Injection-molded capsule bodies and caps based on polymer blends for controlled drug delivery

Youcef Benzine, Florence Siepmann, Christel Neut, Florence Danede, Jean-François Willart, Juergen Siepmann, Youness Karrout

Research article

Injection-molded capsule bodies and caps based on polymer blends for controlled drug delivery

Youcef Benzine[1], Florence Siepmann[1], Christel Neut[2], Florence Danede[3], Jean Francois Willart[3], Juergen Siepmann[1,*], Youness Karrout[1,**]

[1]Univ. Lille, Inserm, CHU Lille, U1008, F-59000 Lille, France
[2]Univ. Lille, Inserm, CHU Lille, U1286-INFINITE Institute for Translational Research in Inflammation, F-59000 Lille, France
[3]Univ. Lille, USTL UMET UMR CNRS 8207, F-59650 Villeneuve d'Ascq, France

*correspondence:
Prof. Juergen Siepmann
College of Pharmacy, INSERM U1008
University of Lille
3 rue du Professeur Laguesse
59006 Lille, France
juergen.siepmann@univ-lille.fr

**correspondence:
Dr. Youness Karrout
College of Pharmacy, INSERM U1008
University of Lille
3 rue du Professeur Laguesse
59006 Lille, France
youness.karrout@univ-lille.fr

Abstract

A variety of polymer:polymer blends was used to prepare hot melt extrudates and empty capsules (bodies and caps) by injection-molding using a benchtop extruder (Babyplast). Kollidon SR:inulin and Carbothane:inulin blends were investigated. The impact of the blend ratio on the water uptake and dry mass loss kinetics upon exposure to 0.1 M HCl, phosphate buffer pH 6.8 and culture medium optionally inoculated with fecal samples from Inflammatory Bowel Disease (IBD) patients were studied. Hot melt extrudates were loaded with up to 60 % theophylline, capsules were filled with drug powder. Increasing the inulin content led to increased water uptake and dry mass loss rates, resulting in accelerated drug release from the dosage forms, irrespective of the type of polymer blend. This can be attributed to the higher hydrophilicity/water-solubility of this polymer compared to Kollidon SR and Carbothane. Interestingly, the presence of fecal samples in culture medium increased the water uptake and dry mass loss of hot melt extrudates to a certain extent, suggesting partial system degradation by bacterial enzymes. However, these phenomena did not translate into any noteworthy impact of the presence of colonic bacteria on *theophylline release* from the investigated extrudates or capsules. Hence, drug release can be expected to be independent of the location "small intestine vs. colon" from these dosage forms, which can be advantageous for long term release throughout the *entire* gastro intestinal tract.

Keywords: Injection-molding; capsule shell; controlled release; polymer blend; polyurethane

1. Introduction

Oral controlled drug delivery systems are of great practical importance. Often, polymers are used to trap the drug and control the resulting release rate [1-3]. Matrix systems as well as reservoir systems can be used for this purpose [4-6]. A variety of physico-chemical phenomena can be involved in the control of drug release, including the diffusion of water into the dosage form [7], drug dissolution [8], polymer swelling [9-11], drug diffusion [12], polymer dissolution [13,14], and polymer degradation [15] to mention just a few. Drug saturation effects can occur *inside* as well as *outside* the dosage form. It has recently been pointed out that perfect sink conditions in the surrounding bulk fluid do not assure the absence of saturation effects *within* the system [16].

The use of polymer blends (instead of single polymers) can be very helpful to easily provide desired system properties: By simply varying the polymer:polymer blend ratio a large spectrum of system properties can often be provided [17,18]. Polymer blends can be used as matrix formers as well as for the preparation of film coatings [19,20]. For example, blends of enteric and non-enteric polymers have been frequently reported for oral controlled drug delivery applications [21,22]. Ali et al. [23] used blends of Kollicoat SR and Eudragit RL for the coating of hydroxypropyl methylcellulose (HPMC) matrix tablets to increase the latter's mechanical robustness. The idea was to combine the flexibility of Kollicoat SR and the permeability of Eudragit RL. Also, differently permeable polymers can be combined and the variation of their blend ratio be used to easily adjust the resulting drug release rate. For instance, Amighi and Moes studied theophylline release from pellets coated with mixtures of more permeable Eudragit RL and less permeable Eudragit RS [24]. Furthermore, the group of Abdul Basit proposed an interesting colon targeting system (Phloral™), based on a coating containing the enteric polymer Eudragit S and maize starch. This allows to combine two colon targeting strategies in the same system: pH-sensitivity and enzymatic degradation in the colon. In case

one triggering mechanisms fails, the other can still allow for site-specific drug delivery to the target site [25].

Different manufacturing techniques can be used to prepare polymeric controlled drug delivery systems, including compression [26,27], 3D printing [28-30], hot melt extrusion [31-34] and injection molding [35,36]. When controlled drug delivery *throughout* the entire gastro intestinal tract of the patient is targeted, particular attention should be paid to the conditions provided during the drug release experiments. Often, only the contents of the upper gastro intestinal tract (stomach and small intestine) are simulated. However, if the drug is also absorbed from the colon and once daily dosing is desired, in addition the contents of the colon should be simulated. One of the key differences between the colon and the upper gastro intestinal tract is the presence of the microbiota, which can potentially substantially impact drug release from a dosage form. For example, certain polymers are degraded by enzymes secreted by colonic bacteria [37].

The aim of this study was to evaluate the potential of Kollidon SR:inulin and Carbothane:inulin blends for the preparation of polymeric controlled release dosage forms. Kollidon SR is a blend of 80% poly(vinyl acetate), 19% poly(vinyl pyrrolidone), sodium lauryl sulfate and colloidal silicon dioxide [38], inulin is a polysaccharide of natural origin [39]. The impact of the polymer:polymer blend ratio on the processability of the mixtures via hot melt extrusion as well as on the key properties of the obtained systems (water uptake, dry mass loss, drug release) was to be investigated. Furthermore, empty capsule shells (caps and bodies) were to be produced, which can be filled with arbitrary drugs, without the need of cost-intensive and time-consuming formulation development (optimization of the resulting drug release kinetics). Special attention was placed on the potential impact of the microbiome in the colon, when longer term drug release throughout the entire gastro intestinal tract is desired.

2. Materials and methods

2.1. Materials

Anhydrous theophylline and Kollidon SR [80% poly(vinyl acetate), 19% poly(vinyl pyrrolidone), sodium lauryl sulfate and colloidal silicon dioxide] (BASF, Ludwigshafen, Germany); Carbothane (Carbothane PC-3575A, a thermoplastic polyurethane; Lubrizol, Wilmington, USA); inulin (Inulin Synergy 1; Beneo, Oreye, Belgium); dibutyl sebacate (DBS; Stearinerie Dubois, Boulogne-Billancourt, France); extracts from beef and tryptone (pancreatic digest of casein; Becton Dickinson, Sparks, USA); yeast extract (Oxoid, Hants, UK); sodium chloride (J.T. Baker, Deventer, Netherlands); L-cysteine hydrochloride hydrate (Acros Organics, Geel, Belgium); Ringer solution (Merck, Darmstadt, Germany); acetic acid glacial (Fisher Bioblock, Illkirch, France); acetonitrile (CWR, Fontenay-sous-Bois, France).

2.2. Preparation of hot melt extrudates

Polymer powders were blended for 10 min at 98 rpm in a Turbula T2A (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland), followed by manual mixing with DBS in a mortar using a pestle. After 24 h plasticization time, the drug was added and the blend further manually mixed in the mortar. The compositions of the formulations were varied as indicated. Polymer:polymer blend ratios are expressed in weight:weight. The indicated plasticizer percentage is referring to the mass of Kollidon SR or Carbothane (mass of Kollidon SR/Carbothane = 100 %). The plasticized blends were kept at room temperature for 24 h, followed by extrusion with a Nano 16 twin screw extruder (Leistritz, Nuremberg, Germany), equipped with a 4 mm diameter die (screw diameter = 16 mm, length/diameter ratio = 26.25). Figure S1 shows the setting of the screw elements. The process temperatures were kept constant at 100 – 100 – 100 – 100 °C [zone 4 (die) – zone 3 – zone 2 – zone 1]. The feed rate was set at 3 mL/min. After cooling, the hot melt extrudates were manually cut into cylinders (1 cm length).

2.3. Preparation of injection-molded capsules

A bench-top micromolding machine was used (BabyPlast 6/10P; Rambaldi, Molteno, Italy), equipped with a capsular mold furnished with a hot-runner and two interchangeable inserts for the manufacturing of matching capsule caps and bodies (600 µm thickness). The cylindrical hot melt extrudates were loaded into the injection-molder, and pushed into the injection chamber by the loading plunger. Afterwards, two different and consecutives injection pressures (P_1 and P_2) were applied and maintained for specific time periods (t_1 and t_2) to inject the polymeric melt into the mold cavity. The operating conditions were as follows: Plasticizing chamber temperature: 100 °C; injecting temperature: 100 °C; nozzle temperature: 100 °C; mold temperature: 107 °C; P_1: 100 bar; P_2: 80 bar; t_1: 6 s; t_2: 5 s; cooling time: 10 s. If indicated, the capsules were manually filled with 10 mg theophylline (and sealed upon wetting with ethanol).

2.4. Optical microscopy

Macroscopic pictures of hot melt extrudates and capsules were taken with an optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan), equipped with a Zeiss camera (Axiocam ICc1; Zeiss, Jena, Germany). Cross-sections of hot melt extrudates were obtained by manual breaking.

2.5. In vitro drug release

Under conditions simulating the *upper* gastro intestinal tract:

Hot melt extrudates and injection-molded capsules (filled with 10 mg drug) were placed into flasks (1 sample per flask), filled with 200 mL 0.1 M HCl and agitated at 80 rpm (in a horizontal shaker, 37 °C; GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). After 2 h, the release medium was completely exchanged with phosphate buffer pH 6.8 (USP 41). At pre-determined time points (indicated in the figures), 3 mL samples were

withdrawn (not replaced, sink conditions being provided throughout the experiments) and analyzed UV-spectrophotometrically (UV-1800; Shimadzu, Kyoto, Japan) at λ = 275 nm for their drug content. All experiments were performed in triplicate. Mean values +/- standard deviations are reported.

