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ScienceDirect
Carbohydrate Polymers 72 (2008) 571–578
Carbohydrate Polymers
www.elsevier.com/locate/carbpol

Characterization and drug delivery behaviour of starch-based hydrogels prepared via isostatic ultrahigh pressure

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Received 29 December 2006; accepted 27 September 2007
Available online 4 October 2007

Abstract

The purpose of our study was to investigate the applicability of isostatic ultra high pressure (IUHP) for the aim of drug formulation. Aqueous suspensions of potato and maize starches containing theophylline as a model drug were subjected to IUHP. The changes in the structure and morphology of potato and maize starches were investigated. The release profile of theophylline from the pressurized samples was also studied. The aqueous suspensions subjected to IUHP turned into highly viscous gels. The crystalline structure of maize starch was changed, while PS pressurized in aqueous medium retained its original X-ray pattern. The sample containing potato starch as a gel-forming polymer exhibited faster drug dissolution compared to an aqueous theophylline suspension used as a reference, while the pressurization of maize starch resulted in a gel exhibiting sustained drug release. The results of the dissolution study can be explained with the changes in structure and morphology of the starches caused by IUHP processing and with the different pressure sensitivities of PS and MS.

Keywords: Drug dissolution; Isostatic ultrahigh pressure; Scanning electron microscopy; Starch; X-ray diffraction

1. Introduction

Ultrahigh pressure (UHP) treatment is known as a potential preservation technique for almost over a century. UHP processing is defined as 'mild technology' because it causes inactivation of microorganisms and enzymes while leaving small molecules, such as flavours and many vitamins intact (Smelt, 1998). This application has also been used for pharmaceutical purposes but isostatic ultrahigh pressure (IUHP) has played only a minor role in pharmaceutical sciences so far (Blümer & Mäder, 2005).

Starches and starch derivatives are important in the formulation of pharmaceutical drug substances. Various starch sources, starch modifications and starch derivatives provide a wide range of solids, which can be used in pharmaceutical applications (Elfstrand et al., 2007; Swarbrick & Boylan, 2002).

Biopolymers, such as starches and proteins, show changes of their native structure under high hydrostatic pressure analogous to the changes occurring at high temperatures. Several authors reported that high pressure could evoke gelatinization of starch granules in starch–water suspensions already at room temperature. However, the pressure-induced gelatinization was significantly different from heat-induced gelatinization. The gelation of starch during heating is defined as phase transition from an ordered state to a disordered one, which is related to granules hydration, rapid swelling and loss of crystallinity and granular shape. According to previous studies, most of the starches subjected to UHP in excess of water retain their granular shape and exhibit limited power of swelling (Bauer, Hartmann, Sommer, & Knorr, 2004; Bauer &

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doi:10.1016/j.carbpol.2007.09.028

Knorr, 2005; Blaszczak, Fornal, Valverde, & Garrido, 2005a; Blaszczak, Valverde, & Fornal, 2005b; Hendrickx & Knorr, 2003; Hibi, Matsumoto, & Hagiwarea, 1993; Katopo, Song, & Jane, 2002; Kawai, Fukami, & Yamamoto, 2007; Liu, Yu, Xie, & Chen, 2006; Muhr & Blanshard, 1982; Muhr, Wetton, & Blanshard, 1982; Stute, Klingler, Boguslawski, Eshtiaghi, & Knorr, 1996).

The aim of our study was to investigate the applicability of ultrahigh pressure for the aim of drug formulation. In this work, aqueous suspensions of potato and maize starches containing theophylline as a model drug were subjected to isostatic ultrahigh pressure (IUHP). The changes in the structure and morphology of potato and maize starches were investigated. The release profile of theophylline from the pressurized samples was evaluated by using different mathematical models.

2. Experimental

2.1. Materials

The experimental materials were potato starch (*PS*), maize starch (*MS*) and anhydrous theophylline (Hungaropharma, Budapest, Hungary).

2.2. Isostatic UHP treatment

For the preformulation studies, approximately 4.0 g samples of starch–water suspensions (potato starch: 30% (w/w), maize starch: 20% (w/w)) were pressurized in a high-pressure device equipped with a temperature control (Mini Foodlab, Stansted Fluid Power Ltd., Stansted, Essex, UK). The samples were pressure-treated at 300 or 700 MPa for 5 or 20 min (Table 1). The highest temperatures measured inside the UHP chamber were 40 °C during pressurization at 300 MPa, and 52 °C during processing at 700 MPa. After the UHP treatment, the starch pastes and gels were dried at room temperature for one day and then milled in a mortar.

