Preparation and evaluation of oral multiparticulate formulations of acid-labile drugs

Inaugural-Dissertation

to obtain the academic degree

Doctor rerum naturalium (Dr. rer. nat.)

submitted to the Department of Biology, Chemistry and Pharmacy

of Freie Universität Berlin

by

FANG HUANG

from Zhejiang, P. R. China

2017

Die vorliegende Arbeit wurde von September 2012 bis April 2017 unter der Leitung von Prof. Dr. Roland Bodmeier im Institut für Pharmazie angefertigt.

1. Gutachter: Prof. Dr. Roland Bodmeier
2. Gutachter: Prof. Dr. Philippe Maincent

Tag der mündlichen Prüfung: 13.06.2017

Acknowledgements

It is time to say a thousand thanks to you all who has been so much a part of this five-year journey.

My gratitude is endless to my supervisor, Prof. Dr. Roland Bodmeier, the one opened my door to this interesting research area. His support has been with me along the way.

My gratitude continues to Prof. Dr. Phillipe Maincent for reviewing this thesis.

I am deeply grateful to Dr. Martin Körber for his smart suggestions, prompt support, encouragement and help in ways too numerous to mention. Many many thanks to Dr. Agnieszka Solik for her translation and proofreading, as well as Reza Goldoozian for wording of my work.

I am so grateful for the pleasant and professional discussions with Dr. Mesut Ciper, Dr. Mathias Walther and Dr. Andrey Dashevsky. The longest thank goes to Dr. Burkhard Dickenhorst, Dr. Anis Chaerunisaa, Dr. Muhaimin, Dr. Rebaz Ali, Dr. Jelena Teodosic, Dr. Gaith M. Zoubari, Dr. May Darwich, Dr. Kathrin Bürki, Dr. Rahul Ashok Sonawane, Dr. Luisa Duque, Cheng Cheng Zhao, Jia Deng, Zoha Hanif, Marina Kolbina, Benjamin Balzus, Marco Bellini, Miriam Colombo, Marius Heck, Lisa Hein, Nadeem Ishaque Khan, Andreas Krause, Stefan Walter and our new fellows for the nice atmosphere, valuable fellowship and time that we had together.

Thanks and blessing to Mrs. Eva Ewest for her timely organized material supply, prompt technical support and tips for managing household; and to Mrs. Gabriela Karsubke for the nice reminders and working assistance with all administrative issues.

My family and the mountain are my endless generator of power, love, care, encouragement and support all the years. Love you all.

Table of contents

Table of tables

Table of figures

Abbreviations

API	Active pharmaceutical ingredient
CDER	Center for Drug Evaluation and Research
DCP	Dicalcium phosphate dihydrate
DSC	Differential scanning calorimetry
EDQM	European Directorate for the Quality of Medicines
EFI	Extended focus imaging
EFT	Enteral feeding tubes
EP	European Pharmacopoeia
EPI	Exocrine pancreatic insufficiency
Fr	French
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GMS	Glycerol monostearate
HCl	Hydrochloride
HPC	Hydroxypropyl cellulose
HPLC	high performance liquid chromatography
HPMC	Hydroxypropylmethylcellulose
ICH	International Conference of Harmonization
JP	Japanese Pharmacopoeia
LOD	Loss on drying
MCC	Microcrystalline cellulose
MgO	Magnesium oxide
MHLW	Ministry of Health, Labour and Welfare
MUPS	Multiple unit pellet system
NaOH	Sodium hydroxide solution
NF	National Formulary
NG	Nasogastric
NSAID	Non-steroidal anti-inflammatory drug
ODTs	Orally disintegrating tablets
OOS	Out-of-specification
PBS	Phosphate buffer solution
PCL	Programmable Logic Controller
PPIs	Proton pump inhibitors
PSD	Particle size distribution
PVA	Polyvinyl alcohol
RH	Relative humidity
SEM	Scanning electron microscopy
T80	Polysorbate 80
TEC	Triethyl citrate
Tg	Glass transition temperature
US FDA	United States Food and Drug Administration
USP	United States Pharmacopeia

1. Introduction

1.1 Multiple unit pellet system (MUPS)

MUPS have flexibility during formulation development. They can be divided into the desired doses without formulation and process changes and can be blended to simultaneously deliver incompatible bioactive agents or particles with different release profiles at different sites within the gastrointestinal (GI) tract. When taken orally, they generally disperse freely in the GI tract, maximize absorption, minimize side effects, and reduce inter- and intra-patient variability (Ghebre-Sellassie, 1994). Newton (2010) also highlighted the advantages of multi-particulate systems as being easy to coat, reducing the risk of dose dumping as well as the risk of local irritation within the GI tract. Particles < 2 mm can pass through the pyloric sphincter even in the fed state, and therefore, behave as a liquid in terms of gastric emptying, which enables particles to distribute evenly through the GI tract. Distribution of particles through the GI tract is generally independent of nutritional status. MUPS can be filled into capsules or be compressed into tablets. MUPS tablets have a lower risk of tampering and less difficulty during esophageal transport than that of capsules. MUPS can be scored without losing the controlled release properties, allowing for a more flexible dosing regimen (Bodmeier, 1997).

1.1.1 MUPS tablets by compression

Compression is a conventional method used to prepare MUPS tablets. Traditional compression processes offer a higher production efficiency at a lower cost than filling pellets into capsules. The expense of maintaining capsule integrity after filling is also eliminated. With reservoir-type coated pellet dosage forms, the polymeric coating of the pellets must remain intact during compression in order to control drug release (Bodmeier, 1997). Proper selection of polymers to withstand the mechanical stresses of compaction and choosing suitable tablet excipients to protect the coated particles from rupture and damage during compression lead to the successful formulation of tablets containing pellets (Abdul et al.,

2010).

Pellets in a MUPS tablet have a mass percentage of 20–70% and range in size from 300 to 2000 μm, with the bulk density of the pellet phase generally greater than 0.7 g/cm^3. In contrast, excipients are typically between 50 and 200 μm with the density of the excipient mixture ranging from 0.4 to 0.6 g/cm^3. These significant differences in average particle size and density make MUPS mixture extremely sensitive to segregation during storage, transport, and feeding of the MUPS formulation into the tablet press, including the point at which the blend is fed into the die for compression. If segregation occurs during transfer, tablets can be produced with an out-of-specification (OOS) pellet concentration and, hence, an OOS active pharmaceutical ingredient (API) content. The content uniformity of the produced batch would subsequently fail quality assurance checks and the batch would be rejected (Vogeleer, 2014). Hosseini et al. (2013) developed segregation-free, ethyl cellulose-coated, extended release MUPS tablets by layering standard tableting excipients onto ethyl cellulose-coated propranolol hydrochloride pellets to form a cushion layer; this eliminated segregation problems and protected the integrity of the brittle ethyl cellulose coating during compression. Vogeleer (2014) introduced an innovative new MUPS production method - a continuous dosing, blending, and compression system - that keeps segregation to an absolute minimum.

1.1.2 MUPS tablets by freeze-drying

Tablets prepared by freeze-drying techniques possess a highly porous structure that enhances the water adsorption and hence facilitates rapid disintegration (Hoang Thi et al., 2015). Freeze drying is a conventional method used to prepare orally disintegrating tablets (ODTs) with the unique property of disintegrating in the mouth within seconds without chewing or the need for water. This method solved some of the problems encountered in administration of drugs to pediatric and elderly patients, who constitute a large proportion of the world's population. However, this process has some disadvantages, including high production costs and long processing time. ODTs prepared using freeze-drying methods are fragile, lack physical resistance in standard blister packs, and have limited capacity or ability to

incorporate high concentrations of active drug (Badgujar et al., 2011).

Freeze drying could be useful in the formulation of multiparticulates into ODTs. However, three major requirements need to be addressed in order to ensure development of a successful formulation. First, a highly viscous liquid formulation is needed that is able to suspend the multiparticulates long enough to complete the formulation and freeze without compromising the disintegration performance. Second, minimum interactions between the liquid formulation and the multiparticulates are required; such interactions may lead to unwanted changes in the original properties of the multiparticulates, such as early drug leakage. For example, the use of a thick hydrophilic environment in the formulation of multiparticulates coated with hydrophobic polymers reduces premature drug release, whereas an acid formulation ensures integrity of enteric-coated multiparticulates. Third, physical protection against possible damage during freezing and annealing as a result of ice crystal growth is required (Alhusban et al., 2011).

Alhusban et al. (2011) lyophilized ODTs containing 120.5 mg of omeprazole enteric-coated pellets (10-mg dose of omeprazole, with a pellet diameter of 710±40 μm) using an 18 mm diameter mold. The tablets disintegrated in less than 19 s and had an average hardness of 17.24 ± 0.74 N (n = 3). The solution was viscous at 172±21.3 m Pa s (n = 3) and was able to suspend the pellets with no obvious settling or aggregation of the pellets before transferring the formulation to the freezer. Moreover, no degradation or color change was noticed throughout the mixing, freezing, and lyophilizing stages. Stange et al. (2015) freeze dried ODTs containing large fractions (717 mg) of taste-masked naproxen sodium granules in blisters using Lyostar® II Smart™ freeze-dryer technology and obtained mechanically stable tablets (33.4±8.8 N) that disintegrate within 3 s without compromising the coating or resulting in deterioration of the taste-masking properties.

1.2 Acid-labile drugs

Acid-labile drugs are easily degraded in acidic medium, which have been mainly formulated

as enteric-coated dosage forms for oral administration. Proton pump inhibitors (PPIs) are a group of such acid-labile drugs.

1.2.1 PPIs

Inappropriate levels of gastric acid underlie several widespread pathological conditions, including gastroesophageal reflux disease (GERD), for which heartburn is the most common symptom, and peptic ulcers, which cause pain and suffering in millions of people. Gastric acid is secreted by parietal cells of the stomach in response to stimuli such as the presence of food in the stomach or intestine and the taste, smell, sight or thought of food. Such stimuli result in the activation of histamine, acetylcholine, or gastrin receptors (H2, M3, and CCK2 receptors, respectively) located in the basolateral membrane of the parietal cells, which initiate signal transduction pathways that converge on the activation of H^+,K^+-ATPase—the final step of acid secretion. Inhibition of this proton pump has an advantage over other pharmacological approaches in that it reduces acid secretion independently of how secretion is stimulated. For example, inhibition of acid secretion by H2 receptor antagonists can be overcome by food-induced stimulation of acid secretion via gastrin or acetylcholine receptors (Fig. 1) (Olbe et al., 2003). Chemically, the basic structure of PPIs consists of a substituted benzimidazole ring and a substituted pyridine ring connected to each other by a methylsulfinyl chain (Jain et al., 2007). These compounds covalently and irreversibly inhibit H^+,K^+-ATPase. Omeprazole, pantoprazole, lansoprazole, rabeprazole, and others (Fig. 2) belong to this class of agents (Olbe, 1999). In an acidic environment (pH ~ 4), protonation of the pyridine and benzimidazole nitrogens results in formation of a tetracyclic sulfenamide, which represents the active form of the drug. The sulfenamide binds to exposed cysteine residues in the alpha subunit of H^+,K^+-ATPase to form covalent disulfide bonds, which inhibit the activity of the pump (Horn, 2000). Relatively few serious adverse effects have been reported for PPIs (Stedman et al., 2000).

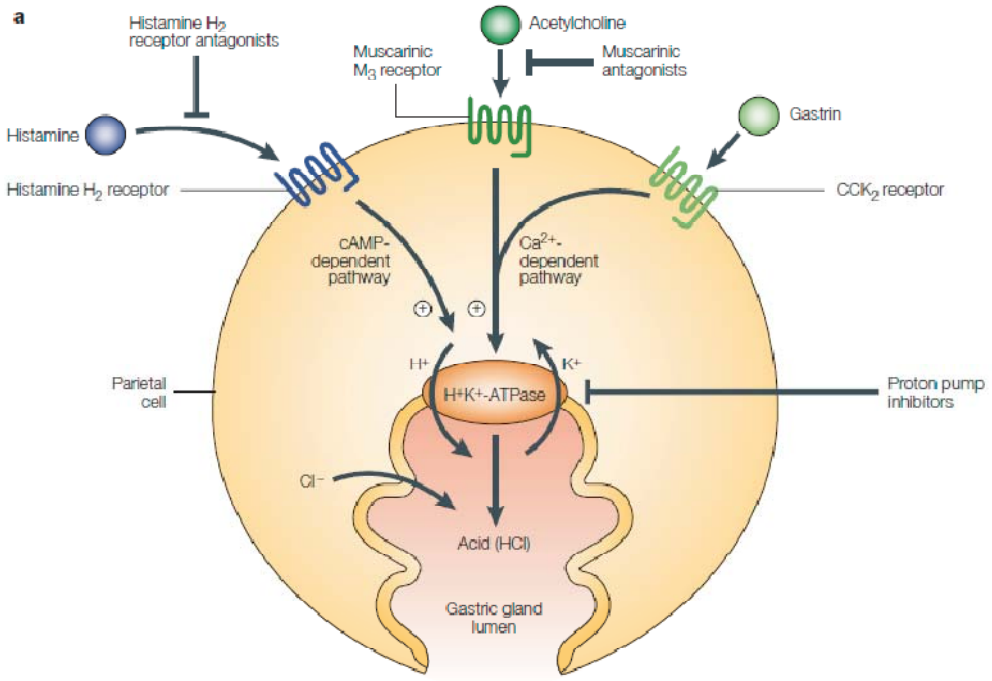


Fig. 1 Proton-pump inhibition (Olbe et al., 2003)

1.2.2 Selection of model drugs

Lansoprazole and rabeprazole are two PPIs that share the parent structure of 2-pyridylmethylsulfinyl benzimidazole, but differ in substitution on the pyridine ring (Fig. 2). The different substitutions on the pyridine or benzimidazole moieties are added to modify solution reactivity or to decrease toxicity (Huber et al., 1995). Lansoprazole is a base that is practically insoluble in water (EDQM, 2016), whereas rabeprazole sodium is very soluble in water (MHLW, 2015). They were chosen as drug pair in this study because of their distinct differences in water solubility, yet similar physicochemical instability and therapeutic effects. Moreover, the newest PPI, ilaprazole (named also as IY-81149) was chosen since it is chemically close to lansoprazole and insoluble in water.

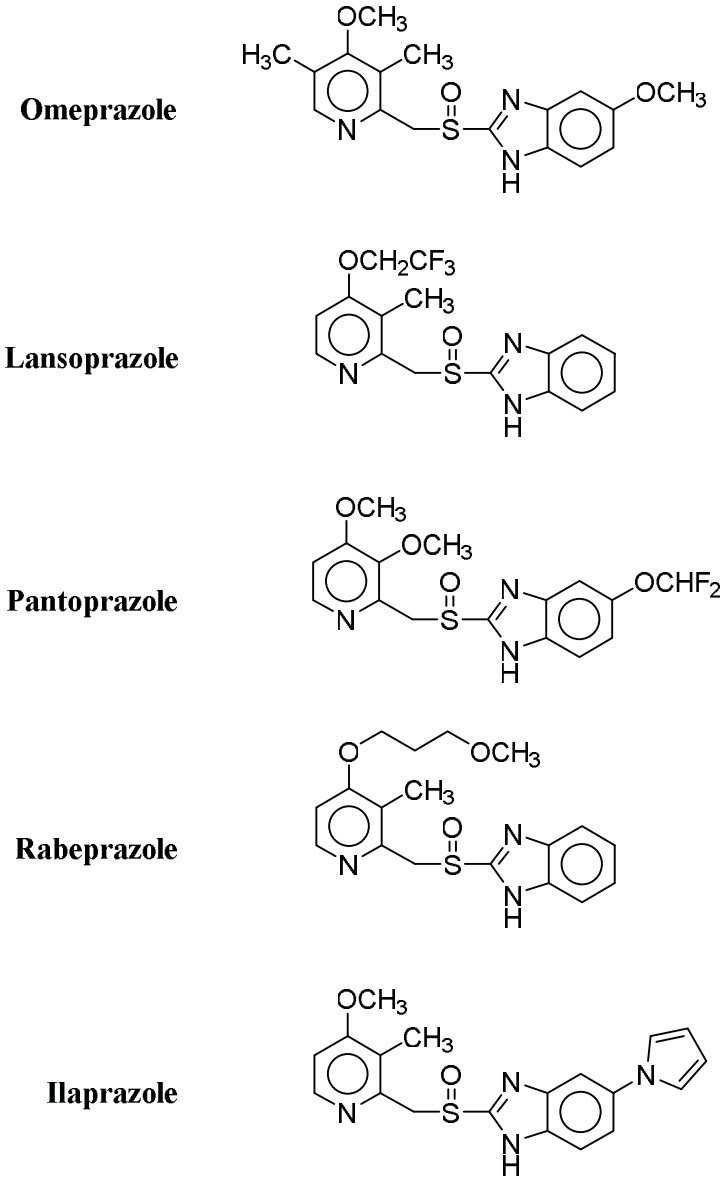


Fig. 2 Chemical structure of PPIs

1.2.2.1 Lansoprazole

Lansoprazole was developed and launched by Takeda Pharmaceutical Co. Ltd. in December 1991. As of April 2017, the available lansoprazole dosage forms include delayed-release capsules, ODTs, and intravenous injections. Lansoprazole is indicated for a number of GI conditions including the short-term treatment of active duodenal and benign gastric ulcers, the eradication of *Helicobacter pylori* to reduce the risk of duodenal ulcer recurrence, the maintenance therapy of healed duodenal ulcers, the short-term treatment of GERD and

erosive esophagitis, the prevention of non-steroidal anti-inflammatory drug (NSAID)-associated gastric and duodenal ulcers, the maintenance of erosive esophagitis, and the long-term treatment of hyper-secretory conditions including Zollinger-Ellison Syndrome. Other therapeutic indications such as gastric secretion inhibition, anticancer, antibacterial, acid pump inhibitor, and anti-ulcerant properties are still under investigation (Thomas Reuter, 2014).