Under conditions simulating the *entire* gastro intestinal tract:

Hot melt extrudates and injection-molded capsules (filled with 10 mg drug) were exposed to 0.1 M HCl for 2 h and subsequently to phosphate buffer pH 6.8 (USP 41) for 6 h, in a USP Apparatus 3 (20 dpm, 37 °C, Bio-Dis; Varian, Paris, France). Afterwards, the extrudates were transferred into 120 mL flasks filled with: (i) 100 mL culture medium inoculated with human fecal samples, or (ii) culture medium free of feces for reasons of comparison. The samples were agitated (50 rpm; Stuart, Cole-Parmer; Villepinte, France) at 37 °C under anaerobic conditions (AnaeroGen 2.5 L; Thermo Scientific; Illkirch, France). 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. Culture medium inoculated with fecal samples was prepared as follows: Human fecal samples (approximately 1 g, from randomly selected IBD patients) were diluted 1:200 with cysteinated Ringer solution; 2.5 mL of this suspension was diluted with culture medium to 100 mL. At pre-determined time points (indicated in the figures), 2 mL samples were withdrawn (not replaced, sink conditions being provided throughout the experiments), centrifuged at 10000 rpm for 10 min (Centrifuge Universal 320; Hettich, Tuttlingen, Germany), filtered (0.45 µm, Millex-HU; Merck Millipore, Tullagreen, Ireland) and analyzed by HPLC for their drug content using a Thermo Fisher Scientific Ultimate 3000, equipped with a LPG 3400 SD/RS pump, an auto sampler (WPS-3000 SL) and a UV-Vis detector (VWD-3400RS) (Thermo Fisher Scientific, Waltham, USA). The mobile phase consisted of 10 % acetonitrile and 90 % water (v/v). Samples were injected into a C18 column (Kinetex 5 µm EVO C18 100 Å, 250 mm x 4.6 mm; Phenomenex, Le Pecq, France) and the flow rate was set at 1.0 mL/min. The drug was

detected UV-spectrophotometrically at λ = 275 nm.

2.6. Water content and dry mass loss kinetics of hot melt extrudates

The water content and the dry mass loss kinetics of hot melt extrudates were measured gravimetrically upon exposure to: (i) simulated gastric fluid (0.1 M HCl pH 1.2), (ii) simulated intestinal fluid (phosphate buffer pH 6.8; USP 41), and (iii) simulated colonic fluid (culture medium inoculated with feces from inflammatory bowel disease patients). The latter was prepared as described in *section 2.5*.

Hot melt extrudates were placed into flasks (1 sample per flask), filled with 200 mL 0.1 M HCl or phosphate buffer pH 6.8 and agitated at 80 rpm (in a horizontal shaker, 37 °C; GFL 3033). At pre-determined time points, extrudate samples were withdrawn and rinsed with water. Excess water was removed by careful blotting with Kimtech precision wipes (Kimberly Clark, Roswell, GA). The extrudates were accurately weighed (wet mass) and dried to constant weight at 60 °C (dry mass). The water uptake and the dry mass (%) at time t were calculated as follows:

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

Erreur ! Cela devrait être un chiffre.

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

where dry mass (t = 0) is the dry extrudate mass before exposure to the medium. All experiments were performed in triplicate. Mean values +/- standard deviations are reported.

2.7. Powder X-ray diffraction (PXRD)

PXRD experiments were conducted with a PanAlytical X'PERT PRO MPD diffractometer (λCuKα = 1.5418 Å for combined Kα1 and Kα2), equipped with an X'celerator detector

(Almlo, The Netherlands). Samples were placed in a spinning (15 rpm) flat sample holder (13 mm diameter, 2 mm depth). The measurements were performed in the Bragg-Brentano θ-θ geometry.

3. Results and discussion

3.1. Kollidon SR:inulin blends

The left column in Figure 1 shows optical macroscopy pictures of hot melt extrudates based on different Kollidon SR:inulin blends before exposure to a release medium. The polymer:polymer blend ratio was varied as indicated on the left hand side. All extrudates were obtained with the same die (diameter = 4 mm), the extrusion temperature was constant (100 °C) and the feed rate set at 3 mL/min. As it can be seen, the "pure" Kollidon SR-based extrudates (plasticized with 30 % DBS) underwent a significant radial expansion upon leaving the die. The addition of inulin substantially decreased the importance of this phenomenon. At very high inulin contents (80 %) the expansion became again somewhat more important. This can likely be attributed to the fact that the two polymers are intimately blended during the hot melt extrusion process and mutually limit relaxation effects with volume increase upon pressure release. Depending on the polymer blend ratio, phases with different compositions are formed, exhibiting different expansion behaviors.

The torque measured during hot melt extrusion was roughly around 30 %, slightly increasing with increasing inulin content (Figure 2a). Figure 2b shows the effect of the theophylline loading on the torque measured during the extrusion of Kollidon SR:inulin 50:50 blends. As it can be seen, the torque remained at about 30 % up to a drug loading of 40 %, and then increased moderately for drug loadings up to 60 %. These values indicate good processability.

Figure 3 shows the X-ray diffractograms of hot melt extrudates based on Kollidon SR:inulin

50:50 blends containing 20 to 60 % theophylline. For reasons of comparison, also the diffraction patterns of drug-free extrudates and of the raw materials (Kollidon SR, inulin and theophylline) are shown. Clearly, the drug was in the crystalline state in all cases, whereas the two polymers and the placebo implants were X-ray amorphous. Furthermore, the angles of the Bragg peaks were the same for the different hot melt extrudates and the theophylline raw material. This indicates that at least parts of the theophylline crystals did not dissolve or undergo phase transitions during the extrusion process.

Dynamic changes in the water content and dry mass of Kollidon SR:inulin-based hot melt extrudates upon exposure to different release media are illustrated in Figure 4. The upper row shows the behavior observed in 0.1 M HCl, simulating the contents of the stomach. The bottom row shows the changes observed in phosphate buffer pH 6.8, simulating the conditions in the small intestine. The Kollidon SR:inulin ratio was varied from 20:80 to 70:30, as indicated. For reasons of comparison, also the behavior of "pure" Kollidon SR extrudates (plasticized with 30 % DBS) is shown. Clearly, the addition of increasing amounts of inulin substantially increased the water uptake and dry mass loss rates and extents of the systems. This is because inulin is water-soluble and increases the hydrophilicity of the extrudates. The visually observed substantial swelling of hot melt extrudates containing 80 % inulin upon exposure to 0.1 M HCl and phosphate buffer pH 6.8 is in good agreement with these observations (pictures in the middle and right column in Figure 1). Importantly, a large range of water uptake and dry mass loss behaviors can easily be provided at low as well as at neutral pH, by simply varying the polymer:polymer blend ratio of the extrudates. Please note that this might also help to effectively adjust desired drug release kinetics reservoir-shaped dosage forms, e.g. from capsules with shells based on Kollidon SR:inulin blends.

The impact of the initial drug loading on theophylline release from hot melt extrudates based on Kollidon SR:inulin 50:50 blends in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8 for 6 h, is shown in Figure 5. As it can be seen, the drug release rate monotonically increased

with increasing theophylline content. This can be attributed to the fact that the density of the polymer network decreases: Once theophylline crystals are released, they are replaced by water, rendering the remaining matrix more permeable for the drug (and water). Please note that sink conditions were provided throughout the experiments. Nevertheless, possible drug saturation effects *within* the polymer matrix are likely [16].

Figure 6 shows the impact of the presence of fecal samples from IBD patients on the water uptake and dry mass loss kinetics of hot melt extrudates based on different Kollidon SR:inulin blends. The black bars represent the results obtained upon 24 h exposure to culture medium free of bacteria, whereas the white bars indicate the water contents and dry mass after 24 h exposure to culture medium inoculated with fecal samples. The polymer:polymer blend ratio was varied as indicated. The behavior of extrudates based on "pure" Kollidon SR (plasticized with 30 % DBS) is illustrated for reasons of comparison. Consistent with the results obtained in media simulating the contents of the upper gastro intestinal tract (Figure 4), the water uptake and dry mass loss increased with increasing inulin content, irrespective of the presence/absence of colonic bacteria (due to the hydrophilicity/water-solubility of this polymer). Interestingly, 50:50 Kollidon SR:inulin blends showed a somewhat higher water uptake in the *presence* of fecal samples, and 50:50, 30:70 and 20:80 blends a somewhat more important dry mass loss in this type of medium. This might eventually be explained by (partial) polymer degradation due to enzymes secreted by the bacteria [40]. Thus, drug release from these extrudates might be faster in the presence of fecal bacteria. However, Figure 7 shows that theophylline release from extrudates based on Kollidon SR:inulin 50:50 blends was not impacted by the presence of fecal samples: Drug release is shown upon exposure to 0.1 M HCl for 2 h, followed by 6 h phosphate buffer pH 6.8 and 10 h culture medium. The latter optionally contained fecal samples from IBD patients. This series of release media was intended to simulate the passage throughout the entire gastro intestinal tract. As it can be seen, the release patterns in the absence and presence of colonic bacteria (dashed and solid curves) were similar. So, the differences observed with

respect to the water uptake and erosion kinetics observed with the hot melt extrudates did not translate into any noteworthy differences in drug release in these cases. Consequently, drug release from this type of advanced drug delivery systems can be expected to be independent of the location “small intestine vs. colon” in a patient’s gastro intestinal tract. It was beyond the scope of this study to investigate the reasons for the apparent insensitivity of inulin to degradation by the bacterial enzymes. Eventually, intense blending with the Kollidon SR might “protect” the inulin.

3.2. Carbothane:inulin blends

The left column in Figure 8 shows optical macroscopy pictures of hot melt extrudates based on Carbothane:inuline blends, prepared at 100 °C and 3 mL/min. The polymer:polymer blend ratio was varied from 10:90 to 40:60, as indicated. Extrudates based on pure Carbothane were studied for reasons of comparison. Interestingly, the extrudate expansion after leaving the 4 mm die was the highest at 60 % inulin content. This can again be attributed to the different compositions of the polymeric phases and their expansion behaviors after pressure release (as discussed above). Figure 2c shows the torque measured during the hot melt extrusion process for these polymer blends, as a function of the blend ratio. Roughly, the torque was about 50 % and no clear impact of the composition on torque was visible.

Theophylline release from hot melt extrudates based on 10:90, 20:80, 30:70 and 40:60 Carbothane:inulin blends in media simulating the conditions in the upper gastro intestinal tract is shown in Figure 9. The initial drug content was 10 %. Clearly, the drug release rate substantially increased with increasing inulin content. This can again be explained by the hydrophilicity/water-solubility of this polymer. From a practical point of view, desired drug release kinetics can be rather easily adjusted by simply varying the Carbothane:inulin blend ratio.

