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MRI study of hydrophilic xanthan tablets with incorporated model drug

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Abstract

Magnetic resonance imaging was used to study swelling dynamics and hydrogel formation of xanthan tablets with or without Pentoxifylline drug in water and HCl pH 1.2 media at two different ionic strengths. Significant changes were observed only in the erosion front positions leading to different hydrogel thicknesses. The impact of the drug on the hydrogel thickness was found to be dependent on the medium conditions at high enough drug amount. The drug does not change the hydrogel thickness in water medium, whereas in acid medium the presence of the drug results in thinner hydrogel. The increased ionic strength in water medium also leads to formation of the thinner hydrogel layer in tablets with high enough drug content, while the effect of NaCl in HCl pH 1.2 medium is very small.

Keywords

MRI, matrix tablets, xanthan, pentoxifylline, hydrogel

1. Introduction

Matrix tablets made of hydrophilic polymers like xanthan are widely used for controlled delivery of drugs. On contact with water or body fluids the outer surface of these tablets hydrates and swells, forming a hydrogel coat around the dry central core. This complex hydrogel coat around d the dry central core regulates the penetration of body fluids into the tablet on one side and the drug release kinetics on the other [1, 2]. Therefore, the penetration of medium into the polymer tablet, the polymer swelling behaviour and the drug dissolution and diffusion out of the tablet are the key factors to understand the drug release mechanism from polymer matrices.

The various layers formed within matrix tablets during hydration are important in controlling the release of the drug. The central dry core is a glassy state polymer. As the medium ingresses into the tablet, a penetration front between the dry glassy and the hydrated glassy polymer appears. As the proportion of the medium increases, the polymer glass

transition temperature is reduced to below the system temperature, and the hydrated glassy polymer is progressively transformed to a rubbery state (hydrogel). The interface between the glassy and rubbery states is called the swelling front. The polymer chains swell as they hydrate, and the eroding front appears as an interface between the swollen tablet and the bulk medium [3, 4].

Xanthan is a well-known biopolymer that adopts a double-strand helix conformation in its native state [5]. In solution the rigid helix-coil structure transforms into flexible coils whose stability and physical properties are strongly influenced by pH and the ionic environment [6].

In our study an impact on the xanthan hydrogel formation by highly soluble model drug Pentoxifylline was investigated. Since it is known that pH and the ionic environment influence the xanthan hydrogel formation and these parameters progressively change in the gastrointestinal tract, the impact on the xanthan hydrogel formation by the model drug was studied in media with different pH and ionic strengths.

2. Materials and Methods

2.1. Materials

Xanthan (XAN) with a molecular weight of $2x10^6$ was obtained from Sigma-Aldrich Chemie, Germany. Pentoxifylline (PF), a methylxanthine derivative, (MW = 278.31) with a solubility in water at 37°C of 191 mg/ml was supplied by Krka, d.d., Slovenia. To study the dependence of hydrogel thickness and drug delivery on pH and ionic strength μ of media, four different media were used: purified H_2O and HCl at pH 1.2 according to Ph. Eur. 6th Ed and the same media with increased ionic strength (11.7 g of NaCl per 1000 ml of each medium). The final ionic strengths of the media were: H_2O (μ = 0 M), H_2O + NaCl (μ = 0.2 M), HCl pH 1.2 (μ = 0.08 M), and HCl pH 1.2 + NaCl (μ = 0.28 M). The ionic strength μ was calculated as $\mu = \frac{1}{2}\sum_{i=1}^{n} c_i z_i^2$ where n is number of all ions in the solution, c_i is the molar concentration measured in mol/l (M) and z_i is the charge number of ion i.

2.2 Preparation of matrix tablets

Xanthan and the drug (PF) were mixed homogeneously using a laboratory model drum blender. Three kinds of circular flat-faced tablets were prepared by direct compression (SP 300, Kilian & co., Cologne, Germany) to form tablets with diameter 12 mm and crushing strength 100 N ± 10 N: tablets with XAN:PF = 3:1 with m = 0.4 g and thickness of 3.23 mm, tablets with XAN:PF = 1:1 with m = 0.7 g and thickness of 4.83 mm and tablets without drug with m = 0.5 g and thickness of 4.00 mm. For MRI experiments tablets were covered with a double layer of an impermeable hydrophobic polymer, leaving only one circular surface exposed for medium penetration.

