Starch-based controlled release matrix tablets: impact of the type of starch

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Research article

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Abstract:

Different types of starches were used to prepare controlled release tablets loaded with diprophylline by direct compression. The impact of the natural origin of the starch, potential chemical modifications (e.g., cross-linking with phosphate or adipate, hydroxypropylation, acetylation to different degrees, partial hydrolysis) and type of pre-gelatinization process (laboratory scale with ethanol and oven drying versus industrial scale drum drying) on the resulting drug release kinetics were studied. Texture analysis of the hydrogels created upon exposure to the release medium, optical and scanning electron microscopy as well as X-ray powder diffraction measurements were used to better understand the observations. Also, a "quick test" using a texture analyzer to rapidly estimate the capacity of a specific starch type to control the resulting drug release rate was proposed. Two types of hydroxypropyl methylcellulose (HPMC K100M and K100 LV) were studied for reasons of comparison. Interestingly, the "quick test" allowed to detect differences in the mechanical strength of the hydrogels formed upon contact with aqueous fluids, which correlated well with the observed drug release patterns from tablets when measured using a USP III ("Bio'-Dis") apparatus at 30 rpm. However, diprophylline release was not very much affected by the investigated starch types when using a USP basket apparatus at 75 rpm. This can be attributed to the much lower mechanical stress experienced by the hydrogels under these conditions. Furthermore, caution must be paid when studying starch types, which are pre-gelatinized at the laboratory scale using ethanol precipitation and oven drying. The obtained starch granules can have significantly different key properties compared to granules obtained by industrial scale drum drying, resulting in substantially different drug release patterns.

Key words: Starch; controlled release; tablet; diprophylline; pre-gelatinization.

1. Introduction

Since decades starches are used as excipients in pharmaceutical dosage forms for different purposes [1-4], e.g. as disintegrants [5], bioadhesive excipients [6,7], binders for twin screw wet granulation [8], in wound dressings [9], in orally disintegrating tablets [10], in colon targeting systems [11–13], in abuse deterrent drug delivery systems [14], and as hydrophilic matrix formers in oral controlled release tablets [15-23], to mention just a few. Starches are renewable materials, biodegradable, biocompatible and abundantly available from different plant sources [24–26]. From a chemical point of view, starches are mainly composed of two homopolymers: *amylose* and *amylopectin*. Both are based on the same monomer: D-glucose. In the case of amylose, the D-glucose units are linked via α-(1,4) bonds, forming linear chains. In the case of amylopectin, the D-glucose units are also linked via α-(1,4) bonds, but in addition, the macromolecules are branched [via α-(1,6) bonds] [27,28]. The presence of numerous free hydroxyl groups renders starches hydrophilic. Different types of *native* starches, as well as a large variety of physically and chemically modified starches, are used in the pharmaceutical field [29,30].

A frequent *physical* modification of starches is "pre-gelatinization": This is a heat treatment which renders starches soluble in cold water. Native starch granules are semi-crystalline and do not dissolve in cold water. When heating an aqueous starch slurry above a critical temperature (which is characteristic for each starch type) ("cooking"), hydrogen bonds are weakened and the starch granules lose their structural integrity. This facilitates the imbibition of larger amounts of water and the granules substantially swell. The granular structure is destroyed and the crystallinity lost [27,31]. Different processes can be used to pre-gelatinize starches, including drum-drying [15,17,32], extrusion [15–17], spray drying [16,17,33,34], and oven drying [21,22,34–36]. At the industrial scale, drum drying is the most commonly applied technique. It has to be pointed out that the conditions during "cooking" and drying can substantially affect the inner and outer structure of the obtained pre-gelatinized starch particles and, thus, their key properties [37]. For example, oven drying is generally relatively slow so that the macromolecules have the possibility to re-associate, creating (again) a more ordered system via numerous hydrogen bonds: The starches partially re-crystallize. This phenomenon is also known as starch *retrogradation* [31]. It occurs more likely in the case of high amylose starches (because of their linear polymeric chains). Furthermore, many studies reporting on pre-gelatinized starches prepared at the laboratory scale add ethanol or acetone to the aqueous starch slurry after "cooking" to precipitate the starch and accelerate

the subsequent oven drying process [20,22,35,38–41]. This can also substantially alter the molecular arrangement of the polymeric systems and, hence, alter their key properties. Retrograded starches have been used as matrix formers in hydrophilic tablets for controlled drug delivery [38–40,42]. The increased polysaccharide crystallinity can lead to increased resistance towards gastro intestinal enzymes [23,43]. For example, Yoon and coworkers studied the effect of starch retrogradation of theophylline-loaded waxy maize starch tablets [42]. The retrogradation process was either isothermal or the temperature was altered in cycles. Generally, the retrogradation of the starch reduced the swelling of the matrix tablet, increased the density of the hydrogel formed upon contact with water and increased the enzymatic resistance of the system, especially in the case of retrograded starches prepared using temperature cycles [42].

Also a variety of *chemical* modifications are frequently used to adjust desired properties of starches for specific pharmaceutical applications, including cross-linking [41] and chemical substitutions with hydroxypropyl, carboxymethyl, aminoethyl, or acetyl groups [20,22,35,44–47]. Different cross-linking agents are used, such as epichlorohydrin, tripolyphosphate and sodium trimetaphosphate [28,48]. In addition, the *degree* of cross-linking can be varied [22,35,46,49]. Highly cross-linked starches are often used as disintegrants [50]. The introduction of acidic groups (e.g., upon carboxymethylation) can provide starches, which are sensitive to pH changes in the gastro intestinal tract [22]. Acetylation renders starches less hydrophilic, limiting system swelling and slowing down enzymatic degradation in biological fluids [51,52]. The chemical modification can be achieved upon reaction with acetic anhydride or vinyl acetate in the presence of alkaline catalyst (e.g., NaOH, KOH) [24], and be carried out in water or organic solvents. Moreover, the degree of substitution can have a significant impact on the properties of the starch type [51].

The aim of this study was to investigate the impact of the botanical origin of starches, the type of pre-gelatinization procedure (industrial scale drum drying versus laboratory scale oven drying following ethanol precipitation) as well as of the degree and type of cross-linking (with phosphate or adipate) and chemical substitution (hydroxypropylation and acetylation) on the resulting drug release kinetics from diprophylline-loaded matrix tablets.

2. Materials and Methods

2.1. Materials

Diprophylline fine powder (BASF, Ludwigshafen, Germany); modified starches produced at the industrial scale as listed in Table 1 as well as low and high viscosity potato dextrins (TACKIDEX® B167, TACKIDEX® B147) and native potato starch SUPRA NP (Roquette Frères, Lestrem, France); hydroxypropyl methylcellulose (HPMC, Methocel K100 LV and K100M; Stobec, Quebec, Canada); magnesium stearate (Baerlocher, Unterschleißheim, Germany); ethanol 96 % and acetonitrile (VWR, Fontenay-sous-Bois, France).

The spray-dried starches produced at the industrial scale (SD C100 and SD CR3010) were prepared as described in more detail by Pitchon et al. [53] and Schara et al. [54]. Briefly, an aqueous suspension (40 % w/w) of starch (native waxy and very highly cross-linked & medium hydropropylated waxy) was pumped at room temperature into the cooking chamber of a spray-cooking nozzle, in which it was exposed to steam water at about 155 °C and 150 Psi. After cooking, the suspension was spray-dried (inlet air temperature = 190 °C, outlet air temperature = 95 °C). Under the given conditions, the starches were fully pre-gelatinized (e.g., no polarization crosses were observable by optical microscopy).

In addition to the starches listed in Table 1, a *laboratory-scale* batch of *pre-gelatinized* potato starch was produced as follows: An aqueous slurry of CLEARAM® PI10 starch powder in purified water (10 %, w:w) was heated to 85 °C in a beaker and stirred for 30 min at 4000 rpm (Eurostar power-b; Ika, Staufen, Germany) to gelatinize the starch. Afterwards, the temperature was decreased to 45 °C (during 10 min). Then, the starch was precipitated adding the same volume of 96 % ethanol, followed by centrifugation for 15 min at 8000 rpm (Sigma™ 3-15; Thermo Scientific™; Illkirch, France). The precipitate was dried in an oven (Air Concept; Froilabo, Meyzieu, France) at 45 °C overnight, and subsequently ground with a laboratory universal grinding mill for 2 min at 20000 rpm (M 20 Ika ®, Staufen, Germany). The obtained powder was passed through a 250 µm sieve (Fritsch, Idar-Oberstein, Germany).

The trademark sign used for a starch type in this article indicates that it is commercially available (being a registered product of Roquette Frères).

2.2. Tablet preparation

Tablets were prepared by direct compression. Diprophylline 30 % (w:w) was manually blended with starch or HPMC powder in a mortar with a pestle. The obtained mixture was passed through a 250 µm sieve (Fritsch, Idar-Oberstein, Germany), followed by further blending in a Turbula mixer (Bachofen AG, Basle, Switzerland) at 49 rpm for 5 min. Upon addition of magnesium stearate (1 %, w/w), the powder blend was further mixed for 3 min at 49 rpm. Cylindrical tablets (400 mg) were prepared with a single-punch rotary press simulator (Stylcam 200R; Medelpharm, Bynost, France) (flat-faced punches, diameter = 10 mm, manual die filling). The hardness of the tablets was kept constant at 100 N, measured with a tablet hardness tester (Pharmatron SmartTest 50, Sotax, Basle, Switzerland). The tablet dimensions were determined using a micrometer gauge (Digimatic Micrometer; Mitutoyo, Tokyo, Japan).