Importantly, the investigated Carbothane:inulin blends also allowed for the preparation of

empty capsule shells, feeding a bench-top injection-molder (Babyplast) with the hot melt extrudates described above (drug-free). Figure 10 shows examples of pictures of capsule bodies and caps (30:70 and 20:80 Carbothane:inulin). These capsules were manually filled with 10 mg theophylline and sealed by wetting with ethanol. Figure 11 shows the resulting drug release kinetics upon exposure to 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. As it can be seen, the resulting release rate increased with increasing inulin content, due to the hydrophilicity/water-solubility of this polymer. However, compared to the drug release rates from the respective hot melt extrudates with a diameter of > 4 mm (Figure 9), theophylline release was substantially slower. This is somewhat surprising, because the capsule shell thickness was only 600 µm. Thus, the pathways to be overcome by most of the water and drug are much shorter. It has to be pointed out that the drug was distributed *throughout* the system in the case of extrudates, whereas the capsule shells were free of theophylline. Thus, for parts of the drug in the extrudates (located in surface near regions) the pathways were shorter compared to the capsules. Looking at Figures 9 and 11, it becomes obvious that drug release from the "larger" extrudates (> 4 mm diameter) was much faster than from the capsules with the thinner shells (600 µm). Eventually, the injection-molding step might alter the inner structure of the polymer:polymer blends. Also, drug released from the extrudates can be expected to be replaced by water, increasing the permeability of the remaining matrix. However, the initial drug loading was only 10 % in these cases.

Figure 12 illustrates the effects of the Carbothane:inulin blend ratio on the water content and dry mass of hot melt extrudates after 24 h exposure to culture medium free of bacteria (black bars) and culture medium inoculated with fecal samples from IBD patients (white bars). For reasons of comparison, also extrudates based on Carbothane only were studied. Clearly, the water content increased and the dry mass decreased with increasing inulin content (due to the hydrophilicity/water-solubility of this polymer). Similar to the Kollidon SR:inulin blends discussed above, a certain (but limited) impact of the presence of fecal samples was observed,

eventually suggesting partial enzymatic inulin degradation, resulting in increased water contents and system erosion. However, as for the Kollidon SR:inulin blends, this did not translate into any noteworthy effects on drug release from the extrudates: The solid curves in Figure 13 show theophylline release from capsules filled with 10 mg drug upon exposure to culture medium free of colonic bacteria, the solid curves in culture medium inoculated with fecal samples from IBD patients. Again, the capsule shells were prepared by injection-molding, feeding a benchtop injection-molder (Babyplast) with drug-free hot melt extrudates. The Carbothane:inulin blend ratio was 10:90, 20:80 or 30:70, as indicated. As it can be seen, the solid and dashed curves are rather similar. Thus, as in the case of extrudates based on Kollidon SR:inulin blends, drug release from capsules with Carbothane:inulin shells is likely not affected by the location "small intestine vs. colon" in the patients gastro intestinal tract to a significant extent. Also in this case, the inulin might be "protected" by the presence of the other polymer against enzymatic attack under the given conditions. Again, the resulting theophylline release rate increased with increasing inulin content, irrespective of the type of release medium, for the reasons discussed above.

4. Conclusion

Kollidon SR:inulin and Carbothane:inulin blends offer an interesting potential for controlled drug delivery throughout the entire gastro intestinal tract. Matrix systems as well as empty capsule shells can be prepared by hot melt extrusion and injection-molding. Interestingly, slight effects of the presence of colonic bacteria on the water uptake and dry mass loss kinetics observed with hot melt extrudates did not translate into noteworthy differences in the resulting drug release patterns. Thus, the location within the gastro intestinal tract "small intestine vs. colon" does probably not alter the resulting drug release rate, which is of particular interest when controlled drug delivery throughout the *entire* gastro intestinal tract is targeted.

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.

References

[1] O.- A. Adeleke, Premium ethylcellulose polymer based architectures at work in drug delivery, Int. J. Pharm. X 1 (2019) 100023.

[2] E. Simon, K.- P. Moll, T. Haefele-Racin, K. Mäder, Safety and robustness of coated pellets: self-healing film properties and storage stability, Pharm. Res. 26 (2009) 1534-1543.

[3] A. Maroni, L. Zema, M.- D. Del Curto, A. Foppoli, A. Gazzaniga, Oral colon delivery of insulin with the aid of functional adjuvants, Adv. Drug Deliv. Rev. 64 (2012) 540-556.

[4] F. Zhang, F. Meng, J. Lubach, J. Koleng, N.A. Watson, Properties and mechanisms of drug release from matrix tablets containing poly(ethylene oxide) and poly(acrylic acid) as release retardants, Eur. J. Pharm. Biopharm. 105 (2016) 97-105.

[5] L. Palugan, M. Cerea, L. Zema, A. Gazzaniga, A. Maroni, Coated pellets for oral colon delivery, J. Drug Deliv. Sc. Technol. 25 (2015) 1-15.

[6] J. Maincent, R.- O. Williams 3rd, Sustained-release amorphous solid dispersions, Drug Deliv. Transl. Res. 8 (2018) 1714-1725.

[7] J. Siepmann, N.- A. Peppas, Hydrophilic matrices for controlled drug delivery: An improved mathematical model to predict the resulting drug release kinetics (the "sequential layer" model), Pharm. Res. 17 (2000) 1290-1298.

[8] J. Siepmann, F. Siepmann, Mathematical modeling of drug dissolution. Int. J. Pharm. 453 (2013) 12-24.

[9] D. Caccavo, G. Lamberti, A.- A. Barba, S. Abrahmsén-Alami, A. Viridén, A. Larsson, Effects of HPMC substituent pattern on water up-take, polymer and drug release: An experimental and modelling study, Int. J. Pharm. 528 (2017) 705-713.

[10] A.- A. Barba, M. d'Amore, S. Chirico, G. Lamberti, G. Titomanlio, Swelling of cellulose derivative (HPMC) matrix systems for drug delivery, Carbohydr. Polymers 78 (2009) 469-474.

[11] C.- S. Brazel, N.- A. Peppas, Mechanisms of solute and drug transport in relaxing, swellable, hydrophilic glassy polymers, Polymer 40 (1999) 3383-3398.

[12] E. Kaunisto, F. Tajarobi, S. Abrahmsen-Alami, A. Larsson, B. Nilsson, A. Axelsson, Mechanistic modelling of drug release from a polymer matrix using magnetic resonance microimaging, Eur. J. Pharm. Sci. 48 (2013) 698-708.

[13] S. Chirico, A. Dalmoro, G. Lamberti, G. Russo, G. Titomanlio, Analysis and modeling of swelling and erosion behavior for pure HPMC tablet, J. Control. Release 122 (2007) 181-188.

[14] E. Kaunisto, S. Abrahmsen-Alami, P. Borgquist, A. Larsson, B. Nilsson, A. Axelsson, A mechanistic modelling approach to polymer dissolution using magnetic resonance microimaging, J. Control. Release 147 (2010) 232-241.

[15] A. Foppoli, A. Maroni, L. Palugan, L. Zema, S. Moutaharrik, A. Melocchi, M. Cerea, A. Gazzaniga, Erodible coatings based on HPMC and cellulase for oral time-controlled release of drugs, Int. J. Pharm. 585 (2020) 119425.

[16] J. Siepmann, F. Siepmann, Sink conditions do not guarantee the absence of saturation effects, Int. J. Pharm. 577 (2020) 119009.

[17] F. Lecomte, J. Siepmann, M. Walther, R.- .J. MacRae, R. Bodmeier, Blends of enteric and GIT-insoluble polymers used for film coating: physicochemical characterization and drug release patterns, J. Control. Release 89 (2003) 457-471.

[18] F. Siepmann, J. Siepmann, M. Walther, R.- J. MacRae, R. Bodmeier, Polymer blends for controlled release coatings, J. Control. Release 125 (2008) 1-15.

[19] N.- C. Ngwuluka, Y.- E. Choonara, P. Kumar, L.- C. du Toit, G. Modi, V. Pillay, A Co-blended Locust Bean Gum and Polymethacrylate-NaCMC Matrix to Achieve Zero-Order Release via Hydro-Erosive Modulation, AAPS PharmaSciTech. 16 (2015) 1377-1389.

[20] Y. El-Malah, S. Nazzal, Novel use of Eudragit® NE 30D/Eudragit® L 30D-55 blends as functional coating materials in time-delayed drug release applications, Int. J. Pharm. 357 (2008) 219-227.

[21] H. Kranz, S. Gutsche, Evaluation of the drug release patterns and long term stability of aqueous and organic coated pellets by using blends of enteric and gastrointestinal insoluble polymers, Int. J. Pharm. 380 (2009) 112-119.

[22] S. Rujivipat, R. Bodmeier, Improved drug delivery to the lower intestinal tract with tablets compression-coated with enteric/nonenteric polymer powder blends, Eur. J. Pharm. Biopharm. 76 (2010) 486-492.

[23] R. Ali, A. Dashevsky, R. Bodmeier, Poly vinyl acetate and ammonio methacrylate copolymer as unconventional polymer blends increase the mechanical robustness of HPMC matrix tablets, Int. J. Pharm. 516 (2017) 3-8.

[24] K. Amighi, A.- J. Moes, Evaluation of thermal and film forming properties of acrylic aqueous polymer dispersion blends: application to the formulation of sustained-release film coated theophylline pellets, Drug Dev. Ind. Pharm. 21 (1995) 2355-2369.

[25] F. Varum, A.- C. Freire, H.- M. Fadda, R. Bravo, A.- W. Basit, A dual pH and microbiota-triggered coating (Phloral™) for fail-safe colonic drug release, Int. J. Pharm. 583 (2020) 119379.

[26] M.- M. Crowley, B. Schroeder, A. Fredersdorf, S. Obara, M. Talarico, S. Kucera, J.- W. McGinity, Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion, Int. J. Pharm. 269 (2004) 509-522.

[27] S. Furlanetto, M. Cirri, F. Maestrelli, G. Corti, P. Mura, Study of formulation variables influencing the drug release rate from matrix tablets by experimental design, Eur. J. Pharm. Biopharm. 62 (2006) 77-84.

[28] M. Elbadawi, T. Gustaffson, S. Gaisford, A.- W. Basit, 3D printing tablets: Predicting printability and drug dissolution from rheological data, Int. J. Pharm. 590 (2020) 119868.

[29] A. Goyanes, A.- B.- M. Buanz, G.-B Hatton, S. Gaisford, A.- W. Basit, 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets, Eur. J. Pharm. Biopharm. 89 (2015) 157-162.

[30] J.- J Ong, A. Awad , A. Martorana, S. Gaisford, E. Stoyanov, A.- W Basit, A. Goyanes, 3D printed opioid medicines with alcohol-resistant and abuse-deterrent properties, Int. J. Pharm. 579 (2020) 119169.

