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

Research article

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Y. Benzine[1], F. Siepmann[1], C. Neut[2], F. Danede[3], J.F. Willart[3], J. Siepmann[1,*], Y. Karrout[1,**]

[1]Univ. Lille, Inserm, CHU Lille, U1008, F-59000 Lille, France

[2]Univ. Lille, Inserm, CHU Lille, U995- LIRIC, 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

Different types of hot melt extrudates were prepared based on a variety of blends of ethylcellulose with a 2nd polysaccharide, namely hydroxypropyl methylcellulose (HPMC), pectin, maize starch, inulin, maltodextrin, guar gum, and chitosan. In selected cases, the polymer:polymer blend ratio was varied from 80:20, 70:30, 60:40, 50:50, 40:60, 30:70 to 20:80. The addition of appropriate amounts of plasticizers allowed reducing the extrusion temperature to about 100 °C. The impacts of the screw speed, extrusion temperature, amount and type of plasticizer as well as of the amount and type of drug (10 to 60 % theophylline or diprophylline) were studied. Drug release was measured in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8 and (optionally) fecal samples to simulate the colon (under anaerobic conditions). DSC measurements and optical microscopy were used to characterize the physical state and morphology of the systems. Interestingly, hot melt extrudates based on ethylcellulose:guar gum blends could be easily prepared at a temperature of 100 °C and offered large spectra of drug release patterns for both: slightly water-soluble theophylline as well as freely water-soluble diprophylline. About constant drug release rates could be obtained during prolonged periods of time. Importantly, the resulting drug release rates from hot melt extrudates based on ethylcellulose:guar gum 80:20 blends were similar in the presence and absence of colonic bacteria, indicating that the ethylcellulose seems to protect the guar gum from degradation upon exposure to fecal samples. Furthermore, these systems were long term stable for at least 1 year under ambient conditions. Thus, they can offer an interesting potential as oral controlled drug delivery systems.

Keywords: Hot melt extrusion; controlled release; ethylcellulose; guar gum; theophylline.

1. Introduction

Polymer blends offer an interesting potential for controlled drug delivery systems [1,2,3,4,5,6], both as matrix formers [7,8,9,10] and as coating materials [11,12,13,14,15]. By simply varying the polymer:polymer blend ratio, the resulting key properties of the systems can be effectively varied, allowing to provide large spectra of possible drug release kinetics [16,17,18]. For example, a variety of blends of enteric and non-enteric polymer blends has been used to control the resulting drug release kinetics from *coated pellets* [19,20]. Importantly, the presence of the non-enteric polymer can effectively hinder the leaching of the enteric polymer out of the film coating at neutral pH [21]. Thus, one polymer can efficiently "mask" key properties of the other polymer, if the two compounds are intimately mixed [22]. The polymer:polymer blend ratio as well as the manufacturing technique (determining the inner system structure) can strongly affect the efficiency of such "masking" phenomena [23]. Polymer:polymer blends have also been used in a variety of controlled drug delivery systems as *matrix formers* [24,25,26]. For example, Zhang et al. [27] studied matrix tablets loaded with theophylline based on blends of polyethylene oxide and Carbopol 907 at different pH values. The resulting drug release kinetics were found to be affected by the pH-dependent interactions between the two polymers. Also, Hamoudi-Ben Yelles et al. [28] added small amounts of hydrophilic polymers (Poloxamer 188 and polyethylene oxide 200 kDa) to poly(lactic-co-glycolic acid) (PLGA)-based implants to alter drug release and the importance of autocatalytic effects. Furthermore, polymer:polymer blends have been proposed as matrix formers in hot melt extrudates for controlled drug delivery. For instance, Verhoeven et al. [29] prepared mini-matrices by hot melt extrusion of ethylcellulose blended with polyethylene glycol/polyethylene oxide to provide a variety of metoprolol tartrate release kinetics.

The type of polymers used, the polymer blend ratio as well as the manufacturing conditions determine the resulting system properties and, thus, the control of drug release.

The basic principle is that the drug is “trapped” within the polymeric system and different types of mass transport phenomena can be involved in the control of drug release, such as water diffusion into the system, drug dissolution and diffusion, polymer swelling and dissolution, osmotic effects, polymer degradation and pore formation upon leaching of water-soluble compounds into the surrounding bulk fluid (to mention just a few). In the case of polymer blends, the properties of both compounds might be decisive, or one of them might dominate. For example, when blending a polymer that is permeable for many drugs with a polymer that is poorly permeable, broad spectra of drug release patterns might be obtained by simply varying the polymer:polymer blend ratio [30]. Also differences in drug solubility or drug loading might be compensated by adjusting the polymer:polymer blend ratio. For example, high loadings of a freely water-soluble drug in a matrix system generally lead to fast drug release. This might be compensated by increasing the portion of the poorly permeable polymer in the dosage form. Also, one polymer might assure the mechanical stability of the drug delivery system within the gastrointestinal tract, whereas the other polymer might trigger drug release in specific segments (e.g. small intestine or colon) [31,32,33,34,35,36]. Furthermore, the solubilities of the two polymers might be complementary: For example, ethylcellulose:guar gum blends have been proposed as film coating materials to provide controlled drug release that is not susceptible to the co-consumption of alcoholic beverages [37,38,39]. The basic idea is that ethylcellulose is not soluble in water, but in ethanol. *Vice-versa*, guar gum is soluble in water, but not in ethanol. Appropriate ethylcellulose:guar gum blends were shown to be able to release theophylline from coated pellets with release rates that were very similar in release media containing 0, 20 or 40 % ethanol.

The aim of this study was to explore the potential of blends of ethylcellulose with a second polysaccharide as matrix former in controlled release hot melt extrudates. Ethylcellulose was chosen to provide good mechanical stability of the systems. But it is known to be poorly permeable for many drugs [40]. Thus, it was combined with different

types and amounts of a more permeable second polysaccharide, namely hydroxypropyl methylcellulose (HPMC), pectin, maize starch, inulin, maltodextrin, guar gum, and chitosan. Optionally, different types and amounts of plasticizers (dibutyl sebacate, triethyl citrate and polyethylene glycol) were added. Theophylline was selected as model drug exhibiting slight water solubility, diprophylline as freely water-soluble model drug. The drug loading was varied from 10 to 60 %. The key manufacturing parameters (temperature and screw speed) as well as the polymer:polymer blend ratio were varied. Drug release was measured under conditions simulating the contents of the upper gastro intestinal tract (0.1 M HCl and phosphate buffer pH 6.8), as well as the colon (upon exposure to human fecal samples).

2. Materials and methods

2.1. Materials

Ethylcellulose (EC, Ethocel Standard 10 premium; Colorcon, Massy, France); hydroxypropyl methylcellulose (HPMC, Methocel E5 Premium LV; Colorcon, Kent, England); pectin and maltodextrin (UniPectin and C*Actistar 11700 Tapioca maltodextrin, Cargill, Krefeld, Germany); maize starch (C*PharmGel 03406; Cargill, Gent, Belgium); guar gum (viscosity of a 1 % solution in water at 25 °C: ~5000 cP; Cooper, Melun, France); inulin (Inulin HPX; Beneo, Oreye, Belgium); chitosan (Crab Shell chitosan, Mw = 800 kDa, degree of deacetylation = 80-90 %; Bio 21, Chonburi, Thailand); triethyl citrate (TEC; Alfa Aesar, Karlsruhe, Germany); polyethylene glycol (PEG 1500; Pluracare E 1500 Flasks; BASF, Ludwigshafen, Germany); dibutyl sebacate (DBS; Stearinerie Dubois, Boulogne-Billancourt, France); anhydrous theophylline and diprophylline (BASF, Ludwigshafen, Germany); 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); sodium acetate (Sodium acetate anhydrous, 99 %, ThermoFisher, Kandel, Germany)

2.2. Preparation of hot melt extrudates

Drug and polymer powders were blended for 10 min at 98 rpm in a Turbula T2A (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland), followed by manual mixing in a mortar with a plasticizer (TEC, DBS or PEG 1500). The compositions were varied as indicated. Polymer:polymer blend ratios are expressed in weight:weight, plasticizer percentages are referring to the mass of ethylcellulose (mass of ethylcellulose = 100 %), drug percentages refer to the total mass of the hot melt extrudates (mass of extrudate = 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 170 – 170 – 170 – 170 °C or 100 – 100 – 100 – 100 °C [zone 4 (die) – zone 3 – zone 2 – zone 1], as indicated. The feed rate was set at 3 mL/min. After cooling, the hot melt extrudates were manually cut into cylinders.

2.3. Optical microscopy

Macroscopic pictures of hot melt extrudates 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.

2.4. In-vitro drug release

Under conditions simulating the *upper* gastro intestinal tract: Hot melt extrudates 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, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically (UV-1800; Shimadzu, Kyoto, Japan) at λ = 275 nm (theophylline) or λ = 274 nm (diprophylline) for their drug content.

Under conditions simulating the *entire* gastro intestinal tract: Hot melt extrudates 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) 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, 2 mL samples were withdrawn, 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). In the case of theophylline, 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. In the case of diprophylline, the mobile phase consisted of 35 % acetonitrile and 65 % 0.01 M aqueous sodium acetate solution (v/v). Samples were injected into a Polar C18 column (Luna Omega 3 µm Polar C18 100 Å, 150 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 = 274 nm.

2.5. Differential scanning calorimetry (DSC)

DSC thermograms were recorded with a Q200 calorimeter (TA Instruments, Guyancourt, France). During all measurements the calorimeter head was flushed with highly pure nitrogen gas. Temperature and enthalpy readings were calibrated using pure indium at the same scan rates as used in the experiments. The samples were placed in hermetic high volume pans, resistant to pressure. Approximately 6 mg samples were heated from - 40 to 300 °C at 10 °C/min.

2.6. 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 into Lindemann glass capillaries (diameter = 0.7 mm) and installed on a rotating sample holder to avoid artifacts due to preferential orientations of crystallites. Heating experiments have been performed in situ, at 10 °C/min, using the furnace HTC 9634 from Huber (Rimsting, Germany).

2.7. Thermogravimetric analysis (TGA)

TGA experiments were conducted with a Q500 TGA from TA Instruments (Guyancourt, France). Samples were placed in open aluminum pans, and the furnace was flushed with highly pure nitrogen gas (50 mL/min). The temperature reading was calibrated using the Curie points of alumel and nickel, while the mass reading was calibrated using balance tare weights provided by TA Instruments. All scans were performed at 10 °C/min.

3. Results and discussion

3.1. Impact of the type of polymer blend and plasticizer addition

Figure 1 shows optical macroscopy pictures of hot melt extrudates based on different types of polymer:polymer blends: Ethylcellulose was blended with a selection of other polysaccharides, as indicated. The ethylcellulose:2nd polysaccharide blend ratio was 80:20 (weight:weight) in all cases. Thirty percent DBS (referring to ethylcellulose) was added as a plasticizer, the systems were loaded with 10 % theophylline, the extrusion temperature was 100 °C in all cases. Cross-sections of the hot melt extrudates (obtained by manual breaking) are shown at the top, pictures of surfaces right below. As it can be seen, the inner structure of all systems appeared to be rather homogeneous and the surface relatively smooth, except for ethylcellulose:chitosan blends, which lead to extrudates with a slightly rough surface and somehow “granular” inner structure.

Importantly, in all cases the torque measured during extrusion was similar (around 30 %), not causing any difficulty during processing (Figure 2a). The resulting drug release kinetics upon exposure to 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8 for 22 h are illustrated in Figure 2b. Clearly, the type of polymer blend had a pronounced effect on theophylline release. This can be attributed to the different chemical structures of the

polysaccharides and the resulting difference in permeability of the polymeric matrices for the drug. In many cases, the observed release rates were too low for oral administration (e.g. less than about 18 % after 24 h). For this reason, only the 3 most rapidly releasing polymer blends were selected for further studies: ethylcellulose:chitosan, ethylcellulose:guar gum and ethylcellulose:pectin.