2.3. In vitro drug release measurements

Drug release was measured using the following experimental set-ups:

USP apparatus I (basket):

The USP apparatus I (AT7 Smart; Sotax) was used at 75 rpm and 37 °C. The release medium was 900 mL 0.1 N HCl or phosphate buffer pH 6.8 (USP 43). At predetermined time points, 5 mL samples were withdrawn (replaced with fresh medium), filtered (PTFF syringe filters, 0.22 µm; GE Healthcare, Kent, UK) and analyzed for their diprophylline content by HPLC-UV, using a method adapted from Hsein et al., 2017: A Waters e2695 apparatus (Waters, Milford, USA), equipped with a UV/Vis detector (λ= 274 nm) and reversed-phase column C18 (Luna Polar 3 µm; 4.8 mm x 150 mm, 30 °C; Phenomenex, Le Pecq, France) were used. The mobile phase was a 90:10 (v/v) blend of 0.01 M acetate buffer pH 4.5: acetonitrile. The flow rate was 1 mL/min. The injection volume was 5 µL.

USP apparatus II (paddle):

The USP apparatus II (AT7 Smart; Sotax) was used at 75 rpm and 37 °C with stainless helix sinkers (diameter = 12 mm; Air Liquide welding, Cergy Pontoise, France). The release medium was 900 mL phosphate buffer pH 6.8 (USP 43). At pre-determined time points, 5 mL samples were withdrawn (replaced with fresh medium), filtered using a blunt fill needle (5 µm FINE-JECT®; VWR) and analyzed for their diprophylline content by UV spectrophotometry (λ= 274 nm; UV-1650 PC; Shimadzu, Kyoto, Japan).

USP apparatus III (Bio-Dis):

The USP apparatus III (Agilent Technologies, Massy, France) was used at 20 or 30 dpm, as indicated. The release medium was 900 mL 0.1 N HCl or phosphate buffer pH 6.8 (USP 43). At predetermined time points, 5 mL samples were withdrawn (replaced with fresh medium), filtered (PTFF syringe filters, 0.22 µm; GE Healthcare), and their drug content was measured using HPLC-UV as described above.

All experiment were conducted in triplicate, mean values +/- standard deviations are reported.

2.4. Scanning electron microscopy

Images were recorded with a Quanta™ 200 FEG scanning electron microscope (SEM) (Thermo Scientific™, Waltham, Massachusetts, USA). Samples were deposited on aluminum stubs and covered with conductive carbon tape. The electron accelerating voltage was 12.5 kV.

2.5. X-ray powder diffraction analysis

X-ray powder diffraction analysis was conducted with a D8 ADVANCE diffractometer (Bruker AXS, Karlsruhe, Germany), equipped with a monochromatic radiation (CuKα = 1.5418 Å). Approximately 5 mg samples were packed tightly in a silicon cavity holder. The samples were exposed to the X-Ray generator running at 40 kV and 25 mA and scanned over a range of 2θ = 5-60 ° with a step interval of 0.02 ° and a scanning rate of 0.1 s/step. The measurements were performed in reflection mode with a LYNXEYE-XE-T detector (Bruker AXS).

2.6. Texture analysis

A texture analyzer (TA.XT.Plus; Stable Micro Systems, Surrey, UK, load cell: 50 kg) equipped with a cylindrical (flat-ended) probe (6 mm: diameter) was used to prepare "compacts" of the investigated polysaccharides (without drug) as follows (also illustrated at the top of Figure 1): The bottom of the barrel of a 5 mL syringe (Terumo™ Three-Part Syringe, Thermo Scientific™) was cut to obtain an open cylinder. The syringe was placed into a 7 mL round-base plastic tube (marked in blue in Figure 1) (Gosselin™; Thermo Scientific™), containing 350 mg starch or HPMC powder (marked in grey). The plunger was driven downwards at 1 mm/s until a force of 500 N was reached to compress the powder, and then driven upwards again at the same speed. The resulting "compacts" trapped in the the barrel, were placed in 10 mL glass vials

(Thermo Scientific™) filled with 8 mL 0.1 N HCl for 4 h. The vials were covered with parafilm (PARAFILM® M; VWR) to prevent evaporation and horizontally shaken at 80 rpm at 37 °C (GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany).

To evaluate the gel strength of the compact (upon removal from the syringe) after 4 h exposure to the release medium, a method adapted from Herman et al., 1989 [16] was used (schematically illustrated at the bottom of Figure 1). A spherical probe (5 mm diameter) was driven downwards at a speed of 0.1 mm/s with a texture analyzer (TA.XT.Plus; load cell: 1 kg). Once in contact with the gel, the applied force was recorded as a function of time. When the probe reached a penetration depth of 2 mm, it was again completely driven upwards at 0.1 mm/s. This is considered as "first compression cycle". After 15 s rest, a "second compression" cycle was run. The diagram at the bottom on the right-hand side of Figure 1 shows a typical force-time record. The *hardness of the gel* is defined as the maximum force measured during the first compression cycle. The *cohesiveness* of the gel is defined as the ratio of the positive force-time area measured during the second compression cycle (A2) to the positive force-time area measured during the first compression cycle (A1) (being dimensionless).

$$\text{Cohesiveness} = \frac{A2}{A1}$$

All experiments were performed 6 times, mean values +/- standard deviations are reported.

2.7. Optical microscopy

Starch granules were observed using a Leica DM RB light microscope (Leica Mikrosysteme, Wetzlar, Germany) before and after exposure to distilled water (70 °C) for 5 min, optionally followed by heating in a microwave (30 s, 850 Watt). A 5 % (w/w) starch dispersion optionally containing iodine for staining (2 mg/mL iodine and 20 mg/mL potassium iodide) was studied.

3. Results and Discussion

3.1. Impact of the botanical origin of the starch

Figure 2 illustrates the diprophylline release profiles from matrix tablets based on pre-gelatinized, chemically non-modified pea starch (*PREGEFLO® L100*), potato starch (*PREGEFLO® P100*) and waxy maize starch (*PREGEFLO® C100*), respectively. Pre-gelatinization and subsequent drying were performed in a drum in all cases (Table 1). The drug loading was kept at 30 %. The release medium was phosphate buffer pH 6.8, the USP apparatus II (paddle) was used with helix sinkers. As it can be seen, the following ranking order was observed with respect to the resulting drug release rate: pea starch > potato starch > waxy maize starch. This order correlates well with the amylose content of these starches: 34 % > 20 % > 0 % (the amylopectin content is increasing accordingly: 66 % < 80 % < 100 %). This is consistent with reports in the literature [17]. But not only the amylose/amylopectin ratio, also other differences (e.g., structural differences) of the investigated starch types might be responsible for the observed differences in the resulting diprophylline release kinetics [22].

3.2. Impact of chemical substitution and cross-linking

The impact of the type and degree of chemical substitution (acetylation and hydroxypropylation; none, extremely low, low, medium, high) and of the type and degree of cross-linking with phosphate or adipate (none, low, medium, highly, very highly) on diprophylline release from starch-based matrix tablets in phosphate buffer pH 6.8 is illustrated in Figure 3 (USP apparatus II, helix sinkers). The following starch types were studied: a) pre-gelatinized potato starch with a medium level of acetylation and a medium, high or very high cross-linking degree (cross-linked with phosphate) (*PREGEFLO® PJ10, PREGEFLO® PJ20, PREGEFLO® PJ30*), b) pre-gelatinized waxy maize starch with a medium cross-linking degree (cross-linked with adipate) and an extremely low level of acetylation (*PREGEFLO® CH10*) or a high cross-linking degree (cross-linked with adipate) and a low level of acetylation (*PREGEFLO® CH20*), and c) pre-gelatinized waxy maize starch with a high level of hydroxypropylation and a low cross-linking degree (cross-linked with phosphate) (*Pregel CR0820*), a medium level of hydroxypropylation and a very high cross-linking degree (cross-linked with phosphate) (*Pregel CR3010*) or a high level of hydroxypropylation and a very high cross-linking degree (cross-linked with phosphate) (*Pregel CR3020*). For reasons of comparison, also drug release

from matrix tablets based on the respective pre-gelatinized, *chemically non-modified* starches are shown (*PREGEFLO® P100* and *PREGEFLO® C100*).

Roughly, cross-linking had a much more pronounced effect on drug release than acetylation or hydroxypropylation in the investigated cases, irrespective of the type of cross-linking (using phosphate or adipate). The higher the degree of starch cross-linking, the faster was drug release. This might at least in part be explained by the action of the cross-linked starches as disintegrants: The molecules are hydrophilic, but cannot dissolve due to the cross-linking. Thus, they take up substantial amounts of water and swell considerably, which favors disintegration. If they were not cross-linked, they would start dissolving, instead of continuing to swell. This was visually confirmed: With increasing cross-linking degree the tablets disintegrated more rapidly. This is also consistent with reports in the literature, e.g. [35].

