HYDROGELS-BASED MATRICES BEHAVIOR: EXPERIMENTAL AND MODELING DESCRIPTION

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ABSTRACT SUMMARY

The use of hydrogels in the development of pharmaceutical forms is widespread. The aim of this work is to describe the phenomena involved in the hydration of a hydrogel-based matrix. Gravimetric analyses have been used to describe the mass evolutions of water, drug, and polymer inside the matrix during the dissolution. Moreover, a texture analysis has been performed to quantify the water absorbed during the matrix dissolution. Finally, a mathematical model able to describe all the phenomena involved has been proposed and compared with the experimental results.

INTRODUCTION

Hydrogels are widely used in pharmaceutical formulations, particularly to develop controlled release dosage forms.

In fact, when this polymer enters in contact with the dissolution medium, water diffusion through the matrix causes a glass-rubber transition and thus the polymer swelling. Then, the drug contained in the swollen region starts to diffuse toward the outer dissolution medium. When the external polymer layers became extremely hydrated the erosion takes place.

Therefore the development and improvement of pharmaceutical systems requires the analysis of all the mechanisms involved during the water uptake and gel layer formation.

Aim of the work

The aim of this work is to describe all the phenomena which take place during the hydrogel-based matrices hydration, using both experimental techniques and a modeling approach.

EXPERIMENTAL METHODS

Matrices composed by HydroxyPropyl MethylCellulose (HPMC) and theophylline (TP) 50% wt/wt have been used. The tablets (175 mg weight, 1 mm diameter) have been glued on a glass slab and immersed into a USP II apparatus at 37°C. During the first 2 hours, to reproduce the acidic stomach environment, a pH 1 solution has been used. Then, the solution has been almost neutralized (pH 6.8) to reproduce the intestinal environment.

Gravimetric analysis

From the difference between hydrate and dry tablets weights, the water absorbed has been evaluated. The residual amount of drug after the dissolution has been obtained dissolving the dried residue and analyzing the solution via HPLC. The polymer mass is obtained through mass difference. The gravimetric analyses performed on the whole tablet at different dissolution times allow to obtain the evolution of water, drug, and polymer contents in the swollen matrices.

Using cylindrical hollow punches, the hydrated swollen tablets have been cut in several annular sections. Analyzing each section by the same previously described method, it has been possible to obtain the average mass fractions profiles as a function of the radial direction.

Mechanical tests

Indentation tests using a texture analyzer have been performed on the swollen matrix. It has been penetrated at several distances from the center. Using a previously developed technique [1], the slope of the force-penetration curve (dF/ds) has been correlated to the water content on the swollen tablet. The water content in the axial direction varies due to the non-uniform hydration of the tablet, as a consequence, the slope of the force-penetration curve is not constant. By this technique, it is possible to determine the water mass content, via the measured force, along the axial direction of the tablet for several radial positions.

MODELING

The dissolution process has been modeled using mass transport equations, to describe the species diffusion, coupled with the ALE (Arbitrary Lagrangian Eulerial) method, to consider the system swelling.

The transport equations employed [2], with the proper initial and boundary conditions, have been reported below, for water (i=1) and drug (i=2), while the polymer (i=3) has been derived from the mass fraction constraint:

$$\begin{cases} \rho\dfrac{\partial \omega_i}{\partial t} = \nabla\cdot(\rho\, D_i\, \nabla\omega_i + \rho\dfrac{\omega_i}{M}\, D_i \nabla M) \\ \omega_3 = 1-(\omega_1+\omega_2) \\ @\, t = 0 \;\; \forall \mathbf{x}\in\Omega \;\; \omega_i = \omega_{i0} \\ @x\in\Gamma 1 \;\forall t > 0 \;\; \mathbf{J_i} = 0 \\ @x\in\Gamma 2 \;\forall t > 0 \;\; \mathbf{J_i} = 0 \\ @x\in\Gamma 3 \;\; \forall t > 0 \;\; \omega_i = \omega_{i,eq} \\ @x\in\Gamma 4 \;\; \forall t > 0 \;\; \omega_i = \omega_{i,eq} \end{cases}$$

With the constitutive equations described by the following equation for the diffusivities:

$$D_i = D_{i,\,eq}\exp\left[-\beta_i\left(1-\frac{\omega_1}{\omega_{1,eq}}\right)\right]$$

and an ideal mixing rule for the specific volume for the system density:

$$\frac{1}{\rho} = \left(\sum \frac{\omega_i}{\rho_i}\right)$$

The swelling velocity can be computed from a flow identity at interface whereas the erosion velocity is accounted as a constant value (fitting parameter).

