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

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1   **Abstract**

2   The aim of this study was to evaluate the potential of a cross-linked pregelatinized potato

3   starch (PREGEFLO® PI10) as matrix former for controlled release tablets. Different types of tablets

4   loaded with diprophylline, diltiazem HCl or theophylline were prepared by direct compression

5   of binary drug:polymer blends. The drug content was varied from 20 to 50%. Two hydroxypropyl

6   methylcellulose grades (HPMC K100LV and K100M) were studied as alternative matrix formers.

7   Drug release was measured in a variety of release media using different types of experimental set-

8   ups. This includes 0.1 N HCl, phosphate buffer pH 6.8 and water, optionally containing different

9   amounts of NaCl, sucrose, ethanol or pancreatin, Fasted State Simulated Gastric Fluid, Fed State

10 Simulated Gastric Fluid, Fasted State Simulated Intestinal Fluid, Fed State Simulated Intestinal Fluid

11 as well as media simulating the conditions in the colon of healthy subjects and patients suffering

12 from Crohn's disease. The USP apparatuses I/II/III were used under a range of operating conditions

13 and optionally coupled with the simulation of additional mechanical stress. Importantly, the drug

14 release kinetics were not substantially affected by the investigated environmental conditions

15 from tablets based on the cross-linked pregelatinized potato starch, similar to HPMC tablets.

16 However, in contrast to the latter, the starch based tablets roughly kept their shape upon exposure the

17 release media (they "only" increased in size) during the observation period, and the water penetration

18 into the systems was much less pronounced. Thus, the investigated cross-linked pregelatinized potato

19 starch offers an interesting potential as matrix former in controlled release tablets.

20

21 **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.

49   Generally, the resulting drug release kinetics from a controlled drug delivery system are measured

50   in vitro under conditions aiming to simulate those encountered in vivo. However, care must be taken

51   when drawing conclusions based on in vitro data, especially in case of highly swollen polymeric matrix

52   systems. This is because the conditions in the gastro intestinal tract in a patient are often complex and

53   not always fully reflected by commonly used in vitro release set-ups. In particular, mechanical stress

54   experienced due to the motility of the stomach and small intestine might favor the disintegration of

55   fragile dosage forms, resulting in accelerated drug release (31,32). Also, the composition of the fluids

56   the controlled release dosage form is exposed to might affect the resulting drug release rate (33–36). For

57   instance, the presence of certain enzymes might lead to the degradation of a polymeric matrix former,

58   e.g. starches can be degraded by amylases (37,38), potentially resulting in accelerated drug release (39).

59   This might not be detected using standard in vitro drug release measurements set-ups and conditions.

60   The major aims of the present study were: (i) to prepare different types of controlled release matrix

61   tablets based on a cross-linked pregelatinized potato starch (PREGEFLO ® PI10), varying the type and

62   amount of drug; (ii) to measure the resulting drug release kinetics using a variety of experimental set-

63   ups (USP apparatuses I, II and III), operation conditions (e.g. dipping speed, medium change) in a range

64   of release media (0.1 N HCl, phosphate buffer pH 6.8, water, FaSSGF, FeSSGF, FaSSIF, FeSSIF, and

65   cell culture medium; optionally containing different amounts of NaCl, sucrose, ethanol, pancreatin or

66   fecal samples from healthy volunteers or Crohn's disease patients), and optionally simulating mechanical

67   stress using a texture analyzer or silicone balls; and (iii) to study HPMC as alternative matrix former for

68   reasons of comparison.

69

70

71   **MATERIALS AND METHODS**

72

73   **Materials**

74   Diprophylline fine powder and theophylline monohydrate fine powder (BASF, Ludwigshafen,

75   Germany); diltiazem hydrochloride (diltiazem HCl; Teva, Netanya, Israel); cross-linked pregelatinized

76   potato starch (PREGEFLO® PI10; Roquette Freres, Lestrem, France); hydroxypropyl methylcellulose

77 (HPMC, METHOCEL™ K100LV and K100M; Stobec, Quebec, Canada); magnesium stearate

78 (Baerlocher, Unterschleissheim, Germany); sodium chloride (NaCl; Cooper, Melun, France); sucrose

79 (Seppic, Paris, France); lecithin (Alfa Aesar, Karlsruhe, Germany); sodium acetate anhydrous, pepsin,

80 ethanol, acetic acid glacial, hydrochloric acid (HCl) and acetonitrile (Fisher, Loughborough, UK);

81 pancreatin from porcine pancreas (8 x more concentrated than the USP 43 specification), sodium

82 taurocholate and trichloroacetic acid (TCA) (Sigma Aldrich, Saint Louis, USA); extracts from beef,

83 yeast, tryptone (= pancreatic digest of casein) (Becton Dickinson, Sparks, USA); L-cysteine

84 hydrochloride hydrate (Acros Organics, Geel, Belgium); cysteinated Ringer solution (Merck,

85 Darmstadt, Germany).

86

87 **Tablet preparation**

88 Tablets were prepared by direct compression. The drug content was varied from 20 to 50 % (w/w).

89 Diprophylline, diltiazem HCl or theophylline powder was blended with cross-linked pregelatinized

90 potato starch or HPMC powder in a Turbula mixer (Bachoven, Basle, Switzerland) at 49 rpm for 5 min.

91 Upon addition of magnesium stearate (1 %, w/w), the powder blend was further mixed for 3 min at

92 49 rpm. Cylindrical tablets (400 mg) were prepared with single-punched rotary press (Stylcam 200 R;

93 Medelpharm, Bynost, France), equipped with flat-faced punches (diameter = 10 mm, manual die filling).

94 The hardness of the tablets was kept constant at 100 N (measured with a tablet hardness tester;

95 Pharmatron SmartTest 50; Sotax, Basle, Switzerland). The tablet dimensions were measured using a

96 micrometer gauge (Digimatic Micrometer; Mitutoyo, Tokyo, Japan).

97

98 **In vitro drug release measurements**

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

100 USP apparatus I (basket):

101 The USP apparatus I (AT7 Smart; Sotax) was used at 75 rpm and 37 °C. The release medium was

102 900 mL demineralized water, 0.1 N HCl or phosphate buffer pH 6.8 (USP 43). At predetermined time

103 points, 5 mL samples were withdrawn (replaced with fresh medium), filtered (PTFF syringe filters,

104 0.22 µm; GE Healthcare, Kent, UK) and analyzed by UV-spectrophotometry (UV-1650 PC; Shimadzu,

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

106   respectively.

107   If indicated, different amounts of NaCl or sucrose were added to the release medium. Or,

108   demineralized water, optionally containing 5 or 20 % ethanol (v/v) (40) was used. In these cases, the

109   diprophylline content of the withdrawn samples was determined by HPLC-UV analysis using a method

110   adapted from Hsein et al. (41). The HPLC system (Waters e2695; Waters, Milford, USA) was equipped

111   with a UV/Vis detector (λ= 274 nm) and reversed-phase column C18 (Luna Polar 3 µm; 4.8 mm x

112   150 mm, 30 °C; Phenomenex, Le Pecq, France). The mobile phase was a 90:10 (v/v) blend of 0.01 M

113   acetate buffer pH 4.5: acetonitrile, the flow rate was 1 mL/min. The injection volume was 5 µL.