3.3. Impact of partial starch hydrolysis

The impact of partial starch hydrolysis on diprophylline release from matrix tablets based on pre-gelatinized pea starch with a high level of hydroxypropylation is illustrated in Figure 4. The tablets were exposed to 0.1 N HCl for 2 h, followed by phosphate pH 6.8 for 6 h using: a) the USP apparatus I (75 rpm), or b) USP apparatus III (30 dpm). The crosses indicate partially hydrolyzed starch (*Pregel LKB020*), the black circles non-hydrolyzed starch (*Pregel LK020*). As it can be seen, under the given conditions there is a small to moderate impact on drug release: The partial hydrolysis leads to a decrease in the polymer molecular weight of the starch and, thus, less entangled networks. This results in slightly faster drug release, irrespective of the experimental setup.

3.4. Pre-gelatinization: Drum drying versus spray drying

Native starches do not extensively swell in cold water [17]. The process of pre-gelatinization is used to render starches swellable in cold water, so that a hydrogel can be formed to control drug release. Figure 5 visualizes this process: Microscopic pictures of native potato starch granules (Potato starch SUPRA NP) are shown before and after exposure to hot (70 °C) water. The photos on the left-hand side were obtained using normal light and iodine staining, the photos on the right-hand side were obtained using polarized light without staining. The top row shows raw granules, the middle row granules after 5 min exposure to hot water, the

bottom row after 5 min exposure to hot water and subsequent heating in a microwave (30 s, 850 Watt). The Maltese crosses which can be observed under polarized light in the raw granules clearly indicate crystalline regions. The latter completely disappear during the pre-gelatinization process. Upon exposure to hot water, the granules substantially swell and disintegrate. The degree of granule transformation depends on the pre-gelatinization conditions. Obviously, this process can affect the inner structure of starch-based tablets and, hence, the resulting drug release kinetics.

Figure 6 illustrates the impact of the type of pre-gelatinization procedure (*drum drying* versus *spray drying*) on drug release from tablets based on chemically non-modified starches or based on highly cross-linked (phosphate) and medium hydroxypropylated starches. The USP apparatus II (paddle with helix sinkers) was used. The release medium was phosphate buffer pH 6.8, the diprophylline loading was 30 %. It has to be pointed out that in all cases the pre-gelatinization process was complete (e.g., no polarization crosses were visible using light microscopy). As it can be seen, the spray-dried starches (dashed curves) showed faster drug release than the drum dried starches (solid curves) in the investigated cases. Please note that diprophylline release from highly cross-linked (phosphate) medium hydroxypropylated drum-dried starch was much faster than from the respective chemically non-modified drum-dried starch (Figure 6). This confirms the above discussed impact of starch cross-linking on drug release. In the case of spray-drying, drug release from the chemically non-modified starch was slightly faster than from the respective highly cross-linked, medium hydroxypropylated starch, but these differences were not very pronounced and drug release was rapid in all cases.

3.5. Pre-gelatinization: Laboratory scale versus industrial scale

It is difficult to simulate the conditions encountered during pre-gelatinization of large amounts of starch at the industrial scale using only small amounts of starch at the laboratory scale. Often, an aqueous starch slurry is simply heated in a beaker to gelatinize the polysaccharide and then cooled. Upon ethanol addition, the starch is precipitated, generally followed by oven drying [20, 22, 35]. However, the properties of the obtained product can be very different from those of the same starch slurry dried in an industrial scale drum, without adding ethanol. In this study, a medium cross-linked (phosphate) potato starch (*CLEARAM® PI10*) was pre-gelatinized at the laboratory scale by heating an aqueous slurry to 85 °C for 30 min, followed by cooling to 45 °C, the addition of 96 % ethanol, centrifugation, oven drying at 45 °C (overnight), grinding and

sieving. This laboratory scale pre-gelatinized starch was compared to *PREGEFLO ® PI10*: the equivalent starch product that is pre-gelatinized in a drum at the industrial scale. Figure 7 shows diprophylline release from tablets based on these two starch types in 0.1 N HCl for 2 h, followed by 6 h in phosphate buffer pH 6.8. The USP basket apparatus was used at 75 rpm. As it can be seen, drug release was rapid from tablets based on the lab-scale starch, whereas it was sustained in the case of the industrial scale starch.

To better understand the observed differences, SEM pictures were taken from the different starch particles as well as from starch granules that were not pre-gelatinized, for reasons of comparison. Furthermore, X-ray powder diffractions patterns were recorded of the two starch types. As it can be seen at the top of Figure 8, the non-gelatinized starch granules were round/oval shaped and relatively small-sized. The oval shape and small size were both lost upon pre-gelatinization at the laboratory scale (Figure 8, middle row): Structures similar to "rocks" are visible, as well as the presence of some granules similar to those observed in non-gelatinized starch (highlighted by the dotted red circles). This suggests that the laboratory scale starch was not fully pre-gelatinized or that it has been retrograded during oven drying at 45 °C. In contrast, the industrial scale, drum dried starch is characterized by irregular, more or less flat plates, the initial granular structure being lost (Figure 8, bottom row). It has been reported that this morphology is typical for starches produced by roll drying or drum drying [55]. These observations are consistent with the X-ray diffraction patterns of the two starch types shown in Figure 9: The pre-gelatinized starch produced via drum drying at the industrial scale is completely amorphous, whereas a few clear diffraction peaks are visible in the case of the pre-gelatinized starch produced at the laboratory scale, indicating the presence of crystalline regions. Thus, this starch was not fully gelatinized or retrograded during oven drying. Hence, caution should be paid when gelatinizing starches at the laboratory scale and drawing conclusions to the performances of the obtained product, e.g. with respect to its capacity to slow down drug release.

3.6. A "quick test" to estimate gel properties and drug release

In order to provide rapid feedback on the drug release kinetics from a specific type of starch-based tablets, a "quick test" as described in the following was applied: As illustrated in Figure 1, a texture analyzer was used to prepare "compacts" based on different starch types. Briefly, 350 mg starch powder were compacted with a syringe barrel in a plastic tube, applying a force of up to 500 N. For reasons of comparison, also HPMC K100LV and K100M compacts were prepared using this set-up. The compacts were exposed to 0.1 N HCl at

37 °C for 4 h (under horizontal agitation at 80 rpm). At pre-determined time points, samples were withdrawn and a texture analyzer was used to drive a spherical probe into the wetted compact. When the probe reached a penetration depth of 2 mm, it was again driven upwards. After 15 s rest, a second "compression cycle" of this type was run. The forces were recorded as a function of time, as shown in Figure 1. The *hardness of the gel* was defined as the maximum force measured during the first "compression cycle". The *cohesiveness* of the gel was defined as the ratio of the positive force-time area measured during the second "compression cycle" (A2) to the positive force-time area measured during the first "compression cycle" (A1).

The diagram at the top of Figure 10 shows the hardness of compacts based on different types of starches and HPMC. Clearly, major differences were observed: HPMC K100M-based compacts exhibited the highest hardness values, "closely" followed by systems based on medium cross-linked potato starch. Compacts based on HPMC K100LV exhibited an "intermediate" hardness value, whereas all other investigated starches led to much lower hardness values. Thus, it might be expected that tablets based on HPMC K100M and medium cross-linked potato starch might slow down drug release more effectively than other starch types, which lead to compacts with low hardness, e.g. chemically non-modified waxy maize starch. However, when diprophylline was measured using the USP I basket apparatus at 75 rpm in phosphate buffer pH 6.8, the release profiles were rather similar for all the investigated polysaccharide types. But when measuring drug release from the same tablets using the USP III apparatus ("Bio-Dis") at 30 dpm, substantial differences in the release rates were observed, which correlated well with the measured hardness values of the compacts: For example, diprophylline was slowest from tablets based on HPMC K100M and medium cross-linked potato starch, and fastest from tablets based on chemically non-modified waxy maize starch. This indicates that the differences in the mechanical strength of the hydrogels that are formed upon contact with aqueous fluids only become important upon exposure to a minimal mechanical stress. In vivo, hydrogel based controlled release tablets are exposed to mechanical stress, due to the motility of the gastro intestinal tract. It can be expected that drug release is likely less variable from hydrogels which are mechanically more stable. If the hydrogel disintegrates into smaller pieces, the diffusion pathway lengths are shortened and drug release is accelerated.

In contrast, the measured cohesiveness values of the hydrated compacts was not very much affected by the polysaccharide type (diagram at the bottom of Figure 10). These values are more consistent with the observed drug release patterns under less mechanical stress (USP basket apparatus, 75 rpm), as discussed above.