In an attempt to simplify the formulation, the plasticizer DBS was omitted. Figure 3 shows macroscopic pictures of cross-sections and surfaces of hot melt extrudates based on ethylcellulose:pectin/guar gum/chitosan blends free of plasticizer. The blend ratio was varied as indicated, hot melt extrudates based “only” on ethylcellulose (loaded with 10 % theophylline) are shown for reasons of comparison. To allow for extrusion without a plasticizer, the processing temperature had to be increased, here to 170 °C. As it can be seen in the top row, this temperature degraded pectin under the given conditions. Also, in the case of hot melt extrudates loaded with high amounts of chitosan some color changes at the systems’ surface was observed (Figure 3, bottom row). Due to the important pectin degradation, these hot melt extrudates were not studied any further. The resulting theophylline release kinetics of systems based on different ethylcellulose:guar gum and ethylcellulose:chitosan blends are illustrated in Figure 4. The release medium was 0.1 M HCl for the first 2 h, followed by phosphate buffer pH 6.8 for the subsequent 6 h. The ethylcellulose:2nd polysaccharide blend ratio was varied as follows: 100:0, 90:10, 80:20, 70:30 and 60:40. As it can be seen, the resulting release rate was very low at all blend ratios in the case of ethylcellulose:chitosan (4 - 15 % after 8 h). Also in the case of ethylcellulose:guar gum blends, theophylline release from the plasticizer-free implants was relatively slow, much slower compared to the respective DBS-plasticized systems extruded at 100 °C: For example, after 8 h only 6 versus 15 % drug was released in the case of ethylcellulose:guar gum 80:20 blends (see also Figure 4b versus Figure 2b). This reduced drug release rate in plasticizer-free systems can at least partially be attributed to the fact that

the presence of the plasticizer increases the mobility of the polymer chains and, thus, also of the drug molecules. For example, Figure S2 shows the DSC thermogram of ethylcellulose plasticized with 30 % DBS. The glass transition temperature decreased from about 130 to 53 °C in the dry state compared to pure ethylcellulose (Figure 5 vs. Figure S2). In addition to DBS, water can also be expected to be acting as a plasticizer for this polymer during drug release. Since the observed release rates were too low in plasticizer-free hot melt extrudates, these systems were not studied any further.

Instead, the suitability of ethylcellulose:guar gum, ethylcellulose:chitosan and ethylcellulose:HPMC E5 blends, plasticized with 30 % DBS was studied in more detail (note that "pectin was replaced by HPMC E5", since it showed important thermal degradation at 170 °C, and similar drug release rates: Figure 3 and Figure 2b). In the presence of the plasticizer, the extrusion temperature was again reduced to 100 °C. Figure 6 shows the resulting theophylline release kinetics from hot melt extrudates based on these polymer:polymer blends, varying the blend ratio from 100:0 to 20:80, in 10 % increments. The release medium was 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8 for 22 h. Clearly, in all cases a broad spectrum of drug release patterns could be obtained, by simply varying the polymer:polymer blend ratio. In the investigated cases, ethylcellulose was less permeable for theophylline than the other polymers. This is why in all cases, the release rate increased with decreasing ethylcellulose content. Since ethylcellulose:guar gum blends showed the largest spectrum of possible drug release patterns (e.g., the highest theophylline release rate at the 20:80 ethylcellulose:2nd polysaccharide blend ratio), this blend was selected for further studies.

3.2. Ethylcellulose:guar gum blends

Figure 7 shows macroscopic pictures of cross-sections and surfaces of different types of ethylcellulose:guar gum based hot melt extrudates: The following parameters were varied:

(i) the type of plasticizer (DBS, TEC and PEG), (ii) the percentage of plasticizer (15, 20 and 30 %), (iii) the extrusion temperature (100 and 170 °C), (iv) the screw speed (30, 60 and 90 rpm), (v) the type of drug (theophylline and diprophylline, being slightly and freely water-soluble), and (vi) the drug loading (10, 30 and 60 %, referring to the total extrudate mass). In all cases, the ethylcellulose:guar gum blend ratio was kept constant: 80:20 (weight:weight). As it can be seen, in all cases rather homogeneous inner system structures and relatively smooth surfaces were obtained. In no case, any visible sign of polymer degradation was observed. Extrudates containing 0, 15 or 20 % plasticizer as well as extrudates loaded with 60 % drug were hard and brittle. All other systems were flexible.

Figure 8a shows the torque values measured during the extrusion of ethylcellulose:guar gum 80:20 blends plasticized with 15 % PEG (PEG 1500), DBS or TEC. The systems were loaded with 10 % theophylline. For reasons of comparison, also the torque values observed with “pure” ethylcellulose hot melt extrudates (loaded with 10 % theophylline) are shown. Please note that it was not possible to extrude plasticizer-free and 15 % PEG containing formulations at 100 °C (the torque values were too high). This is why these extrudates were obtained at 170 °C processing temperature. In contrast, blends plasticized with 15 % DBS or TEC could be obtained at 100 °C processing temperature, although the corresponding torque values were high (Figure 8a). The respective theophylline release kinetics from these hot melt extrudates are illustrated in Figure 8b. As it can be seen, the following rank order with respect to the resulting drug release rate was observed: 15 % PEG > 15 % DBS > 15 % TEC > no plasticizer. Thus, the plasticizer facilitates drug release, probably due to increased polymer chain mobility and/or plasticizer leaching into the surrounding bulk fluid. Please note that a direct comparison of PEG with DBS & TEC should be viewed with caution, since the extrusion temperature was different. In all cases, the resulting drug release rates were rather low (e.g., less than 36 % after 6 h).

Figure 9a shows the impact of varying the plasticizer content (here DBS and TEC) on the torque measured during extrusion of ethylcellulose:guar gum 80:20 blends, loaded with 10 % theophylline. The extrusion temperature was 100 °C. Clearly, the torque values substantially decreased with increasing plasticizer level, irrespective of the type of plasticizer. The theophylline release kinetics from the obtained hot melt extrudates are shown in Figure 9b. Interestingly, the freely water-soluble plasticizer TEC lead to slower drug release rates than the lipophilic plasticizer DBS. Thus, in these cases, the increase in polymer chain mobility seems to play a more important role than potential plasticizer leaching into the surrounding bulk fluid (eventually creating water-filled pores). TEC seems to be a more efficient plasticizer for the polymeric matrix than DBS, resulting in a denser (and less permeable) system (overcompensating potential increased drug mobility effects). But again, in all cases the resulting theophylline release rates were rather low (e.g., less than 27 % drug was released after 6 h).

The effects of varying the screw speed when manufacturing ethylcellulose:guar gum 80:20 based hot melt extrudates loaded with 10 % theophylline at 100 °C (plasticized with 30 % DBS) on: a) the torque measured during extrusion, and b) drug release in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8 for subsequent 6 h, are illustrated in Figure 10. Clearly, the variation of the screw speed in the investigated range (30 – 60 – 90 rpm) did neither substantially impact the torque, nor theophylline release.

Furthermore, the impact of the type of drug and drug loading was studied (Figure 11): The percentages of slightly water-soluble theophylline and freely water-soluble diprophylline were varied from 10 to 60 %. Figure 11a shows the respective torque values observed during extrusion (at 100 °C, with 30 % DBS). Figure 11b shows the resulting drug release kinetics in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8 for 22 h. As it can be seen, the torque values increased with increasing drug loading (especially in the case of theophylline). This can probably be attributed to the fact that both drugs do not melt at 100 °C (Figure 5) and that

the relative amounts of more easily extrudable, plasticized polymer blends in the formulations decrease. Figure 11b shows that also the resulting drug release rates clearly increased with increasing drug loading. This can at least partially be explained by the fact that less drug release retarding polymer is present in the systems. Or, in other words: Upon drug release, the systems become more and more porous and remaining drug can more easily diffuse out. This is very important from a practical point of view: Most of the drug is released after 24 h at an initial drug loading of 60 %. Also, as it can be seen, about zero order release kinetics can be provided during major parts of the release periods: Theophylline and diprophylline were released at a rate of approximately 3 %/h during 24 h. Please note that perfect sink conditions were provided throughout the experiments. Thus, the observed relatively *constant* drug release rates can probably be attributed to drug saturation effects *within* the hot melt extrudates: The amounts of water penetrating into the systems are limited and most likely not sufficient to dissolve the entire drug loadings. Thus, *non-dissolved* and *dissolved* drug co-exist within the systems. Importantly, only dissolved drug is available for diffusion. This results in about constant drug concentration differences: saturated solutions *inside* the hot melt extrudates and perfect sink conditions in the surrounding bulk fluids.

Figure 5 shows DSC thermograms of hot melt extrudates loaded with 10 to 60 % diprophylline or theophylline, based on ethylcellulose:guar gum 80:20 blends plasticized with 30 % DBS prepared at 100 °C. For reasons of comparison, also the DSC thermograms of the following raw materials (as received) are illustrated: ethylcellulose, guar gum, DBS, diprophylline and theophylline. Pure ethylcellulose showed 2 thermal events: (i) a glass transition (Tg) at about 130 °C, which is in good agreement with data reported in the literature [e.g., 41], and (ii) an exothermic event at approximately 185 °C. Lai et al. [42] have shown that for “Ethocel Standard 100 Premium” (an ethylcellulose with a higher molecular weight than the investigated polymer) (Dow, Midland, MI, USA) a similar exotherm corresponded to an oxidative degradation (the pans were hermetically closed, the nitrogen flushing was

outside the pans), which masks the melting of a small crystalline fraction. The presence of a small crystalline fraction in the ethylcellulose raw material was further confirmed by X-ray powder diffraction measurements (Figure S3). A Bragg peak was visible at about 2 Θ = 12 °. Also, Huang et al. [43] reported a Bragg peak for another ethylcellulose ("N7 viscosity grade", 48.0 – 49.5 w/w ethoxyl groups) (Hercules, Wilmington, DE, USA) in this range. Furthermore, TGA revealed thermal degradation of ethylcellulose above 200 ° (Figure S4).

The guar gum raw material was X-ray amorphous (Figure S3). The DSC thermogram showed a glass transition at about 60 °C and an exothermic event between 250 and 300 °C, corresponding to thermal degradation, as confirmed by TGA (Figure S4). This is also consistent with data reported in the literature [e.g., 44]. The TGA curve also indicates a mass loss of about 10 % between 20 °C and approximately 125 °C, likely corresponding to water loss. DBS is a liquid at room temperature, melting at approximately -10 °C. Diprophylline and theophylline showed sharp melting endotherms at about 162 and 275 °C, respectively, indicating their crystalline nature. In the different types of hot melt extrudates (except for hot melt extrudates loaded with 10 % theophylline) such endotherms could also be observed, but shifted toward lower temperatures (probably corresponding more to the dissolution of drug crystallites into their amorphous environment, rather than to melting). So, the diprophylline is at least partially distributed in the form of small crystals throughout the hot melt extrudates at all the investigated drug loadings. In contrast, theophylline is likely completely dissolved and/or amorphous at 10 % drug loading, and at least partially dispersed in the form of small crystals at 30 and 60 % drug loading.

Since guar gum has been reported to be preferentially degraded by enzymes secreted by bacteria present in the colon [e.g., 45,46,47] and since the provided drug release periods were rather long, it was important to evaluate whether or not the exposure to fecal samples potentially altered the resulting drug release kinetics from the investigated hot melt extrudates. Due to the intimate mixture of guar gum with ethylcellulose, it might be that the

latter effectively protects the guar gum against enzymatic degradation. For this reason, hot melt extrudates loaded with 60 % theophylline or 60 % diprophylline, based on ethylcellulose:guar gum 80:20 blends (plasticized with 30 % DBS) were prepared at 100 °C and exposed to 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8 for 6 h, and fecal samples for 10 h (the latter under anaerobic conditions). For reasons of comparison, the extrudates were also exposed to 0.1 M HCl and phosphate buffer pH 6.8, followed by culture medium free of fecal bacteria. The 0.1 M HCl was intended to simulate the conditions in the stomach, the phosphate buffer pH 6.8 in the small intestine, and the fecal samples the conditions in the colon. The solid curves in Figure 12 show the experimentally measured drug release rates with this set up using fecal samples, whereas the dashed curves show the respective release rates observed with culture medium free of feces. As it can be seen, the presence of fecal bacteria did not have a noteworthy impact on drug release, irrespective of the type of drug.