On the basis of the preformulation studies, pressurization at 700 MPa for 5 min was chosen to prepare gel samples containing theophylline as an active pharmaceutical ingredient. The profile of theophylline release was investigated from hydrogels containing 8% (w/w) theophylline, 32% (w/w) starch and 60% (w/w) water, produced via IUHP treatment at 700 MPa for 5 min (PS-T; MS-T).

Table 1
Conditions of processing of starch samples

Samples	Starch	Applied pressure [MPa]	Duration of pressure treatment [min]
$PS_{300\text{-}5}$	PS	300	5
$PS_{700\text{-}5}$	PS	700	5
$PS_{700\text{-}20}$	PS	700	20
$MS_{300\text{-}5}$	MS	300	5
$MS_{700\text{-}5}$	MS	700	5
$MS_{700\text{-}20}$	MS	700	20

2.3. Morphology of the processed samples

The morphology of the starch suspensions and gels generated by IUHP was analysed with a *stereomicroscope* (Zeiss KL 1500 LCD, Jena, Germany) after drying at room temperature. The texture of the processed samples was investigated with a *scanning electron microscope* (Hitachi 2400 S, Hitachi Scientific Instruments Ltd., Tokyo, Japan). A polaron sputter coating apparatus (Bio-Rad SC502, VG Microtech Uckfield, UK) was applied to create electric conductivity on the surface of the samples. The air pressure was 1.3–13.0 mPa.

2.4. X-ray diffraction

X-ray diffraction examinations of the samples were performed with a D4 Endeavour diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) under the following conditions: radiation source: CuKα; angle of diffraction scanned: from 1° to 30°; step size: 0.01°; step time: 8 s.

2.5. In vitro drug diffusion studies: diffusion cell method

In vitro drug release studies were performed by means of a vertical diffusion cell method (Hanson SR8-Plus™ Dissolution Test Station, Hanson Research Corporation, Chatsworth CA, USA). 0.50 g of sample was placed as a donor phase on the Porafil membrane filter with a pore diameter of 0.45 μm. The effective diffusion surface area was 7.069 cm^2. 70 ml buffer (pH 5.43) was used as acceptor phase to ensure sink conditions. The pH of the applied buffer approaches the natural pH value of human skin. Therefore, this kind of buffer is usually used as dissolution medium for the investigation of transdermal drug delivery. The membranes were soaked in buffer for 15 min before starting the tests. Investigations were performed at 37 °C for 6 h. The quantitative determination of theophylline was carried out with a UV–VIS spectrophotometer (Unicam Heλios-α, Spectronic Unicam, UK) at a wavelength of $\lambda = 271$ nm. In order to compare dissolution profiles, an aqueous suspension of theophylline (T) was used as a reference. The measurements were made in triplicate.

2.6. Characterization of the mechanism of drug release

The following mathematical models were evaluated considering the dissolution profiles of the samples (Costa & Lobo, 2001; Dredán, Antal, & Rácz, 1996; Dredán, Zelkó, Antal, Bihari, & Rácz, 1998):

2.6.1. First-order model

The drug activity within the reservoir is assumed to decline exponentially and the release rate is proportional to the residual activity:

$$\frac{M_t}{M_\infty} = 1 - \exp(-kt) \quad (1)$$

where M_t is the amount of drug released at time t, M_∞ is the initial drug amount and k is the rate constant of drug release.

2.6.2. Higuchi square root time model

The most widely used model to describe drug release from matrices, derived from Higuchi for a planar matrix, however, it is applicable for systems of different shapes too:

$$\frac{M_t}{M_\infty} = kt^{\frac{1}{2}} \tag{2}$$

2.6.3. Hixson–Crowell model

The model describes the release from systems showing dissolution rate limitation and does not dramatically change in shape as release proceeds. When this model is used, it is assumed that the release rate is limited by the drug particle dissolution rate and not by the diffusion that might occur through the polymeric matrix.