2.3 MR imaging of xanthan tablets during swelling

MR images were recorded at room temperature on a TecMag Apollo (USA) MRI spectrometer with a superconducting 2.35 T horizontal bore magnet (Oxford Instruments, UK) equipped with gradients and RF coils for MR microscopy (Bruker, Germany). To be able to accurately determine penetration, swelling and erosion fronts during tablets swelling two different MRI methods were used. The 2D MR images were taken using a standard multi-echo pulse sequence [7] with an echo time (*TE*) of 6.2 ms, number of echoes (*N*) 50 and a repetition time (*TR*) of 200 ms. The field of view was 50 mm with in-plane resolution of 200 μm and slice thickness of 3 mm. To measure short T_2 times (tablet at room humidity, hydrated glassy polymer and hydrogels with high polymer concentration), a one dimensional single

point imaging (1D SPI) T_2 mapping sequence was used [8]. A single point on the free induction decay was sampled at the encoding time t_p = 0.17 ms after the radiofrequency detection pulse $\alpha = 20^o$. *TR* was 200 ms and the inter-echo time was varied from 0.3 ms to 10 ms. The field of view was 45 mm with in-plane resolution of 350 μm.

To follow changes within the tablets during swelling, 2D MRI and 1D SPI sequences were used after medium was added to a tablet inserted in a container. For MRI experiments tablets were covered with an impermeable hydrophobic polymer, leaving only one circular surface exposed for medium penetration. A tablet at room humidity was used as reference. The first MR image was taken approximately 10 minutes after the tablet came in contact with medium and then every 30 minutes for 15 hours. The measurements were repeated at least three times for each kind of tablets and each medium.

T_2 mapping was obtained at different swelling times. T_2 values at each point in the 2D MR image were determined by fitting the signal intensities at different echo times to a single-exponential function. In the regions with T_2 values shorter than 5 ms, T_2 was obtained from 1D SPI measurements.

3. Results and Discussions

To follow the polymer swelling a combination of different MRI techniques was used for accurately determining moving fronts as described in ref. [9]. The border between dry and hydrated glassy xanthan – the penetration front – was determined from 1D SPI signal intensity profiles. The swelling front, where xanthan is transformed from a glassy to a rubbery state (hydrogel formation), was determined from T_2 profiles. The erosion front was obtained from signal intensity profiles of T_1-weighted spin-echo MR images. Since the incorporated drug changes the relaxation times, the T_2 values at which the xanthan is transformed from a glassy to a rubbery state was determined to be 2.7 ms for the XAN tablets and 2.1 ms for the XAN tablets containing the drug.

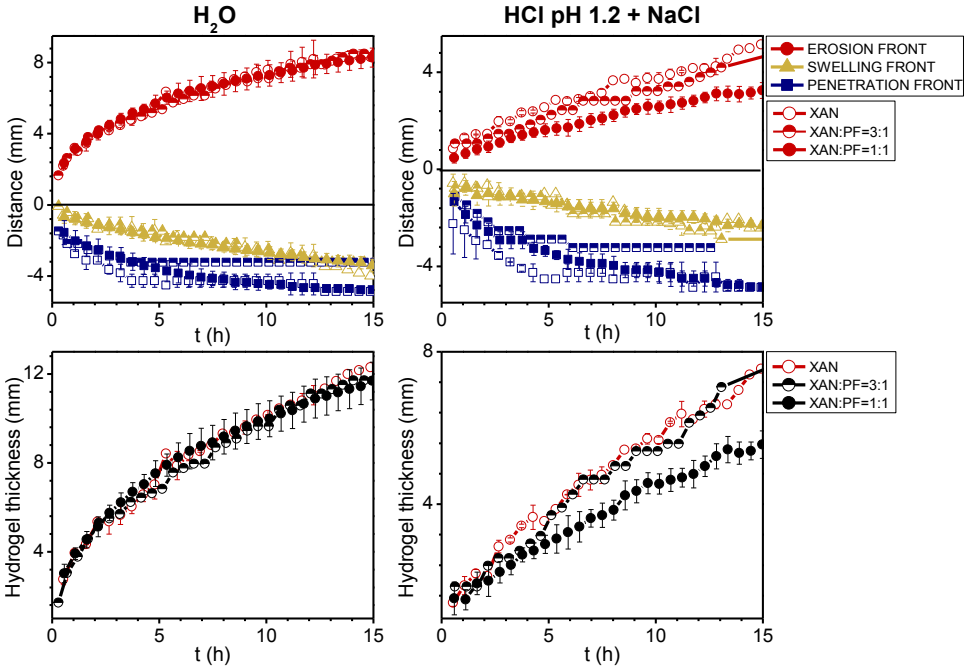

Figure 1: The positions of erosion, swelling and penetration fronts together with the increase of hydrogel layer thickness (difference between the erosion and swelling front positions) formed in xanthan matrix tablets during swelling for pure xanthan tablets and for xanthan tablets with incorporated Pentoxifylline drug in water and in acid media. Each point represents the mean value of at least three measurements and error bars show ±SD.