Furthermore, the long term stability of the investigated hot melt extrudates was studied. Figure S5 shows the release rates of diprophylline and theophylline from ethylcellulose:guar gum 80:20-based systems in 0.1 M HCl for 2 h, followed by 22 h in phosphate buffer pH 6.8. The drug loading were varied from 10 to 60 %, the extrudates were prepared at 100 °C and contained 30 % DBS. The solid curves illustrate drug release prior to storage, the dashed curves drug release after 1 year storage at ambient conditions. In all cases, drug release did not change to a noteworthy extent.

4. Conclusion

Hot melt extrudates based on ethylcellulose:guar gum blends offer an interesting potential as controlled drug delivery systems: They can be prepared at temperatures of about 100 °C, provide broad spectra of drug release patterns (in particular about constant drug release rates) and are long term stable. The ethylcellulose can effectively protect the guar gum against potential enzymatic degradation in the colon.

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Conflicts of interest

One of the authors is the Editor-in-Chief of this journal. The manuscript has been subject to all of the journal's usual procedures, including peer review, which has been handled independently of the Editor-in-Chief.

Figure captions

Fig. 1: Macroscopic pictures of hot melt extrudates (cross-sections and surfaces) based on ethylcellulose and different types of a 2nd polymer (indicated in the figure). The polymer:polymer blend ratio was 80:20, the extrudates were extruded at 100 °C, loaded with 10 % theophylline and plasticized with 30 % DBS. For reasons of comparison, also hot melt extrudates based "only" on ethylcellulose (loaded with 10 % theophylline, and plasticized with 30 % DBS) are illustrated.

Fig. 2: Impact of the type of polymer blend (indicated in the diagrams) used as matrix former on: a) the torque generated during hot melt extrusion, and b) theophylline release from the extrudates in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The extrudates were extruded at 100 °C, loaded with 10 % drug and plasticized with 30 % DBS.

Fig. 3: Macroscopic pictures of hot melt extrudates (cross-sections and surfaces) based on ethylcellulose and different types of a 2nd polymer (indicated in the figure). The polymer:polymer blend ratio is indicated in the figure, the extrudates were extruded at 170 °C, loaded with 10 % theophylline and free of plasticizer.

Fig. 4: Impact of the polymer:polymer blend ratio (indicated in the diagrams) on theophylline release from hot melt extrudates based on ethylcellulose:guar gum or ethylcellulose:chitosan blends (as indicated) in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The extrudates were extruded at 170 °C, loaded with 10 % drug and free of plasticizer.

Fig. 5: DSC thermograms of hot melt extrudates based on 80:20 ethylcellulose:guar gum blends. The type and amount of drug were varied as indicated. The extrusion temperature was 100 °C, the extrudates were plasticized with 30 % DBS. For reasons of comparison, also the DSC thermograms of the pure drugs, polymer powders and DBS (all as received) are illustrated.

Fig. 6: Impact of the polymer:polymer blend ratio (indicated in the figure) on theophylline release from hot melt extrudates based on ethylcellulose and different types of a 2nd polysaccharide in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The extrudates were extruded at 100 °C, loaded with 10 % drug and plasticized with 30 % DBS.

Fig. 7: Macroscopic pictures of hot melt extrudates (cross-sections and surfaces) based on 80:20 ethylcellulose:guar gum blends. The types and amounts of drug and plasticizer, extrusion temperature and screw speed were varied as indicated.

Fig. 8: Impact of the type of plasticizer and extrusion temperature on: a) the generated torque, and b) theophylline release from extrudates in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The systems were based on 80:20 ethylcellulose:guar gum blends, the drug loading was 10 %.

Fig. 9: Impact of the type and amount of plasticizer on: a) the generated torque, and b) theophylline release from extrudates in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The systems were based on 80:20 ethylcellulose:guar gum blends, the extrusion temperature was 100 °C and the drug loading 10 %.

Fig. 10: Impact of the screw speed during extrusion of 80:20 ethylcellulose:guar gum blends on: a) the generated torque, and b) theophylline release from extrudates in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The extrusion temperature was 100 °C, the extrudates were plasticized with 30 % DBS, and the drug loading was 10 %.

Fig. 11: Impact of the theophylline or diprophylline loading on: a) the generated torque, and b) drug release from extrudates in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The systems were based on 80:20 ethylcellulose:guar gum blends, the extrusion temperature was 100 °C, the extrudates were plasticized with 30 % DBS.

Fig. 12: Drug release from hot melt extrudates based on 80:20 ethylcellulose:guar gum 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 human fecal samples (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). The drug loading was 60 %, the extrusion temperature 100 °C. The extrudates were plasticized with 30 % DBS.

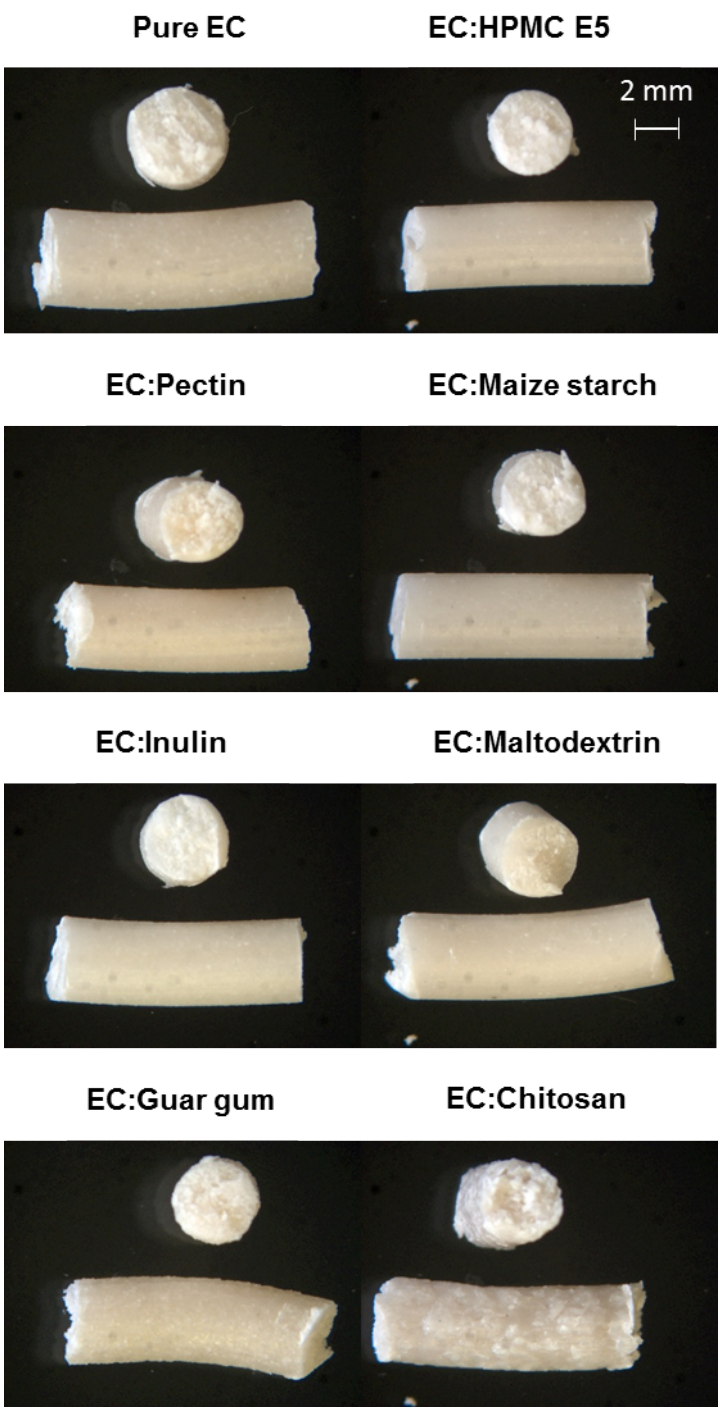

Pure EC
EC:HPMC E5
2 mm
EC:Pectin
EC:Maize starch
EC:Inulin
EC:Maltodextrin
EC:Guar gum
EC:Chitosan

Figure 1

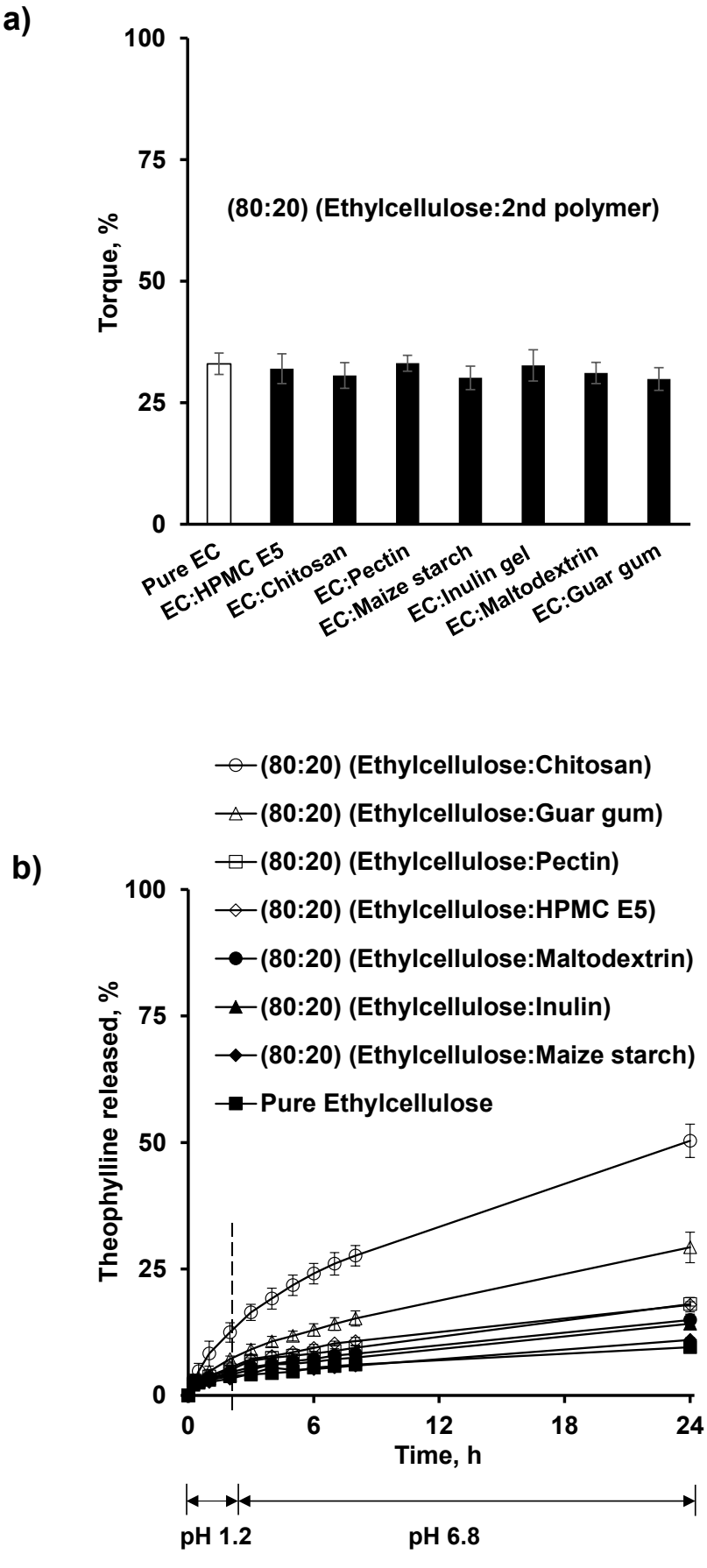

a)
100
75
50
25
0
Torque, %
(80:20) (Ethylcellulose:2nd polymer)
Pure EC
EC:HPMC E5
EC:Chitosan
EC:Pectin
EC:Maize starch
EC:Inulin gel
EC:Maltodextrin
EC:Guar gum
b)
(80:20) (Ethylcellulose:Chitosan)
(80:20) (Ethylcellulose:Guar gum)
(80:20) (Ethylcellulose:Pectin)
(80:20) (Ethylcellulose:HPMC E5)
(80:20) (Ethylcellulose:Maltodextrin)
(80:20) (Ethylcellulose:Inulin)
(80:20) (Ethylcellulose:Maize starch)
Pure Ethylcellulose
Theophylline released, %
100
75
50
25
0
0
6
12
18
24
Time, h
pH 1.2
pH 6.8

