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Published in:
International Journal of Pharmaceutics

DOI:
10.1016/j.ijpharm.2018.11.019

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2019

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PII: S0378-5173(18)30835-4
DOI: https://doi.org/10.1016/j.ijpharm.2018.11.019
Reference: IJP 17912

To appear in: *International Journal of Pharmaceutics*

Received Date: 17 August 2018
Revised Date: 3 November 2018
Accepted Date: 7 November 2018

Please cite this article as: B. Gareb, G. Dijkstra, J.G.W. Kosterink, H.W. Frijlink, Development of novel zero-order release budesonide tablets for the treatment of ileo-colonic inflammatory bowel disease and comparison with formulations currently used in clinical practice, *International Journal of Pharmaceutics* (2018), doi: https://doi.org/10.1016/j.ijpharm.2018.11.019

Title

Development of novel zero-order release budesonide tablets for the treatment of ileo-colonic inflammatory bowel disease and comparison with formulations currently used in clinical practice

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Keywords

ColoPulse, budesonide, IBD, drug targeting, ileo-colonic

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abbreviations

$AUC_{0\text{-}24h}$: Area under the curve during 24 hours

CD: Crohn's disease

CS: croscarmellose sodium

CV: coefficient of variation

ECCO: European Crohn's and Colitis Organisation

GI: gastrointestinal

GISS: gastrointestinal simulation system

GIT: gastrointestinal tract

HPMC: hydroxypropyl methylcellulose

IBD: inflammatory bowel disease

MAN: mannitol

MC: microcrystalline cellulose

MMX: Multi-Matrix system

PEG: polyethylene glycol

SSF: sodium stearyl fumarate

UC: ulcerative colitis

Abstract

Up to 50% of Crohn's disease and ulcerative colitis patients suffer from ileo-colonic inflammation. Topically delivered budesonide is an effective treatment but *in vitro* as well as clinical data suggest that oral formulations currently used in clinical practice are not optimal to treat the ileo-colon. The aim of this *in vitro* study was to develop ileo-colonic-targeted zero-order sustained-release tablets containing 3 mg or 9 mg budesonide. Targeted delivery was achieved by coating the tablets with the ColoPulse technology (ColoPulse 3 mg or ColoPulse 9 mg, respectively). Tablet were tested in a 10-h gastrointestinal simulation system for site-specific release, zero-order release kinetics ($R^2 \geq 0.950$), release rate, and completeness of release (≥80%). Release profiles of the novel formulations were compared with Entocort, Budenofalk, and Cortiment (budesonide MMX). ColoPulse 3 mg and 9 mg were targeted to the simulated ileo-colon, budesonide release was complete and in a sustained zero-order manner, and both formulations complied with a 6-month accelerated stability study. None of the formulations currently used in clinical practice targeted the ileo-colon. These *in vitro* results are discussed in light of clinical data. ColoPulse 3 mg and 9 mg are novel interesting formulations for the treatment of the entire ileo-colon in inflammatory bowel disease.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are debilitating inflammatory bowel diseases (IBD). Both are chronic diseases affecting the gastrointestinal tract (GIT) and are characterized by their relapsing behavior. CD is characterized by transmural inflammation and can affect the entire GIT whereas in UC the inflammation is limited to the mucosa and can affect the rectum and colon. The exact pathogenesis of IBD is not completely elucidated but it is thought to be the result of an aberrant immune response of a genetically susceptible host against the hosts commensal gut microflora. This abnormal immune response involves both branches of the innate and adaptive immune system (Foersch et al., 2013), both contributing to tissue injury as a result of excessive production of pro-inflammatory mediators such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α). A prolonged inflammatory response against the gut epithelium may result in epithelial injury and therefore could lead to increased exposure to the gut microflora, amplifying the immune response (Abraham and Cho, 2009; Baumgart and Sandborn, 2012; Danese and Fiocchi, 2011; Ungaro et al., 2017). Therefore, anti-inflammatory and immune suppressive drugs that attenuate the aberrant immune and inflammatory response are efficacious is IBD. The choice of treatment depends on disease severity and location. Therapy aims to induce and thereafter maintain remission (Gomollón et al., 2017; Harbord et al., 2017). Approximately 50% of CD patients suffer from ileo-colonic inflammation and up to 45% of UC patient suffer from extensive colitis in which the entire colon can be affected (Peppercorn and Kane, 2018; Ungaro et al., 2017).

The European Crohn's and Colitis Organisation (ECCO) states that oral budesonide is the first-line treatment for mild-to-moderately active ileo-colonic CD. Oral budesonide is currently only advised in left-sided and extensive UC if aminosalicylate therapy fails

(Gomollón et al., 2017; Harbord et al., 2017). Budesonide is a potent glucocorticosteroid possessing a broad range of anti-inflammatory properties (Clark, 2007; Prantera, 2013; Rhen and Cidlowski, 2005). Due to its extensive first-pass metabolism by the gut mucosa and liver, budesonide acts primarily topically in the GIT with substantially less systemic side effects compared to traditional glucocorticosteroid (Kuenzig et al., 2014; Rezaie et al., 2015; Sherlock et al., 2015). To achieve local drug delivery in the distal inflamed GIT, budesonide release from oral formulations must be modified. In addition, since the inflammation in IBD is more often than not diffuse, drug release should cover the entire inflamed region instead of just one site. This can only be realized through a sustained drug release profile targeting the inflamed region during gastrointestinal (GI) transit. However, a major disadvantage of this approach is incomplete drug release from the formulation due to faster transit times as a result of frequent bowel movements, which is a common symptoms of active IBD. (Abraham and Cho, 2009; Baumgart and Sandborn, 2012; Ungaro et al., 2017).

Commercially available oral budesonide formulations apply different strategies to target the site of inflammation. Table 1 shows the oral budesonide formulations currently used in clinical practice (Kuenzig et al., 2014; Rezaie et al., 2015; Sherlock et al., 2015). These formulations are generally modified-release cores or granules coated with a pH-sensitive polymer. They intend to treat specific parts of the GIT. Table 1 shows that the *in vitro* data do not correlate well with the observed clinical data. *In vitro-in vivo* correlation is challenging and depends on several factors such as physiochemical properties of the drug, formulation, and type of *in vitro* model (Dressman and Reppas, 2000; Goyanes et al., 2015b; Lu et al., 2011). However, *in vitro* as well as clinical data suggest that these formulations are not optimally suited to treat the entire ileo-colon in IBD. Furthermore, none of these formulations is suited to treat the colon descendens. These observations imply that a great portion of IBD

patients may benefit from a novel oral budesonide formulation that aims to treat the entire ileo-colon.

