A COMBINED EXPERIMENTAL AND COMPUTATIONAL APPROACH FOR THE DESIGN OF 4D GASTRORETENTIVE DRUG DELIVERY SYSTEMS

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Introduction

The use of gastroretentive drug delivery systems (GRDDSs) is a widely employed approach for the treatment of local diseases and for increasing the bioavailability of drugs poorly stable in the intestinal environment, since it can address several challenges associated with conventional oral dosage forms. Among the different strategies to attain GRDDSs, those relying on pharmaceutical-grade shape memory polymers (SMPs) have gained special attention. In fact, thermo-responsive SMPs allow to develop systems administered in a collapsed configuration and able to self-expand upon interaction with gastric fluid at body temperature, thus preventing passage through the pylorus. Moreover, recent advances in 4D printing technology open promising opportunities to develop customized self-expandable GRDDSs based on SMPs [1].
The present work aims at investigating a combined experimental and computational approach for the assisted design of shape memory expandable GRDDSs manufactured via fused deposition modeling 3D printing and extrusion.

Methodology

A pharmaceutical formulation is selected, composed of a semi-crystalline SMP (i.e., poly(vinyl alcohol) (PVA) of pharmaceutical grade) and a plasticizer (i.e., glycerol), with the possibility of loading also an active ingredient (i.e., Allopurinol) [1-2]. A comprehensive thermal, mechanical, and shape memory characterization is first performed under different testing conditions and on different sample geometries. Then, a GRDDS prototype consisting of an S-shaped device is fabricated, deformed in a temporary collapsed configuration, and tested. A three-dimensional visco-elastic model under finite strain is considered in a finite element framework [3] to support the design of the device. Results from the experimental investigation are used to calibrate the constitutive model and validate numerical results.

Results

Experimental data demonstrate that the investigated SMP is suitable for the prototyping of GRDDSs, by programming a temporary shape, which can be fitted inside commercially available capsules, and by exploiting the recovery of the permanent shape (upon contact with simulated gastric fluid at 37°C) to achieve retention and controlled release of the conveyed drug. Moreover, a good matching is observed by comparing numerical and experimental isothermal and thermally-stimulated recovery curves. In particular, the results clearly highlight the importance of a correct model calibration, based on the investigated application and on the type of associated testing environment.

Conclusions

The present work confirms the possibility to employ PVA as base material for shape-changing GRDDs realized by means of 4D printing and provides new insights concerning the application of the chosen constitutive model to this pharmaceutical formulation. Combining experimental and computational approaches turns out to be an effective methodology for achieving a complete understanding of the complex behavior of pharmaceutical-grade SMPs and for the design of related delivery systems.

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References

[1] Melocchi A., Uboldi M., Inverardi N., et al. Expandable drug delivery system for gastric retention based on shape memory polymers: development via 4D printing and extrusion. Int. J. Pharm., 571, p. 118700, 2019.

[2] Inverardi N., Scalet G., Melocchi A., et al. Experimental and computational analysis of a pharmaceutical-grade shape memory polymer applied to the development of gastroretentive drug delivery systems. J. Mech. Behav. Biomed. Mater. 124, p. 104814, 2021.

[3] Diani, J., Gilormini, P., Frédy, C., Rousseau I. Predicting thermal shape memory of crosslinked polymer networks from linear viscoelasticity. Int. J. Solid Struct., 49(5), p. 793-799, 2012.