$$\left(1 - \frac{M_t}{M_\infty}\right)^{\frac{1}{3}} = 1 - kt \tag{3}$$

2.6.4. Korsmeyer–Peppas model

Ritger and Peppas proposed an equation to describe drug release kinetics from drug delivery systems controlled by swelling (Baumgartner, Planinsek, Srcic, & Kristl, 2006; Ritger & Peppas, 1987). The equation is based on a power law dependence of the fraction released on time and has the following form:

$$\frac{M_t}{M_\infty} = kt^n \tag{4}$$

where n is the diffusional exponent, which can range from 0.43 to 1 depending on the release mechanism and the shape of the drug delivery device. Based on the value of the diffusional exponent, the drug transport in slab geometry is classified either as Fickian diffusion ($n = 0.5$), non-Fickian or anomalous transport ($0.5 < n < 1$), or Case II transport ($n = 1$), where the dominant mechanism for drug transport is due to polymer relaxation during gel swelling. Anomalous transport occurs due to a coupling of Fickian diffusion and polymer relaxation.

In the anomalous processes of drug release, Fickian diffusion through the hydrated layers of the matrix and polymer chain relaxation/erosion are both involved (Baumgartner et al., 2006; Dürig & Fassihi, 2002). The contribution of these two mechanisms to the overall release are considered to be additive. The empirical model of Peppas and Sahlin describes these phenomena (Peppas & Sahlin, 1989):

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{5}$$

where M_t/M_∞ represents the drug fraction released in time t (<60%), k_1 and k_2 the kinetic constants associated with diffusional and relaxational release, respectively, and m is the purely Fickian diffusion exponent. For the geometry of our devices $m = 0.475$ was appropriate. To calculate the percentage of drug release due to the Fickian mechanism, the following equation was introduced:

$$F = \frac{1}{1 + (k_2/k_1) \cdot t^m} \tag{6}$$

F is the Fickian release fraction released due to the Fickian mechanism. The ratio of relaxation to the Fickian contributions can be expressed as follows:

$$\frac{R}{F} = \frac{k_2}{k_1} \cdot t^m \tag{7}$$

2.6.5. Weibull distribution

A general empirical equation described by Weibull was adapted to the dissolution/release process. This equation can be successfully applied to almost all kinds of dissolution curves and is commonly used in these studies (Langenbucher, 1972):

$$\frac{M_t}{M_\infty} = 1 - \exp\left\{-\left[(t - t_0)/\tau\right]^\beta\right\} \tag{8}$$

where t_0 is the lag time of the drug dissolution, τ is the mean dissolution time, when 63.2% of M_∞ has been released and β is a shape parameter of the dissolution curve.

2.7. Release profiles comparison

In order to compare the dissolution profiles of the samples, two fit factors were determined, as described by Moore and Flanner (1996). The difference factor (f_1) measures the percent error between two curves over all time points:

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \tag{9}$$

where n is the sampling number, R_j and T_j are the percent dissolved of the reference and test products at each time point j.

The similarity factor (f_2) as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared differences of drug percent dissolved between the test and the reference products (15):

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{j=1}^{n} \left|R_j - T_j\right|^2\right]^{-0.5} \times 100\right\} \tag{10}$$

In general, f_1 values lower than 15 (0–15) and f_2 values higher than 50 (50–100) show the similarity of the dissolution profiles.

2.8. Wettability of the samples

The wetting properties of the samples were determined by contact angle measurements with bidistilled water using

the OCA 20 Optical Contact Angle Measuring System (Dataphysics, Filderstadt, Germany). Ten parallel measurements were carried out.

3. Results and discussion

3.1. Preformulation study

Starch–water suspensions pressurized at 300 MPa did not exhibit visible changes. SEM analysis confirmed that the granules of PS and MS treated at 300 MPa retained their granular shape and smooth surface (Figs. 1 and 2).

The samples subjected to 700 MPa turned into highly viscous gels, although the temperature in the pressure chamber did not reach the starch gelatinization temperature known from the literature (~72 °C). The majority of the particles of PS pressurized at 700 MPa did not display apparent changes in shape or surface characteristics. However, some particles were characterized by significant surface damage and deformations (Fig. 3). Treatment at 700 MPa led to an irreversible loss of the particle structure of MS. $MS_{700\text{-}5}$ and $MS_{700\text{-}20}$ revealed a high level of destruction of the particle integrity. Fig. 4 demonstrates clear network-like gel structures. These observations are closely related to those of a previous study on high pressure-treated starches (Blaszczak et al., 2005a, 2005b).

