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Short communication

Measurements of water content in hydroxypropyl-methyl-cellulose based hydrogels via texture analysis

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ABSTRACT

In this work, a fast and accurate method to evaluate the water content in a cellulose derivative-based matrix subjected to controlled hydration was proposed and tuned. The method is based on the evaluation of the work of penetration required in the needle compression test. The work of penetration was successfully related to the hydrogel water content, assayed by a gravimetric technique. Moreover, a fitting model was proposed to correlate the two variables (the water content and the work of penetration). The availability of a reliable tool is useful both in the quantification of the water uptake phenomena, both in the management of the testing processes of novel pharmaceutical solid dosage forms.

1. Introduction

The use of cellulose derivative, in particular of HPMC, in the preparation of pharmaceutical solid dosage forms is widely diffused (Siepmann & Peppas, 2001). After swallowing, matrices based on HPMC undergo several subsequent phenomena. Water diffusion through the matrix causes the polymer swelling, therefore the drugs in the hydrated hydrogel begin to diffuse and to pass in the gastro-intestinal environment, then the most hydrated external polymer layers are subjected to disentanglement and erosion actions and, at last, they dissolve in the physiological fluids. Dynamics of these phenomena have been investigated by several methods, both experimental and theoretical.

In the experimental field, an image analysis method was proposed and applied to matrices made of HPMC and buflomedil pyridoxal phospate (BPP) a colored (yellow) drug (Colombo, Bettini, & Peppas, 1999). More recently, an integrated approach, based on gravimetric and image analysis methods, was proposed, working with matrices made of pure HPMC (Barba, d'Amore, Chirico, Lamberti, & Titomanlio, 2009b; Chirico, Dalmoro, Lamberti, Russo, & Titomanlio, 2007), and, furthermore, it was successfully applied on HPMC matrices loaded by theophylline (Barba, Dalmoro, Santis, & Lamberti, 2009; Barba, D'Amore, et al., 2009; Barba, d'Amore, et al., 2009). Other approaches were based on NMR measurements (Kaunisto et al., 2010), and on texture analysis (Pillay & Fassihi, 1999), demonstrating, thus, a vivid interest in this kind of control. The main point is that the hydration plays a fundamental role during the drug release from different drug delivery systems, also based on other carbohydrates such as alginates, alone or in combination with Pluronics® (Barba, Dalmoro, Santis, et al., 2009; Barba, D'Amore, et al., 2009; Barba, d'Amore, et al., 2009; Dalmoro, Barba, Lamberti, & d'Amore, 2012; Dalmoro, Barba, Lamberti, Grassi, & d'Amore, 2012), chitosan (Dalmoro, Barba, Lamberti, & d'Amore, 2012; Dalmoro, Barba, Lamberti, Grassi, et al., 2012), or on other kinds of materials (Barba, Dalmoro, Santis, et al., 2009; Barba, D'Amore, et al., 2009; Barba, d'Amore, et al., 2009; Dalmoro, Lamberti, Titomanlio, Barba, & d'Amore, 2010).

Even if some of the works above mentioned include modeling approaches, an excerpt from literature regarding the modeling of water uptake and drug release from cellulose based hydrogels shows that the applied approaches range from the simple 1D method based on finite differences (Acierno, Barba, & d'Amore, 2004; Barba, d'Amore, Chirico, Lamberti, & Titomanlio, 2009a), to the more complex 2D methods based on finite differences (Siepmann, Podual, Sriwongjanya, Peppas, & Bodmeier, 1999), or on finite volumes (Grassi & Grassi, 2005). These last two approaches were based on affine deformation (i.e. because of the water uptake and of the erosion, the matrices increase and then decrease their size, without any modification in their shape). Recently and independently, two full models were proposed, able to take into account also for non-affine deformations, i.e. the change in shape due to

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hydration, swelling and erosion (Kaunisto, Marucci, Borgquist, & Axelsson, 2011; Lamberti, Galdi, & Barba, 2011).