114   Furthermore, pancreatin with an α-amylase activity of 108.000 IU/L was optionally added to the

115   phosphate buffer pH 6.8 (42). In these cases, the withdrawn samples were centrifuged (5 min, 8000 rpm)

116   prior to filtering and HPLC-UV analysis.

117   In addition, Fasted State Simulated Gastric Fluid (FaSSGF), Fed State Simulated Gastric Fluid

118   (FeSSGF), Fasted State Simulated Intestinal Fluid (FaSSIF) or Fed State Simulated Intestinal Fluid

119   (FeSSIF) (43) were used as release media. In these cases, the diprophylline content in the withdrawn

120   samples was determined upon precipitation with an aqueous 10 % (w/v) trichloroacetic acid solution

121   (sample: trichloroacetic acid solution ratio = 1:2). The mixtures were vortexed (30 s), centrifuged

122   (15 min at 8000 rpm) and filtered prior to HPLC-UV analysis (44).

123   If indicated, tablet samples were mechanically stressed at each sampling time point (adapted from

124   31) as follows: The tablets were placed into Petri dishes and a texture analyzer (TA.XT.Plus, 1 kg load

125   cell; Stable Micro Systems, Surrey, UK), equipped with a 40 mm flat-ended plate probe, was used to

126   exert a force of up to 2 N onto the axial surface of the tablet. One "compression cycle" was as follows:

127   The probe was driven downwards at a speed of 0.5 mm/s. Once in contact with the surface of the tablet,

128   a steadily increasing force was exerted until a value of 2 N was reached. The probe was subsequently

129   driven upwards at a speed of 10 mm/s. Three or five "compression cycles" were run, as indicated. The

130   tablets were carefully placed back into the vessels. The Petri dishes were rinsed with 5 mL release

131   medium. The drug content in the samples was determined by HPLC-UV as described above.

132

133 USP apparatus II (paddle):

134   The USP apparatus II (AT7 Smart; Sotax) was used at 75 rpm and 37 °C. The release medium was

135 900 mL 0.1 N HCl or phosphate buffer pH 6.8, as indicated. At pre-determined time points, 5 mL

136 samples were withdrawn (replaced with fresh medium) and analyzed for their diprophylline content by

137 UV spectrophotometry (UV-1650 PC) at λ= 274.

138 USP apparatus III (Bio-Dis):

139   The USP apparatus III (Agilent Technologies, Massy, France) was used at 5 and 20 dpm and 37 °C.

140 The release medium was 200 mL 0.1 N HCl during the first 2 h, followed by 200 mL phosphate buffer

141 pH 6.8. At predetermined time points, 5 mL samples were withdrawn (replaced with fresh medium) and

142 drug release was measured using HPLC-UV spectrophotometry (as described above). If indicated,

143 silicone balls (17 mm diameter, 4.5 g) were added to the vessels (1 ball per vessel) to **better** simulate

144 the mechanical stress experienced in the gastrointestinal tract.

145 USP apparatus I, followed by inoculation with fecal samples:

146   Tablets were exposed to 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 for 2 h in a USP

147 apparatus I, as described above. The tablets were then transferred into 120 mL flasks, filled with 100 mL

148 culture medium inoculated with fecal samples from healthy subjects or patients suffering from Crohn's

149 disease. Culture medium was prepared by dissolving 1.5 g beef extract, 3 g yeast extract, 5 g tryptone,

150 2.5 g NaCl and 0.3 g L-cysteine hydrochloride hydrate in 1 L distilled water (pH 7.0 ± 0.2) and

151 subsequent sterilization in an autoclave. Fresh fecal samples from patients suffering from Crohn's

152 disease as well as from healthy subjects were diluted 1:200 with cysteinated Ringer solution; 2.5 mL of

153 this suspension was diluted with culture medium to 100 mL (45). The flasks were agitated at 50 rpm

154 and 37 °C under anaerobic conditions (AnaeroGen 2.5 L; Thermo Fisher Scientific; Illkirch, France).

155 At predetermined time points, 2 mL samples were withdrawn, centrifuged (5 min at 8000 rpm), filtered

156 and analyzed by HPLC-UV as described above.

157   All in vitro drug release experiments were conducted in triplicate, mean values +/- standard

158 deviations are reported.

159

160 **Swelling and erosion studies**

161   The swelling kinetics of the tablets were monitored upon exposure to 0.1 N HCl and phosphate

162 buffer pH 6.8 using the USP apparatus I (37 °C, 75 rpm; AT7 Smart). At predetermined time points,

163 specimen were withdrawn and excess surface water was gently removed with absorbent tissue (Kimtech,

164 Kimberly-Clark, Reigate, UK). The tablets were weighed [*wet mass (t)*] and dried to constant weight at

165 60 °C in an oven [*dry mass (t)*]. The dynamic changes in the system's water content and dry mass loss

166 were calculated as follows:

167
$$\text{water content (\%) (t)} = \frac{\text{wet mass (t)} - \text{dry mass (t)}}{\text{wet mass (t)}} \cdot 100\ \% \tag{1}$$

168

169
$$\text{dry mass loss (\%) (t)} = \frac{\text{dry mass (t = 0) - dry mass (t)}}{\text{dry mass (t = 0)}} \cdot 100\ \% \tag{2}$$

170

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

172   Assuming that the amounts of ions penetrating from the release media into the tablets are negligible,

173 the following equation was used to estimate the polymer mass loss over time:

174

175
$$\text{estimated polymer mass loss (\%) (t) =} \tag{3}$$
$$\frac{\text{(dry mass (t=0) - (dry mass (t) + amount of drug released (t))}}{\text{polymer mass (t = 0)}} \cdot 100\ \%$$

176 where *amount of drug released (t)* is the amount of drug released at time *t*, and *polymer mass (t=0)* is

177 the polymer mass in the tablets before exposure to the release medium.

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

179   In addition, withdrawn tablet samples were deep-frozen at -20 °C and cut into halves using a scalpel

180 (Feather, Osaka, Japan). Pictures of cross-sections were taken with an Axiovision Zeiss Scope-A1

181 microscope, equipped with an AxioCam ICc1 (Carl Zeiss, Jena, Germany).

182

183 **Drug solubility measurements**

184   Excess amounts of drugs (as received) were exposed to 10 mL 0.1 N HCl, phosphate buffer pH 6.8

185 or demineralized water, optionally containing up to 20 % ethanol (as indicated) in flasks and horizontally

186 shaken at 37°C at 80 rpm (GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At pre-

187 determined time points, samples were withdrawn, immediately filtered (PTFE syringe filters, 0.45 µm;

188 GE Healthcare) and diluted. The drug contents of the samples were determined by UV-

189 spectrophotometry, as described above. Samples were withdrawn until equilibrium was reached. Each

190 experiment was conducted in triplicate, mean values +/- standard deviations are reported.

