Robustness of controlled release tablets based on a cross-linked pregelatinized potato starch matrix

Dhouha Elgaied, N. Descamps, P. Lefevre, Asta Rahama Mackin Mohamour, Christel Neut, Florence Siepmann, Juergen Siepmann, Susanne Florin Muschert

Robustness of Controlled Release Tablets Based on a Cross-linked Pregelatinized Potato Starch Matrix

D. Elgaied-Lamouchi, N. Descamps, P. Lefèvre, A. R. Mackin-Mohamour, C. Neut, F. Siepmann, Juergen Siepmann & S. Muschert

Abstract

The aim of this study was to evaluate the potential of a cross-linked pregelatinized potato starch (PREGEFLO® PI10) as matrix former for controlled release tablets. Different types of tablets loaded with diprophylline, diltiazem HCl or theophylline were prepared by direct compression of binary drug:polymer blends. The drug content was varied from 20 to 50%. Two hydroxypropyl methylcellulose grades (HPMC K100LV and K100M) were studied as alternative matrix formers. Drug release was measured in a variety of release media using different types of experimental set-ups. This includes 0.1 N HCl, phosphate buffer pH 6.8 and water, optionally containing different amounts of NaCl, sucrose, ethanol or pancreatin, Fasted State Simulated Gastric Fluid, Fed State Simulated Gastric Fluid, Fasted State Simulated Intestinal Fluid, Fed State Simulated Intestinal Fluid as well as media simulating the conditions in the colon of healthy subjects and patients suffering from Crohn's disease. The USP apparatuses I/II/III were used under a range of operating conditions and optionally coupled with the simulation of additional mechanical stress. Importantly, the drug release kinetics were not substantially affected by the investigated environmental conditions from tablets based on the cross-linked pregelatinized potato starch, similar to HPMC tablets. However, in contrast to the latter, the starch based tablets roughly kept their shape upon exposure the release media (they "only" increased in size) during the observation period, and the water penetration into the systems was much less pronounced. Thus, the investigated cross-linked pregelatinized potato starch offers an interesting potential as matrix former in controlled release tablets.

Keywords: Starch; controlled drug release; matrix tablet; diprophylline; HPMC

INTRODUCTION

Hydrophilic polymeric matrix tablets are frequently used to control drug release (1,2). A broad range of polymers can be used as matrix formers for this purpose, such as hydroxypropyl methylcellulose (HPMC) (3,4), starches and starch derivatives (5,6), polyethylene oxide (7), poly(vinyl acetate)/poly(vinyl pyrrolidone) blends (8), gums (9) and other types of polysaccharides (10,11). The underlying drug release mechanisms can be rather complex, including water diffusion into the system, polymer swelling, drug dissolution & diffusion, polymer chain disentanglement and diffusion through the liquid unstirred layer surrounding the device, to mention just a few (12–14). Importantly, the diffusion coefficients of the respective species might strongly depend on time and position (e.g., in a system undergoing substantial polymer swelling). The relative importance of the different phenomena depends on the type of drug, type of matrix former, tablet composition (e.g. the potential presence of other excipients, such as lactose) (15–18) and eventually the type of preparation technique (e.g. direct compression, wet & dry granulation, hot melt extrusion or 3D printing) (19–21).

HPMC is frequently used as matrix former in controlled release tablets. Various HPMC grades are available, differing for example in the average polymer molecular weight and substitution patterns (22,23). Interestingly, starch is the second most abundant organic compound in nature (after cellulose) and offers an interesting potential as matrix formers for controlled release tablets (24,25). A large variety of native and physically and/or chemically modified starches is available and can be used in pharmaceutical dosage forms. For example, Te Wierik et al. (26) proposed a retrograded, pre-gelatinized potato starch prepared by gelatinization, partial enzymatic degradation, retrogradation, filtration and washing with ethanol for the preparation of controlled release matrix tablets. Also, retrograded waxy maize starch was used by Yoon et al. (27) to control the release of theophylline from matrix tablets. Furthermore, Onofre et al. (28) studied different types of cross-linked corn starches with varying amylose contents as matrix former in controlled release tablets for propranolol hydrochloride. Recently, Recife et al. (29) used retrograded high amylose starch to control diclofenac sodium release from matrix tablets, and Ravenelle and Rahmouni (30) proposed chemically and physically modified high-amylose corn starch to prepare controlled release tablets.

Generally, the resulting drug release kinetics from a controlled drug delivery system are measured in vitro under conditions aiming to simulate those encountered in vivo. However, care must be taken when drawing conclusions based on in vitro data, especially in case of highly swollen polymeric matrix systems. This is because the conditions in the gastro intestinal tract in a patient are often complex and not always fully reflected by commonly used in vitro release set-ups. In particular, mechanical stress experienced due to the motility of the stomach and small intestine might favor the disintegration of fragile dosage forms, resulting in accelerated drug release (31,32). Also, the composition of the fluids the controlled release dosage form is exposed to might affect the resulting drug release rate (33–36). For instance, the presence of certain enzymes might lead to the degradation of a polymeric matrix former, e.g. starches can be degraded by amylases (37,38), potentially resulting in accelerated drug release (39). This might not be detected using standard in vitro drug release measurements set-ups and conditions.

The major aims of the present study were: (i) to prepare different types of controlled release matrix tablets based on a cross-linked pregelatinized potato starch (PREGEFLO ® PI10), varying the type and amount of drug; (ii) to measure the resulting drug release kinetics using a variety of experimental set-ups (USP apparatuses I, II and III), operation conditions (e.g. dipping speed, medium change) in a range of release media (0.1 N HCl, phosphate buffer pH 6.8, water, FaSSGF, FeSSGF, FaSSIF, FeSSIF, and cell culture medium; optionally containing different amounts of NaCl, sucrose, ethanol, pancreatin or fecal samples from healthy volunteers or Crohn's disease patients), and optionally simulating mechanical stress using a texture analyzer or silicone balls; and (iii) to study HPMC as alternative matrix former for reasons of comparison.

MATERIALS AND METHODS

Materials

Diprophylline fine powder and theophylline monohydrate fine powder (BASF, Ludwigshafen, Germany); diltiazem hydrochloride (diltiazem HCl; Teva, Netanya, Israel); cross-linked pregelatinized potato starch (PREGEFLO® PI10; Roquette Freres, Lestrem, France); hydroxypropyl methylcellulose

(HPMC, METHOCEL™ K100LV and K100M; Stobec, Quebec, Canada); magnesium stearate (Baerlocher, Unterschleissheim, Germany); sodium chloride (NaCl; Cooper, Melun, France); sucrose (Seppic, Paris, France); lecithin (Alfa Aesar, Karlsruhe, Germany); sodium acetate anhydrous, pepsin, ethanol, acetic acid glacial, hydrochloric acid (HCl) and acetonitrile (Fisher, Loughborough, UK); pancreatin from porcine pancreas (8 x more concentrated than the USP 43 specification), sodium taurocholate and trichloroacetic acid (TCA) (Sigma Aldrich, Saint Louis, USA); extracts from beef, yeast, tryptone (= pancreatic digest of casein) (Becton Dickinson, Sparks, USA); L-cysteine hydrochloride hydrate (Acros Organics, Geel, Belgium); cysteinated Ringer solution (Merck, Darmstadt, Germany).

Tablet preparation

Tablets were prepared by direct compression. The drug content was varied from 20 to 50 % (w/w). Diprophylline, diltiazem HCl or theophylline powder was blended with cross-linked pregelatinized potato starch or HPMC powder in a Turbula mixer (Bachoven, 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 single-punched rotary press (Stylcam 200 R; Medelpharm, Bynost, France), equipped with 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 measured using a micrometer gauge (Digimatic Micrometer; Mitutoyo, Tokyo, Japan).

In vitro drug release measurements

Drug release from the tablets was measured using different experimental set-ups and release media:

<u>USP apparatus I (basket):</u>

The USP apparatus I (AT7 Smart; Sotax) was used at 75 rpm and 37 °C. The release medium was 900 mL demineralized water, 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 by UV-spectrophotometry (UV-1650 PC; Shimadzu,

Kyoto, Japan) at λ= 274, 237 and 271 nm in the case of diprophylline, diltiazem HCl and theophylline, respectively.

If indicated, different amounts of NaCl or sucrose were added to the release medium. Or, demineralized water, optionally containing 5 or 20 % ethanol (v/v) (40) was used. In these cases, the diprophylline content of the withdrawn samples was determined by HPLC-UV analysis using a method adapted from Hsein et al. (41). The HPLC system (Waters e2695; Waters, Milford, USA) was 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). 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.

Furthermore, pancreatin with an α-amylase activity of 108.000 IU/L was optionally added to the phosphate buffer pH 6.8 (42). In these cases, the withdrawn samples were centrifuged (5 min, 8000 rpm) prior to filtering and HPLC-UV analysis.

In addition, Fasted State Simulated Gastric Fluid (FaSSGF), Fed State Simulated Gastric Fluid (FeSSGF), Fasted State Simulated Intestinal Fluid (FaSSIF) or Fed State Simulated Intestinal Fluid (FeSSIF) (43) were used as release media. In these cases, the diprophylline content in the withdrawn samples was determined upon precipitation with an aqueous 10 % (w/v) trichloroacetic acid solution (sample: trichloroacetic acid solution ratio = 1:2). The mixtures were vortexed (30 s), centrifuged (15 min at 8000 rpm) and filtered prior to HPLC-UV analysis (44).

