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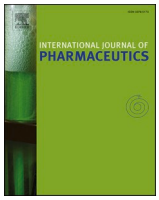

In vitro evaluation of the gastrointestinal delivery of acid-sensitive pancrelipase in a next generation enteric capsule using an exocrine pancreatic insufficiency disease model

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ABSTRACT

The dissolution characteristics of five capsules (Next Generation Enteric [NGE], Vcaps® Enteric [VCE], VCE DUOCAP® [VCE/VCE] system, Hard Gelatin Capsule [HGC] as negative control, and Creon® 10,000 U as market reference) were evaluated using an *in vitro* simulation of the stomach and upper intestinal tract with an acidic duodenal incubation (pH 4.5 for the first 10 min, pH 6 for the remaining 17 min) to simulate exocrine pancreatic insufficiency. Caffeine was a marker of capsule dissolution, and tributyrin to butyrate conversion measured pancrelipase activity. All capsules were filled with pancrelipase; the NGE, VCE, VCE/VCE, and HGC capsules also contained 50 mg caffeine. Caffeine was released first from the HGC capsule, followed by the VCE, NGE, and VCE/VCE capsules. Pancrelipase activity followed this trend and demonstrated a similar activity level over time for the NGE, VCE/VCE, and Creon® capsules. The HGC formulation confirmed gastric degradation of unprotected pancrelipase. NGE capsules provided similar protection to the simple fill formulation as observed for the complex formulation of the Creon® capsule in a setting with increased pepsin activity and may hasten the time needed to go from formula development to first-in-human studies for pH sensitive drugs or those requiring small intestine targeting.

1. Introduction

Oral drug delivery is often preferred over other routes, including intravenous, intranasal, and intradermal, given that oral formulations may have controlled delivery; easier and more convenient administration, facilitating greater patient compliance; and the capability of accommodating solid formulations (Homayun et al., 2019). Despite this attractiveness, there are some challenges associated with oral delivery (Vinarov et al., 2021). One such challenge is the passage of medication through the upper gastrointestinal tract where the pH changes quite drastically from the highly acidic pH of the stomach (~pH 2) to around pH 6 in the duodenum with a gradual increase to around 7.4 in the ileum (Fallingborg, 1999). The low pH environment of the stomach may denature or depurinate molecules, reducing their effectiveness. Additionally, the presence of gastric enzymes such as pepsin may degrade proteins and peptides, greatly dampening their activity (Bruno et al., 2013). Drugs that are poorly stable with an acidic pH or that would be prone to degradation by pepsin, which is active at an acidic pH, must be protected as they transit through the low pH environment of the stomach (Alqahtani et al., 2021). Several strategies for effective oral drug delivery have been developed, including coating or encapsulation in single capsules and the DUOCAP® system (Marzorati et al., 2021; Rump et al., 2021; Varum et al., 2020a; Varum et al., 2020b). When developing encapsulated medications, capsule dissolution characteristics are

Abbreviations: GC, gas chromatography; GC-FID, gas chromatography-flame ionization detector; HGC, Hard Gelatin Capsule; HPLC, high-pressure liquid chromatography; HPMC, hydroxypropyl methylcellulose; HPMC-AS, hydroxypropyl methylcellulose acetate succinate; HPMC-P, hydroxypropyl methylcellulose phthalate; NGE, Next Generation Enteric; SHIME®, Simulator of the Human Intestinal Microbial Ecosystem; SI, small intestine; ST, stomach; VCE, Vcaps® Enteric capsule; VCE/VCE, Vcaps® Enteric in Vcaps® Enteric DUOCAP® system.

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important to consider, as they will affect drug bioavailability and therapeutic effectiveness.

After the stomach the drug product will be emptied into the small intestine where most of lipid digestion and absorption occurs. Bile salts stabilize emulsified lipids which are then digested by pancreatic lipase (Kiela and Ghishan, 2016), an enzyme that is most active at a near neutral pH (Borgstrom and Erlanson, 1973). Bicarbonate secretion by the pancreas and biliary tree neutralizes stomach acids, thus facilitating the activity of pancreatic lipase in the small intestine (Allen and Flemstrom, 2005). Bile salts, which are also essential for lipid digestion, lower the pH and thus reduce the effectiveness of pancreatic lipase (Borgstrom and Erlanson, 1973). People who suffer from exocrine pancreatic insufficiency, such as those with chronic pancreatitis or cystic fibrosis-derived pancreatic juice insufficiency, experience inadequate pancreatic secretion of digestive enzymes (mainly pancreatic lipase) which impedes lipid digestion (Ghodeif and Azer, 2022). Additionally, secretion of bicarbonate by ductal epithelial cells may be impaired which results in a reduced and delayed pH neutralization in the small intestine; the pH in the duodenum can be 4 or lower for some of these patients (Waldthaler et al., 2019). Supplementation with pancreatic enzymes (e.g., pancrelipase) is commonly used as a treatment for patients with exocrine pancreatic insufficiency (Ghodeif and Azer, 2022). However, it is important that these enzymes are protected from the acidic environment of the stomach as they transit to the intestine.