The chemical formula for lansoprazole is 2-[[[3-methyl- 4-(2,2,2-trifluoroethoxy)-2-pyridyl]-methyl]sulfinyl] benzimidazole [CAS. 103577-45-3], with an empiric formula of $C_{16}H_{14}F_3N_3O_2S$ and molecular weight of 369.36. The compound differs from omeprazole and esomeprazole on the pyridine and benzimidazole rings. It has been suggested that this modification may account for the greater bioavailability of lansoprazole than that of omeprazole (Thomas Reuter, 2014).

In a randomized, double-blind, multicenter study with a total of 3510 patients over 8 weeks, lansoprazole 30 mg once daily relieved heartburn symptoms faster and more effectively than omeprazole 20 mg once daily in patients with erosive esophagitis (Richter et al., 2001). Another randomized, 2 period, crossover design study assessed the effects of dexlansoprazole, lansoprazole, esomeprazole, and omeprazole on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers (Frelinger et al., 2012). This study demonstrated that generation of clopidogrel active metabolites and inhibition of platelet function were reduced less by co-administration of dexlansoprazole or lansoprazole with clopidogrel than by co-administration of esomeprazole or omeprazole, suggesting that the potential for PPIs to attenuate the efficacy of clopidogrel could be minimized by the use of dexlansoprazole or lansoprazole rather than esomeprazole or omeprazole (Thomas Reuter, 2014).

1.2.2.2 Rabeprazole sodium

Rabeprazole sodium is a fast-acting PPI with a 24-h duration of action that was co-developed and launched by Eisai and Johnson & Johnson in 1997. Rabeprazole sodium is currently

marketed globally under the trade names Aciphex® Sprinkle™ (rabeprazole sodium) delayed-release capsules (5 mg or 10 mg) and Aciphex® (rabeprazole sodium) delayed-release tablets (10 mg or 20 mg). Aciphex® rabeprazole sodium delayed-release tablets are indicated in adults for healing of erosive or ulcerative GERD, maintenance of healing of erosive or ulcerative GERD, treatment of symptomatic GERD, healing of duodenal ulcers, *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence, and treatment of pathological hyper-secretory conditions including Zollinger-Ellison Syndrome. Aciphex® Sprinkle™ delayed-release capsules are indicated for pediatric patients 1 to 11 years of age for treatment of GERD for up to 12 weeks.

Rabeprazole is a monosodium with a chemical formula of (RS)-2-({[4- (3-methoxypropoxy) -3-methylpyridin-2-yl]methyl}sulfinyl)-1H-benzoimidazolide [CAS. 117976-90-6], an empiric formula of $C_{18}H_{20}N_3NaO_3S$, and a molecular weight of 381.42 (MHLW, 2015).

Besancon et al. (1997) found that rabeprazole inhibits ATPase activity faster than that of omeprazole and lansoprazole. Further, proton transport of rabeprazole correlates with the degree of acid stability to a greater extent than that of omeprazole and lansoprazole. Willians et al. (1998) assessed the effects of 8 days of dosing with rabeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in 24 young healthy male subjects in a placebo-controlled trial, concluding that rabeprazole 20 mg once daily has a significantly faster onset of anti-secretory activity than omeprazole 20 mg once daily. On day 8 of dosing, the decrease in 24-h intragastric acidity was greater with rabeprazole than that of omeprazole, but the difference was not statistically significant. Pantoflickova et al. (1998) compared acid inhibition of four PPIs on the first day of dosing in a cross-over, double-blind, randomized study performed in 18 *H. pylori*-negative subjects. The intragastric pH (3.4) and time at pH > 4 during the 24-h post-dose (8.0 h) were significantly greater with rabeprazole than with lansoprazole, pantoprazole, omeprazole capsule, omeprazole MUPS tablets, or placebo. Daytime and nighttime pH values were higher with rabeprazole and lansoprazole than with pantoprazole, omeprazole capsule, and omeprazole MUPS tablet. Rabeprazole was shown to

be the most potent acid inhibitor of all the PPIs tested during the first day of dosing. Willians et al. (1998) concluded that rabeprazole has more effective *in-vitro* antibacterial properties against *Helicobacter pylori* than those of either lansoprazole or omeprazole.

1.2.2.3 Ilaprazole

Ilaprazole (IY-81149) was developed and launched by Il-Yang Pharm. Co., Ltd, Korea, in December 2009. In January 2017, the enteric-coated tablet was approved for peptic ulcers, including *Helicobacter pylori*-induced stomach ulcers, reflux esophagitis, and erosive esophagitis (Thomas Reuter, 2017). Ilaprazole is currently marketed globally with the trade names of Yi Li An® ilaprazole enteric-coated tablets, Alwel® ilaprazole tablets, and Noltec® ilaprazole tablets.

Ilaprazole (2-[[(4-methoxy-3-methyl)-2-pyridinyl]methyl]sulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole (CAS: 172152-36-2) has an empirical formula of $C_{19}H_{18}N_4O_2S$ and molecular weight of 366.43 g/mol. The structure contains a methoxy group at the C4 position and a methyl group at the C3 position of the pyridine ring and a pyrrole ring at the C5 position of the benzimidazole ring; these small substituents strongly affect the pKa value of the pyrimidine N of ilaprazole (Kwon et al., 2001).

Ilaprazole has been demonstrated as a strong PPI with superior potency against gastric acid secretion than omeprazole (Kwon et al.,2001). In a randomized, parallel, double-blind, double-dummy, and omeprazole-controlled phase III clinical trial in 496 patients over 4 weeks, ilaprazole (10 mg/day) was as effective as omeprazole (20 mg/day) in the treatment of duodenal ulcers with similar side effects. The efficacy of ilaprazole was unaffected by CYP2C19 polymorphisms (Wang et al., 2012). Ji et al. (2014) performed a meta-analysis of randomized controlled trials comparing the efficacy and tolerance of ilaprazole and other PPIs in the treatment of duodenal ulcers, which indicated that the adverse effect rate in the ilaprazole group was lower than that in the control group, but the difference was not significant. Bortoli et al. (2013) concluded that further studies were required to assess the clinical advantages of ilaprazole in patients with GERD and other acid-related

gastrointestinal disorders.

1.3 Influence of core type on drug layering and drug release

1.3.1 Core type

The starting cores could consist of several different compositions and with different particle size distribution (PSD). For example, Nonpareil® from Freund Corporation includes four core types made from purified sucrose and corn starch (Nonpareil®-101), purified sucrose (Nonpareil®-103), lactose and microcrystalline cellulose (MCC) (Nonpareil®-105), and D-mannitol (Nonpareil®-108), respectively (Freund Corporation, 2016). Celphere™ is a 100% MCC spherised core from Asahi Kasei Chemicals. Suglets®(Colorcon) is made of sucrose and starch. There is a growing interest toward applying sugar substitutes (polyols, polyalcohols) as excipients for pharmaceutical formulations (Kállai-Szabó et al., 2014). Examples included isomalt cores and cores made of isomalt and MCC mixtures.

Cores can also be classified as water-soluble or water-insoluble according to the solubility of their constituents. A higher yield without the formation of undesirable agglomerates was observed for cores composed of MCC because of their insolubility in water during drug layering (Gryczová et al., 2008). Sugar spheres have long been used as inert cores and are monographed in the major pharmacopeias (EP, USP, JP). MCC, the gold standard for extrusion-spheronization, is widely used, but possesses various disadvantages such as drug adsorption to the surface of its fibers, chemical incompatibility with a number of drugs, and a lack of disintegration when used in matrix pellets. Isomalt, a polyol produced from sucrose, is a novel potential carrier core exhibiting multiple health benefits attributable to it having a low glycemic and low insulinemic response, and thus is suitable for diabetics. Another advantage of the isomalt polyol is that it does not contain a carbonyl group, making Maillard reactions impossible; hence, it is chemically more stable than related saccharides (Kállai et al., 2010).

1.3.2 Core deformation and fragmentation

Maganti et al. (1993) found that powders compacted by plastic deformation produce strong compacts, whereas their pellets (500-1000 μm) exhibit elastic deformation and brittle fragmentation, resulting in compacts of lower tensile strength. Johansson et al. (1995) investigated the compression behavior and compactability of MCC cores (710-1000 μm) produced by extrusion-spheronization in relation to their pore structure and mechanical properties. They found that the MCC cores were compressed by permanent deformation rather than fragmentation. The degree of core deformation increased with increasing original core porosity, while the mechanical strength of the cores was not a primary factor in their compression behavior. Core porosity determined the degree of their deformation during compression, which in turn controlled the pore structure and the tensile strength of the compact. Johansson et al. (1996) quantified the degree of deformation and densification of cores during compression with two sets of MCC cores (710–1000 μm) with marked differences in intra-granular porosity. They found that high porosity cores showed both a high compression-induced change in shape and a marked decrease in core porosity. The low porosity cores showed only limited local permanent deformation during the compression, and the pellet porosity was unaffected by the compression. Bead cores should deform and recover after compression without damage to the coating. The core size also affects the compaction properties (Bodmeier, 1997). Johansson et al. (1998) prepared and compacted MCC cores (size fractions 425–500 μm and 1250–1400 μm, porosity 38%), concluding that the original size of the cores does not affect the volume or porosity changes of the tablet with tablet formation pressure. Consequently, the degree of densification of individual pellets during compression is independent of the original core size. However, the degree of deformation of individual cores during compression is higher for larger cores. Therefore, there is a different dependence on core size for the dominating mechanisms of compression for this type of aggregate.

Miller et al. (1999) found that most mechanical properties of tablets compressed from coated

spheres are comparable to those of tablets compressed from uncoated spheres (namely, sugar spheres NF, Nu-Pareil 14/18 mesh, corresponding to 1000-1410 μm). Bashaiwoldu et al. (2011) found that the compressibility and compactability of the various type of cores was significantly influenced by the nature of the excipient combinations and binder liquids used to prepare the pellet cores (1000–1180 μm). Nicklasson et al. (1999) compared tableting behavior between pellets (710–1000 mm) made of a 4:1 mixture of dicalcium phosphate dihydrate (DCP) and MCC pellets, concluding that the DCP/MCC pellets were more rigid and underwent a different mode of deformation during tableting than the MCC pellets. The DCP/MCC pellets tended to yield tablets of a lower mechanical strength.

1.3.3 Influence of core type on drug layering

Pašić (2008) used sugar pellets Suglets® (850–1000 μm) and MCC pellet Ethispheres® 850 (710-1000 μm) as starter cores for developing stable lansoprazole pellets using a bottom spraying process with a fluidized-bed. He et al. (2010) used nonpareil sugar spheres (500-700 μm) for investigating the influence of sodium carbonate on physicochemical properties of lansoprazole in designed multiple coating pellets. Fang et al. (2014) used nonpareil sugar spheres (500-700 μm) for developing Eudragit L/HPMCAS blend enteric-coated lansoprazole pellets. Takeda Pharmaceutical Co. Ltd. launched Prevacid® (lansoprazole) delayed-release capsules with a sugar core and SoluTab™ (lansoprazole) delayed-release ODTs with a lactose monohydrate-MCC core (Takeda, 2016). Gryczová et al. (2008) compared the influence of sucrose spheres (500-600 μm), Celphere® CP 507 MCC cores (500-700 μm), Cellets® 500 MCC cores (500-700 μm), and self-produced lactose/MCC cores (65:35 w/w, 500-800 μm) on yield using a highly concentrated drug layering solution. The highest yield (85.66-89.41%) was obtained for cores composed of MCC, attributable to their insolubility in water and good mechanical properties. In contrast, soluble and brittle sucrose cores partially dissolved during the process, forming undesirable agglomerates and giving a lower yield (76.2%).

1.3.4 Influence of core type on drug release

Kállai et al. (2010) investigated the effect of isomalt starter pellets (galenIQ™980, 700-1000 μm), sugar spheres (pharm-a-spheres®, 850–1000 μm), and MCC spheres (Ethispheres® 850, 710-1000 μm) on the *in-vitro* drug release kinetics of diclofenac sodium sustained release pellets. The results proved that inert cores were adequate for further processing, and the release mechanism was also influenced by the core type. Sugar- and isomalt-type pellet cores demonstrated similar drug release profiles. Luhn et al. (2012) investigated the effect of MCC cores (Ethispsheres®850, 710–1000 μm) and isomalt-MCC starter pellets (700–1000 μm) (consisting of 100, 50, 30, or 10 % w/w isomalt) on the drug release profile of sodium diclofenac. The results demonstrated that isomalt used in the composite core decreased the vulnerability of the dissolution kinetics to the changes in the osmotic environment.

1.4 Solution drug layering

Based on API solubility, solution drug layering means that the API dissolves in the aqueous binder solution. In contrast, suspension layering occurs when the API is partially soluble or insoluble in the aqueous binder solution. Solution layering is a good choice for drugs with reasonable solubility and viscosity; suspension layering is more flexible than solution layering because of the low viscosity and capability for extensive drug loading (Teng et al., 2010). Striking porous structures were seen when ethanol was used as the solvent for layering tramadol solutions onto non-pareils. These pores are deep, smooth-walled, and of similar size; further, they are distributed throughout the drug layer and are responsible for an increase in surface area of the pellets (McConnell et al., 2009). When an aqueous drug solution was sprayed onto sugar spheres, the surface sucrose was partially dissolved, making the spheres sticky. Pellets are then “glued” together, and after the solvent was removal during drying, larger agglomerates that are irregular in shape and size were formed (Gryczová et al., 2008).

1.5 Water-soluble subcoating polymers

Interactions between a substrate and functional coating can be prevented by the application of

a separating subcoat. A subcoat may also be applied to prevent the migration of a drug substance through the film of a functional polymer coating or to increase the diffusional path length that drug substances must travel for dissolution to occur (Bruce et al., 2008). U.S. patent 4,786,505 (Lovgren, 1988) describes the function of the subcoat as a pH-buffering zone in which hydrogen ions diffusing from the outside towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles. The claim included pharmaceutically acceptable, water soluble, inert polymers, including polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose (HPC), methylcellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose or hypromellose (HPMC), and polyvinyl acetal diethylaminoacetate. The aqueous coating materials that are currently used for pharmaceutical products are predominantly either cellulose derivatives or low-viscosity grades of HPMC (Remuñán-López et al., 1996).

Bruce et al. (2003) observed that the drug release of a highly water-soluble drug, chlorpheniramine maleate, from enteric-coated pellets in acidic media correlated with the water vapor transmission rates derived for the aqueous polymeric subcoated films Eudragit RD 100, Eudragit RS 30D, and Opadry AMB. The subcoat can seal a water-soluble substrate to prevent the migration of the active into the enteric polymer film and prevent the degradation of acid-labile compounds, such as omeprazole (Lovgren et al., 1988). However, it may not always be effective in the improvement of gastric resistance, which necessitates the application of a large weight of enteric-coating. However, subcoated sodium valproate pellets with Methocel E5 to act as a barrier between the water-soluble drug and the enteric film coating and to increase the diffusional path length between the pellet core and the dissolution medium, still failed the USP enteric test conditions, which resulted in a requirement for increased application of the enteric polymer (Bruce et al., 2003).

Water-soluble polymers with low vapor permeability are often combined with hydrophobic additives to act as moisture barriers for immediate release tablets. The vapor transmission rates of HPMC and HPC have been reported as 1.59 and 0.6 g/100 cm^2/day, respectively.

HPMC and HPC are often combined in coatings in order to exploit the adhesiveness and flexibility of HPC and the high mechanical stability of HPMC films (Warnke, 2012).

1.5.1 HPMC

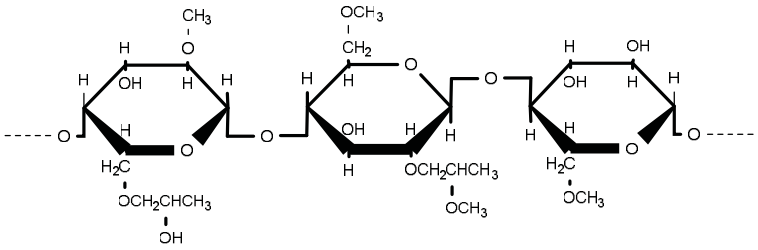
Hypromellose (HPMC) is a methyl and hydroxypropyl mixed ether of cellulose (Table 1) (The United States Pharmacopeial Convention, 2016). The ether-linked methoxy and hydroxypropyl side group substituents are attached through ether linkages to the cellulose chain hydroxy groups (Fig. 3). The first two numbers in the name (HPMC 2208, HPMC 2906, and HPMC 2910) designate the average methoxy content and the last two numbers represent the average percentage of hydroxypropyl substitution (Ford, 2014). The investigation of free films of HPMC prepared from Methocel E5 and Methocel E15 by Nagarsenker et al. (1999) confirmed that the water vapor permeability of the films decreased with a decrease in viscosity. Remuñán-López et al. (1996) concluded that the mechanical and water vapor transmission properties of HPMC films were less influenced by the variables of polymer type, viscosity, plasticizer type, and plasticizer concentration.

Table 1 Methoxy and hydroxypropoxy substitution of hypromellose

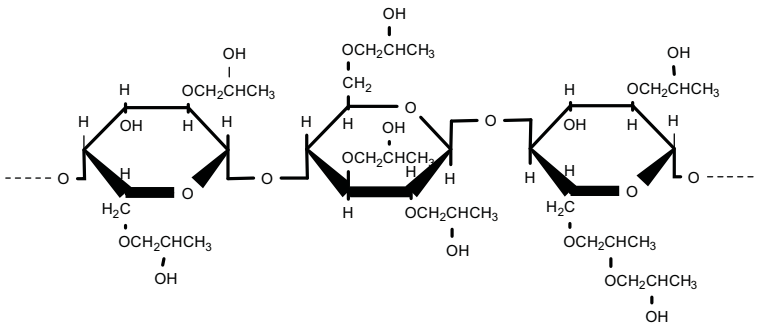
Substitution Type	Methoxy (%)		Hydroxypropoxy (%)	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

Hypromellose 2910 USP grade (Methocel E Premium products) are preferred for use in aqueous film coatings. These products tend to have the best clarity, color, and film-forming properties (The Dow Chemical Company, 2002) with cloud points of approximately 56°C in aqueous 2% w/w gels (Mitchell et al., 1993). The glass transition temperature (Tg) of free HPMC films was found to be 159°C (Bley et al., 2009) and the Tg of HPMC E5 was reduced from 155°C to approximately 72°C as the moisture content was increased from zero to approximately 15% w/w (Hancock et al., 1994). Tablets coated with Methocel E5 showed the

highest water uptake rates in the investigated polymers at early time points (up to 1.46%/day), which can be attributed to the relatively high hydrophilicity of HPMC and its significant swelling capacity (Bley et al., 2009).



