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RESEARCH ARTICLE

Non-coated multiparticulate matrix systems for colon targeting

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Abstract

Background: Colon specific drug delivery can significantly improve the efficacy of local treatments of inflammatory bowel diseases. Film coatings containing the starch derivative Nutriose have recently been reported to minimize 5-ASA release in media simulating the upper gastro intestinal tract (GIT), while releasing the drug in a time-controlled manner upon contact with feces from Crohn's Disease and Ulcerative Colitis patients. It was the aim of this study to prepare Nutriose-containing matrix pellets and mini tablets in order to avoid a film coating step.

Methods: Highly dosed matrix pellets were prepared by extrusion-spheronization, highly dosed mini tablets by compression. Various types of lipids were added and drug release measured in 0.1 N HCl and phosphate buffer pH 6.8, optionally containing pepsin and pancreatin.

Results: The type of added lipid and the preparation technique, in particular the curing conditions, significantly affected the resulting drug release kinetics. Glyceryl palmitostearate containing pellets and mini tablets showed the most promising results upon appropriate curing, minimizing premature drug release in media simulating the upper GIT.

Conclusion: The proposed novel multiparticulates do not require a film coating step and show an interesting potential for site-specific drug delivery to the colon of inflammatory bowel disease patients.

Keywords: Colon targeting, matrix pellets, mini tablets, controlled release, nutriose

Introduction

The local treatment of inflammatory bowel diseases (e.g., Crohn's Disease and Ulcerative Colitis) is highly challenging, because conventional dosage forms rapidly release the drug in the upper gastro intestinal tract (GIT). Upon absorption into the blood stream, the drug is distributed throughout the human body, resulting in potentially severe side effects. In addition, the drug concentration at the site of action—the inflamed colon—is low, leading to low therapeutic efficacies. To overcome these restrictions, drug release from the dosage form should ideally be suppressed in the stomach and small intestine, but set on as soon as the target site is reached[1–3].

Different interesting approaches have been described in the literature to allow for site-specific drug delivery to the colon upon oral administration[3–10]. Generally, a drug reservoir is surrounded by a film coating, which is poorly permeable for the drug in the upper GIT, but becomes permeable as soon as the colon is reached[11–13]. The change in drug permeability of the film coating might be caused by: (i) the change in the pH of the contents of the GIT (stomach—intestine—colon[12,14–16]), (ii) degradation of the film coating by enzymes, which are secreted by colonic bacteria[17,18], or (iii) structural changes in the film coating as soon as the target site is reached (e.g., rupturing after a certain lag time, due to a steadily increasing hydrostatic pressure within the dosage form[19]). Furthermore, drug release might start right after oral administration at a rate which is sufficiently small in order to assure that drug is still present in the dosage form once the colon is reached[20,21].

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However, great care must be taken, because the conditions in the GIT of a patient suffering from Crohn's Disease or Ulcerative Colitis might significantly differ from those in a healthy subject. In particular, the pH values and transit times within the various GIT segments as well as the quality and quantity of the colonic microflora can be very different from those under physiological conditions[22,23]. Thus, a dosage form which might reliably deliver a drug specifically to the colon in a healthy subject might fail in a patient. Also, the intra- and inter-variability of the dosage form's performance can be expected to be considerable if the onset of drug release is not induced in the disease state. Recently, Nutriose-containing film coatings have been proposed for colon targeting in inflammatory bowel disease patients[24–26]. Nutriose is a water-soluble, branched dextrin with high fiber contents obtained from wheat starch[27–29]. Importantly, it serves as a substrate for enzymes secreted from colonic bacteria present in the feces of patients suffering from Crohn's Disease and Ulcerative Colitis[24]. However, so far only Nutriose-based film coatings have been described.

Yet, the potential of matrix systems containing this colon targeting compound is unknown. The latter offer the advantage of not necessitating a coating step during production. In these cases, the drug is embedded within the release rate controlling material[30,31]. Since Nutriose as well as the most frequently used drug for the local treatment of inflammatory bowel diseases [5-aminosalicylic acid (5-ASA)] are water-soluble at 37°C, an additional, water-insoluble excipient is needed for instance a lipid[32–34]. Multi Matrix MMX is a technology used in the commercial product Lialda aiming at colon specific delivery of 5-ASA. The idea is to embed the drug within a lipid matrix (carnauba wax and stearic acid) and to disperse this phase within a hydrogel consisting mainly of sodium carboxymethylcellulose and sodium starch glycolate. The drug-lipid-hydrogel mixture is compressed into tablets, which are film coated with Eudragit S and Eudragit L. Thus, this system requires a coating step, and it is a single unit dosage form, suffering from the all-or-nothing effect and an eventually nonhomogeneous distribution within the contents of the GIT.

The aim of this study was to prepare and characterize novel, non-coated, multiparticulate dosage forms (matrix pellets and mini tablets) containing the colon targeting compound Nutriose and high doses of 5-ASA. The high drug content is of major practical importance, because up to 4.8 g 5-ASA is administered per day[35–37]. Different types of lipids were added to minimize premature drug release in the upper GIT and the effects of various formulation and processing parameters was studied.

Materials and methods

Materials

5-aminosalicylic acid (5-ASA; Falk Pharma, Freiburg, Germany); glyceryl behenate (Compritol 888 ATO) and glyceryl palmitostearate (Precirol ATO 5) (Gattefosse, St. Priest, France); hydrogenated soybean oil (Sterotex HM) and hydrogenated cottonseed oil (Sterotex NF) (Abitec, Janesville, WI); glyceryl trimyristate/ glyceryl tripalmitate/ glyceryl tristearate/ hardened soybean oil (Dynasan 114/116/118/120) and synthetic hard paraffins (Sasolwax Spray 30 and Synthetic Wax) (Sasol, Witten, Germany); Nutriose FB 06 (Nutriose, a water-soluble, branched dextrin with high fiber contents obtained from wheat starch; Roquette Freres, Lestrem, France); microcristalline cellulose (MCC, Avicel PH 101; FMC BioPolymer, Brussels, Belgium); poly(vinylpyrrolidone) (PVP, Povidone 30) (Cooperation Pharmaceutique Francaise, Melun, France); chitosan (Protasan CL 213; 75–90% degree of deacetylation, average molecular weight = 150–400 kDa; Novamatrix, FMC BioPolymer, Drammen, Norway); Microwax HG and Microwax HW (Paramelt, Heerhugowaard, The Netherlands); pancreatin (from mammalian pancreas = mixture of amylase, protease and lipase) and pepsin (Fisher Bioblock, Illkirch, France).