191

192

193 **RESULTS AND DISCUSSION**

194

195 **Tablet swelling**

196   Figure 1 shows optical macroscopy pictures of cross-sections of matrix tablets loaded with 30 %

197 diprophylline upon exposure to 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 for 6 h. The

198 USP apparatus I (basket) was used. The tablets were based on cross-linked pregelatinized potato starch,

199 HPMC K100LV or HPMC K100M, as indicated at the top. The time periods of exposure to the release

200 media are given on the left hand side. As it can be seen, the swelling behavior of the cross-linked

201 pregelatinized potato starch-based tablets substantially differed from the swelling behavior of HPMC

202 K100LV- and K100M-based tablets: The rectangular shape of the cross-sections of the cylindrical

203 systems remained almost unaltered ("only" the size increased) in the case of the investigated starch

204 derivative. In contrast, the corners of the HPMC-based tablets rapidly became round and the original

205 tablet shape got lost, irrespective of the HPMC grade. Interestingly, the same was true for the geometry

206 of the "dry tablet cores", which were visible at the center of the systems: The geometry of the cross-

207 sections of these "dry cores" remained rectangular in the case of tablets based on pregelatinized potato

208 starch, they became more and more round in the case of HPMC-based tablets. In addition, the thickness

209 of the swollen hydrogel layer continuously increased when using pregelatinized potato starch as matrix

210 former, whereas this was not the case with the HPMC K100LV- and HPMC K100M-based tablets. The

211 thickness of the swollen HPMC K100LV layer even decreased at later time points. This indicates

212 significant erosion of the HPMC matrices during drug release.

213 To better understand whether these substantial differences in polymer swelling (starch derivative

214 versus HPMC) translate into differences in the resulting drug release kinetics from these matrix tablets,

215 various types of systems (loaded with different types and amounts of drugs) were prepared and drug

216 release was monitored under a variety of experimental conditions.

217

218 **Impact of the type of polymer**

219 The resulting diprophylline release kinetics from matrix tablets based on cross-linked pregelatinized

220 potato starch, HPMC K100LV or HPMC K100M in 0.1 N HCl and phosphate buffer pH 6.8 are

221 illustrated in Figure 2. The USP apparatuses I, II and III were used: basket, paddle or "Bio-Dis". The

222 release medium was optionally changed after 2 h (as indicated). In the case of the USP III apparatus, the

223 dipping speed was set at 5 or 20 dpm.

224 As it can be seen, the three types of polymers were able to control the release of the freely water-

225 soluble drug during more than 8 h under all conditions. When using the USP basket apparatus or the

226 "Bio-Dis" apparatus at 5 dpm, the release rates from cross-linked pregelatinized potato starch- and

227 HPMC K100LV-based tablets were rather similar, while diprophylline from HPMC K100M-based

228 tablets was somewhat slower. When using the USP paddle apparatus, drug release was fastest from the

229 starch-based tablets, followed by HPMC K100LV- and HPMC K100M-based tablets. In contrast, when

230 using the USP III apparatus at 20 dpm, diprophylline release was fastest from HPMC K100LV-based

231 tablets, followed by the starch-based systems and the HPMC K100M-based tablets. Interestingly, the

232 optional complete medium change after 2 h from 0.1 N HCl to phosphate buffer pH 6.8 did not affect

233 drug release to a noteworthy extent, irrespective of the type of polymer (left versus right diagram at the

234 top of Figure 2).

235

236 **Effects of the type of release medium**

237 Figure 3 shows the impact of adding 5 or 20 % ethanol to water as the release medium on

238 diprophylline release from tablets based on cross-linked pregelatinized potato starch, HPMC K100LV

239   or HPMC K100M. The drug loading was 30 %, the USP apparatus I was used. Clearly, diprophylline

240   release was not affected to a noteworthy extent in the case of the investigated starch derivative. For

241   HPMC K100LV and HPMC K100M, a slight decrease in the release rates was observed with increasing

242   ethanol content of the release medium. The solubility of diprophylline in water containing 0, 5 and 20 %

243   ethanol at 37 °C was found to be equal to 206 ± 13.5, 210 ± 18 and 220 ± 11 mg/mL, respectively. This

244   suggests that the presence of up to 20 % ethanol in the release medium does not affect the capacity of

245   cross-linked pregelatinized potato starch to a noteworthy extent.

246   The impact of the addition of different amounts of NaCl and sucrose on diprophylline release from

247   matrix tablets based on cross-linked pregelatinized potato starch or HPMC K100M is illustrated in

248   Figure 4. The USP apparatus I (basket) was used, the release medium was 0.1 N HCl during the first

249   2 h, followed by phosphate buffer pH 6.8 for the subsequent 6 h. The aim was to evaluate the sensitivity

250   of drug release from these types of controlled release matrix tablets to variations in the osmolality of the

251   contents of the gastro intestinal tract. As it can be seen, in none of the cases there was a noteworthy

252   effect under the given in vitro conditions.

253   When using a starch derivative as a matrix former in controlled release tablets, it is very important

254   to evaluate the potential impact of the presence of pancreatin in the release medium on system

255   performance: Pancreatin contains α-amylase which can degrade starches and, thus, potentially affect the

256   resulting drug release kinetics. In practice, the α-amylase secretion in the patients' gastro intestinal tract

257   varies. Hence, in the case of amylase-sensitive starches, in vivo variability of drug release might result

258   from variable starch degradation. Importantly, the diagram at the left hand side at the top of Figure 5

259   shows that diprophylline release from tablets based on the investigated cross-linked pregelatinized

260   potato starch is not sensitive to the presence of pancreatin. The open diamonds illustrate drug release in

261   the presence of pancreatin (with an α-amylase activity of 108.000 IU/L), the filled diamonds show the

262   respective release kinetics in the absence of pancreatin. The release medium was 0.1 N HCl for the first

263   2 h, followed by phosphate buffer pH 6.8. The USP apparatus I was used. The drug loading was 30 %.

264   As it can be seen on the right hand side at the top of Figure 5, also drug release from HPMC K100M-

265   based tablets was insensitive to the presence of pancreatin (as expected). The diagrams in the middle of

266   Figure 5 show diprophylline release from these tablets upon exposure to Fasted State Simulated Gastric

267 Fluid (FaSSGF) or Fed State Simulated Gastric Fluid (FeSSGF) for 2 h, followed by Fasted State

268 Simulated Intestinal Fluid (FaSSIF) or Fed State Simulated Intestinal Fluid (FeSSIF) for the subsequent

269 6 h. Again, the USP apparatus I was used. Furthermore, diprophylline release was measured upon

270 exposure to 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 for 6 h and a release medium

271 simulating the conditions in the colon of a patient suffering from Crohn's disease (dotted curves) or in

272 the colon of a healthy subject (solid curves). In these cases, fecal samples from patients/healthy subjects

273 were incubated under anaerobic conditions and used as release media. For reasons of comparison, also

274 drug release into 0.1 N HCl (2 h), followed by phosphate buffer pH 6.8 (22 h) is shown (filled

275 diamonds). The diagrams on the left hand side show diprophylline release from tablets based on cross-

276 linked pregelatinized potato starch, the diagrams on the right hand side illustrate the release kinetics

277 from HPMC K100M-based tablets. As it can be seen, in all cases no noteworthy effects were observed

278 with respect to the type of release medium: FaSSGF, FeSSGF, FeSSGF, FeSSIF and colonic media from

279 patients or healthy subjects. This is important, especially in the case of the investigated starch derivative,

280 because starches might be preferentially degraded by bacterial enzymes present in the colon.