If indicated, tablet samples were mechanically stressed at each sampling time point (adapted from 31) as follows: The tablets were placed into Petri dishes and a texture analyzer (TA.XT.Plus, 1 kg load cell; Stable Micro Systems, Surrey, UK), equipped with a 40 mm flat-ended plate probe, was used to exert a force of up to 2 N onto the axial surface of the tablet. One “compression cycle” was as follows: The probe was driven downwards at a speed of 0.5 mm/s. Once in contact with the surface of the tablet, a steadily increasing force was exerted until a value of 2 N was reached. The probe was subsequently driven upwards at a speed of 10 mm/s. Three or five “compression cycles” were run, as indicated. The tablets were carefully placed back into the vessels. The Petri dishes were rinsed with 5 mL release medium. The drug content in the samples was determined by HPLC-UV as described above.

USP apparatus II (paddle):

The USP apparatus II (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, as indicated. At pre-determined time points, 5 mL samples were withdrawn (replaced with fresh medium) and analyzed for their diprophylline content by UV spectrophotometry (UV-1650 PC) at λ= 274.

USP apparatus III (Bio-Dis):

The USP apparatus III (Agilent Technologies, Massy, France) was used at 5 and 20 dpm and 37 °C. The release medium was 200 mL 0.1 N HCl during the first 2 h, followed by 200 mL phosphate buffer pH 6.8. At predetermined time points, 5 mL samples were withdrawn (replaced with fresh medium) and drug release was measured using HPLC-UV spectrophotometry (as described above). If indicated, silicone balls (17 mm diameter, 4.5 g) were added to the vessels (1 ball per vessel) to **better** simulate the mechanical stress experienced in the gastrointestinal tract.

USP apparatus I, followed by inoculation with fecal samples:

Tablets were exposed to 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 for 2 h in a USP apparatus I, as described above. The tablets were then transferred into 120 mL flasks, filled with 100 mL culture medium inoculated with fecal samples from healthy subjects or patients suffering from Crohn's disease. Culture medium was prepared by dissolving 1.5 g beef extract, 3 g yeast extract, 5 g tryptone, 2.5 g NaCl and 0.3 g L-cysteine hydrochloride hydrate in 1 L distilled water (pH 7.0 ± 0.2) and subsequent sterilization in an autoclave. Fresh fecal samples from patients suffering from Crohn's disease as well as from healthy subjects were diluted 1:200 with cysteinated Ringer solution; 2.5 mL of this suspension was diluted with culture medium to 100 mL (45). The flasks were agitated at 50 rpm and 37 °C under anaerobic conditions (AnaeroGen 2.5 L; Thermo Fisher Scientific; Illkirch, France). At predetermined time points, 2 mL samples were withdrawn, centrifuged (5 min at 8000 rpm), filtered and analyzed by HPLC-UV as described above.

All in vitro drug release experiments were conducted in triplicate, mean values +/- standard deviations are reported.

Swelling and erosion studies

The swelling kinetics of the tablets were monitored upon exposure to 0.1 N HCl and phosphate buffer pH 6.8 using the USP apparatus I (37 °C, 75 rpm; AT7 Smart). At predetermined time points, specimen were withdrawn and excess surface water was gently removed with absorbent tissue (Kimtech, Kimberly-Clark, Reigate, UK). The tablets were weighed [*wet mass (t)*] and dried to constant weight at 60 °C in an oven [*dry mass (t)*]. The dynamic changes in the system's water content and dry mass loss were calculated as follows:

$$\text{water content (\%) (t)} = \frac{\text{wet mass (t)} - \text{dry mass (t)}}{\text{wet mass (t)}} \cdot 100\ \% \quad (1)$$

$$\text{dry mass loss (\%) (t)} = \frac{\text{dry mass (t = 0)} - \text{dry mass (t)}}{\text{dry mass (t = 0)}} \cdot 100\ \% \quad (2)$$

where *dry mass (t = 0)* is the tablets' dry mass before exposure to the release medium.

Assuming that the amounts of ions penetrating from the release media into the tablets are negligible, the following equation was used to estimate the polymer mass loss over time:

$$\text{estimated polymer mass loss (\%) (t)} = \frac{(\text{dry mass (t=0)} - (\text{dry mass (t)} + \text{amount of drug released (t)})}{\text{polymer mass (t = 0)}} \cdot 100\ \% \quad (3)$$

where *amount of drug released (t)* is the amount of drug released at time *t*, and *polymer mass (t=0)* is the polymer mass in the tablets before exposure to the release medium.

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

In addition, withdrawn tablet samples were deep-frozen at -20 °C and cut into halves using a scalpel (Feather, Osaka, Japan). Pictures of cross-sections were taken with an Axiovision Zeiss Scope-A1 microscope, equipped with an AxioCam ICc1 (Carl Zeiss, Jena, Germany).

Drug solubility measurements

Excess amounts of drugs (as received) were exposed to 10 mL 0.1 N HCl, phosphate buffer pH 6.8 or demineralized water, optionally containing up to 20 % ethanol (as indicated) in flasks and horizontally shaken at 37°C at 80 rpm (GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At pre-determined time points, samples were withdrawn, immediately filtered (PTFE syringe filters, 0.45 µm; GE Healthcare) and diluted. The drug contents of the samples were determined by UV-spectrophotometry, as described above. Samples were withdrawn until equilibrium was reached. Each experiment was conducted in triplicate, mean values +/- standard deviations are reported.

RESULTS AND DISCUSSION

Tablet swelling

Figure 1 shows optical macroscopy pictures of cross-sections of matrix tablets loaded with 30 % diprophylline upon exposure to 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 for 6 h. The USP apparatus I (basket) was used. The tablets were based on cross-linked pregelatinized potato starch, HPMC K100LV or HPMC K100M, as indicated at the top. The time periods of exposure to the release media are given on the left hand side. As it can be seen, the swelling behavior of the cross-linked pregelatinized potato starch-based tablets substantially differed from the swelling behavior of HPMC K100LV- and K100M-based tablets: The rectangular shape of the cross-sections of the cylindrical systems remained almost unaltered (“only” the size increased) in the case of the investigated starch derivative. In contrast, the corners of the HPMC-based tablets rapidly became round and the original tablet shape got lost, irrespective of the HPMC grade. Interestingly, the same was true for the geometry of the “dry tablet cores”, which were visible at the center of the systems: The geometry of the cross-sections of these “dry cores” remained rectangular in the case of tablets based on pregelatinized potato starch, they became more and more round in the case of HPMC-based tablets. In addition, the thickness of the swollen hydrogel layer continuously increased when using pregelatinized potato starch as matrix former, whereas this was not the case with the HPMC K100LV- and HPMC K100M-based tablets. The

thickness of the swollen HPMC K100LV layer even decreased at later time points. This indicates significant erosion of the HPMC matrices during drug release.

To better understand whether these substantial differences in polymer swelling (starch derivative versus HPMC) translate into differences in the resulting drug release kinetics from these matrix tablets, various types of systems (loaded with different types and amounts of drugs) were prepared and drug release was monitored under a variety of experimental conditions.

Impact of the type of polymer

The resulting diprophylline release kinetics from matrix tablets based on cross-linked pregelatinized potato starch, HPMC K100LV or HPMC K100M in 0.1 N HCl and phosphate buffer pH 6.8 are illustrated in Figure 2. The USP apparatuses I, II and III were used: basket, paddle or "Bio-Dis". The release medium was optionally changed after 2 h (as indicated). In the case of the USP III apparatus, the dipping speed was set at 5 or 20 dpm.

As it can be seen, the three types of polymers were able to control the release of the freely water-soluble drug during more than 8 h under all conditions. When using the USP basket apparatus or the "Bio-Dis" apparatus at 5 dpm, the release rates from cross-linked pregelatinized potato starch- and HPMC K100LV-based tablets were rather similar, while diprophylline from HPMC K100M-based tablets was somewhat slower. When using the USP paddle apparatus, drug release was fastest from the starch-based tablets, followed by HPMC K100LV- and HPMC K100M-based tablets. In contrast, when using the USP III apparatus at 20 dpm, diprophylline release was fastest from HPMC K100LV-based tablets, followed by the starch-based systems and the HPMC K100M-based tablets. Interestingly, the optional complete medium change after 2 h from 0.1 N HCl to phosphate buffer pH 6.8 did not affect drug release to a noteworthy extent, irrespective of the type of polymer (left versus right diagram at the top of Figure 2).

Effects of the type of release medium

Figure 3 shows the impact of adding 5 or 20 % ethanol to water as the release medium on diprophylline release from tablets based on cross-linked pregelatinized potato starch, HPMC K100LV

or HPMC K100M. The drug loading was 30 %, the USP apparatus I was used. Clearly, diprophylline release was not affected to a noteworthy extent in the case of the investigated starch derivative. For HPMC K100LV and HPMC K100M, a slight decrease in the release rates was observed with increasing ethanol content of the release medium. The solubility of diprophylline in water containing 0, 5 and 20 % ethanol at 37 °C was found to be equal to 206 ± 13.5, 210 ± 18 and 220 ± 11 mg/mL, respectively. This suggests that the presence of up to 20 % ethanol in the release medium does not affect the capacity of cross-linked pregelatinized potato starch to a noteworthy extent.