Preparation of matrix pellets

Matrix pellets containing 60% 5-ASA were prepared by extrusion-spheronization. The drug, Nutriose and the respective lipid(s) were blended and granulated manually with demineralized water in a mortar with a pestle. The obtained wet mass was extruded using a cylinder extruder with two counter-rotating rollers (1 mm orifice, 3 mm thickness, extrusion speed = 32 rpm, GA 65 extruder; Alexanderwerk, Remscheid, Germany). The extrudates were subsequently spheronized (Caleva model 15; Caleva, Dorset, UK) for 180 s at 364 rpm. The obtained pellets were dried for 24 h in an oven at 40°C and sieved (fraction: 0.71–1.00 mm). If indicated, the pellets were cured for specific time periods at defined temperatures in an oven. The homogeneity of the drug content of the pellets was very good (data not shown).

Preparation of mini tablets

5-ASA, Nutriose and the respective lipid(s) were blended manually in a mortar with a pestle. Mini tablets (50% drug loading) were prepared by:

1. direct compression on a Frank 81802 (Karl Frank, Birkenau, Germany), equipped with a 2-mm diameter punch set (Korsch, Berlin, Germany), or
2. compression of granules obtained via melt granulation. If not otherwise stated, the respective compounds were heated and mixed on a water bath at 85°C. After cooling to room temperature, the obtained mass was ball milled, sieved (fraction 50–100 μm) and compressed using the same equipment as in 1.

The tablet height was 2 mm. Optionally, the tablets were cured in an oven for different time periods at various temperatures, as indicated.

Drug release measurements

Drug release from matrix pellets was measured in 120 mL cylindrical plastic flasks (diameter: 5.5 cm, height: 6.5 cm)

containing 100 mL release medium: 0.1 N HCl (optionally containing 0.32% w/v pepsin) for 2 h and phosphate buffer pH 6.8 (USP 34) (optionally containing 1.0% w/v pancreatin) for 8 h (complete medium change after 2 h). The flasks were agitated in a horizontal shaker (37°C, 80 rpm, $n = 3$) (GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At pre-determined time points, 3-mL samples were withdrawn (replaced with fresh medium), filtered and analyzed UV-spectrophotometrically at $\lambda = 302.4$ nm (0.1 N HCl), or $\lambda = 331.2$ nm (phosphate buffer pH 6.8) (UV-1650PC; Shimadzu, Champs-sur-Marne, France). In the presence of enzymes, the samples were centrifuged at 13,000 rpm for 10 min (Universal 320 centrifuge; Hettich, Tuttlingen, Germany) and filtered (0.2 µm, PTFE) prior to UV measurements.

Drug release from mini tablets was measured using the USP 34 apparatus 3 (BioDis; Varian, Les Ulis, France) (37°C, 5 dpm, $n = 3$) in 200 mL release medium: 0.1 N HCl for 2 h and phosphate buffer pH 6.8 (USP 34) for 8 h (complete medium change after 2 h). At pre-determined time points, 3-mL samples were withdrawn (replaced with fresh medium), filtered and analyzed UV-spectrophotometrically as described above.

Determination of drug solubility

Excess amounts of 5-aminosalicylic acid were placed in contact with 0.1 N HCl and phosphate buffer pH 6.8 at 37°C in a horizontal shaker (80 rpm, GFL 3033). Samples were withdrawn every 12 h, filtered and analyzed for their drug content as described in section 2.4. until equilibrium was reached.

DSC analysis

Thermograms of different types of pellets and raw materials (for reasons of comparison) were measured by differential scanning calorimetry (DSC1; STARe Software; Mettler Toledo SAS, Viroflay, France). Pellets were gently crushed in a mortar with a pestle and approximately 7-mg samples were heated in sealed aluminum pans (investigated temperature range: 20–90°C, heating rate: 10°C/min).

Results and discussion

Nutriose-containing matrix pellets

Extrusion-spheronization allowed obtaining spherical pellets in all cases. The systems contained 60% 5-ASA, 15% Nutriose and 25% lipid(s) (optionally partially replaced by MCC or PVP). The high drug loading is of great practical importance, because 5-ASA is highly dosed (up to 4.8 g per day). The presence of Nutriose in the pellets aims at providing colon specific drug delivery: This polymer has been reported to be degraded by enzymes present in feces of inflammatory bowel disease patients.[24] The lipids, MCC and PVP aim at avoiding immediate drug release upon contact with aqueous body fluids (note that the drug and Nutriose are both water-soluble at 37°C).

Figure 1 shows the release of 5-ASA from pellets containing 25% (w/w) of the following lipids: (a) hardened soybean oil, (b) glyceryl tristearate, (c) Sasolwax or Synthetic Wax, or (d) Microwax HG or Microwax HW. The systems were cured at different temperatures for 1, 2 or 3 min (as indicated) in order to allow for a more homogeneous lipid distribution, more efficient embedding of the drug particles and eventually the (partial) transformation of a lipid into a more stable modification. The melting points of the investigated lipids (glyceryl tristearate: 70–73°C, hardened soybean oil: 67-72°C, Sasolwax: 96-100°C, Synthetic Wax: 94-97°C, Microwax HG: 80-86°C, Microwax HW: 75-80°C) were close to or well below the investigated curing temperatures. As it can be seen in Figure 1, immediate drug release is avoided and the release rate generally decreased with increasing curing temperature and time, irrespective of the type of lipid. Thus, in principle the applied strategy is successful. However, in all cases drug release was too rapid, and most of the drug was released during the observation period (corresponding to the simulated transit period through the upper GIT; note that long residence times have been assumed, simulating unfavorable conditions for the drug delivery system). Hence, premature drug release *in vivo* is highly likely. The fact that after complete medium change (at $t = 2$ h), the release rate decreased in most cases can probably (at least partially) be attributed to the lower aqueous solubility of 5-ASA in phosphate buffer pH 6.8 compared to 0.1 N HCl at 37°C: 4.4 mg/mL vs. 10 mg/mL.