281   In practice, the observed insensitivity of the drug release kinetics to variations in the composition

282 of the release media is promising, because the contents of the gastro intestinal tract of a patient varies

283 intra-individually and inter-individually. Thus, in vivo rather consistent drug release kinetics might be

284 expected. However, since the investigated matrix tablets substantially swell upon contact with the

285 aqueous release media (Figure 1), variations in the mechanical stress experienced during the transit

286 throughout the gastro intestinal tract might potentially alter the resulting drug release rates. For instance,

287 in the case of mechanically fragile gels, forces exerted on the tablets by the stomach or small intestine

288 might lead to accelerated system disintegration and, thus, faster drug release. Importantly, the

289 mechanical stress encountered in a patient's gastro intestinal tract might significantly vary intra-

290 individually and inter-individually. To evaluate the potential impact of such effects on system

291 performance, diprophylline release was measured from starch- and HPMC-based tablets using the USP

292 apparatuses I and III, optionally adding silicone balls or using a texture analyzer to simulate contraction

293 forces of the stomach and small intestine.

294

Impact of mechanical stress on drug release

295

296   The diagrams on the left hand side of Figure 6 show the release kinetics of diprophylline from tablets

297   based on cross-linked pregelatinized potato starch (top) or HPMC K100M (bottom) upon exposure to

298   0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 in a USP apparatus I (basket). To simulate

299   mechanical stress encountered in the gastro intestinal tract of the patient, the tablets were withdrawn

300   from the release medium at each sampling time point and underwent 3 or 5 "compression cycles" (as

301   indicated) using a texture analyzer. In brief, one "compression cycle" was as follows: The tablets were

302   placed on a Petri dish and a cylindrical probe was driven downwards at a speed of 0.5 mm/s. As soon as

303   the flat face of the probe got into contact with the flat face of the tablet, a steadily increasing force was

304   exerted onto the tablet. Once this forced reached 2 N, the probe was driven upwards. For reasons of

305   comparison, the diagrams in Figure 6 also show drug release from tablets that did not undergo such

306   "compression cycles". In addition, the USP apparatus III ("Bio-Dis") was used to monitor drug release

307   from these tablets at 5 and 20 dpm, optionally adding a silicone ball (17 mm diameter, 4.5 g) to each

308   vessel. The resulting diprophylline release rates are shown in the diagrams on the right hand side of

309   Figure 6. As it can be seen, in all cases the overall impact of mechanical stress on drug release from the

310   investigated tablets was limited. This indicates that the swollen polymer gels (Figure 1) are mechanically

311   stable and can resist the pressure they were exposed to. This is again promising with respect to the

312   variability of the resulting drug release kinetics that can be expected in vivo from these systems: It is

313   unlikely that the motility of the gastro intestinal tract substantially affects the resulting drug release rates

314   (provided that the encountered mechanical stress is similar).

315

Effects of the amount and type of drug

316

317   The diagrams in Figure 7 show the resulting diprophylline release kinetics from tablets based on

318   cross-linked pregelatinized potato starch (top) or HPMC K100M (bottom) upon exposure to 0.1 N HCl

319   for 2 h, followed by phosphate buffer pH 6.8 in a USP apparatus I. The initial drug loading was varied

320   from 20 to 50 %, as indicated. It has to be pointed out that the tablets were essentially based on binary

321   drug: polymer blends (only 1 % magnesium stearate was added as lubricant). Thus, the starch

322   derivative/HPMC content decreased accordingly from about 80 to 50 %. Nevertheless, the resulting drug

323 release kinetics (relative release rates) were unaffected, irrespective of the type of matrix former. This

324 is a further indication for the robustness of the hydrated macromolecular networks that are formed upon

325 contact with aqueous fluids. It also provides flexibility with respect to dose adjustments from this type

326 of controlled release tablets.

327   The diagrams in Figure 8 show (from the top to the bottom): the (i) dry mass loss kinetics,

328 (ii) estimated polymer mass loss kinetics, and (iii) dynamic changes in the water contents of tablets

329 based on cross-linked pregelatinized potato starch (left hand side) or HPMC K100M (right hand side)

330 upon exposure to 0.1 N HCl and phosphate buffer pH 6.8. The USP apparatus I (basket) was used. The

331 initial diprophylline loading was 30 or 40 %, as indicated. As it can be seen, the variation of the drug

332 content did not substantially affect the resulting mass loss kinetics of the tablets or matrix former, neither

333 the time-dependent changes in the water contents of the systems. This is consistent with the robustness

334 of the relative drug release kinetics discussed above. Interestingly, the observed dry mass loss of the

335 tablets essentially corresponded to the amounts of drug that were released into the surrounding bulk

336 fluid in the observation period. The polymeric matrix former did not dissolve to a noteworthy extent in

337 any of the investigated systems. This might at least in part explain the observed robustness of the

338 resulting drug release kinetics under the various investigated conditions: types of release media, types

339 of release apparatuses and conditions for drug release (including the application of mechanical stress).

340 Both, the investigated starch derivative as well as HPMC K100M seem to form mechanically stable

341 polymer networks that do not dissolve during the observation period. Interestingly, the two diagrams at

342 the bottom of Figure 8 indicate that the water uptake of tablets based on the investigated cross-linked

343 starch derivative was much less pronounced than the water uptake of the respective HPMC K100M-

344 based tablets.

345   From a practical point of view, an "ideal" polymeric matrix former for controlled release tablets

346 should be able to control the release of very different types of drugs, exhibiting for instance substantially

347 different solubility in aqueous media. For this reason, also diltiazem HCl and theophylline containing

348 tablets were prepared, based on cross-linked pregelatinized potato starch or HPMC K100M. The

349 solubility of diprophylline, theophylline and diltiazem HCl were determined to be equal to 199 ± 12,

350 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

351   buffer pH 6.8 at 37 °C, respectively. Figure 9 shows the resulting drug release kinetics in the two media

352   (complete exchange after 2 h). The USP apparatus I was used, the initial drug content was 30 % in all

353   cases. As it can be seen, the investigated starch derivative as well as HPMC K100M were able to

354   effectively control the resulting drug release kinetics, irrespective of the type of drug. The release rate

355   was lowest for theophylline (red curves in Figure 9), irrespective of the type of matrix former. This can

356   at least partially be attributed to the relatively low solubility of this drug in aqueous media and the fact

357   that only dissolved drug is available for diffusion: Upon water penetration into the systems, probably

358   not all of the theophylline can be dissolved. Thus, dissolved and non-dissolved theophylline co-exist.

359   Importantly, only the *dissolved* drug contributes to the concentration gradients that are the driving forces

360   for drug release. Please note that even in the case of freely water-soluble drugs, limited solubility effects

361   might be of importance (46,47). Interestingly, diltiazem HCl release was slower than diprophylline

362   release in the present study, despite of its higher solubility in the investigated release media. This was

363   true for both types of matrix formers. Hence, other phenomena must (also) be of importance. For

364   instance, the molecular weight of diltiazem H^+ ions is much higher than the molecular weight of

365   diprophylline (451 versus 254 Da). Consequently, the mobility (diffusion coefficient) of dissolved

366   diltiazem H^+ ions is likely smaller than the mobility of dissolved diprophylline molecules, resulting in

367   lower drug release rates.