3.7. Starch:dextrin blends

Blending different types of polymeric matrix formers can be an efficient means to adjust desired drug release kinetics [56,57]. Since dextrins are water-soluble, diprophylline release from purely dextrin-based tablets can be expected to be very fast. On the other hand, diprophylline release from tablets based on chemically non-modified potato starch (*PREGEFLO ® P100*) is slow (e.g., less than 75 % drug is released after 8 h exposure to 0.1 N HCl/phosphate buffer pH 6.8: crosses in Figure 11). The idea was to blend this chemically non-modified potato starch with two types of potato dextrins (a low viscosity grade: *Tackidex® B167* and a high viscosity grade: *Tackidex® B147*) to provide potentially intermediate drug release rates. The dashed curves in Figure 11 show the resulting diprophylline release kinetics from tablets based on 50:50 starch:dextrin blends in 0.1 N HCl, followed by phosphate buffer pH 6.8. As it can be seen, drug release was rapid in both cases, thus, the water-soluble dextrins were dominant, at least at this blend ratio.

4. Conclusion

The obtained insight on the importance of the type of starch (botanical origin, potential chemical modification, type and scale of the pre-gelatinization process) on the resulting drug release kinetics from matrix tablets can help facilitating the development of novel advanced drug delivery systems of this type. For example, caution should be paid when studying pre-gelatinized starches prepared at the laboratory scale using ethanol and oven drying: Their key properties can be different from those obtained upon drum drying at the industrial scale, leading to substantially different drug release rates.

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Conflicts of interests

Some of the co-authors of this article are employees of the company Roquette, commercializing several of the investigated starch derivatives. The Editor-in-Chief of the journal is one of the co-authors of this article. The manuscript has been subject to all of the journal's usual procedures, including peer review, which has been handled independently of the Editor-in-Chief.

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Table 1:

Investigated starches produced at the industrial scale. *Drum dried*: simultaneous cooking and drying of the starch slurry in a drum. *Spray dried*: spray drying of the starch slurry. Maize starches were "waxy" (cut granules having a waxy appearance), containing > 99% amylopectin. The trademark sign indicates that the products are commercially available. The other starch types were also produced at the industrial scale, but are currently not for sale. Pregel L KB020 is partly hydrolyzed Pregel L K020.

Origin	**Pre-gelatinization & drying process**	**Chemical modifications**		**Name**
		Cross-linking: Agent; Degree	**Substitution: Type; Degree**	
Maize (waxy)	Drum drying	Not modified		PREGEFLO® C100
	Spray drying	Not modified		SD C100
	Drum drying	Adipate; Medium	Acetylation; Extremely low	PREGEFLO® CH10
	Drum drying	Adipate; High	Acetylation; Low	PREGEFLO® CH20
	Drum drying	Phosphate; Low	Hydroxypropylation; High	Pregel CR0820
	Drum drying	Phosphate; Very high	Hydroxypropylation; Medium	Pregel CR3010
	Drum drying	Phosphate; Very high	Hydroxypropylation; High	Pregel CR3020
	Spray drying	Phosphate; Very high	Hydroxypropylation; Medium	SD CR3010
Potato	Drum drying	Not modified		PREGEFLO® P100
	Drum drying	Phosphate; Medium	No	PREGEFLO® PI10
	Drum drying	Phosphate; Medium	Acetylation; Medium	PREGEFLO® PJ10
	Drum drying	Phosphate; High	Acetylation; Medium	PREGEFLO® PJ20
	Drum drying	Phosphate; Very high	Acetylation; Medium	PREGEFLO® PJ30
	None	Phosphate; Medium	No	CLEARAM® PI10
Pea	Drum drying	Not modified		PREGEFLO® L100
	Drum drying	No	Hydroxypropylation; High	Pregel L K020
	Drum drying	No	Hydroxypropylation; High	Pregel L KB020

Figure captions

Fig. 1 Schematic presentation of the set-ups used to prepare "compacts" of the investigated starches and HPMC and to determine the mechanical key properties of the gels formed upon "compact" swelling in 0.1 N HCl for 4 h. The diagram shows a typical force-time measurement during 2 compression cycles. Details are described in the text.

Fig. 2 Influence of the botanical origin of the starch type (pre-gelatinized, chemically non-modified starches: *PREGEFLO ® L100, PREGEFLO ® C100* and *PREGEFLO ® P100*) on diprophylline release from matrix tablets in phosphate buffer pH 6.8. The USP apparatus II with helix sinkers was used. Mean values ± standard deviations are indicated (n=3).

Fig. 3 Impact of cross-linking and substitution: Diprophylline release in phosphate buffer pH 6.8 from matrix tablets based on: a) pre-gelatinized potato starch with a medium level of acetylation and a medium, high or very high cross-linking degree (phosphate) (*PREGEFLO ® PJ10, PREGEFLO ® PJ20, PREGEFLO ® PJ30*), b) pre-gelatinized waxy maize starch with a medium cross-linking degree (adipate) and an extremely low level of acetylation (*PREGEFLO ® CH10*) or a high cross-linking degree (adipate) and a low level of acetylation (*PREGEFLO ® CH20*), and c) pre-gelatinized waxy maize starch with a high level of hydroxypropylation and a low cross-linking degree (phosphate) (*Pregel CR0820*), a medium level of hydroxypropylation and a very high cross-linking degree (phosphate) (*Pregel CR3010*) or a high level of hydroxypropylation and a very high cross-linking degree (phosphate) (*Pregel CR3020*). For reasons of comparison, also drug release from matrix tablets based on the respective pre-gelatinized *chemically non-modified* starches is shown (*PREGEFLO ® P100* and *PREGEFLO ® C100*). The USP apparatus II with helix sinkers was used. Mean values ± standard deviations are indicated (n=3).

Fig. 4 Impact of partial starch hydrolysis: Diprophylline release in 0.1 N HCl for 2 h, followed by phosphate pH 6.8 for 6 h from matrix tablets based on a pre-gelatinized pea starch with a high level of hydroxypropylation: Non-hydrolyzed (*Pregel LK020*) or partially hydrolyzed (under acidic conditions) (*Pregel LKB020*). Two different drug release apparatuses were used: a) the USP

apparatus I, 75 rpm, and b) the USP apparatus III, 30 dpm. Mean values ± standard deviations are indicated (n=3).

Fig. 5 Microscopic pictures of native potato starch granules (*Potato starch SUPRA NP*): a) before exposure to water (70 °C), b) after 5 min exposure to water (70 °C), and c) after 5 min exposure to water (70 °C) and subsequent heating in a microwave (30 s, 850 Watt). Normal light and iodine staining (left column) or polarized light without staining (right column) was used.

Fig. 6 Impact of pre-gelatinization technique: Diprophylline release in phosphate pH 6.8 from matrix tablets based on *drum dried* pre-gelatinized chemically non-modified waxy maize starch (*PREGEFLO ® C100*) or *drum dried* pre-gelatinized waxy maize starch with a very high level of cross-linking (phosphate) and medium degree of hydroxypropylation (*Pregel CR3010*), or the respective *spray-dried* starches (*SD C100 and SD CR3010*). The USP apparatus II with helix sinkers was used. Mean values ± standard deviations are indicated (n=3).

Fig. 7 Pre-gelatinization at the laboratory versus the industrial scale: Diprophylline release from tablets based on medium cross-linked (phosphate) potato starch (*CLEARAM ® PI10*) upon pre-gelatinization at the laboratory scale or based on the equivalent starch product pre-gelatinized at the industrial scale (drum drying) (*PREGEFLO ® PI10*). The USP apparatus I was used. The release medium was 0.1 N HCl for the first 2 h, followed by phosphate pH 6.8 for the subsequent 6 h. Mean value ± standard deviations are indicated (n=3)

Fig. 8 SEM pictures of: a) non-gelatinized, medium cross-linked (phosphate) potato starch particles (*CLEARAM ® PI10*), b) pre-gelatinized starch particles obtained at the laboratory scale upon heating an aqueous slurry of a medium cross-linked (phosphate) potato starch (*CLEARAM ® PI10*), cooling, addition of ethanol and oven drying, and c) pre-gelatinized starch particles (PREGEFLO ® PI10) obtained at the industrial scale upon drum drying of an aqueous slurry of medium cross-linked (phosphate) potato starch.

Fig. 9 X-ray diffraction patterns of pre-gelatinized starch obtained at the laboratory scale upon heating an aqueous slurry of a medium cross-linked (phosphate) potato starch (*CLEARAM ® PI10*), cooling, addition of ethanol and oven drying, and pre-gelatinized starch particles (*PREGEFLO ® PI10*) obtained at the industrial scale upon drum drying of an aqueous slurry of medium cross-linked (phosphate) potato starch.

Fig. 10 Results obtained with a "quick test" to estimate the capacity of different starch types (*PREGEFLO ® C100, Pregel CR0820, PREGEFLO ® CH10, Pregel LK020, Pregel LKB020, PREGEFLO ® P100, PREGEFLO ® PI10, PREGEFLO ® PJ10*) to control drug release from diprophylline matrix tablets. For reasons of comparison also HPMC K100LV and HPMC K100M were used as matrix formers. The impact of the type of polysaccharide on the strength and the cohesiveness of the hydrogel formed upon 4 h exposure of a compact to 0.1 N HCl are shown at the top and bottom, respectively. In the middle, the drug release rates measured using the USP I basket apparatus (75 rpm) and USP III apparatus ("Bio-Dis") from tablets are shown in 2 h 0.1 N HCl and 6 h phosphate buffer pH 6.8. Mean value ± standard deviations are indicated (n = 6 for hardness and cohesiveness measurements, n = 3 for drug release measurements).