In order to reduce the undesired premature drug release in 0.1 N HCl and phosphate buffer pH 6.8, parts of the lipid were substituted by MCC or PVP. Figure 2 shows 5-ASA release from pellets containing 60% drug, 15% Nutriose, 15% hardened soybean oil and 10% MCC or PVP. For reasons of comparison, also drug release from MCC/PVP-free systems (containing 25% hardened soybean oil) is shown. All pellets were cured for 3 min at 70, 80 or 90°C (as indicated). Interestingly, the replacement of 10% (w/w, referred to the total system mass) lipid by MCC resulted in accelerated drug release, irrespective of the curing conditions. Thus, the lipid is more efficient in hindering drug release from these pellets than MCC. In contrast, the partial replacement of hardened soybean oil by PVP led to slightly/moderately decreased drug release rates, if the systems were cured at 70 and 80°C. However, upon curing at 90°C, also in this case drug release was accelerated upon lipid substitution. Thus, these approaches are not suitable to effectively minimize premature drug release in the upper GIT.

In a further attempt to avoid the observed undesired drug release in 0.1 N HCl and phosphate buffer pH 6.8, a short-term curing for 3 min at 90°C was followed by a long-term curing at 40°C for 7 days. Figure 3 shows 5-ASA release from pellets containing 25% glyceryl trimyristate, hardened soybean oil, glyceryl behenate, glyceryl palmitostearate, glyceryl tripalmitate, hydrogenated cottonseed oil, or glyceryl tristearate upon exposure to 0.1 N

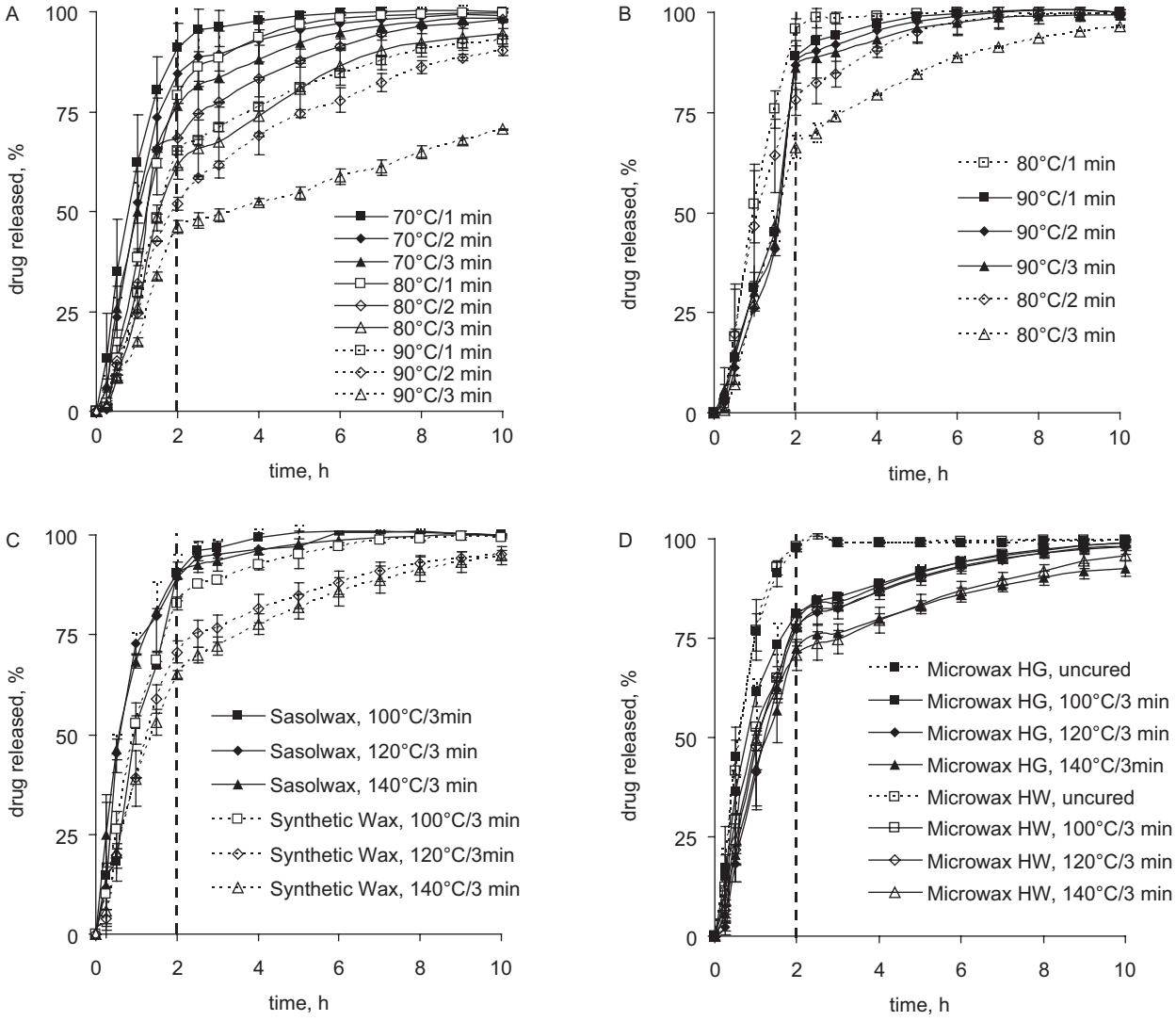

Figure 1. 5-ASA release from pellets consisting of 60% drug, 15% Nutriose and 25% lipid: (A) hardened soybean oil, (B) glyceryl tristearate, (C) Sasolwax or Synthetic Wax, or (D) Microwax HG or Microwax HW. The release medium was 0.1 N HCl (for the first 2 h) and phosphate buffer pH 6.8 (for the subsequent 8 h). The curing conditions are indicated in the diagrams.

