OUTPUT 6	Advanced drug delivery systems for colon targeting
Project specific objective	1) Innovative pharmaceutical formulations and technologies
Output description	The delivered products will be ready to use in pharmaceutical applications. Prototypes and comprehensive data bases on their physico chemical key properties and optimized processing parameters will be available. 1 patent is targeted.
Project Output Target	1
Expected project specific result (s)	New products: Development of advanced drug delivery systems with enhanced properties (expected gain 100% in therapeutic efficacy) for colon targeting. The delivered products will be ready to use in pharmaceutical applications and will increase of the competitiveness of SMEs. 1 Patent is targeted
Partner responsible	LP 12 (University of Lille)
Other Partners involved	OP 1 (Foundation DigestScience)

Summary of the objectives, activities and achievements obtained during the project

The main object of this output was to develop innovative drug delivery systems allowing for "colon targeting": This means that the drug product upon oral administration does not release major portions of the drug in the stomach and small intestine, but only once the colon is reached. This can be highly advantageous if diseases of the colon are to be treated, such as inflammatory bowel diseases (e.g. Crohn's disease and ulcerative colitis). Most of the drug should be trapped within the dosage form until the target site is reached.

To achieve this objective a large variety of polymer:polymer blends was investigated. The basic idea was to identify a suitable polymer blend that allows a substantially different drug release rate in non-colonic conditions versus colonic conditions. To simulate these conditions, bacterial culture medium was inoculated with fecal human samples. For reasons of comparison, culture medium free of samples was studied. Different drugs were incorporated within various polymer:polymer blends using different manufacturing techniques, such as film casting, hot melt extrusion and injection molding. No single polymer has been reported that could provide the desired release properties. However, a combination of appropriate polymers was to be identified: One of the polymers should be affected by the colonic bacteria, while the other polymer should avoid the undesired premature dissolution of the first polymer under conditions simulating the contents of the upper gastro intestinal tract. The first polymer is preferentially degraded by bacterial enzymes: This allows the "colon targeting approach: In the stomach and small intestine, the number of bacteria is low (and, thus, the concentration of enzymes secreted by these bacteria), whereas in the colon the number of bacteria is very high (and, thus, the concentration of bacterial enzymes). Importantly, a blend of the water insoluble polymer ethylcellulose and a second polysaccharide was identified to provide the desired properties: It could be shown that polymeric systems based on these compounds show a substantially higher drug release rate upon exposure to release media containing faecal human samples compared to release media free of bacteria.

1) Description of the scientific and technological achievements

The basic idea was to use a large variety of polymer:polymer blends to prepare advanced drug delivery systems exhibiting higher drug release rates under conditions as encountered in the human colon compared to the upper gastro intestinal tract. In fact, polymer blends offer an interesting potential for controlled drug delivery systems [1], both as matrix formers [2] and as coating materials [3]. 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 [4]. 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* [5]. 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 [6]. Thus, one polymer can efficiently "mask" key properties of the other polymer, if the two compounds are intimately mixed [7]. 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 [8]. Polymer:polymer blends have also been used in a variety of controlled drug delivery systems as *matrix formers* [9]. For example, Zhang et al. [10] 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. [11] 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. [12] 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 [13]. 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) [14]. 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 [15]. 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.