HPMC



HPC

Fig. 3 Chemical structure of HPMC and HPC

1.5.2 HPC

HPC is a highly substituted cellulose ether, with 3.4–4.1 moles of hydroxypropyl substituent per mole of anhydroglucose backbone units (Fig. 3). The hydroxypropyl substituent groups comprise up to 80% of the mass of HPC. This high level of substitution renders HPC more thermoplastic and less hygroscopic than other water-soluble cellulose ethers. Chan et al. (2010) determined the water solubility of HPC was temperature dependent with a cloud point of approximately 45°C.

Klucel HPC is a nonionic polymer. The viscosity of the solutions was unchanged as the pH is varied from 2.0 to 11.0. For the optimum storage stability, the pH should be maintained between 6.0 and 8.0. Klucel has a low affinity for water. At any given relative humidity (RH),

it has a lower equilibrium moisture content than most other water-soluble polymers, with an equilibrium moisture content of 4% at 50% RH and 23°C and an equilibrium moisture content of 12% at 84% RH and 23°C. Films of Klucel are inherently flexible with good heat sealability (Aschland, 2012).

Bergstrand et al. (1999) found that using a certain quality of HPC, with a cloud point of not less than 40°C, preferably 41°C, as a constituent of the layer separating a core material comprising omeprazole from the enteric-coating layer could fulfill the criteria on release rate stability. A range of Tg values (19°C, 20°C, and 21°C) has been reported in the literature (Nyamweya et al., 2000). Picker-Freyer et al. (2007) found that HPC was a semicrystalline polymer with a Tg between -25°C and 0°C as the moisture content was varied from approximately 10% to 1%. Samuels (1969) found that morphologically, water-cast HPC films had 15% crystallinity. The HPC molecule has a cellulosic backbone of anhydroglucose units twisted into an irregular 31 helix. There are three anhydroglucose units per 15.0 Å repeat. The poly (propylene oxide) side chains are intramolecularly hydrogen-bonded to the cellulosic backbone to produce a stiff, rodlike molecule; the bonding reduces the reactivity of this group.

1.5.3 Blends of HPMC and HPC

Although there are similarities in the chemical structures of HPC and HPMC, HPMC/HPC blends were found to be immiscible owing to the absence of favorable interactions between the polymers (Nyamweya et al., 2000). When used alone, the HPC film may be tacky and cause problems in sticking or picking of tablets. But when HPC used in combination with hypromellose, the HPC product imparts better adhesion (The Dow Chemical Company, 2016). Films prepared with HPMC and HPC blends in the ratios of 9:1 and 8:2 significantly lowered the moisture permeability, with the maximum adhesion demonstrated from 8:2 blends (Shin et al., 2015).

1.6 Acid resistance of enteric-coated MUPS

Delayed-release formulations are designed to protect an acid-labile drug substance from

degradation in the stomach or to protect stomach tissues from irritation. The coating polymer is chosen not only to resist dissolution in the lower pH of the gastric environment, but also to dissolve in the higher pH intestinal environment (The United States Pharmacopeial Convention, 2016). The dissolution method of delayed release dosage forms with apparatus 1 (basket) and apparatus 2 (paddle) described in USP is composed of an acid stage and a buffer stage. Method A (750 mL) or method B (1000 mL) using 0.1 N hydrochloric acid (HCl) at a temperature of 37 ± 0.5°C is used for the acid stage. An aliquot of the fluid in 0.1 N HCl after 2 h of operation is obtained to determine the test dosage form's acid resistance (The United States Pharmacopeial Convention, 2016). In acid resistance test, numbers of enteric-coated PPIs pellets are individually exposed to acid for 2 h, the tablets or pellets are collected and dissolved in an alkaline solution, and the amount of drug remaining intact after acid exposure is determined (Olbe, 1999). In a USP monograph of lansoprazole delayed-release capsules, the capsules were placed into 0.1 N HCl (500 mL, apparatus 2) rotating at 75 rpm for 60 min, and then a 25-mL aliquot was withdrawn at 60 minutes to measure UV absorption. No more than 10% of the labeled amount of lansoprazole should be dissolved within 60 minutes (The United States Pharmacopeial Convention, 2016). In a draft monograph of rabeprazole sodium delayed-release tablets, the tablet was placed in 0.1 N HCl (750 mL, apparatus 2) rotating at 100 rpm for 2 h, and then the remaining rabeprazole tablet is determined using an high performance liquid chromatography (HPLC) method. No more than 10% of the labeled amount should be dissolved (The United States Pharmacopeial Convention, 2012). No compendial method for acid resistance test of ilaprazole product was found.

In-vitro release testing may be used as a surrogate to demonstrate consistent availability of the drug substance from the formulated dosage (The United States Pharmacopeial Convention, 2016). Therefore, knowing the amount of drug remaining intact after acid exposure is important to ensure availability. The integrity of the enteric-coating and intrinsic stability affect the amount of intact drug remaining inside enteric-coated units. Rabeprazole sodium degrades rapidly at pH 6.8 and 7.5 during the first hour (30% and 13.4%, respectively) (Garcia et al., 2006). Slight permeations of the acidic medium during the acid stage of the

dissolution test may not destroy the integrity of the enteric-coating, but may cause rabeprazole sodium to degrade inside the intact pellets to a greater extent than that of lansoprazole. Therefore, in this study, an acid stage of one hour was used for the acid resistance test of lansoprazole and rabeprazole sodium from the pellets and pellet-tablets to alleviate interference attributable to the instability of rabeprazole sodium during the membrane performance tests. An acid stage of 2 hours was kept for ilaprazole pellets and pellet-tablets.

1.7 Suspending agent

Suspending agents help reduce the sedimentation rate of particles in a suspension. They also act as thickening agents, increasing the viscosity of the solution. A good suspension should have well-developed thixotropy (shear thinning). At rest (low-shear rates), the solution should be sufficiently viscous to prevent sedimentation of the particles. When agitation is applied, the viscosity should decrease to provide good flow characteristics. Oral suspensions and syrups are examples of “thickened” liquid dosage forms that may be found desirable by patients who have difficulty in swallowing tablets or capsules (e.g., very young children) (Kulkarni et al., 2016). For enteral tube feeding, prominent shear thinning can ensure the complete delivery of the suspension.

1.7.1 Sodium hyaluronate

Hyaluronic acid, hyaluronan, and sodium hyaluronate are similar names for a linear natural polysaccharide that occurs in many biological tissues and matrices, forming a group of natural, very complex glycosaminoglycans with repeating units of N-acetyl-D- glucosamine and D-glucuronide (Kupská et al., 2014). Their function in the body is, amongst other things, to bind water and lubricate movable parts of the body, such as joints and muscles (Necas et al., 2008). These glycosaminoglycans can be used as humectants, lubricants, and sustained-release agents (Rowe et al., 2006). The physical properties and functions of sodium hyaluronate are based on its ability to form viscoelastic aqueous solutions (Haxaire

et al. 2000). Sodium hyaluronate solutions manifest very unusual rheological properties and are exceedingly lubricious and very hydrophilic (Necas et al., 2008). The bulk viscosity (zero shear viscosity) of sodium hyaluronate solutions is strongly dependent on concentration and molecular weight. A 2-fold increase in concentration or molecular weight results in a 10-fold increase in bulk viscosity (Bothner et al., 1987). The cohesive properties of sodium hyaluronate in solution have been found to correlate with the high frequency complex viscosity and high frequency loss modulus independent of molecular weight (Falcone et al., 2006). When the concentration decreases and the molecules are not crowded or when the average molecular weight is very low, the frequency dependence of the viscosity drastically decreases (Balazs, 2004). Increasing the pH of a neutral salt solution of sodium hyaluronate to 12.5 produces a rapid drop in viscosity which is reversible upon restoring the pH to neutrality (Mathews et al., 1977). Around pH 2.5, a gel-like behavior is shown and is attributed to cooperative interchain interactions due to the reduction of the polymer net charge and may be the protonation of the acetamido groups (Gatej et al., 2005). High pseudo-plasticity facilitates injection of sodium hyaluronate through a small-gauge cannula (Higashide et al., 2008).

1.7.2 Xanthan gum

Xanthan gum is a high-molecular-weight polysaccharide gum produced by a pure-culture fermentation. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid (The United States Pharmacopeial Convention, 2016). Xanthan gum is used as a gelling agent, stabilizing agent, suspending agent, sustained-release agent, and viscosity-increasing agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range. Xanthan gum gels show pseudoplastic behavior, with shear thinning being directly proportional to shear rate. Viscosity returns to normal immediately upon release of shear stress (Rowe et al., 2006). These applications stem from the ability of xanthan gum to induce high viscosity at low polymer concentrations in aqueous solutions (Li et al., 2015). Xanthan

gum solutions prepared with tap water and ground water have much lower viscosity compared to solutions prepared with deionized water, presumably owing to the ionic strength and composition of these waters (Zhong et al., 2013).

1.7.3 Rheological behavior of polymer solutions

The viscosity of a solution is related to shear rate and shear stress. Shearing occurs whenever a fluid is moved or made to flow, as in mixing, pouring, and flowing through a cannula. The shear rate is of special importance for understanding the rheological behavior of solutions containing flexible polysaccharide molecules such as sodium hyaluronate. These solutions exhibit a shear thinning (pseudoplastic) behavior. That is, with increasing shear rate, the flexible molecules will deform and align in the streamlines of flow. Therefore, the flow will be affected to a lesser extent and viscosity will decrease in an inverse proportion to the increasing shear rate. Viscosity at high shear rates is important; for example, when considering the force required to push a solution through a thin cannula. In such circumstances, the shear rate is in the order of 1000–10000 L/s, and the viscosity should preferably be very low to allow easy handling of the solution. At low shear rates, the viscosity levels approach a constant value, i.e. the zero shear viscosity at steady-state (Bothner et al. 1987). At very high shear rates, non-Newtonian shear thinning fluids behave like Newtonian fluids with constant viscosity similar to the solvent (Safari et al., 2016).

In many cases, polysaccharide mixtures exhibit rheological behavior that is not simply a linear combination of individual contributions (Florjancic et al., 2002).

1.8 Pellet suspension

Troy (2005) summarized three major concerns associated with using suspensions: 1) ensuring adequate dispersion of the particles in vehicle; 2) minimizing settling of the dispersed particles; and 3) preventing caking of these particles when sediments form. Stokes' law and the Einstein equation are two classic laws interpreting the sedimentation and viscosity of rigid, spherical particle suspensions in very dilute systems.

1.8.1 Stokes' law

Assuming that all dispersed particles are of uniform shape and size and that the particles are sufficiently far apart so that the movement of one does not affect the neighboring particles, the rate of sedimentation of particles can be determined by Stokes' law:

$$V = \frac{d^2(\rho_1 - \rho_2)g}{18\eta_0} \qquad \text{Eq. 1}$$

where, V is the terminal velocity of sedimentation (cm/s); d is the diameter of the particle (cm); ρ_1 and ρ_2 are the densities of the suspended particles and the medium, respectively; g is the acceleration attributable to gravity; and η_0 is the viscosity of the medium (Kulshreshtha et al., 2009). Stokes' law is valid for diluted pharmaceutical suspensions that are composed of no more than 2% solids (Martin, 2006).

From the Stokes' equation, reduction of particle size and increased viscosity of dispersion medium decreases the velocity of sedimentation of the suspended particles. Meanwhile, to retain the desirable syringability of suspensions for enteral tube feeding, an ideal suspension should have high viscosity during standing and low viscosity during injection.

1.8.2 Einstein equation

Einstein's inaugural dissertation of 1906 can be considered as the starting point of suspension rheology. According to Einstein (1906, 1911), the effective viscosity of a dilute suspension of rigid, non-interacting spherical particles is:

$$\eta = \eta_0(1 + 2.5\phi) \qquad \text{Eq. 2}$$

where, ϕ denotes volume fraction, η is the effective (i.e. macroscopic) suspension viscosity, and η_0 is the viscosity of the suspending medium (pure liquid) (Pabst, 2004).

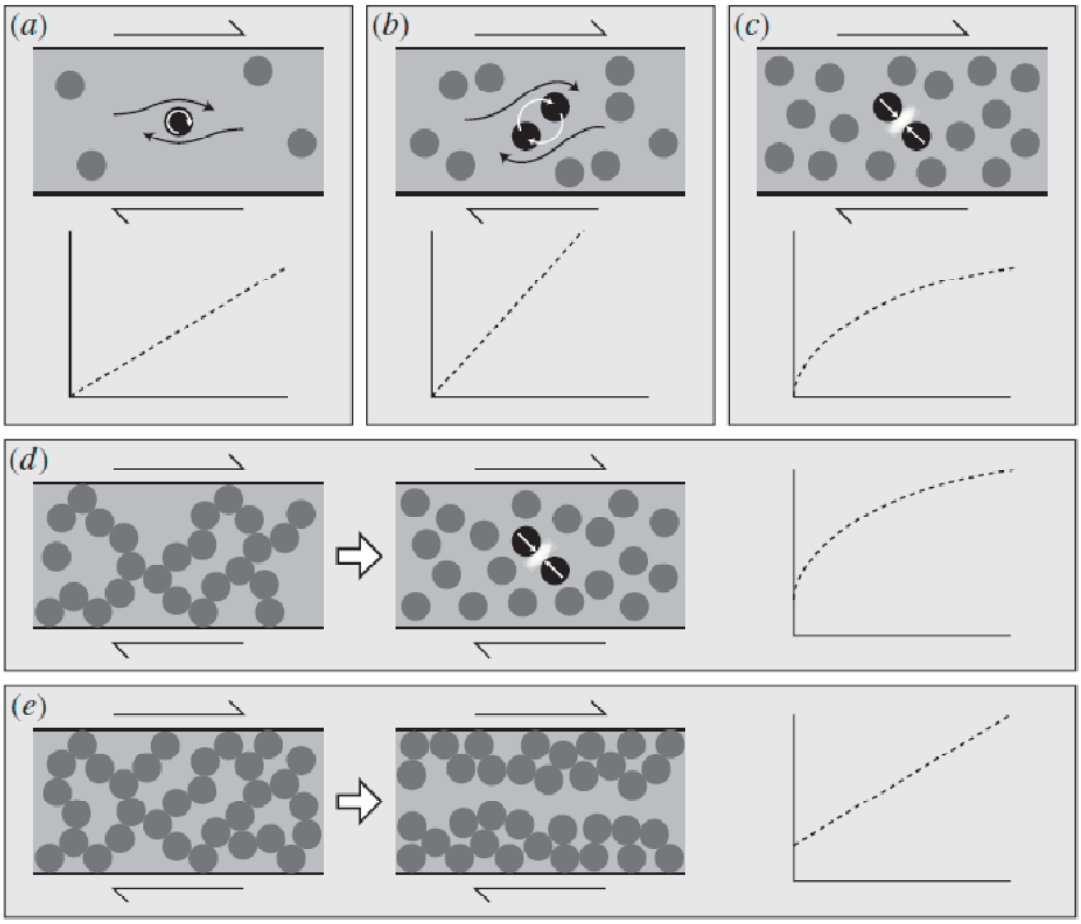


Fig. 4 Rheology change of particle suspension as particle volume fraction ϕ increases from (a) to (e). Each regime is illustrated with a sketch showing the microstructural processes that control rheology and a typical flow curve τ (γ) (Mueller et al., 2010).

Mueller et al. (2010) produced a microstructural explanation (Fig. 4) for the observed rheological changes as ϕ increases. They observed shear-thinning at intermediate particle volume fractions (n<1). The typical minimum separation between particles is sufficiently small that squeezing-flow in the small gaps between approaching particles causes local viscous heating, lubricating the passage of the particles and leading to a decrease in viscosity at high strain rates.

1.9 Applicability of MUPS dosage forms

Some approved MUPS can be prescribed for nasogastric (NG) tube feeding (Table 2). Interestingly, most of these drugs are PPIs. Among them, only Nexium® esomeprazole magnesium for delayed-release oral suspension, Prevacid® SoluTab™ lansoprazole delayed-release ODTs, Dexilant® SoluTab™ dexlansoprazole delayed-release ODTs, and Prilosec® omeprazole for delayed-release oral suspension are prescribed for 8-Fr (French) NG tube feeding.

Among 345 products approved from 2010 to 2016 in Germany, 142 products were indicated for use in children younger than 24 months, and solutions and suspensions turned out to be the most used oral dosage forms (Fig. 5) (Verband Forschender Arzneimittelhersteller e.V., 2016). Multiple-unit dosage forms (e.g. pellets or granules) may be advantageous if the drug is unstable in liquid formulations, the taste of the drug is unacceptable to the child, there is a lack of suitable excipients for children, or controlled release mechanisms are favorable (Schirm et al., 2003). Standing et al. (2005) prospected that (mini) tablets, chewable tablets, dispersible tablets, or oral liquids are more suitable for children based on their ability to swallow and preferences. Multiparticulate formulations offer an alternative to solid and liquid dosage forms in order to meet the needs of the heterogeneous pediatric population. Patients older than 6 months of age may be able to swallow multiparticulates in soft food, although the occurrence of chewing and the significance of grittiness of the formulation must be considered for taste masked, enteric-coated, or modified release particles (Bowles et al., 2010). MUPS products approved for administration to children younger than 24 months are summarized in Table 3.