The ColoPulse technology is an innovative coating that is characterized by the incorporation of a superdisintegrant in the coating matrix to yield fast and site-specific coating disintegration. This coating was developed to specifically target the ileo-colonic region in humans. Previously, we have shown with stable isotope experiments and through comparative profiling with the IntelliCap capsule that ColoPulse-coated tablets and capsules target the ileo-colon in healthy subjects as well as CD patients. Additionally, food and time of food intake did not substantially influence the targeting performance in healthy subjects and CD patients (Maurer et al., 2015, 2013, 2012, Schellekens et al., 2010, 2009).

The aim of this *in vitro* study was to develop novel zero-order sustained-release tablets containing 3 mg or 9 mg budesonide intended to treat the entire ileo-colon in IBD. The target product profile is given in table 2. The desired release profile was characterized by site-specific drug release followed by a sustained release rate ensuring the treatment of left-sided colitis as well. The novel formulations were compared with all oral budesonide formulations currently used in clinical practice.

Table 1: Overview of all oral budesonide formulations currently used in clinical practice for the treatment of IBD.

Formulation	Technology	Intend to treat	Clinical data	*In vitro* data
Entocort 3 mg	Sustained release granules coated with pH-dependent coating (pH threshold >5,5)	Ileum and colon ascendens	40% absorbed in ileum and colon ascendens (SmPC, 2017a).	80-90% released in jejunum. 10-20% in ileo-colon. First-order release (Goyanes et al., 2015a; Klein et al., 2005).
Budenofalk 3 mg and 9 mg	Granules coated with pH-dependent coating (pH threshold >6,0)	Ileum and colon ascendens	70% absorbed in ileum and colon ascendens (SmPC, 2017b).	95% immediately released in distal jejunum/proximal ileum (Klein et al., 2005).
Cortiment (MMX) 9 mg	Sustained release tablet coated with pH-dependent coating (pH threshold >7,0)	Entire colon	Only 42% initial tablet disintegration observed in ileum; 96% of released dose absorbed in colon. However, released dose is highly variable and estimated to be small (Brunner et al., 2006).	Slow and incomplete release. Only 7% to 30% of dose released in colon (Gareb et al., 2016; Goyanes et al., 2015a).

Table 2: Target product profile for ColoPulse 3 mg and 9 mg budesonide formulations. The requirements to comply with the accelerated stability study (6 months at 40 °C/75% RH) were the same.

Parameter	Requirement
Content	95-105% of dose
Lag time	≤5% released at t240 min in GISS (end of simulated jejunum, start of simulated ileum)
Completeness of release[a]	≥80% at t600 min in GISS (6 h in simulated ileo-colon)
Release kinetics	Correlation coefficient: R^2 ≥0.950[b]
Uncoated tablet mass	300 mg
Applied coating[c]	5 mg/cm^2
Tablet shape	Biconvex, round, 9 mm

a: Desired release was ≥80% after 300 min at pH 6 for non-coated tablet cores (Ph. Eur., 2018a).
b: To comply with zero-order release kinetics, coefficient was arbitrarily set to ≥0.950.
c: Expressed as mg Eudragit S100 per cm^2

2. Material and methods

2.1 Chemicals

Budesonide (Sofotec Almirall, Bad Homburg, Germany), methacrylic acid–methyl methacrylate copolymer 1:2 (Eudragit S100, Evonik, Essen, Germany), hydroxypropyl methylcellulose (HPMC, Sigma-Aldrich, St. Louis, USA), polyethylene glycol 6000 (PEG 6000, Fagron, Capelle aan de IJssel, The Netherlands), sodium stearyl fumarate (SSF, JRS Pharma, Rosenberg, Germany), methanol (Biosolve, Dieuze, France), acetone, sodium hydroxide, hydrochloric acid 37% (VWR, Fontenay-sous-Bois, France), talc, potassium dihydrogen phosphate, sodium chloride (Spruyt-Hillen, IJsselstein, The Netherlands), croscarmellose sodium (CS, FMC, Brussels, Belgium), sodium dihydrogen phosphate dihydrate, disodium monohydrogen phosphate dihydrate (Merck, Darmstadt, Germany), microcrystalline cellulose (MC, DMV Fonterra Excipients, Foxhol, The Netherlands), mannitol (Roquette, Nord-Pas-de-Calais, France), Cortiment 9 mg (budesonide MMX, Ferring Pharmaceuticals, Hoofddorp, The Netherlands, lot LI114), Budenofalk 3 mg capsules (Dr. Falk Pharma Benelux B.V., Breda, The Netherlands, lot 16D18706L), Budenofalk 9 mg granules (Dr. Falk Pharma GmbH, Freiburg, Germany, lot 17A11778L), and Entocort 3 mg (Tillotts Pharma GmbH, Rheinfelden, Germany) were all used as received from their respective suppliers.

2.2 Target product profile and product development

The desired formulation was obtained by first developing different uncoated tablet cores containing 9 mg budesonide. Release profiles of these cores were tested in dissolution

medium pH 6, the assumed average pH of the colon (Freire et al., 2011; McConnell et al., 2008; Nugent et al., 2001; Press et al., 1998; Schellekens et al., 2007). Subsequently, the same formulation containing 3 mg budesonide was produced and investigated to ensure similar release profiles for both doses. Both formulations were tested for tablet hardness and friability. Thereafter, both formulations were coated with the ColoPulse coating and release profiles were investigated in the gastrointestinal simulation system (GISS). Release profiles of the oral budesonide formulations currently used in clinical practice (table 1) were investigated in the GISS as well and compared to the novel formulations. Finally, stability and product integrity of the novel formulations were investigated in a 6-months accelerated stability study (ICH, 2003).

Table 3 shows the composition of the different formulations. HPMC was used as the polymer hydrogel matrix for the sustained release of budesonide. It is cheap, easy to process, and non-toxic and therefore a suitable excipient in controlled-release formulations (Li et al., 2005). MAN and MC were respectively used as water-soluble and water-insoluble fillers as well as excipients to control budesonide release rate. Both excipients are cheap, have good flowability, and are widely applied in pharmaceutical formulations. SFF was added as the lubricant due to good blending characteristics, less sensitivity to overblending, and high degree of drug compatibility (JRS Pharma, 2018). The tablet cores with the desired release profile were coated with the ColoPulse coating to target the simulated ileo-colon (Maurer et al., 2013).

2.3 Tablet cores

Dry powder mixtures were blended in a Turbula mixer (Bachoven, Basel, Switzerland) at 90 rpm. All excipients (except SSF) were mixed for 10 min. Subsequently, SSF was added and

mixed for an additional 2 min. Biconvex 9 mm tablets of 300 mg were compacted at 20 kN with a rate of 2 kN/s (Instron, Norwood, USA).