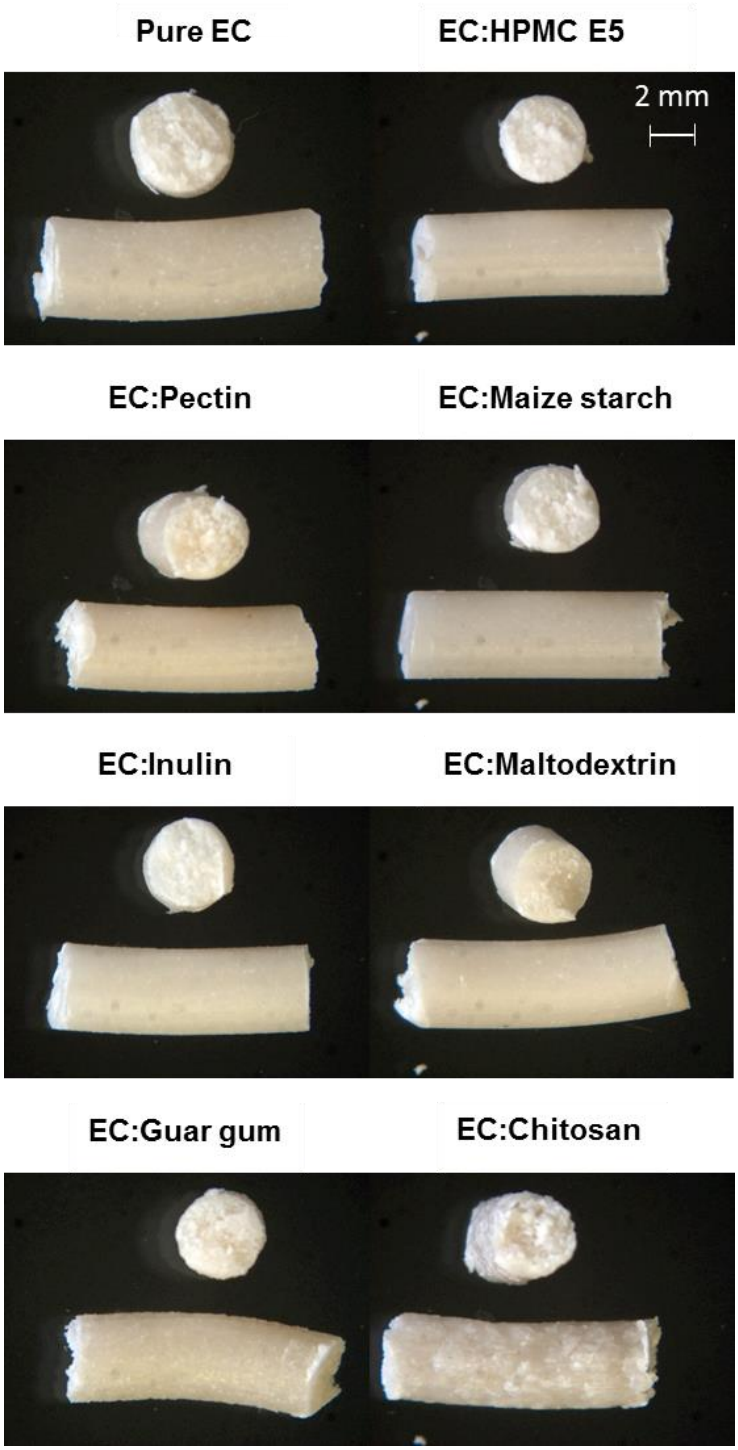


Figure 1 shows optical macroscopy pictures of hot melt extrudates based on different types of polymer:polymer blends: Ethylcellulose was blended with a selection of other polysaccharides, as indicated. The ethylcellulose:2nd polysaccharide blend ratio was 80:20 (weight:weight) in all cases. Thirty percent 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.

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 (referring to ethylcellulose). For reasons of comparison, also hot melt extrudates based "only" on ethylcellulose (loaded with 10 % theophylline, and plasticized with 30 % DBS) are illustrated.

Importantly, in all cases the torque measured during extrusion was similar (around 30 %), not causing any difficulty during processing. The resulting theophylline release kinetics of systems based on different ethylcellulose:guar gum and ethylcellulose:chitosan blends are illustrated in Figure 2. 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).