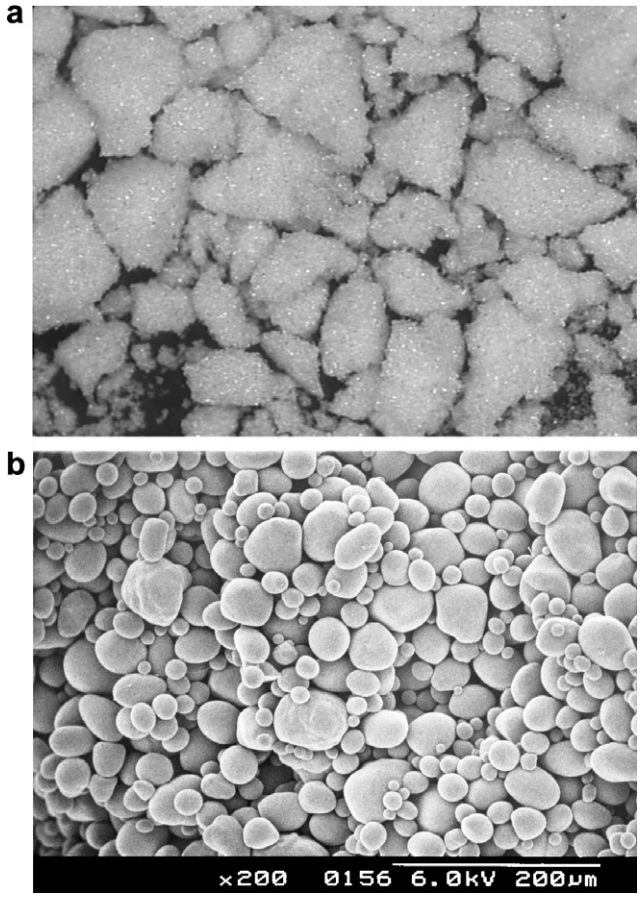

Fig. 1. Stereomicrograph (magnification: 10×) (a) and SEM picture of $PS_{300\text{-}5}$ (b).

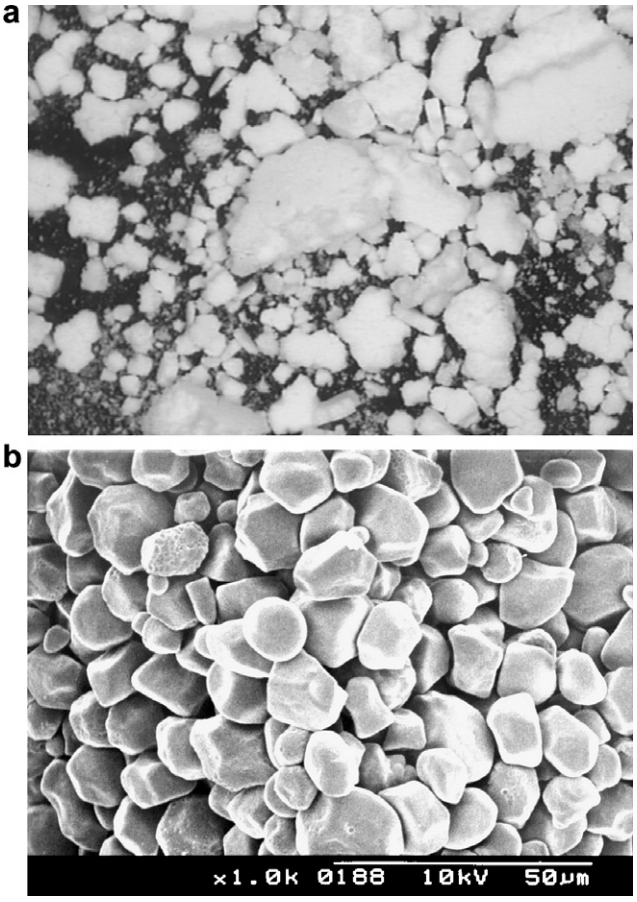

Fig. 2. Stereomicrograph (magnification: 10×) (a) and SEM picture of $MS_{300\text{-}5}$ (b).

