OUTPUT 5	Bio-based matrix solid dosage form for oral controlled drug delivery
Project specific objective	1) Innovative pharmaceutical formulations and technologies
Output description	Products will be ready to use for pharmaceutical applications in animals. Prototypes and comprehensive data based on their physico chemical key properties and optimized processing parameters.
Project Output Target	1
Expected project specific result (s)	1 new excipient for use in release formulations using bio-based products such as zein produced by PP11 (ROQUETTE). The developed product will increase the competitiveness of industries in the field and create new jobs opportunities. 1 Patent is targeted
Partner responsible	PP11 (Roquette)
Other Partners involved	LP 12 (University of Lille)

Summary of the objectives, activities and achievements obtained during the project
(in an understandable style for non-specialists) (1/2 to 1 page max)

There are 5 deliverables composing the Output 5 :

- D 1.5.1: Review on polymeric excipients (submitted 31/12/2017)
- D 1.5.2: Preparation of bio-based excipients (submitted 31/12/2018)
- D 1.5.3: Evaluation of the potential of new bio-based excipients in various formulations (under submission)
- D 1.5 4: Filed patent application related to Output O.5.1
- D 1.5.5: Granted patent related to Output O.5.1

The research work in this project was done by PP11 and PL12. It consisted in researching new plant-based excipients for sustained release matrix tablets.
The first part of this project consisted in a huge screening step to evaluate the properties of starch derivatives polymers with various chemical or physical modifications. At the end of this stage, a very good candidate for such application was identified. In addition, precise knowledge is now established on the critical parameters driving the functionalities of starch derivatives in such application.
The second part of this project consisted in improving further the properties of this candidate. Actually, this product being initially developed for food applications, this amelioration step is essential to fulfil with pharmaceutical requirements in term of processability.
Finally, we have a new excipient to use in sustained release formulations having good processability properties as required in the pharmaceutical industry.

This report presents into detail the great ability and the robustness of the identified candidate for sustained release matrix tablets applications in various conditions of release.
Concerning the improvement step for processability, it is described in D 1.5.3.
Concerning patentability, we identified after a deep literature and patent review that the candidate found during this work is not patentable (see D 1.5.4). Therefore, it was decided to publish the obtained results.

1) Description of the scientific and technological achievements

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 and water, optionally containing different amounts of NaCl, sucrose, ethanol or pancreatin, FaSSGF, FeSSGF, FaSSIF, FeSSIF and 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.

Experimental Section

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™ K100 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:

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 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), 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. (40). 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 (41). 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) (42) 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) trichloracetic acid solution (sample: trichloracetic acid solution ratio = 1:2). The mixtures were vortexed (30 s), centrifuged (15 min at 8000 rpm) and filtered prior to HPLC-UV analysis (43).

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 or phosphate buffer pH 6.8, as indicated. 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 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 (44). 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, Kimberely-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:

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

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

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:

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

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 demineralized water 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 K100 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 K100- 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.
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.