Fig. 1 shows the penetration, swelling and erosion fronts positions as well as hydrogel thickness at different swelling times for all three types of tablets in water and HCl pH 1.2 + NaCl media. The highly soluble drug does not change the position of the swelling front in any media, while it slightly slows the medium penetration in the tablet irrespective of the media pH, ionic strength and the drug content. Slower medium penetration can be explained by high solubility of the PF drug that uses some water to dissolve. The polymer erosion does not change within the experimental error at lower drug content, i.e. for the XAN:PF=3:1 tablets, in any of the media used in the study. At higher drug content (XAN:PF = 1:1) the polymer erosion is strongly influenced by the media pH and ionic strength. In water medium the drug does not change the polymer erosion rate. In water medium with added NaCl (μ = 0.2 M) the erosion is slightly slowed by the drug (data not shown). The impact of the drug on erosion is more pronounced in acid media, where the increase of the ionic strength does not further change the erosion rate. The hydrogel thickness (the difference between the erosion and swelling front positions) of the xanthan tablets follows the differences of the erosion front movement (Fig. 1). The hydrogel thickness dependence on the pH and ionic strength does not change with the incorporated drug. It decreases as follows: H_2O > H_2O+NaCl>HCl pH 1.2> HCl pH 1.2+NaCl for all three types of the tablets. However, since the drug does not influence the erosion in water medium where the hydrogel is the thickest and it decreases the hydrogel layer in the other three media the differences in the hydrogel thicknesses between different media increase at higher drug content (Fig. 2).

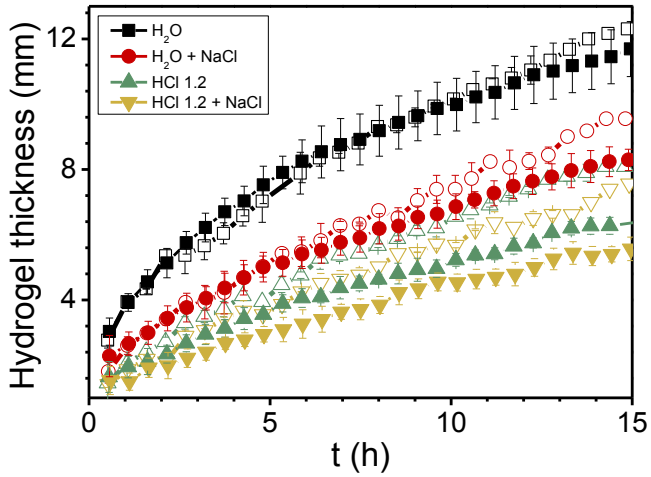

Figure 2: The hydrogel thicknesses of xanthan tablets without drug (open symbols) and of XAN:PF = 1:1 tablets (solid symbols) in different media. Each point represents the mean value of at least three measurements and error bars show ±SD.

The impact of a drug on the hydrogel formation has been studied for different polymers. In highly amylose starch with 10 wt % of drug no effect on swelling was observed owing to too low drug content [10], while the higher swelling rate was observed at higher drug contents [11]. In a non-ionic semi-synthetic polymer HPMC the studies with high soluble excipient (mannitol) and low soluble excipient (dicalcium phosphate) in ratio of 40% HPMC and 60% drug were performed [12]. It was shown that the hydrogel thickness slightly increases in the case of mannitol and significantly decreases in the case of dicalcium phosphate. The similar results, i.e. the increase of polymer hydration in the case of highly soluble drug antipyrine and its decrease when the polymer was loaded with low soluble drug hesperetin was observed in tablets made of HPMC or PVP in water [13]. In the case of HPMC tablets loaded with a tetracycline hydrochloride swelled in an acid medium (pH 2), the hydrogel thickness increases with the increase of the amount of the loaded drug [14, 15]. The wider hydrogel layer was also observed in the presence of drug in hydroxypropylcellulose (LH41) [*16*]. The studies of the effect of a high molecular weight drug peptide on the medium uptake kinetics in a

poly(glycolide-co-lactide) showed that the drug slows the buffer uptake [17]. Different impacts of the drug on the hydrogel thickness can be attributed to different hydrogel structures formed by different polymers and different drug-polymer interactions that can alter medium penetration and polymer chain mobility causing different swelling behaviour. It has been previously shown that the medium penetration, the hydrogel formation rates, the drug release, as well as the medium pH and ionic strengths dependence on the hydrogel formation are different for ionic-polymer xanthan than for non-ionic polymers like HPMC [9]. Our study shows that not only the amount of the incorporated drug that has to be high enough to influence the polymer swelling, but also the medium properties (pH and ionic strength) are important at least in the case of ionic-polymer xanthan.

4. Conclusions

The studies showed that the incorporated hydrophilic drug has some influence on the positions of the moving fronts at high enough drug content. However, the drug influence does not depend only on the drug content, but also on the medium pH and ionic strength. The medium penetration into the tablet is slightly slowed by the drug regardless of the medium conditions, while the drug has no effect on the hydrogel formation. The largest impact of the drug is observed in the erosion front position which is reflected in different thicknesses of the hydrogel layers. The hydrogel thickness depends on the amount of the incorporated drug as well as on the medium conditions.

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