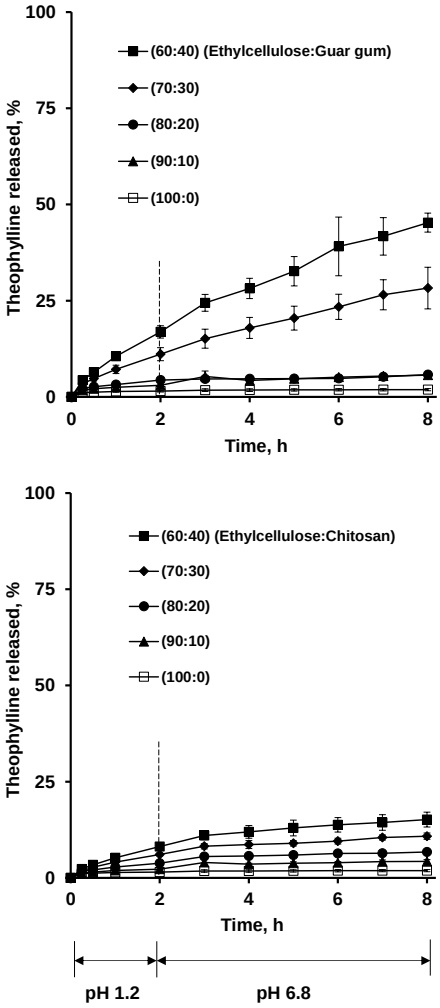


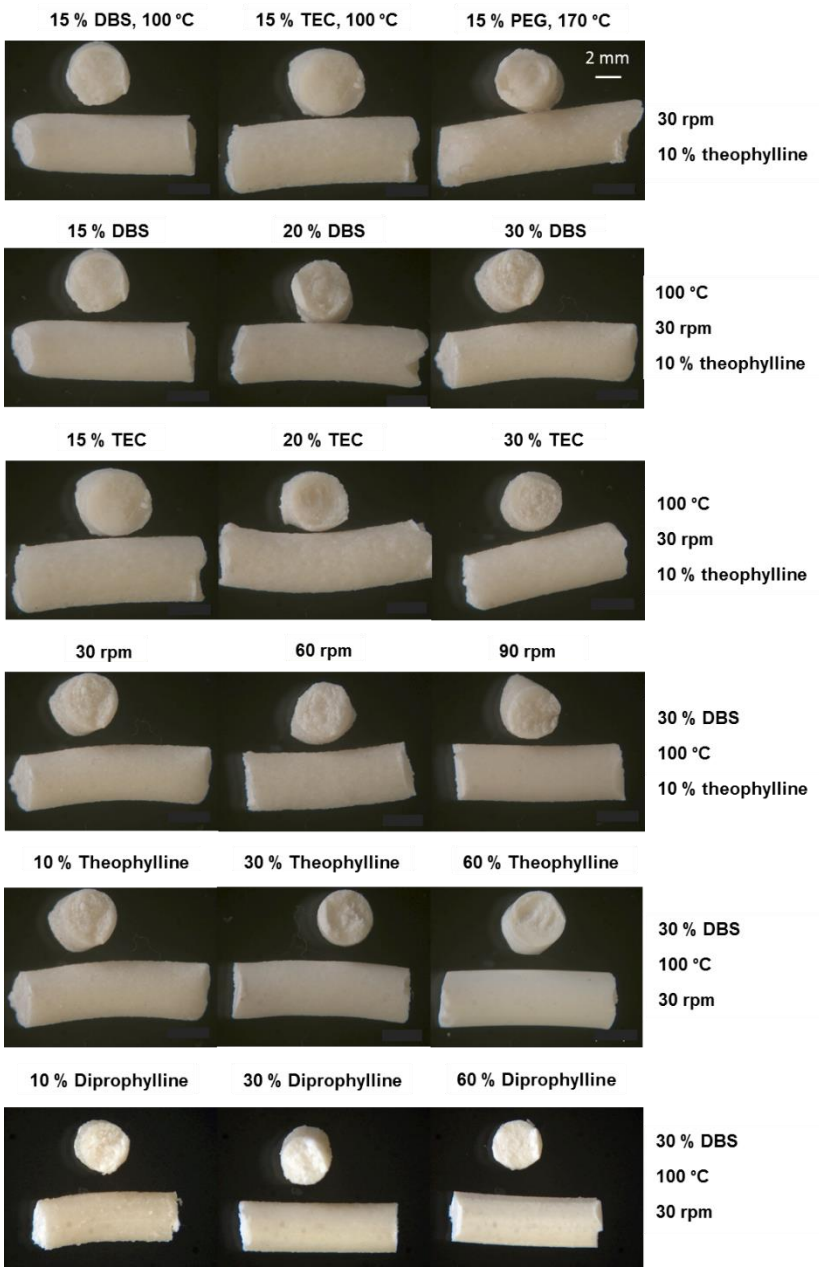
Fig. 2: Impact of the polymer:polymer blend ratio (indicated in the diagrams) on theophylline release from hot melt extrudates based on ethylcellulose:guar gum or ethylcellulose:chitosan blends (as indicated) in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The extrudates were extruded at 170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

Based on the obtained information, the suitability of ethylcellulose:guar gum, ethylcellulose:chitosan and ethylcellulose:HPMC E5 blends, plasticized with 30 % DBS (referring to ethylcellulose) were 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 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 %, referring to ethylcellulose), (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 4a 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 4a). The respective theophylline release kinetics from these hot melt extrudates are illustrated in Figure 4b. 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).