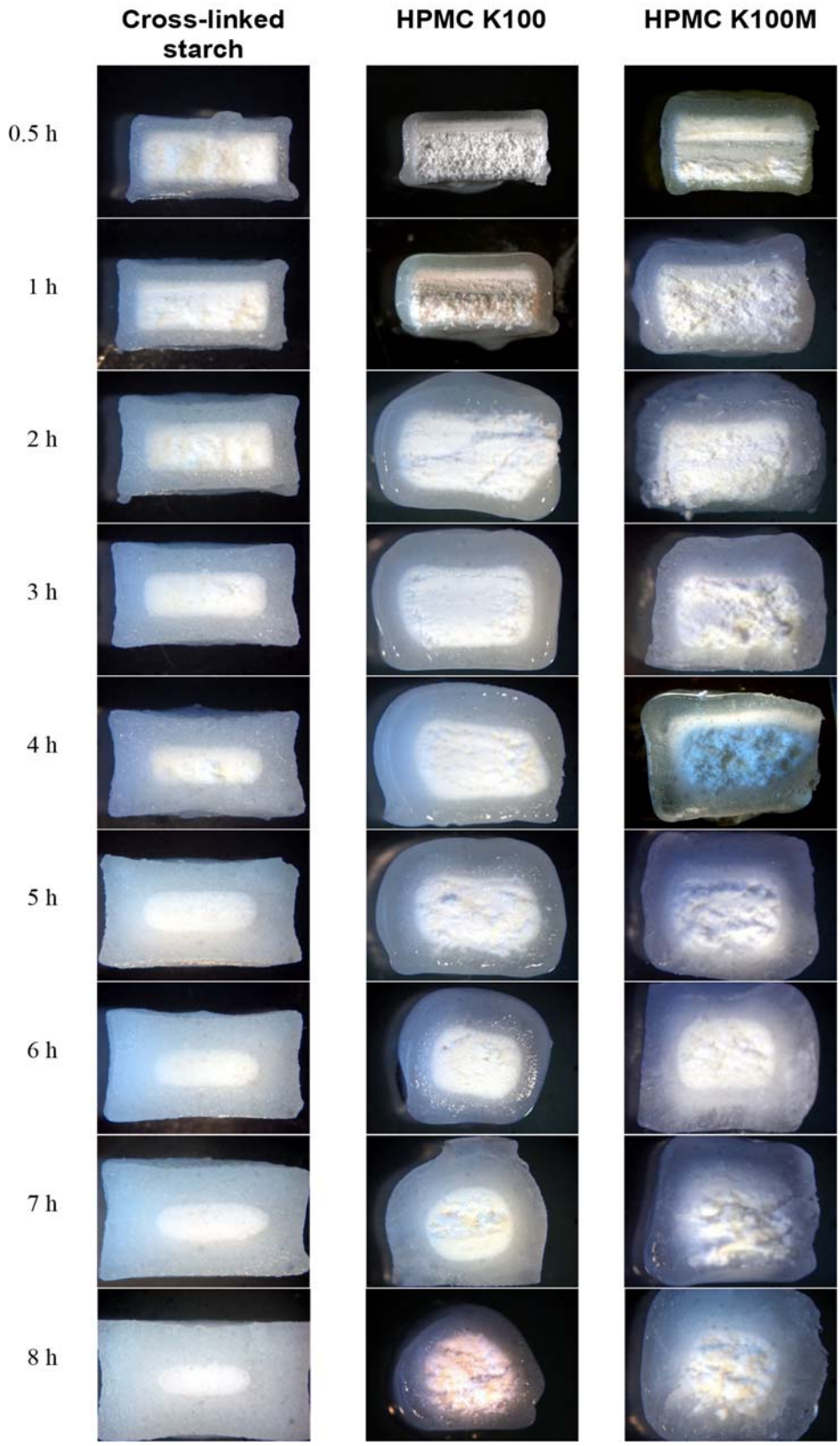

Fig. 1 Optical macroscopy pictures of cross-sections of tablets based on cross-linked pregelatinized potato starch, HPMC K100 or HPMC K100M upon exposure for different time periods (indicated on the left hand side) to the release medium: 0.1 N HCl for the first 2 h, followed by phosphate buffer pH 6.8. The USP apparatus I was used. The tablets contained 30 % diprophylline.