The impact of the addition of different amounts of NaCl and sucrose on diprophylline release from matrix tablets based on cross-linked pregelatinized potato starch or HPMC K100M is illustrated in Figure 4. The USP apparatus I (basket) was used, the release medium was 0.1 N HCl during the first 2 h, followed by phosphate buffer pH 6.8 for the subsequent 6 h. The aim was to evaluate the sensitivity of drug release from these types of controlled release matrix tablets to variations in the osmolality of the contents of the gastro intestinal tract. As it can be seen, in none of the cases there was a noteworthy effect under the given in vitro conditions.

When using a starch derivative as a matrix former in controlled release tablets, it is very important to evaluate the potential impact of the presence of pancreatin in the release medium on system performance: Pancreatin contains α-amylase which can degrade starches and, thus, potentially affect the resulting drug release kinetics. In practice, the α-amylase secretion in the patients' gastro intestinal tract varies. Hence, in the case of amylase-sensitive starches, in vivo variability of drug release might result from variable starch degradation. Importantly, the diagram at the left hand side at the top of Figure 5 shows that diprophylline release from tablets based on the investigated cross-linked pregelatinized potato starch is not sensitive to the presence of pancreatin. The open diamonds illustrate drug release in the presence of pancreatin (with an α-amylase activity of 108.000 IU/L), the filled diamonds show the respective release kinetics in the absence of pancreatin. The release medium was 0.1 N HCl for the first 2 h, followed by phosphate buffer pH 6.8. The USP apparatus I was used. The drug loading was 30 %. As it can be seen on the right hand side at the top of Figure 5, also drug release from HPMC K100M-based tablets was insensitive to the presence of pancreatin (as expected). The diagrams in the middle of Figure 5 show diprophylline release from these tablets upon exposure to Fasted State Simulated Gastric

Fluid (FaSSGF) or Fed State Simulated Gastric Fluid (FeSSGF) for 2 h, followed by Fasted State Simulated Intestinal Fluid (FaSSIF) or Fed State Simulated Intestinal Fluid (FeSSIF) for the subsequent 6 h. Again, the USP apparatus I was used. Furthermore, diprophylline release was measured upon exposure to 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 for 6 h and a release medium simulating the conditions in the colon of a patient suffering from Crohn's disease (dotted curves) or in the colon of a healthy subject (solid curves). In these cases, fecal samples from patients/healthy subjects were incubated under anaerobic conditions and used as release media. For reasons of comparison, also drug release into 0.1 N HCl (2 h), followed by phosphate buffer pH 6.8 (22 h) is shown (filled diamonds). The diagrams on the left hand side show diprophylline release from tablets based on cross-linked pregelatinized potato starch, the diagrams on the right hand side illustrate the release kinetics from HPMC K100M-based tablets. As it can be seen, in all cases no noteworthy effects were observed with respect to the type of release medium: FaSSGF, FeSSGF, FeSSGF, FeSSIF and colonic media from patients or healthy subjects. This is important, especially in the case of the investigated starch derivative, because starches might be preferentially degraded by bacterial enzymes present in the colon.

In practice, the observed insensitivity of the drug release kinetics to variations in the composition of the release media is promising, because the contents of the gastro intestinal tract of a patient varies intra-individually and inter-individually. Thus, in vivo rather consistent drug release kinetics might be expected. However, since the investigated matrix tablets substantially swell upon contact with the aqueous release media (Figure 1), variations in the mechanical stress experienced during the transit throughout the gastro intestinal tract might potentially alter the resulting drug release rates. For instance, in the case of mechanically fragile gels, forces exerted on the tablets by the stomach or small intestine might lead to accelerated system disintegration and, thus, faster drug release. Importantly, the mechanical stress encountered in a patient's gastro intestinal tract might significantly vary intra-individually and inter-individually. To evaluate the potential impact of such effects on system performance, diprophylline release was measured from starch- and HPMC-based tablets using the USP apparatuses I and III, optionally adding silicone balls or using a texture analyzer to simulate contraction forces of the stomach and small intestine.

Impact of mechanical stress on drug release

The diagrams on the left hand side of Figure 6 show the release kinetics of diprophylline from tablets based on cross-linked pregelatinized potato starch (top) or HPMC K100M (bottom) upon exposure to 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 in a USP apparatus I (basket). To simulate mechanical stress encountered in the gastro intestinal tract of the patient, the tablets were withdrawn from the release medium at each sampling time point and underwent 3 or 5 "compression cycles" (as indicated) using a texture analyzer. In brief, one "compression cycle" was as follows: The tablets were placed on a Petri dish and a cylindrical probe was driven downwards at a speed of 0.5 mm/s. As soon as the flat face of the probe got into contact with the flat face of the tablet, a steadily increasing force was exerted onto the tablet. Once this forced reached 2 N, the probe was driven upwards. For reasons of comparison, the diagrams in Figure 6 also show drug release from tablets that did not undergo such "compression cycles". In addition, the USP apparatus III ("Bio-Dis") was used to monitor drug release from these tablets at 5 and 20 dpm, optionally adding a silicone ball (17 mm diameter, 4.5 g) to each vessel. The resulting diprophylline release rates are shown in the diagrams on the right hand side of Figure 6. As it can be seen, in all cases the overall impact of mechanical stress on drug release from the investigated tablets was limited. This indicates that the swollen polymer gels (Figure 1) are mechanically stable and can resist the pressure they were exposed to. This is again promising with respect to the variability of the resulting drug release kinetics that can be expected in vivo from these systems: It is unlikely that the motility of the gastro intestinal tract substantially affects the resulting drug release rates (provided that the encountered mechanical stress is similar).

Effects of the amount and type of drug

The diagrams in Figure 7 show the resulting diprophylline release kinetics from tablets based on cross-linked pregelatinized potato starch (top) or HPMC K100M (bottom) upon exposure to 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 in a USP apparatus I. The initial drug loading was varied from 20 to 50 %, as indicated. It has to be pointed out that the tablets were essentially based on binary drug: polymer blends (only 1 % magnesium stearate was added as lubricant). Thus, the starch derivative/HPMC content decreased accordingly from about 80 to 50 %. Nevertheless, the resulting drug

release kinetics (relative release rates) were unaffected, irrespective of the type of matrix former. This is a further indication for the robustness of the hydrated macromolecular networks that are formed upon contact with aqueous fluids. It also provides flexibility with respect to dose adjustments from this type of controlled release tablets.

The diagrams in Figure 8 show (from the top to the bottom): the (i) dry mass loss kinetics, (ii) estimated polymer mass loss kinetics, and (iii) dynamic changes in the water contents of tablets based on cross-linked pregelatinized potato starch (left hand side) or HPMC K100M (right hand side) upon exposure to 0.1 N HCl and phosphate buffer pH 6.8. The USP apparatus I (basket) was used. The initial diprophylline loading was 30 or 40 %, as indicated. As it can be seen, the variation of the drug content did not substantially affect the resulting mass loss kinetics of the tablets or matrix former, neither the time-dependent changes in the water contents of the systems. This is consistent with the robustness of the relative drug release kinetics discussed above. Interestingly, the observed dry mass loss of the tablets essentially corresponded to the amounts of drug that were released into the surrounding bulk fluid in the observation period. The polymeric matrix former did not dissolve to a noteworthy extent in any of the investigated systems. This might at least in part explain the observed robustness of the resulting drug release kinetics under the various investigated conditions: types of release media, types of release apparatuses and conditions for drug release (including the application of mechanical stress). Both, the investigated starch derivative as well as HPMC K100M seem to form mechanically stable polymer networks that do not dissolve during the observation period. Interestingly, the two diagrams at the bottom of Figure 8 indicate that the water uptake of tablets based on the investigated cross-linked starch derivative was much less pronounced than the water uptake of the respective HPMC K100M-based tablets.

From a practical point of view, an “ideal” polymeric matrix former for controlled release tablets should be able to control the release of very different types of drugs, exhibiting for instance substantially different solubility in aqueous media. For this reason, also diltiazem HCl and theophylline containing tablets were prepared, based on cross-linked pregelatinized potato starch or HPMC K100M. The solubility of diprophylline, theophylline and diltiazem HCl were determined to be equal to 199 ± 12, 12 ± 0.9 and 667 ± 14 mg/mL in 0.1 N HCl and 190 ± 20, 12 ± 0.3 and 497 ±11.5 mg/mL in phosphate

buffer pH 6.8 at 37 °C, respectively. Figure 9 shows the resulting drug release kinetics in the two media (complete exchange after 2 h). The USP apparatus I was used, the initial drug content was 30 % in all cases. As it can be seen, the investigated starch derivative as well as HPMC K100M were able to effectively control the resulting drug release kinetics, irrespective of the type of drug. The release rate was lowest for theophylline (red curves in Figure 9), irrespective of the type of matrix former. This can at least partially be attributed to the relatively low solubility of this drug in aqueous media and the fact that only dissolved drug is available for diffusion: Upon water penetration into the systems, probably not all of the theophylline can be dissolved. Thus, dissolved and non-dissolved theophylline co-exist. Importantly, only the *dissolved* drug contributes to the concentration gradients that are the driving forces for drug release. Please note that even in the case of freely water-soluble drugs, limited solubility effects might be of importance (46,47). Interestingly, diltiazem HCl release was slower than diprophylline release in the present study, despite of its higher solubility in the investigated release media. This was true for both types of matrix formers. Hence, other phenomena must (also) be of importance. For instance, the molecular weight of diltiazem H^+ ions is much higher than the molecular weight of diprophylline (451 versus 254 Da). Consequently, the mobility (diffusion coefficient) of dissolved diltiazem H^+ ions is likely smaller than the mobility of dissolved diprophylline molecules, resulting in lower drug release rates.