368

369   **CONCLUSION**

370   The investigated cross-linked pregelatinized potato starch offers an interesting potential as matrix

371   former for controlled release matrix tablets: It can be used to effectively control the release rates of

372   different types of drugs (at different initial loadings) during several hours. Importantly, the resulting

373   drug release kinetics are not affected to a noteworthy extent by variations in the type of release medium

374   (including the presence of pancreatin) and the applied experimental set-up (USP apparatus I, II and III)

375   under a broad range of operating conditions, including optional simulation of mechanical stress (using

376   silicone balls or a texture analyzer). Thus, the resulting drug release kinetics in vivo might also be rather

377   robust.

378

379

ACKNOWLEDGEMENTS

384

385

CONFLICT OF INTERESTS

387   Several co-authors of this article are employees of the company Roquette, commercializing

388   the investigated starch derivative.

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519

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),

547		followed by phosphate buffer pH 6.8 (22 h) is illustrated. Mean values ± standard deviations
548		are indicated (n=3).
549	Fig. 6	Impact of mechanical stress on diprophylline release in 0.1 N HCl (first 2 h), followed by
550		phosphate buffer pH 6.8. The results on the left-hand side were obtained with the USP
551		apparatus I and optional compression cycles with a texture analyzer. The results on the right
552		hand side were obtained with the USP apparatus III, optionally adding a silicone ball to the
553		vessel. Details are described in the text. Mean values ± standard deviations are indicated
554		(n=3).
555	Fig. 7	Impact of the initial drug content on diprophylline release from tablets based on cross-linked
556		potato starch or HPMC K100M. The USP apparatus I was used, the release medium was 0.1 N
557		HCl for the first 2 h, followed by phosphate pH 6.8. Mean values ± standard deviations are
558		indicated (n=3).
559	Fig. 8	Dry mass loss (%), estimated polymer mass loss (%) and water content (%) of tablets based
560		on cross-linked potato starch or HPMC K100M upon exposure to 0.1 N HCl (first 2 h),
561		followed by phosphate pH 6.8. The USP apparatus I was used. Mean values ± standard
562		deviations are indicated (n=3). The tablets contained 30 or 40 % diprophylline, as indicated.
563	Fig. 9	Influence of the type of drug (indicated in the diagrams) on drug release from tablets based
564		on cross-linked potato starch or HPMC K100M upon exposure to 0.1 N HCl (first 2 h),
565		followed by phosphate pH 6.8. The USP apparatus I was used. The initial drug content was
566		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

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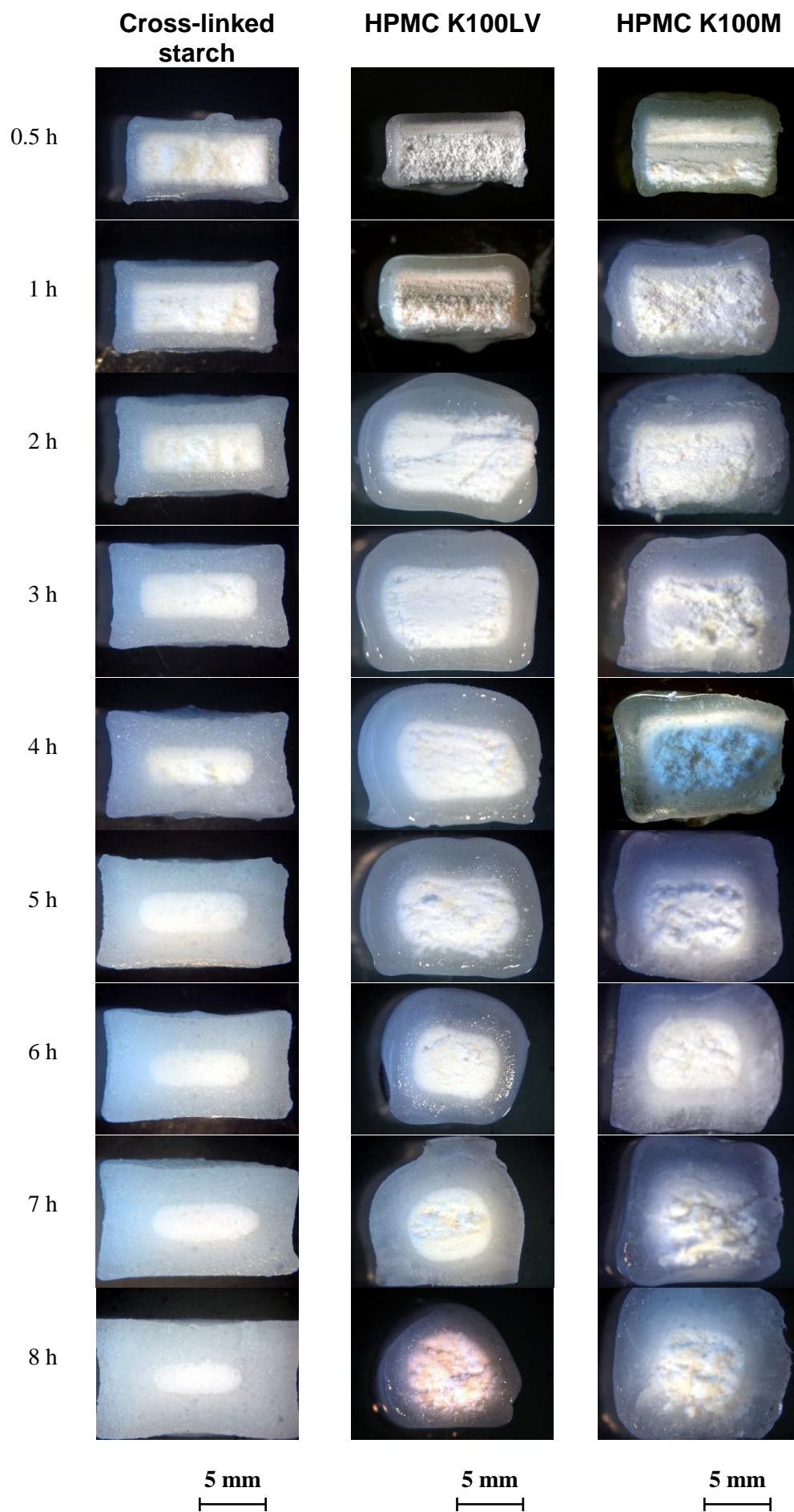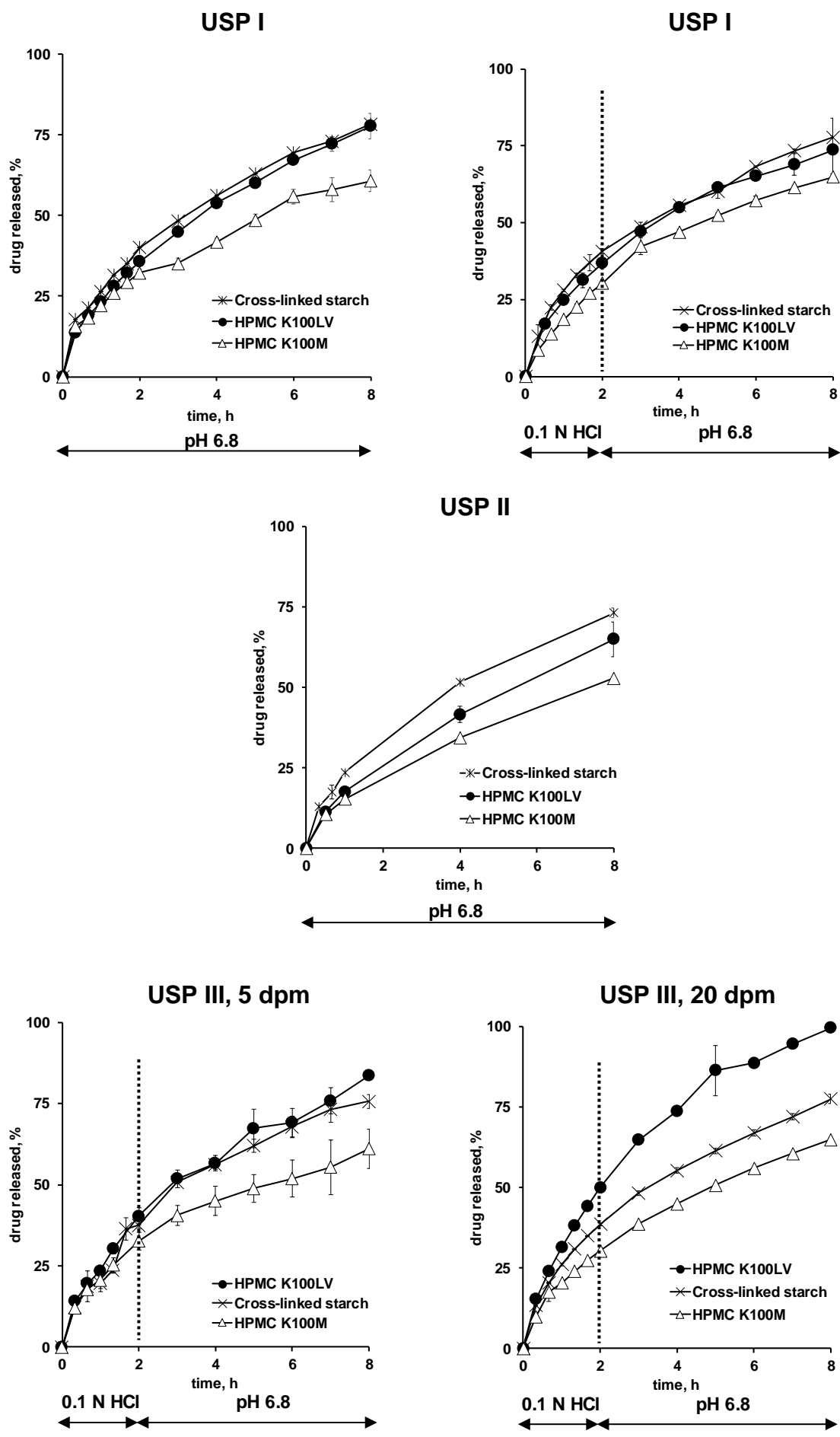
Figure 2