Impact of the type of polymer

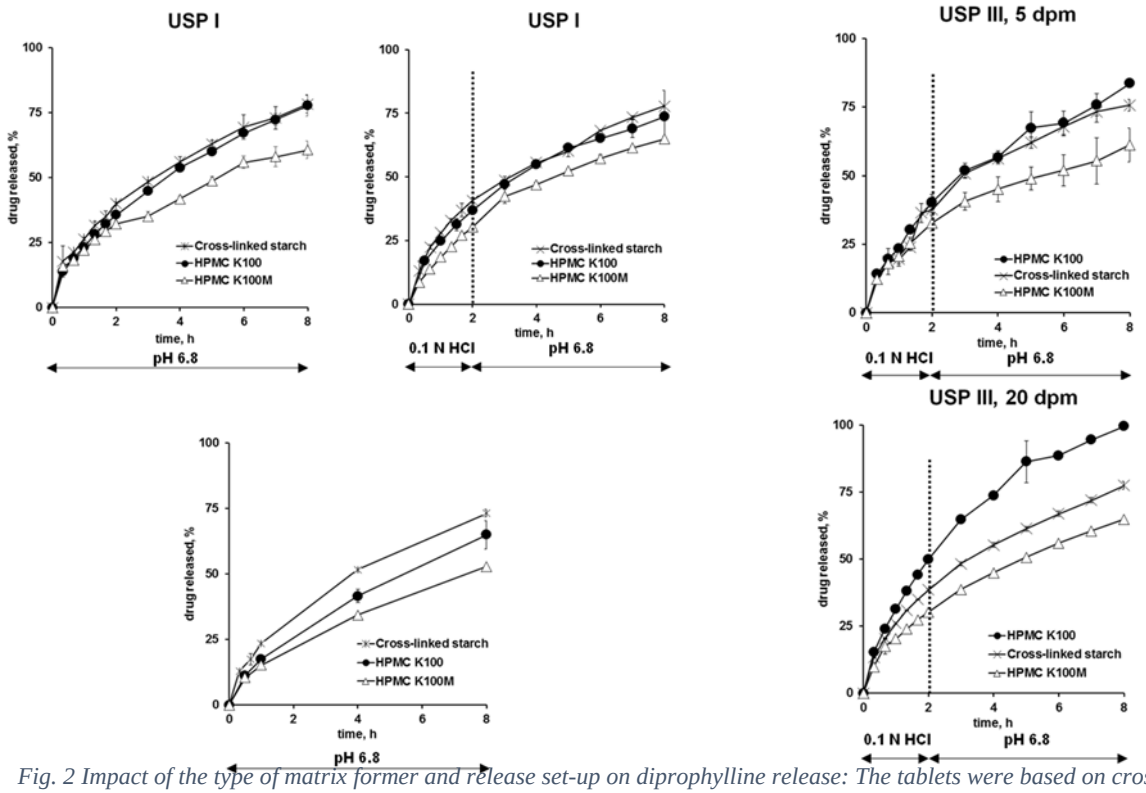

Fig. 2 Impact of the type of matrix former and release set-up on diprophylline release: The tablets were based on cross-linked pregelatinized potato starch, HPMC K100 or HPMC K100M, as indicated in the diagrams. The USP apparatuses I, II, and III were used. The release medium was 0.1 N HCl or phosphate buffer pH 6.8, as indicated. Mean values ± standard deviations are indicated (n=3).

The resulting diprophylline release kinetics from matrix tablets based on cross-linked pregelatinized potato starch, HPMC K100 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 K100-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 K100- and HPMC K100M-based tablets. In contrast, when using the USP III apparatus at 20 dpm, diprophylline release was fastest from HPMC 100K-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

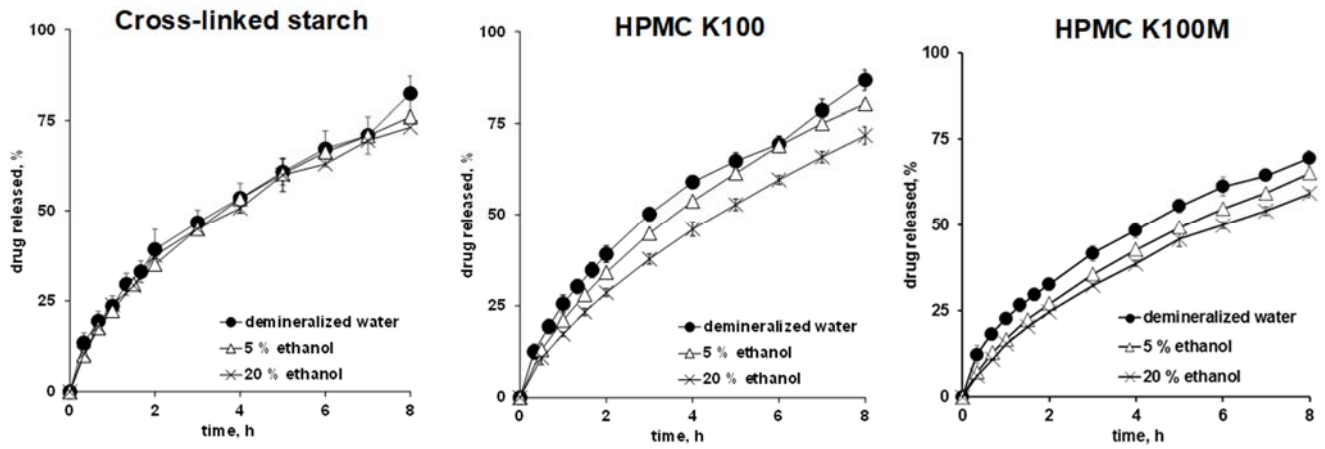

Fig. 3 Impact of the addition of ethanol to water as the release medium on diprophylline release from tablets based on cross-linked pregelatinized potato starch, HPMC K100 or HPMC K100M. The USP apparatus I was used. Mean values ± standard deviations are indic

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 K100 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 K100 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.