In vitro models that simulate the human upper gastrointestinal tract are important tools for the preclinical evaluation of oral drug transit (Marzorati et al., 2021) and can be useful for studying the stability and behavior of enzymes along the upper gastrointestinal tract. The Simulator of the Human Intestinal Microbial Ecosystem (SHIME®) technology platform can be adapted to simulate the physiological conditions of the stomach and small intestine and serves as an excellent tool for the evaluation of capsule dissolution characteristics and enzyme activity during upper gastrointestinal tract transit (e.g., Blancquaert et al., 2019; Marzorati et al., 2021; Marzorati et al., 2022). This model can further be adapted to simulate disease states of the upper gastrointestinal tract. In the present study, the SHIME® technology platform was utilized to simulate an acidic disease model of the upper gastrointestinal tract, with small intestine conditions similar to those observed in patients with exocrine pancreatic insufficiency. The aim was to investigate the capsule dissolution of five different capsules filled with pancrelipase, and to determine the lipid digestion properties of pancrelipase during passage through the upper gastrointestinal tract under fasted conditions to evaluate the efficiency of protection of the fill formulation against acid and pepsin degradation. Five capsules were compared and included the Next Generation Enteric (NGE), Vcaps® Enteric (VCE), VCE DUOCAP® (VCE/VCE) system, Hard Gelatin Capsule (HGC), and Creon® 10,000 U capsules.

2. Materials and methods

2.1. Test products and composition of the capsule systems

Five different capsules were tested for their dissolution behavior; the enzymatic activity of the released contents (pancrelipase) was also evaluated and compared to blank. The NGE, VCE, VCE/VCE, and HGC capsules contained a powder mixture of 450 mg pancrelipase (pancreatin from porcine pancreas 8 × USP, Sigma-Aldrich, France) and 50 mg caffeine (Reagent Plus, Sigma-Aldrich, France). The two powder components were mixed and homogenized. All capsules were filled by hand on a laboratory scale to the target fill weight of 500 mg. All capsules containing the powder formulation are of the same size (size #0). In the case of the VCE/VCE DUOCAP system the capsule size #0 is over-encapsulated in a capsule size #00 manually. The capsule shell thickness of the enteric capsules is the same as for standard capsules and all sizes, 100 μm (±10%). In addition, the capsules were not sealed nor banded and were supplied by Lonza Capsules & Health Ingredients (Colmar, France). The market reference capsule, Creon® 10,000 U (Abbvie, USA), contained pancrelipase (10,000 lipase units) but no caffeine. The tributyrin lipase activity of the enteric capsules and HGC capsule filled with pancrelipase and caffeine was 31% lower than observed for the Creon® capsule (market reference capsule), as measured by pH-stat using the method described by Fernandez et al. (Fernandez et al., 2007). This lower lipase activity is related to the use of reduced enzymatic activity enzymes in the enteric capsule formulations.

The NGE and VCE are enteric capsules composed of hydroxypropyl methylcellulose (HPMC) and HPMC acetate succinate (HPMC-AS). The VCE capsules contain HPMC-AS L-grade, a pH-dependent enteric polymer that can dissolve in media with pH > 5.5. The NGE capsules contain HPMC-AS H-grade, an enteric polymer with a lower concentration of succinyl groups versus L-grade that induces a dissolution in higher pH media (pH > 6.5). The VCE/VCE is a DUOCAP® system composed of VCE-in-VCE capsules. The HGC capsules are immediate release capsules composed of gelatin. Finally, the Creon® pellets are composed of an enteric formulation containing HPMC phthalate (HPMC-P), an enteric polymer (solubility pH > 5); macrogol 4,000 (polyethylene glycol 4,000), a binder that slows the hydration of the formulation especially in acidic media (hydration rate: neutral pH > acidic pH); cetyl alcohol; triethyl citrate; and dimethicone 1,000; all contained within an immediate release gelatin capsule.