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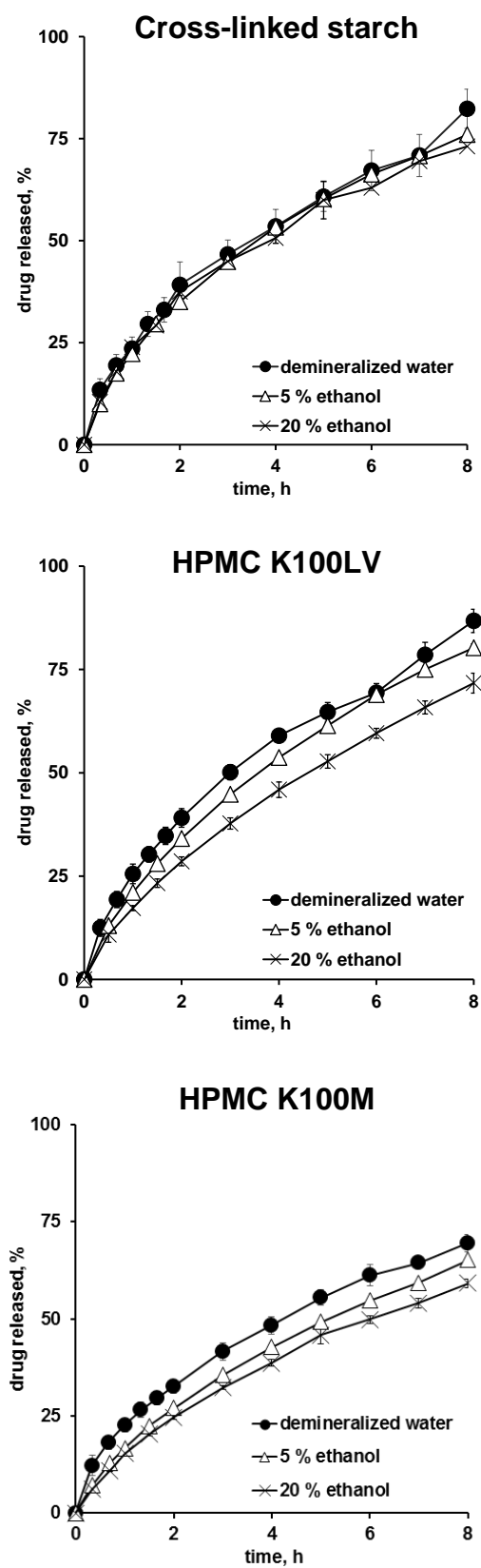
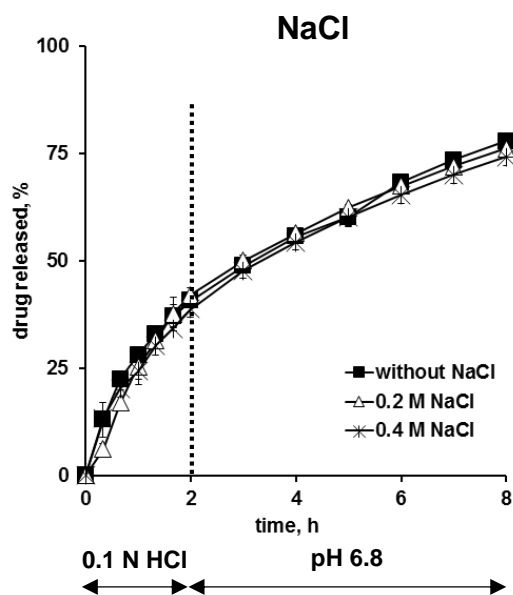Figure 3