Figure 2

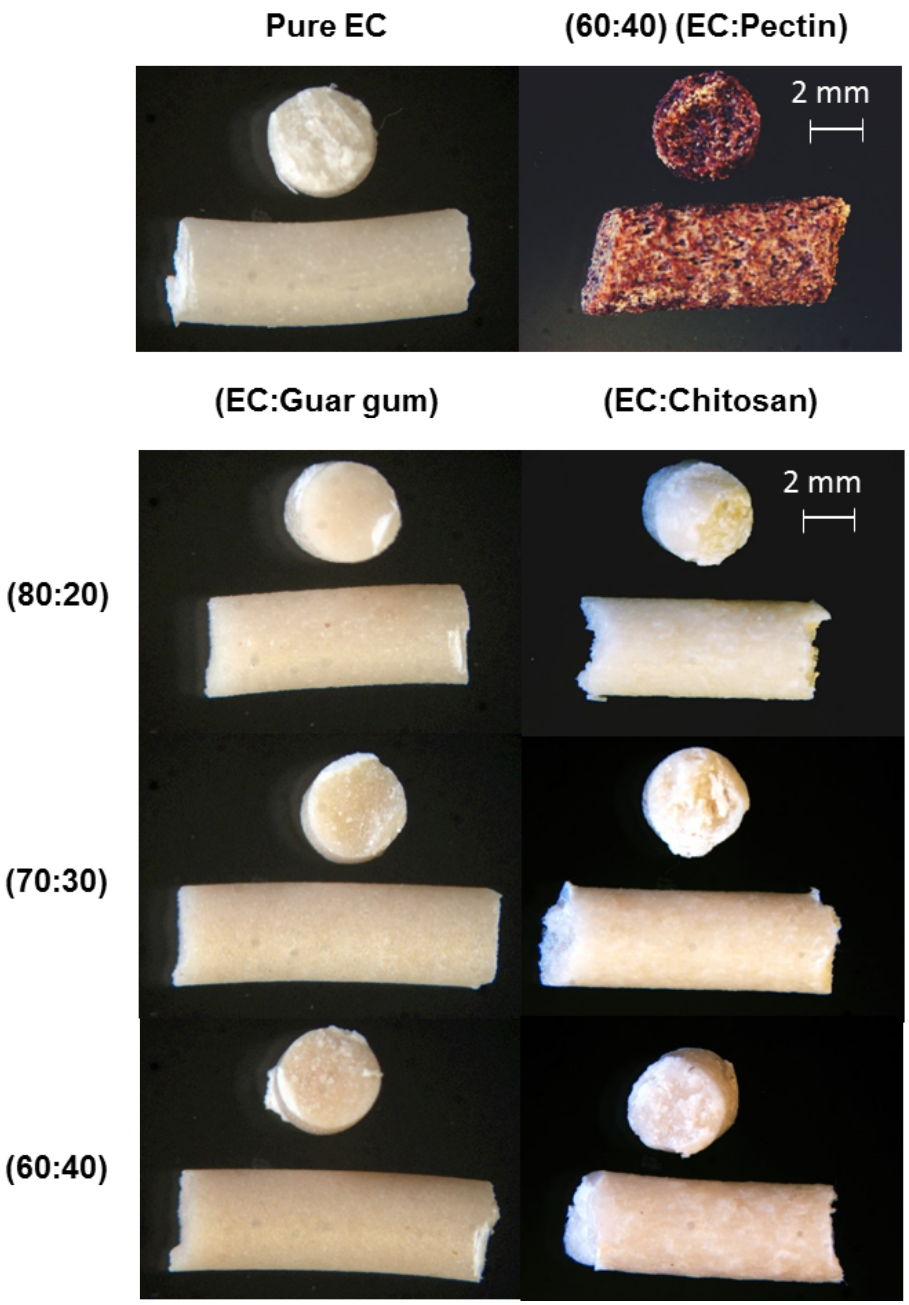

Pure EC
(60:40) (EC:Pectin)
2 mm
(EC:Guar gum)
(EC:Chitosan)
2 mm
(80:20)
(70:30)
(60:40)

Figure 3

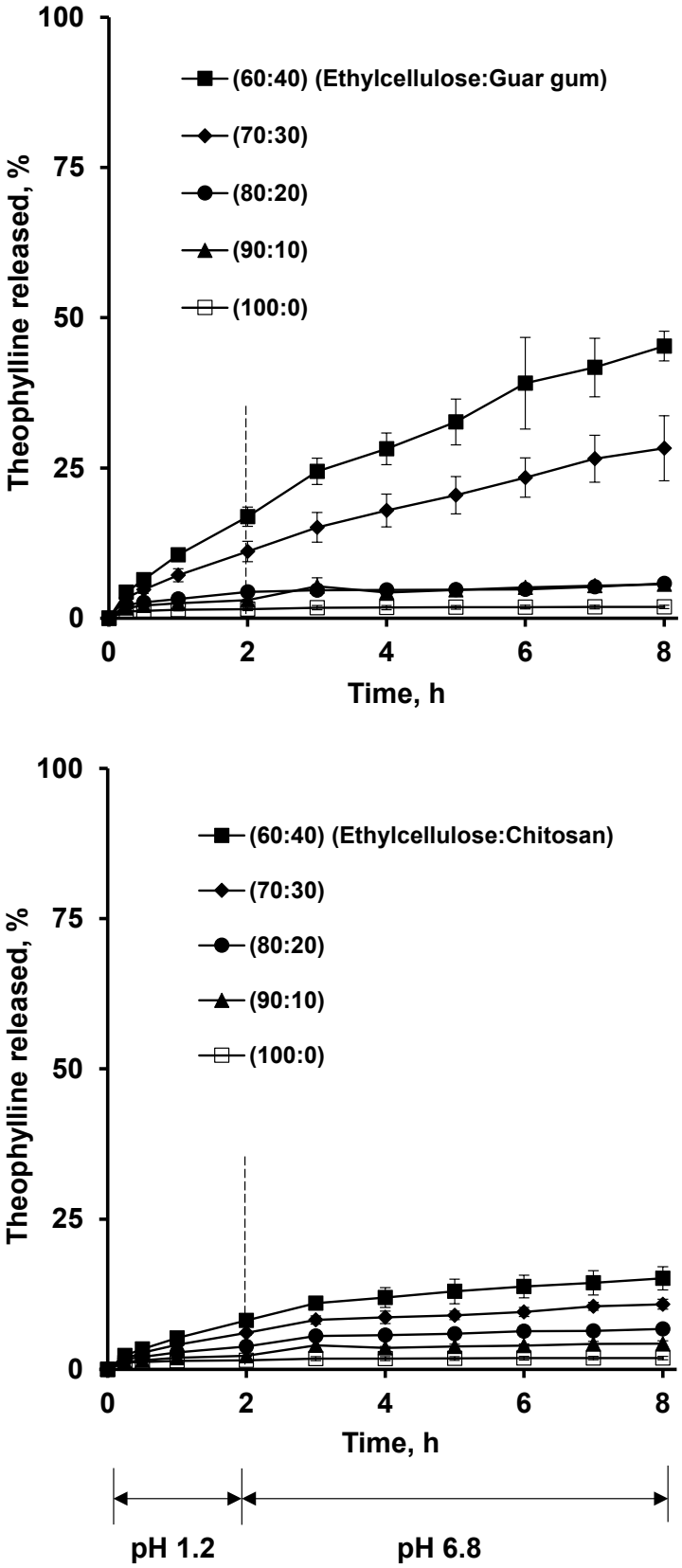

100
75
50
25
0
Theophylline released, %
(60:40) (Ethylcellulose:Guar gum)
(70:30)
(80:20)
(90:10)
(100:0)
0
2
4
6
8
Time, h
100
75
50
25
0
Theophylline released, %
(60:40) (Ethylcellulose:Chitosan)
(70:30)
(80:20)
(90:10)
(100:0)
0
2
4
6
8
Time, h
pH 1.2
pH 6.8

Figure 4

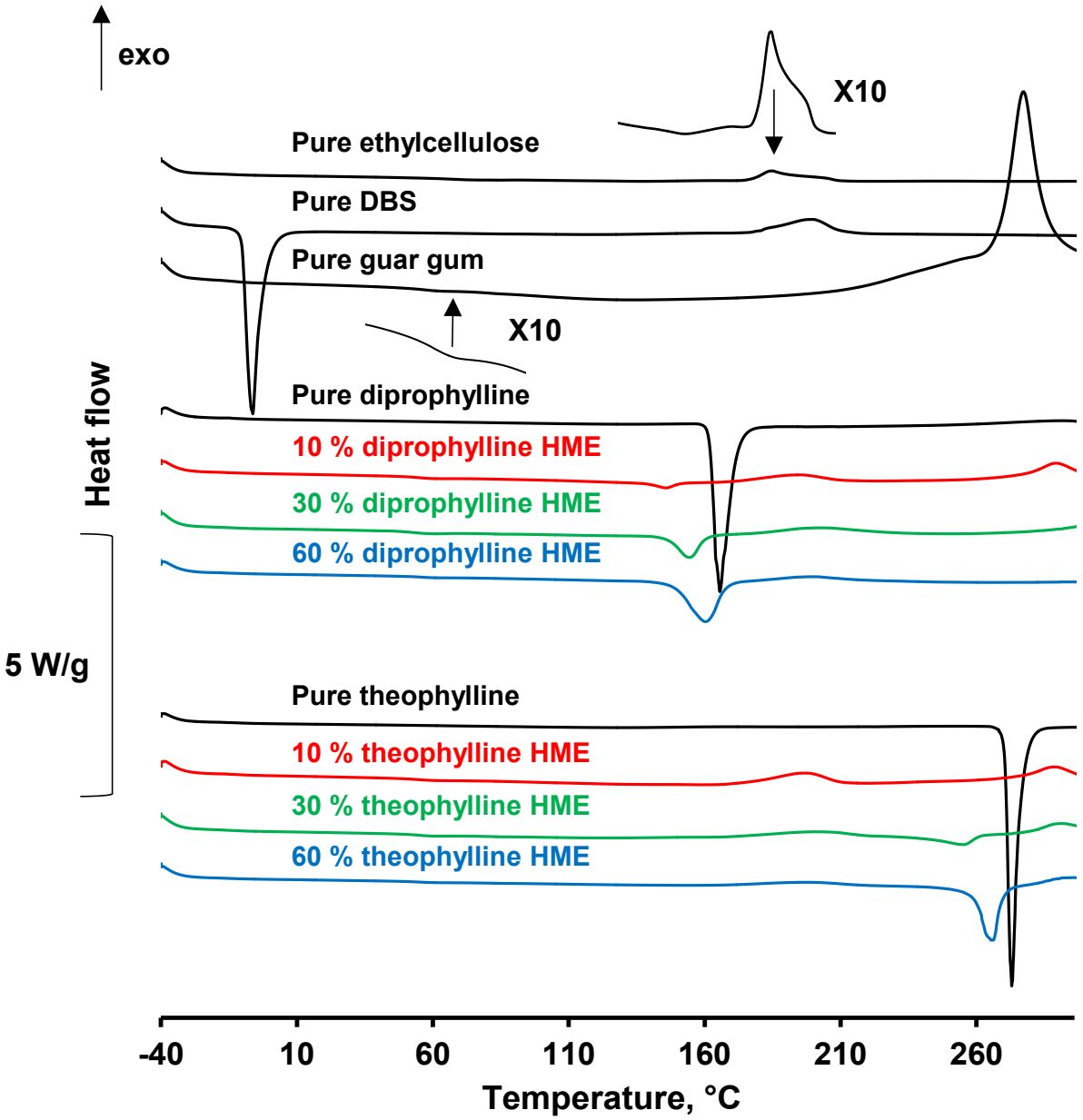

exo
X10
Pure ethylcellulose
Pure DBS
Pure guar gum
X10
Heat flow
Pure diprophylline
10 % diprophylline HME
30 % diprophylline HME
60 % diprophylline HME
5 W/g
Pure theophylline
10 % theophylline HME
30 % theophylline HME
60 % theophylline HME
-40
10
60
110
160
210
260
Temperature, °C