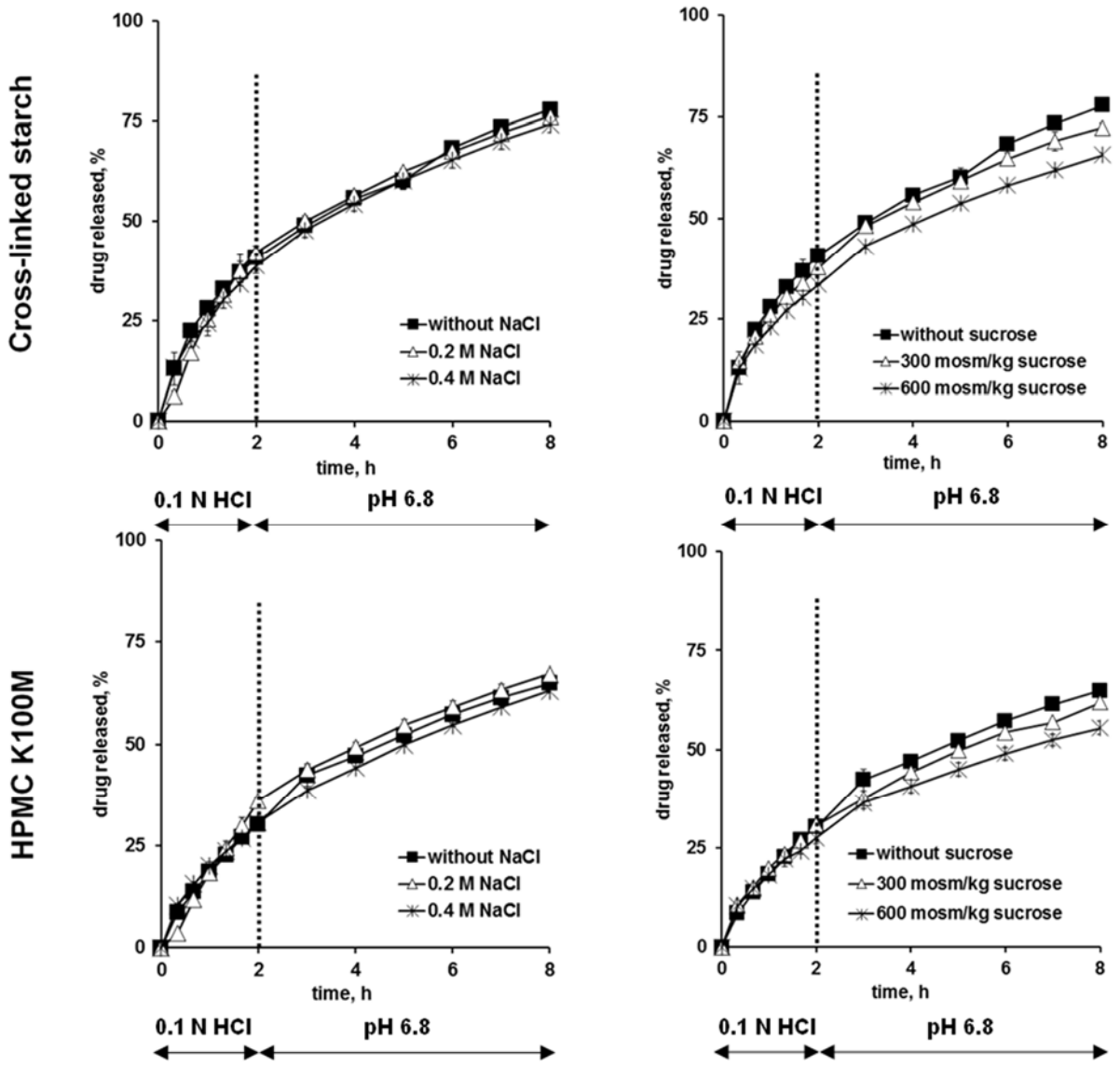

Fig. 4 Impact of the osmolality of the release medium on diprophylline release from tablets based on cross-linked pregelatinized potato starch or HPMC K100M. The USP apparatus I was used, the release medium was 0.1 N HCl during the first 2 h, followed by by phosphate buffer pH 6.8. Both media optionally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

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.

