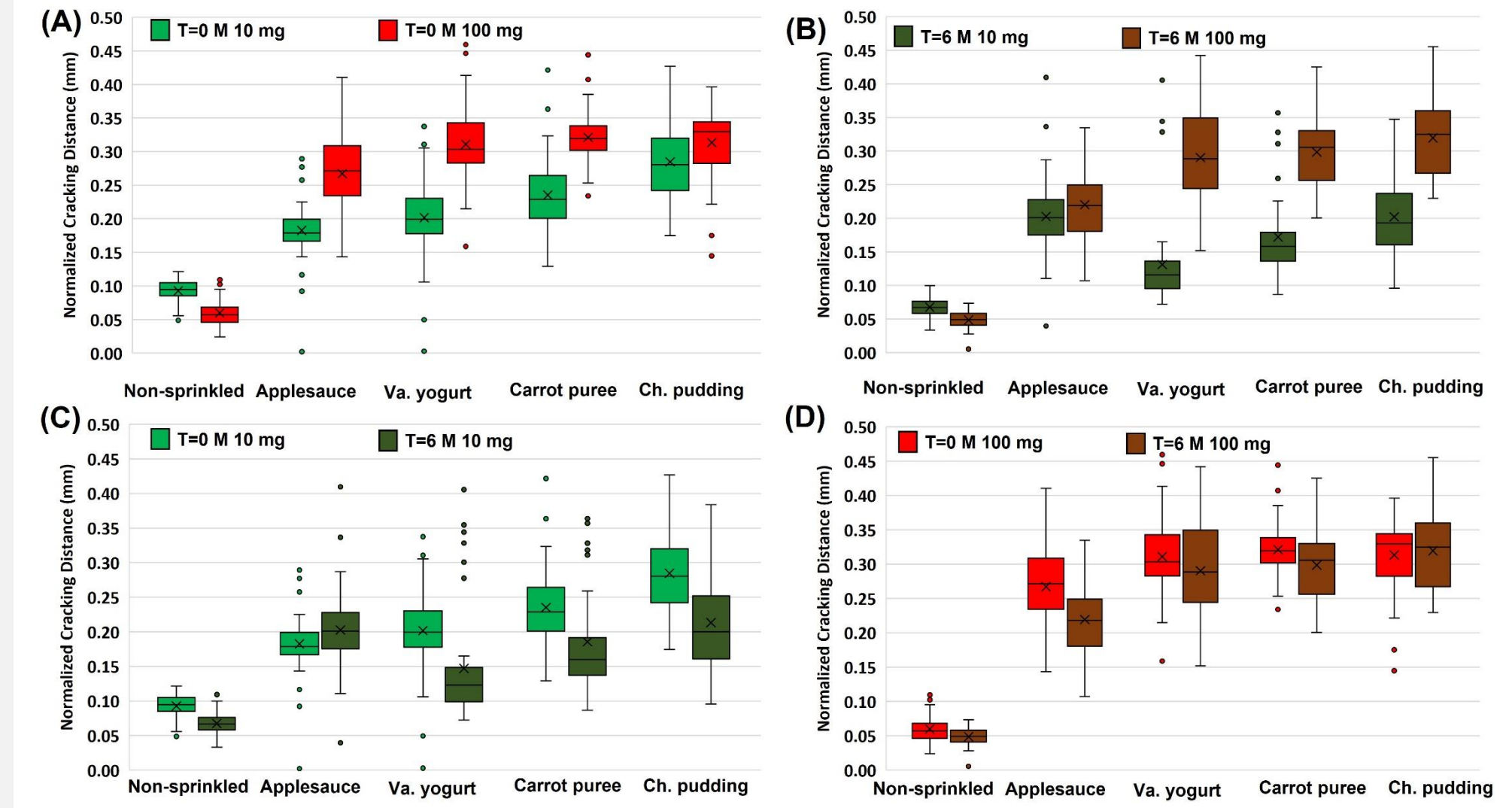


Figure 8. Box & Whisker Plot showing normalized cracking distance (n=40) for all test groups with contact times of 2 h for (A) T=0 M, 10 mg vs. 100 mg, (B) T=6 M 10 mg vs. 100 mg, (C) 10 mg, T=0 M vs. T=6 M, and (D) 100 mg, T=0 M vs. T=6 M. The pellets cracked under lower forces and longer cracking distances when sprinkled on high pH soft foods.

Conclusion

High pH foods including carrot puree and Ch. pudding appeared to associate with higher water content, greater pellet deformation under lower stress force, and slightly elevated MS dissolution in the early time points of the sprinkled pellets for both 10 mg and 100 mg strengths at T=0 M and T=6 M. However, all conditions tested passed USP dissolution testing which ensures drug quality is maintained regardless of soft food selection, formulation, and storage. These results may help in interpreting the soft food effect on drug products with similar ER mechanisms.

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Reference

- [1] Cho, S.Y., et al., Neurogastroenterol. & Motil., 2015. 27(2): 212-219.
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