Table 3: Composition of all the produced formulations. ColoPulse coating is expressed as mg Eudragit S100 per cm^2. HPMC: hydroxypropyl methylcellulose. MAN: mannitol. MC: microcrystalline cellulose. SSF: sodium stearyl fumarate.

Formulation	Budesonide (mg)	Excipients (%)	ColoPulse coating
10/90-HPMC/MAN 9 mg	9	9,5% HPMC, 89,5% MAN, 1% SSF	No
10/90-HPMC/MC 9 mg	9	9,5% HPMC, 89,5% MC, 1% SSF	No
15/85-HPMC/MAN 9 mg	9	14,5% HPMC, 84,5% MAN, 1% SSF	No
23/77-HPMC/MAN 3 mg	3	22,5% HPMC, 76,5% MAN, 1% SSF	No
23/77-HPMC/MAN 9 mg	9	22,5% HPMC, 76,5% MAN, 1% SSF	No
50/50-HPMC/MAN 9 mg	9	49,5% HPMC, 49,5% MAN, 1% SSF	No
ColoPulse 3 mg	3	22,5% HPMC, 76,5% MAN, 1% SSF	5 mg/cm^2
ColoPulse 9 mg	9	22,5% HPMC, 76,5% MAN, 1% SSF	5 mg/cm^2

2.4 Tablet coating

Tablet cores were coated with the ColoPulse coating. The coating suspension consisted of Eudragit S100/PEG 6000/CS/talc in a ratio of 7/1/3/2 (w/w) in a solvent mixture of acetone/water 97/3 (v/v). First, PEG600 was gently heated until it was completely melted and acetone was added. This mixture was stirred until PEG 6000 dissolved in acetone. Thereafter, Eudragit S100 was added and dissolved in the mixture. Finally, CS and talc was added, resulting in the coating suspension. Tablet cores in a mini-rotating drum were continuously sprayed with the coating suspension. A hot air blower was aimed at the mini-rotating drum for mild heating to induce solvent mixture evaporation and film formation.

2.5 Tablet hardness and friability tests

Tablet hardness and friability were investigated for the uncoated and coated formulations with the desired release profiles. Tablet hardness was determined with a tablet hardness tester (Erweka, Heusenstamm, Germany). Friability was tested as described in the Ph. Eur. in a friability apparatus (Erweka, Heusenstamm, Germany). Twenty-two tablets (mass of 6.6 g) and 20 tablets (mass of 6.5 g) were used per friability experiment for the uncoated and coated tablets, respectively (Ph. Eur., 2018b).

2.6 Budesonide dissolution at pH 6

An USP dissolution apparatus II (Sotax, Basel, Switzerland) was used for all dissolution experiments. Dissolution medium, medium temperature, and paddle speed were 1 L phosphate buffer pH 6 (67 nM), 37 ºC, and 50 rpm respectively. Before each experiment pH was measured, and if needed, adjusted to ensure the right pH. Budesonide release profiles of the produced formulation were determined by an online UV-VIS spectrophotometer (Thermo Fisher, Madison, USA) equipped with 10-mm cuvettes measured at a wavelength of 247 nm.

2.7 GISS

The GISS simulates GI transit in a simple *in vitro* model and is described in detail elsewhere (Schellekens et al., 2007). It simulates transit through stomach (pH 1.2 for 2 h), jejunum (pH 6.8 for 2 h), ileum (pH 7.5 for 30 min), and colon (pH 6 for 5.5 h). The same dissolution apparatus, medium temperature, and paddle speed were applied as described in section 2.6. Medium constituent and volume were variable as buffers were added for the pH change.

Initial volume was 500 mL (stomach) and end volume was 1000 mL (colon). Before and during the experiments pH was measured, and adjusted if needed, to ensure the right pH.

Budesonide release profiles from the ColoPulse formulations were determined by an online UV-VIS spectrophotometer equipped with 10-mm cuvettes measured at a wavelength of 247 nm. Budesonide release profiles from the commercially available formulations were determined by reversed-phase HPLC (Zorbax Extend-C18, Agilent Technologies, USA) coupled to UV detection (Dionex, Germering, Germany) since the formulation excipients interfered with UV-VIS analysis (data not shown). Wavelength, injection volume, flow rate, column temperature, run time, and mobile phase were 244 nm, 50 µL, 1.0 ml/min, 22 ºC, 5 min, and methanol/water 80/20 (v/v), respectively.

2.8 Accelerated stability study

ColoPulse tablets containing 3 mg or 9 mg budesonide packed in polypropylene containers were placed at 40 ºC and 75% RH. Tablets were tested for content and release profile in the GISS at t0 months, t3 months, and t6 months (ICH, 2003). The requirements to comply with the stability study are depicted in table 2. GISS experiments were conducted as described in section 2.7. For the content analysis, a tablet was placed in a 500.0-ml volumetric flask filled with methanol/water 80/20 (v/v). This was stirred overnight, filtered through a 0.45-µm filter, and analyzed by the HPLC method described in section 2.7.

2.9 Calculations

The correlation coefficient (R^2) was calculated by the least squares methods. R^2 was calculated from t0 min till t300 min for the dissolution experiments at pH 6. R^2 was calculated

from the first point (0% release) before initial release was observed till t600 min during the GISS experiments.

3. Results

3.1 Tablet cores

Figure 1 shows the release profiles of the five different formulations containing 9 mg budesonide in dissolution medium pH 6. Table 4 summarizes the release characteristics of these formulations. The release profiles of 10/90-HPMC/MAN 9 mg and 15/85-HPMC/MAN 9 mg showed complete budesonide release from these formulations but could not be classified as zero-order (86% release with R^2=0.520 and 89% release with R^2=0.836, respectively). The release profile of 50/50-HPMC/MAN could be classified as zero-order (R^2=1.00). However, budesonide release from this formulation was slow and incomplete (30%). Budesonide release from 10/90-HPMC/MC 9 mg was the lowest (16%) and could not be classified as zero-order (R^2=0.886). Formulation 23/77-HPMC/MAN 9 mg had the desired release profile as release was complete (81%) and could be classified as zero-order (R^2=0.954). The 3 mg budesonide core with the same formulation (23/77-HPMC/MAN 3 mg) showed similar release characteristics. Budesonide release from this formulation was complete (100%) and could be classified as zero-order (R^2=0.989) as well. Both formulations 23/77-HPMC/MAN 9 mg and 23/77-HPMC/MAN 3 mg complied with the friability tests and tablet hardness was on average 202 N (range 195-210 N).