Fig. 11 Diprophylline release from tablets based on 50:50 blends of chemically non-modified potato starch (*PREGEFLO ® P100*) and low or high viscosity potato dextrins (*Tackidex® B167* and *Tackidex® B147*). The USP apparatus I was used. Mean value ± standard deviations are indicated (n=3).

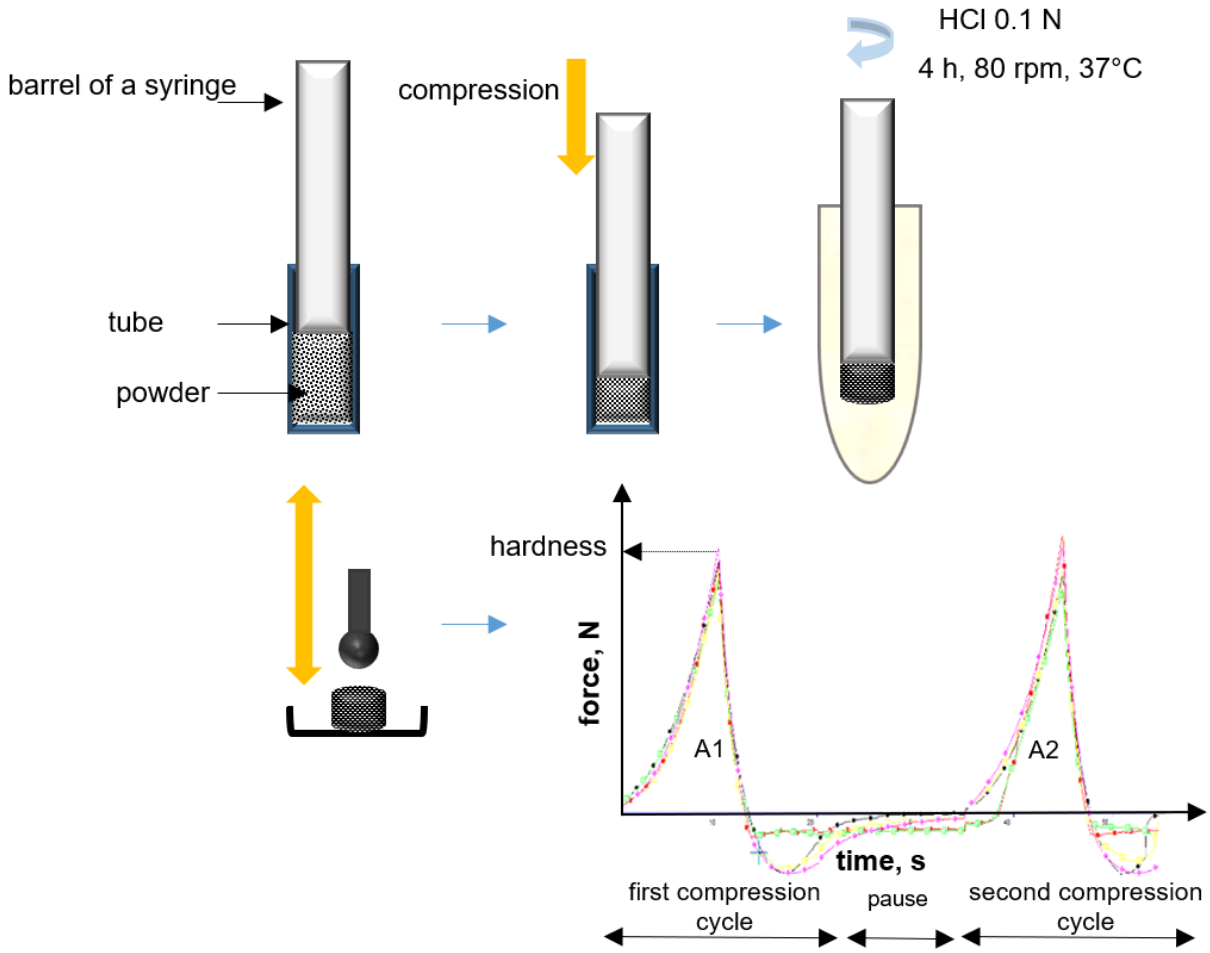

barrel of a syringe
compression
HCl 0.1 N
4 h, 80 rpm, 37°C
tube
powder
hardness
force, N
A1
A2
time, s
first compression cycle
pause
second compression cycle

Figure 1

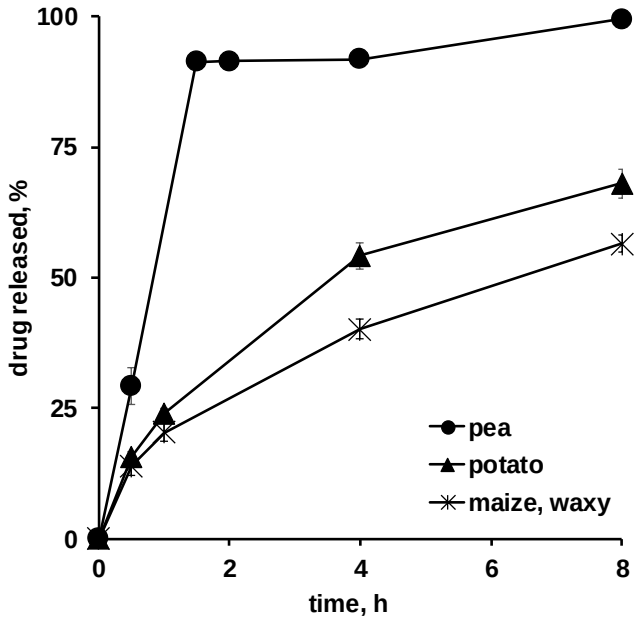
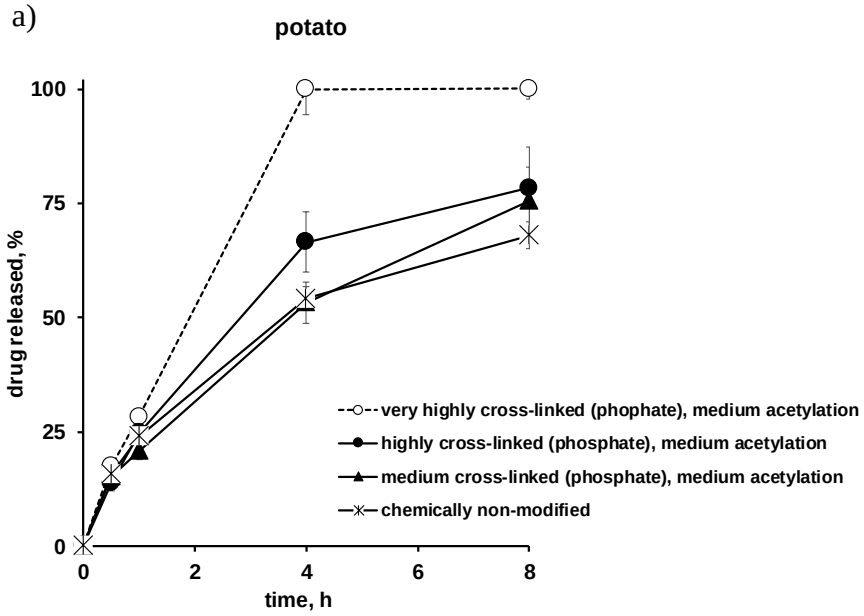
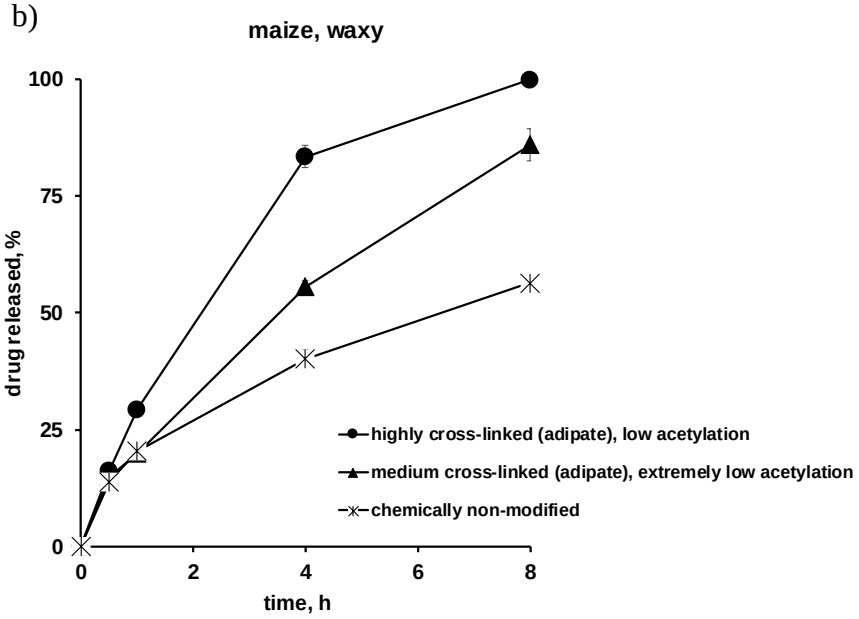