[31] E. Verhoeven, T.- R.- M. De Beer, E. Schacht, G. Van den Mooter, J.- P. Remon, C. Vervaet, Influence of polyethylene glycol/polyethylene oxide on the release characteristics of sustained-release ethylcellulose mini-matrices produced by hot melt extrusion: in vitro and in vivo evaluations, Eur. J. Pharm. Biopharm. 72 (2009) 463-470.

[32] R. Thakkar, R. Thakkar, A. Pillai, E.- A. Ashour, M.- A. Repka, Systematic screening of pharmaceutical polymers for hot melt extrusion processing: a comprehensive review Int. J. Pharm. 576 (2020) 118989.

[33] P. Srinivasan, M. Almutairi, N. Dumpa, S. Sarabu, S. Bandari, F. Zhang, E. Ashour, M.- A. Repka, Theophylline-nicotinamide pharmaceutical co-crystals generated using hot melt extrusion technology: Impact of polymeric carriers on processability, J. Drug Deliv. Sci. Technol. 61 (2020) 102128.

[34] Y. Benzine, F. Siepmann, C. Neut, F. Danede, J.- F. Willart, J. Siepmann, Y. Karrout, Hot melt extruded polysaccharide blends for controlled drug delivery, J. Drug Deliv. Sci. Technol. 54 (2019) Article 101317.

[35] J.- A.- C. Barbosa, M.- M. Al-Kauraishi, A.- M. Smith, B.- R. Conway, H.- A. Merchant, Achieving gastroresistance without coating: Formulation of capsule shells from enteric polymers, Eur. J. Pharm. Biopharm.144 (2019) 174-179.

[36] S. Deshmukh, A. Paradkar, S. Abrahmsén-Alami, R. Govender, A. Viridén, F. Winge, H. Matic, J. Booth, A. Kelly, Injection moulded controlled release amorphous solid dispersions: Synchronized drug and polymer release for robust performance Int. J. Pharm. 575 (2019) 118908.

[37] Y. Karrout, C. Neut, D. Wils, F. Siepmann, L. Deremaux, L. Dubreuil, P. Desreumaux, J. Siepmann, Colon targeting with bacteria-sensitive films adapted to the disease state, Eur. J. Pharm. Biopharm. 73 (2009) 74-81.

[38] I. Ozgüney, D. Shuwisitkul, R. Bodmeier, Development and characterization of extended release Kollidon SR mini-matrices prepared by hot-melt extrusion Eur. J. Pharm. Biopharm.73 (2009) 140-145.

[39] S. Chadha, A. Kumar, S.- A. Srivastava, T. Behl, R. Ranjan, Inulin as a delivery vehicle for targeting colon-specific cancer, Cur. Drug Deliv. 17 (2020) 651-674.

[40] S. Giri, P. Dutta T.- K. Giri, Inulin-based carriers for colon drug targeting, J. Drug Deliv. Sc. Technol. 64 (2021) 102595.

Figure captions

Fig. 1: Macroscopic pictures of hot melt extrudates based on Kollidon SR:inulin blends before and after exposure to 0.1 M HCl pH 1.2 for 2 h, optionally followed by phosphate buffer pH 6.8 for 6 h. The polymer:polymer blend ratio was varied as indicated on the left hand side. The potential exposure to the release media is indicated at the top. The extrudates were free of drug.

Fig. 2: Torque generated during the preparation of hot melt extrudates based on: a) Kollidon SR:inulin blends (the blend ratio is indicated in the diagram), b) Kollidon SR:inulin (50:50) blends, loaded with 10 to 60 % theophylline, and c) Carbothane:inulin blends (the blend ratio is indicated in the diagram).

Fig. 3: X-ray diffractograms of hot melt extrudates based on Kollidon SR:inulin (50:50) blends, loaded with different amounts of theophylline (as indicated). For reasons of comparison, also the X-ray diffractograms of hot melt extrudates free of drug as well as of the raw materials (theophylline, Kollidon SR and inulin) are illustrated.

Fig. 4: Dynamic changes in the water content and dry mass of hot melt extrudates based on different Kollidon SR:inulin blends (the blend ratio is indicated in the diagrams) upon exposure to: a) 0.1 M HCl and b) phosphate buffer pH 6.8. Extrudates consisting "only" of Kollidon SR (plasticized with 30 % DBS) are shown for reasons of comparison.

Fig. 5: Impact of the theophylline loading on drug release from hot melt extrudates in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The systems were based on Kollidon SR:inulin (50:50) blends.

Fig. 6: Water content and dry mass of hot melt extrudates based on different Kollidon SR:inulin blends upon 24 h exposure to culture medium or culture medium inoculated with feces of patients suffering from inflammatory bowel diseases. Extrudates

consisting “only” of Kollidon SR (plasticized with 30 % DBS) were studied for reasons of comparison.

Fig. 7: Theophylline release from hot melt extrudates based on Kollidon SR:inulin (50:50) blends under conditions simulating the transit through the entire gastro intestinal tract: 2 h in 0.1 M HCl, followed by 6 h in phosphate buffer pH 6.8, followed by culture medium inoculated with feces of patients suffering from inflammatory bowel diseases (solid curve). For reasons of comparison also drug release in 0.1 M HCl, phosphate buffer pH 6.8 and culture medium without fecal samples is shown (dotted curve). The drug loading was 10 %.

Fig. 8: Macroscopic pictures of hot melt extrudates based on different Carbothane:inulin blends before and after exposure to 0.1 M HCl pH 1.2 for 2 h, optionally followed by phosphate buffer pH 6.8 for 6 h. The polymer:polymer blend ratio was varied as indicated on the left hand side. The potential exposure to the release media is indicated at the top. The extrudates were free of drug.

Fig. 9: Theophylline release from hot melt extrudates based on different Carbothane:inulin blends in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The polymer:polymer blend ratio was varied as indicated. The drug loading was 10 %.

Fig. 10: Macroscopic pictures of injecting-molded empty capsules (caps and bodies) based on Carbothane:inulin blends. The polymer:polymer blend ratio was varied as indicated.

Fig. 11: Theophylline release from injection-molded capsules based on different Carbothane:inulin blends in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The polymer:polymer blend ratio was varied as indicated.

Fig. 12: Water content and dry mass of hot melt extrudates based on different Carbothane:inulin blends upon 24 h exposure to culture medium or culture medium inoculated with feces of patients suffering from inflammatory bowel diseases. The

polymer:polymer blend ratio was varied as indicated. Extrudates consisting “only” of Carbothane (plasticized with 30 % DBS) were studied for reasons of comparison.

Fig. 13: Theophylline release from injection-molded capsules based on different Carbothane:inulin blends under conditions simulating the transit through the entire gastro intestinal tract: 2 h in 0.1 M HCl, followed by 6 h in phosphate buffer pH 6.8, followed by culture medium inoculated with feces of patients suffering from inflammatory bowel diseases (solid curves). For reasons of comparison also drug release in 0.1 M HCl, phosphate buffer pH 6.8 and culture medium without fecal samples is shown (dotted curves).

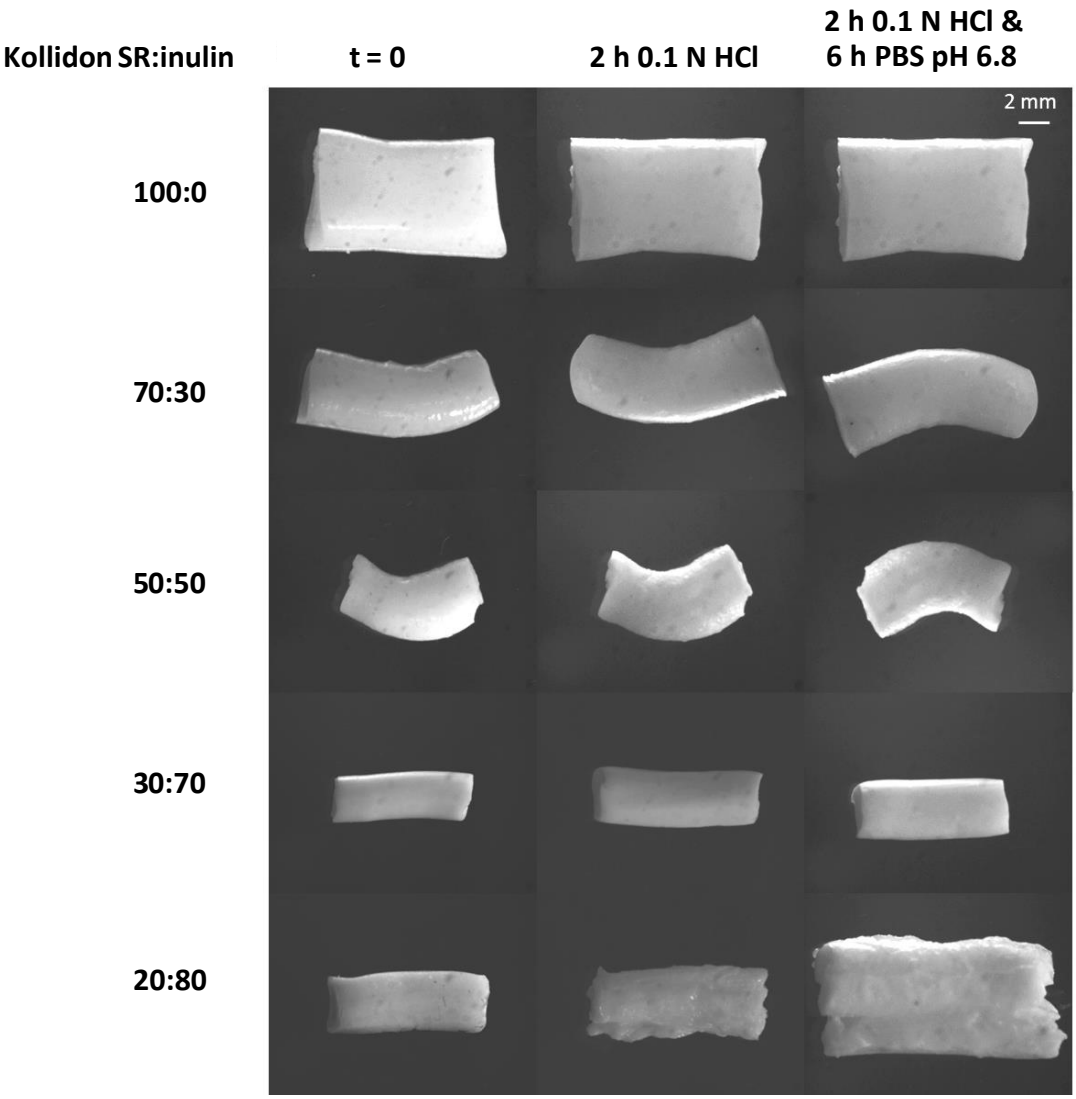

Kollidon SR:inulin
t = 0
2 h 0.1 N HCl
2 h 0.1 N HCl &
6 h PBS pH 6.8
2 mm
100:0
70:30
50:50
30:70
20:80