Fig. 3: Macroscopic pictures of hot melt extrudates 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.

Figure 5a 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 5b. 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).

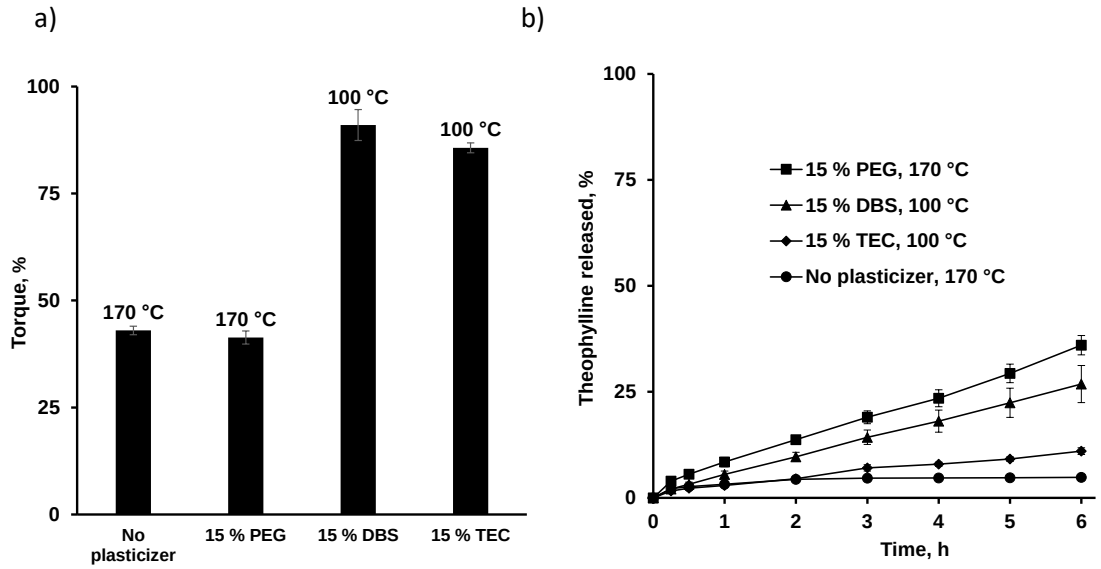


Fig. 4: Impact of the type of plasticizer and extrusion temperature on: a) the generated torque, and b) theophylline release from extrudates in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The systems were based on 80:20 ethylcellulose:guar gum blends, the drug loading was 10 %.