100
75
50
25
0
drug released, %
0
2
4
6
8
time, h
pea
potato
maize, waxy

Figure 2

a)


potato
drug released, %
time, h
very highly cross-linked (phophate), medium acetylation
highly cross-linked (phosphate), medium acetylation
medium cross-linked (phosphate), medium acetylation
chemically non-modified

b)


maize, waxy
drug released, %
time, h
highly cross-linked (adipate), low acetylation
medium cross-linked (adipate), extremely low acetylation
chemically non-modified

c)

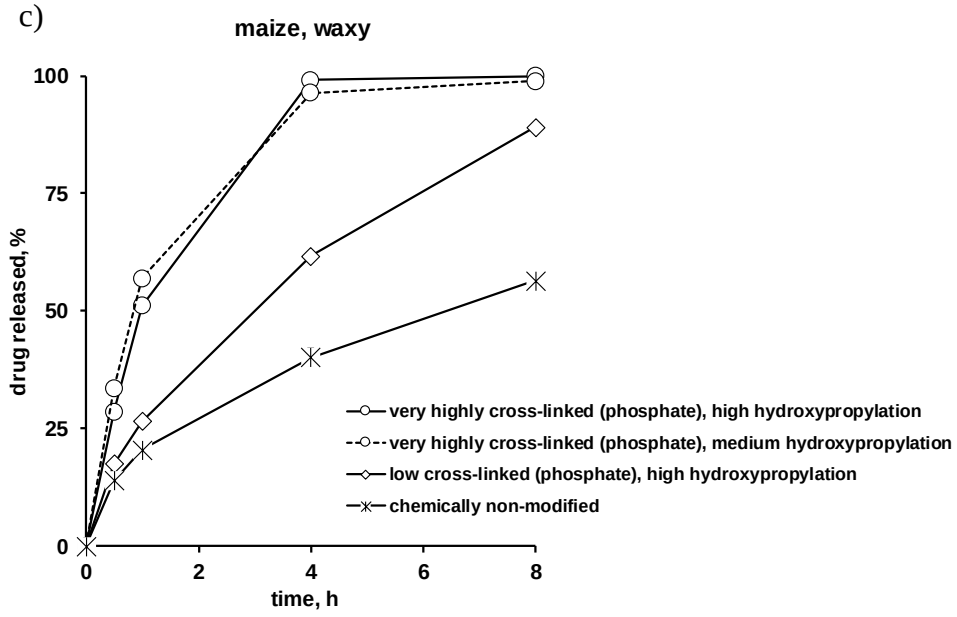

maize, waxy
drug released, %
time, h
very highly cross-linked (phosphate), high hydroxypropylation
very highly cross-linked (phosphate), medium hydroxypropylation
low cross-linked (phosphate), high hydroxypropylation
chemically non-modified

Figure 3

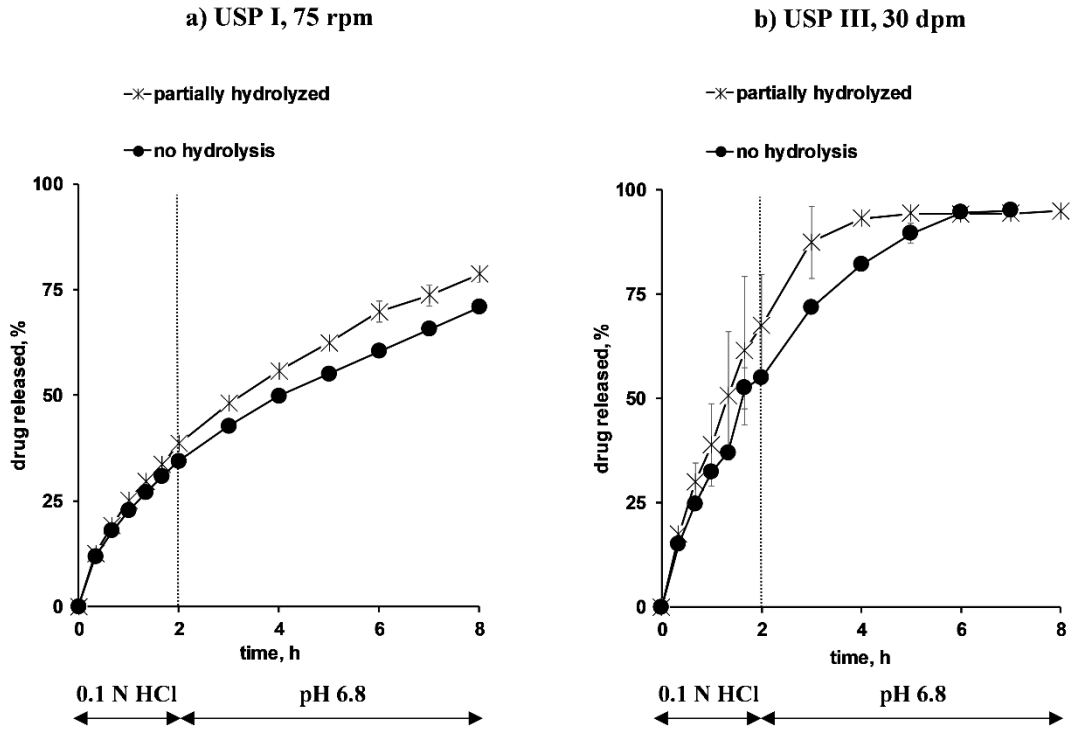

a) USP I, 75 rpm
b) USP III, 30 dpm
partially hydrolyzed
no hydrolysis
drug released, %
time, h
0.1 N HCl
pH 6.8

Figure 4

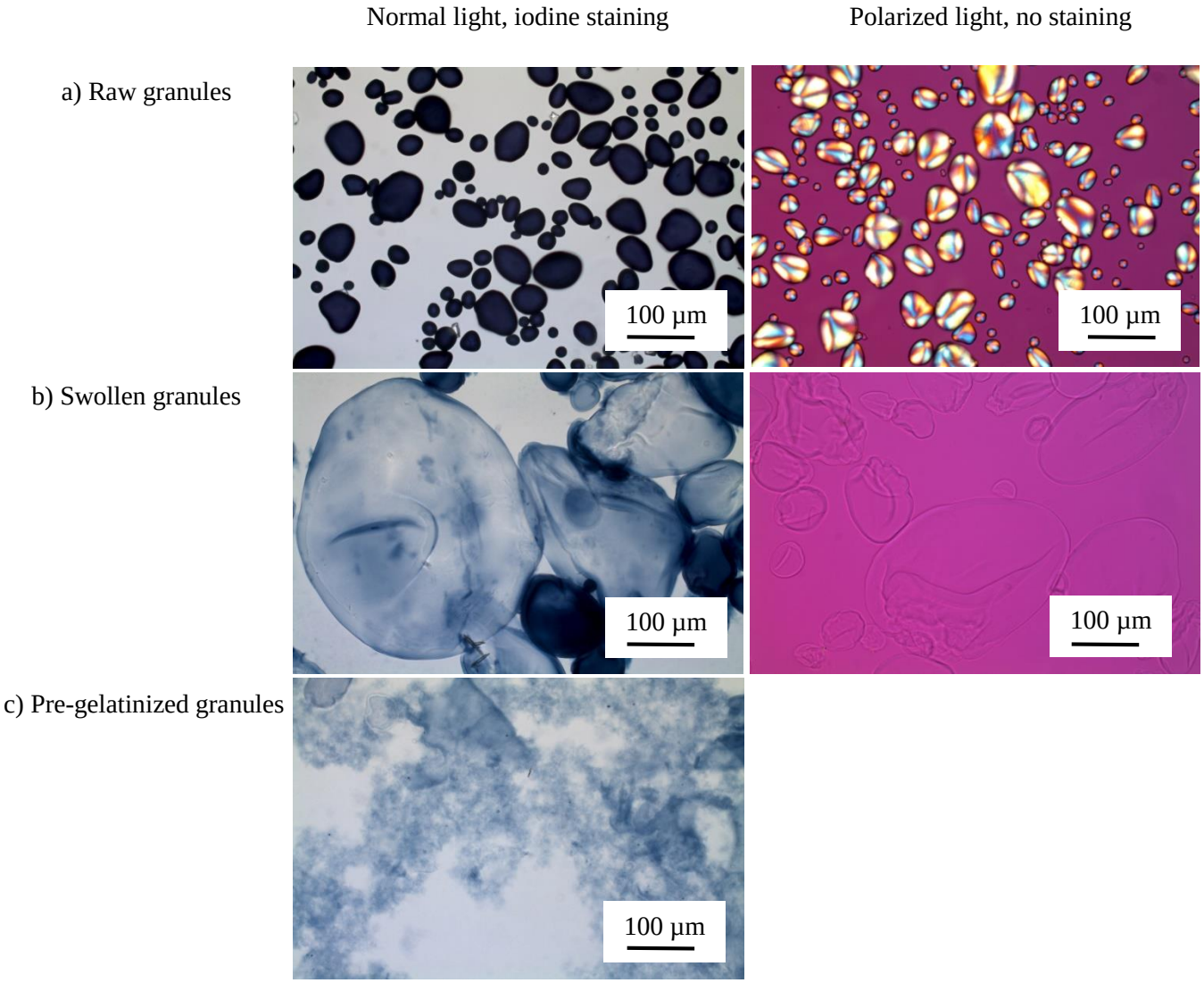

Normal light, iodine staining
Polarized light, no staining
a) Raw granules
b) Swollen granules
c) Pre-gelatinized granules
100 µm
100 µm
100 µm
100 µm
100 µm