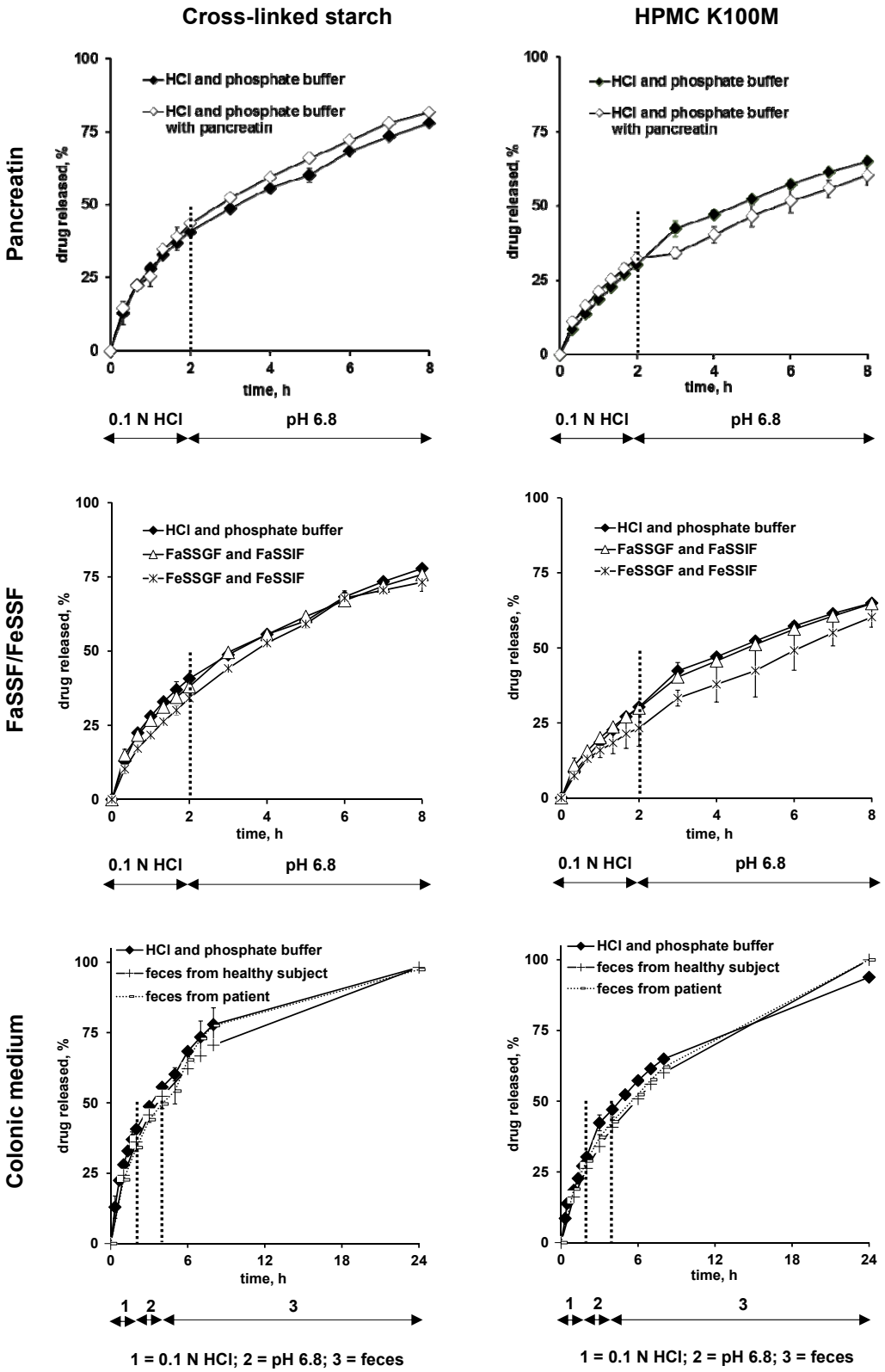

Fig. 5 Effects of the addition of pancreatin, use of FaSSF or FeSSF, or "colonic medium" on diprophylline release from cross-linked potato starch and HPMC K100M matrix tablets. The USP apparatus I was used, the release medium was a) 2 h 0.1 N HCl, followed by 6 h phosphate pH 6.8, both optionally containing pancreatin; b) 2 h FaSSGF or FeSSGF, followed by 6 h FaSSIF or FeSSIF; and c) 2 h 0.1 N HCl, followed by 2 h phosphate buffer pH 6.8, followed by 4 h (in plastic flasks) inoculum of fecal samples from patients or healthy 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).