As expected from the previous findings, MS (possessing an A-type X-ray diffraction pattern) proved to be more sensitive to UHP, while PS (with a B-type crystal structure) was more stable toward UHP treatment (Buléon, Colonna, Planchot, & Ball, 1998; Hibi et al., 1993; Stute et al., 1996). PS pressurized in aqueous medium retained its original X-ray pattern. Nevertheless, the intensity of the peaks was decreased after treatment at 700 MPa, which can be attributed to the loss of crystallinity during pressurization (Fig. 5). The X-ray diffractogram of MS pressurized at 300 MPa indicates marked changes (Fig. 6). Fig. 6 demonstrates the change in the crystalline structure of MS from A- to B-type upon treatment at 700 MPa ($MS_{700\text{-}5}$). The single peak at 22° 2θ characteristic of A-type starches remained unchanged. The X-ray curve of $MS_{700\text{-}5}$ reveals a peak at around 6° 2θ and the transformation from a double peak to a single peak at around 17.5°, which are characteristic of the B-type pattern (peaks denoted by arrows) (Szepes et al., 2005). These observations might be explained in terms of the differences in amylopectin structure and water content of the A-type and B-type starches. In the B-type crystallite, water fills up the channel in the unit cell and stabilizes the crystalline structure. For A-type starches,

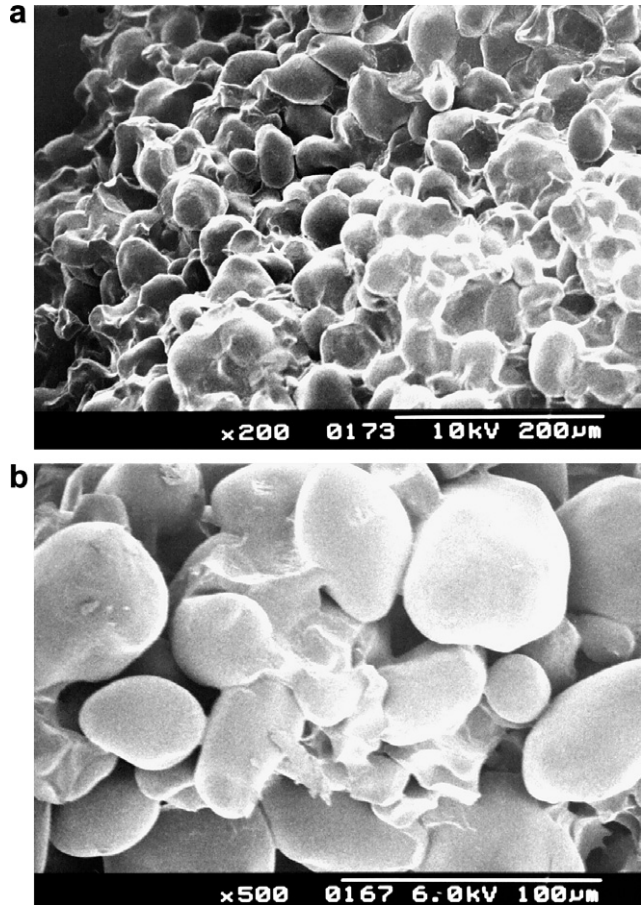

Fig. 3. SEM micrographs of $PS_{700\text{-}5}$.

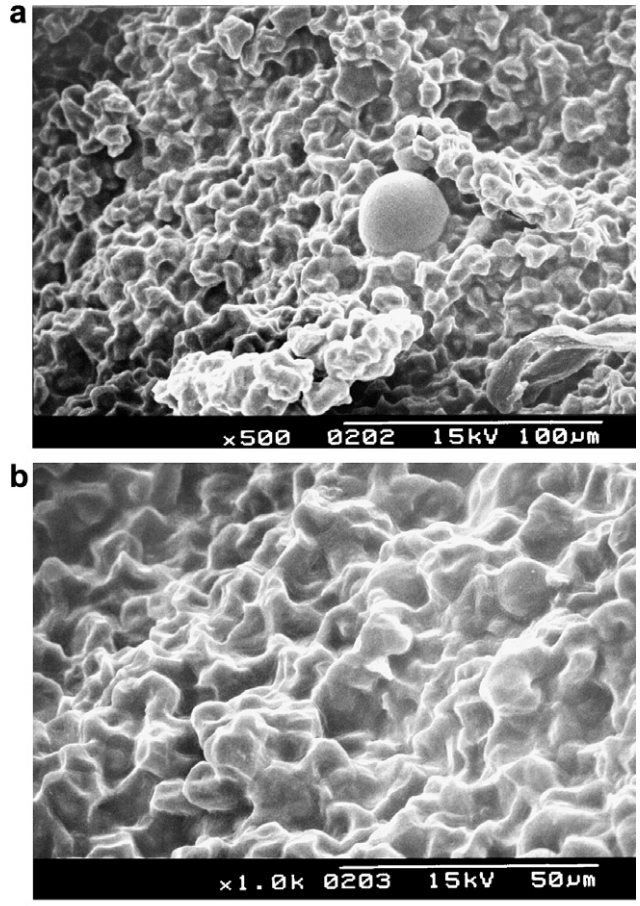

Fig. 4. SEM pictures of $MS_{700\text{-}5}$.

the more scattered branching structure of amylopectin is more flexible and allows rearrangements of the double helices, which permits a structure transformation (Katopo et al., 2002).