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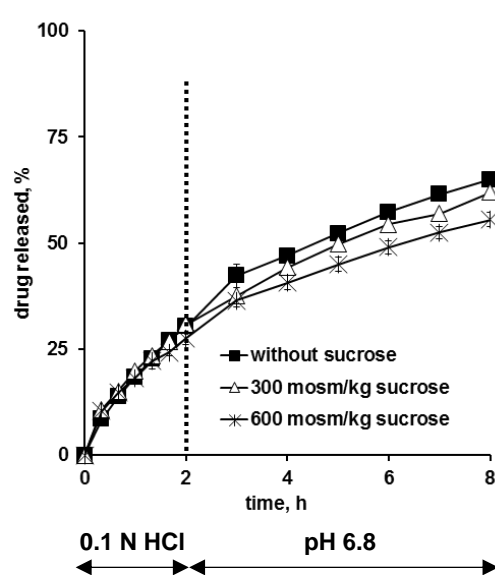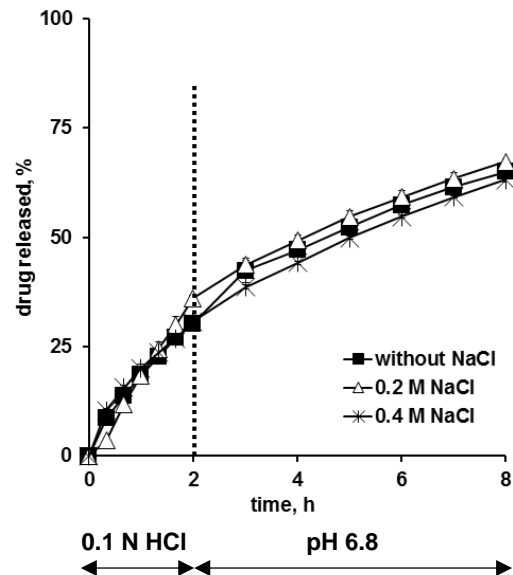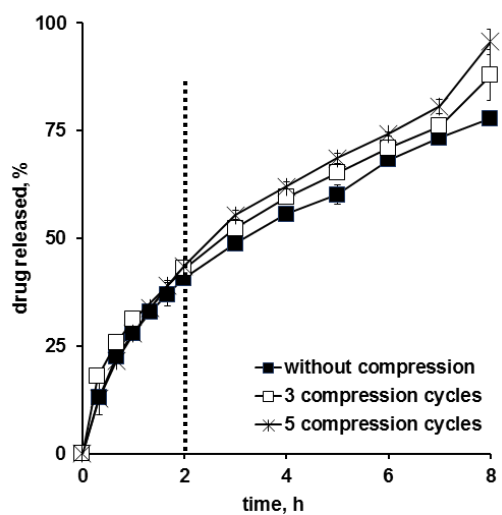
Cross-linked starch

HPMC K100M

Figure 4

a)

Cross-linked starch

HPMC K100M

Pancreatin

FaSSGF/FeSSIF

Colonic Medium

b)

c)
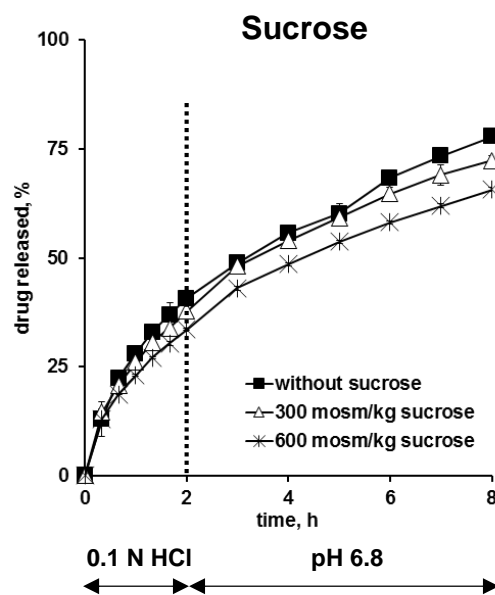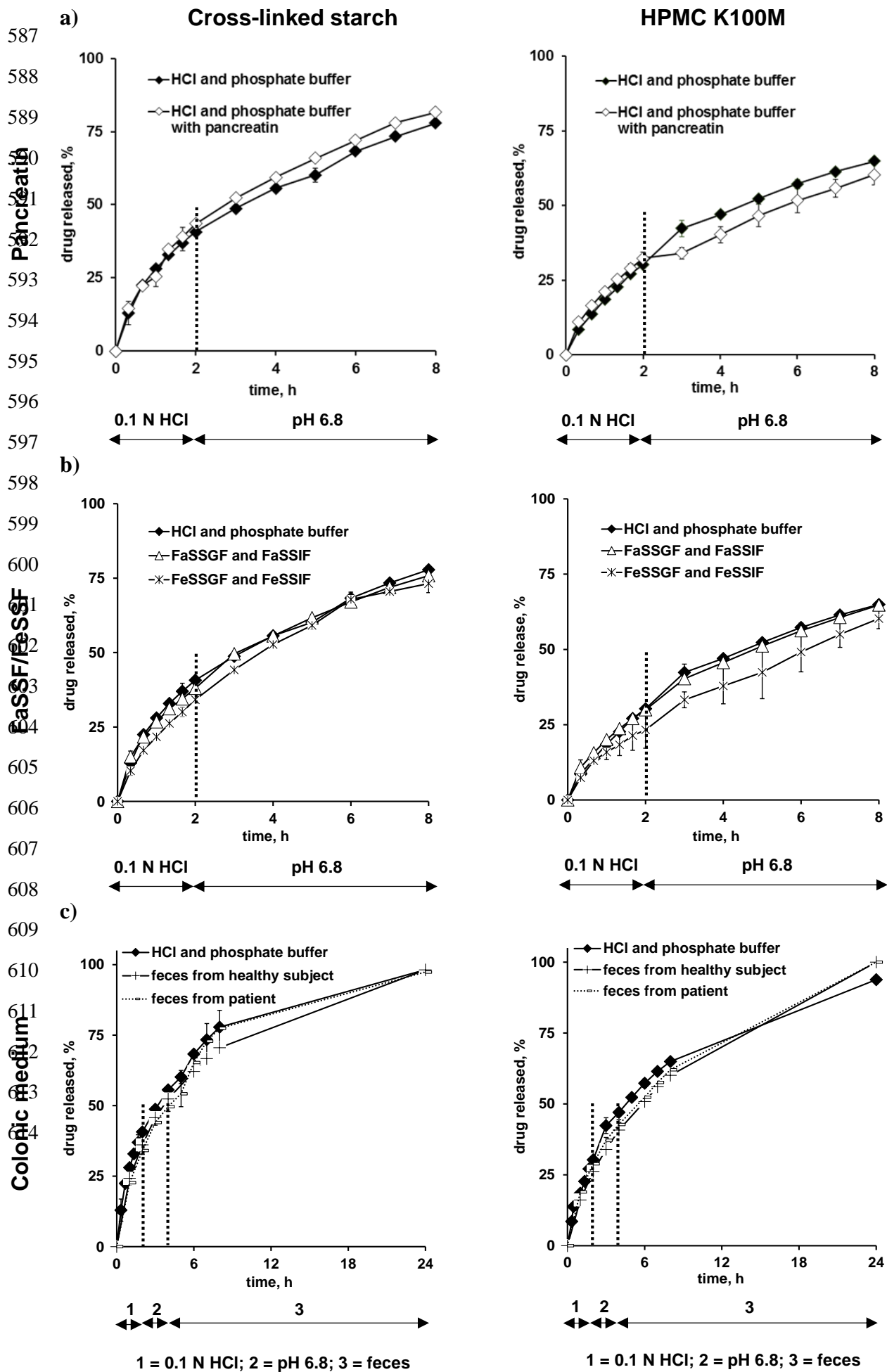
Figure 5