2.2. Upper gastrointestinal tract simulation

The conditions of the upper gastrointestinal tract simulation were modified from those used to simulate the healthy upper gastrointestinal tract (Marzorati et al., 2021) to those that would simulate the upper gastrointestinal tract of an individual with chronic pancreatitis or cystic fibrosis-derived pancreatic juice insufficiency. A double-jacketed reactor, sequentially simulating the stomach and small intestine digestion conditions, was used to perform the upper gastrointestinal tract simulation (Fig. 1). The reactor was held at 37℃ with continuous magnetic stirring (300 rpm). Fasted (i.e., consumption of the product before a meal) conditions were used for this study. All experimental conditions were selected based on the InfoGest consensus method (Mackie and Rigby, 2015). A 45 min incubation was used to simulate stomach digestion. Prior to the start of gastric incubation, gastric fluid (68 mL, pH 2) containing KCl 0.74 g/L, NaCl 4.06 g/L and mucin 4.41 g/L, 0.4 mL of lecithin (Carl Roth GmbH + Co. KG, Germany) (3.4 g/L), and 5.76 mL pepsin (Chem Lab, Zedelgem, Belgium) (16 g/L) were added to each reactor. A single capsule was added to each reactor using capsule sinkers. These capsule sinkers were positioned in the middle of the liquid, perpendicular to the stirring direction. As such, the capsules were exposed to shear stress, mimicking the mechanical forces encountered during *in vivo* digestion. Continuous pH control was accomplished using a Senseline pH meter F410 (ProSense, Oosterhout, The Netherlands); HCl (0.5 M) or NaOH (0.5 M) was used to maintain pH 2. At the end of the stomach incubation, MilliQ water was added to bring the gastric digestion volume to 100 mL. Afterwards, 35.2 mL simulated pancreatic juice (Oxgall 2.2 g/L; Difco™ Oxgall, BD, Erembodegem, Belgium) and 20 mL MilliQ water was added to the reactor to initiate the small intestinal incubation. Oxgall contains bovine bile, which is a closer match to human than porcine in terms of tauro- and glycocholate. To simulate the duodenal incubation, the pH was increased gradually from 2 to 4.5 and then maintained at 4.5 for 10 min (to simulate the more acidic condition of the duodenum in patients with exocrine pancreatic insufficiency) followed by another gradual increase to pH 6.0 which was maintained for 17 min. Next, there was a stepwise pH increase (0.1 pH unit/4.5 min for 63 min) to a final pH of 7.5 to simulate jejunal digestion. Ilial digestion was simulated for 90 min, during which the pH was maintained at 7.5. $NaHCO_3$ (8.4 g/L) was used to achieve pH increases (40 mL over the first 100 min). In total the incubation of capsules lasted for 225 min (45 min of gastric incubation and 180 min of intestinal incubation), and the final volume is 200 mL. Tributyrin (8 mL) was

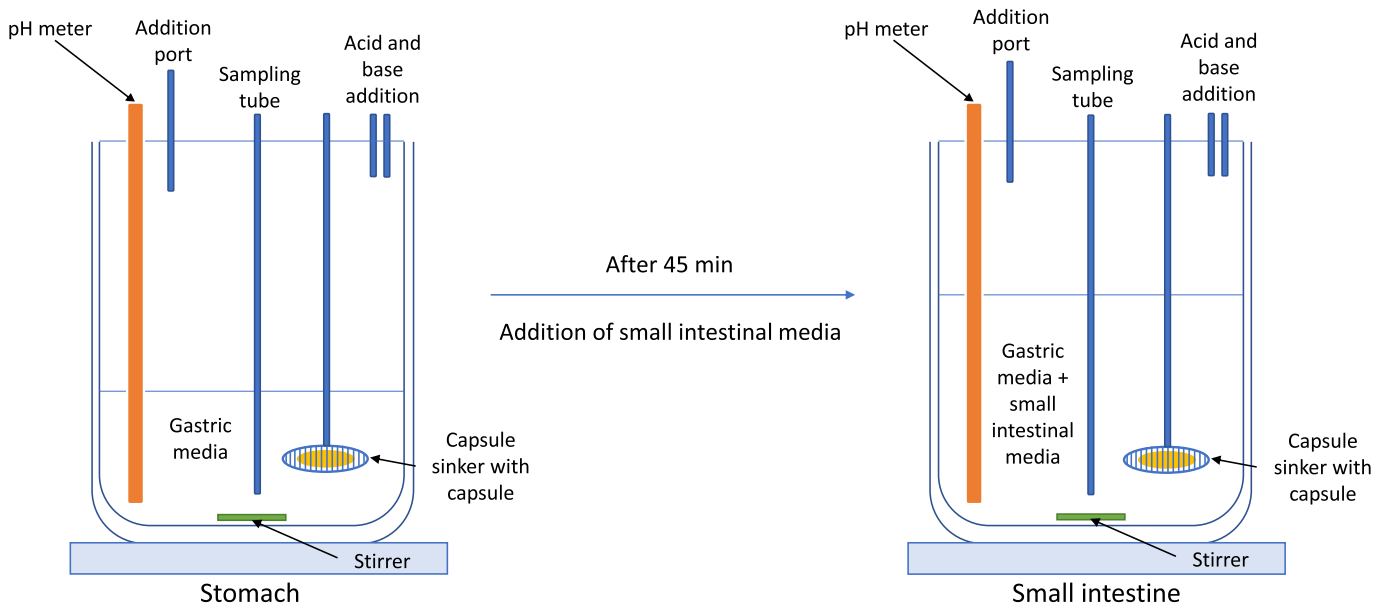

Fig. 1. General scheme of the SHIME® system used to simulate the gastrointestinal fate of a test product during passage through the upper GIT tract.