HCl for 2 h, followed by phosphate buffer pH 6.8 for 8 h (dotted curves). For reasons of comparison, also drug release from pellets, which were only cured for 3 min at 90°C are shown (solid curves). Clearly, the release rate significantly decreased in most cases upon long-term curing. This can at least partially be attributed to changes in the modifications of the lipids: Figure 4 shows exemplarily DSC thermograms of pellets consisting of 60% 5-ASA, 15% Nutriose and 25% glyceryl palmitostearate or tripalmitate (as indicated). The pellets were cured for 3 min at 90°C and optionally subsequently for 7 days at 40°C. For reasons of comparison, also thermograms of 5-ASA, Nutriose and of the lipid powders as received are shown in Figure 4. The melting peaks of the powders as received correspond to the melting peaks of the stable β-modifications of these lipids[38,39]. In contrast, pellets which were only cured for 3 min at 90°C also showed the melting/transformation of a less stable modification, irrespective of the type of lipid. Importantly, pellets cured for 7 days at 40°C again only showed the melting of the stable lipid modification (in both cases). It has to be pointed out that the curing temperature during long-term curing was well below the melting point of the respective lipids. Hence, the observed changes in the resulting drug release rates during long-term curing are probably not caused by potential local redistributions of the lipids.

As lipids were used to slow down drug release within the upper part of the GIT, it was important to measure the effects of the presence of enzymes in the bulk fluids on drug release. Figure 5 shows 5-ASA release from pellets consisting of 60% drug, 15% Nutriose and 25% hydrogenated cottonseed oil, glyceryl tripalmitate or glyceryl palmitostearate (as indicated). The release medium was either 0.1 N HCl for the first 2 h, followed by phosphate buffer pH 6.8 for the subsequent 8 h (solid curves), or 0.1 N HCl containing 0.32% w/v pepsin for the first 2 h, followed by phosphate buffer pH 6.8 containing 1% w/v pancreatin for the subsequent 8 h (dotted curves). All pellets were cured for 3 min at 90°C, followed by 7 days at 40°C. Clearly, drug release significantly increased in

the presence of enzymes in the case of hydrogenated cottonseed oil and glyceryl tripalmitate, due to the (at least partial) degradation of these lipids. In contrast, the release rate only slightly increased in the case of glyceryl palmitostearate. Thus, this lipid seems to be much less affected by the added enzymes under these conditions. For this reason, glyceryl palmitostearate was used as standard lipid in all further experiments (if not otherwise stated).

When developing controlled drug delivery systems, special care needs to be taken with respect to potential changes in the systems' properties during long-term storage. Modifications in the molecular structures might alter the resulting matrix permeability for the drug and, thus, the release rate. For these reasons, it is of great practical importance to measure drug release before and after long-term storage from such dosage forms. Storage under stress conditions (e.g., elevated temperature) can allow obtaining results more rapidly than under ambient conditions. Figure 6 shows the release of 5-ASA from pellets consisting of 60% drug, 15% Nutriose and 25% glyceryl palmitostearate. The pellets were cured for 3 min at 90°C, followed by 7 days at 37, 40 and 45°C (as indicated) (the melting range of glyceryl palmitostearate is 53-57°C). For reasons of comparison, also drug release from pellets, which were only cured for 3 min at 90°C and from pellets, which were cured for 3 min at 90°C, followed by 6 months at 37, 40 and 45°C is illustrated. Clearly, a 7-days curing is required to slow down drug release, irrespective of the curing temperature. Interestingly, the resulting release profiles do not overlap, indicating possible differences in the lipid distribution within the system. Importantly, drug release further slowed down when increasing the curing period to 6 month in the case of curing at 37°C, but not in the case of curing at 40 or 45°C. Thus, the latter pellets are likely to be stable during long-term storage at room temperature.

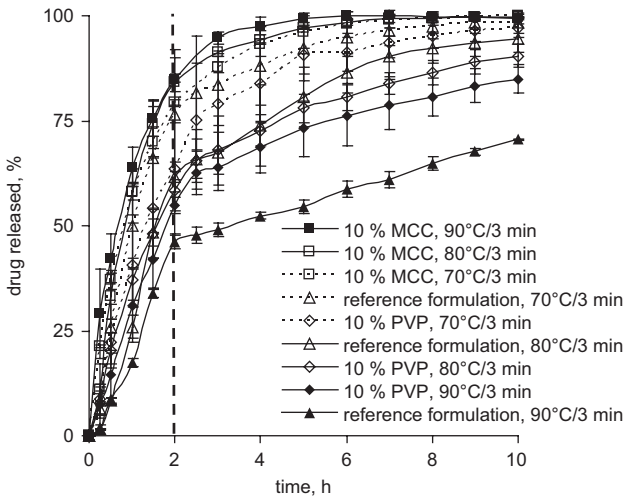

Figure 2. Effects of the replacement of 10% hardened soybean oil by MCC or PVP (as indicated) on 5-ASA release from pellets containing 60% drug and 15% Nutriose. The reference formulations contained 25% hardened soybean oil. The curing conditions are indicated in the diagram, the release medium was 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 for 8 h.

Nutriose-containing mini tablets

As an alternative to matrix pellets, also mini tablets (diameter: 2 mm; height: 2 mm) consisting of 50% 5-ASA, 15% Nutriose and 35% lipid were prepared. Again, the high drug loading was important because of the high daily doses of 5-ASA. Nutriose was the colon targeting compound, and the lipid was intended to minimize drug release in the upper GIT. To evaluate the suitability of different types of lipids in these dosage forms, hardened soybean oil, glyceryl tristearate, glyceryl tripalmitate, glyceryl behenate, glyceryl palmitostearate, hydrogenated cottonseed oil as well as hydrogenated soybean oil were studied (Figure 7). The mini tablets were prepared by direct