CONCLUSION

The investigated cross-linked pregelatinized potato starch offers an interesting potential as matrix former for controlled release matrix tablets: It can be used to effectively control the release rates of different types of drugs (at different initial loadings) during several hours. Importantly, the resulting drug release kinetics are not affected to a noteworthy extent by variations in the type of release medium (including the presence of pancreatin) and the applied experimental set-up (USP apparatus I, II and III) under a broad range of operating conditions, including optional simulation of mechanical stress (using silicone balls or a texture analyzer). Thus, the resulting drug release kinetics in vivo might also be rather robust.

ACKNOWLEDGEMENTS

This project has received funding from the Interreg 2 Seas programme 2014-2020, co-funded by the European Regional Development Fund under subsidy contract 2S01-059_IMODE. The authors are very grateful for this support.

CONFLICT OF INTERESTS

Several co-authors of this article are employees of the company Roquette, commercializing the investigated starch derivative.

REFERENCES

1. Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. J Controlled Release. 2011; 154(1):2–19.
2. Zhang X, Li Y, Huang Z, Cui Y, Zhao Z, Yue X, et al. Development and pharmacokinetics evaluation of quetiapine fumarate sustained-release tablets based on hydrophilic matrix. J Drug Deliv Sci Technol. 2019; 54:101322.
3. Li CL, Martini LG, Ford JL, Roberts M. The use of hypromellose in oral drug delivery. J Pharm Pharmacol. 2005; 57(5):533–46.
4. Ward A, Walton K, Mawla N, Kaialy W, Liu L, Timmins P, et al. Development of a novel method utilising dissolution imaging for the measurement of swelling behaviour in hydrophilic matrices. Int J Pharmaceut. X. 2019; 1:100013.
5. Lenaerts V, Moussa I, Dumoulin Y, Mebsout F, Chouinard F, Szabo P, et al. Cross-linked high amylose starch for controlled release of drugs: recent advances. J Controlled Release. 1998; 53(1):225–234.
6. Hattori Y, Takaku T, Otsuka M. Mechanochemical effect on swelling and drug release of natural polymer matrix tablets by X-ray computed tomography. Int J Pharmaceut. 2018; 539(1):31–8.
7. Xu X, Siddiqui A, Srinivasan C. et al. Evaluation of Abuse-Deterrent Characteristics of Tablets Prepared via Hot-Melt Extrusion. AAPS PharmSciTech. 2019; 20(6):230.
8. Siepmann F, Eckart K, Maschke A, Kolter K, Siepmann J. Modeling drug release from PVAc/PVP matrix tablets. J Controlled Release. 2010; 141(2):216–22.
9. Lazzari A, Kleinebudde P, Knop K. Xanthan gum as a rate-controlling polymer for the development of alcohol resistant matrix tablets and mini-tablets. Int J Pharmaceut. 2018; 536(1):440–9.

10. Vlachou M, Tragou K, Siamidi A, Kikionis S, Chatzianagnostou A-L, Mitsopoulos A, et al. Modified in vitro release of the chronobiotic hormone melatonin from matrix tablets based on the marine sulfated polysaccharide ulvan. J Drug Deliv Sci Technol. 2018; 44:41–8.
11. Layek B, Mandal S. Natural polysaccharides for controlled delivery of oral therapeutics: a recent update. Carbohydr Polym. 2019; 115617.
12. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev. 2001; 48(2):139–157.
13. Borgquist P, Körner A, Piculell L, Larsson A, Axelsson A. A model for the drug release from a polymer matrix tablet—effects of swelling and dissolution. J Controlled Release. 2006; 113(3):216–25.
14. Kaunisto E, Abrahmsen-Alami S, Borgquist P, Larsson A, Nilsson B, Axelsson A. A mechanistic modelling approach to polymer dissolution using magnetic resonance microimaging. J Controlled Release. 2010; 147(2):232–41.
15. Siepmann J, Karrout Y, Gehrke M, Penz FK, Siepmann F. Predicting drug release from HPMC/lactose tablets. Int J Pharmaceut. 2013; 441(1):826–34.
16. Controlled release tablets based on HPMC:lactose blends. Pharma Excip [Internet]. 2019 May 21 [cited 2019 Nov 27]; Available from: https://www.pharmaexcipients.com/oral-excipients/hpmclactose-blends/.
17. Xi Z, Sharma N, Paprikar A, Lin S. Development and evaluation of dipyridamole sustained release tablets containing micro-environmental pH modifiers. J Drug Deliv Sci Technol. 2019; 54:101231.
18. Panainte AD, Gafitanu C, Stoleriu I, Tarțău LM, Popescu M-C, Lisa G, et al. New modified release tablets of bisoprolol fumarate for the treatment of hypertension: characterization and in vitro evaluation. J Drug Deliv Sci Technol. 2019; 50:402–9.

438 19. Krkobabić M, Medarević D, Cvijić S, Grujić B, Ibrić S. Hydrophilic excipients in digital
439 light processing (DLP) printing of sustained release tablets: Impact on internal structure
440 and drug dissolution rate. Int J Pharmaceut. 2019; 572:118790.
441 20. Cui M, Yang Y, Jia D, Li P, Li Q, Chen F, et al. Effect of novel internal structures on
442 printability and drug release behavior of 3D printed tablets. J Drug Deliv Sci Technol.
443 2019; 49:14–23.
444 21. Yi S, Wang J, Lu Y, Ma R, Gao Q, Liu S, et al. Novel Hot Melt Extruded Matrices of
445 Hydroxypropyl Cellulose and Amorphous Felodipine–Plasticized Hydroxypropyl
446 Methylcellulose as Controlled Release Systems. AAPS PharmSciTech. 2019; 20(6):219.
447 22. Caccavo D, Lamberti G, Barba AA, Abrahmsén-Alami S, Viridén A, Larsson A. Effects
448 of HPMC substituent pattern on water up-take, polymer and drug release: An experimental
449 and modelling study. Int J Pharmaceut. 2017; 528(1):705–13.
450 23. Zhu C, Xu S, Han X. Sustained Release Bilayer Tablet of Ibuprofen and Phenylephrine
451 Hydrochloride: Preparation and Pharmacokinetics in Beagle Dogs. AAPS PharmSciTech.
452 2019; 20(2):86.
453 24. Ashogbon AO, Akintayo ET. Recent trend in the physical and chemical modification of
454 starches from different botanical sources: A review. Starch - Stärke. 2014; 66(1–2):41–
455 57.
456 25. Hong Y, Liu G, Gu Z. Recent advances of starch-based excipients used in extended-
457 release tablets: a review. Drug Deliv. 2016; 23(1):12–20.
458 26. Te Wierik GHP, Eissens AC, Bergsma J, Arends-Scholte AW, Bolhuis GK. A new
459 generation starch product as excipient in pharmaceutical tablets: III. Parameters affecting
460 controlled drug release from tablets based on high surface area retrograded pregelatinized
461 potato starch. Int J Pharmaceut. 1997; 157(2):181–187.

462 27. Yoon H-S, Lee JH, Lim S-T. Utilization of retrograded waxy maize starch gels as tablet
463 matrix for controlled release of theophylline. Carbohydr Polym. 2009; 76(3):449–53.
464 28. Onofre FO, Mendez-Montealvo G, Wang Y-J. Sustained release properties of cross-linked
465 corn starches with varying amylose contents in monolithic tablets. Starch - Stärke. 2010;
466 62(3–4):165–72.
467 29. Recife ACD, Meneguin AB, Cury BSF, Evangelista RC. Evaluation of retrograded starch
468 as excipient for controlled release matrix tablets. J Drug Deliv Sci Technol. 2017; 40:83–
469 94.
470 30. Ravenelle F, Rahmouni M. Contramid®: High-Amylose Starch for Controlled Drug
471 Delivery. In: Polysaccharides for Drug Delivery and Pharmaceutical Applications.
472 American Chemical Society; 2006; 79–104. (ACS Symposium Series; vol. 934).
473 Available from: http://dx.doi.org/10.1021/bk-2006-0934.ch004.
474 31. Takieddin M, Fassihi R. A Novel Approach in Distinguishing Between Role of
475 Hydrodynamics and Mechanical Stresses Similar to Contraction Forces of GI Tract on
476 Drug Release from Modified Release Dosage Forms. AAPS PharmSciTech. 2014;
477 16(2):278–83.
478 32. Vrbanac H, Krese A. The influence of different mechanical stress on the release properties
479 of HPMC matrix tablets in sucrose-NaCl media. J Drug Deliv Sci Technol. 2019;
480 54:101246.
481 33. Parojčić J, Vasiljević D, Ibrić S, Djurić Z. Tablet disintegration and drug dissolution in
482 viscous media: Paracetamol IR tablets. Int J Pharmaceut. 2008; 355(1):93–9.
483 34. Klein S. The Use of Biorelevant Dissolution Media to Forecast the In Vivo Performance
484 of a Drug. AAPS J. 2010; 12(3):397–406.
485 35. Nokhodchi A, Asare-Addo K. Drug release from matrix tablets: physiological parameters
486 and the effect of food. Expert Opin Drug Deliv. 2014; 11(9):1401–18.