Figure 5

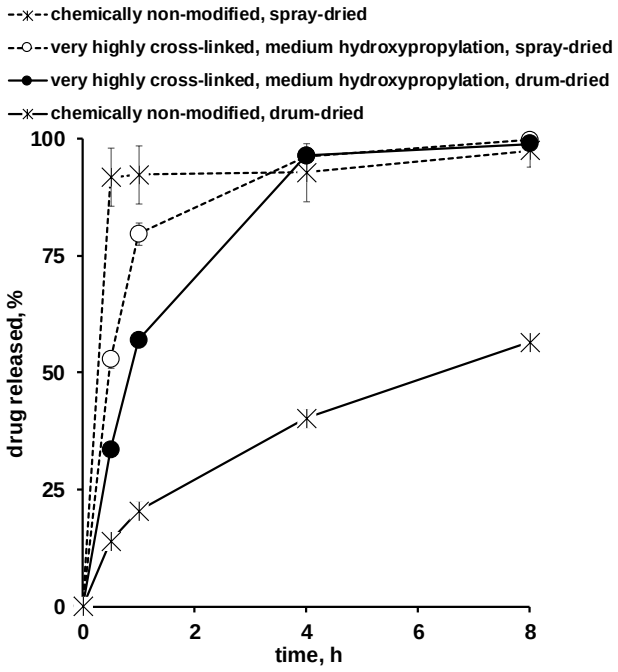

chemically non-modified, spray-dried
very highly cross-linked, medium hydroxypropylation, spray-dried
very highly cross-linked, medium hydroxypropylation, drum-dried
chemically non-modified, drum-dried
drug released, %
100
75
50
25
0
0
2
4
6
8
time, h

Figure 6

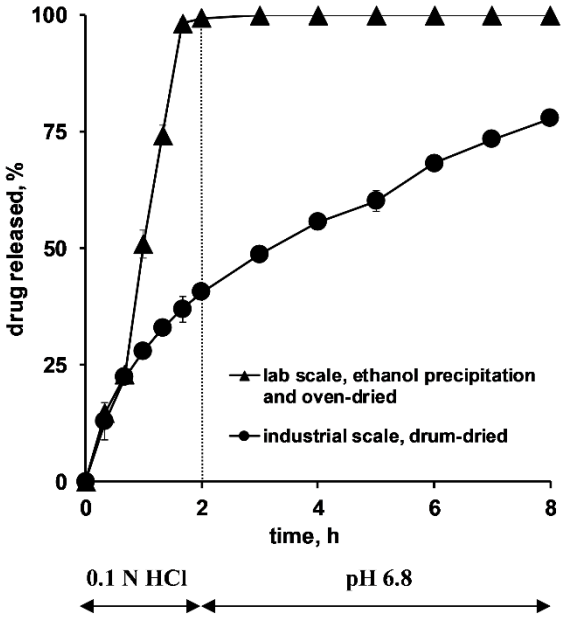

100
75
50
25
0
drug released, %
0
2
4
6
8
time, h
lab scale, ethanol precipitation and oven-dried
industrial scale, drum-dried
0.1 N HCl
pH 6.8

Figure 7

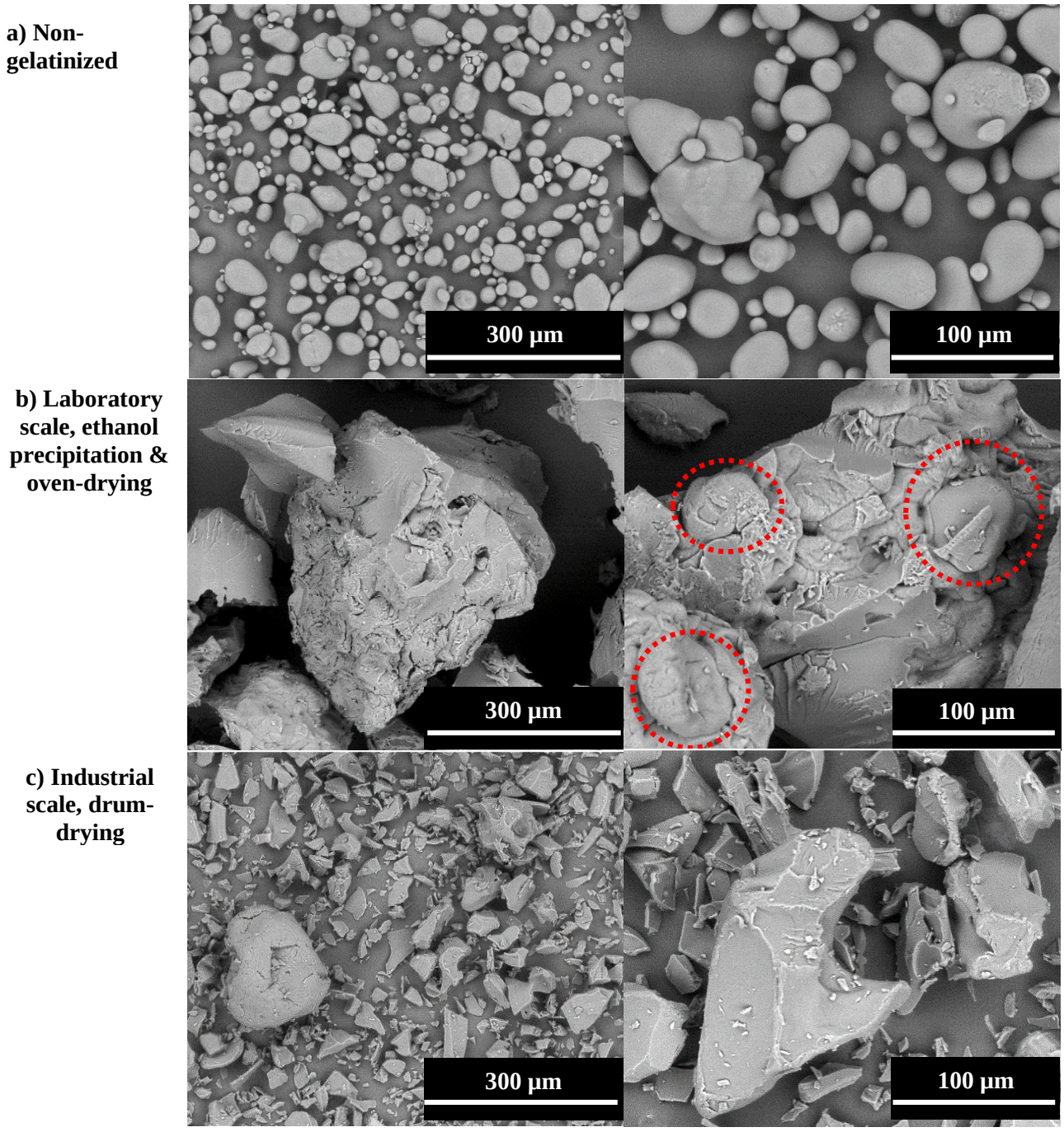

a) Non-gelatinized
300 µm
100 µm
b) Laboratory scale, ethanol precipitation & oven-drying
300 µm
100 µm
c) Industrial scale, drum-drying
300 µm
100 µm