Figure 1

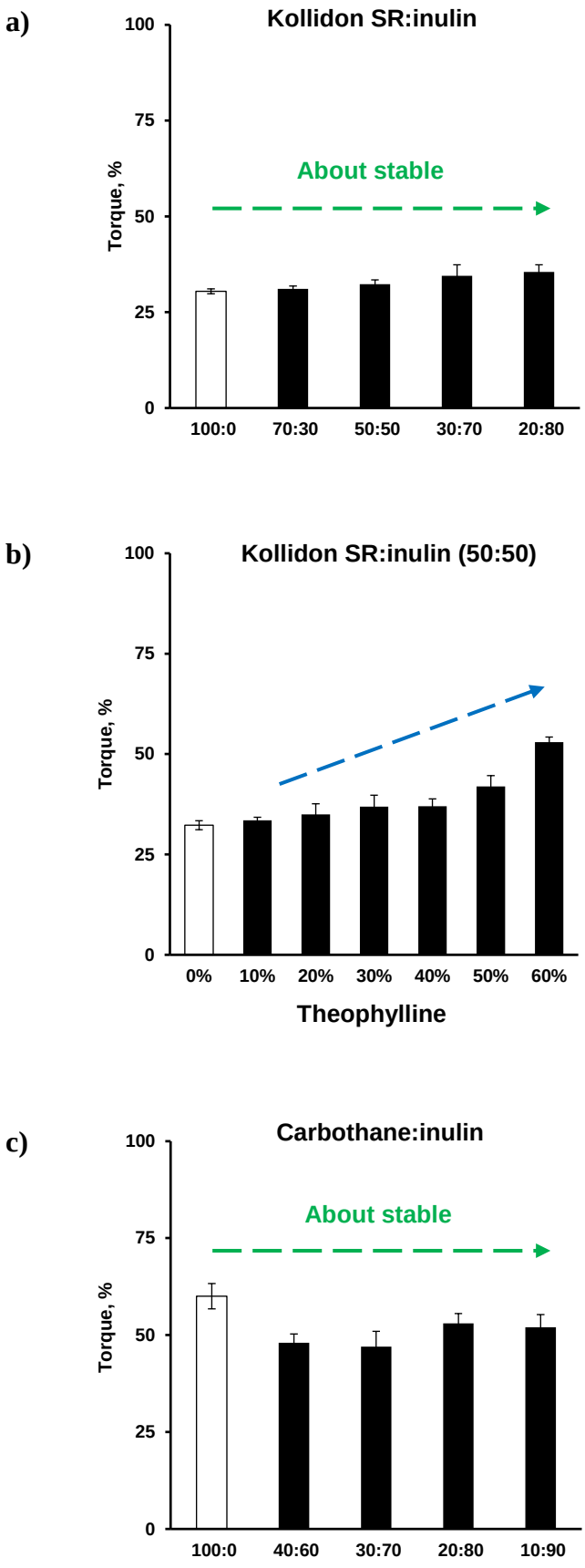

a)
Kollidon SR:inulin
About stable
Torque, %
100
75
50
25
0
100:0
70:30
50:50
30:70
20:80
b)
Kollidon SR:inulin (50:50)
Torque, %
0%
10%
20%
30%
40%
50%
60%
Theophylline
c)
Carbothane:inulin
About stable
Torque, %
100:0
40:60
30:70
20:80
10:90

Figure 2

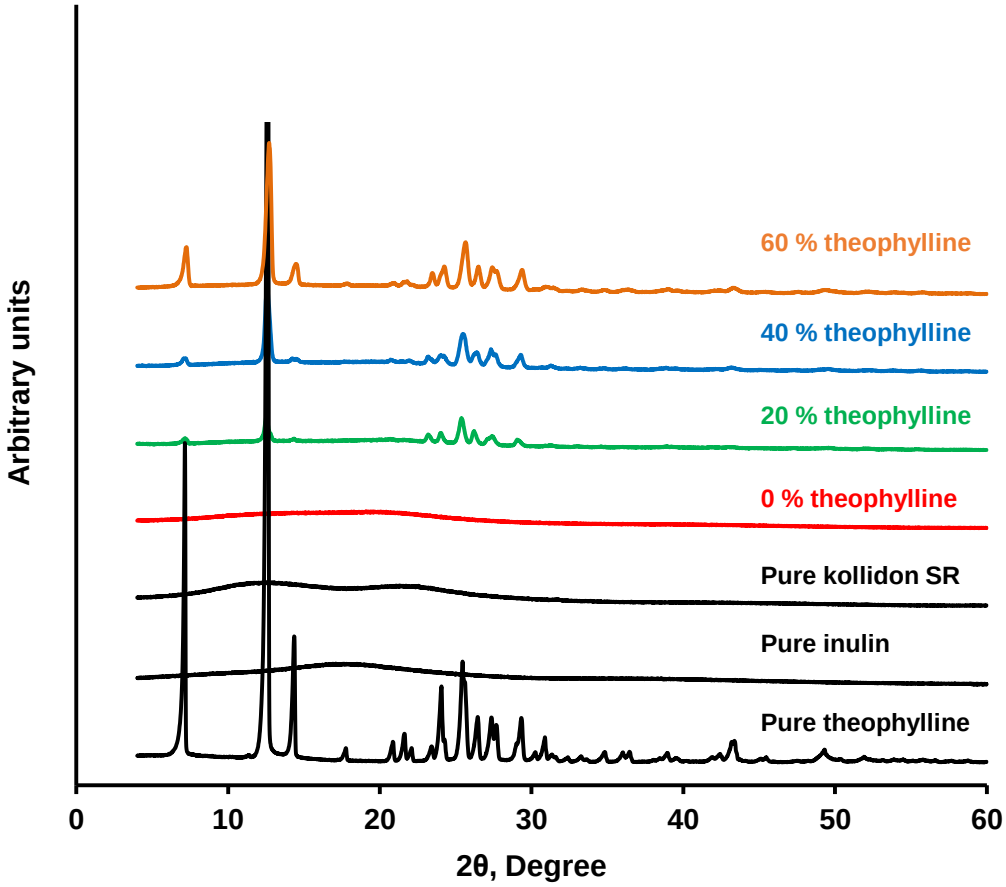

Arbitrary units
60 % theophylline
40 % theophylline
20 % theophylline
0 % theophylline
Pure kollidon SR
Pure inulin
Pure theophylline
0
10
20
30
40
50
60
2θ, Degree

Figure 3

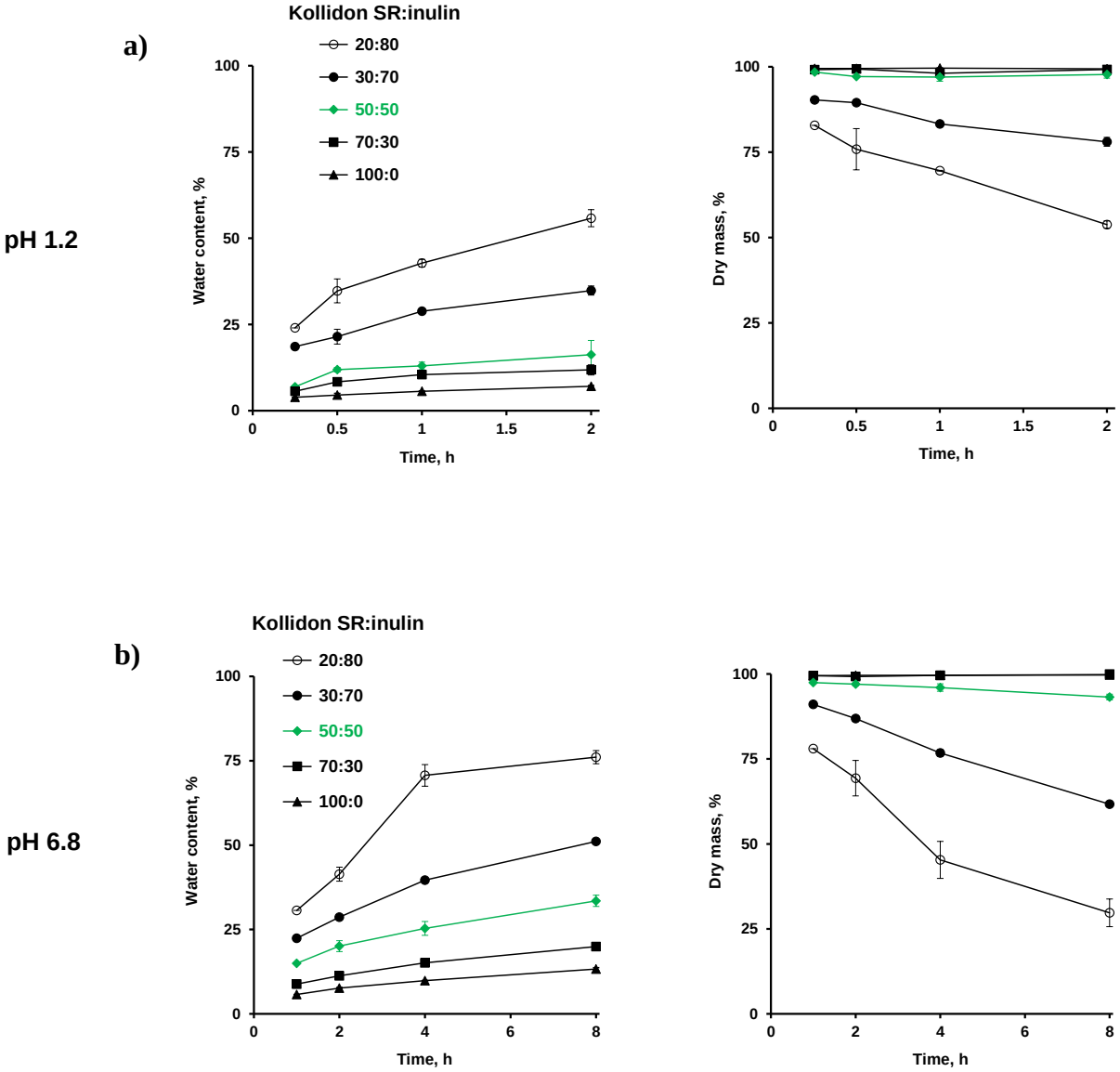

a)
pH 1.2
Kollidon SR:inulin
20:80
30:70
50:50
70:30
100:0
Water content, %
Dry mass, %
Time, h
b)
pH 6.8
Kollidon SR:inulin
20:80
30:70
50:50
70:30
100:0
Water content, %
Dry mass, %
Time, h