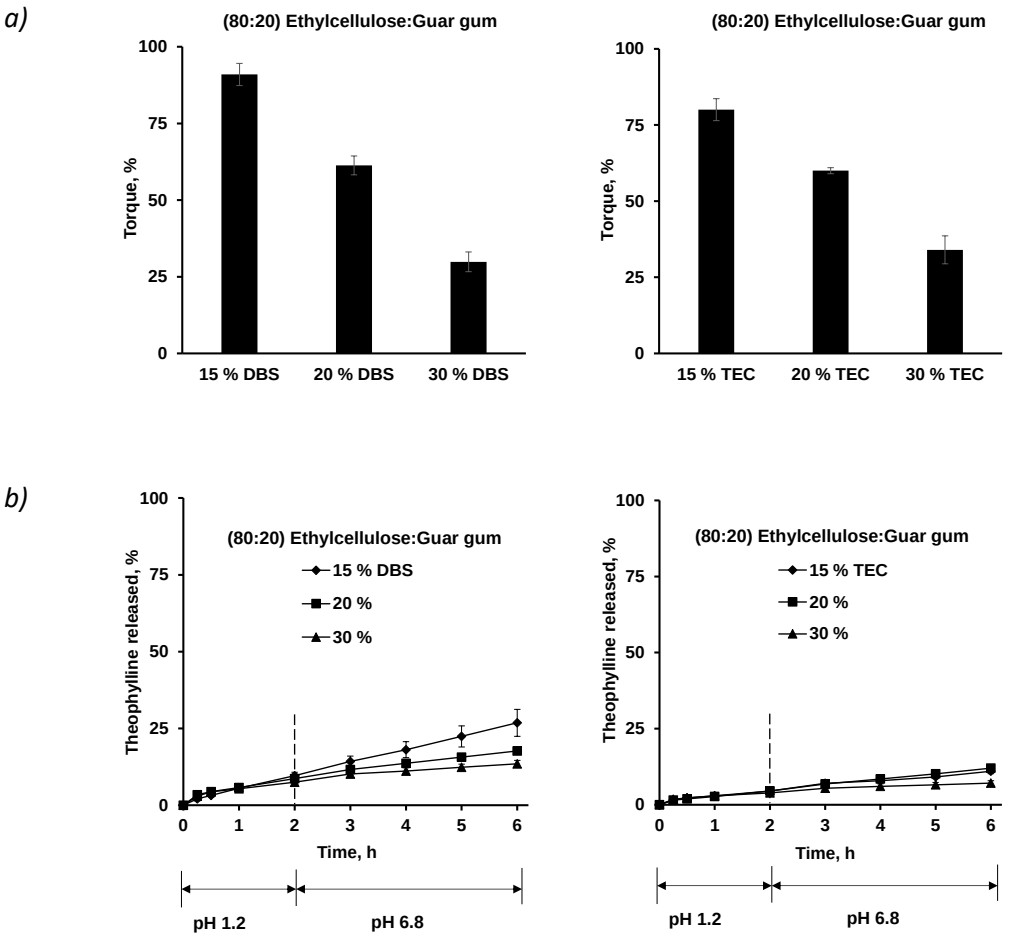


Fig. 5: Impact of the type and amount of plasticizer on: a) the generated torque, and b) theophylline release from extrudates in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The systems were based on 80:20 ethylcellulose:guar gum blends, the extrusion temperature was 100 °C and the drug loading 10 %.

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 6. 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 7): The percentages of slightly water-soluble theophylline and freely water-soluble diprophylline were varied from 10 to 60 %.

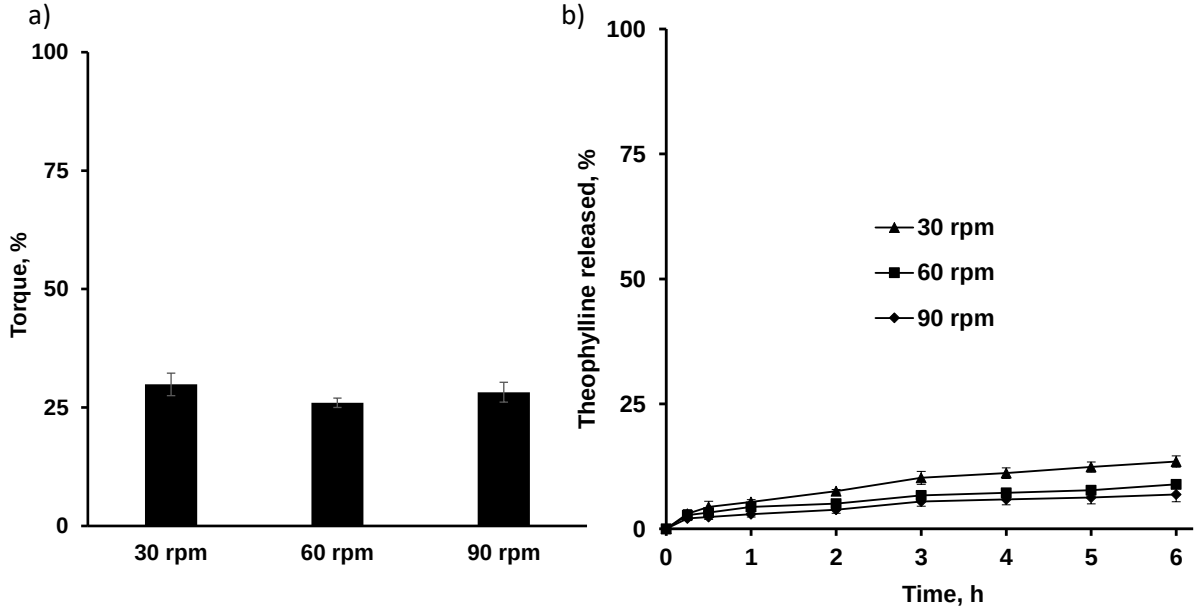


Fig. 6: Impact of the screw speed during extrusion of 80:20 ethylcellulose:guar gum blends on: a) the generated torque, and b) theophylline release from extrudates in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The extrusion temperature was 100 °C, the extrudates were plasticized with 30 % DBS (referring to ethylcellulose), and the drug loading was 10 %.