Figure 5

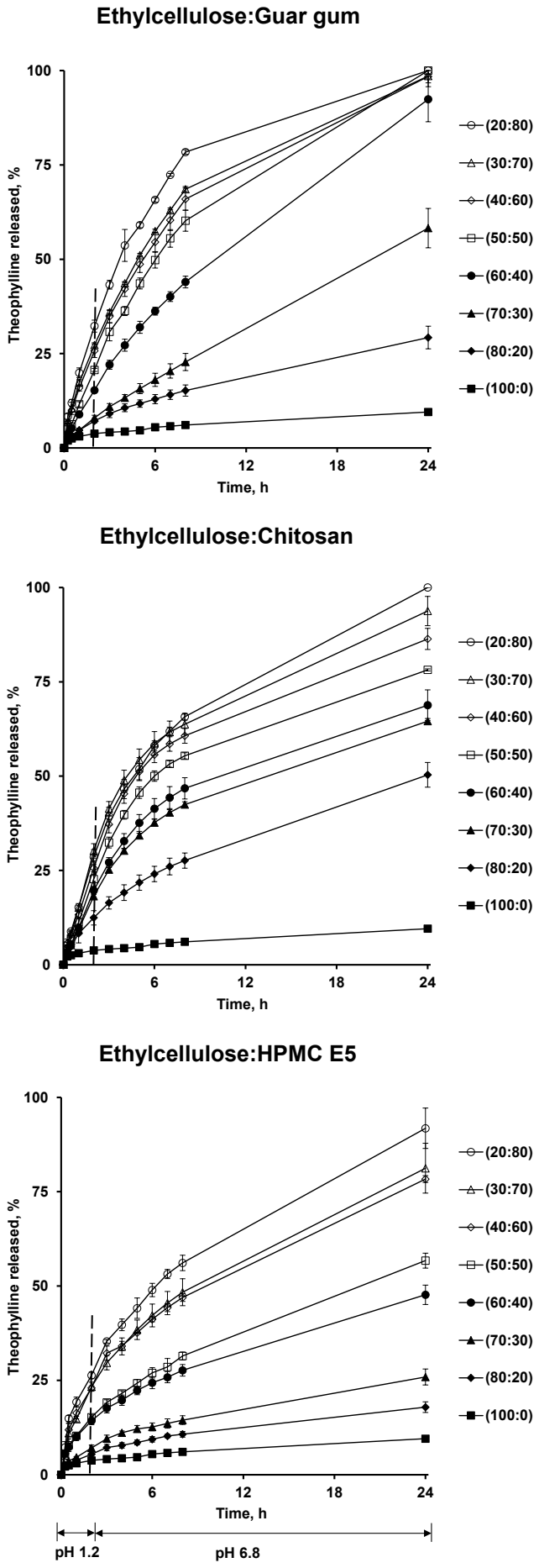

Ethylcellulose:Guar gum
Theophylline released, %
Time, h
(20:80)
(30:70)
(40:60)
(50:50)
(60:40)
(70:30)
(80:20)
(100:0)
Ethylcellulose:Chitosan
Theophylline released, %
Time, h
(20:80)
(30:70)
(40:60)
(50:50)
(60:40)
(70:30)
(80:20)
(100:0)
Ethylcellulose:HPMC E5
Theophylline released, %
Time, h
pH 1.2
pH 6.8
(20:80)
(30:70)
(40:60)
(50:50)
(60:40)
(70:30)
(80:20)
(100:0)

Figure 6

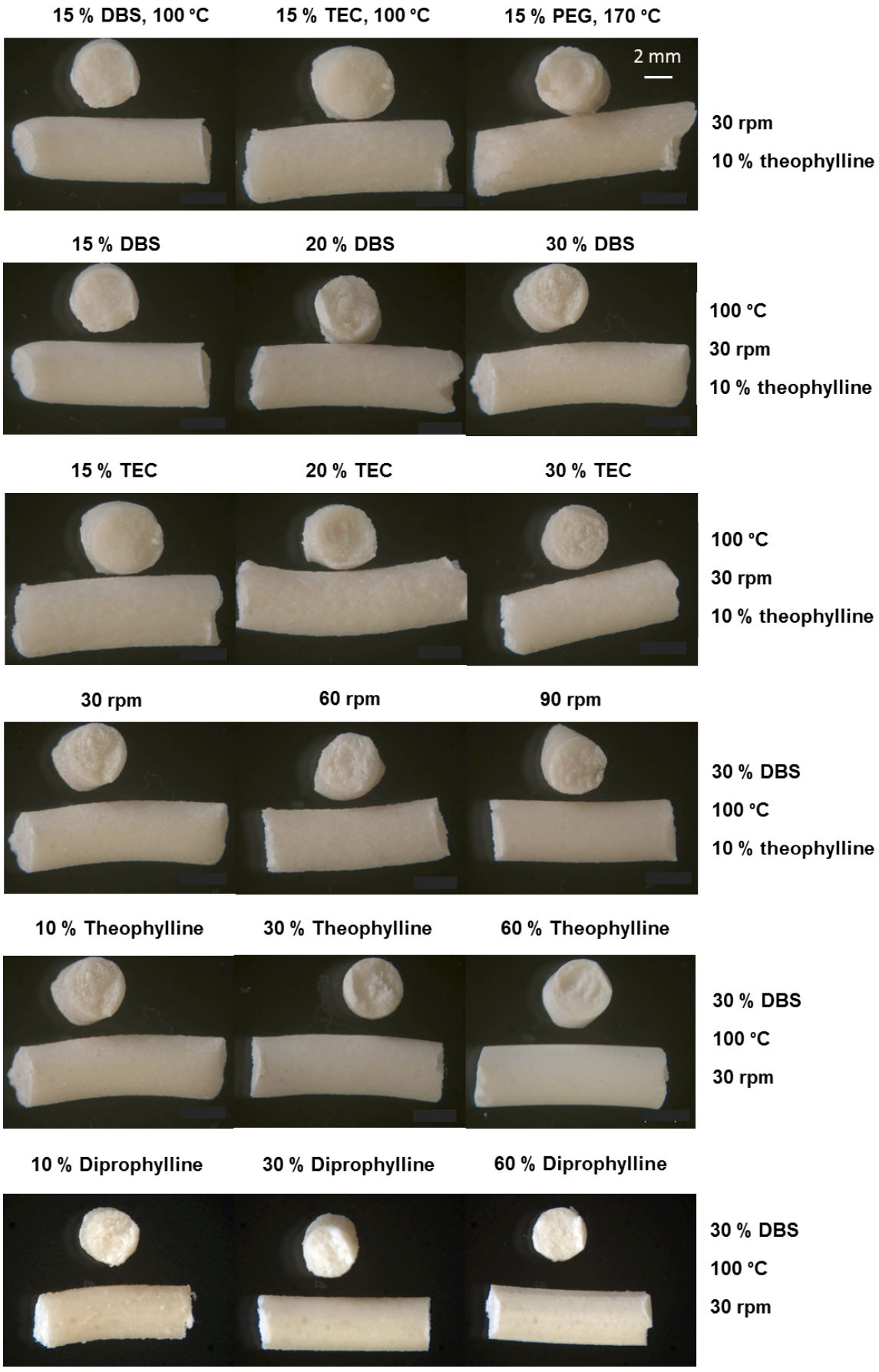

15 % DBS, 100 °C
15 % TEC, 100 °C
15 % PEG, 170 °C
2 mm
30 rpm
10 % theophylline
15 % DBS
20 % DBS
30 % DBS
100 °C
30 rpm
10 % theophylline
15 % TEC
20 % TEC
30 % TEC
100 °C
30 rpm
10 % theophylline
30 rpm
60 rpm
90 rpm
30 % DBS
100 °C
10 % theophylline
10 % Theophylline
30 % Theophylline
60 % Theophylline
30 % DBS
100 °C
30 rpm
10 % Diprophylline
30 % Diprophylline
60 % Diprophylline
30 % DBS
100 °C
30 rpm

Figure 7

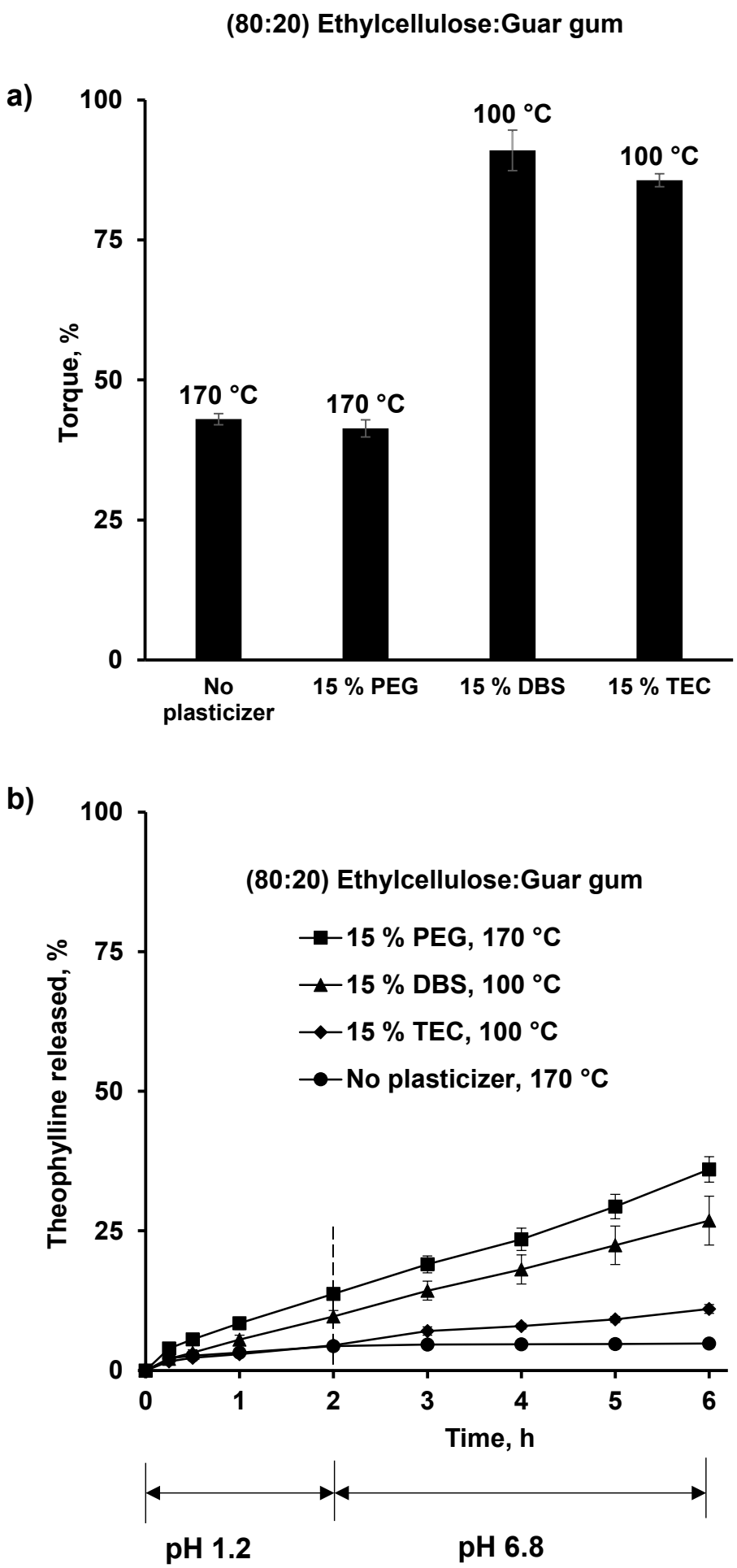

(80:20) Ethylcellulose:Guar gum
a)
100
75
50
25
0
Torque, %
170 °C
170 °C
100 °C
100 °C
No plasticizer
15 % PEG
15 % DBS
15 % TEC
b)
(80:20) Ethylcellulose:Guar gum
15 % PEG, 170 °C
15 % DBS, 100 °C
15 % TEC, 100 °C
No plasticizer, 170 °C
Theophylline released, %
0
1
2
3
4
5
6
Time, h
pH 1.2
pH 6.8