Figure 4

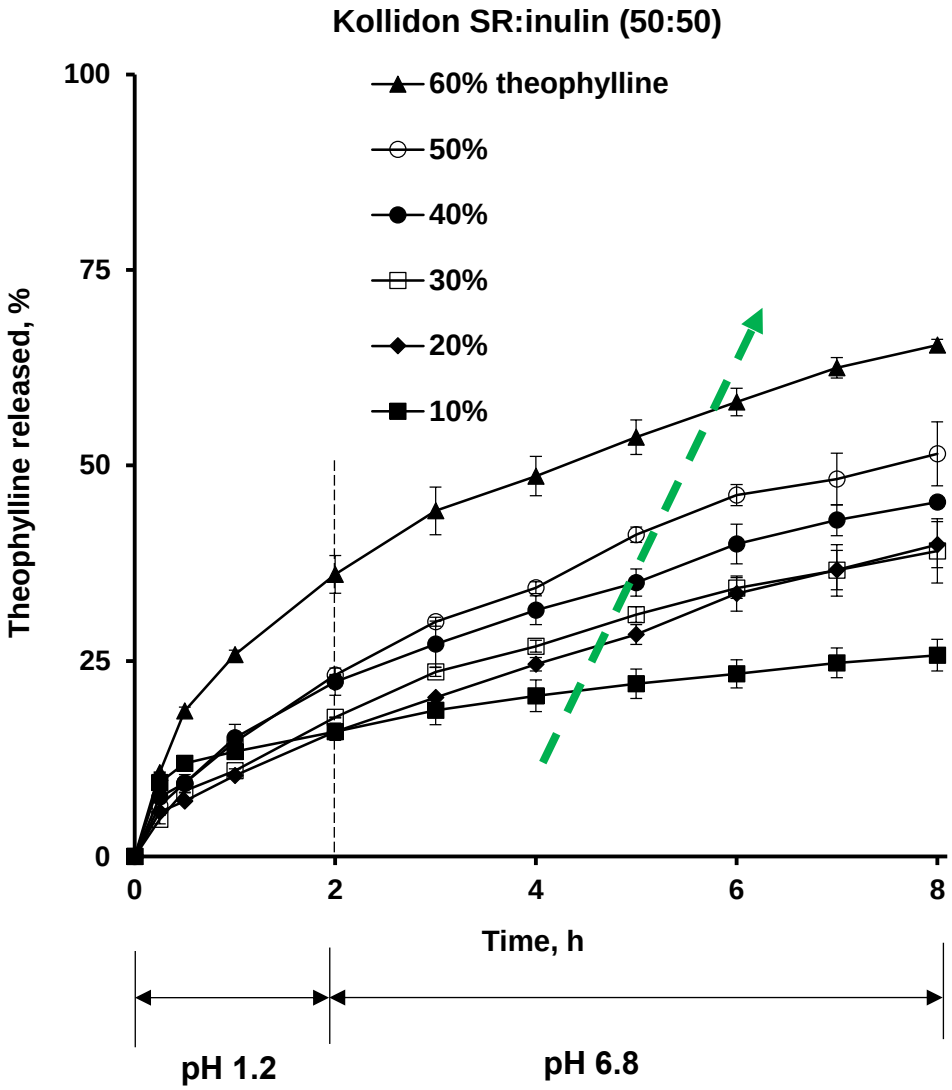

Kollidon SR:inulin (50:50)
60% theophylline
50%
40%
30%
20%
10%
Theophylline released, %
100
75
50
25
0
0
2
4
6
8
Time, h
pH 1.2
pH 6.8

Figure 5

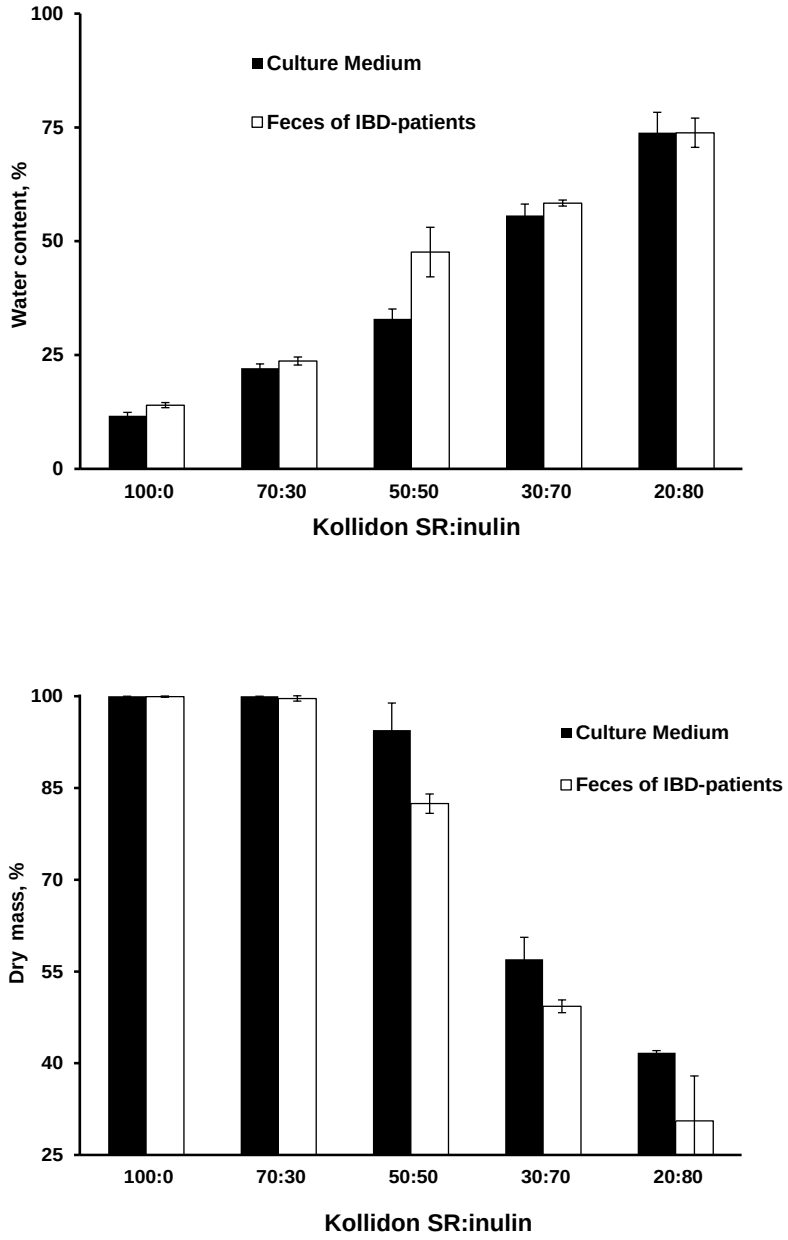

100
75
50
25
0
Water content, %
Culture Medium
Feces of IBD-patients
100:0
70:30
50:50
30:70
20:80
Kollidon SR:inulin
100
85
70
55
40
25
Dry mass, %
Culture Medium
Feces of IBD-patients
100:0
70:30
50:50
30:70
20:80
Kollidon SR:inulin

Figure 6

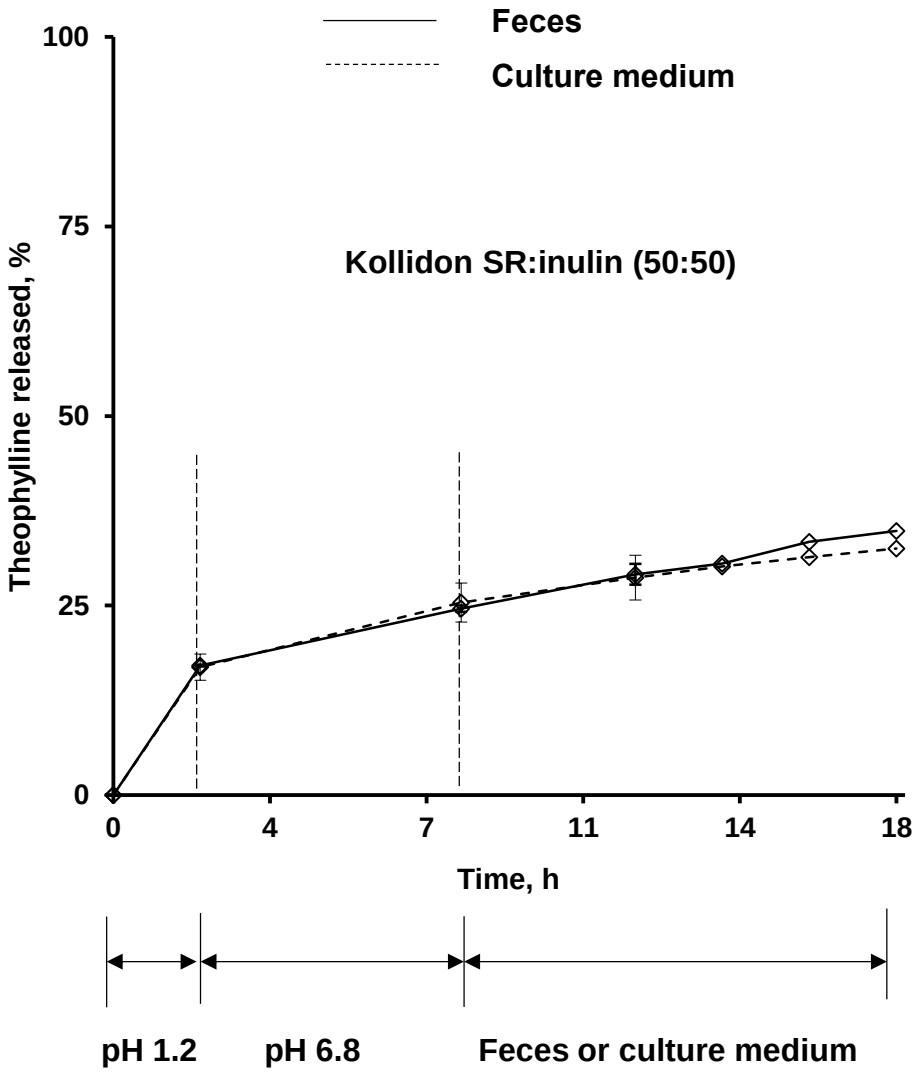

Feces
Culture medium
Kollidon SR:inulin (50:50)
Theophylline released, %
100
75
50
25
0
0
4
7
11
14
18
Time, h
pH 1.2
pH 6.8
Feces or culture medium