Table 2 Approved MUPS for NG tube feeding

Brand	Product name	Medium	NG tube	Population	Source
Nexium	Esomeprazole magnesium delayed release capsule	Water 50 mL	-	> 1 month	AstraZeneca, 2014
Nexium	Esomeprazole magnesium for delayed-release oral suspension	Water 5/15 mL	> 6 Fr	> 1 month	AstraZeneca, 2014
Prevacid	Lansoprazole delayed -release capsules	Apple juice 40 mL	≥16 Fr	> 1 year	Takeda, 2016
Prevacid SoluTab	Lansoprazole delayed -release ODTs	Water 4/10 mL	≥8 Fr	> 1 year	Takeda, 2016
Dexilant	Dexlansoprazole delayed -release capsules	Water 20 mL	≥16 Fr	> 1 year	Takeda, 2016
Dexilant SoluTab	Dexlansoprazole delayed-release ODTs	Water 20 mL	≥8 Fr	-	Takeda, 2016
Prilosec	Omeprazole for delayed -release oral suspension	Water 5/15 mL	≥6 Fr	> 1 month	AstraZeneca, 2016
Zegerid	Omeprazole/sodium bicarbonate powder for oral suspension	Water 20 mL	-	> 18 years	Santarus, 2014
Protonix	Pantoprazole for delayed -release oral suspension	Apple juice 10 mL	≥16 Fr	> 1 year	Wyethpharms, 2014
Kadian	Morphine sulfate extended -release capsules	Water 10 mL	≥16 Fr	> 18 years	Actavis, 2014

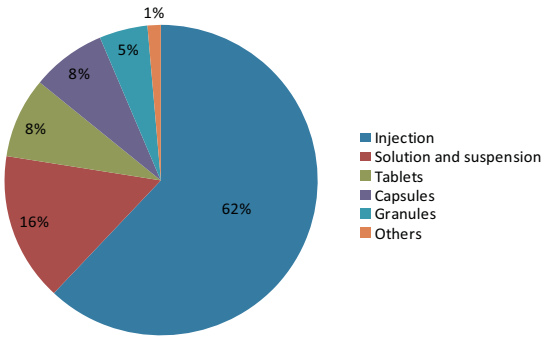


Fig. 5 Ratio of dosage forms in Germany approved for children < 24 months (2010–2016) reproduced from 'Zulassungen und Zulassungserweiterungen für Arzneimittel oder Applikationshilfen für Kinder und Jugendliche seit 2001' (Verband Forschender Arzneimittelhersteller e.V., 2016)

Table 3 MUPS approved by US FDA for children < 24 months

Product Name	Indication	Age	Manufacturer	Approval
Prilosec® (omeprazole) delayed-release capsules	GERD	＞1 year	AstraZeneca Pharms	1989
Prilosec® (omeprazole magnesium) for delayed-release oral suspension	GERD	＞1 year	AstraZeneca Pharms	1989
Zmax® (azithromycin extended release) for oral suspension	Community -acquired Pneumonia	＞3 months	PF Prism CV	1991
Prevacid® (lansoprazole) delayed-release capsules	GERD	＞1 year	Takeda Pharms	1995
Prevacid® SoluTab™ (lansoprazole) delayed-release ODTs	GERD	＞1 year	Takeda Pharms	1995
Nexium® (esomeprazole magnesium) delayed-release capsules	GERD	＞1 month	AstraZeneca Pharms	2001
Nexium® (esomeprazole magnesium) for delayed-release oral suspension	GERD	＞1 month	AstraZeneca Pharms	2001
Creon® (pancrelipase) delayed-release capsules	EPI	＞12 months	Abbvie	2009
Zenpep® (pancrelipase) delayed release capsules	EPI	＞12 months	Forest Labs Inc.	2009
Pancreaze® (pancrelipase) delayed-release capsules	EPI	＞12 months	Janssen Pharms	2010
Ultresa® (pancrelipase) delayed-release capsules	EPI	＞12 months	Forest Labs Inc.	2012
Pertzye® (pancrelipase) delayed-release capsules	EPI	＞12 months	Digesive Care Inc.	2012
Aciphex® Sprinkle™ (rabeprazole sodium) delayed-release capsules	GERD	＞1 year	Eisai Inc.	2013

Patients include those with swallowing disorders, such as motor neuron disease and multiple sclerosis; those with physical obstruction to swallowing, such as esophageal tumors; those unable to ingest food, such as head injury or stroke patients; and those with anorexia due to an underlying disease, such aschronic lung disease, irritable bowel disease, orcancer. Dysphagic patients and those with anorexia, malabsorption, or excessive catabolism may also need long term enteral feeding (Pearce et al., 2002). The enteral feeding tubes (EFT) are typically classified by site of insertion (e.g., nasal, oral, or percutaneous) and location of the distal tip of the feeding tube (e.g., stomach, duodenum, or jejunum), in which NG tube feeding is generally more convenient, less costly, and less labor intensive than other enteral feeding methods. Stomach can tolerate various medications and enteral formulas, including hypertonic preparations (Williams, 2008).

Tube occlusion is a common complication of EFTs, occurring in 23–35% of cases.

Accumulation of viscous feeding formula and/or improperly administered medications, inadequate flushing, and/or small lumen tubing are thought to contribute to feeding tube occlusions (Dandeles et al., 2011); larger bore tubes can be used but often result in patient discomfort and frequent self-extubation (American Gastroenterological Association, 1995). NG tubes made of polyurethane, silicone, and Tygon (sized 5-18 Fr) were approved by the United States Food and Drug Administration (US FDA) for clinical use (Cui, 2014). Among relevant patients, children represent the most challenging group for NG feeding. The recommended NG tube sizes for children are shown in Table 4.

Table 4 Recommended NG tube sizes

Population	**Body weight (kg)**	**Size of NG tube (Fr)**
Small infant	6-7	5-8
Infant	8-9	5-8
Toddler	10-11	8-10
Small child	12-14	10
Child	15-18	10
Child	19-23	12-14
Large child	24-29	14-18
Adult	30-36	16-18

(modified from the reprint version, Children's Hospital of University of Iowa, 2016)

Delivery of pellets through NG tubes could be affected by many factors such as bore size, material of feeding tube, length of the feeding tube, delivery method, liquid volume for reconstitution, liquid volume for flushing, shaking time, size of the pellets, and weight of the pellets. Larson et al. (1996) compared the bioavailability and efficacy of omeprazole as encapsulated enteric-coated granules or as enteric-coated granules delivered via a NG tube (16-Fr) in 10 healthy subjects. The first volunteer's NG tube was removed owing to a large amount of omeprazole granules clumped in the distal tip. The remaining volunteers were administered the granules by flushing 6–10 granules at a time, using a total of 140 mL of water; a long administration time and large fluid volumes were used in this study. Chun et al. (1996) investigated the bioequivalence of a single 30-mg lansoprazole capsule swallowed intact and 30 mg of lansoprazole granules injected through a 16-Fr NG tube with total volume of 120 mL, which essentially allowed complete delivery of the dose in

approximately 3 to 5 minutes. Dunn et al. (1999) found that delivery of omeprazole and lansoprazole granules through 14-Fr NG tubing *in-vitro* was generally poor and highly variable. White et al. (2002) found that delivery of esomeprazole magnesium enteric-coated pellets through 14-Fr NG tubes is more effective when 50 mL of fluid is drawn into the catheter-tip syringe in one-step than when 25 mL of water is initially drawn followed by the addition of another 25 mL of water. The one-step method improved delivery from the syringe to the tube, rather than reducing the number of pellets lodged in the tube. Pellet delivery was significantly different when using 14-Fr NG tubes than when using 8-Fr NG tubes; differences in pellet delivery between 8-Fr NG tubes and other bore-sizes were related to reduced delivery of the pellets into the tube rather than an increase in pellets lodged within the tubes. Freston et al. (2004) delivered a 30-mg lansoprazole orally disintegrating tablet with 10 mL water via an 8-Fr NG feeding tube, which was administered more easily comparing to deliver the pellets from capsule. Shah et al. (2006) found that esomeprazole magnesium enteric-coated pellets dispersed in 30% Ora-Plus, a thick multi-ingredient suspension liquid, showed the best pellet delivery in their study through 14-Fr NG tubes *in-vitro*. When esomeprazole magnesium enteric-coated pellets were used along with water in the 8-Fr NG tubes, retention of 988 pellets in the water dispersion group was observed in one of the 10 trials. This suggests that there is potential for syringe clogging with water-only medium. The Ora-Plus method may require less syringe shaking than tap water, which may help reduce variability among administrators.

In pediatric care, flushing and solution volumes are kept intentionally low in order to prevent gastric overload; the sum of liquid volumes administered does not exceed 15 mL (Ponrouch et al., 2010). A mean acid resistance greater than 94% was reported when infant feeding tubes (6-Fr, 105 cm) and Dobhoff feeding tubes (8-Fr, 109 cm) were used (Bladh et al., 2007). Four PPIs (Mopral®omeprazole 10 mg (AstraZeneca), Nexium® esomeprazole 20 mg (AstraZeneca), Ogast®lansoprazole 15 mg (Takeda), and Ogastro® lansoprazole orally disintegrating tablet 15 mg (Takeda) were administered through NG tubes with 2 mL or 5 mL of water to dissolve or suspend, respectively, and with 2 mL, 5 mL, or 10 mL of water to

flush-through. All NG tubes (6-Fr) were obstructed by the PPIs. The mean recovery of active ingredients through 8-Fr NG tubes was 86.2% for lansoprazole orally disintegrating tablet and 36.9% for esomeprazole; however, only 7.1% was recovered for lansoprazole and 3.9% for omeprazole (Ponrouch et al., 2010).

1.10 Objectives

The objective of this study was to prepare oral multiparticulate formulations of acid-labile drugs, which are promising in delivery of multiparticulate combinations to populations with ingestion problems, such as infants or patients with sucking and swallowing problems, through the administration of intact tablets, via an oral syringe or through EFTs. Three studies were included:

1) Delayed-release pellets of lansoprazole and rabeprazole sodium, based on four type of cores containing different weight ratio of microcrystalline cellulose (MCC) (% w/w) [CP-102 (100% MCC) >laboratory-made cores (45% MCC) > Nonpareil-105 (30% MCC) > PF 053 (0% MCC)], were compressed or lyophilized with sodium hyaluronate and xanthan gum into MUPS tablets. The influence of core type and drugs on drug layering, and swelling, acid resistance, drug release of the top-coated pellets and pellet-tablets was investigated.

2) Ilaprazole delayed-release pellets, subcoated with HPMC, HPC, HPMC-HPC (80:20), respectively, were compressed with sodium hyaluronate and xanthan gum granules. The influence of subcoat and top-coat on water vapor absorption/desorption, acid resistance, drug release of the top-coated ilaprazole pellets and pellet-tablets was assessed.

3) Hyaluronic sodium and xanthan gum as thickening agents and lubricant in the pellet mixture or pellet-tablets had provided anti-sedimentation, shear-thinning, and lubrication effects, which were essential in ensuring swallowability or blockage-free feeding through small-bore feeding tubes.

2. Materials and methods

2.1 Materials

All materials used for the formulations were of pharmaceutical grade. Purified water was used for all preparations.

2.1.1 Drugs

Ilaprazole (< 3 μm) was provided by Hubei Xinyuanshun Pharmaceutical Chemical Co., Ltd. (Wuhan, China). Rabeprazole sodium and lansoprazole were purchased from Rundu Pharmaceutical Co., Ltd. (Zhuhai, China).

2.1.2 Cores

100% MCC cores (Celphere®CP-102, 106–212 μm, Asahi Kasei Chemicals, Tokyo, Japan), 30% MCC cores (70:30 w/w, Nonpareil-105 (150), 106–212 μm, Freund Corporation, Tokyo, Japan), 0% MCC cores (sucrose/starch=85:15 % w/w, Suglets® PF 053 180/250, 180–250 μm, Colorcon, Stoughton, USA), and Suglets® PF 002 (355-425μm, Colorcon, Stoughton, USA) were purchased from the respective suppliers. Laboratory-made cores (45% MCC cores) composed of 55% w/w lactose monohydrate (FlowLac®100, Molkerei Meggle Wasserburg GmbH & Co. KG, Wasserburg, Germany) and 45% w/w MCC (Avicel®PH-101, FMC BioPolymer, Philadelphia, USA) were prepared in the study.

2.1.3 Polymers for coating

Methacrylic acid copolymers (Eudragit® L 30 D-55, Evonik Industries AG, Darmstadt, Germany), hydroxypropylmethylcellulose (HPMC, Methocel®E5 Premium LV, The Dow Chemical Company, Los Angeles, USA), hydroxypropylcellulose (HPC, Klucel® EF, Ashland Inc., Kentucky, USA) were used as purchased.

2.1.4 Coating additives

Magnesium oxide light (MgO, USP, Tomita Pharmaceutical, Tokushima, Japan), sodium

hydroxide (NaOH, Guangzhou Chemical Reagent Factory, Guangzhou, China), talc (Longsheng Huamei Talc Development Co., Ltd., Guangxi, China), triethyl citrate (TEC, Bengbu bbca Tushan Pharmaceutical Co., Ltd., Anhui, China), glycerol monostearate (GMS, Hunan Furong Pharmaceutical Co., Ltd., Hunan, China), Polysorbate 80 (T80, Zhaoqing Chaoneng Industrial Co., Ltd., Zhaoqing, China) and mannitol (Pearlitol 160 C, Roquette Freres, Lestrem, France) were used as purchased.

2.1.5 Thickening excipients

Sodium hyaluronate (≈1,000 kDa, Freda® HA, Bloomage Freda Biopharm Co., Ltd., Jinan, China), and xanthan gum (Gedian Humanwell Pharmaceutical Excipients Co., Ltd., Hubei, China) were used as thickening agents.

2.1.6 Other excipients

Colorants (Shanghai Dyestuffs Research Institute Co., Ltd., Shanghai, China), mannitol (Pearlitol®100SD and Pearlitol 160 C, Roquette Freres, Lestrem, France), microcrystalline cellulose (MCC, Avicel®PH-102, FMC BioPolymer, Philadelphia, USA), crospovidone (PVPP XL, Ashland Inc., Kentucky, USA), magnesium stearate (Anhui Sunhere Pharmaceutical Excipients Co., Ltd., Anhui, China) and citrate acid anhydrous (Er-Kang Pharmaceutical Co., Ltd., Hunan, China) were also used.

® and ™ are not used in the following text.

2.2 Preparation methods

2.2.1 45% MCC cores

Micronized lactose monohydrate FlowLac 100 and MCC Avicel PH-101were mixed at a weight ratio of 55:45 and granulated (G10, Xinyite Science and Technology Co., Ltd., Shenzhen, China) in the following conditions: paddle speed, 120 rpm; chopper speed, 2500 rpm; water (40% based on dry materials) spraying, 1 g/s, for 5 minutes. The granulates were subsequently fluidized (DPL-IIA, Jinggong Pharmaceutical Machinery Co., Ltd., Chongqing,

China) at: rotating speed, 1300 rpm to 500 rpm; process air, 150 m^3/h; atomizing air pressure, 1.0 bar; water spray, 10 g/min; and dried at: inlet temperature, 80°C; product temperature, 60°C; air flow rate, 200 m^3/h; loss on drying (LOD) < 2.0%. The 125–250 μm fraction was used in this study as 45% MCC cores.

2.2.2 Preparation of delayed-release ilaprazole pellets

A bottom-spray fluidized bed coater (DPL-IIA, Jinggong Pharmaceutical Machinery Co., Ltd., Chongqing, China) was used for the coating: nozzle, 1.0 mm; air flow, 150 m^3/h; start pellets, 500 g; product temperature for drying, 55°C.

Drug pellets (8.67% w/w ilaprazole) were prepared by layering drug suspension (0.005% w/w NaOH, 16.13% w/w ilaprazole, 3.23% w/w HPMC) on PF 002 cores. Drug pellets were subcoated with suspension [8.33% w/w talc, 4.17% w/w HPMC or HPC or HPMC-HPC (80:20)] to a weight gain 22% based on weight of drug pellets. Besides, 30% weight gain of HPMC subcoat was prepared also. The subcoated pellets were enteric-coated with emulsion (16.56% w/w Eudragit L30 D-55 in solid content, 3.30% w/w TEC, 0.83% w/w GMS, 0.33% w/w T80) to a weight gain 45% based on weight of subcoated pellets. The enteric-coated pellets were top-coated with HPMC solution (9.51% w/w pearlitol 160C, 4.80% w/w HPMC) to a weight gain 10% based on weight of enteric-coated pellets. The LOD of each type of pellets was < 2.0%. The coating parameters were shown in Table 5.

Table 5 Coating parameters for ilaprazole pellets

Parameters	Drug layering	Subcoating	Enteric-coating	Top-coating
Atomization pressure, bar	2.0	2.0	1.8	2.0
Inlet temperature, °C	65 ± 2	65 ± 2	35 ± 2	65 ± 2
Product temperature, °C	40 ± 2	40 ± 2	30 ± 2	40 ± 2
Steady spray rate, g/min	4.0–8.0	6.1–6.8	3.6–5.0	3.1–4.9
Cut-off size, μm	300-500	300-500	355-710	355-710

2.2.3 Preparation of delayed-release lansoprazole and rabeprazole sodium pellets

Bottom-spray fluidized bed coater (DPL-IIA, Jinggong Pharmaceutical Machinery Co., Ltd., Chongqing, China) was used for the coating: nozzle, 1.0 mm; air flow, 150 m^3/h; start pellets,

500 g; product temperature at drying, 55°C.

Drug pellets (22.4% w/w drug) were prepared by layering drug solution/suspension (10.81% w/w drug, 4.86% w/w HPMC, 4.32% w/w MgO, 0.04% colorant) on four cores (100% MCC, 45% MCC, 30% MCC, and 0% MCC, respectively). The resulted eight type of drug cores were equally mixed by weight for subsequent subcoating, enteric-coating and top-coating. The resulted pellets were marked as "all cores" in case of necessary. Drug pellets (all cores) were subcoated with suspension (8.00% w/w talc, 4.00% w/w HPMC) to a weight gain 60% based on weight of drug pellets. The subcoated pellets were enteric-coated with emulsion (16.56% w/w Eudragit L30 D-55 in solid content, 3.30% w/w TEC, 0.83% w/w GMS, 0.33% w/w T80) to a weight gain 100% based on weight of subcoated pellets. The enteric-coated pellets were top-coated with HPMC solution (6.67% w/w pearlitol 160C, 3.33% w/w HPMC) to a weight gain 10% based on weight of enteric-coated pellets. The LOD of each type of pellets was < 2.0%. The coating parameters were shown in Table 6.