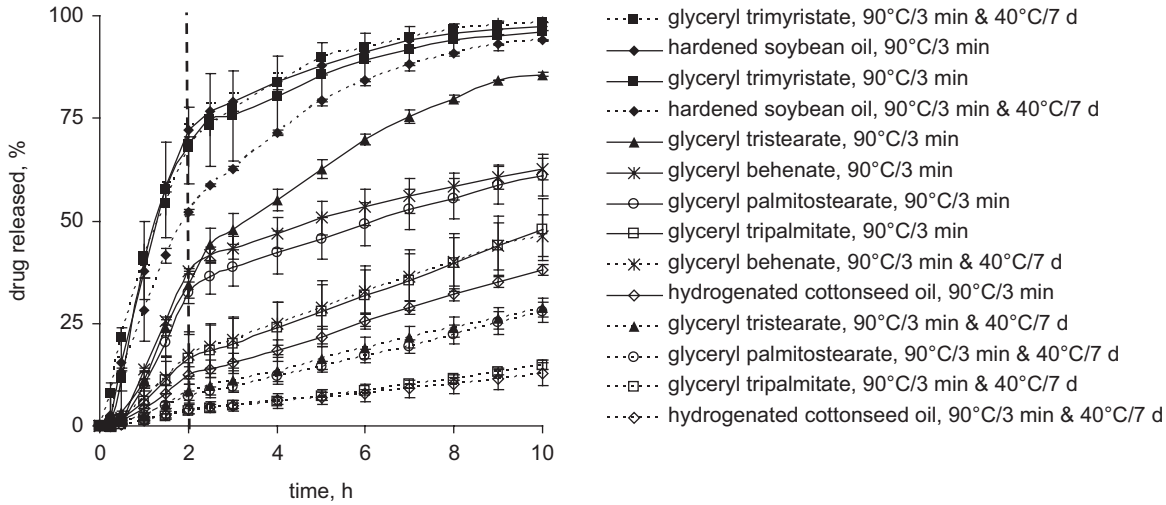

Figure 3. Effects of an additional long-term curing on drug release from pellets consisting of 60% 5-ASA, 15% Nutriose and 25% lipid (the type is indicated in the diagram) upon exposure to 0.1 N HCl (for 2 h) and phosphate buffer pH 6.8 (for 8 h). The solid curves indicate drug release from pellets, which were only cured for 3 min at 90°C. The dotted curves show drug release from pellets, which were additionally cured for 7 days at 40°C.

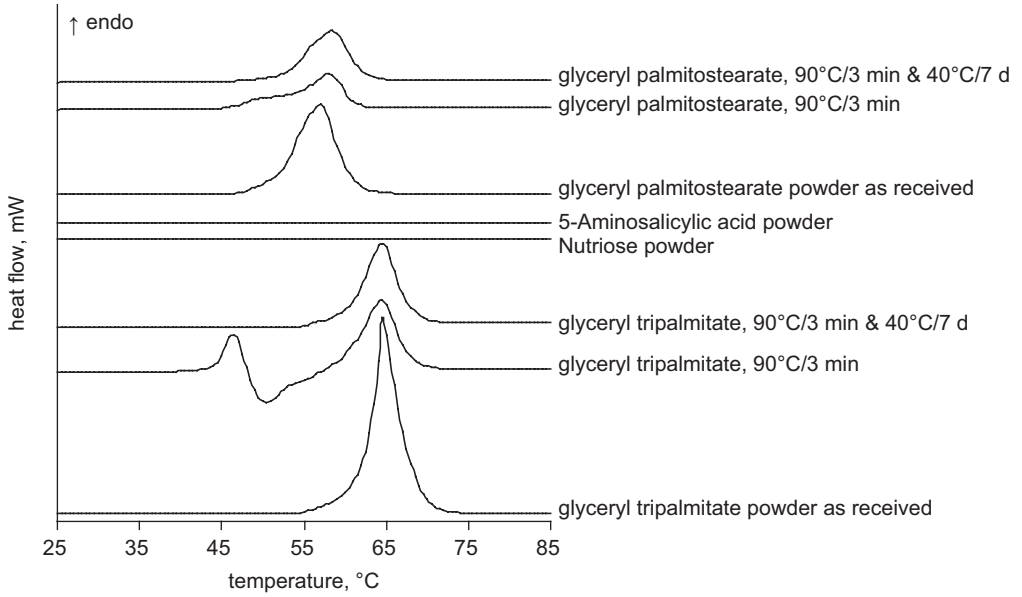

Figure 4. DSC thermograms of pellets consisting of 60% 5-ASA, 15% Nutriose and 25% glyceryl palmitostearate or tripalmitate. The curing conditions are indicated in the diagram. For reasons of comparison, also thermograms of 5-ASA, Nutriose and the lipid powders as received are shown.

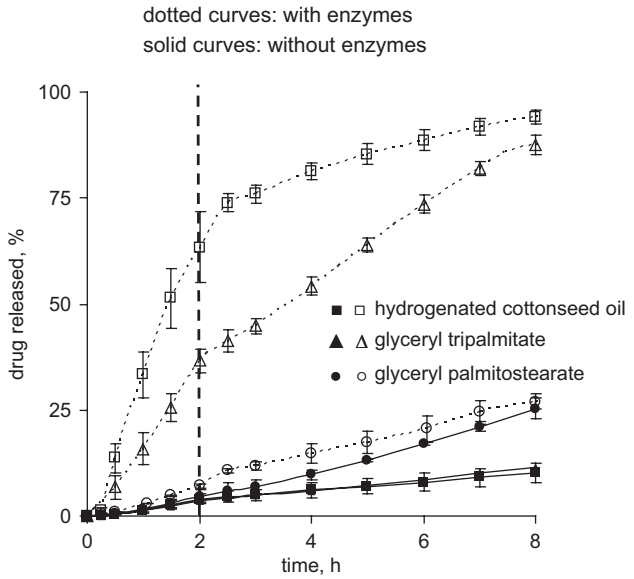

Figure 5. Impact of the presence of enzymes in the bulk fluid [0.32% w/v pepsin in 0.1 N HCl (for 2 h), and 1% w/v pancreatin in phosphate buffer pH 6.8 (for 8 h)] on 5-ASA release from pellets consisting of 60% drug, 15% Nutriose and 25% lipid (the type is indicated in the diagram). All pellets were cured at 90°C for 3 min, followed by 7 days at 40°C.

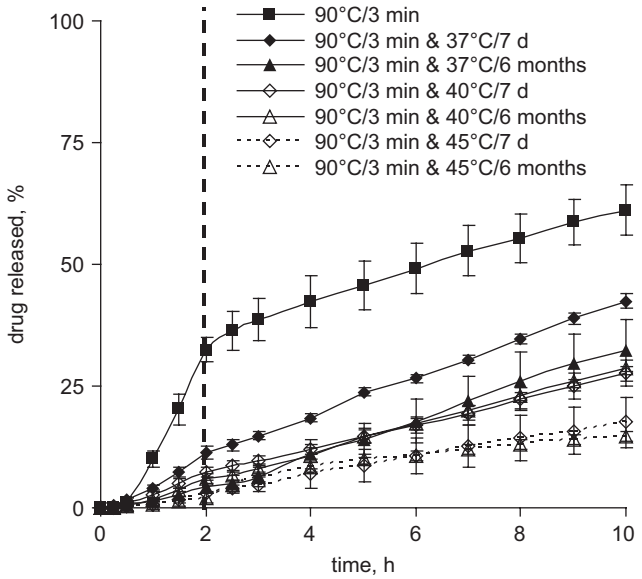

Figure 6. Long-term stability (under stress conditions) of pellets containing 60% 5-ASA, 15% Nutriose and 25% glyceryl palmitostearate: Drug release in 0.1 N HCl (for 2 h) and phosphate buffer pH 6.8 (for 8 h) from systems, which were cured for 3 min at 90°C, optionally followed by 7 days or 6 month at 37, 40 or 45°C (as indicated).