The 23/77-HPMC/MAN 3 mg and 23/77-HPMC/MAN 9 mg formulations were coated with 5 mg/cm^2 of ColoPulse coating, resulting respectively in the ColoPulse 3 mg and ColoPulse 9 mg formulations.

[INSERT FIGURE 1 HERE]

Table 4: Summary of the release characteristics of the different produced tablet cores. Release profiles are shown in figure 1. t300 min: mean±SD (n=3) percentage of budesonide dose released at time point 300 min. R^2: correlation coefficient. N.a.: not applicable.

Formulation	R^2	t300 min (%)	Hardness (N)[a]	Friability (%)[b]
10/90-HPMC/MAN 9 mg	0.520	86±2	N.a	N.a.
10/90-HPMC/MC 9 mg	0.886	16±6	N.a	N.a.
15/85-HPMC/MAN 9 mg	0.836	89±3	N.a	N.a.
23/77-HPMC/MAN 3 mg	0.989	100±3	200 (195-205)	0.08
23/77-HPMC/MAN 9 mg	0.954	81±4	204 (197-210)	0.10
50/50-HPMC/MAN 9 mg	1.00	30±1	N.a	N.a.

a: average (range).
b: Requirement is <1% (Ph. Eur., 2018b).

3.2 GISS

Figure 2 shows the release profiles of ColoPulse 3 mg, Entocort 3 mg, and Budenofalk 3 mg in the GISS. Table 5 summarizes the release characteristics of these formulations. ColoPulse 3 mg did not release any budesonide in the simulated stomach and release in the simulated jejunum was negligible (3%). Coating disintegration in the simulated ileum was rapid and complete, resulting in zero-order sustained-release (R^2=0.988) of budesonide throughout the entire simulated ileo-colon. Release in the simulated ileum and colon was respectively 17% and 84%. The release was complete (104%) with a constant release rate of 0.5 mg/h. This formulation complied with the friability test and had an average hardness of 423 N (table 6). Release from Entocort 3 mg started in the simulated jejunum and was not zero-order (R^2=0.733). Release before the simulated ileum was 77% and only 24% of the dose was released in the simulated ileo-colon with a time-dependent release rate. Budesonide release from Budenofalk 3 mg in the simulated stomach was negligible (2%). This formulation released 17% in the simulated jejunum. In the simulated ileum, the bulk of the dose (74%) was immediately released. Consequently, no substantial release was observed in the simulated colon. Release from Budenofalk 3 mg was not zero-order (R^2=0.781).

Figure 3 shows the release profiles of ColoPulse 9 mg, Budenofalk 9 mg, and Cortiment 9 mg in the GISS. Table 5 summarizes the release characteristics of these formulations. Release from ColoPulse 9 mg before the simulated ileum was negligible (2%). Release started in the simulated ileum and was zero-order (R^2=0.980) and sustained throughout the entire simulated ileo-colon. In the simulated ileum, 9% was released whereas 74% was released in the simulated colon. Release was complete (85%) with a constant release rate of 1.2 mg/h. This formulation complied with the friability test and had an average hardness of 424 N (table 6). Budenofalk 9 mg had, as expected, a similar non-zero-order (R^2=0.798) release profile as Budenofalk 3 mg. This formulation also had negligible release in the simulated stomach (1%), released 12% in the simulated jejunum, and released the

[INSERT FIGURE 2 HERE]

[INSERT FIGURE 3 HERE]

Table 5: Summary of release characteristics of the different formulations in the GISS. Release profiles are depicted in figure 2 and 3. Budesonide release is expressed as percentage (mean±SD) of dose released in simulated region (n=3). R^2: zero-order correlation coefficient.

Formulation	R^2	Stomach (%)	Jejunum (%)	Ileum (%)	Colon (%)	Total (%)
Entocort 3 mg	0.733	1±0	76±2	16±5	8±4	101±5
Budenofalk 3 mg	0.781	2±2	17±3	74±9	7±3	100±2
ColoPulse 3 mg	0.988	0±0	3±0	17±2	84±3	104±3
Cortiment 9 mg	0.984	0±0	0±0	0±0	6±1	6±1
Budenofalk 9 mg	0.798	1±0	12±0	69±7	11±4	93±4
ColoPulse 9 mg	0.980	0±0	2±0	9±1	74±3	85±4

majority of the dose (69%) immediately in the simulated ileum with only 11% release in the simulated colon. Cortiment 9 mg had the lowest and slowest release. Substantial release (5%) was observed at t=540 min, 4.5 h in the simulated colon. Release at the end of the experiment was 6% and release after 24 h in the GISS was 20% (data not shown). Although release was in a sustained and zero-order manner (R^2=0.984), the release rate was extremely slow (0.10 mg/h).

3.3 Accelerated stability study

Figures 4 and 5 show the release profiles of ColoPulse 3 mg and 9 mg from the accelerated stability study. Table 6 summarizes the release characteristics, content, friability, and hardness results of these formulations. The release profiles of ColoPulse 3 mg as well as ColoPulse 9 mg did not differ substantially at t0 months, t3 months, and t6 months. Release started in the simulated ileum and showed zero-order release kinetics (range R^2=0.975-0.988) throughout the simulated ileo-colon. Furthermore, release was complete (range 81-104%) for both formulations. Tablet hardness and friability did not change substantially during the stability study. Finally, all content values during the different time points were within the 95-105% range.

[INSERT FIGURE 4 HERE]

[INSERT FIGURE 5 HERE]

Table 6: Summary of the release characteristics (n=3), content (n=3), friability, and hardness results (n=3) of ColoPulse 3 mg and 9 from the accelerated 6-month stability study at 40 ºC/75% RH. R^2: correlation coefficient. t240 min: mean±SD percentage of budesonide dose released at time point 240 min (end of simulated jejunum, start of simulated ileum). t600 min: mean±SD percentage of budesonide dose released at time point 600 min (end of experiment, 6 h in simulated ileo-colon).

Formulation/time	Content (%)[a]	R^2	t240 min (%)	t600 min (%)	Hardness (N)[b]	Friability (%)[c]
3 mg t0 months	102 (101-103)	0.988	3±1	104±3	423 (412-430)	0.06
3 mg t3 months	100 (98-103)	0.984	3±2	102±9	430 (419-445)	0.05
3 mg t6 months	100 (97-101)	0.984	1±0	95±5	436 (429-442)	0.05
9 mg t0 months	102 (100-104)	0.980	2±0	85±4	424 (410-436)	0.05
9 mg t3 months	100 (98-102)	0.975	1±1	80±4	432 (421-444)	0.07
9 mg t6 months	100 (100-101)	0.979	1±0	81±1	429 (425-436)	0.06

a: average value as percentage of dose (range)
b: average (range)
c: Requirement is <1% (Ph. Eur., 2018b).