Table 6 Coating parameters for lansoprazole and rabeprazole sodium pellets

Parameters	Drug layering	Subcoating	Enteric-coating	Top-coating
Atomization pressure, bar	2.0	2.0	1.8	2.0
Inlet temperature, °C	65 ± 2	65 ± 2	32 ± 2	65 ± 2
Product temperature, °C	40 ± 2	38 ± 2	30 ± 2	40 ± 2
Steady spray rate, g/min	4.0–6.0	5.8–6.1	3.6–5.2	3.1–4.5
Cut off size, μm	250-325	270-325	325-425	325-425

Besides, delayed-release rabeprazole sodium pellets (0% MCC cores) were prepared the same, but with weight gain of subcoat 60% and 80% respectively, based on the weight of drug pellets. Further, 60%-subcoated rabeprazole sodium pellets (0% MCC cores) was enteric-coated with a weight gain of 108% based on the weight of 60%-subcoated pellets.

2.2.4 Pellet compression

2.2.4.1 Preparation of sodium hyaluronate-xanthan gum granules

Sodium hyaluronate - xanthan gum granules were prepared by adding 115 g HPMC solution (5% w/w) at 1 g/s into 300 g mixture (3.33% w/w sodium hyaluronate, 3.33% w/w xanthan

gum, 86.67% w/w mannitol, 6.67% w/w crospovidone) in a high shear granulator (G10, Xinyite Science and Technology Co., Ltd., Shenzhen, China) at: paddle speed, 420 rpm; chopper speed, 2800 rpm; granulation time, 6 minutes. The granulates were subsequently dried in an oven (DHG-9140A, Shanghai Yiheng Machinery Co., Ltd., Shanghai, China) at 70°C till LOD was < 2.0%. The resultant granules were 0.8 mm sieved (P100G10, Xinyite Science and Technology Co., Ltd., Shenzhen, China) and used as a filler for pellet compression.

2.2.4.2 Compression

Ilaprazole enteric-coated pellets, top-coated pellets, lansoprazole and rabeprazole sodium top-coated pellets were mixed with other excipients (Table 7, Table 8) in a 3D rotational mixer (HD-20B, Xiaolun Pharmaceutical Machinery Co., Ltd., Zhejiang, China) at 20 rpm for 10 minute before adding magnesium stearate and mixed for another 3 minutes. The mixture was compressed with an 8-punch rotation tabletting machine (ZP S008, Tianxiang Co., Ltd., Shanghai, China) into 8.5 mm flat-faced round tablets. The tablets were dried at 55°C until the LOD was <2.0%. Tablet weights, content uniformity and disintegration of the tablets were checked .

Table 7 Compression of ilaprazole pellets

Ingredients	Without sodium hyaluronate-xanthan gum g (% w/w)	With sodium hyaluronate-xanthan gum g (% w/w)
Pellets	500.00 (37.42)	500 .00 (37.42)
MCC PH102	378.61(28.34)	-
Pearlitol 100SD	378.61(28.34)	-
Sodium hyaluronate-xanthan gum granules	-	810.40 (60.65)
PVPP XL	66.54 (4.98)	13.36 (1.00)
Citrate acid anhydrous	4.94 (0.37)	4.94 (0.37)
Magnesium stearate	7.48(0.56)	7.48 (0.56)
Total:	1336.19 (100)	1336.19 (100)

Table 8 Compression of lansoprazole and rabeprazole top-coated pellets

Ingredients	Without sodium hyaluronate-xanthan gum g (% w/w)	With sodium hyaluronate-xanthan gum g (% w/w)
Top-coated pellets	500.00 (42.13)	500 .00 (42.13)
MCC PH102	308.37 (25.98)	-
Pearlitol 100SD	308.37 (25.98)	-
Sodium hyaluronate-xanthan gum granules	-	660.79 (55.68)
PVPP XL	59.09 (4.98)	15.03 (1.27)
Citrate acid anhydrous	4.41 (0.37)	4.41 (0.37)
Magnesium stearate	6.61 (0.56)	6.61 (0.56)
Total:	1186.84 (100)	1186.84 (100)

2.2.5 Preparation of freeze-dried pellet tablets

126.39 g of lansoprazole and rabeprazole sodium top-coated pellets (all cores) was well dispersed into 450.00 g polymer solution (1.20% w/w sodium hyaluronate, 1.20% w/w xanthan gum, 9.76% w/w mannitol, 0.24% w/w citrate acid anhydrous). 500 μL of the resulting pellet suspension was dispensed into aluminum blister (d=11.5 mm), frozen with liquid nitrogen, and then lyophilized with Unicryo MC6L (Uniequip, Martinsried, Germany): -50°C, 0.033 mbar, 18 h.

2.3 Characterization methods

2.3.1 Appearance

The appearance of the cores, APIs, pellets and tablets were observed with optical light microscope (Mshot MJ32, Guangzhou Micro-shot Technology Co., Ltd., Guangzhou, China). The extended focus imaging (EFI) surface of the drug pellet was created with the built-in Olympus Stream of the optical light microscope (Olympus BX51, Olympus Corporation, Tokyo, Japan). For cross-sectional images, the top-coated pellets were fixed on an adhesive band and cut with a blade in the center.

2.3.2 Scanning electron microscopy (SEM)

The cores and pellets for SEM observation were coated with a fine gold layer under an argon

atmosphere before observing with SEM (S-3000N, Hitachi, Tokyo, Japan). For cross-sectional images, the pellets were fixed on an adhesive band and cut with a blade in the center before gold coating.

2.3.3 Bulk density and tapped density

Cores, drug pellets and subcoated pellets (approximately 100 g, n=2) were carefully introduced into a dry graduated 250 mL cylinder (readable to 2 mL) and then leveled without compacting. The unsettled apparent volume (V_0) was read to the nearest graduated unit. The bulk density in g/mL was calculated with the formula m/V_0. The filled cylinder was secured in the holder of the tapped density tester (SVM 202, Erweka GmbH, Heusenstamm, Germany) and tapped at a fixed drop of 3 ± 0.2 mm at a nominal rate of 250 taps per minute for 5 minutes. The tapped density (g/mL) was calculated with the formula m/V_F, in which V_F is the final tapped volume.

The compressibility index and Hausner ratio of cores were calculated as defined in USP 38 <616> Measures of Powder Compressibility (The United States Pharmacopeial Convention, 2016).

$$\text{Compressibility index} = \frac{V_0 - V_F}{V_0} \times 100 \qquad \text{Eq. 3}$$

$$\text{Hausner Ratio} = \frac{V_0}{V_F} \qquad \text{Eq. 4}$$

2.3.4 Deformability

100% MCC, 45% MCC, 30% MCC, and 0% MCC cores were mixed with a yellowish indicator before compression. First, each type of cores was compressed with an 8-punch rotation compression machine (ZP S008, Tianxiang Jiantai Pharmacy Machinery Co., Ltd., Shanghai, China) with round, flat-faced punches (d=8.5 mm) at increasing compression force. Five tablets at each compression force setting were sampled after discarding the first 10 tablets after each change in compression force. Second, each type of core was mixed with

40% (w/w) MCC Avicel PH-102 and compressed in the same manner. Thickness at compression (H_1) was read from the programmable logic controller (PLC) system. The thickness of the tablet after relaxation (H_2) and its hardness were measured by Multicheck (Erweka GmbH, Heusenstamm, Germany). The corresponding compression ratio, compression ratio after relaxation, and elasticity of the tablets were calculated with Eq. 5, Eq. 6, and Eq. 7. The tablets were manually broken, and the cross sections were examined with Mshot MJ32 microscope (Guangzhou Micro-shot Technology Co., Ltd., Guangzhou, China). The percentage of broken pellets from five images was calculated with Eq. 8.

$$Compression\ ratio\ = \frac{H_0}{H_1} \quad \text{Eq. 5}$$

$$Compression\ ratio\ after\ relaxation\ = \frac{H_0}{H_2} \quad \text{Eq. 6}$$

$$Elasticity\ (\%) = \frac{H_2}{H_1} \times 100 \quad \text{Eq. 7}$$

$$Brokage\ (\%)\ = \frac{Broken\ pellets}{Total\ pellets} \quad \text{Eq. 8}$$

where, H_0 is filling depth (mm); H_1 is the thickness at compression (mm); and H_2 is the thickness of the tablet after relaxation.

2.3.5 Particle size and PSD

Optical light microscope (Olympus BX51, Olympus Corporation, Tokyo, Japan) was used for image capturing. Microtrac (S 3550, Microtrac Inc., Florida, USA) with the Turbotrac dry powder system and sample delivery controller was used to characterize particle size and PSD of the pellets with the laser diffraction method.

2.3.6 pH

pH of solutions and suspensions (n=2) was measured with a pH meter (S210+InLab Routine Pro, Mettler-Toledo, Zurich, Switzerland) at room temperature. Standard buffer solutions

(Thermo Fisher Scientific, Massachusetts, USA) of pH 4.01 and pH 6.86 were used for calibration before measurements. For suspensions, 50 mL of suspension was centrifuged (TG16-WS, Changsha Xiangzhi Centrifuge Instruments Co., Ltd., Changsha, China) at 11000 rpm for 5 min before the supernatant was collected and measured.

2.3.7 Viscosity

The viscosity of the solution and suspensions (n=2) was measured with a viscometer (DVS+, Brookfield Engineering Labs., Inc., Middleboro, MA, USA).

For drug layering suspensions, 30 mL of samples were equilibrated at 25°C and measured with a cylinder shaped spindle (#61 LV, C-diameter 18.84 mm, D 65.1 mm, F 80.97 mm) at rotational speed 50 rpm.

The viscosity of polymer solutions (Table 9) at various rotational speeds was measured. Pearlitol 160C and citrate acid anhydrous were dissolved into the purified water before adding polymer. The polymer solutions were well mixed by overnight continuous stirring (T18 digital, IKA, Staufen, Germany) at room temperature. 30 mL of samples were equilibrated to 25°C and measured with the same spindle but at rotational speeds of 10, 12, 20, 30, 50, 60, and 100 rpm, respectively. Viscosity, % torque, and rotational speed were recorded. The pellets suspension was prepared by suspending freeze-dried lansoprazole and rabeprazole sodium pellet-tablet in 5 ml purified water, in which the concentration of sodium hyaluronate and xanthan gum was 0.1% w/w individually.

Table 9 Polymer solutions for rheological evaluation

Composition \ Samples	Sodium hyaluronate (0.1% w/w), %	Xanthan gum (0.1% w/w), %	Sodium hyaluronate-xanthan gum (0.1%-0.1% w/w), %
Pearlitol 160C	0.82	0.82	0.82
Citrate acid anhydrous	0.02	0.02	0.02
Xanthan gum	0.10	-	0.10
Sodium hyaluronate	-	0.10	0.10
Purified water	99.06	99.06	98.96
Total	100	100	100

2.3.8 LOD

The LOD of the samples was determined with a moisture analyzer (HX204, Mettler-Toledo, Zurich, Switzerland): 105°C for 5 minutes, n=2.

2.3.9 Differential scanning calorimetry (DSC)

Lansoprazole and rabeprazole sodium (approximately 55 mg) were weighed (MX5, Mettler-Toledo, Zurich, Switzerland) into an aluminum crucible and sealed. The samples were scanned with a differential scanning calorimeter (DSC 6000, PerkinElmer, Shelton, USA) from 20°C to 100°C with a heating rate of 20°C/min and from 100°C to 250°C with a heating rate of 10°C/min.

2.3.10 High-performance liquid chromatography (HPLC) methods

2.3.10.1 Simultaneous determination of lansoprazole and rabeprazole content

HPLC (LC-20AT, Shimadzu, Tokyo, Japan), equipped with an ultraviolet detector (SPD-20A, Shimadzu, Tokyo, Japan) and an Agilent Zorbax Extend-C18 column (250 mm x 4.6 mm, 5 μm) was used to simultaneously determine the content of lansoprazole and rabeprazole with an isocratic mobile phase 0.015 mol/L Na_2HPO_4 (pH 6.0) solution: acetonitrile [68:32 (v/v)], flow rate 1.0 mL/min, column temperature 30°C, injection volume 10 μL, UV absorbance 290 nm. Test samples and standard solutions (10 μg/mL) were prepared by dissolving the samples (10 mg drug) with 60 mL NaOH (0.05 mol/L) and made up to 100 mL with acetonitrile. 5 mL aliquot was drawn and diluted 10 times with NaOH (0.05 mol/L): acetonitrile (2:1 v/v) mixture. All samples were filtered with 0.45-μm nylon filters (Jinteng Laboratory Equipment Co., Ltd., Tianjin, China) before injection.

2.3.10.2 Determination of ilaprazole content

HPLC (LC-20AT, Shimadzu, Tokyo, Japan), equipped with an ultraviolet detector (SPD-20A, Shimadzu, Tokyo, Japan) and an Agilent Zorbax Extend-C18 column (250 mm x 4.6 mm, 5 μm) was used to determine the ilaprazole content with isocratic mobile phase 60:40 (v/v)

0.025 mol/L K_2HPO_4 solution (pH 8.3): acetonitrile, flow rate 1.0 mL/min, column temperature 25°C, injection volume 20 μL, UV absorbance 237 nm, test samples and standard solutions (5 μg/mL) were prepared with mobile phase (4°C). All samples were filtered with 0.45-μm nylon filters before injection. The samples for preparation and injection were kept at 4°C.

2.3.11 pH-dependent stability of lansoprazole and rabeprazole sodium solution

10 mg lansoprazole and 10 mg rabeprazole sodium were weighed into 900 ml phosphate buffer solution (PBS) pH 6.8, PBS pH 7.5, sodium hydroxide solution (NaOH) pH 10.0, NaOH pH 12.0, respectively, in a dissolution tester (ADFC8MC, Tianda Tianfa Technology, Tianjin, China): 37°C, paddle 50 rpm, n=2. 3 mL drug solution was withdrawn at predetermined time points and immediately basified with 1 mL NaOH (0.5 mol/L) before HPLC determination. Recovery was calculated by percentage based on initial drug content.

2.3.12 Stability of lansoprazole and rabeprazole sodium in drug layering solution/suspension

200 mg lansoprazole drug layering suspension or rabeprazole sodium drug layering solution at room temperature (light protected) (n=2) was drawn at predetermined time points, dissolved with 120 mL NaOH (0.05 mol/L), and made up to 200 mL with acetonitrile. 5 mL aliquot was drawn and diluted 10 times with NaOH (0.05 mol/L): acetonitrile (2:1 v/v) mixture. All samples were filtered with 0.45-μm nylon filters (Jinteng Laboratory Equipment Co., Ltd., Tianjin, China) before HPLC determination. The recovery of lansoprazole and rabeprazole sodium was calculated by percentage based on initial drug content. When the recovery was 98.0–102.0% of the initial content. Drug solution/suspension was deemed stable.

2.3.13 Solubility of lansoprazole in drug suspension

50 mL of lansoprazole drug suspension was drawn and centrifuged (TG16-WS, Changsha Xiangzhi Centrifuge Instruments Co., Ltd., Changsha, China) at 10000 rpm for 5 minutes.

The supernatant was collected and filtered with 0.45 μm fiber filters before HPLC determination. Rabeprazole sodium was very soluble in the medium.

2.3.14 Moisture absorption/desorption of subcoated ilaprazole pellets

Subcoated ilaprazole pellets (10 g, n=3) was preequilibrated in a dried Petri dish (d= 5 cm, ca. 45 g) at 50°C until the weight change was < 0.02 %. The Petri dishes were then transferred to a closed desiccator (25°C, RH 93% given by a solution of saturated potassium nitrate). The moisture content of the samples was determined by weighing samples at predetermined time points and was calculated as percent based on the preequilibrated pellet weight. At 360 min, the Petri dishes were transferred to an oven at 50°C for desorption. The moisture content (%) was plotted against time.

$$Moisture\ (de)sorption\ (\%) = \frac{W_t - W_0}{w_0} \times 100 \qquad \text{Eq. 9}$$

where, W_0 is the preequilibrated weight of the Petri dish with pellets (mg); W_t is the weight of the Petri dish with pellets at time point t (mg); and w_0 is the preequilibrated weight of the pellets (mg).

2.3.15 Determination of cloud point of subcoat solution by UV

Subcoating polymer, namely HPMC, HPMC-HPC (80:20) and HPC respectively, was dissolved in PBS pH 6.8 at a 1.0% w/w and determined with UV-visible spectroscopy (CARY8453, Agilent Technologies, Waldbronn, germany): sample amount, 80 μL; temperature range, 30°C ~ 65.0°C; heating rate, 1.0°C/min; UV, 240 nm; n=2. The starting polymer solution was defined as light transmission 100%. The cloud point was defined as the temperature where the light transmission reduced to 95%. The transmission (%T) was converted from absorbance (A) with Eq.10:

$$A = 2 - \log_{10} \%T \qquad \text{Eq. 10}$$

2.3.16 Swelling of top-coated pellets in 0.1 N HCl

Top-coated ilaprazole pellets (n=3), subcoated with HPMC, HPC, HPMC-HPC (80:20) respectively, were fixed gently on a 5-cm Petri dish before adding 10 mL 0.1 N HCl solution (45°C) and observed using optical light microscope (Mshot MJ32, Guangzhou Micro-shot Technology Co., Ltd, Guangzhou, China) with heated sample platform which maintained the medium at 45±2°C.