Therefore, a lot of work was done in order to clarify the phenomena taking place during cellulose-based matrix hydration. However, experimental protocols defined are cumbersome and time-consuming. There is still the need a fast and accurate method to estimate the water content in different position of the matrix during their hydration. The method should be based on a technique fast, reliable and easy to carry out using common apparatuses. Thus, aim of this work is to propose a new method with the features above reported, and to tune it by comparison with experimental data coming from a different technique of water uptake measurement.

2. Experimental

2.1. Materials

Powders of hydroxypropyl methylcellulose (HPMC, Methocel K15M, Colorcon, Varese, Italy) and theophylline (TP, Sigma–Aldrich, Milan, Italy) were used to produce hydrogel model tablets. Distilled water was used as dissolution medium.

2.2. Methods

2.2.1. Matrices preparation

Both HPMC and drug powders were used as provided and shaped in cylindrical matrices (tablets, radius 6.5 mm and thickness 2.1 mm) through powders mixing (25% TP, 75% HPMC) and compression, using, for this latter operation, a tableting machine (Specac PN3000, equipped with flat-faced punches, diameter 13 mm and with a Carver Press), working with a loading force of 50 kN kept for 5 min.

2.2.2. Matrices hydration

To allow the water uptake only through radial direction, the tablets were confined between two glass slides. These "sandwiches" were placed in a thermostatic bath (vessels of USP 2 apparatus AT7 Smart, Sotax, Allschwil, Switzerland), in which the dissolution medium was distilled water, stirred and kept at 37 °C. All the runs were performed in triplicate.

2.2.3. Gravimetric method

The method was developed previously and presented elsewhere in details (Barba et al., 2009b). Here, just a brief summary is given. At given immersion times, each sample was withdrawn from the bath, the cover slide was carefully removed, and the swollen tablet was cut by several thin-walled metallic punches, the gel layer external to each punch wall was carefully recovered and quantitatively transferred on a glass holder. The cutting were repeated by using punches of decreasing radius, obtaining several annuli and a central core, which could not be further cut. Each single annulus, and the central core, were placed on a different glass holder. All the samples were dried in an oven at 105 °C until they reached a constant weight. The amounts of water and of polymer in each sample were thus obtained. By this method, the water mass fraction and the polymer mass fraction were obtained as functions of the radial direction. For different immersion times, the mass fractions were obtained as function of time. Therefore, the technique here outlined allows to obtain the evolutions of mass fractions with both the time and the radial direction. All the runs were performed in triplicate, and results were given in graphs as their average values, with error bars whose size are the standard deviation of data.

2.2.4. Texture analysis method

In parallel, different sets of hydrated matrices were used for texture analysis. Needle penetration tests were carried out using a texture analyser (TA.XT Plus, Stable Micro Systems, Ltd., Godalming, UK) equipped with a 2 mm diameter stainless steel needle probe (P/2N) and a 5 kg loading cell. The needle was punched into the hydrated matrix at several radial positions, recording the compression force and the needle position. The rate of needle advancement was 30 μm/s and the maximum strain allowed was 90% (i.e. the needle penetrated for 90% of the hydrated thickness). A recording rate of 500 point/s was set. Each run takes about 100 s to be completed (the thickness of hydrated matrices being around 3.3 mm). All the runs were performed in triplicate, and results were given in graphs as their average values, with error bars whose size are the standard deviation of data.