On the basis of the preformulation studies, pressurization at 700 MPa for 5 min was chosen in order to formulate gel samples containing theophylline as an active pharmaceutical ingredient, since the gelatinization of the starch suspensions and the structural conversion of MS occurred completely using the given process parameters.

3.2. Investigation of theophylline dissolution from starch gels prepared by IUHP treatment

A considerable difference could be observed between the profiles of theophylline release from the starch gels and the reference (Fig. 7). The correlation coefficients of different kinetic equations are included in Table 2. The dissolution mechanism from the aqueous theophylline suspension used as a reference (T) can be characterized preferably by a first-order kinetic, while the release from PS-T fits mostly to the Hixson–Crowel model. On the basis of these results, it can be assumed that the drug release from PS occurs only in vertical direction relative to the matrix surface and the matrix maintains its original shape during the release progress (Costa & Lobo, 2001). The release mechanism of theophylline from MS-T can be characterized with the Korsmeyer–Peppas model. The results of fitting to Eq. (5) are summarized in Table 3. The diffusional exponent ($n = 0.6351$) signified a non-Fickian or anomalous mechanism of drug release. Drug dissolution occurring via Fickian diffusion proved to be essential, because the diffusional rate constant (k_1) is much larger than the relaxational constant (k_2). As shown in Fig. 8, the Fickian contribution to the overall release process decreased with increasing amount of released drug. Hence, the relaxation of the polymer chains became more pronounced (Fig. 9). These results can be explained with the simultaneous water up-take during the dissolution process, which enables polymer relaxation (Baumgartner et al., 2006). It must be noted that the first three measuring points of the dissolution curve of MS-T coincide with those of T, which may be probably due to the presence of free drug particles on the sample's surface easily accessible for the dissolution medium.

The values of the characterized dissolution time (τ) evidenced the promoted drug release from PS-T as compared to the reference (T) (Table 4). The τ value of PS-T, which was calculated from the slope and the intercept values after linearized regression and transformation of the Rosin-Rammler-Sperling-Bennett-Weibull distribution, is

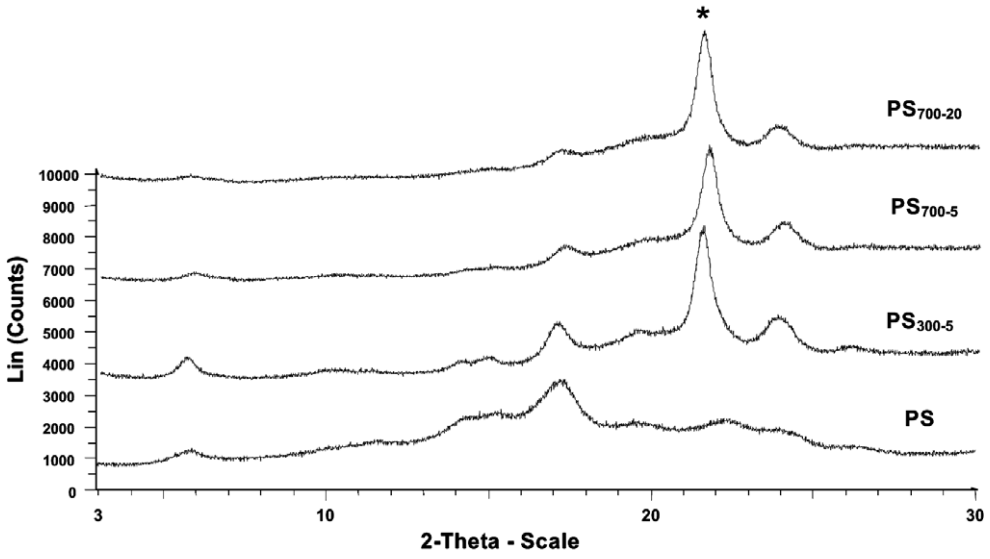

Fig. 5. X-ray curves of potato starch samples (*Peak of the sample protection foil).