Lansoprazole top-coated pellets and rabeprazole sodium top-coated pellets (n=2) from each type of cores were soaked in 10 mL 0.1 N HCl solution (37°C) in glass dishes (d=8 cm) and observed with the microscope (Mshot MJ32, Guangzhou Micro-shot Technology Co., Ltd, Guangzhou, China) with heated sample platform which maintained the medium at 37±2°C. The diameter of the tested pellets was determined from the microscopic images taken at predetermined time points. Changes in volume were then calculated with Eq.11:

$$\frac{\Delta V}{V_0}, \% = \left(\frac{d_t^3}{d_0^3} - 1\right) \times 100 \qquad \text{Eq. 11}$$

where, V_0 is the volume of the pellet, ΔV is the volume change of the pellet, d_0 is the diameter of pellet before soaking, d_t is the diameter of the pellet at measured time point.

2.3.17 Acid resistance test

Acid resistance test was performed in a dissolution tester (ADFC8MC, Tianda Tianfa Technology, Tianjin, China) with 500 mL 0.1 N HCl (37°C, paddle 75 rpm, n=3).

For lansoprazole and rabeprazole sodium top-coated pellets and pellet-tablets containing 5 mg of lansoprazole and 5 mg of rabeprazole sodium, the HCl solution was carefully removed at 60 minute and NaOH solution (1000 mL, 0.05 mol/L) was added to extract the remaining actives. The paddles were kept stirring at 100 rpm for 10 minute. Aliquots (10 mL) of the solution were withdrawn and filtered with 0.45 µm fiber filters before injecting into the HPLC for determination.

For ilaprazole top-coated pellets and pellet-tablets containing 5 mg of ilaprazole, the HCl solution was carefully removed at 120 minute and 200 mL mobile phase for content determination was used to extract the remaining actives. Aliquots were withdrawn, diluted five times, and filtered with 0.45 µm nylon filters before injecting into the HPLC for determination.

2.3.18 Drug release

2.3.18.1 Drug release of lansoprazole and rabeprazole sodium

Pellets or pellet-tablet containing 5 mg of lansoprazole and 5 mg of rabeprazole sodium were released in the dissolution tester (ADFC8MC, Tianda Tianfa Technology Co., Ltd., Tianjin, China): paddle, 75 rpm, 900 mL PBS pH 6.8 with SDS (1 mmol/L) or NaOH solution pH 12, 37°C, n=3. Aliquots (3.0 mL) were drawn at predeterimined time points and filtered with 0.45 µm fiber filters before HPLC determination. The rabeprazole samples from PBS pH 6.8 were immediately basified with NaOH solution (1.0 mL, 0.5 mol/L). Standard solutions with concentrations of 10%, 20%, 40%, 80%, 100%, 120% of the nominal 100% content were prepared and used for determination.

2.3.18.2 Drug release of ilaprazole

Pellets containing 5 mg of ilaprazole were released in the dissolution tester (ADFC8MC, Tianda Tianfa Technology Co., Ltd., Tianjin, China): paddle, 100 rpm, 900 mL PBS pH 6.8/isopropanol (72:28), 37°C, n=3. Aliquots (3.0 mL) were drawn at predeterimined time points and filtered with 0.45 µm nylon filters before HPLC determination. Standard solutions with concentrations of 10%, 20%, 40%, 80%, 100%, 120% of the nominal 100% content were prepared and used for determination.

2.3.19 Characterization of pellet-tablets

Tablet weight and weight uniformity, and tablet hardness was monitored with a hardness tester (Multicheck, Erweka GmbH, Heusenstamm, Germany).

Pellet-tablets (n=6) were tested with a disintegration tester (KB-1, Tianda Tianfa Technology Co., Ltd., Tianjin, China) containing 900 mL purified water at 37±1°C. One tablet each time was placed in the sample basket (long, 30 mm; diameter, 13.0 mm), the stainless steel wire mesh in bottom in a plain square shape with a 710 μm aperture. The constant raising and lowering (moving distance 10±1 mm) frequency was set at 30 cycles per minute. When there was no residue remaining on the screen, the time was recorded as the disintegration time. The averaged disintegration time was reported.

2.3.20 NG tube studies

An 8-Fr NG tube coupled with a catheter tipped syringe (5 mL) was used for NG feeding (Fig. 6). The MUPS mixture or tablet was charged into the syringe barrel after removing the syringe plunger, and thereafter replacing the plunger. After drawing 5 mL distilled water, the syringe was shaken till a homogeneous suspension was formed, the time was recorded as the thickening time. The syringe was placed perpendicular onto the bench tip up, the settle time was recorded when the level of the solid mass was reduced to less than half of the height. The syringe was well-shaken again and then connected with the NG tube to inject the contents through NG tube. The syringe was twice flushed with 5 mL distilled water. Recovery was calculated by percentage based on initial drug content. The study was repeated twice.

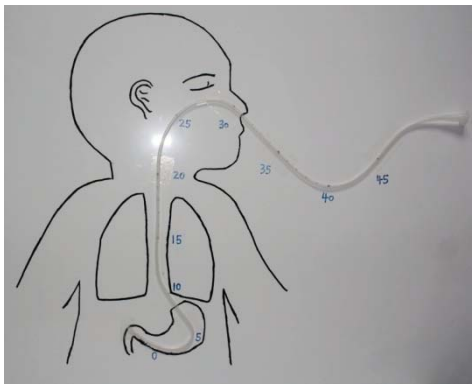


Fig. 6 Layout of NG feeding tube

3. Results and discussion

3.1 Core type and drug influence on drug layering and properties of top-coated pellets

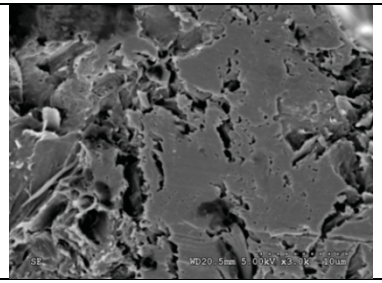
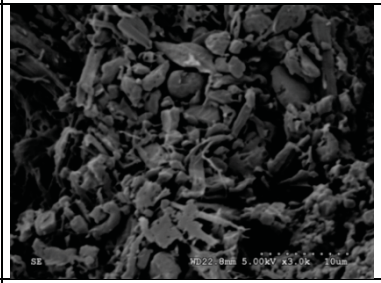
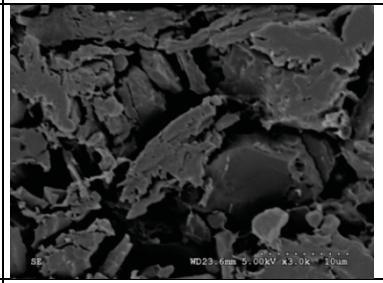
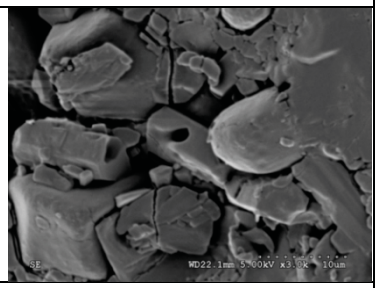
3.1.1 Properties of cores

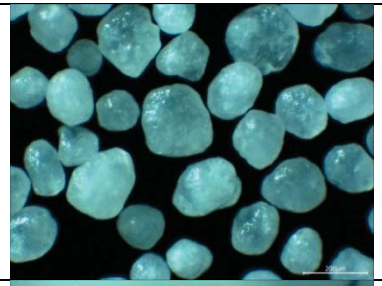
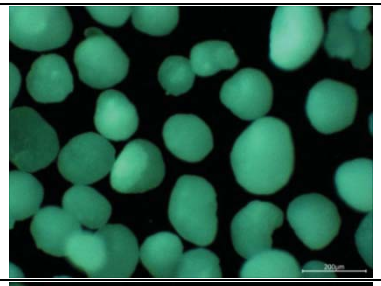
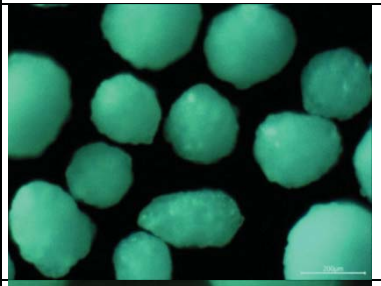
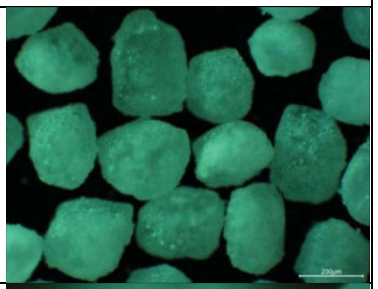
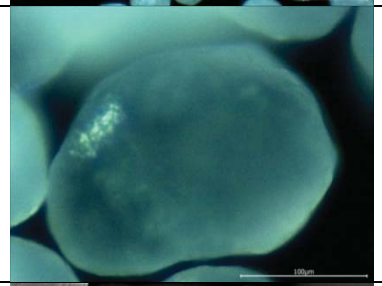
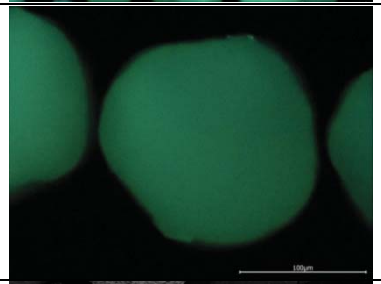
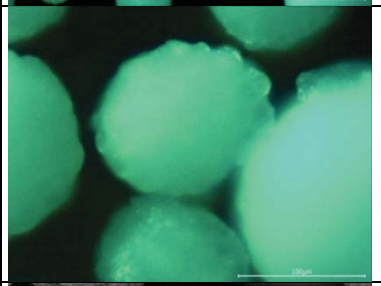
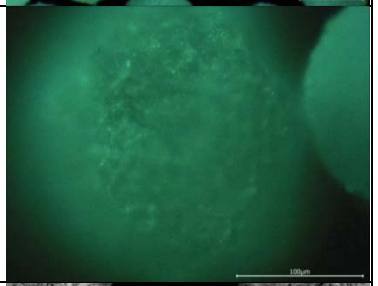
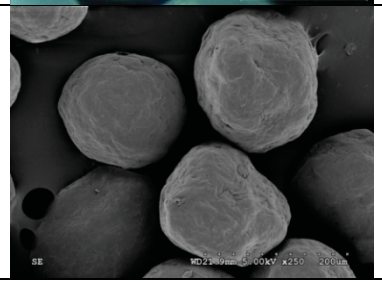
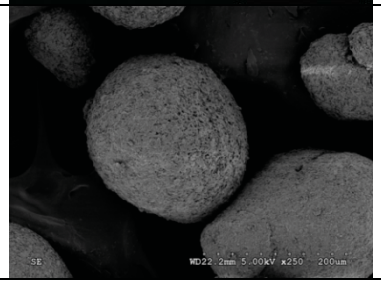
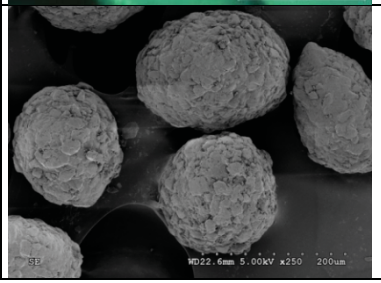
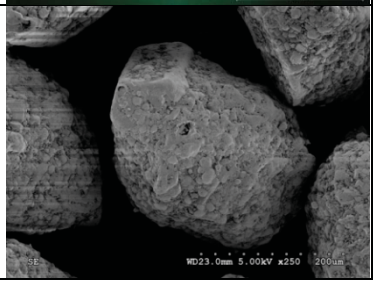
Three commercially-available cores (CP-102, Nonpareil-105, and PF 053) and one laboratory made core were used in this study to investigate the core type influence on drug layering, pellet compression, acid resistance, and drug release. The percentages of MCC (% w/w) in the cores were in descending order of: CP-102 (100%) > laboratory made (45%) > Nonpareil-105 (30%) > PF 053 (0%), thereafter referred as 100% MCC cores, 45% MCC cores, 30% MCC cores, and 0% MCC cores, respectively. The physicochemical properties of the four type of cores are summarized in Table 10.

Microscopy and laser diffraction were used to determine particle size and PSD. The laser diffraction method measures d_{90}, d_{50}, and d_{10} indirectly by measuring the angular variation in intensity of light scattered as a laser beam passes through a dispersed particulate sample (Malvern, 2016). The particle size is reported as a volume-equivalent sphere diameter. Disperse pressure and shape of the particles may affect the reported PSD. Microscopy directly measures the diameter. Nevertheless, the cores used in this study were not perfectly spherical, which may cause deviation with reported dimension data. The particle sizes of investigated cores in ascending order were as follows: 30% MCC < 100% MCC < 45% MCC < 0% MCC. The difference in particle size is partially responsible for the variability in drug layering process, and affects further coating of the pellets. The tapped densities of the cores decreased in the following order: 100% MCC > 0% MCC > 30% MCC > 45% MCC.

Crystals on the surface of 30% MCC cores and 0% MCC cores were visible. 100% MCC cores was transparent, even and with smooth surface. 45% MCC exhibited amorphous and homogenous with rough surface (Table 10).

Table 10 Properties of the cores

Name	**100% MCC**	**45% MCC**	**30% MCC**	**0% MCC**
Type	CP-102	Laboratory made	Nonpareil-105	PF 053
Composition	100% MCC	45% MCC 55% lactose	30% MCC 70% lactose	0% MCC 85% sucrose, 15% starch
Size, (µm)	106-212	125-250	106-212	180-250
PSD, LD (µm)	d_{90}: 218 d_{50}: 169 d_{10}: 125	d_{90}: 238 d_{50}: 165 d_{10}: 104	d_{90}: 184 d_{50}: 142 d_{10}: 114	d_{90}: 309 d_{50}: 260 d_{10}: 214
PSD, microscopy (µm)	d_{90}: 210 d_{50}: 156 d_{10}: 130	d_{90}: 186 d_{50}: 149 d_{10}: 111	d_{90}: 176 d_{50}: 142 d_{10}:119	d_{90}: 353 d_{50}: 297 d_{10}: 251
Bulk density, g/cm^3	0.88	0.62	0.72	0.82
Tapped density, g/cm^3	0.94	0.69	0.77	0.86
SEM, cross section				
Compressibility index,%	0.06	0.10	0.06	0.05
Hausner ratio	1.07	1.11	1.07	1.05
LOD, %	2.76	3.22	1.76	1.67

Name	100% MCC	45% MCC	30% MCC	0% MCC
Appearance, by microscopy				
Surface, microscopy				
Surface, SEM				

3.1.1.1 Core compressibility with and without filler

The relationship between the hardness of the resulted compacts and the compression force for compressing the cores without filler (Fig. 7) indicated that the compressibility of the cores improved with the decreasing MCC% w/w in the core in an order of: 100% MCC < 45% MCC < 30% MCC < 0% MCC. Fragmentation of the plastic material and its ratio in the cores (namely lactose in laboratory made cores and Nonpareil-105, and sucrose in PF 053) contributed to the compressibility of the cores.

Top-coated pellets were supposed to be compressed with filler and other excipients. With 40% w/w MCC PH-102 as cushion for compression, the relationship between the hardness of the resulted compacts and compression force (Fig. 8) showed that all cores could be compressed with smaller compression forces into harder tablets than that without filler. The influence of core type on core compressibility was leveled with 40% MCC PH-102 as cushion material. It may have implied that 40% w/w MCC PH-102 was adequate to fill the inter-granular void of all four cores during the densification, and bound together well to compensate for the core influence.

Elasticity versus compression force for four type of cores compressed without and with filler (Fig. 9 and Fig. 10) disclosed that 100% MCC cores exhibited the most elasticity and 0% MCC cores the least elasticity among the four cores compressed without filler. The difference was attributed to the intrinsic elasticity and plasticity of the composition. The scattering of the elasticity decreased to 5-10% with lower and narrower amplitude of compression force when 40% MCC PH-102 was used for compression. The influence of core type on elasticity after compression was compromised by adding the cushion material. Therefore, the potential damage resulted from the mechanical properties of the cores could be minimized by including highly compressible excipient in the compression.