Figure 7

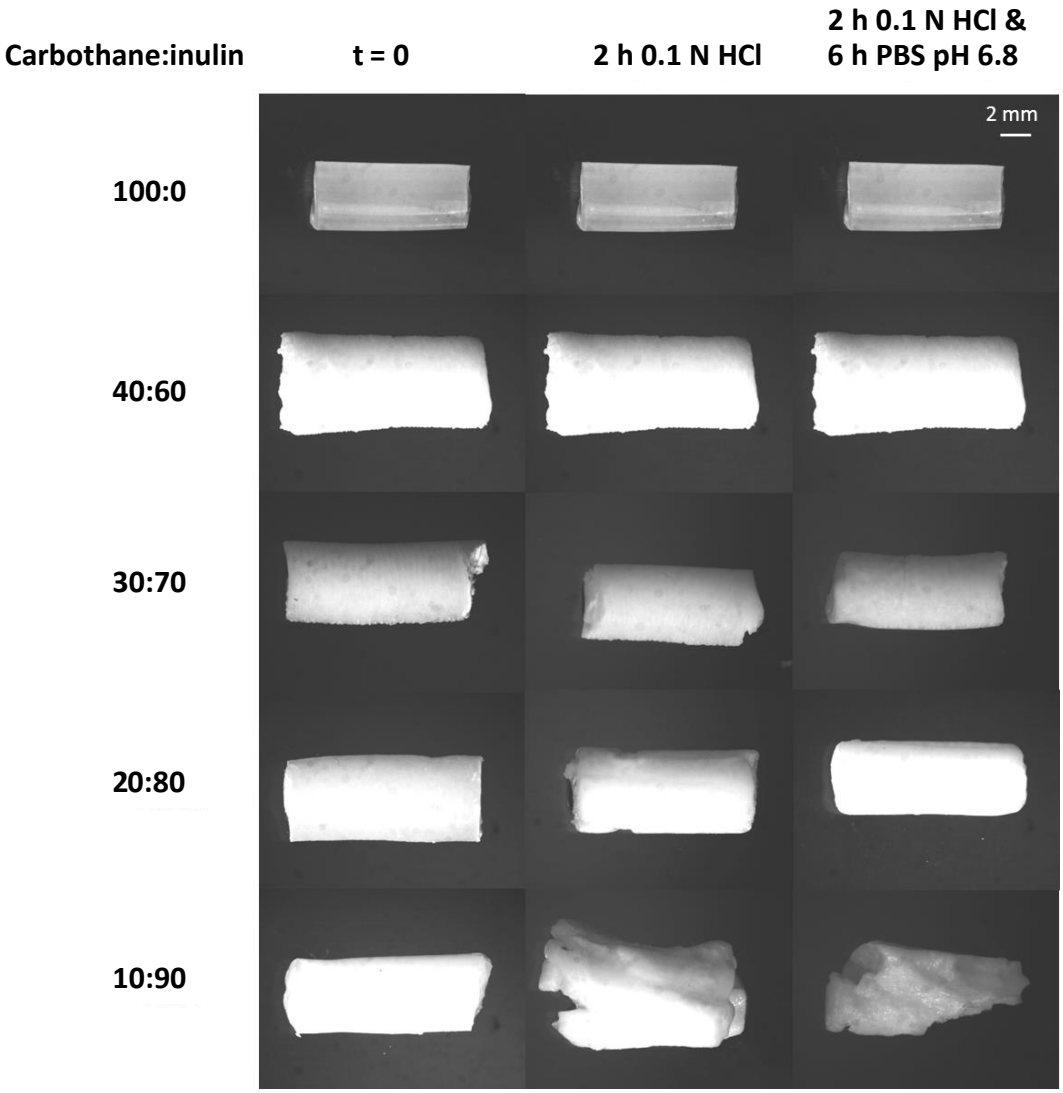

Carbothane:inulin
t = 0
2 h 0.1 N HCl
2 h 0.1 N HCl &
6 h PBS pH 6.8
2 mm
100:0
40:60
30:70
20:80
10:90

Figure 8

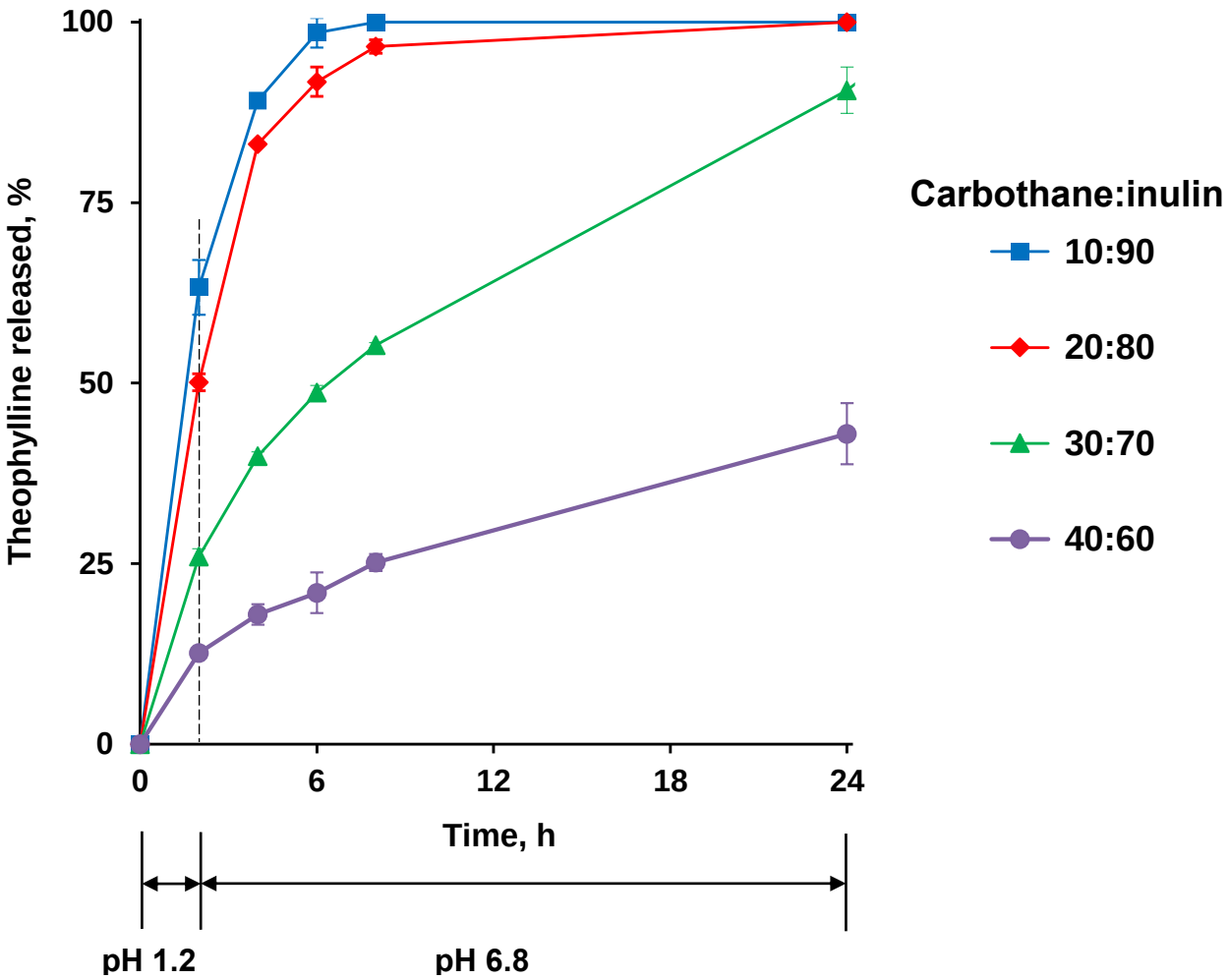

100
75
50
25
0
Theophylline released, %
0
6
12
18
24
Time, h
pH 1.2
pH 6.8
Carbothane:inulin
10:90
20:80
30:70
40:60