Figure 8

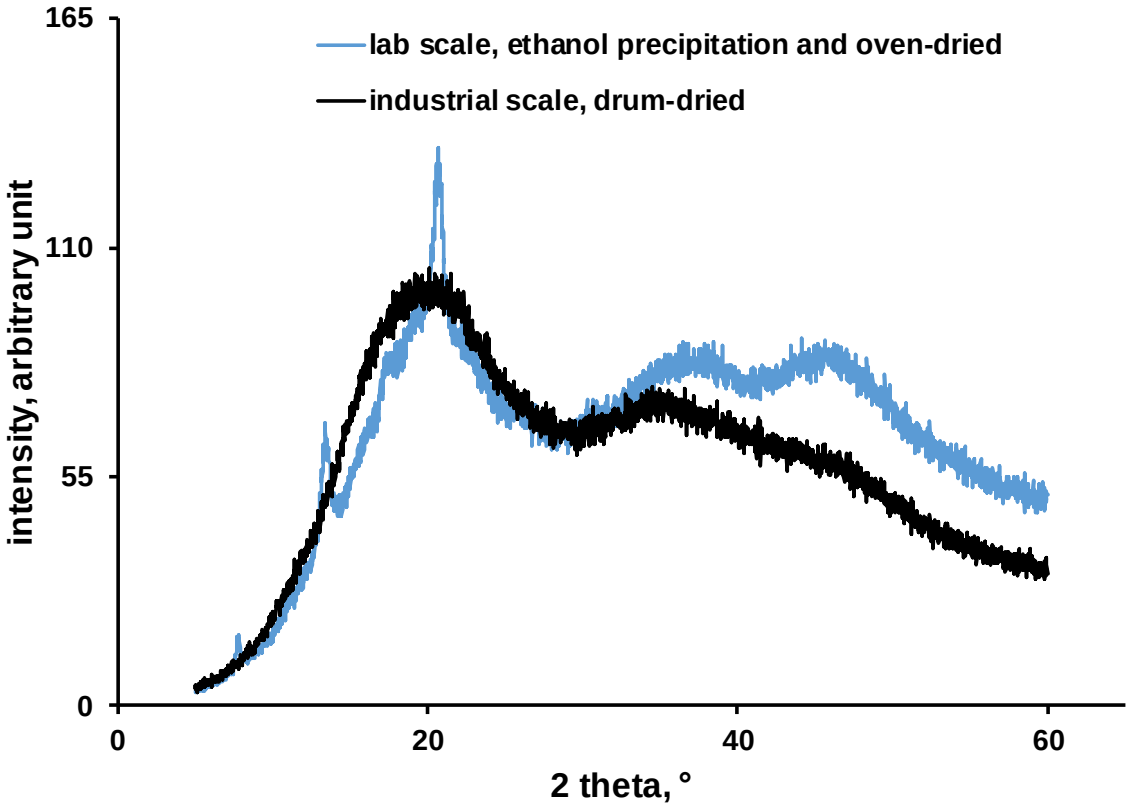

lab scale, ethanol precipitation and oven-dried
industrial scale, drum-dried
intensity, arbitrary unit
165
110
55
0
0
20
40
60
2 theta, °

Figure 9

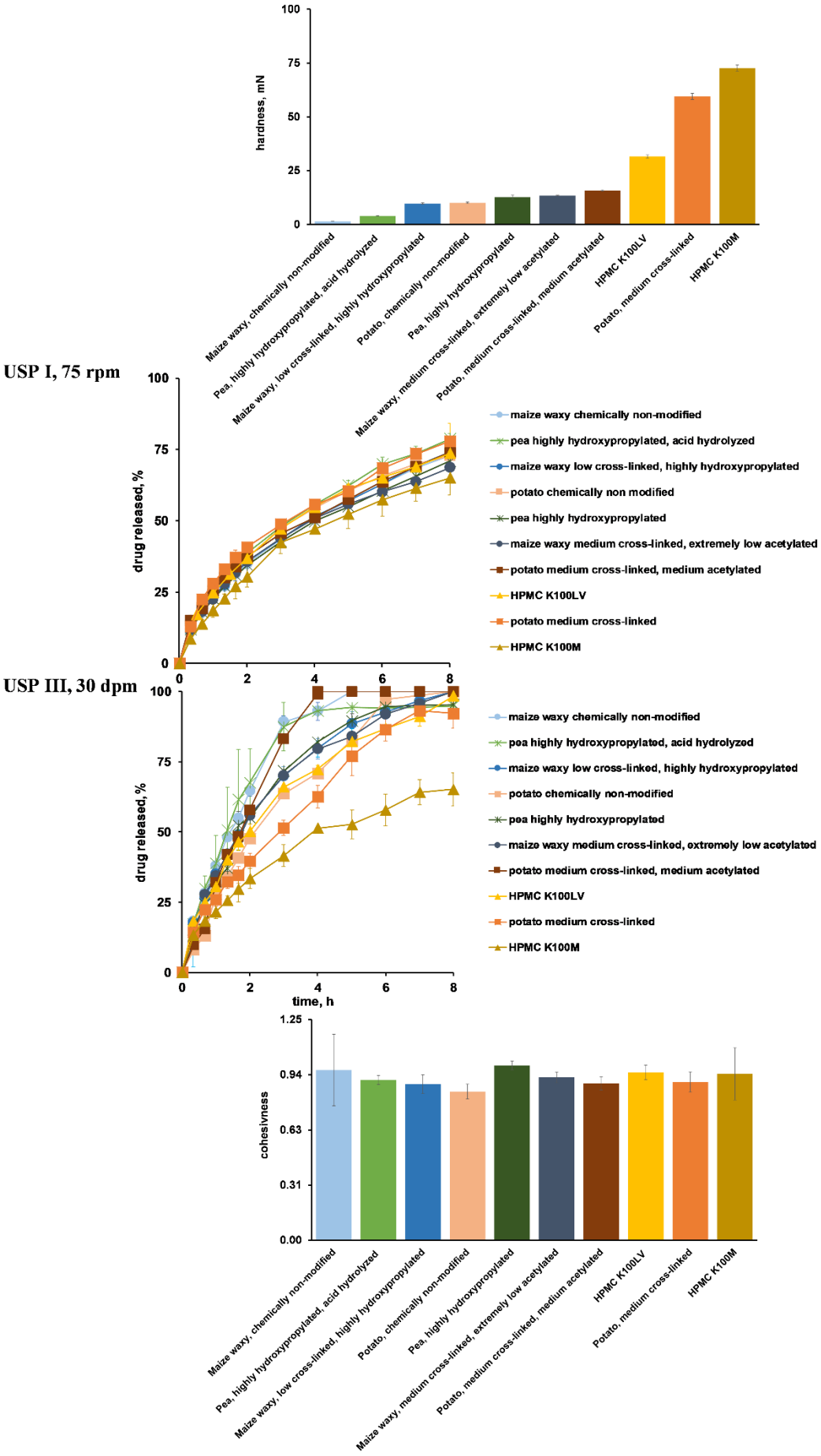

hardness, mN
100
75
50
25
0
Maize waxy, chemically non-modified
Pea, highly hydroxypropylated, acid hydrolyzed
Maize waxy, low cross-linked, highly hydroxypropylated
Potato, chemically non-modified
Pea, highly hydroxypropylated
Maize waxy, medium cross-linked, extremely low acetylated
Potato, medium cross-linked, medium acetylated
HPMC K100LV
Potato, medium cross-linked
HPMC K100M
USP I, 75 rpm
drug released, %
time, h
maize waxy chemically non-modified
pea highly hydroxypropylated, acid hydrolyzed
maize waxy low cross-linked, highly hydroxypropylated
potato chemically non modified
pea highly hydroxypropylated
maize waxy medium cross-linked, extremely low acetylated
potato medium cross-linked, medium acetylated
HPMC K100LV
potato medium cross-linked
HPMC K100M
USP III, 30 dpm
drug released, %
time, h
maize waxy chemically non-modified
pea highly hydroxypropylated, acid hydrolyzed
maize waxy low cross-linked, highly hydroxypropylated
potato chemically non-modified
pea highly hydroxypropylated
maize waxy medium cross-linked, extremely low acetylated
potato medium cross-linked, medium acetylated
HPMC K100LV
potato medium cross-linked
HPMC K100M
cohesivness
1.25
0.94
0.63
0.31
0.00
Maize waxy, chemically non-modified
Pea, highly hydroxypropylated, acid hydrolyzed
Maize waxy, low cross-linked, highly hydroxypropylated
Potato, chemically non-modified
Pea, highly hydroxypropylated
Maize waxy, medium cross-linked, extremely low acetylated
Potato, medium cross-linked, medium acetylated
HPMC K100LV
Potato, medium cross-linked
HPMC K100M

Figure 10

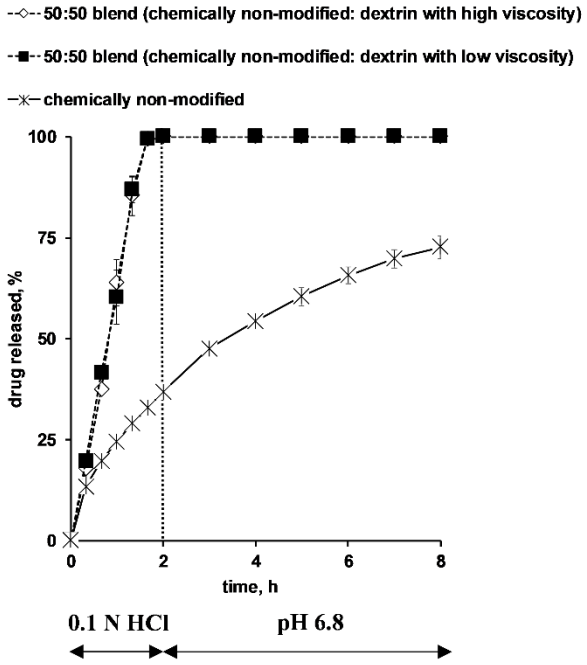

50:50 blend (chemically non-modified: dextrin with high viscosity)
50:50 blend (chemically non-modified: dextrin with low viscosity)
chemically non-modified
drug released, %
100
75
50
25
0
0
2
4
6
8
time, h
0.1 N HCl
pH 6.8

Figure 11