36. Koziolek M, Kostewicz E, Vertzoni M. Physiological Considerations and In Vitro Strategies for Evaluating the Influence of Food on Drug Release from Extended-Release Formulations. AAPS PharmSciTech. 2018; 19(7):2885–97.
37. Fredriksson H, Bjorck I, Andersson R, Liljeberg H. Studies on α-amylase degradation of retrograded starch gels from waxy maize and high-amylopectin potato - ScienceDirect. Carbohydr Polym. 2000; 43(1):81–7.
38. Cai L, Shi Y-C, Rong L, Hsiao BS. Debranching and crystallization of waxy maize starch in relation to enzyme digestibility. Carbohydr Polym. 2010; 81(2):385–93.
39. Rahmouni M, Chouinard F, Nekka F, Lenaerts V, Leroux JC. Enzymatic degradation of cross-linked high amylose starch tablets and its effect on in vitro release of sodium diclofenac. Eur J Pharm Biopharm. 2001; 51(3):191–8.
40. Rubbens J, Brouwers J, Wolfs K, Adams E, Tack J, Augustijns P. Ethanol concentrations in the human gastrointestinal tract after intake of alcoholic beverages. Eur J Pharm Sci. 2016; 86:91-5.
41. Hsein H, Garrait G, Tamani F, Beyssac E, Hoffart V. Denatured Whey Protein Powder as a New Matrix Excipient: Design and Evaluation of Mucoadhesive Tablets for Sustained Drug Release Applications. Pharm Res. 2017; 34(2):365–77.
42. Onofre FO, Wang Y-J. Hydroxypropylated starches of varying amylose contents as sustained release matrices in tablets. Int J Pharmaceut. 2010; 385(1–2):104–12.
43. Jantratid E, Janssen N, Reppas C, Dressman JB. Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update. Pharm Res. 2008; 25(7):1663–76.
44. Baxevanis F, Kuiper J, Fotaki N. Strategic drug analysis in fed-state gastric biorelevant media based on drug physicochemical properties. Eur J Pharm Biopharm. 2018; 127:326–41.

45. Karrout Y, Neut C, Wils D, Siepmann F, Deremaux L, Dubreuil L, et al. Colon targeting with bacteria-sensitive films adapted to the disease state. Eur J Pharm Biopharm. 2009; 73(1):74–81.

46. Siepmann F, Karrout Y, Gehrke M, Penz FK, Siepmann J. Limited drug solubility can be decisive even for freely soluble drugs in highly swollen matrix tablets. Int J Pharmaceut. 2017; 526(1-2):280–90.

47. Siepmann J, Siepmann F. Sink conditions do not guarantee the absence of saturation effects. Int J Pharmaceut. 2020; 577:119009.

520 **FIGURE CAPTIONS**

521

522 Fig. 1 Optical macroscopy pictures of cross-sections of tablets based on cross-linked pregelatinized
523 potato starch, HPMC K100LV or HPMC K100M upon exposure for different time periods
524 (indicated on the left hand side) to the release medium: 0.1 N HCl for the first 2 h, followed
525 by phosphate buffer pH 6.8. The USP apparatus I was used. The tablets contained 30 %
526 diprophylline.

527 Fig. 2 Impact of the type of matrix former and release set-up on diprophylline release: The tablets
528 were based on cross-linked pregelatinized potato starch, HPMC K100LV or HPMC K100M,
529 as indicated in the diagrams. The USP apparatuses I, II, and III were used. The release medium
530 was 0.1 N HCl or phosphate buffer pH 6.8, as indicated. Mean values ± standard deviations
531 are indicated (n=3).

532 Fig. 3 Impact of the addition of ethanol to water as the release medium on diprophylline release from
533 tablets based on cross-linked pregelatinized potato starch, HPMC K100LV or HPMC K100M.
534 The USP apparatus I was used. Mean values ± standard deviations are indicated (n=3).

535 Fig. 4 Impact of the osmolality of the release medium on diprophylline release from tablets based
536 on cross-linked pregelatinized potato starch or HPMC K100M. The USP apparatus I was
537 used, the release medium was 0.1 N HCl during the first 2 h, followed by phosphate buffer
538 pH 6.8. Both media optionally contained different amounts of NaCl or sucrose, as indicated.
539 Mean values ± standard deviations are indicated (n=3).

540 Fig. 5 Effects of the addition of pancreatin, use of FaSSGF, FaSSIF, FeSSGF, FeSSIF, or “colonic
541 medium” on diprophylline release from cross-linked potato starch and HPMC K100M matrix
542 tablets. The USP apparatus I was used, the release medium was: a) 2 h 0.1 N HCl, followed
543 by 6 h phosphate pH 6.8, both optionally containing pancreatin; b) 2 h FaSSGF or FeSSGF,
544 followed by 6 h FaSSIF or FeSSIF; and c) 2 h 0.1 N HCl, followed by 2 h phosphate buffer
545 pH 6.8, followed by 4 h (in plastic flasks) inoculum of fecal samples from patients or healthy
546 subjects (as indicated). For reasons of comparison, also drug release into 0.1 N HCl (2 h),

followed by phosphate buffer pH 6.8 (22 h) is illustrated. Mean values ± standard deviations are indicated (n=3).

Fig. 6 Impact of mechanical stress on diprophylline release in 0.1 N HCl (first 2 h), followed by phosphate buffer pH 6.8. The results on the left-hand side were obtained with the USP apparatus I and optional compression cycles with a texture analyzer. The results on the right hand side were obtained with the USP apparatus III, optionally adding a silicone ball to the vessel. Details are described in the text. Mean values ± standard deviations are indicated (n=3).

Fig. 7 Impact of the initial drug content on diprophylline release from tablets based on cross-linked potato starch or HPMC K100M. 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. Mean values ± standard deviations are indicated (n=3).

Fig. 8 Dry mass loss (%), estimated polymer mass loss (%) and water content (%) of tablets based on cross-linked potato starch or HPMC K100M upon exposure to 0.1 N HCl (first 2 h), followed by phosphate pH 6.8. The USP apparatus I was used. Mean values ± standard deviations are indicated (n=3). The tablets contained 30 or 40 % diprophylline, as indicated.

Fig. 9 Influence of the type of drug (indicated in the diagrams) on drug release from tablets based on cross-linked potato starch or HPMC K100M upon exposure to 0.1 N HCl (first 2 h), followed by phosphate pH 6.8. The USP apparatus I was used. The initial drug content was 30 %. Mean values ± standard deviations are indicated (n=3).

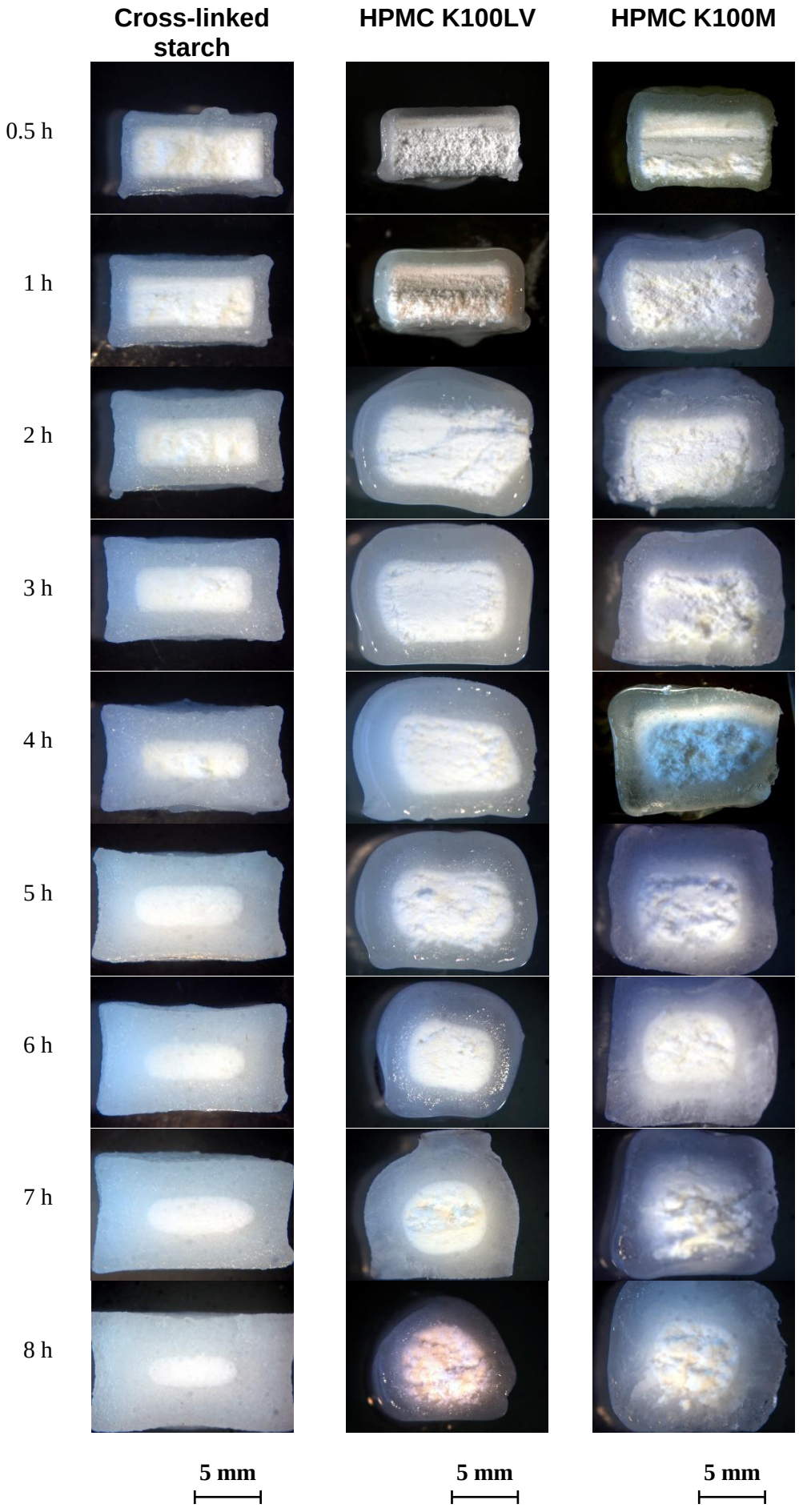
Cross-linked starch
HPMC K100LV
HPMC K100M
0.5 h
1 h
2 h
3 h
4 h
5 h
6 h
7 h
8 h
5 mm
5 mm
5 mm