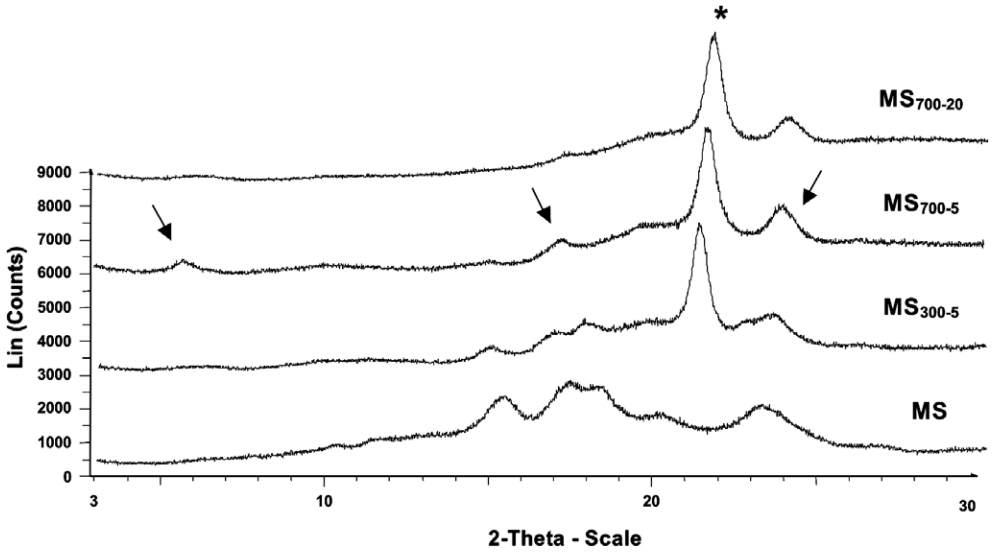

Fig. 6. X-ray curves of maize starch samples (*Peak of the sample protection foil).

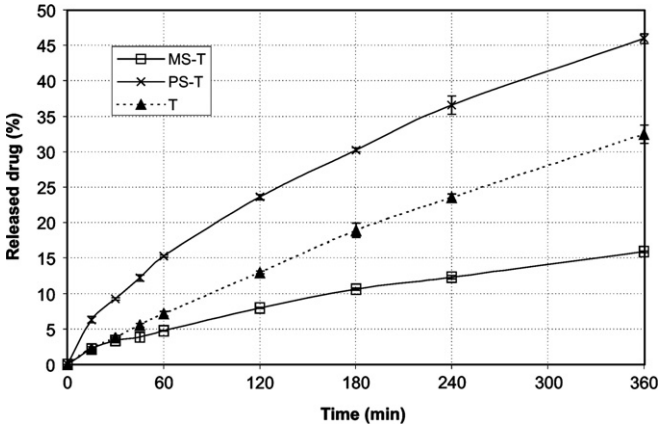

Fig. 7. Dissolution profile of theophylline from the gels (PS-T; MS-T) and the reference (T).

significantly smaller than those of the reference, while the characterized dissolution time of MS-T is more than seven times higher than the τ value of T.

On the basis of the obtained values of f_1 and f_2 (Table 5), the dissolution profiles of the gels can be considered different compared to each other and the reference.

According to the literature, the process of drug release in an aqueous medium is strongly influenced by the wettability of the sample's surface (Pepin, Blanchon, & Couarraze, 1999). The results of contact angle measurements shown in Table 6 confirmed that the gels containing starches as hydrophilic polysaccharides exhibit smaller contact angle values compared to the pure active drug substance. Smaller contact angles correspond to better wetting properties, which can contribute to the faster drug release from PS-T.

Table 2
Correlation coefficients of different kinetic equations

Sample	First-order kinetics	Higuchi model	Hixson–Crowell model	Korsmeyer–Peppas model
MS-T	0.9735	0.9468	0.9709	0.9943
PS-T	0.9867	0.9321	0.9922	0.9606
T	0.9990	0.9958	0.9976	0.9989

Table 3
Diffusional exponent (n) (Eq. (4)), diffusional (k_1) and relaxational (k_2) kinetic constants (Eq. (5)) and Pearson's coefficient (R^2) for MS-T

	n	R^2	k_1 [$h^{-0.475}$]	k_2 [$h^{-0.95}$]	R^2
MS-T	0.6351	0.9943	4.2088	0.3754	0.9987