Figure 7a shows the respective torque values observed during extrusion (at 100 °C, with 30 % DBS). Figure 7b 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 and that the relative amounts of more easily extrudable, plasticized polymer blends in the formulations decrease.

Figure 7b 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.

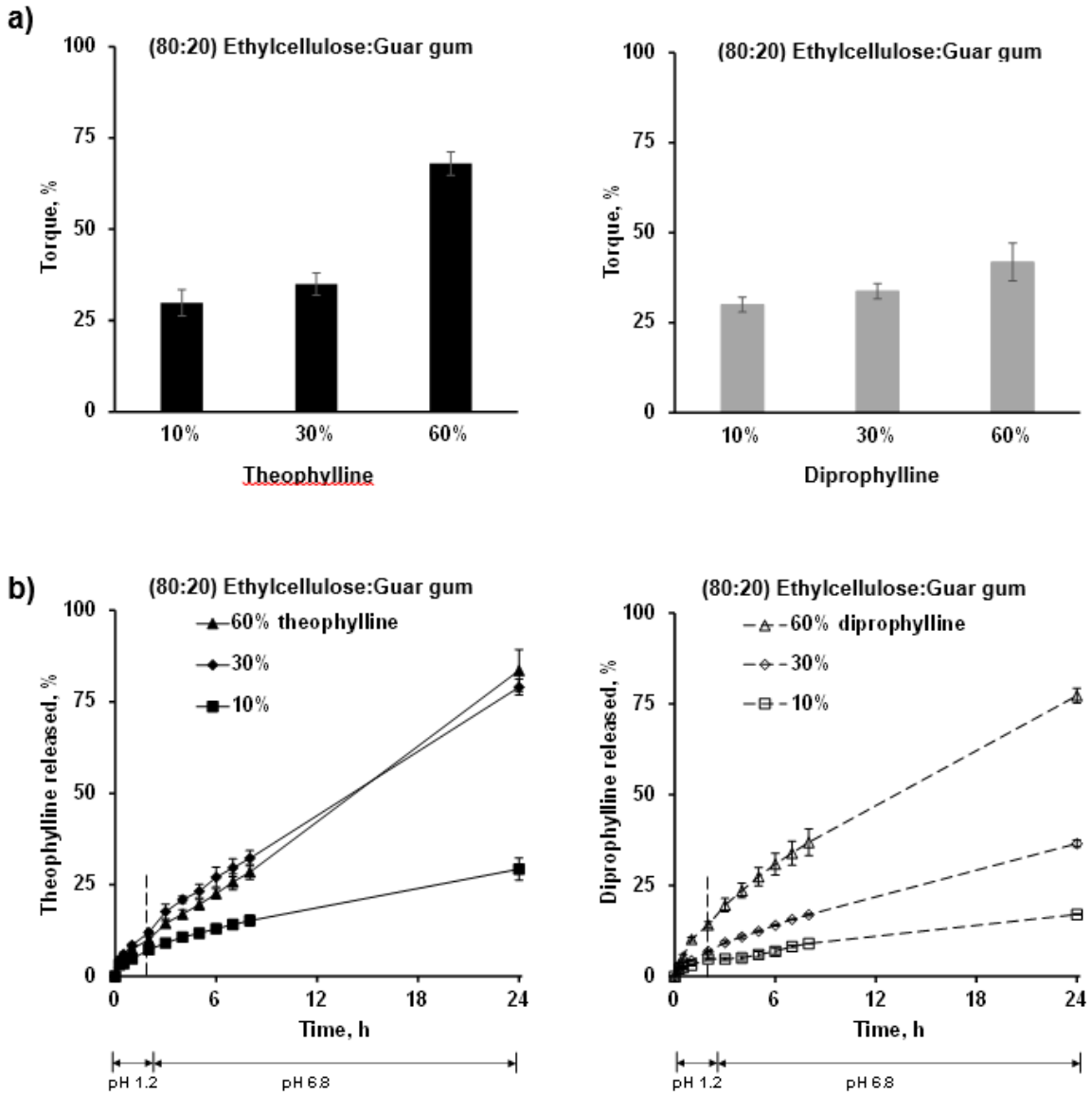


Fig. 7: Impact of the theophylline or diprophylline loading on: a) the generated torque, and b) drug release from extrudates in 0.1 M HCl for 2 h, followed by phosphate buffer pH 6.8. The systems were based on 80:20 ethylcellulose:guar gum blends, the extrusion temperature was 100 °C, the extrudates were plasticized with 30 % DBS.