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: FaSSF, FeSSF, 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

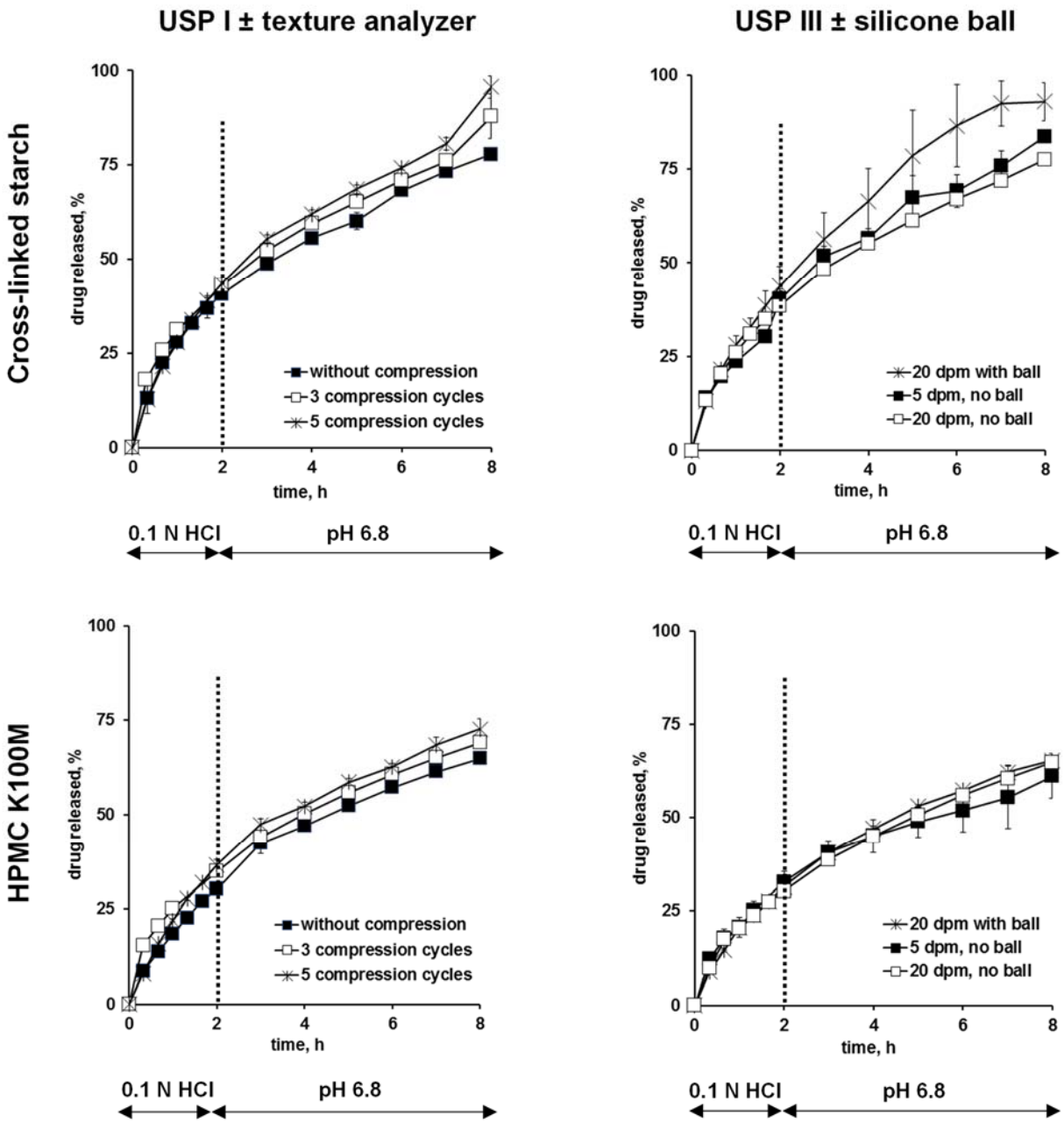

Fig. 6 Impact of mechanical stress on diprophylline release in 0.1 N HCl (first 2 h), followed by phosphate buffer pH 6.8. The results on the left-hand side were obtained with the USP apparatus I and optional compression cycles with a texture analyzer. The results on the left-hand side were obtained 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).

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: Drug release is likely not substantially affected by the motility of the gastro intestinal tract (at least within the investigated force ranges and under similar conditions).