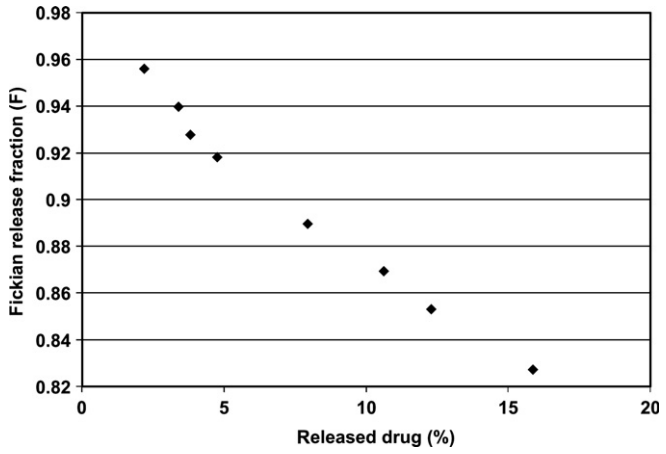

Fig. 8. Fickian release fraction (F) (Eq. (6)) as a function of released theophylline from MS-T.

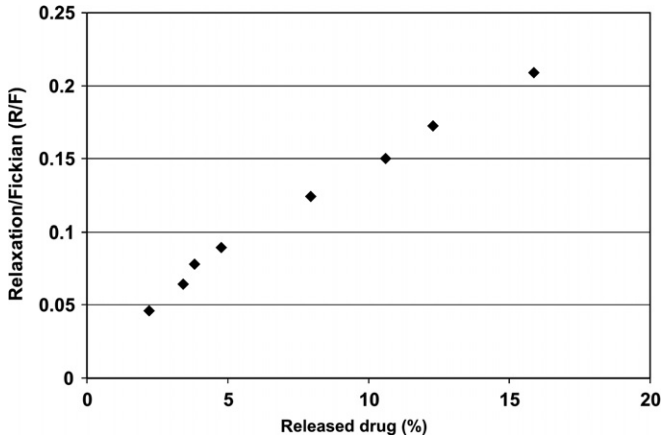

Fig. 9. Ratio between relaxational (R) and diffusional (F) contributions to release of theophylline from MS-T (Eq. (7)).

However, the improved wettability of MS-T did not result in promoted drug dissolution. Therefore, it is reasonable to assume that the sustained drug release from MS-T can be attributed to the changes in morphology and structure of the gel-forming polymer caused by IUHP processing.

Table 4
Parameters of rates of dissolution by RRSBW distribution

Sample	β shape parameter	τ value [min]	R^2
MS-T	0.6582	5324	0.9938
PS-T	0.7171	734	0.9982
T	0.9108	1023	0.9988

Table 5
Fit factor values obtained for the gels prepared by IUHP processing

Sample	Difference factor (f_1) [%]	Similarity factor (f_2)
MS-T/T	42.86	56.06
PS-T/T	68.25	51.86
MS-T/PS-T	66.04	30.47

Table 6
Contact angle of the samples measured with bidistilled water (Θ_{water})

Sample	Θ_{water} [°]
MS-T	16.12 ± 0.86
PS-T	16.73 ± 0.81
T	36.13 ± 2.22

4. Conclusion

IUHP treatment of potato and maize starch in presence of water generated highly viscous gels. The process was accompanied by the structural conversion of maize starch. The results of the morphological and structural studies carried out in this work were in good agreement with previous studies, which reported a difference in pressure sensitivity depending on the botanical origin of starch as one of the major benefits of pressure-induced gelatinization.

The profile of drug release from the gels prepared by IUHP processing could be characterized by different kinetics. The hydrogel containing potato starch as a gel-forming polymer exhibited faster drug dissolution compared to the aqueous theophylline suspension used as a reference, while the pressurization of maize starch resulted in a gel exhibiting sustained drug release. Our experimental results allow the conclusion that the morphological and structural changes caused by pressurization have a significant influence on the dissolution process.

The different pressure sensitivities of the starches permit the use of IUHP treatment as a selective non-conventional means of starch modification. The modified features of the pressurized starches might well promote their application in drug formulation and development.

Acknowledgements

This study was supported by the *German Academic Exchange Service* and the *Hungarian Scholarship Committee*, and by the *Hungarian National Research Foundation* (OTKA T-047166), for which the authors express their thanks.

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