Hot melt extrudates loaded with 60 % theophylline or 60 % diprophylline, based on ethylcellulose:guar gum 80:20 blends (plasticized with 30 % DBS referred to ethylcellulose) 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 8 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. Thus, these systems are not suitable for colon targeting.

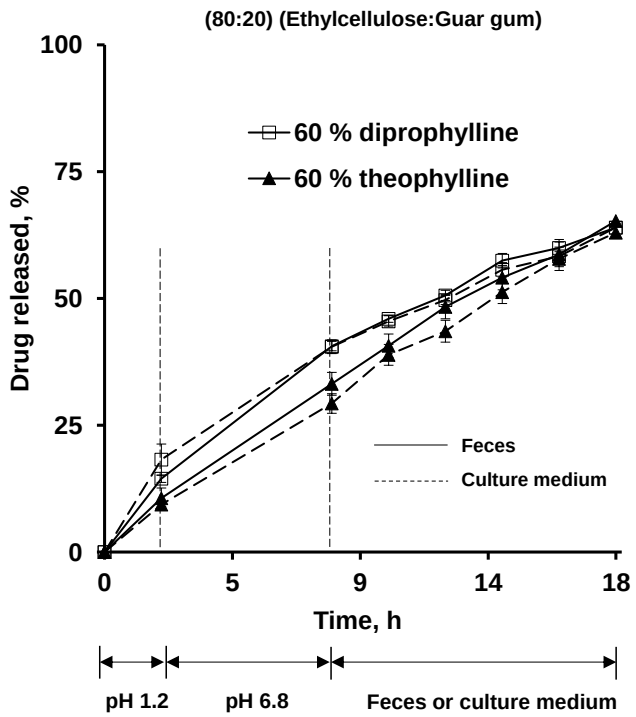


Fig. 8: Drug release from hot melt extrudates based on 80:20 ethylcellulose:guar gum blends under conditions simulating the transit through the entire gastro intestinal tract: 2 h in 0.1 M HCl, followed by 6 h in phosphate buffer pH 6.8, followed by culture medium inoculated with human fecal samples (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 (referring to ethylcellulose).

However, other polymer:polymer blends could successfully be prepared allowing for more rapid drug release under colonic conditions compared to environments simulating the contents of the stomach and small intestine.

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2) Description of the results obtained for the output in term of specific results category and specific result type

Specific results category And Specific result type	Description of the specific results
Knowledge - Created/Increased skill and capacities New products: Development of advanced drug delivery systems with enhanced properties (expected gain 100% in therapeutic efficacy) for colon targeting.	Innovative polymeric systems have been developed allowing for site-specific drug delivery to the colon. They can be used to enable new therapeutic treatments, because they can avoid undesired premature drug in the upper gastro intestinal tract leading to drug absorption into the blood stream. Consequently, the drug does not reach its target site: the colon. With the new polymeric films this can be avoided and the drug can reach the site of action. These successful results in terms of "colon targeting" concern only a part of the overall obtained results: Many investigated systems failed to release the drug in the desired way. This illustrates the significant challenge that had to be overcome. It has to be pointed out that these "colon targeting failures" are nevertheless interesting, for a different perspective: They allow controlled drug delivery within the gastro intestinal tract without being affected by colonic bacteria. In other words: If colon targeting is not desired, these systems are of interest, since they are "insensitive" to the bacterial environment and provide more reliable drug release kinetics. This is way these results are not "lost", but of interest for scientists working on oral controlled drug delivery systems other than "colon targeting" systems. It was not possible to patent these results, for this reason they have been disseminated at international scientific conferences and a research article published in a peer-reviewed international journal: The Journal of Drug Delivery Science and Technology. Another article is in preparation. Also, a PhD thesis was defended in December 2019. PhD thesis: Youcef Benzine Enzymatically triggered polymeric drug delivery systems for colon targeting University of Lille, defended on 18th December 2019 Scientific articles: Benzine, Y; Siepmann, F; Neut, C; Danede, F; Willart, JF; Siepmann, J; Karrout, Y. Hot melt extruded polysaccharide blends for controlled drug delivery. Journal of Drug Delivery Science and Technology 54, 101317, 1-11, 2019. A second article is under preparation.