Effects of the amount and type of drug

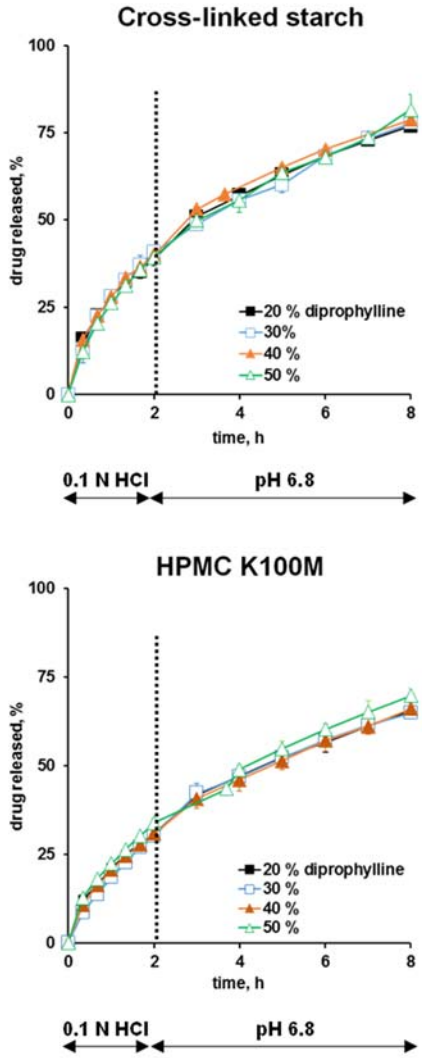

Fig. 7Impact of the initial drug content on diprophylline release from tablets based on cross-linked potato starch or HPMC K100M. The USP apparatus I was used, the release medium was 0.1 N HCl for the first 2 h, followed by phosphate pH 6.8. Mean values ± standard deviations are indicated (n=3).

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.