added to each reactor at the start of the stomach incubation as the lipid source to measure pancrelipase activity. While this may be considered a low concentration, we note that lipases may be inhibited by excessive lipid concentrations and therefore used a conservative amount of tributyrin to limit the possibility of lipase inhibition in the study. Capsule sinkers designed for capsule dissolution studies (ProSense, Oosterhout, The Netherlands) were used to mount capsules in the reactor; dosing occurred at the start of the gastric phase. A blank control without capsules, caffeine, or pancrelipase was included in all the assays as a background media for the caffeine high-pressure liquid chromatography (HPLC) analysis. All assays were performed in triplicate.

2.3. Study endpoints

2.3.1. Analysis of caffeine

Samples collected from the stomach (ST) incubation at ST 0, ST 15, ST 30, ST 45, and from the small intestine (SI) incubation at SI 30, SI 60, SI 90, SI 120, SI 150, SI 180 were evaluated for caffeine concentration using a method previously described in Marzorati et al. (Marzorati et al., 2021). In brief, caffeine was quantified by HPLC-UV/Vis (Hitachi Chromaster HPLC-DAD, Hitachi High-Tech Corporation, Japan) using an isocratic separation method (25% methanol:75% water) on a Kinetex® C18 LC column (5 μm,100 Å, LC Column 100 × 4.6 mm, solid support of Core-shell Silica) (Phenomenex, Belgium) at a controlled column temperature of 25.0 ± 0.1 °C. A 10 μL injection volume was used and the total run time per sample was 7 min. The UV/Vis detector was operated at 272 nm. Caffeine was quantified using external standards (Sigma-Aldrich, Merck KGaA, Darmstadt, Germany). Samples were centrifuged for 15 min at 5000 g prior to injection on the column. Finally, the supernatant was filtered (0.2 μm) and placed into HPLC vials. Given that caffeine was not included in the blank control or the Creon® capsule, these samples were not tested for caffeine.

2.3.2. Tributyrin and butyrate analysis

Samples (1 mL at each timepoint) were collected for tributyrin and butyrate analysis at ST 0, ST 15, ST 30, ST 45, SI 30, SI 60, SI 90, SI 120, SI 150, and SI 180. After collection, samples were immediately flash-frozen in liquid nitrogen. Prior to analysis, samples were thawed and extracted as follows. A small amount of NaCl was added to the sample followed by the addition of 1000 μL acetonitrile extraction mix (acetonitrile, formic acid, methyl hexanoic acid). The samples were then homogenized and shaken for 15 min using an orbital shaker, followed by centrifugation for 15 min at 15,080 g. Finally, 100 μL of the supernatant was transferred to a vial for gas chromatography (GC) analysis. Tributyrin and butyrate concentrations were determined using a GC-flame ionization detector (GC-FID) (GC2030, Schimadzu, Japan). The GC injector port was installed with an enduro blue injector septum and inlet liner with a standard split (Shimadzu 221–75189, glass insert liner with quartz wool and deactivation) and a BP21 (FFAP) GC column was used (length, 30 m length; inside diameter, 0.32 mm; film thickness, 0.25 μm). The carrier gas was nitrogen (flow rate, 1.98 mL/min) and the sample was split 40:1 at the inlet. The injection volume was set at 1 μL and the run time was 20 min with the following oven temperature conditions: initial temperature, 70 °C; temperature ramp 10 °C/min to 220 °C; held for 5 min. The injector and detector temperatures were set at 200 °C and 240 °C, respectively. The peak area output signal was computed via integration using Lab solutions DB software (Shimadzu).

2.4. Statistical analysis

For each test condition, statistically significant differences in caffeine, tributyrin, and butyrate concentrations were determined for each timepoint and compared with the preceding timepoint to evaluate changes over time. Percent caffeine release and percent butyrate conversion were compared for each capsule, using a student's *t*-test to compare sequential values. A p-value < 0.05 was considered significant with a confidence interval of 95%. Analyses were performed using GraphPad Prism software, version 9.0 (GraphPad Software, CA, USA).

3. Results

3.1. Characterization of capsule release behavior during the upper gastrointestinal tract passage under fasted conditions

Capsule dissolution over time was evaluated using caffeine as an active marker during both the stomach and small intestine digestion-like environment. After 45 min in the stomach (ST 45), 100.0% (standard deviation [SD] 4.1%) of the theoretical caffeine contained in the HGC capsule was already released into the environment. For the VCE capsule, only 2.0% (standard deviation [SD] 0.3%) was released, which gradually increased through the SI 30 timepoint (9.5% ± 8.2%) and most of the caffeine contents were released by SI 60 (95.9% ± 4.8%) (Fig. 2).