	Poster presentations at international scientific meetings: Benzine, Y; Siepmann, F; Siepmann, J; Karrout, Y. Hot melt extrudates for colon targeting. 11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Granada, Spain, Proceedings, 2018. Benzine, Y; Siepmann, F; Siepmann, J; Karrout, Y. Ethylcellulose: guar gum hot melt extrudates for controlled drug release: Impact of plasticizers and processing parameters. 3rd European Conference on Pharmaceutics, Bologna, Italy, Proceedings, 2019. Benzine, Y; Siepmann, F; Siepmann, J; Karrout, Y. Hot melt extruded polysaccharide blends for controlled drug delivery. 3rd European Conference on Pharmaceutics, Bologna, Italy, Proceedings, 2019. Benzine, Y; Siepmann, F; Neut, C; Danede, F; Willart, JF; Siepmann, J; Karrout, Y. Polymer blends for hot melt extruded and injection molded controlled drug delivery systems. Oral presentations at national and international scientific meetings: Benzine, Y; Siepmann, F; Siepmann, J; Karrout, Y. Hot melt extrudates for colon targeting. 12th PSSRC Annual Meeting "Pharmaceutical Solid State Research Cluster", Leuven, Belgium, 2018. Benzine, Y; Siepmann, F; Neut, C; Danede, F; Willart, JF; Siepmann, J; Karrout, Y. Polymer blends for hot melt extruded and injection molded controlled drug delivery systems. Biofit, Marseille, France, 2019.
Socio-Economic -Increased business activities/capacities (new products, processes, services, techniques) The delivered products will be ready to use in pharmaceutical applications and will increase of the competitiveness of SMEs.	Since the results on the successful colon targeting systems were obtained only very recently, we did not yet communicate on them. Patent protection must be assured before (please see below). The results on the "non-colon targeting systems" have been discussed with a variety of pharmaceutical companies.
Socio-Economic -Patent applications 1 Patent	We believe that it would be premature at this stage to apply for a patent application for the identified polymer:polymer blend. We will continue working on this system and intend to file a patent in the next 3 years, based on more comprehensive data. A premature disclosure now (or in the next few months) would not be in our favour.

List of documents enclosed as annex

Images	A colon targeting film.
Reports and high impact publications	PhD thesis: Youcef Benzine Enzymatically triggered polymeric drug delivery systems for colon targeting University of Lille, defended on 18th December 2019 Research article: Benzine, Y; Siepmann, F; Neut, C; Danede, F; Willart, JF; Siepmann, J; Karrout, Y. Hot melt extruded polysaccharide blends for controlled drug delivery. Journal of Drug Delivery Science and Technology 54, 101317, 1-11, 2019. A second article is under preparation.
Communications in European and/ or international events	Benzine, Y; Siepmann, F; Siepmann, J; Karrout, Y. Hot melt extrudates for colon targeting. 11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Granada, Spain, Proceedings, 2018. Benzine, Y; Siepmann, F; Siepmann, J; Karrout, Y. Ethylcellulose: guar gum hot melt extrudates for controlled drug release: Impact of plasticizers and processing parameters. 3rd European Conference on Pharmaceutics, Bologna, Italy, Proceedings, 2019. Benzine, Y; Siepmann, F; Siepmann, J; Karrout, Y. Hot melt extruded polysaccharide blends for controlled drug delivery. 3rd European Conference on Pharmaceutics, Bologna, Italy, Proceedings, 2019. Benzine, Y; Siepmann, F; Neut, C; Danede, F; Willart, JF; Siepmann, J; Karrout, Y. Polymer blends for hot melt extruded and injection molded controlled drug delivery systems. 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Vienna, Austria, Proceedings, 2020. Oral presentations at national and international scientific meetings: Benzine, Y; Siepmann, F; Siepmann, J; Karrout, Y. Hot melt extrudates for colon targeting. 12th PSSRC Annual Meeting “Pharmaceutical Solid State Research Cluster”, Leuven, Belgium, 2018. Benzine, Y; Siepmann, F; Neut, C; Danede, F; Willart, JF; Siepmann, J; Karrout, Y. Polymer blends for hot melt extruded and injection molded controlled drug delivery systems. Biofit, Marseille, France, 2019. Please note that these abstracts had to follow templates, which do not allow the inclusion of logos. The logos were included in the posters and slides.
Patent prior art search & patent preparation	
Patent	
Official letters from company(ies)	

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