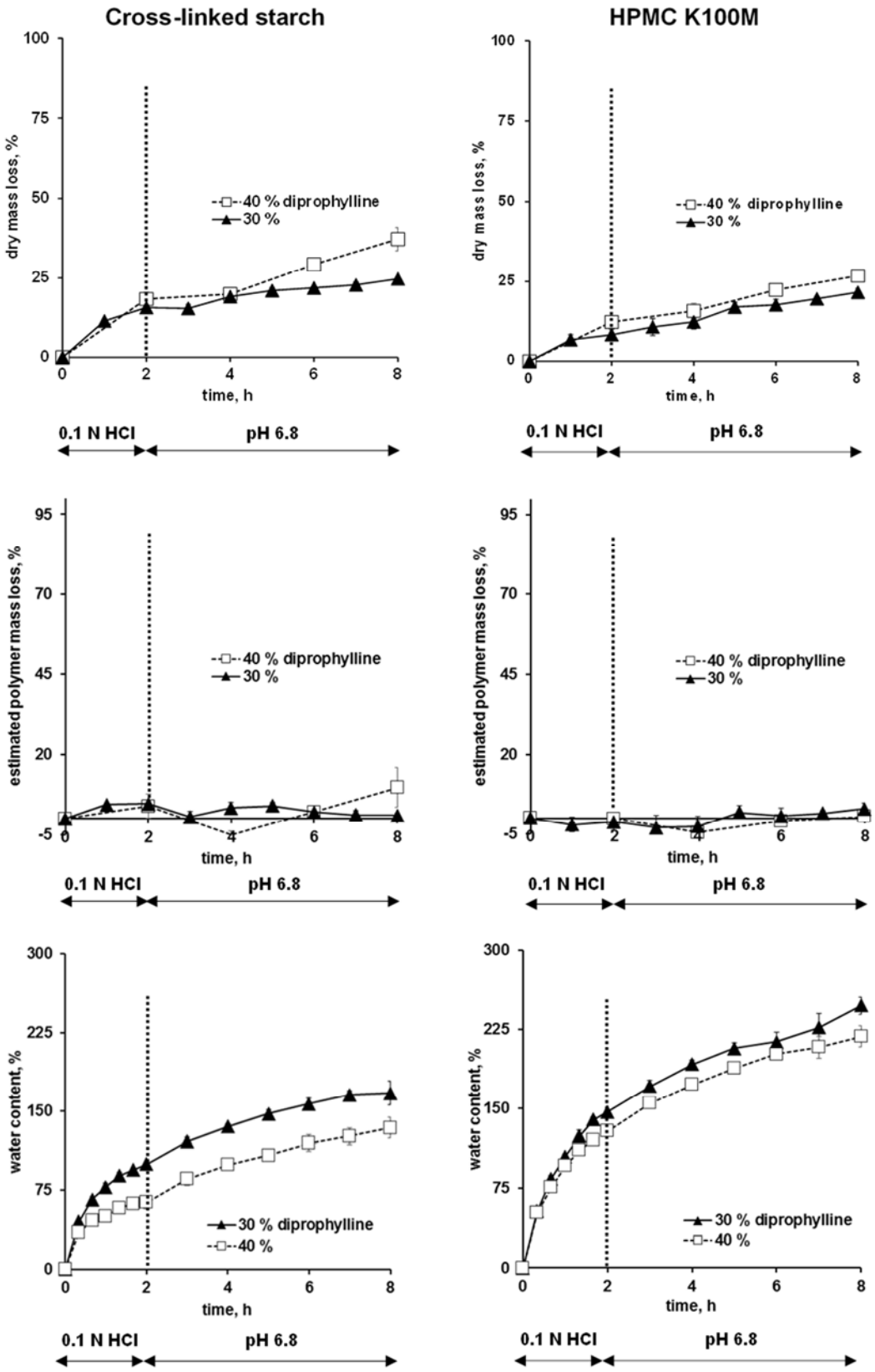

Fig. 8 Dry mass loss (%), estimated polymer mass loss (%) and water content (%) of tablets based on cross-linked potato starch or HPMC K100M upon exposure to 0.1 N HCl (first 2 h), followed by phosphate pH 6.8. The USP apparatus I was used. Mean values ± standard deviations are indicated (n=3). The tablets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

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 (45,46). 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.

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2) Description of the results obtained for the output in term of specific results category and specific result type (1 to 3 pages). Use the following table.

Specific results category And Specific result type	Description of the specific results
Knowledge - Created/Increased skill and capacities 1 new excipient for use in release formulations using bio-based products such as zein produced by PP11 (ROQUETTE).	Measured by the end of the project: 1 PhD thesis via examination and manuscript. Since no patent can be filled at this stage (see D1.5.4), it was decided to publish the work done. First article ("Robustness of controlled release tablets based on a cross-linked pregelatinized potato starch matrix") was submitted on December 31th 2019 to the AAPS PharmSciTech. Three more articles are being written and will be submitted in 2020. International communication was made at the 8th BioFIT conference in Marseille, France (December 10th 2019) (annex "Presentation BioFIT") In addition, 4 abstracts for posters were submitted to the 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, March 23rd-26th 2020 in Vienna: • Sustained release matrix tablets based on starches: Impact of the starch nature and chemical modifications (annex "Poster 1 PBP") • Cross-linked potato starch matrix tablets for controlled drug delivery (annex "Poster 2 PBP") • Robustness of drug release from cross-linked potato starch-based controlled release tablets (annex "Poster 3 PBP") • Co-processed starch/mannitol as a promising excipient for direct compression of controlled release tablets (annex "Poster 4 PBP")
Socio-Economic -Increased business activities/capacities (new products, processes, services, techniques) The developed product will increase the competitiveness of industries in the field.	Measured on mid/long-term basis (2022- 2024): Product sales will be the indicator of increased activity/business and new products used by targeted groups.
Socio-Economic – Increased employability The developed product will create new jobs opportunities.	Measured on mid/long-term basis (2022- 2024): New job creation will be the results of sales and expected in the same time frame as increased activity/business.

List of documents enclosed as annex

Images	
Reports and high impact publications	"Robustness of controlled release tablets based on a cross-linked pregelatinized potato starch matrix", submitted on December 31th 2019 to the AAPS PharmSciTech (annex "Article"
Communications in European and/ or international events	• Oral communication: STARCH MATRIX TABLETS FOR CONTROLLED DRUG DELIVERY 8th BioFIT conference in Marseille, France (December 10th 2019) (annex "Presentation BioFIT") • Abstract for posters Submitted to the 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, March 23rd-26th 2020 in Vienna: - Sustained release matrix tablets based on starches: Impact of the starch nature and chemical modifications (annex "Poster 1 PBP") - Cross-linked potato starch matrix tablets for controlled drug delivery (annex "Poster 2 PBP") - Robustness of drug release from cross-linked potato starch-based controlled release tablets (annex "Poster 3 PBP") - Co-processed starch/mannitol as a promising excipient for direct compression of controlled release tablets (annex "Poster 4 PBP")
Patent prior art search & patent preparation	
Patent	
Official letters from company(ies)	
…	…