compression, followed by a curing for 24 or 48 h at 60, 65, 70 or 75°C (as indicated), according to the melting points of the lipids: hardened soybean oil 67-72°C, glyceryl tristearate 70-73°C, glyceryl tripalmitate 61-63°C, glyceryl behenate 69-74°C, glyceryl palmitostearate 53-57°C, hydrogenated cottonseed oil 60-62.5°C hydrogenated soybean oil 66.5-69.5°C. As it can be seen in Figure 7, drug release upon 2-h exposure to 0.1 N HCl, followed by 8-h exposure to phosphate buffer pH 6.8 is considerable in all cases. Generally, the release rate decreased with increasing curing time and temperature, due to altered lipid modifications and/or lipid distribution within the system. As in the case of matrix pellets, glyceryl palmitostearate showed the most promising potential as release rate controlling lipid. For this reason, it was studied in more detail.

In order to minimize the undesired, premature drug release in the upper GIT, the curing time and temperature were further increased. Figure 8 shows 5-ASA release from mini tablets consisting of 50% drug, 15%

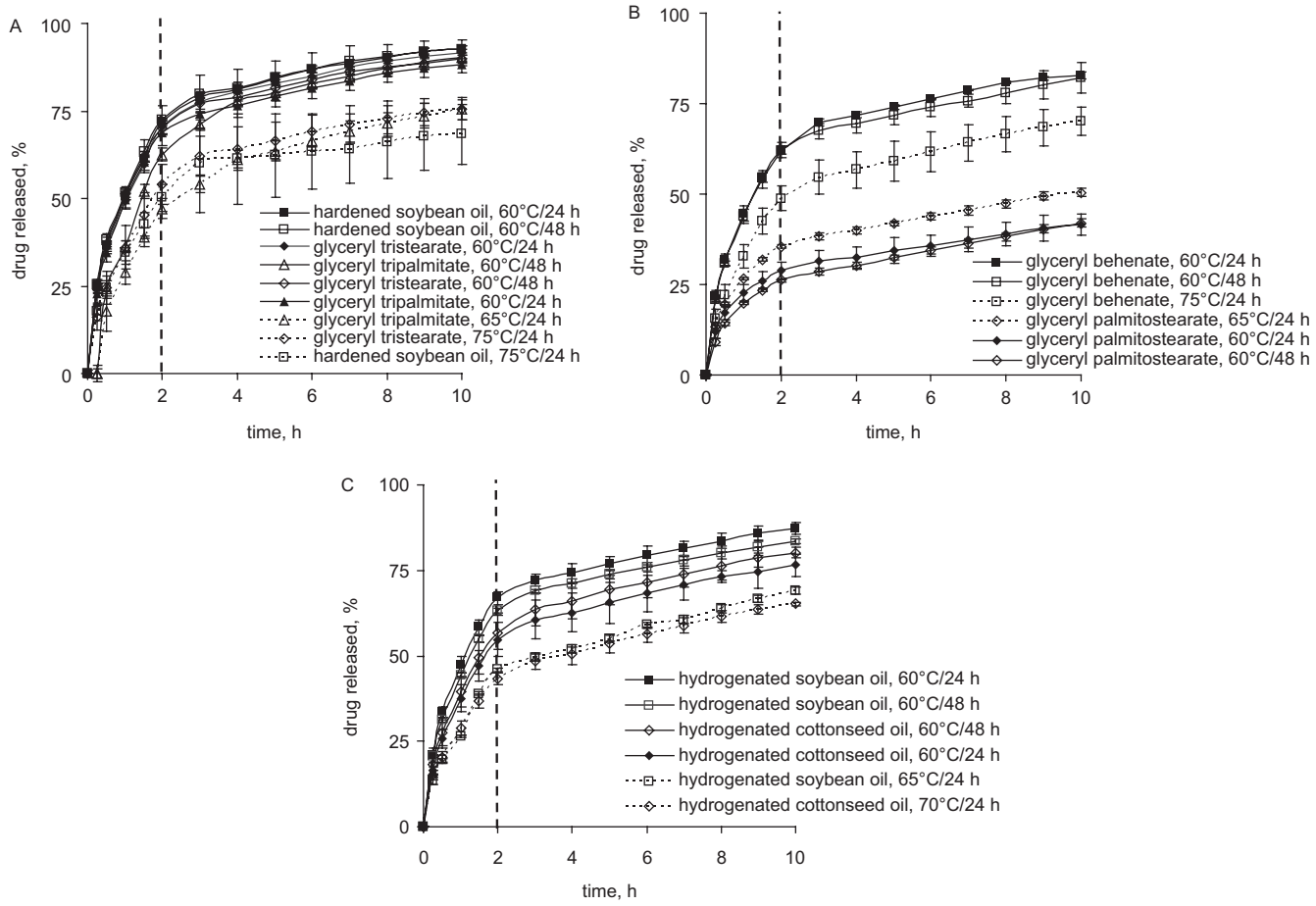

Figure 7. 5-ASA release from mini tablets consisting of 50% drug, 15% Nutriose and 35% lipid: (A) glyceryl tripalmitate, glyceryl tristearate, or hardened soybean oil, (B) glyceryl behenate or glyceryl palmitostearate, (C) hydrogenated cottonseed or hydrogenated soybean oil. Drug release was measured in 0.1 N HCl for 2 h and phosphate buffer pH 6.8 for 8 h. The curing conditions are indicated in the diagrams. All tablets were prepared by direct compression.

Nutriose and 35% glyceryl palmitostearate. The systems were cured for 3 min at 90°C, followed by 7 days, 14 days or 1 month at 40°C, or by 12, 24 or 48 h at 60°C. For reasons of comparison, also 5-ASA release from mini tablets cured for 24 h at 60°C is shown. Clearly, the release rate was not very much affected by the curing conditions, except for the 1-month curing. As the latter is difficult to realize at an industrial scale and as the release rate still remains considerable, this approach was not further investigated.