Figure 8

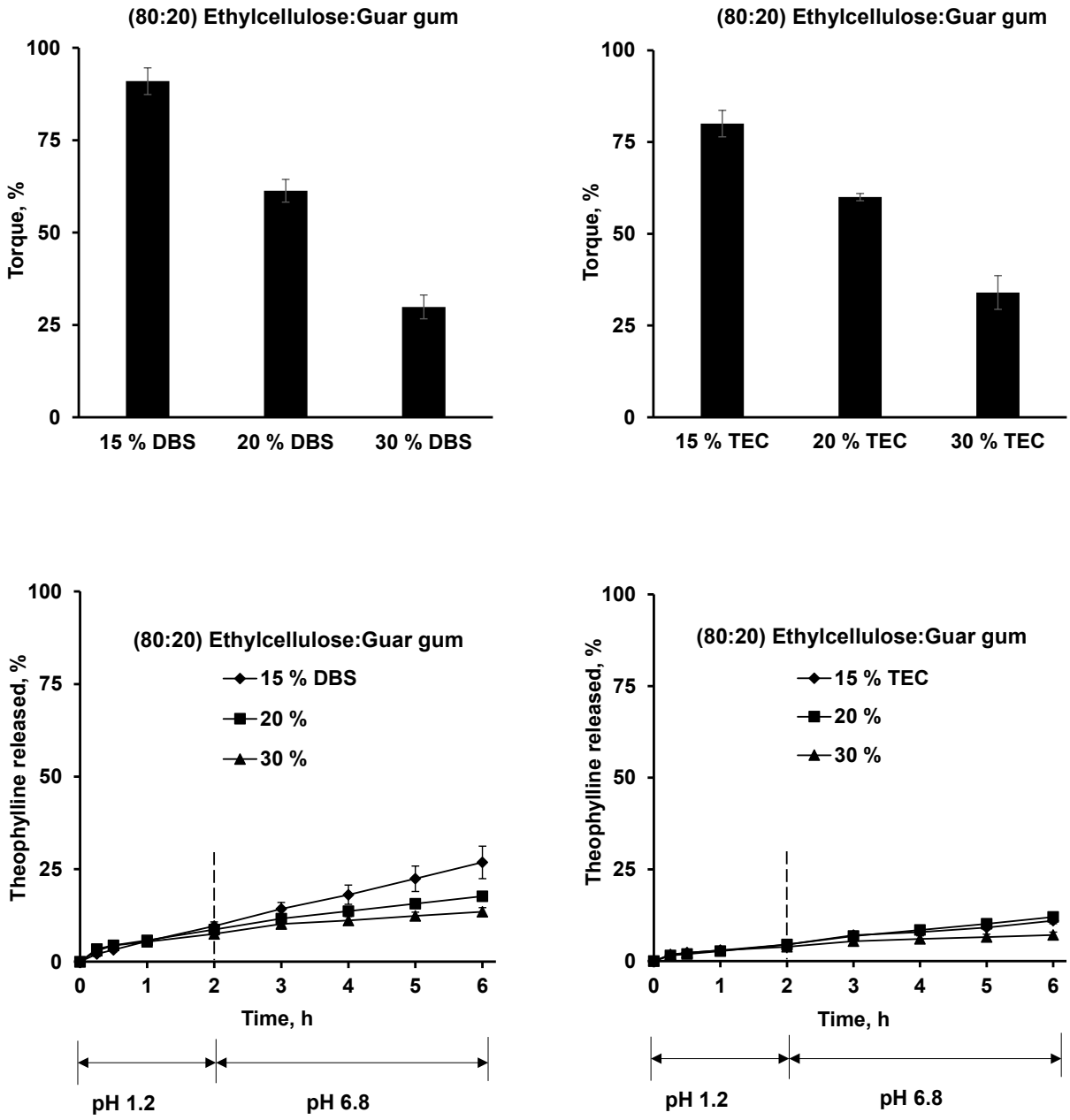
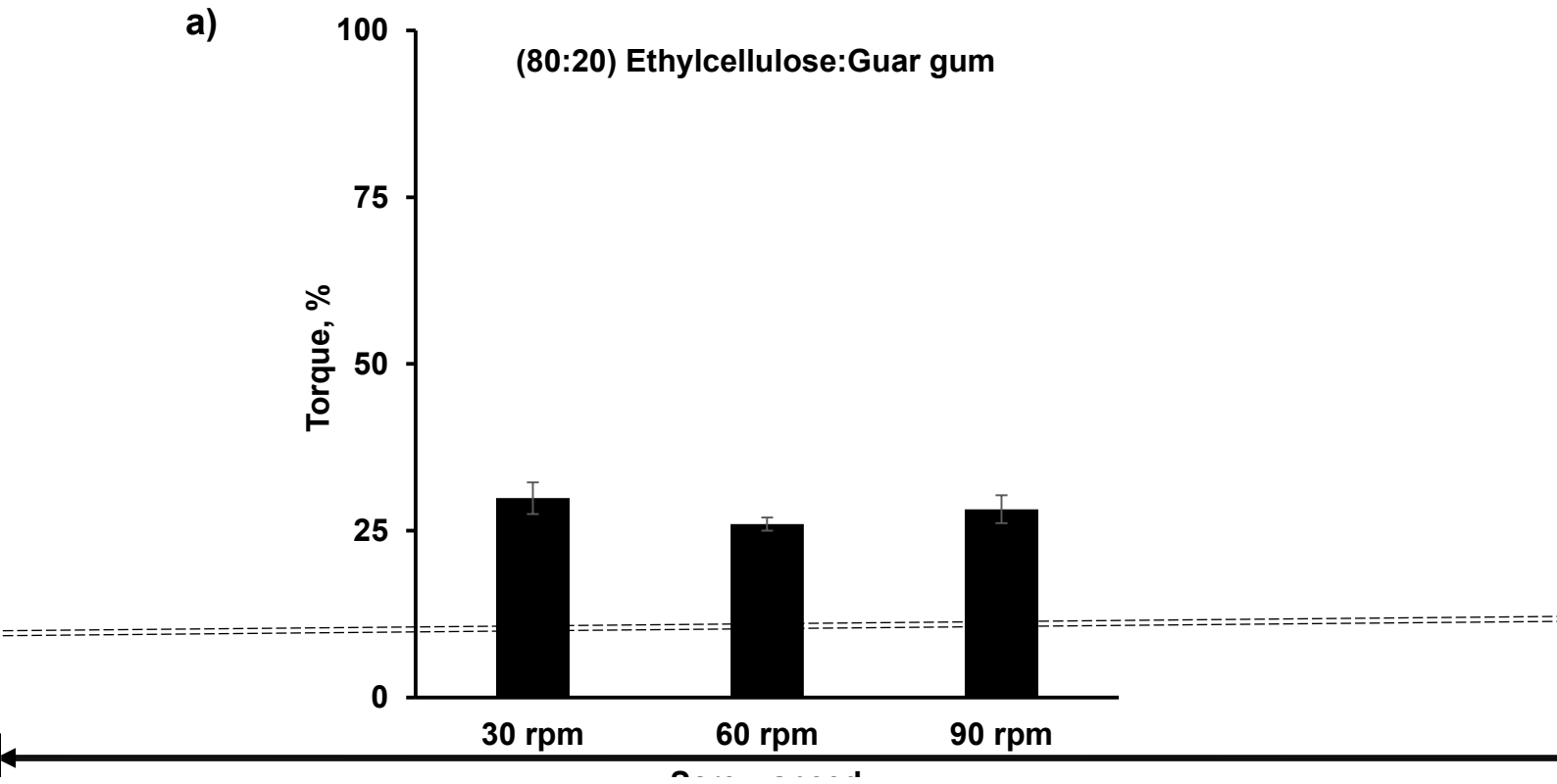

(80:20) Ethylcellulose:Guar gum
Torque, %
100
75
50
25
0
15 % DBS
20 % DBS
30 % DBS
(80:20) Ethylcellulose:Guar gum
Torque, %
100
75
50
25
0
15 % TEC
20 % TEC
30 % TEC
(80:20) Ethylcellulose:Guar gum
Theophylline released, %
15 % DBS
20 %
30 %
0
25
50
75
100
0
1
2
3
4
5
6
Time, h
pH 1.2
pH 6.8
(80:20) Ethylcellulose:Guar gum
Theophylline released, %
15 % TEC
20 %
30 %
0
25
50
75
100
0
1
2
3
4
5
6
Time, h
pH 1.2
pH 6.8

Figure 9


a)
(80:20) Ethylcellulose:Guar gum
Torque, %
100
75
50
25
0
30 rpm
60 rpm
90 rpm

P

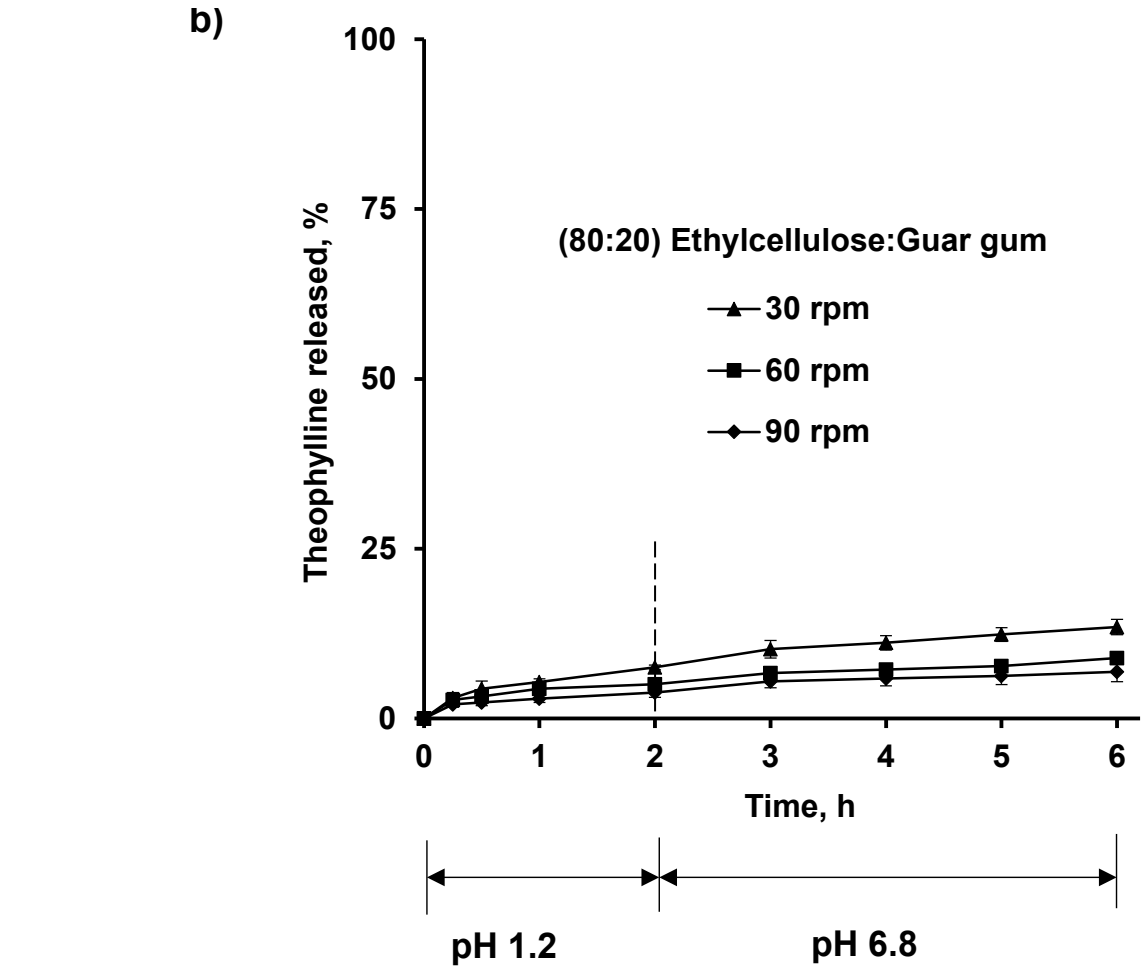

b)
(80:20) Ethylcellulose:Guar gum
Theophylline released, %
30 rpm
60 rpm
90 rpm
100
75
50
25
0
0
1
2
3
4
5
6
Time, h
pH 1.2
pH 6.8