4. Discussion

The results showed that the newly developed ColoPulse 3 mg and 9 mg formulations met the target product profile (table 2). In view of treating ileo-colonic IBD, both formulations showed superior *in vitro* release profiles compared with the oral budesonide formulations currently used in clinical practice. The novel formulation was cheap and easy to produce from commonly applied excipient and complied with the accelerated stability study, making it a feasible new treatment option for ileo-colonic IBD.

Budesonide release from the different tablet cores could be modified by varying type and amount of excipients. Zero-order sustained and complete release was achieved by the formulation containing 23% HPMC and 77% MAN. This core formulation had a hardness of 202 N, which increased noticeably after coating. Comparing the release profiles of 10/90-HPMC/MC 9 mg and 10/90-HPMC/MAN 9 mg shows that replacing the insoluble MC by the soluble MAN substantially increased the budesonide release rate. Budesonide dissolution from 10/90-HPMC/MAN 9 mg was faster and more complete compared to 9 mg non-formulated budesonide (data not shown), even though the former contained the gel former HPMC. It is assumed that MAN hydration and dissolution combined with the water in the HPMC gel matrix aided in the wetting and solvation of the lipophilic budesonide.

The novel ColoPulse 3 mg and 9 mg formulations had similar release profiles. Negligible budesonide release before the simulated ileum was observed, indicating targeted delivery to the simulated ileo-colonic region. Furthermore, release was complete with a constant release rate throughout the simulated ileo-colon. The majority of the dose was released in the simulated ileo-colon (101% and 83% respectively). Both formulations complied with all the requirements set for the accelerated stability study and product integrity was shown by hardness and friability tests. The *in vitro* data indicate that this formulation

would be suitable to treat ileo-colonic IBD. Additionally, since release rate was constant and substantial throughout the simulated ileo-colon, the formulations might be used to treat left-sided UC, a disease currently treated with enemas (Harbord et al., 2017). Enemas have been associated with poor patient adherence and acceptance and oral treatment may therefore be more suitable for these patients (Cohen, 2006).

The *in vitro* results showed that none of the oral budesonide formulations currently used in clinical practice showed the optimal release profile for treating ileo-colonic IBD. Budenofalk 3 mg and 9 mg released a substantial amount of budesonide before the simulated ileum (~15%) and the majority of the dose (~70%) was released immediately in the simulated ileum, with only a small remainder of the dose released in the simulated colon. Although a different GI model was used, similar results have been reported elsewhere (Klein et al., 2005). Clinical data in accordance with these *in vitro* results have also been described (SmPC, 2017b), rendering this formulation only suitable to treat the inflamed ileum and proximal part of the colon, which is in accordance with the indication for Budenofalk.

Entocort 3 mg released budesonide after the simulated stomach with first-order release kinetics. The majority of the dose (77%) was released in the jejunum with the remainder released in the simulated ileum. Similar results have been observed elsewhere in different GI models (Goyanes et al., 2015a; Klein et al., 2005). However, clinical data show that 40% of the dose is absorbed in the ileum and colon ascendens, illustrating that *in vitro* results do not always correlate well with *in vivo* data (SmPC, 2017a). Still, only 40% of the dose reaching the ileum and colon ascendens is far from optimal in treating the entire ileo-colon. This formulation would be better suited to treat IBD in which the small bowel, ileum, and/or colon ascendens are affected. This is partly in accordance with the indication for Entocort as it is not registered to treat the small bowel.

Release from Cortiment 9 mg was slow and incomplete. With a release rate of 0.10 mg/h, only 20% of the dose was released after 24 h in the GISS. Slow and incomplete release has been observed as well in a dynamic *in vitro* model simulating GI transit (Goyanes et al., 2015a). In this study, total budesonide release from Cortiment 9 mg was 50% after a 10-h experiment of which 30% was released in the simulated colon. The difference in budesonide release compared to the present study could be explained by the different model used, which simulated GI transit with different buffers, volumes, and regional pH as well as transit times. Although the dynamic *in vitro* model simulated *in vivo* GI transit more accurately, budesonide release from Cortiment 9 mg was still far from complete. This formulation uses the MMX technology consisting of lipophilic and hydrophilic excipients. We hypothesized that the lipophilic budesonide rather stays in the lipophilic parts instead of dissolving in the aqueous medium. This is supported by data showing fast and complete mesalazine dissolution—a readily water soluble drug—from Mezavant, which uses the same MMX technology (Gareb et al., 2016).

Cortiment 9 mg intends to treat the entire colon during transit but the observed slow and incomplete release questions whether sufficient amounts of budesonide is released during transit to treat the inflamed area. More so as transit can be fast as a result of frequent bowel movements in active IBD. Clinical data show that the release from Cortiment 9 mg started in the ileum in only 42% of the investigated healthy subjects; release before the ileo-colonic region was observed as well. Furthermore, absorbed dose ($AUC_{0\text{-}24h}$ values), an indication of released dose, was highly variable (40% CV) (Brunner et al., 2006). Assuming linear pharmacokinetics for budesonide and based on the $AUC_{0\text{-}24h}$ of intravenously administered budesonide, we calculated that the absorbed dose was on average 0.7 mg with a range of 0.2-1 mg (Edsbäcker et al., 2003; Edsbäcker and Andersson, 2004). In case of complete release, it is expected that 0.9 mg budesonide is absorbed taking a bioavailability of 10% into account

(Edsbäcker and Andersson, 2004). The authors stated that 96% of the released Cortiment 9 mg dose was absorbed in the colon but this does not provide any insight as to how much budesonide was actually released (in mg) in the colon and what parts of the colon were actually treated by the drug (proximal, distal, or entire colon). Clinical efficacy has been shown in mild-to-moderate UC. In these studies, Cortiment 9 mg was compared to Asacol, (Balzola et al., 2012) Entocort, (Travis et al., 2014) and placebo. The therapeutic advantage was modest and it can even be questioned why a glucocorticoid was compared to low dose mesalazine (2.4 g Asacol instead of 4.8 g) in moderately active UC or a budesonide formulation with a completely different release profile (Entocort, see figure 2 and 3) (Prantera, 2014; Prantera and Scribano, 2014; Sherlock et al., 2015). We therefore think that this formulation is not optimally suited to treat ileo-colonic IBD.