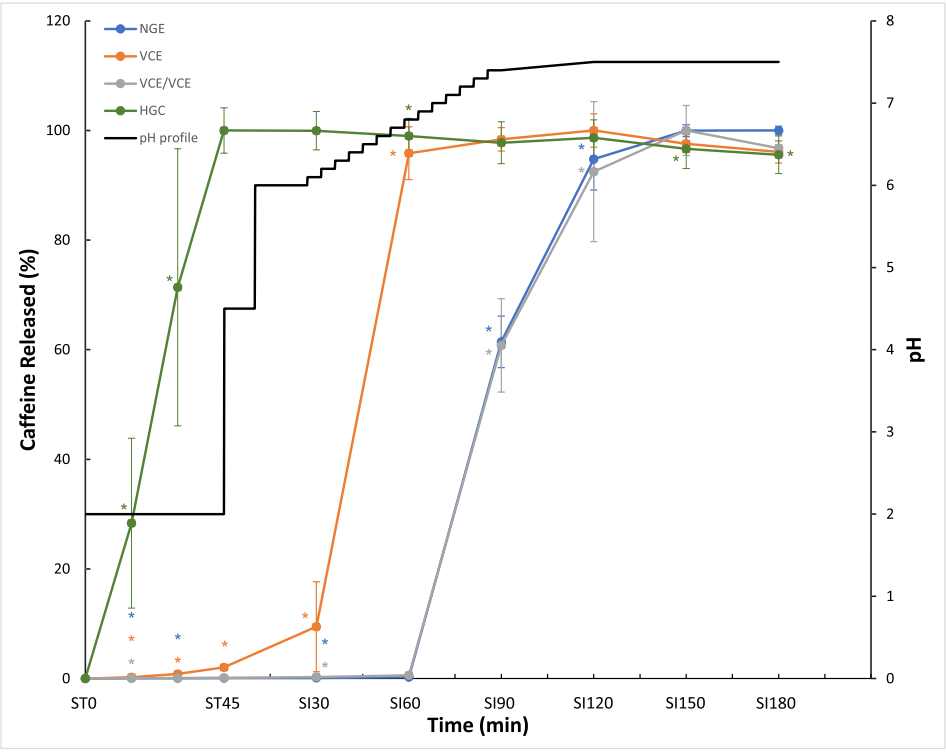

Fig. 2. Effect of capsule configuration and pH on caffeine release during the stomach and small intestinal simulated digestion in fasted conditions. Dots represent caffeine release at different time points (%, n = 3); values are presented on the left Y axis. The black line represents pH; values are presented on the right Y axis. Student's *t*-test was used to determine significant differences from the preceding time point; * = $p < 0.05$. NGE = Next Generation Enteric capsule; HGC = Hard Gelatin Capsule; SI = small intestine; ST = stomach; VCE = Vcaps® Enteric capsule; VCE/VCE = Vcaps® Enteric DUOCAP® system.

<1% of the theoretical caffeine contained in both the NGE and VCE/VCE capsules was detected in the stomach digestion-like environment. A respective 61.4% ± 4.7% and 60.1% ± 8.5% was released at SI 90 and most of the contents were released by SI 120 (94.8% ± 5.6% and 92.5% ± 12.8%, respectively). When considering the pH at each timepoint, the VCE capsule was somewhat affected by the lower pH of the stomach-like condition and both the NGE and VCE/VCE capsules had a higher integrity as they were resistant to the lower pH, with caffeine release not apparent until the pH was above 7. As HGC capsules are intended to dissolve in <20–30 min, full release of the caffeine content occurred at gastric pH (i.e., pH 2).

3.2. Pancrelipase activity

Pancrelipase activity was evaluated by measuring the conversion of tributyrin to butyrate. Similar to caffeine release, pancrelipase activity was observed earlier with the VCE capsule compared with the others (NGE, VCE/VCE, and Creon®) (Fig. 3). A small amount of butyrate conversion was observed with the VCE capsule at SI 30 (1.1% ± 1.9%), which increased to 51.9% ± 8.5% at SI 60, reaching maximum activity at SI 90 (70.0% ± 2.7%). The Creon® capsule converted a small amount of butyrate (9.0% ± 7.3%) at SI 60, which increased to 47.2% ± 4.0% at SI 90, reaching maximum conversion at SI 180 (65.3% ± 1.2%). While