Figure 10

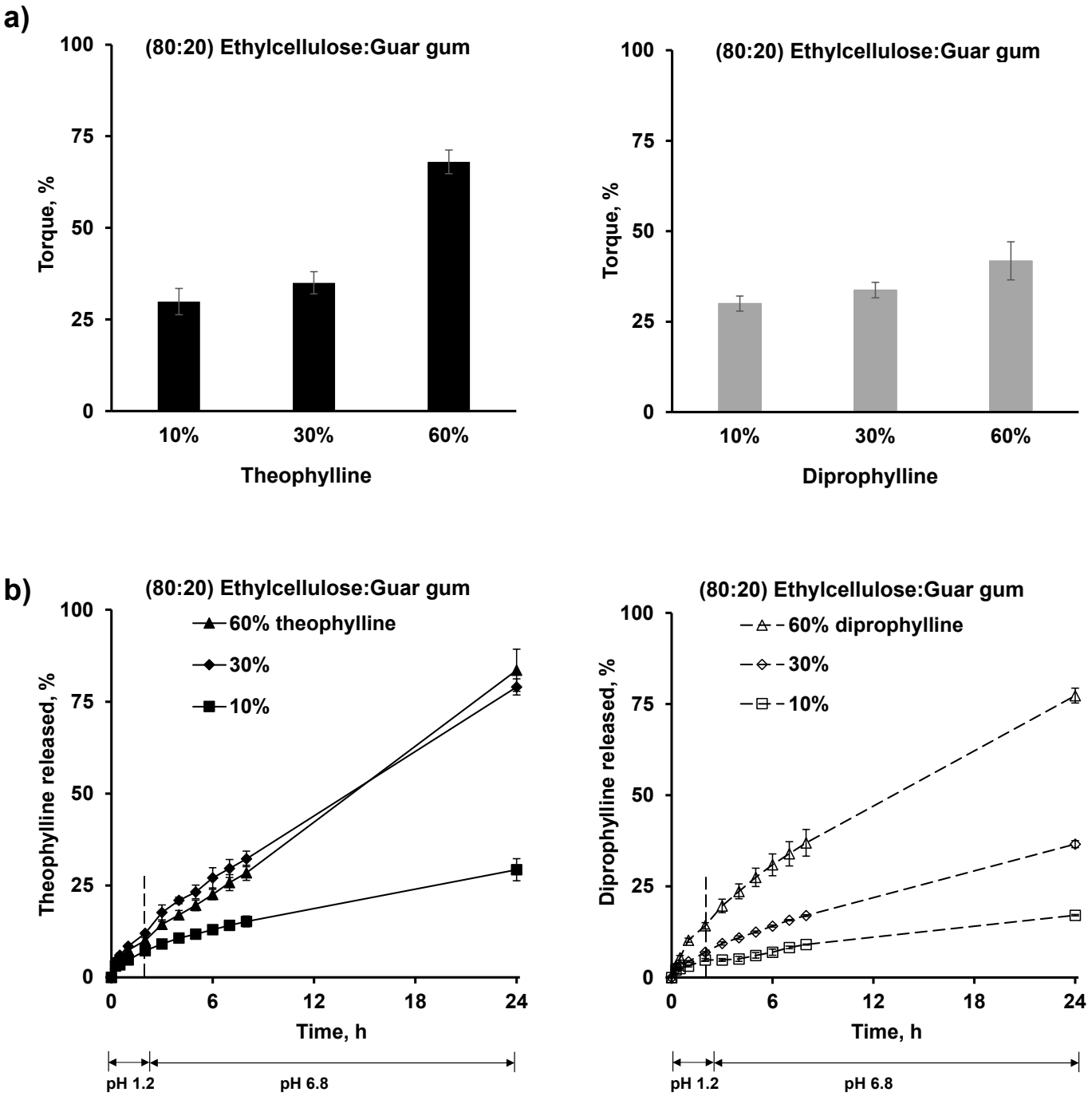

a)
(80:20) Ethylcellulose:Guar gum
Torque, %
100
75
50
25
0
10%
30%
60%
Theophylline
(80:20) Ethylcellulose:Guar gum
Torque, %
100
75
50
25
0
10%
30%
60%
Diprophylline
b)
(80:20) Ethylcellulose:Guar gum
60% theophylline
30%
10%
Theophylline released, %
100
75
50
25
0
0
6
12
18
24
Time, h
pH 1.2
pH 6.8
(80:20) Ethylcellulose:Guar gum
60% diprophylline
30%
10%
Diprophylline released, %
100
75
50
25
0
0
6
12
18
24
Time, h
pH 1.2
pH 6.8

Figure 11

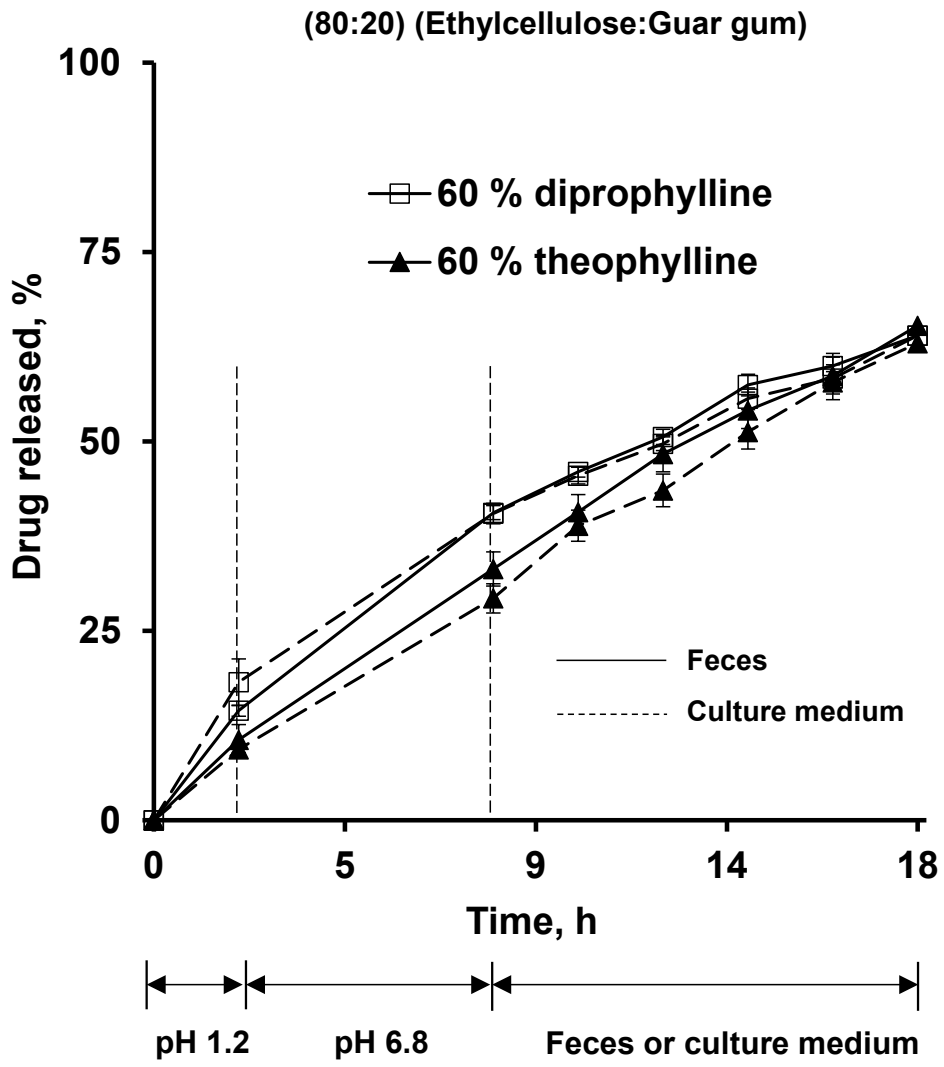

(80:20) (Ethylcellulose:Guar gum)
100
75
50
25
0
Drug released, %
60 % diprophylline
60 % theophylline
Feces
Culture medium
0
5
9
14
18
Time, h
pH 1.2
pH 6.8
Feces or culture medium

Figure 12

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Supplementary material

Hot melt extruded polysaccharide blends for controlled drug delivery

Y. Benzine[1], F. Siepmann[1], C. Neut[2], F. Danede[3], J.F. Willart[3], J. Siepmann[1], Y. Karrout[1]

[1] *Univ. Lille, Inserm, CHU Lille, U1008, F-59000 Lille, France*

[2] *Univ. Lille, Inserm, CHU Lille, U995- LIRIC, F-59000 Lille, France*

[3] *Univ. Lille, USTL UMET UMR CNRS 8207, F-59650 Villeneuve d'Ascq, France*

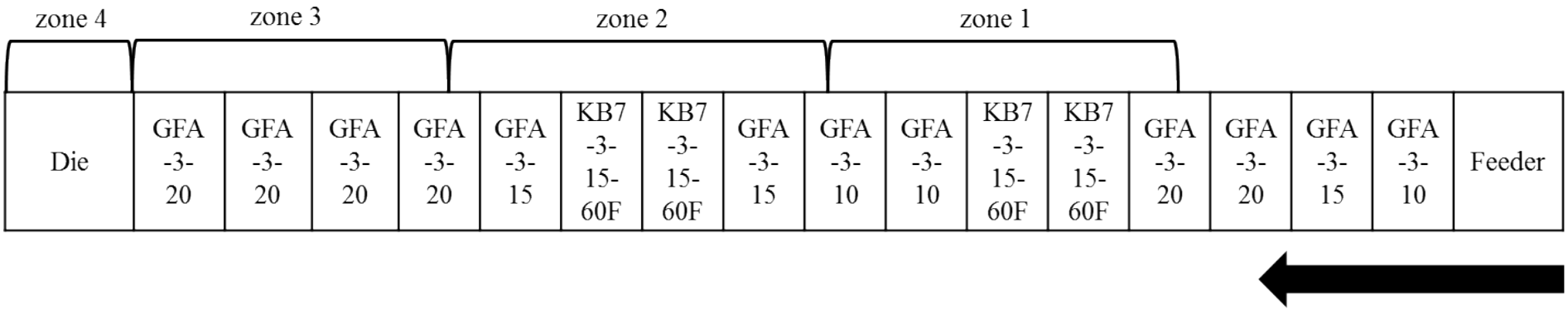

Figure S1: Setting of the screw elements used for hot melt extrusion.