RESULTS AND DISCUSSION

By the gravimetric analysis the evolution of the three components in the swollen matrices has been obtained, and the results are shown in Figure 1. Moreover, the drug release evolution has been evaluated.

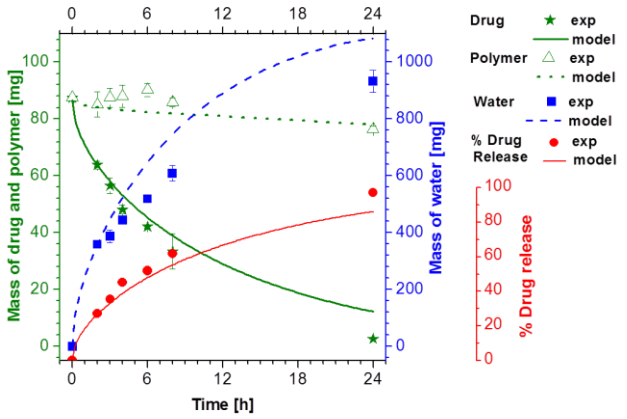

Figure 1. Mass of drug, polymer (green) and water (blue) inside the tablet at different dissolution times. In red the percentage of drug release.

In Figure 1 the results of the model, after a proper tuning, have been compared with the experimental data, showing that the model well describe the macroscopic mass variations of the tablet during the dissolution.

The so tuned model has been used to evaluate the mass fractions inside the swollen matrix and compared to microscopic experimental results, obtained by the measurements of the matrix components in each section. The results are shown in Figure 2.

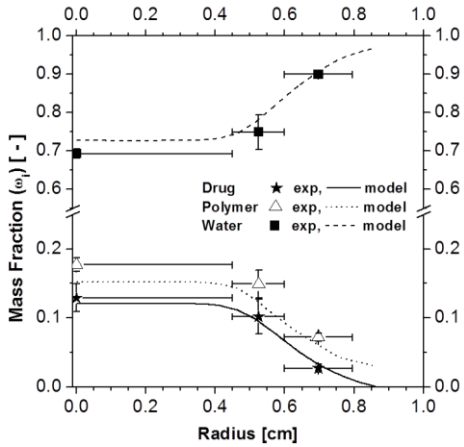

Figure 2. Water, drug and polymer mass fraction along the radius direction after 6h of dissolution.

The swollen matrices have been subjected to texture analyses to obtain the hydration level. The technique gives information on the water content along the axial distance: repeating the analysis at several radii it is possible to build a contour plot that shows the hydration level in the whole swollen tablet.

However these simple analyses give detailed information on the internal water content that can be compared with pictures of the swollen tablet as well as with modeling results. In Figure 3 a swollen tablet picture (top left part) with texture analysis results (top right part), and modeling water mass fraction distribution (bottom right part) after 6 hours dissolution time is shown.

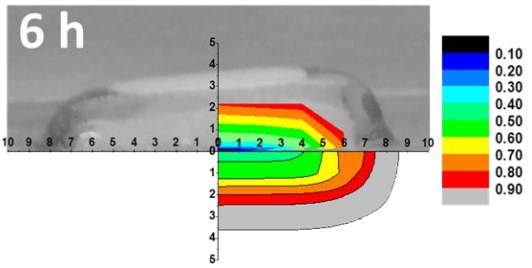

Figure 3. Tablet picture after 6h dissolution time is compared with texture analysis results (top) and modeling results (bottom). The dimensions are in mm.

Both the texture and the modeling data are expressed in terms of water mass fraction content, starting from zero (black) in the dry regions up to more than 0.9 in the fully swollen regions (light gray). From these graphs it is possible to see that the internal tablet hydration level, as well as the final swollen tablet shape, are quantitatively well predicted by the model thanks to the comparison with the texture analysis results and the swollen matrix pictures, respectively. Thus this model is able to predict in a satisfactorily manner all the phenomena involved in a tablet dissolution process.

CONCLUSIONS

The behavior of hydrogel-based matrices has been completely characterized experimentally using texture and gravimetric analyses. A mathematical model has been conceived and tuned showing a good agreement with experimental results.

REFERENCES

[1] Cascone, S.; Lamberti, G.; Titomanlio, G.; d'Amore, M.; Barba, A.A. Measurements of non-uniform water content in hydroxypropyl-methyl-cellulose based matrices via texture analysis, Carbohydrate Polymers, 103(1), 348-354 (2014).

[2] Caccavo, D.; Cascone, S.; Lamberti, G.; Barba, A.A. Modeling the drug release from hydrogel-based matrices, in press on Molecular Pharmaceutics (2015).

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