Figure 1

568
569
570
571

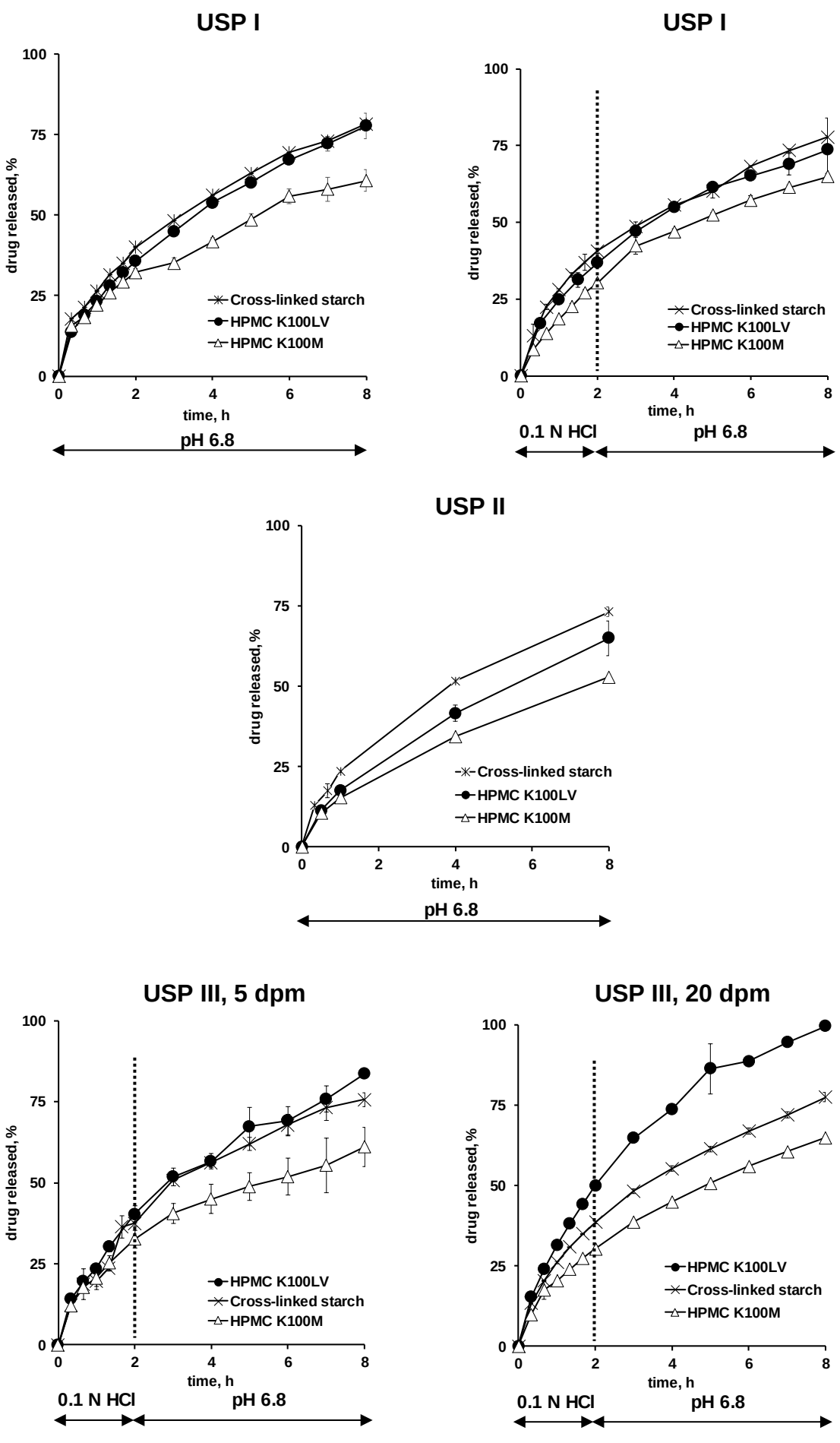

Figure 2

572

573

574

575

576

577

578

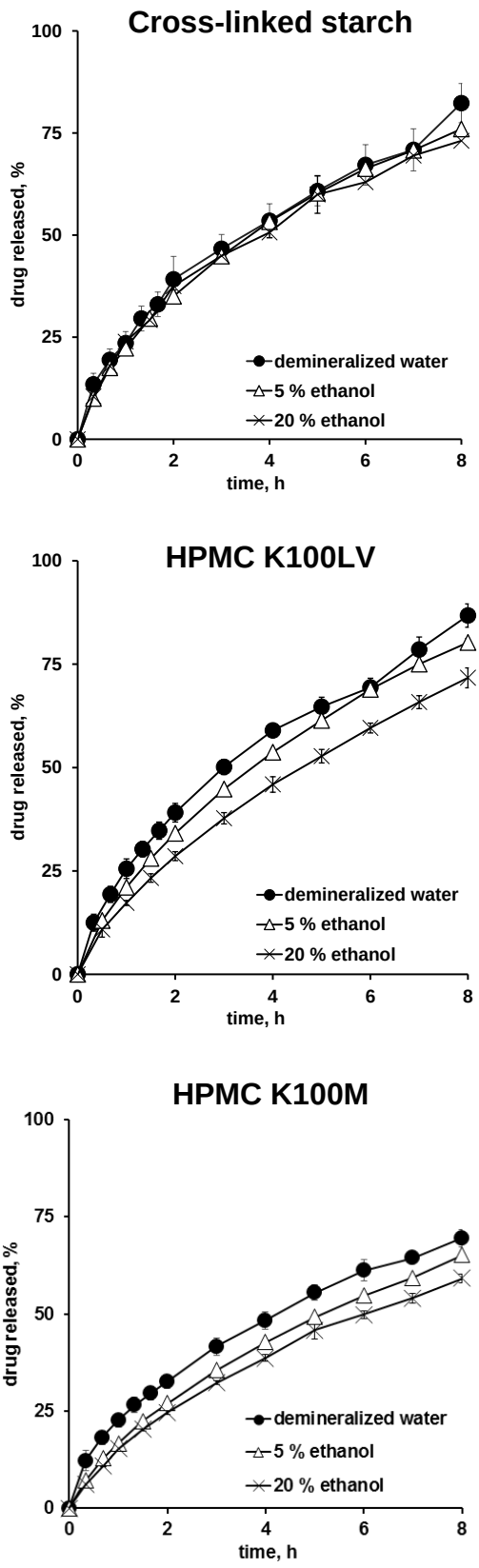

Figure 3

579
580
581
582
583
584
585
586

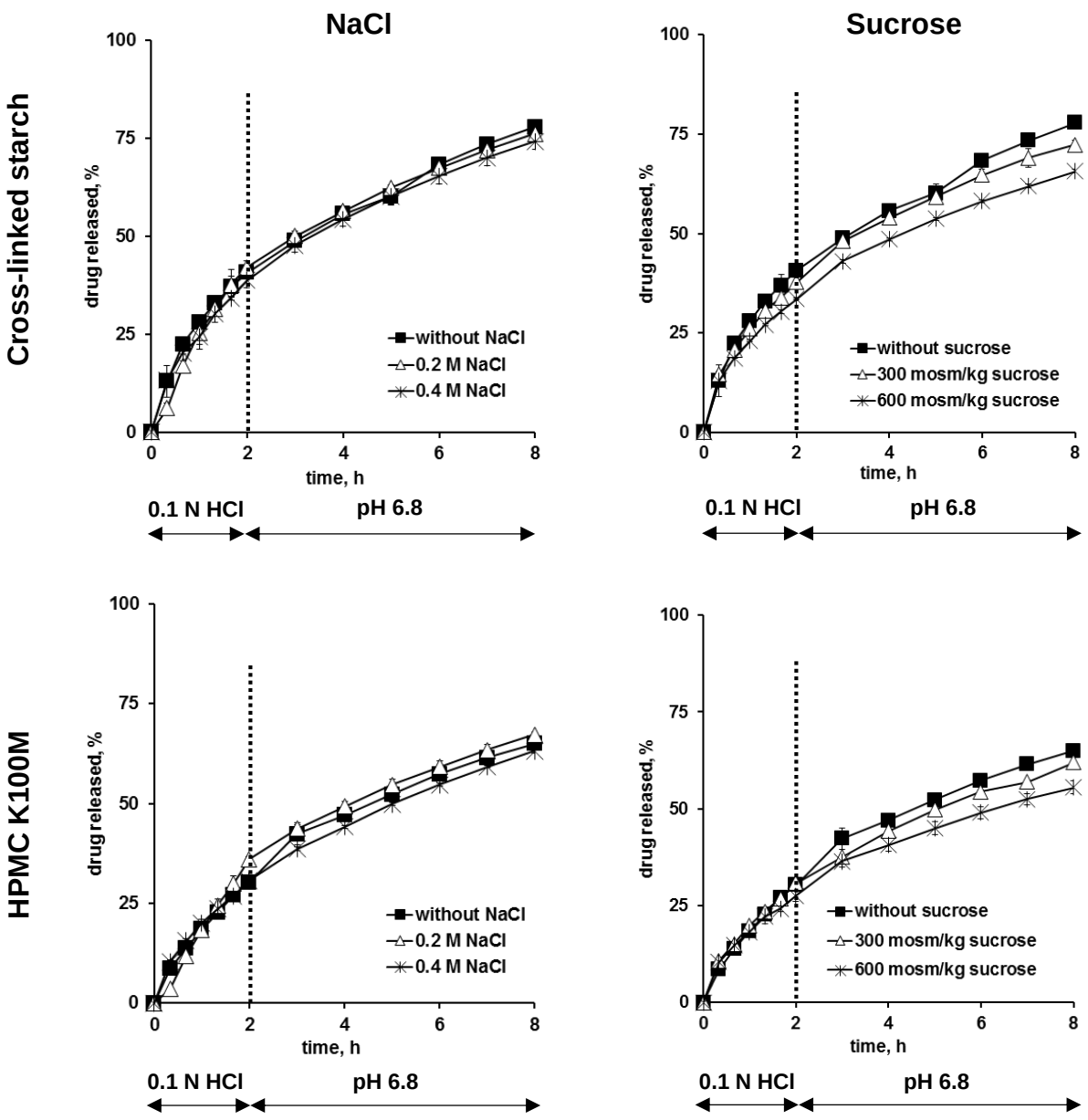

Figure 4

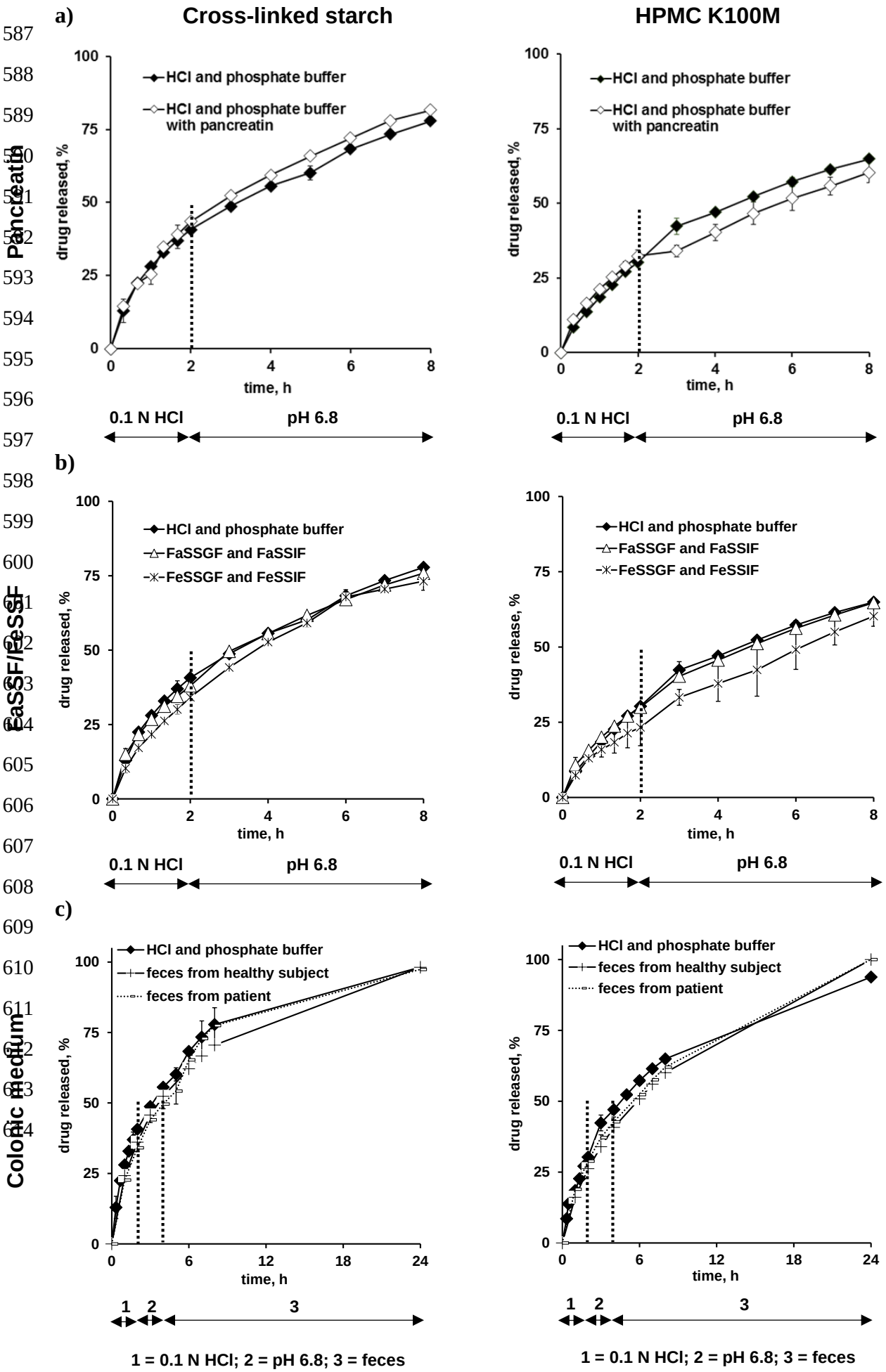
a)
Cross-linked starch
HPMC K100M
HCl and phosphate buffer
HCl and phosphate buffer with pancreatin
drug released, %
time, h
0.1 N HCl
pH 6.8
Pancreatin
b)
HCl and phosphate buffer
FaSSGF and FaSSIF
FeSSGF and FeSSIF