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Cross-linked Starch
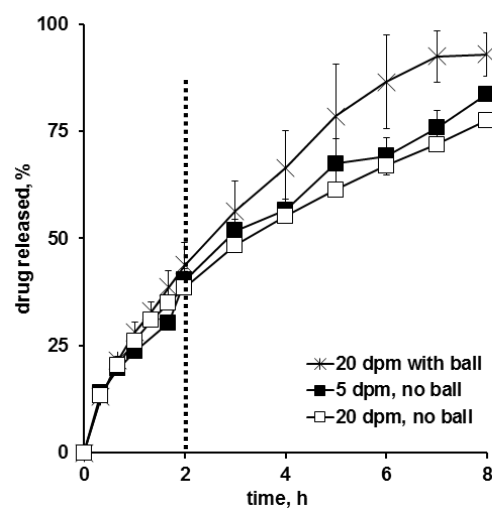
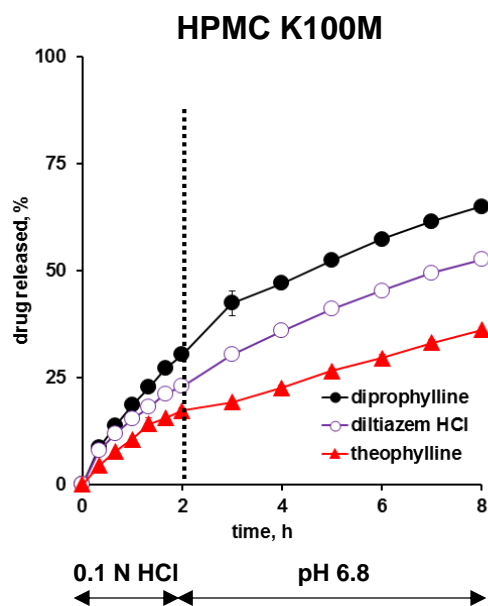**HPMC K100M**
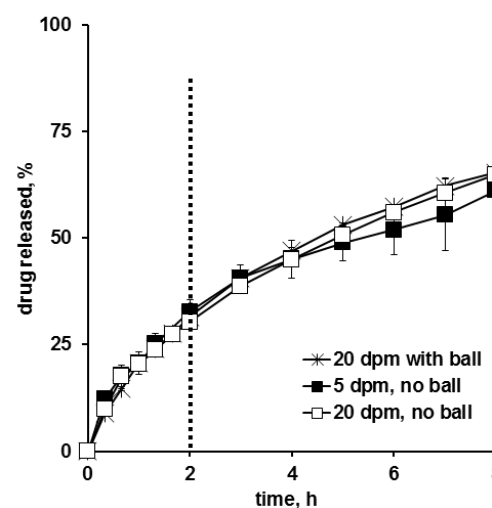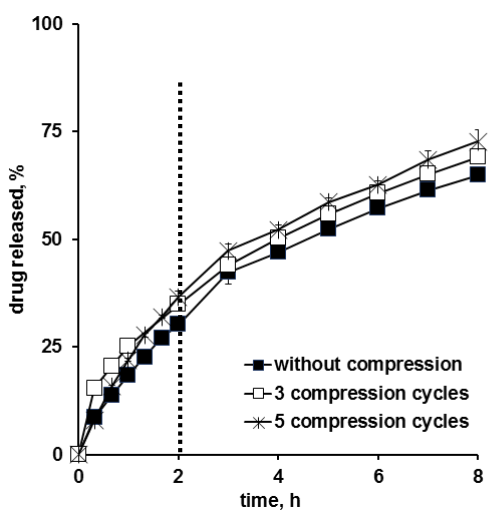
Figure 6

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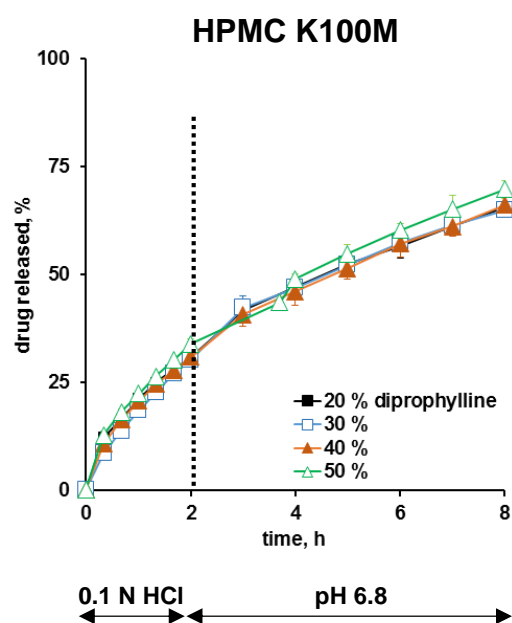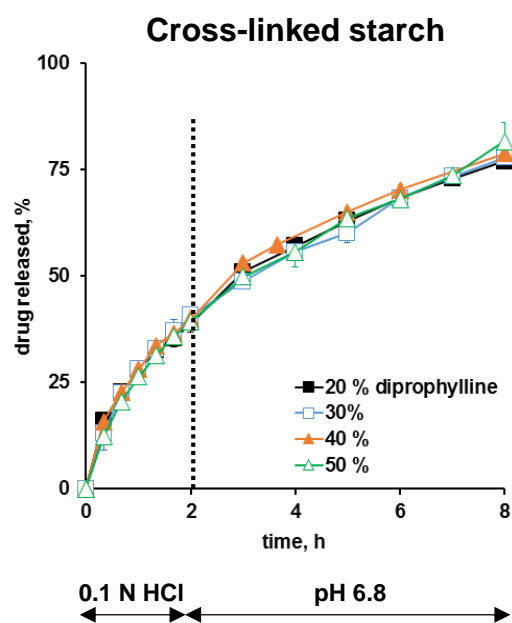
Figure 7

Figure 8

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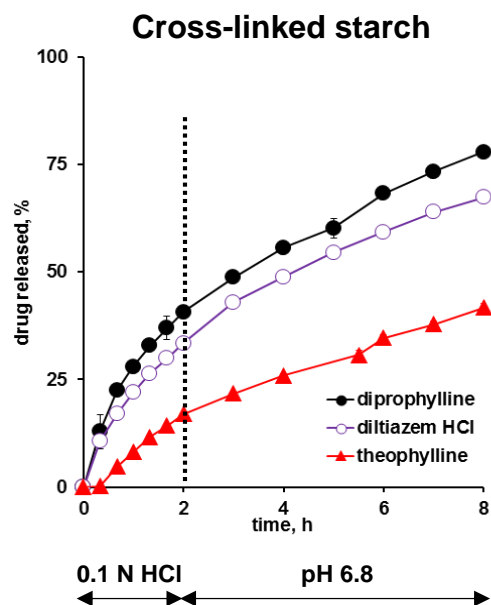

Cross-linked starch

HPMC K100M

Figure 9