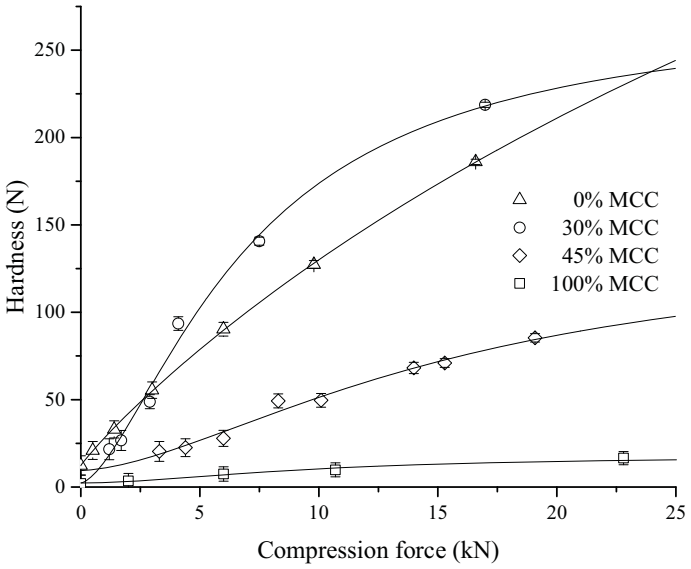


Fig. 7 Core compressibility without filler

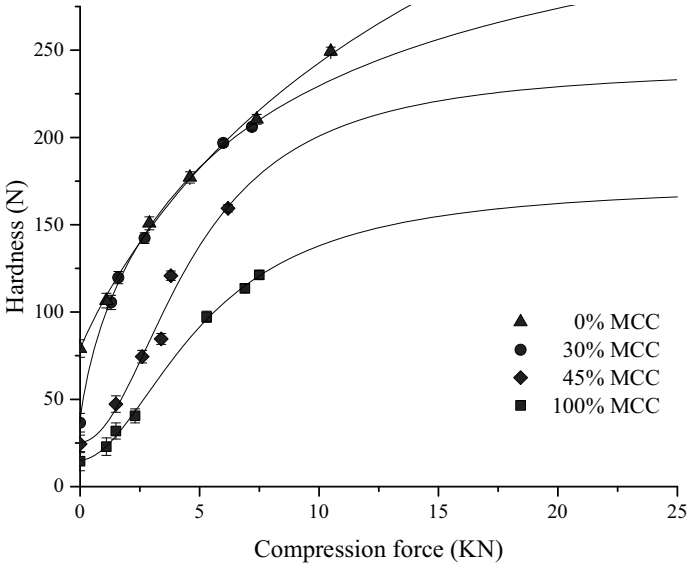


Fig. 8 Core compressibility with filler

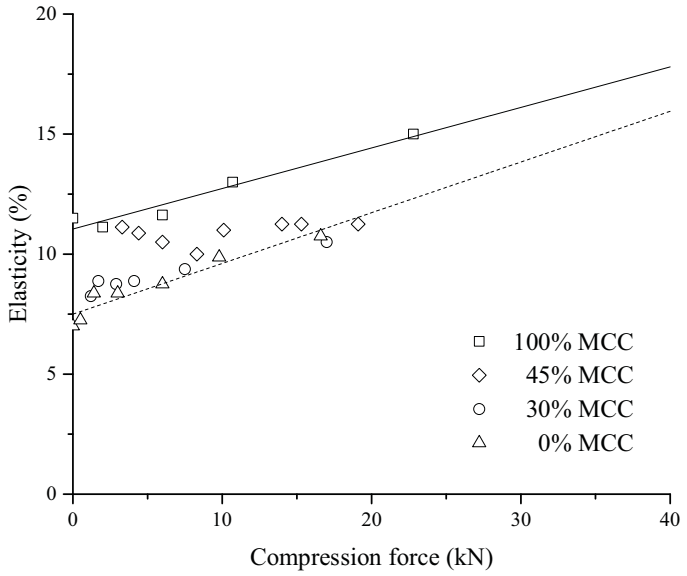


Fig. 9 Elasticity of core compacts without filler

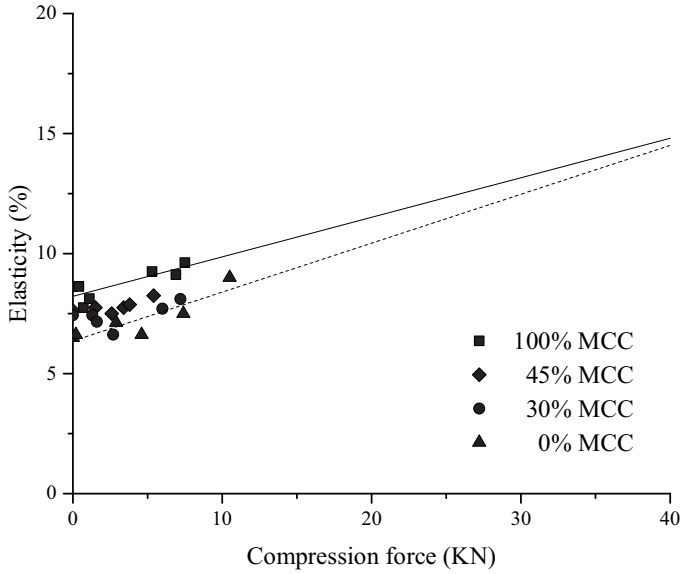


Fig. 10 Elasticity of core compacts with filler

3.1.1.2 Core breakage in compacts with and without filler

The influence of MCC % w/w in cores and hardness on core breakage without and with filler (Fig. 11) could support the selection of the core type and the amount of cushion material and project potential hardness range of the resulting compacts.

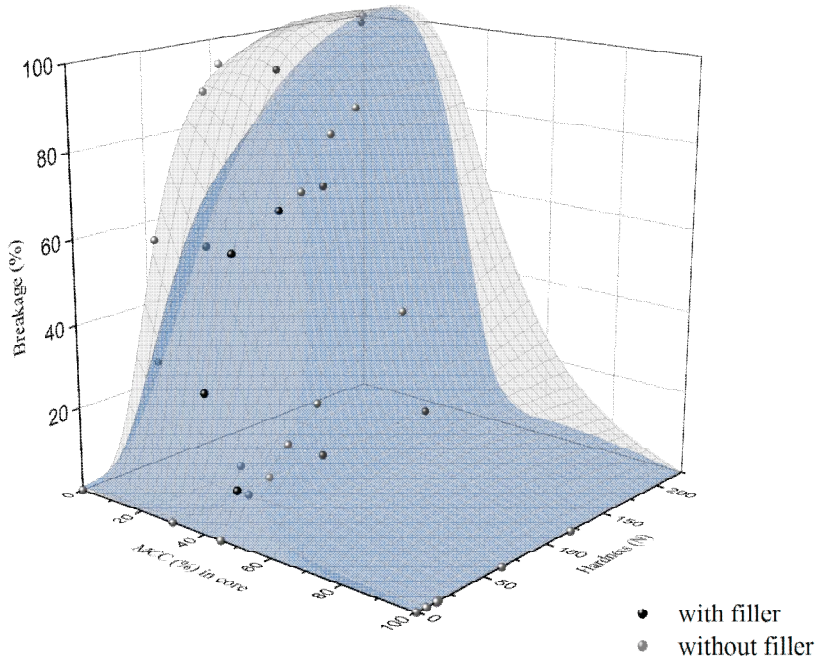


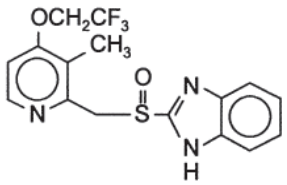
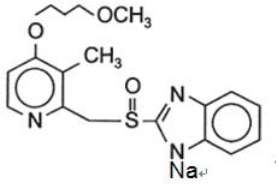
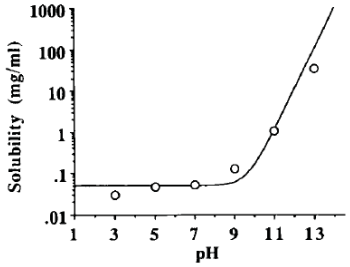
Fig. 11 Influence of MCC% in the core on core breakage

3.1.2 Lansoprazole and rabeprazole sodium

3.1.2.1 Physicochemical properties of lansoprazole and rabeprazole sodium

Lansoprazole and rabeprazole sodium were selected as drug pair for comparison purpose because they shared the same parent structure, but exhibit opposite solubility and different stability, retaining individual characteristics and specific pharmacological effects (Table 11). Both compounds are acid-labile.

Table 11 Physicochemical properties of lansoprazole and rabeprazole sodium

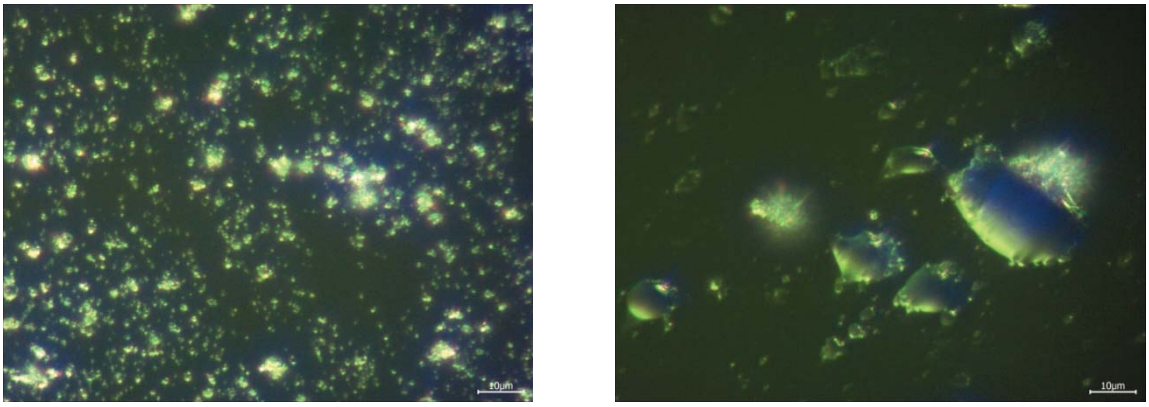
Compounds	Lansoprazole	Rabeprazole sodium
CAS Number	103577-45-3	117976-90-6
Chemical name	2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]-methyl]sulfinyl] benzimidazole	Monosodium (RS)-2-({[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl}sulfinyl)-1H-benzoimidazolide
Chemical structure	 (Olbe, 1999)	 (Olbe, 1999)
BCS classification	Class II (Pašić, 2008)	Class III (Actavis, 2014)
Appearance	White to brownish-white odorless crystalline powder	White to light yellow crystalline powder
Solubility	pH 5 = 0.00006 mol/L pH 7 = 0.00008 mol/L (Kristl et al., 2000)  (Tabata et al., 1992)	H_2O pH 6.6 = 428.07 mg/mL PBS pH 6.8 = 0.83 mg/mL PBS pH 8.0 = 1.41 mg/mL PBS pH 9.0 = 2.96 mg/mL PBS pH11.0 = 407.40 mg/mL (Abbott Laboratories, 2014)
pKa	pKa_1: 8.84 pKa_2: 4.15 pKa_3: 1.33 (Kristl, 2009)	pKa_1: 4.53 pKa_2: 17.33 (Abbott Laboratories, 2014)
Log P	2.8 (Kromer et al., 1998)	0.6 (Abbott Laboratories, 2014)
Hygroscopicity	Not hygroscopic (Axon, 1995)	Very hygroscopic (Chinese Pharmacopoeia Commission, 2015)

3.1.2.2 Polymorphisms of lansoprazole and rabeprazole sodium

Lansoprazole and rabeprazole sodium both have polymorphisms. Rabeprazole sodium has ten crystalline polymorphic forms (crystalline form II, form X, form Y, form Z, crystalline

hydrate α form, hydrate β form, hydrate γ form, form V, form VI, form F) and anamorphous form (Tripathi et al., 2010). As a result of the spray coating process used in this study, the dissolved rabeprazole sodium may undergo phase conversion because of water, heat, stress, and interaction with polymeric binder during drug layering process.

Lansoprazole was observed as fine crystals (1-2 μm) and rabeprazole sodium was observed as bigger crystals (< 20 μm) that instantly exhibited a wet surface after exposure to the air (Fig.12).



Lansoprazole Rabeprazole sodium

Fig. 12 Microscopy images of lansoprazole and rabeprazole sodium

In DSC curves (Fig. 13), lansoprazole displayed an endothermic peak followed by an exothermic peak, which may partially overlap. The endothermic peak corresponds to a melting point 178.84-182.63°C, and the exothermic peak corresponds to the decomposition process. Surprisingly, rabeprazole sodium displayed no endothermic peak, but showed an exothermic peak with a rather wide temperature range. The endothermic peak and exothermic peaks may also overlap owning to the PSD of the various crystallites of rabeprazole sodium.

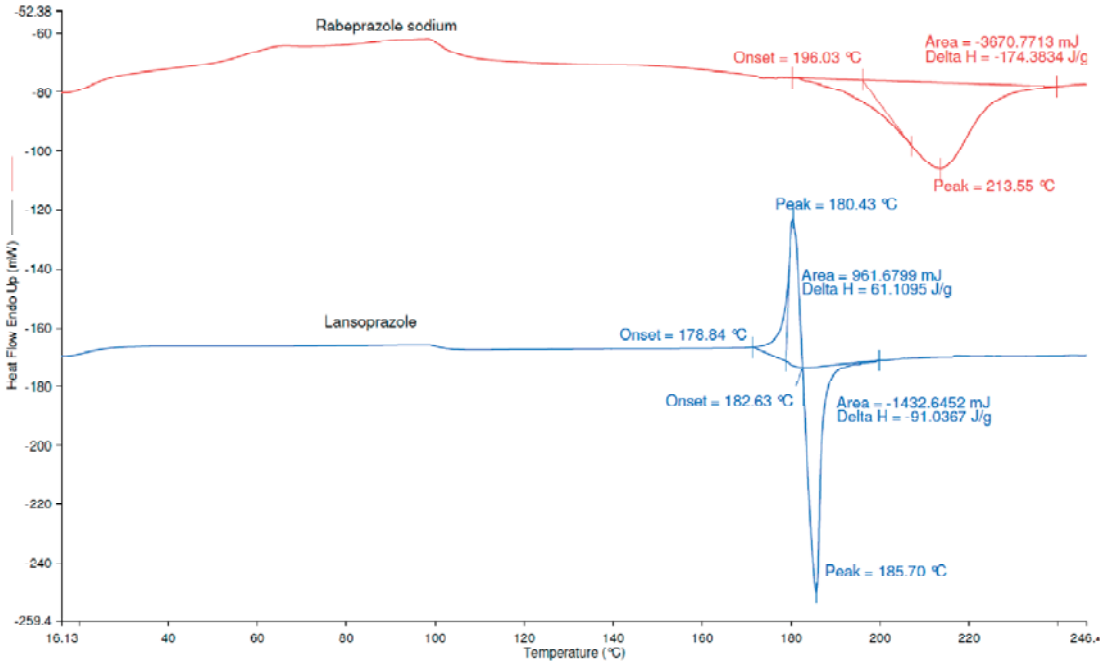


Fig. 13 DSC of lansoprazole and rabeprazole sodium

3.1.2.3 pH-dependent stability of lansoprazole and rabeprazole sodium

Lansoprazole is stable when exposed to light for up to two months. The rate of degradation of the compound in aqueous solution increases with decreasing pH. The degradation half-life of the drug in aqueous solution at 25°C is approximately 0.5 h at pH 5.0 and approximately 18 h at pH 7.0. M (package insert of Prevacid lansoprazole delayed-release capsules and delayed-release ODTs, Takeda, 2016).

The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acidic media, and is more stable under alkaline conditions (package insert of Aciphex rabeprazole sodium delayed-release tablets and Sprinkle rabeprazole sodium delayed-release capsules, Eisai, 2014). Garcia et al. (2006) observed that rabeprazole sodium rapidly degraded at pH 6.8 and 7.5, even during the first hour (30% and 13.4%, respectively); however, it was more stable at pH 9.0, degrading only 1.3% in the first hour. Kromer et al. (1998) found that the activation half-life of rabeprazole at pH 1.2 was 1.3 min, while the half-life at pH 5.1 was 0.12 h.

The pH-dependence of the stability of lansoprazole and rabeprazole sodium was different, rabeprazole sodium was much more acid-labile to the decreasing pH of the medium than

lansoprazole was (Fig. 14 and Fig. 15).

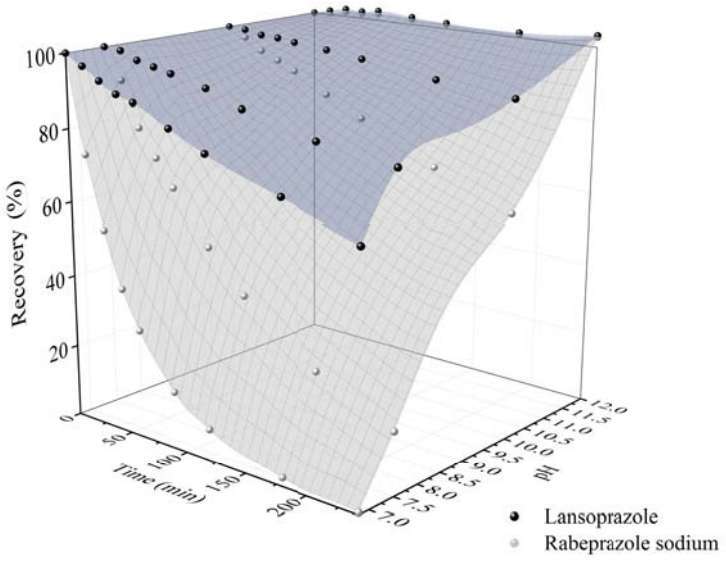


Fig. 14 The pH-dependent stability of lansoprazole and rabeprazole sodium

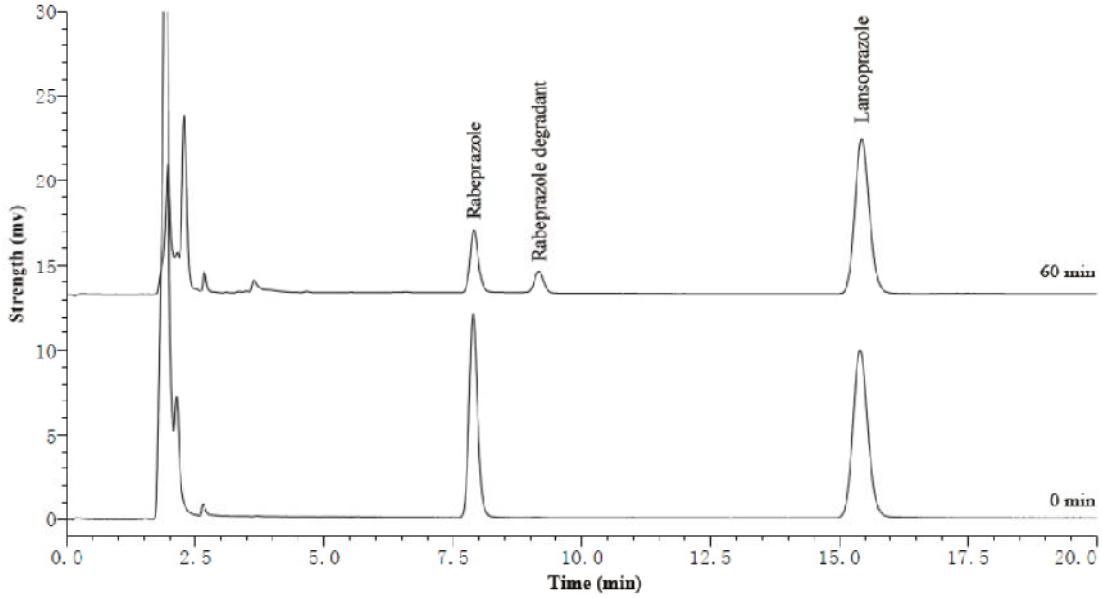


Fig. 15 Degradation of lansoprazole and rabeprazole in PBS pH 6.8 (HPLC)

The recovery of rabeprazole sodium in PBS pH 6.8 as a function of time was extrapolated using Eq.12 and Eq.13. It followed first order degradation function.

$$\text{Recovery}, \% = \frac{M_t}{M} = e^{-kt} \qquad \text{Eq.12}$$

$$\ln \frac{M_t}{M} = -kt \qquad \text{Eq.13}$$

where, M is the total amount of drug, M_t is the remaining amount of drug at time t, k is a constant related to degradation rate; k (lansoprazole) was obtained from the curve as 0.002 and k (rabeprazole sodium) 0.02.