drug released, %
drug release, %
time, h
0.1 N HCl
pH 6.8
FaSSGF/FeSSGF
c)
HCl and phosphate buffer
feces from healthy subject
feces from patient
drug released, %
time, h
1 2 3
1 = 0.1 N HCl; 2 = pH 6.8; 3 = feces
Colonic medium

Figure 5

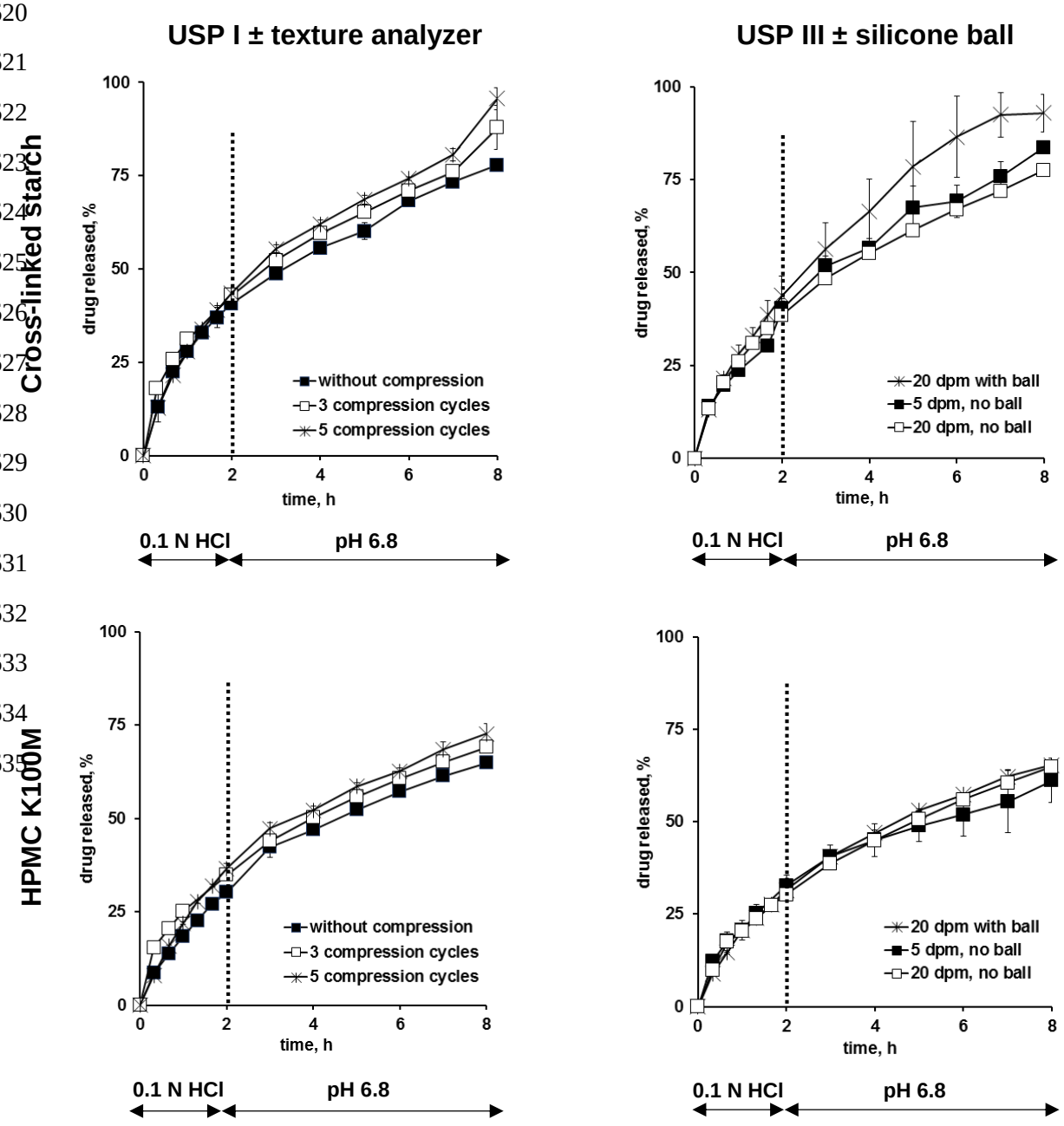
USP I ± texture analyzer
USP III ± silicone ball
Cross-linked starch
HPMC K100M
drug released, %
time, h
without compression
3 compression cycles
5 compression cycles
20 dpm with ball
5 dpm, no ball
20 dpm, no ball
0.1 N HCl
pH 6.8