The GI environment in humans is highly variable and complex. Moreover, this environment can be influenced by a plethora of factors such as the microbiome, sex, age, fed state, diseases, and drugs. GI fluid volume and composition, pH, and transit time vary greatly between and even within individuals. In humans, on average, the pH of the stomach is 1-2, which rises to 6.5-6.8 in the small bowel. Thereafter, pH rises for a short period of time to 7.5 in the ileum after which it drops to 6.0-6.5 in the colon. During colonic transit, pH rises slightly to 7. Similar pH values have been reported in IBD patients. GI transit times however are more variable and affected by disease state. This makes it impossible to accurately simulate the GI environment *in vitro* as there is not one GI environment (Freire et al., 2011; Graff et al., 2001; Haase et al., 2016; McConnell et al., 2008; Nugent et al., 2001; Press et al., 1998; Sjögren et al., 2014; Varum et al., 2013).

Thus, the limitation of our study was the use of a simple *in vitro* model. This model applies standardized simple aqueous buffers of set volumes, pH values, and standardized transit times to simulate GI transit whereas these parameters can vary greatly in humans and

505 can affect drug dissolution from a given formulation. More so from a sustained-release formulation since a faster transit time could correspond to incomplete drug release and part of the dose excreted with the feces. In addition, no efforts were made to simulate the complex composition of GI fluids, which contain enzymes, bile salts, bacteria, and other electrolytes. The GISS does not reflect the complex and highly variable GI environment (Freire et al., 510 2011; McConnell et al., 2008).

However, during the first stages of product development it aids in formulating and the comparison of different release profiles. Even though the GISS is a simple *in vitro* model, we applied it for quality assurance of ColoPulse coating performance in several clinical trials. We have shown that ColoPulse coating performance *in vitro* correlates with coating performance 515 *in vivo*, although this does not assure the same *in vivo* budesonide release profile from the novel formulations (Maurer et al., 2015, 2013, 2012, Schellekens et al., 2010, 2009). This should be investigated in a clinical trial. Therefore, we are currently preparing a clinical trial to investigate the efficacy and safety of the novel ColoPulse 3 mg and 9 mg budesonide formulations in ileo-colonic IBD.

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5. Conclusion

Based on *in vitro* data, the novel ColoPulse 3 mg and 9 mg budesonide formulations had similar release profiles. The tablets started to release budesonide in the simulated ileum and 525 release rate was constant throughout the entire simulated colon until drug release was complete. Furthermore, the formulations were shown to be stable. The *in vitro* results indicate that the oral budesonide formulations currently used in clinical practice were not optimally suited for the treatment of ileo-colonic IBD. The developed formulations are interesting

treatment options for ileo-colonic IBD. A clinical trial is needed to test the therapeutic efficacy and safety of the new formulations.

6. Acknowledgements

None.

7. Declarations of interest

None.

8. Figure captions

Figure 1: The release profiles of the different produced tablet cores (n=3) in dissolution medium pH 6. Budesonide release is expressed as percentage of the dose (mean±SD). Formulation composition is given in table 3.

Figure 2: The release profiles of Entocort 3 mg (n=3), Budenofalk 3 mg (n=3), and ColoPulse 3 mg (n=3) in the GISS. pH change over time is depicted as well. Budesonide release is expressed as percentage of the dose (mean±SD).

Figure 3: The release profiles of Cortiment 9 mg (n=3), Budenofalk 9 mg (n=3), and ColoPulse 9 mg (n=3) in the GISS. pH change over time is depicted as well. Budesonide release is expressed as percentage of the dose (mean±SD).

Figure 4: The release profiles of ColoPulse 3 mg (n=3) in the GISS at different time points during the accelerated stability study. pH change over time is depicted as well. Budesonide release is expressed as percentage of the dose (mean±SD).

Figure 5: The release profiles of ColoPulse 9 mg (n=3) in the GISS at different time points during the accelerated stability study. pH change over time is depicted as well. Budesonide release is expressed as percentage of the dose (mean±SD).

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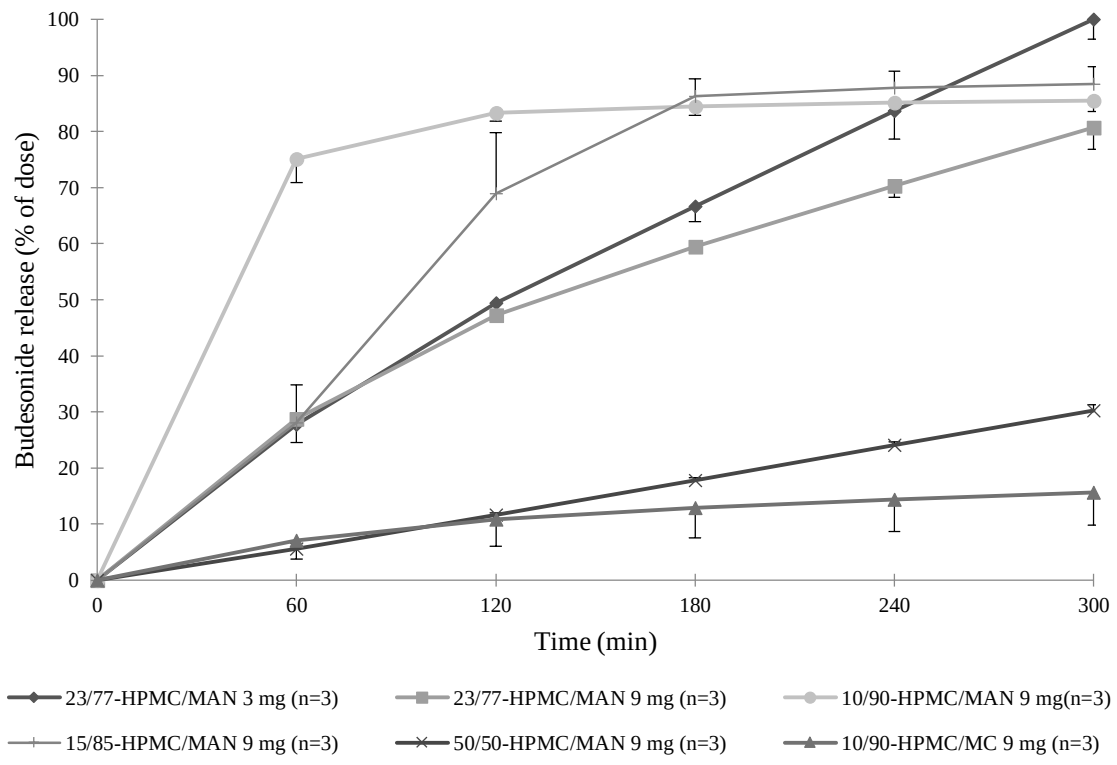