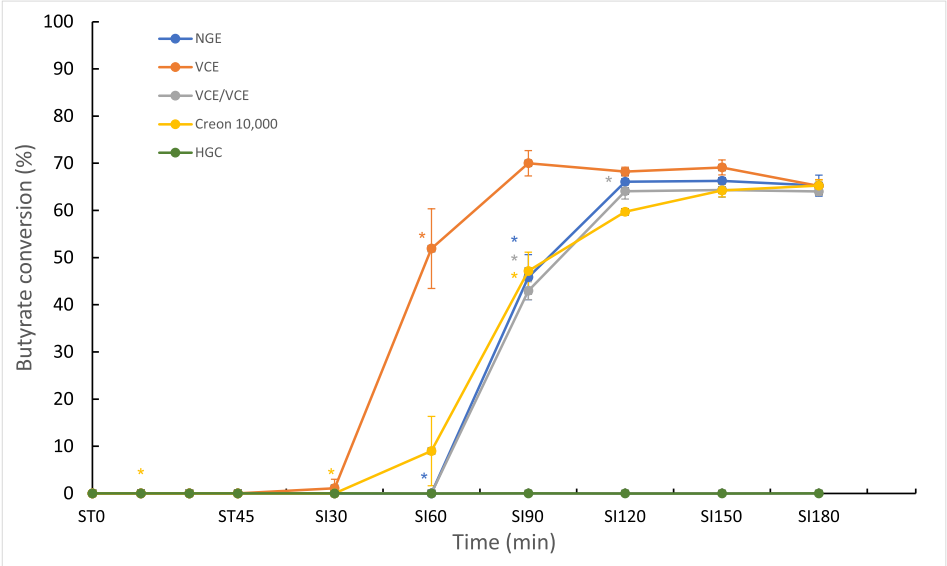

Fig. 3. Effect of capsule configuration on pancrelipase activity. Dots represent the conversion of tributyrin to butyrate (%) as an indication of pancrelipase activity at different timepoints (n = 3). Student's *t*-test was used to determine significant differences from the preceding time point; * = $p < 0.05$. NGE = Next Generation Enteric capsule; HGC = Hard Gelatin Capsule; SI = small intestine; ST = stomach; VCE = Vcaps® Enteric capsule; VCE/VCE = Vcaps® Enteric DUOCAP® system.

no butyrate conversion was observed at SI 60 for the NGE and VCE/VCE capsules, conversion was similar to the Creon® capsule at SI 90 (45.9% ± 4.8% and 43.0% ± 1.9%, respectively). For the NGE and VCE/VCE capsules, conversion remained at around 65% from SI 120 through SI 180. No conversion of butyrate was observed with the HGC capsule.

4. Discussion

In this study, the dissolution characteristics of different capsules (i.e., caffeine release), as well as the enzyme activity of pancrelipase during upper gastrointestinal transit were evaluated using an *in vitro* simulation of the upper gastrointestinal tract adapted to simulate the harsher duodenal pH and the increased pepsin concentration in the stomach observed in patients with exocrine pancreatic insufficiency. A good correlation between caffeine release and the pKa of the enteric polymers used in the capsules (i.e., pH from which the polymer starts to dissolve in the aqueous media), as well as the thickness of the capsule (i.e., the double layer for VCE/VCE) was observed. The pancrelipase activity followed a similar trend, with activity being observed earliest with the VCE capsule, followed by the NGE, VCE/VCE, and Creon® capsules for which a similar level of activity over time was observed. No pancrelipase activity was observed with the HGC capsules, despite full release of the capsule content being obtained by the end of the stomach incubation.

The maximum level of tributyrin conversion observed in the upper gastrointestinal tract simulations was 70%, which is similar to what is observed *in vivo (*Bakala N'Goma et al., 2012*)*. Indeed, the pancreatic lipase can hydrolyze fatty acids in the *sn*-1 and *sn*-3 positions to release a 2-monoglyceride and two fatty acids. The remaining monoglycerides are not broken down but can be absorbed during gastrointestinal transit. This result indicates that the pancrelipase was fully active and was protected from low pH exposure during upper gastrointestinal tract transit with the NGE, VCE, VCE/VCE, and Creon® capsules. The pancrelipase formulation in the different enteric capsules did not contain any enzyme protective adjuvant. As such, the observed protection of pancrelipase was achieved solely as a result of the capsule shell of the VCE and NGE capsules. These findings demonstrate a targeting of pancrelipase to the jejunum by the NGE, VCE, and VCE/VCE capsules and the marketed drug product, which is the target site for this medication, as it is in the upper part of the small intestine that the pH is appropriate for the pancreatic lipase activity and where there is a co-occurrence of nutrient absorption and macromolecule degradation (Karnik and Jan 2022). In addition, the *in vivo* performance of the NGE capsules has recently been demonstrated using two independent techniques (MRI and caffeine in saliva) in eight human volunteers (Rump et al. 2022). The capsules disintegrated in the distal part of the small intestine (jejunum and ileum) and the average disintegration time was 54 ± 28 min after gastric emptying (MRI). In that regard the start of caffeine release and lipase activity seen during the SHIME simulation between 60 and 90 min after the end of the gastric phase reflect well what was observed *in vivo*. The absence of pancrelipase activity with the HGC capsule confirms the importance of targeted release as degradation of the enzymes clearly occurred during gastric incubation. As mentioned before, this can be related with protein denaturation at the low gastric pH and enzymatic degradation by the activity of pepsin.