Figure 6

636

637

638

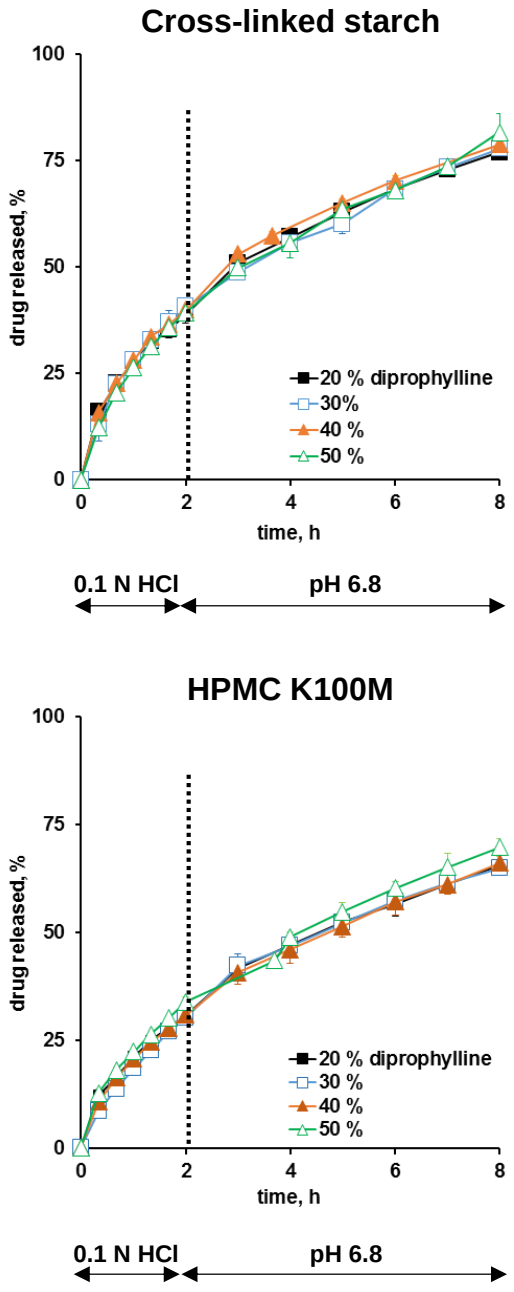

Figure 7

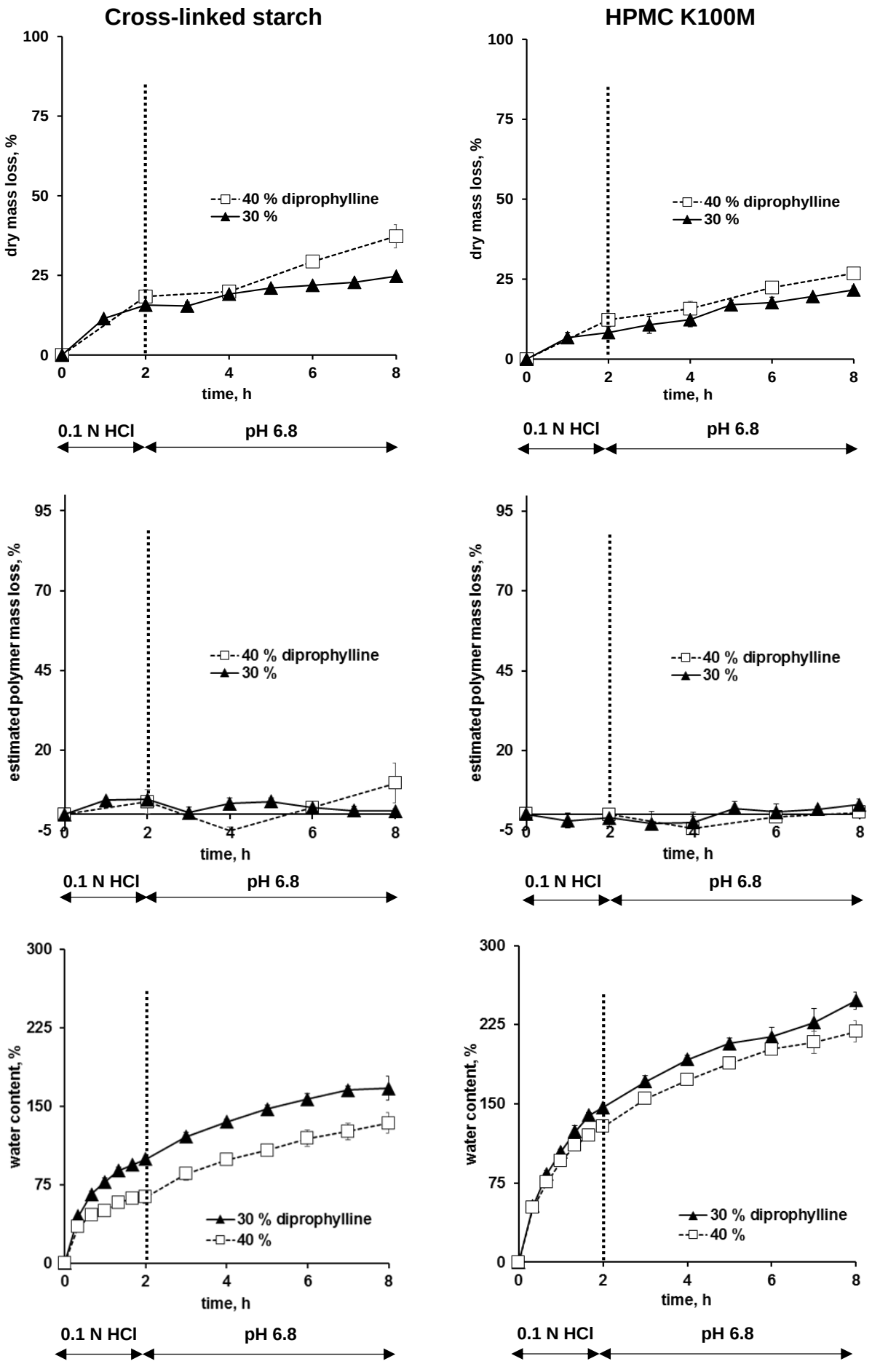
Cross-linked starch
HPMC K100M
dry mass loss, %
estimated polymer mass loss, %
water content, %
time, h
40 % diprophylline
30 %
30 % diprophylline
40 %
0.1 N HCl
pH 6.8

Figure 8

655

656

657

658

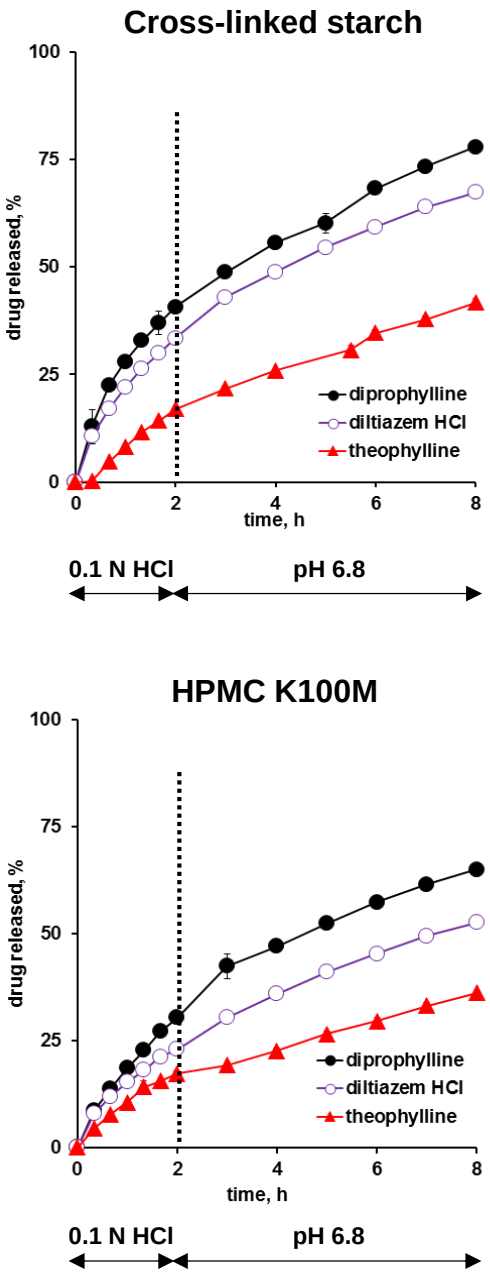

Figure 9