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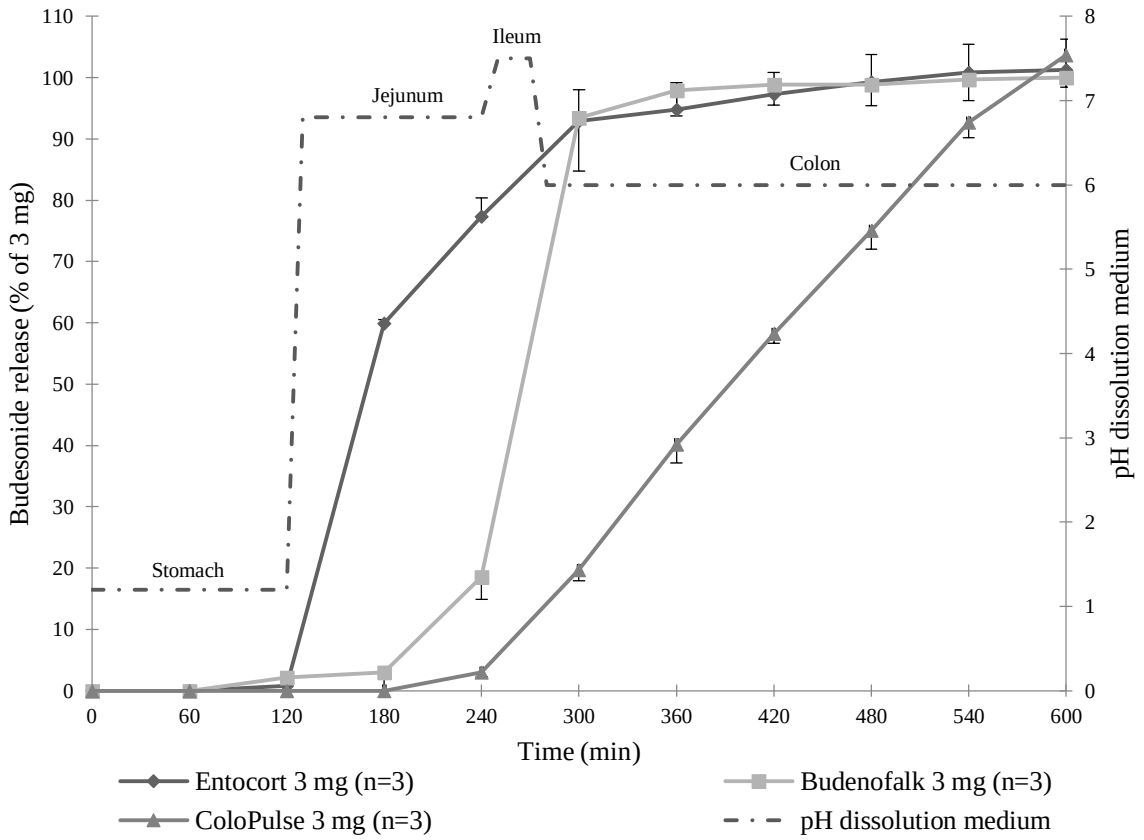

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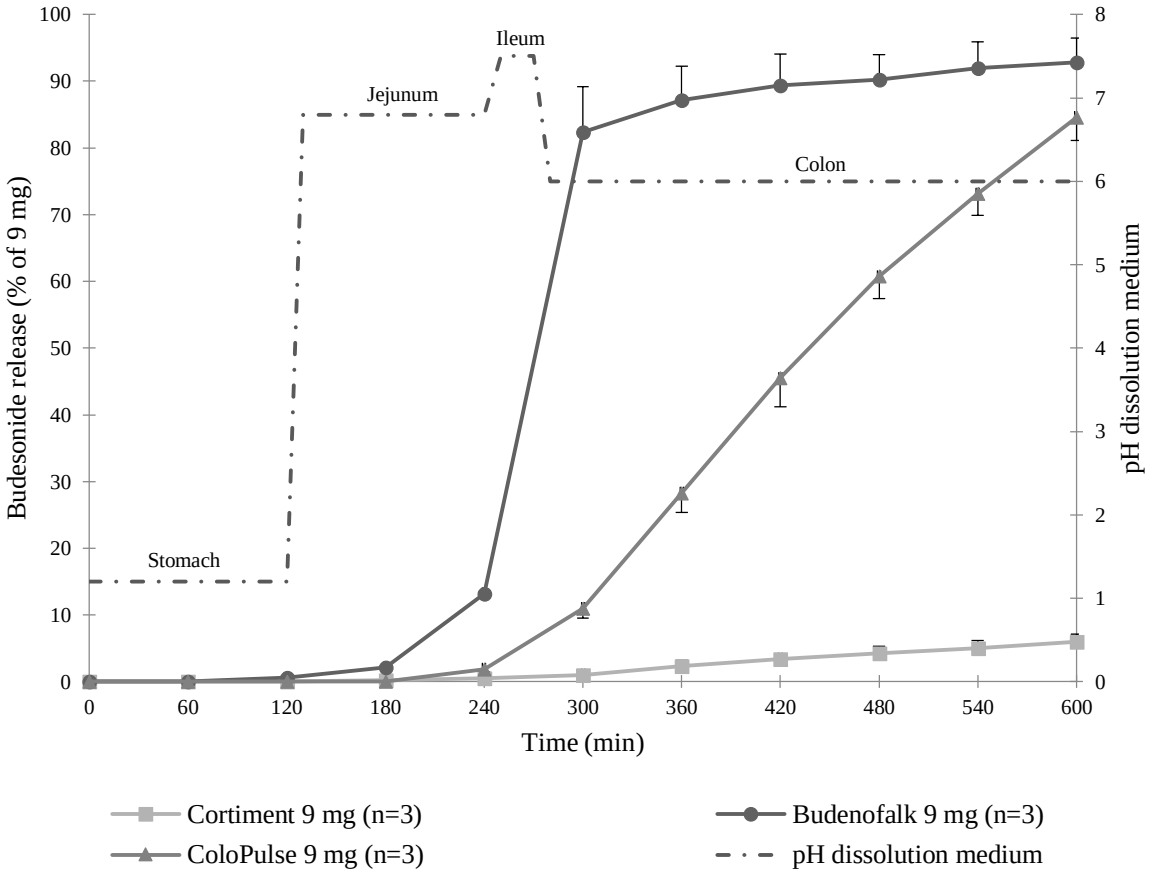