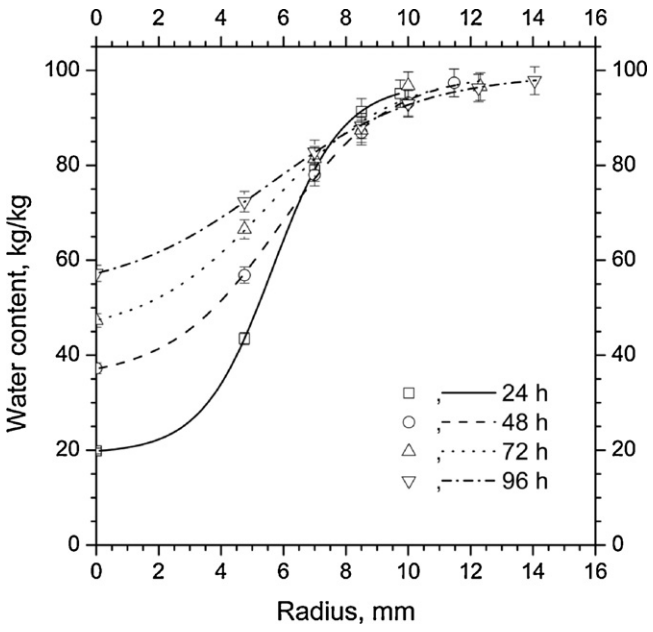

Fig. 1. Water content profiles along the matrix radius as function of immersion times. Symbols, experimental data; curves, fitting by a Boltzmann-type equation. Vertical error bars are the standard deviation of data.

3. Results and discussion

The matrices were tested by immersion for several times: 24 h, 48 h, 72 h and 96 h (1, 2, 3 and 4 days). Results of the gravimetric tests (as described in the previous section) were reported in Fig. 1. The symbols are the average values of three measurements, experimental data, the error bars being the standard deviation of the data. The curves are sigmoidal fits (Boltzmann equation was used, fitting parameters are not reported here). The full analytical protocol (Barba, Dalmoro, Santis, et al., 2009; Barba, D'Amore, et al., 2009; Barba, d'Amore, et al., 2009) allows also the determination of the drug content and thus the quantification of the water and the drug fluxes during the hydration process (which mimics what happens to the matrix after the swallowing). These data are not reported here, since they are not of interest for the purpose of the present work. The fitting procedure was needed because water content and penetration work measurements were not performed exactly at same radial positions. Obviously, the water content is an increasing function of the matrix radius, since the hydration proceeds from the outside (high radius) toward the matrix's core (low radius).

For each immersion times, three other tablets were used to measure the work of penetration (as described in Section 2). Results of three runs are reported as average values in Fig. 2, symbols connected by lines, the lines being drawn only as a guide for the eyes. The error bars are the standard deviation of data. As expected, the

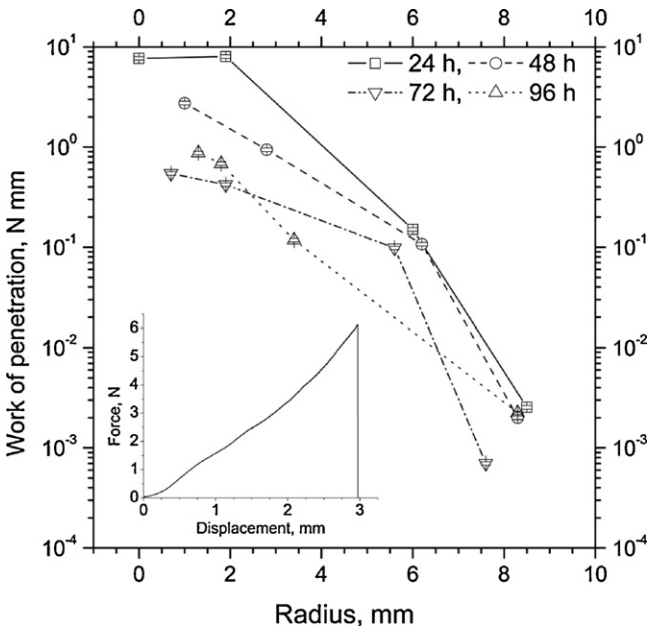

Fig. 2. Work of penetration profiles along the matrix radius as function of immersion times. Connected symbols, experimental data. In the inset: an example of the penetration force versus the displacement during a needle penetration run. Vertical error bars are the standard deviation of data.