This study demonstrates that NGE capsules have a competitive advantage in that they protect acid-sensitive compounds without the need to develop special formulations. This new capsule has the advantage to match the release of the marketed product (vs VCE showing an earlier drug release) while using only one capsule shell and hence simplify the encapsulation process (vs VCE/VCE). Most current formulations of pancreatic enzymes utilize enteric-coated microspheres or some other type of enteric coating to protect the enzymes against stomach acids (Brennan and Saif, 2019). However, the development of such technologies requires both time and resources. NGE capsules have this technology built in, allowing drug makers to streamline activities leading in to first-in-human studies for new products. In addition, the NGE capsules can provide enteric protection to fragile active pharmaceutical ingredients that cannot withstand the process conditions of enteric formulation or coating.

As noted in the methods, this study used a low concentration of tributyrin, meaning that it may be possible that even if some enzyme was degraded, the residual amount was adequate to reach the same concentration of butyrate. Nonetheless, the release and activity patterns of the test capsules was similar to the market drug reference, Creon®. It is worth reiterating that similar patterns were achieved despite the 31% lower tributyrin lipase activity of the enteric capsules versus the Creon® capsule, which might be linked with the strong release of the capsule content of the Creon® product by the end of the gastric incubation, resulting in reduction of the enzymatic activity of pancrelipase due to contact with the harsh environmental conditions in the stomach.

5. Conclusions

Using an improved and modified SHIME® model to simulate the gastrointestinal tract conditions of patients with exocrine pancreatic insufficiency and caffeine as a marker for capsule release and disintegration, we showed that the NGE and VCE/VCE capsules led to a slower release profile than observed with the VCE capsule. For the NGE and VCE/VCE capsules, notable caffeine release was observed at SI90, indicating that targeted delivery to the jejunum was possible. The NGE, VCE, and VCE/VCE capsules resulted in concentrations of tributyrin below the limit of quantification and butyrate conversion was stable at around 65% by the SI 180 timepoint which is similar to the marketed drug product Creon® used as reference. The NGE capsule allowed a simple powder formulation of pancrelipase to achieve a similar release profile, enzyme protection, and efficiency as achieved by the market reference capsule, Creon®, which contained a complex formulation of pancrelipase.

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CRediT authorship contribution statement

Vincent Jannin: Methodology, Writing – review & editing, Funding acquisition. **Cindy Duysburgh:** Formal analysis, Data curation, Writing – review & editing. **Vanessa Gonzalez:** Resources. **Marlies Govaert:** Formal analysis, Investigation, Data curation, Writing – review & editing. **Marine Agisson:** Resources. **Massimo Marzorati:** Supervision, Writing – original draft. **Nicolas Madit:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: At the time of the study, Vanessa Gonzalez, Marine Agisson, Nicolas Madit, and Vincent Jannin were employees of Capsugel France SAS, a company from Lonza Capsules & Health Ingredients Division, manufacturing and selling capsules used in this study.

Data availability

Data will be made available on request.

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References

Allen, A., Flemstrom, G., 2005. Gastroduodenal mucus bicarbonate barrier: protection against acid and pepsin. Am. J. Physiol. Cell Physiol. 288, C1–C. https://doi.org/10.1152/ajpcell.00102.2004.

Alqahtani, M.S., Kazi, M., Alsenaidy, M.A., Ahmad, M.Z., 2021. Advances in oral drug delivery. Front. Pharmacol. 12, 618411 https://doi.org/10.3389/fphar.2021.618411.

Bakala N'Goma, J.C., Amara, S., Dridi, K., Jannin, V., Carriere, F., 2012. Understanding the lipid-digestion processes in the GI tract before designing lipid-based drug-delivery systems. Ther Deliv 3, 105–124. https://doi.org/10.4155/tde.11.138.

Blancquaert, L., Vervaet, C., Derave, W., 2019. Predicting and Testing Bioavailability of Magnesium Supplements. Nutrients 11, 1663. https://doi.org/10.3390/nu11071663.

Borgstrom, B., Erlanson, C., 1973. Pancreatic lipase and co-lipase. Interactions and effects of bile salts and other detergents. Eur. J. Biochem. 37, 60–68. https://doi.org/10.1111/j.1432-1033.1973.tb02957.x.

Brennan, G.T., Saif, M.W., 2019. Pancreatic enzyme replacement therapy: a concise review. J.O.P. 20, 121–125.