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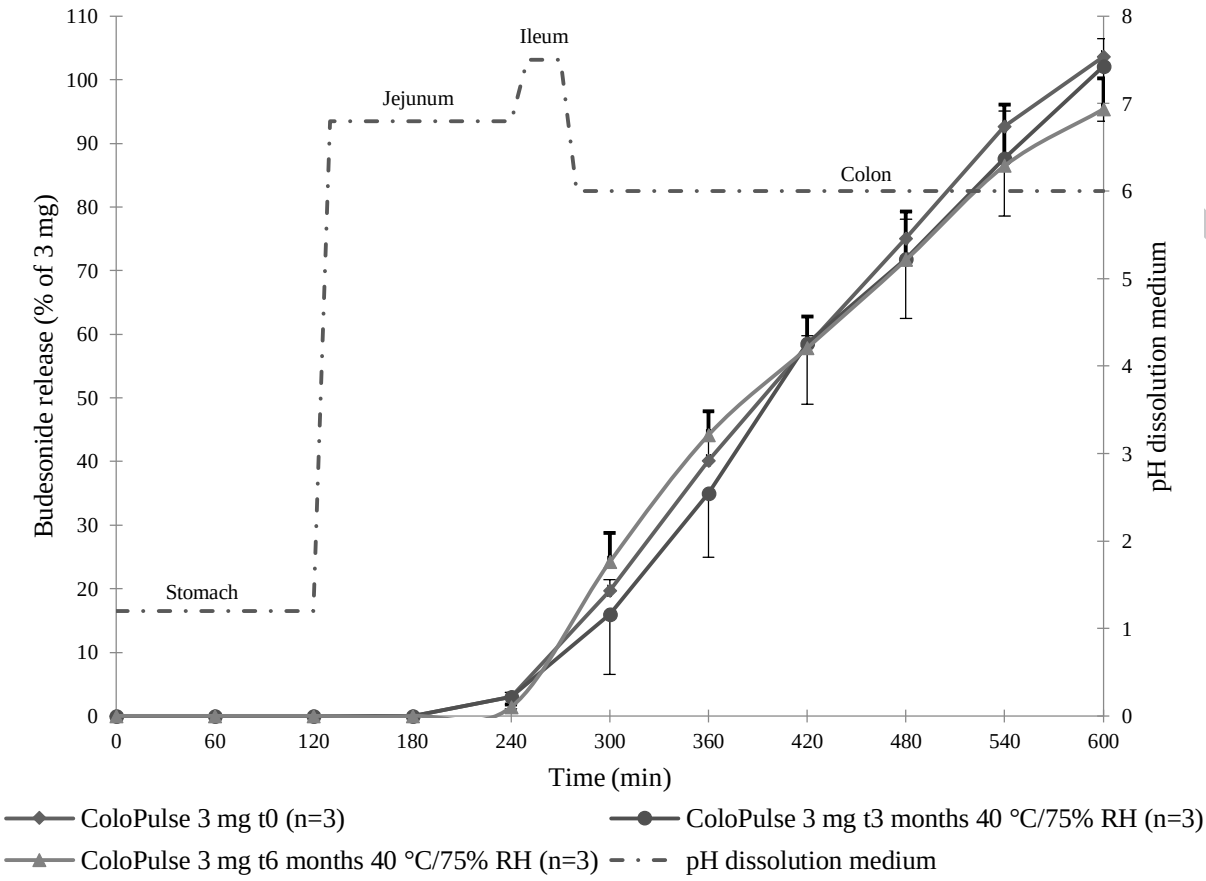

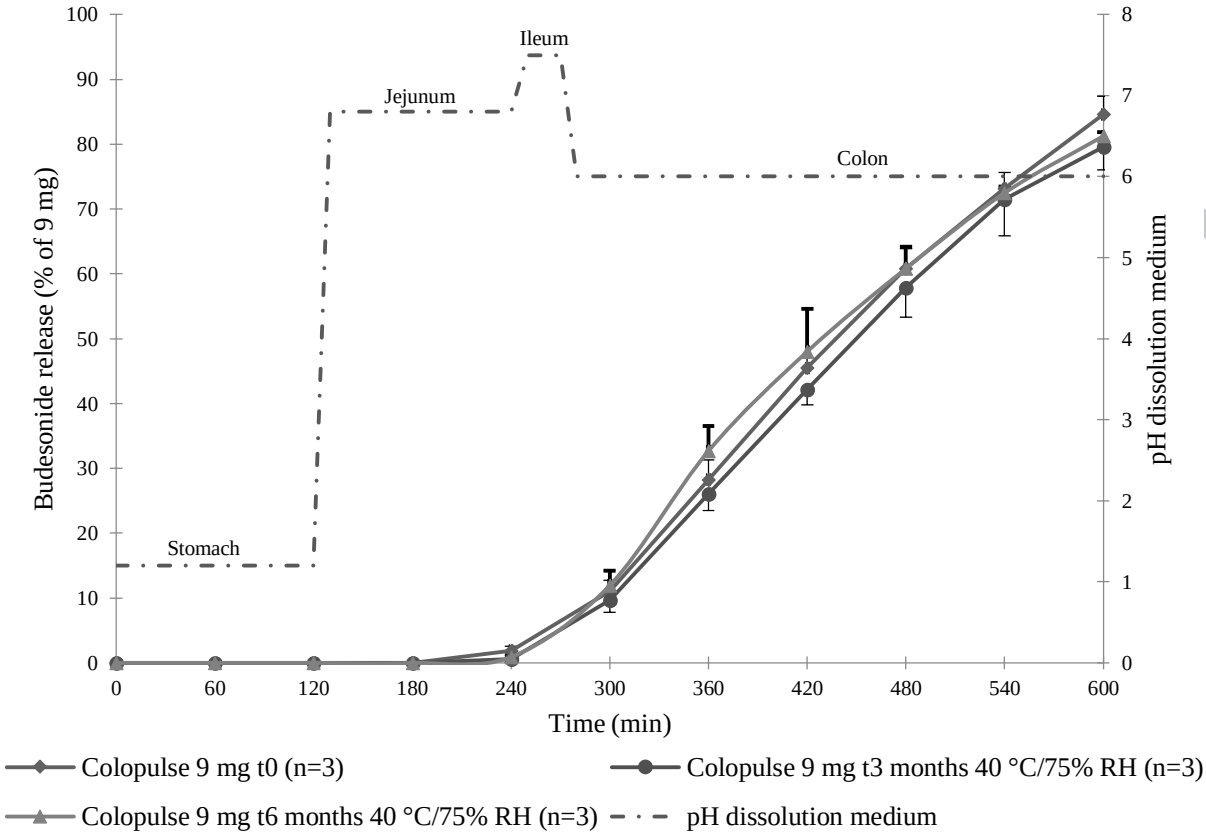

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical abstract