Since the distribution of the lipid within the mini tablets can be expected to significantly alter its ability to hinder drug release, four different preparation techniques were studied, which are likely to result in a more or less intense embedding of the drug within the glyceryl palmitostearate: (i) direct compression, (ii) partial melt granulation and compression, (iii) separate melt granulation and compression, and (iv) melt granulation and compression. In the case of "partial melt granulation and compression", 5-ASA, Nutriose and 60% of the glycerol palmitostearate were molten at 85°C on a water bath, cooled down to room temperature, ball milled and sieved (fraction 50–100 μm). The obtained powder was blended with the remaining glyceryl palmitostearate and compressed. In the case of "separate melt granulation and compression", glyceryl palmitostearate and Nutriose were blended in equal parts and molten at 85°C on a water bath. The remaining glyceryl palmitostearate was blended with the drug, and also

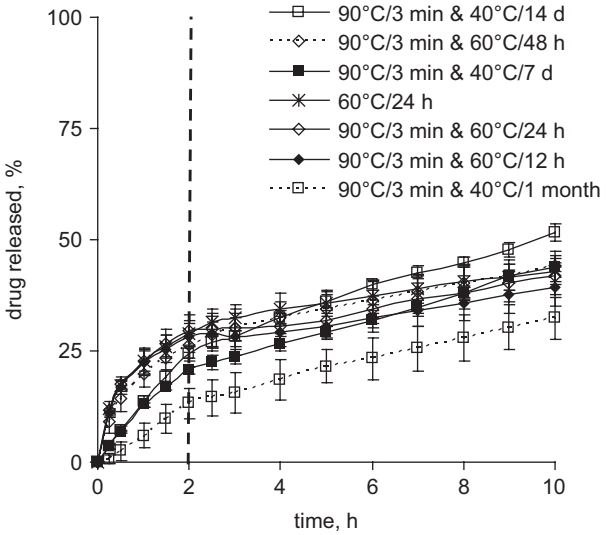

Figure 8. Effects of the curing conditions on 5-ASA release from mini tablets consisting of 50% drug, 15% Nutriose and 35% glyceryl palmitostearate in 0.1 N HCl (for 2 h) and phosphate buffer pH 6.8 (for 8 h). All tablets were prepared by direct compression.

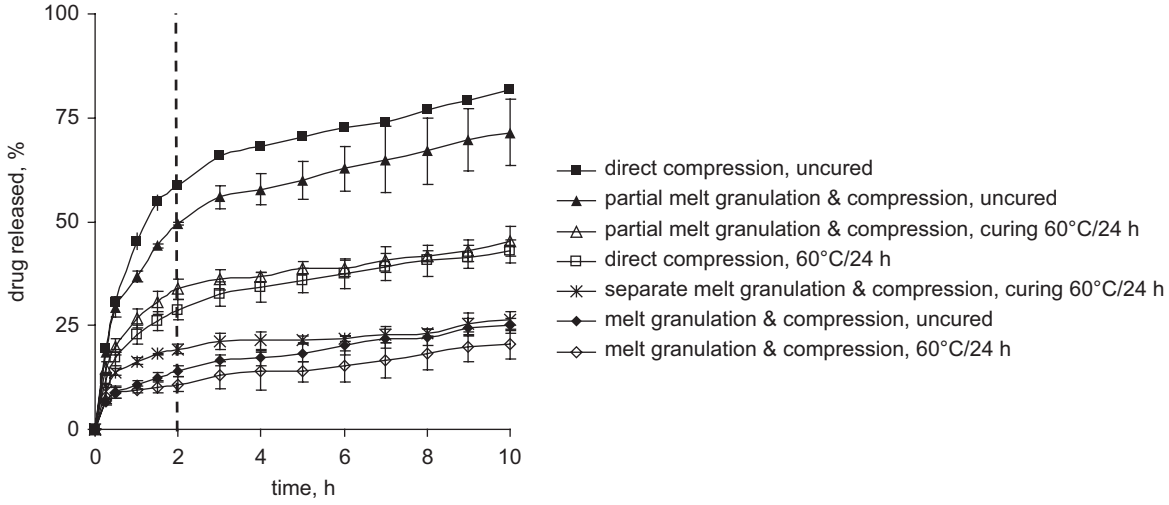

Figure 9. Effects of the type of preparation method: direct compression versus partial melt granulation and compression vs. separate melt granulation and compression vs. melt granulation and compression. Details on the different preparation methods are given in the text. The mini tablets consisted of 50% drug, 15% Nutriose and 35% glyceryl palmitostearate. The release medium was 0.1 N HCl during the first 2 h, followed by phosphate buffer pH 6.8 during the subsequent 8 h.

this blend was molten at 85°C on a water bath. Both melts were cooled down to room temperature, ball milled, sieved (fraction 50–100 μm), blended and compressed. In the case of "melt granulation and compression", all compounds were molten together at 85°C on a water bath, cooled down to room temperature, ball milled, sieved (fraction 50–100 μm) and compressed. The mini tablets were optionally cured for 24 h at 60°C. As it can be seen in Figure 9, the drug release rate decreased in the following ranking order: direct compression > partial melt granulation and compression > separate melt granulation and compression > melt granulation and compression. This was true for uncured as well as for cured mini tablets and can probably be attributed to a more and more intense embedding of the drug within the lipid.

As also chitosan has been reported to allow for site-specific drug delivery to the colon[40–42], the partial substitution of glyceryl palmitostearate by chitosan was studied. Figure 10 shows drug release from mini tablets consisting of 50% ASA, 15% Nutriose, 30% glyceryl palmitostearate and 5% chitosan. For reasons of comparison, also drug release from mini tablets free of chitosan (containing 35% glyceryl palmitostearate) is shown. All systems were prepared by melt granulation and compression. The tablets were either uncured or cured for 24 h at 60°C (as indicated). Clearly, the presence of only 5% chitosan significantly increased the resulting drug release rate, leading to undesired, premature drug release. This was true for uncured as well as for cured tablets and can be attributed to the higher permeability of the hydrogel chitosan for the low molecular weight drug 5-ASA and/or rapid leaching of this compound into the surrounding bulk fluid at low pH. It has to be pointed out that an enteric coating can avoid an undesired dissolution of chitosan at low pH. However, as the objective of this work was to optimize non-coated multiparticulates, only Nutriose was maintained as "colon targeting compound" in this work.