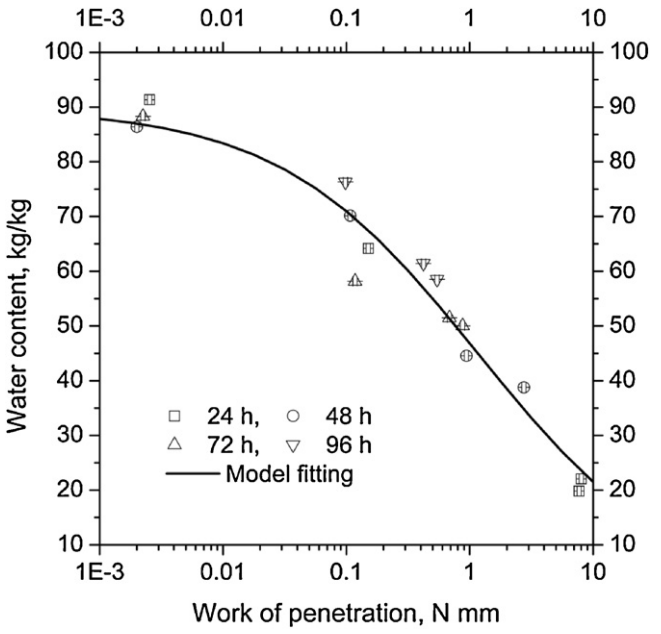

Fig. 3. Water content versus work of penetration for all the experimental data obtained during this work. Symbols are differentiated for different immersion times. Horizontal bars are the standard deviation of data (the water contents, estimated by a fitting procedure, were intended to be error-free, then no vertical bars are plotted). The curve is the model fitting by Eq. (1).

outer layers of the matrices, being more hydrated, require very limited amount of work to be penetrated, while the inner layers, being less hydrated, are more rigid and they requires substantial amount of work to be penetrated (the ordinate scale in Fig. 2 is thus logarithmic). The inset in Fig. 2 reports an example of the texture analyzer test output (24 h, $r = 1.9$ mm).

Therefore, the data from gravimetric method (Fig. 1) and from texture analysis (Fig. 2) can be compared to search for a relationship between them. This comparison process is not straightforward, since the two kinds of measurements hardly can be performed exactly at same radial position. However, the fitting curves in Fig. 1 allow to overcome this obstacle. Indeed, it is possible to compare the experimental work of penetration, obtained for some known radius values, with the water content calculated by the fitting functions at the same radial positions. By this way the couple of data $\{W_P, \omega\}$ were easily obtained and they were drawn in Fig. 3. In this graph, since the water content is the result of a calculation, the error bars (standard deviation of the data) are reported only for the work of penetration (horizontal error bars). The expected trend was obtained (the work of penetration decreases increasing the water content), and a model curve was fitted to these data, according with:

$$\omega(W_P) = \frac{a_1}{1 + (a_2 W_P)^{a_3}} \quad (1)$$

In Eq. (1) ω is the water mass fraction, W_P is the penetration work, $\{a_1 = 89.785,\ a_2 = 0.853\ [\mathrm{N^{-1}\,mm^{-1}}],\ a_3 = 0.539\}$ are the model parameters. Eq. (1) can be seen as the main result of this work: the simple measurement of the work of penetration, W_P, allows to estimate the (less experimentally accessible) water content by Eq. (1). In principle, the tool works also the other way around: once the water content was measured, the work of penetration can be estimated inverting Eq. (1).

4. Conclusions

The measurement of water content within a hydrating matrix based on cellulose derivative hydrogel is an interesting goal for the study of pharmaceutical solid dosage forms, as well as for other applications of hydrogels (for example, in the food and cosmetic industries). Several methods are available to measure the water content in a hydrogel matrix, but all of them are cumbersome and time consuming.

In this work a simple, accurate and fast method was proposed relating the work of penetration to the water content. For matrices shaped as cylinders, hydrated allowing the water up-take only through the lateral surface, the water content was assayed via a gravimetric method, and the work of penetration as function of the matrix radius was measured by a Texture Analyzer. Then, the two measurements (water content and work of penetration) were successfully correlated, and a fitting equation was also proposed and tuned. Therefore, following the proposed protocol, the fast measurements of the work of penetration allows an effective estimation of the hydrogel water content.

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