Figure 9

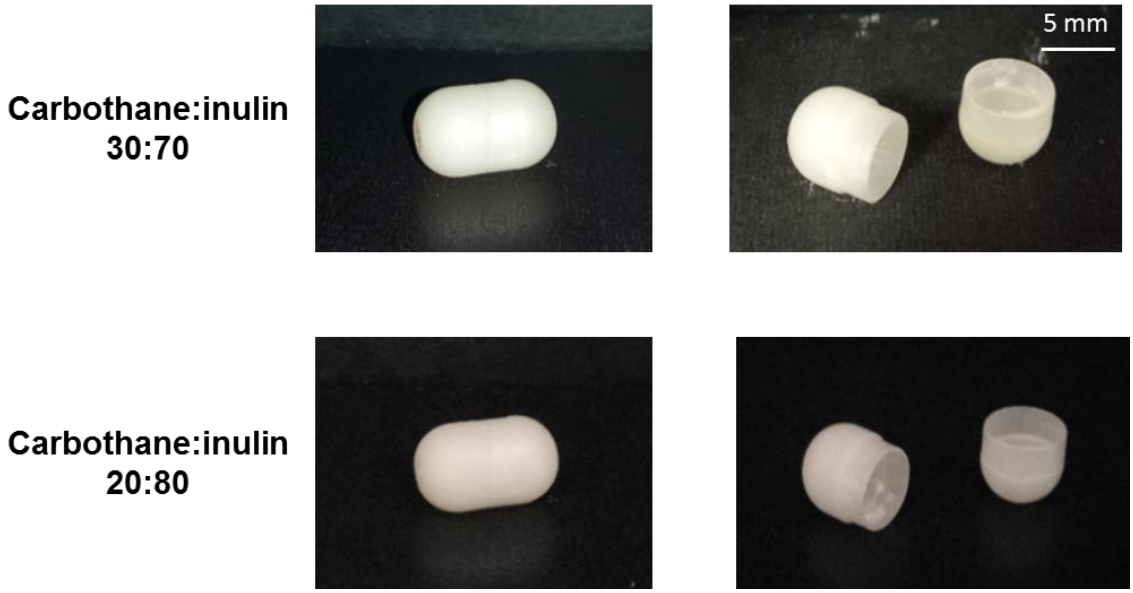


Figure 10

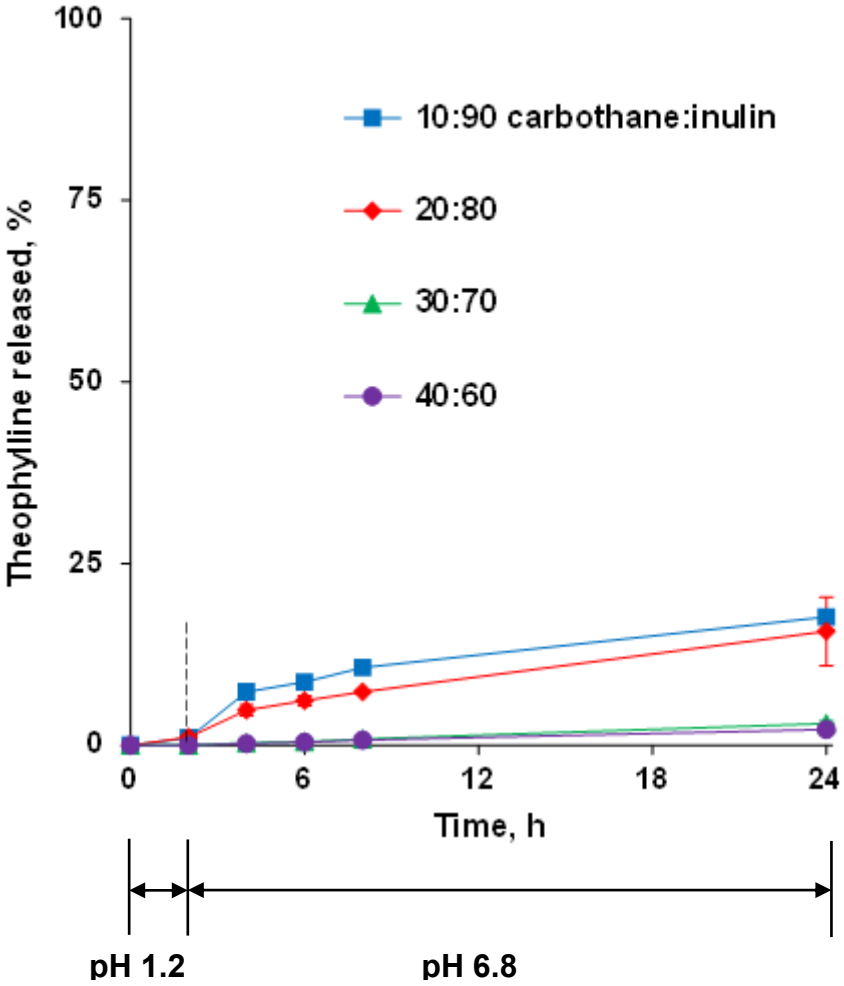
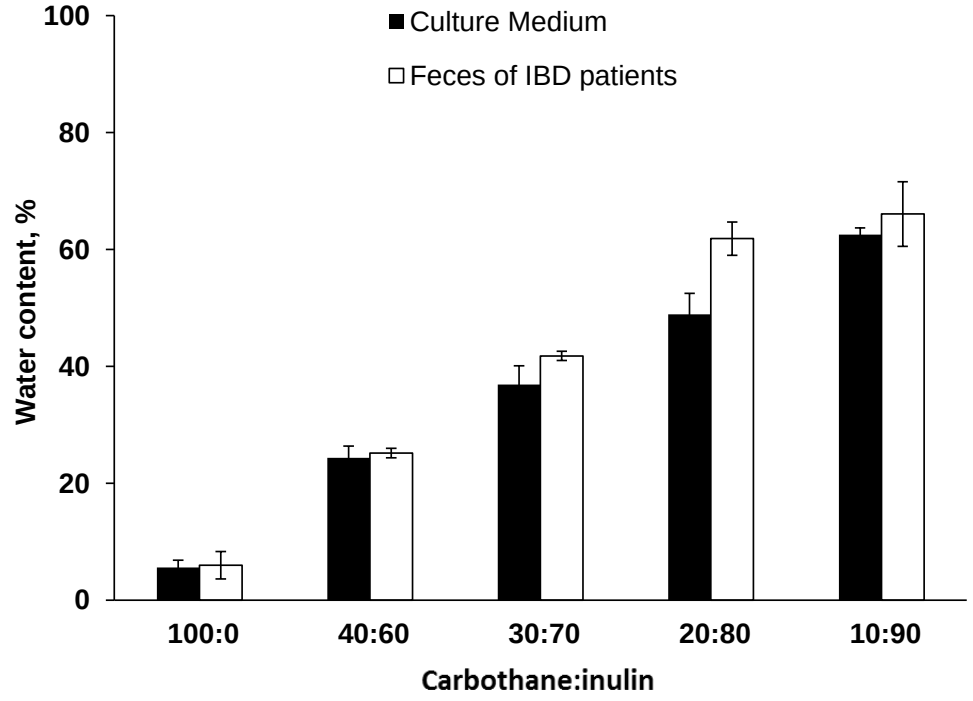

100
75
50
25
0
Theophylline released, %
10:90 carbothane:inulin
20:80
30:70
40:60
0
6
12
18
24
Time, h
pH 1.2
pH 6.8

Figure 11


Culture Medium
Feces of IBD patients
Water content, %
100
80
60
40
20
0
100:0
40:60
30:70
20:80
10:90
Carbothane:inulin

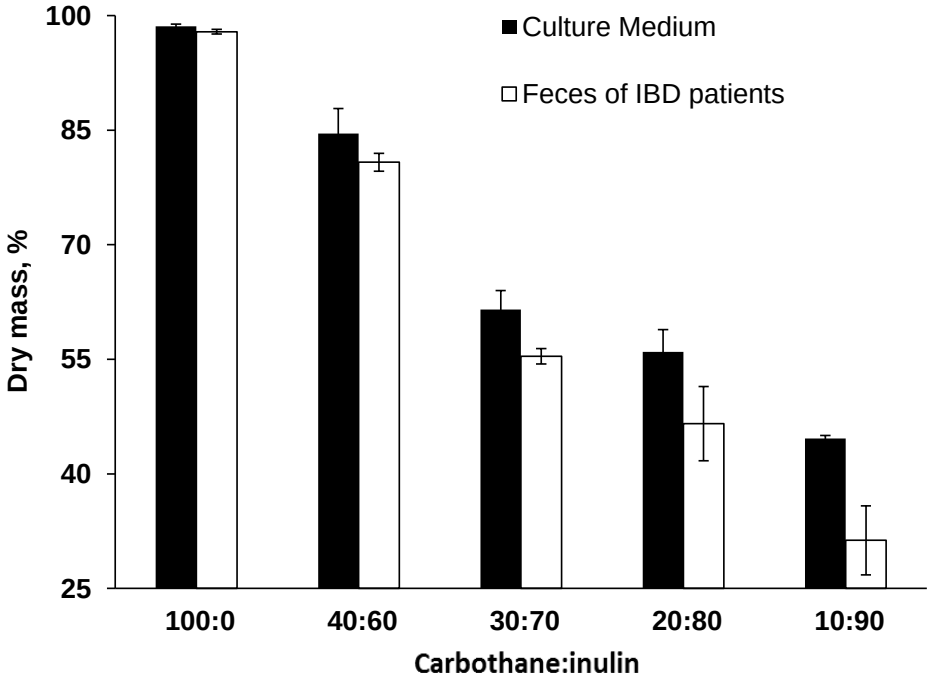

Culture Medium
Feces of IBD patients
Dry mass, %
100
85
70
55
40
25
100:0
40:60
30:70
20:80
10:90
Carbothane:inulin

Figure 12

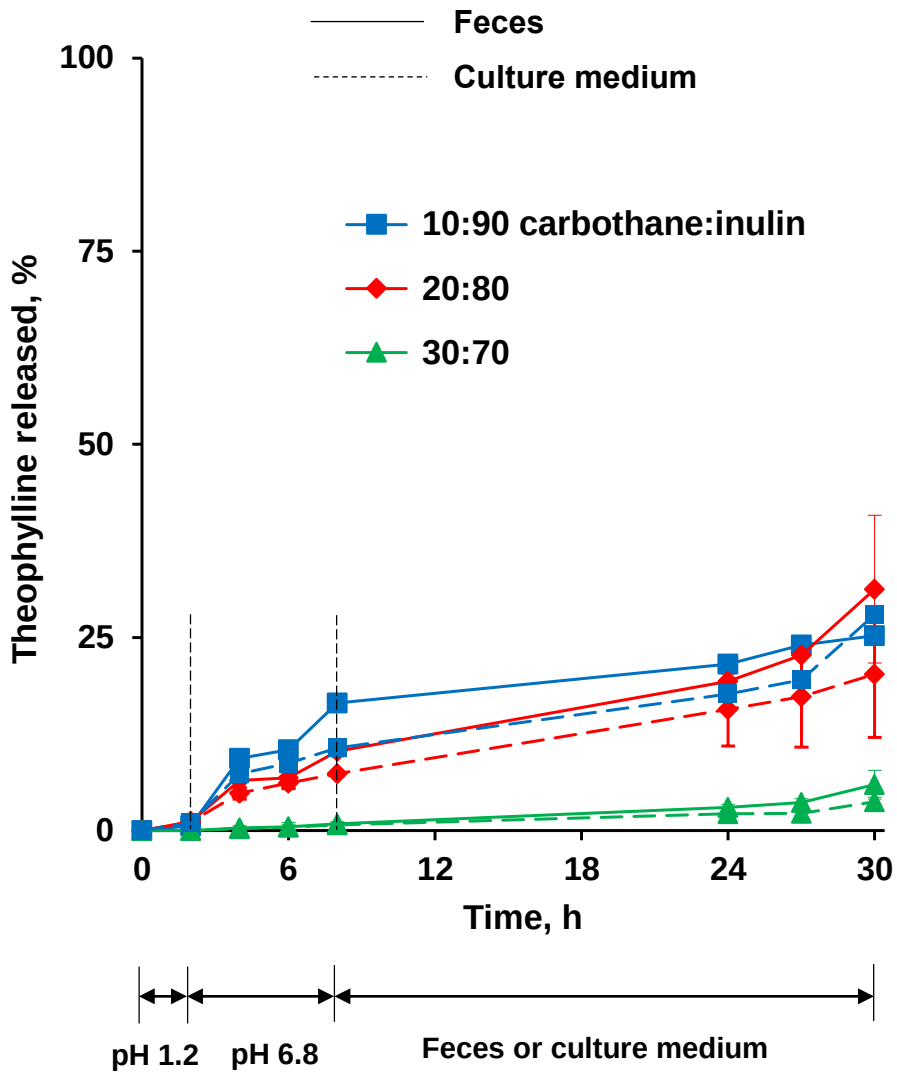

Feces
Culture medium
10:90 carbothane:inulin
20:80
30:70
Theophylline released, %
100
75
50
25
0
0
6
12
18
24
30
Time, h
pH 1.2
pH 6.8
Feces or culture medium

Figure 13