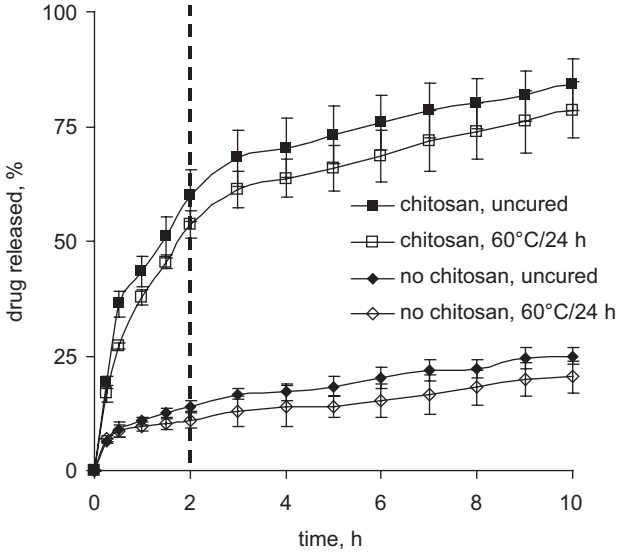

Figure 10. Effects of the replacement of 5% glyceryl palmitostearate by chitosan on 5-ASA release from mini tablets (prepared by melt granulation and compression). The systems consisted of 50% drug, 15% Nutriose and 35% glyceryl palmitostearate [5% of which was replaced by chitosan, if indicated]. The release medium was 0.1 N HCl during the first 2 h, followed by phosphate buffer pH 6.8 during the subsequent 8 h.

Figure 11 shows the effects of the Nutriose content (while keeping the "Nutriose + glyceryl palmintostearate content" constant at 50%) and of the curing conditions on the resulting drug release kinetics from mini tablets prepared by melt granulation and compression upon exposure to 0.1 N HCl for 2 h and subsequent exposure to phosphate buffer pH 6.8 for 8 h. The Nutriose content was increased from 15% to 25% (while the glyceryl palmitostearate content was decreased from 35% to 25%), the tablets were optionally cured for 24 or 48 h at 60°C (as indicated). As it can be seen, the release rate increased with increasing Nutriose content, because

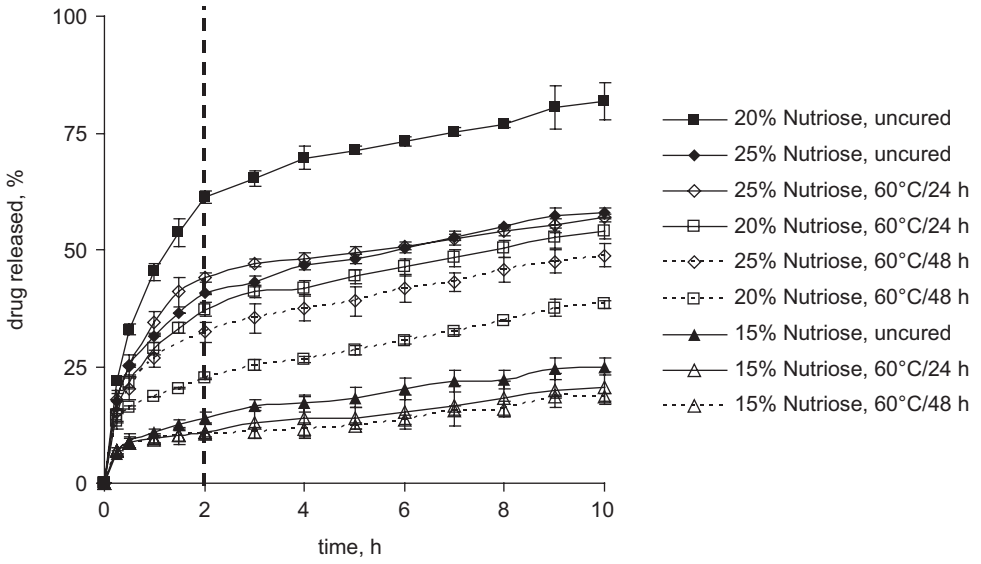

Figure 11. Impact of the Nutriose content and curing conditions on 5-ASA release from mini tablets containing 50% drug and 50% "Nutriose + glyceryl palmitostearate" in 0.1 N HCl (for 2 h) and phosphate buffer pH 6.8 (for 8 h). The curing conditions are indicated in the diagram. All tablets were prepared by melt granulation and compression.

glyceryl palmitostearate is more effectively hindering drug release than Nutriose. Note that Nutriose is more effectively hindering drug release than chitosan in this type of dosage forms: When comparing 5-ASA release from mini tablets cured for 24 h at 60°C, containing 50% drug, 30% glyceryl palmitostearate and 20% Nutriose (open squares and solid curves in Figure 11) vs. 15% Nutriose + 5% chitosan (open squares in Figure 10), it can be seen that drug release was slower in the case of 20% Nutriose. Furthermore, the release rate decreased with increasing curing temperature and time, irrespective of the Nutriose content (Figure 11). Importantly, at a Nutriose level of 15%, 5-ASA release from mini tablets cured at 60°C for 24, and 48 h is virtually overlapping (open triangles: dotted and solid curves), indicating that a stable system is likely to be achieved. Thus, mini tablets consisting of 50% 5-ASA, 15% Nutriose and 35% glyceryl palmitostearate prepared by melt granulation and compression and subsequent curing for 24 h at 60°C show an interesting potential for colon specific drug delivery.

Conclusions

The presented non-coated matrix pellets and mini tablets contain high doses of 5-ASA and effectively minimize drug release in media simulating the transit through the upper GIT. Containing the starch derivative Nutriose, which is known to be degraded by bacterial enzymes present in the colon of inflammatory bowel disease patients, they can be expected to show an interesting potential for site-specific drug delivery to the colon in the disease state. The absence of a film coating simplifies industrial production. Being multiparticulates, the all-or-nothing effect of single unit dosage forms is avoided and a more homogeneous spreading throughout the GIT *in vivo* is highly likely.

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Declaration of interest

Two of the authors are employees of the company commercializing Nutriose.

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