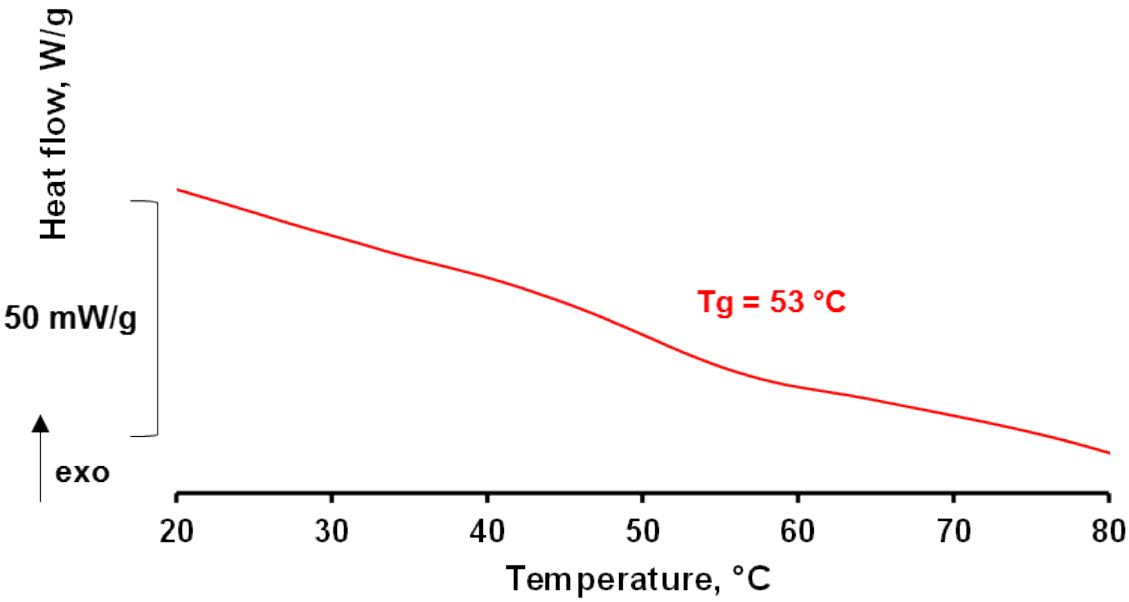

Figure S2: DSC thermogram of ethylcellulose plasticized with 30 % DBS.

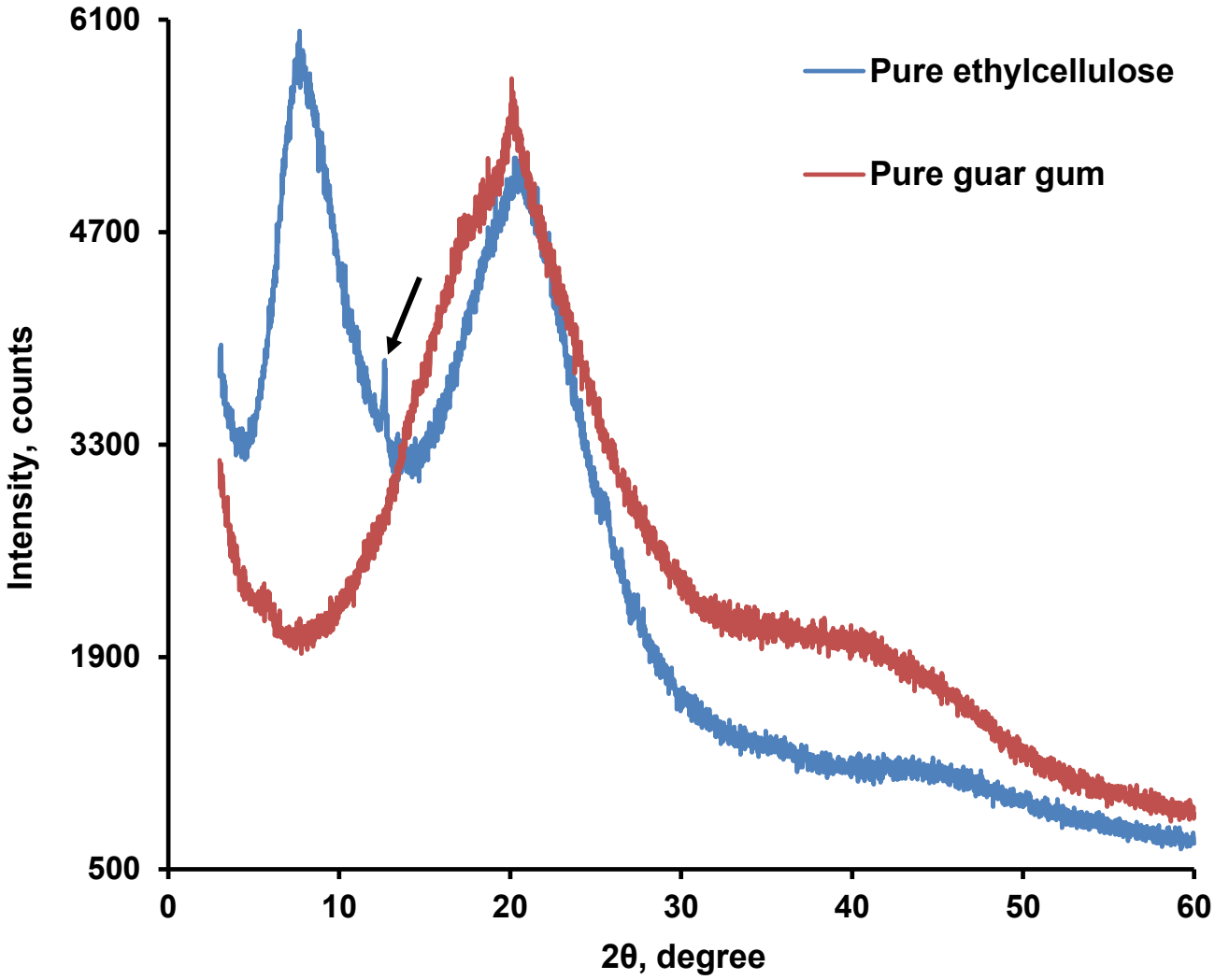

Figure S3: X-ray diffractograms of pure ethylcellulose and pure guar gum powders (as received).

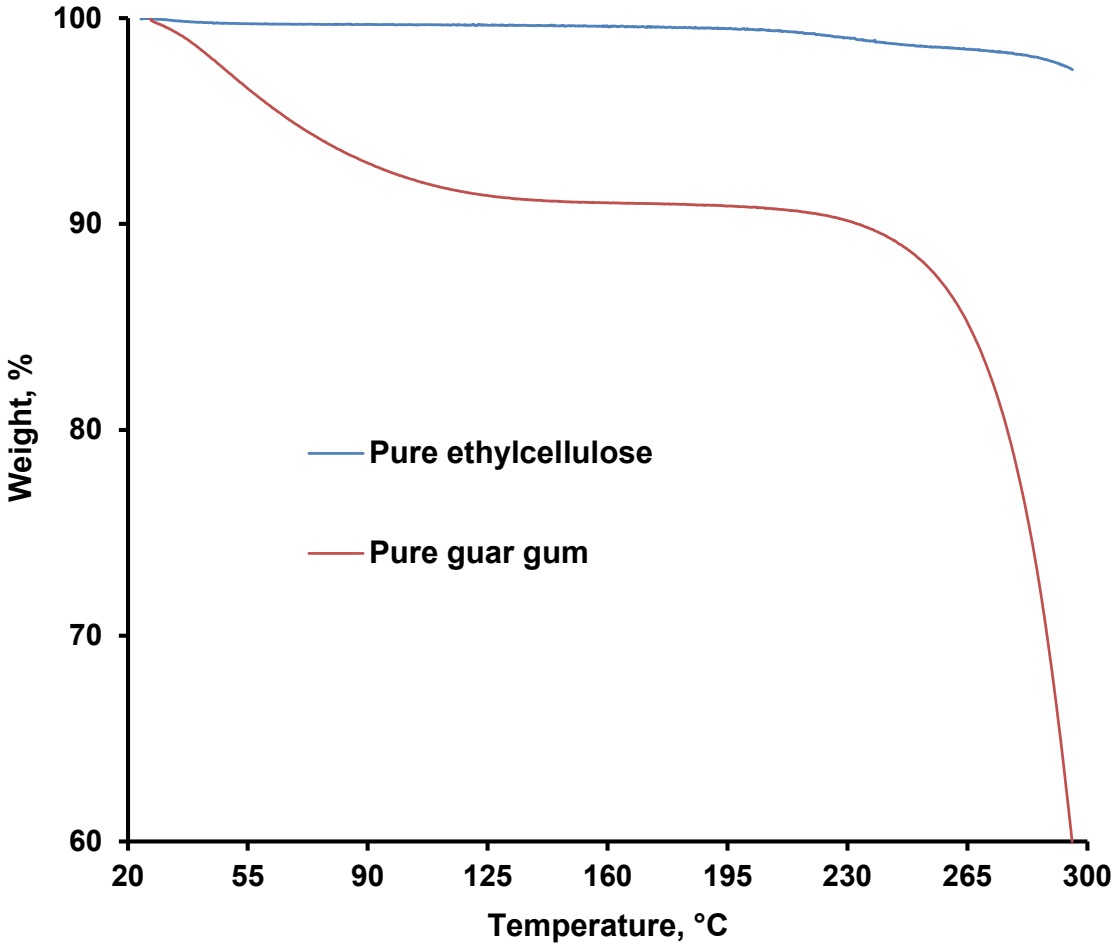

Figure S4: TGA thermograms of pure ethylcellulose and pure guar gum powders (as received).

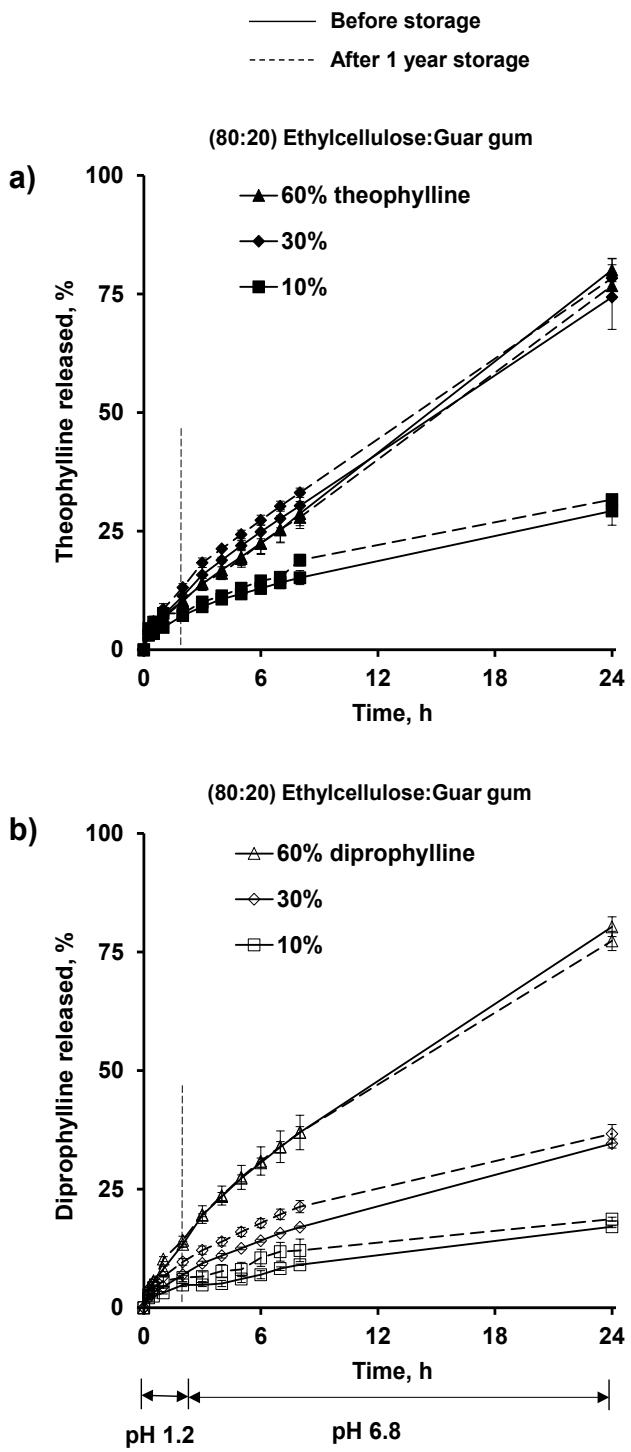

Figure S5: Storage stability of hot melt extrudates based on 80:20 ethylcellulose:guar gum blends loaded with: a) theophylline, or b) diprophylline. The extrusion temperature was 100 °C, the extrudates were plasticized with 30 % DBS. Drug release was measured in 0.1 M HCl (for 2 h), followed by phosphate buffer pH 6.8 before (solid curves) and after 1- year open storage at ambient conditions (dotted curves).