Bruno, B.J., Miller, G.D., Lim, C.S., 2013. Basics and recent advances in peptide and protein drug delivery. Ther. Deliv. 4, 1443–1467. https://doi.org/10.4155/tde.13.104.

Fallingborg, J., 1999. Intraluminal pH of the human gastrointestinal tract. Dan. Med. Bull. 46, 183–196.

Fernandez, S., Jannin, V., Rodier, J.D., Ritter, N., Mahler, B., Carriere, F., 2007. Comparative study on digestive lipase activities on the self emulsifying excipient Labrasol, medium chain glycerides and PEG esters. Biochim Biophys Acta 1771, 633–640. https://doi.org/10.1016/j.bbalip.2007.02.009.

Ghodeif, A.O., Azer, S.A., 2022. Pancreatic insufficiency. StatPearls, Treasure Island (FL).

Homayun, B., Lin, X., Choi, H.J., 2019. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. Pharmaceutics 11. https://doi.org/10.3390/pharmaceutics11030129.

Karnik, N.P., Jan, A., 2022. Pancrelipase, StatPearls, Treasure Island (FL).

Kiela, P.R., Ghishan, F.K., 2016. Physiology of intestinal absorption and secretion. Best Pract. Res. Clin. Gastroenterol. 30, 145–159. https://doi.org/10.1016/j.bpg.2016.02.007.

Mackie, A., and Rigby, N., 2015. InfoGest Consensus Method. In 'The Impact of Food Bioactives on Health', Springer International Publishing, 13–22. 10.1007/978-3-319-16104-4_2.

Marzorati, M., Calatayud, M., Rotsaert, C., Van Mele, M., Duysburgh, C., Durkee, S., White, T., Fowler, K., Jannin, V., Bellamine, A., 2021. Comparison of protection and release behavior of different capsule polymer combinations based on L. acidophilus survivability and function and caffeine release. Int. J. Pharm. 607, 120977 https://doi.org/10.1016/j.ijpharm.2021.120977.

Marzorati, M., Bubeck, S., Bayne, T., Krishnan, K., Giusto, M., 2022. Effects of combined prebiotic, probiotic, IgG and amino acid supplementation on the gut microbiome of patients with inflammatory bowel disease. Future Microbiol. 17, 1307–1324. 0.2217/fmb-2022-0066.

Rump, A., Kromrey, M.-L., Scheuch, E., Jannin, V., Rehenbrock, L., Tzvetkov, M.V., Weitschies, W., Grimm, M., 1999. In Vivo Evaluation of a Gastro-Resistant HPMC-Based "Next Generation Enteric" Capsule. Pharmaceutics 2022, 14. https://doi.org/10.3390/pharmaceutics14101999.

Rump, A., Weiss, F.N., Schulz, L., Kromrey, M.L., Scheuch, E., Tzvetkov, M.V., White, T., Durkee, S., Judge, K.W., Jannin, V., Bellamine, A., Weitschies, W., Grimm, M., 2021. The effect of capsule-in-capsule combinations on in vivo disintegration in human volunteers: A combined imaging and salivary tracer study. Pharmaceutics 13. https://doi.org/10.3390/pharmaceutics13122002.

Varum, F., Freire, A.C., Bravo, R., Basit, A.W., 2020a. OPTICORE, an innovative and accurate colonic targeting technology. Int. J. Pharm. 583, 119372 https://doi.org/10.1016/j.ijpharm.2020.119372.

Varum, F., Freire, A.C., Fadda, H.M., Bravo, R., Basit, A.W., 2020b. A dual pH and microbiota-triggered coating (Phloral) for fail-safe colonic drug release. Int. J. Pharm. 583, 119379 https://doi.org/10.1016/j.ijpharm.2020.119379.

Vinarov, Z., Abrahamsson, B., Artursson, P., Batchelor, H., Berben, P., Bernkop-Schnurch, A., Butler, J., Ceulemans, J., Davies, N., Dupont, D., Flaten, G.E., Fotaki, N., Griffin, B.T., Jannin, V., Keemink, J., Kesisoglou, F., Koziolek, M., Kuentz, M., Mackie, A., Melendez-Martinez, A.J., McAllister, M., Mullertz, A., O'Driscoll, C.M., Parrott, N., Paszkowska, J., Pavek, P., Porter, C.J.H., Reppas, C., Stillhart, C., Sugano, K., Toader, E., Valentova, K., Vertzoni, M., De Wildt, S.N., Wilson, C.G., Augustijns, P., 2021. Current challenges and future perspectives in oral absorption research: An opinion of the UNGAP network. Adv. Drug Deliv. Rev. 171, 289–331. https://doi.org/10.1016/j.addr.2021.02.001.

Waldthaler, A., Valente, R., Arnelo, U., Lohr, J.M., 2019. Endoscopic and conservative management of chronic pancreatitis and its complications. Visc. Med. 35, 98–108. https://doi.org/10.1159/000499611.