3.1.2.4 Stability of drug solution/suspension

An appropriate basic environment was very important to keep acid-labile drugs from degradation during the drug layering process. He et al. (2010) used sodium carbonate in an alkaline layer to provide protection of lansoprazole against degradation. Tabata et al. (1992) concluded that a suitable pH region existed for stabilizing lansoprazole and magnesium carbonate was suitable better than sodium bicarbonate or potassium carbonate for the purpose. As shown in Fig. 14, rabeprazole sodium could keep stable with a stabilizer that could basify the drug suspension higher than pH 12, and similarly higher than pH 10 for lansoprazole was desirable.

The binder solution stabilized with light magnesium oxide resulted in a pH of 12.3 (Table 12), which was higher than the magnesium carbonate-saturated solution (pH 9.1) (Tabata et al., 1992). After adding in drug, the lansoprazole suspensions and rabeprazole sodium solution exhibited pH of 10.6 and 12.0, respectively. Rabeprazole sodium was fully dissolved in the aqueous suspension, while only 0.12% of lansoprazole was dissolved. Thereafter, solution drug layering was referred in case of rabeprazole sodium, while suspension drug layering for lansoprazole thereafter. Lansoprazole suspension was stable at room temperature for at least 72 h, but rabeprazole sodium solution was only stable for around 48 h (Table 12). A higher molar ratio of magnesium oxide may help to stabilize rabeprazole sodium better.

Table 12 Properties of drug layering solution/suspension

	Lansoprazole	**Rabeprazole sodium**
pH, binder solution	5.4	5.4
pH, stabilized binder solution	12.3	12.3
pH, drug solution/suspension	10.6	12.0
Drug in suspension, %	0.12	Dissolved
Stability	> 72 h	< 48 h

3.1.3 Drug layering

3.1.3.1 Drug layering parameters

The total dissolved content in rabeprazole sodium drug solution accounted for 15.67 % w/w, with viscosity of the drug solution of 92.05 mPa.s. On the contrary, lansoprazole was insoluble in the binder solution with only 4.86 % w/w binder as dissolved content, with viscosity of the drug suspension of 80.24 mPa.s. The higher viscosity of drug layering solution may result in increased stickiness among the drug pellets, but less loss in spray coating process.

Gryczová et al. (2008) compared the actual drug content in pellets with the theoretical content of DHCl, and concluded that the pellets from sucrose cores contained the highest amount of DHCl; thus, sucrose cores were concluded to have a more effective layering process. The outcomes in this study (Table 13) disclosed a different meaning. When lansoprazole and rabeprazole sodium were layered on to 45% MCC cores and 0% MCC cores, the actual drug contents (by HPLC method) of the resultant drug pellets were higher than theoretical drug contents; the ratio of actual drug content to theoretical drug content was 103.24% for lansoprazole (45% MCC cores) and 105.61% for rabeprazole sodium (45% MCC cores); 101.02% for lansoprazole (0% MCC cores) and 104.75% for rabeprazole sodium (0% MCC cores). This implied that core breakage or crumbling was dominant in drug layering of 45% MCC cores and 0% MCC cores. Solution drug layering of rabeprazole sodium may have caused more severe loss of the 45% MCC cores and 0% MCC cores, or it may have underwent less spray drying compared with suspension drug layering of

lansoprazole. In contrast, when the drug loss dominated, and the ratio of actual drug content to theoretical drug content lower than 100% was observed (drug pellets with 100% MCC cores and 30% MCC cores). Therefore, in contrast to the observations by Gryczová et al. (2008), we believed that a high ratio of actual drug contents to theoretical drug content reflects the relationship between core loss and drug loss instead of the layering efficiency.

Table 13 Drug layering outcomes

Parameters	Cores / Drug	100% MCC	45% MCC	30% MCC	0% MCC
Actual drug contents/ theoretical drug content, %	Lansoprazole	96.88	103.24	96.86	101.02
	Rabeprazole	96.73	105.61	95.83	104.75
Coating level by weight, % w/w (theoretical 71.20%)	Lansoprazole	66.66	54.23	65.80	56.61
	Rabeprazole	65.32	48.02	63.12	47.44
Actual coating level, by HPLC, %	Lansoprazole	67.46	75.23	67.44	72.44
	Rabeprazole	67.29	78.30	66.25	77.17
Actual coating level / theoretical coating level, %	Lansoprazole	94.75	105.66	94.72	101.74
	Rabeprazole	94.51	109.99	93.05	108.38
Coating efficiency, %	Lansoprazole	93.60	76.15	92.39	79.48
	Rabeprazole	91.71	67.43	88.63	66.61
Yield, %	Lansoprazole	95.34	90.08	95.84	91.46
	Rabeprazole	93.55	86.45	92.27	84.11
Bulk density, g/cm^3	Lansoprazole	0.81	0.71	0.73	0.77
	Rabeprazole	0.85	0.73	0.75	0.79
Tapped density, g/cm^3	Lansoprazole	0.88	0.78	0.80	0.97
	Rabeprazole	0.89	0.80	0.82	1.00

$$\text{Coating level, \% w/w} = \frac{\text{Weight of drug pellets} - \text{Weight of cores}}{\text{Weight of cores}} \times 100 \qquad \text{Eq. 14}$$

$$\text{Actual coating level, \%} = \frac{\text{Actual drug content}}{\text{Drug content in drug layering mass (dry)} - \text{Actual drug content}} \times 100 \qquad \text{Eq. 15}$$

$$\text{Coating efficiency, \%} = \frac{\text{Weight of drug pellets} - \text{Weight of cores}}{\text{Drug layering mass (dry)}} \times 100 \qquad \text{Eq. 16}$$

The coating level by weight reflected the summation of core loss and loss of drug-containing mass (Eq. 14). The coating levels of rabeprazole sodium drug pellets with 45% MCC cores and 0% MCC cores were lower than those of lansoprazole drug pellets with the same cores,

and much lower than those of both type of drug pellets from the 100% MCC cores and 30% MCC cores. This implied that the 45% MCC cores had the least mechanical strength and that 0% MCC cores were strong enough for layering lansoprazole, but not strong enough for layering rabeprazole sodium. The higher viscosity of drug layering solution may have resulted in larger droplets at the same spraying conditions as those for lansoprazole suspension, which may have formed hard shell due to recrystallization of rabeprazole sodium and caused harder collision force, lower deformation ability, and poorer spreading over the surface of the cores, which resulted in more core breakage and more drug loss from friction. Meanwhile, compared to lansoprazole-containing droplets, the core surface could be better wet with rabeprazole sodium-containing droplets, which led to more lose in friction. The core crumbling and drug loss caused by friction and collision between the cores, and between the cores and hard inner surface of the fluid bed chamber were accounted for the low coating level by weight.

The actual coating level, determined with HPLC, reflected the true coating level. When the core loss dominated, the coating level by weight decreased, while actual coating level increased. When the drug loss dominated, the coating level by weight decreased, and actual coating level also decreased. The decrease in coating level/actual coating level reflected an increase of core loss. Coating efficiency and yield reflect the extent of drug loss and core loss. Due to the higher viscosity and higher content of dissolved content, drug layering solution may have caused a more severe mass loss during the process than drug suspension did.

The poor mechanical strength of 45% MCC cores originated from the irregular shape and porous structure of the cores (Fig. 16); the cores may have crumbled easily in continuous high speeds of air flow carrying viscous drug-containing droplets, and in friction and collision between cores or between cores and hard surfaces of the inner chamber. 0% MCC cores (Fig. 17) were in better symmetrical shape and size distribution, with a condensed surface that resulted in stronger mechanical properties than those of 45% MCC cores.

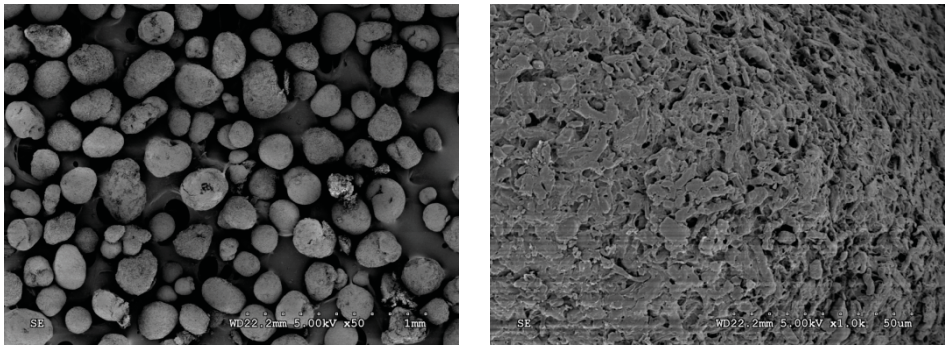


Fig. 16 SEM of 45% MCC cores

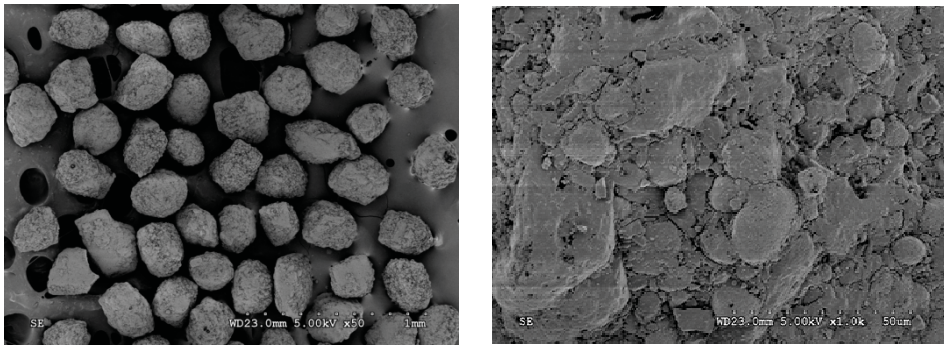


Fig. 17 SEM of 0% MCC cores

3.1.3.2 Appearance of drug pellets

All lansoprazole pellets had rough, non-transparent surfaces with a regular shape, while rabeprazole sodium pellets exhibited smooth, shiny surfaces and transparent fine crystals (Fig. 18). Rabeprazole sodium may have recrystallized into polycrystalline forms (Tripathi et al., 2010) in process of spray coating, while lansoprazole remained unchanged. The visible dents, broken parts, and cracks on the surface of rabeprazole sodium pellets evidenced core crumbling or breakage. In contrast, lansoprazole drug pellets did not show obvious surface defects.

SEM images (Fig. 19) showed distinguishable granules, pores, and a worn-out surface of lansoprazole drug pellets but an even, smooth, continuous, and dense surface of rabeprazole sodium pellets. Compared to the organic coating, which led to very uneven, pockmarked core surfaces which rendered the subsequent extended release coating impossible (McConnell et al., 2009), the aqueous drug layering system in this study achieved strong drug pellets with even surfaces. A faster and more convenient EFI method was used to obtain the surface structures

in this study (Fig. 20). This method did not need sample treatment and captured the authentic surface characteristics.

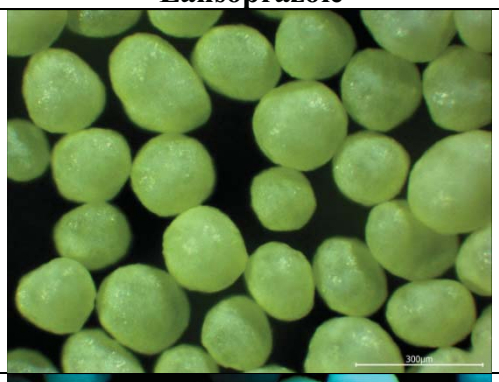
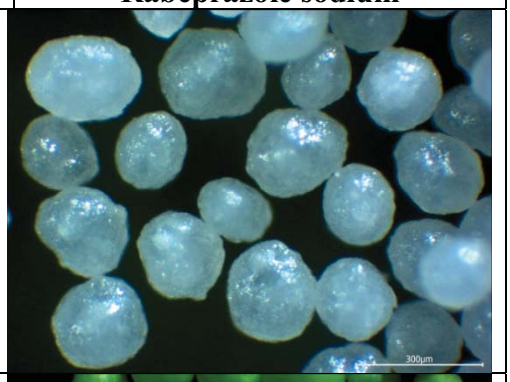
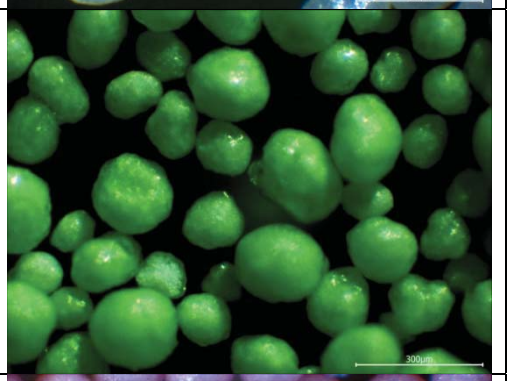
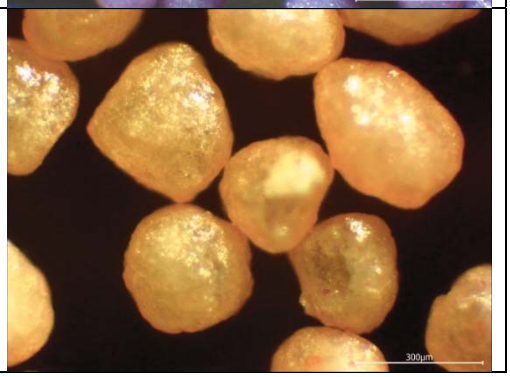
Core	Lansoprazole	Rabeprazole sodium
100% MCC		
45% MCC		
30% MCC		
0% MCC		

Fig. 18 The appearance of drug pellets (microscopy)

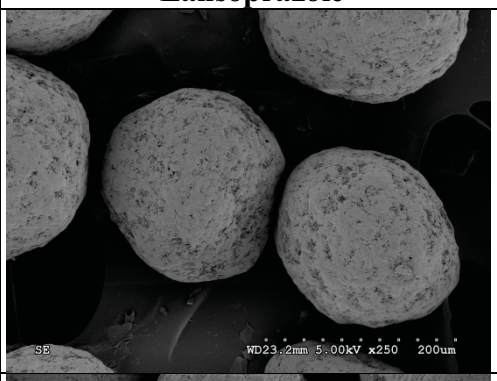
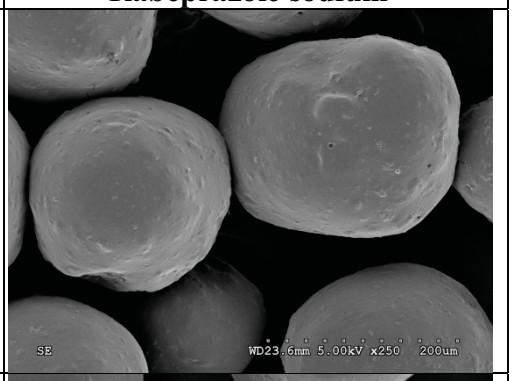
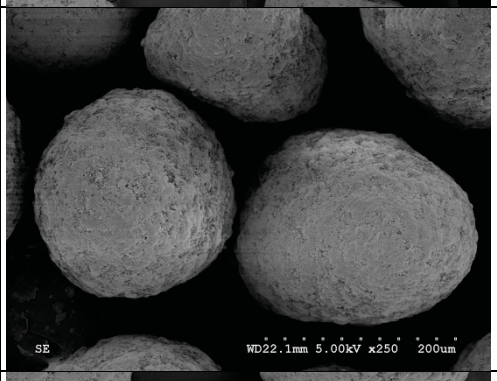
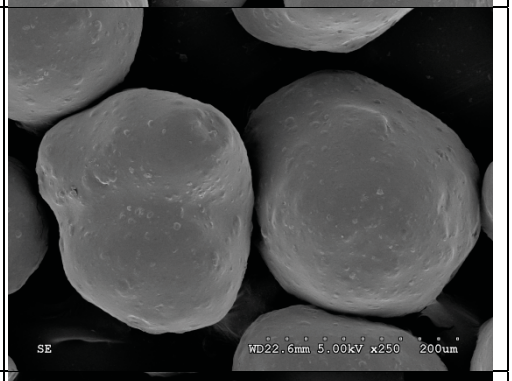
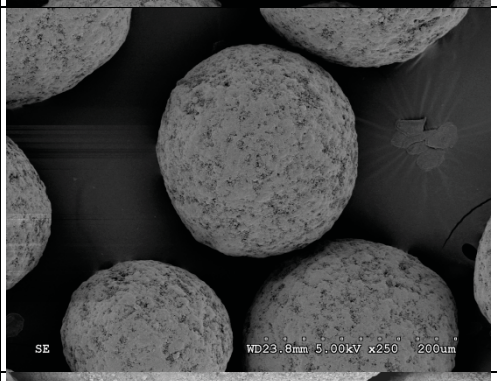
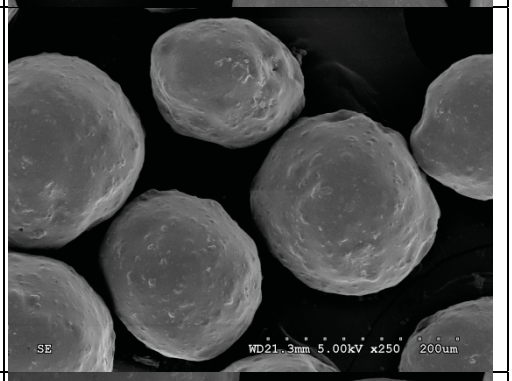
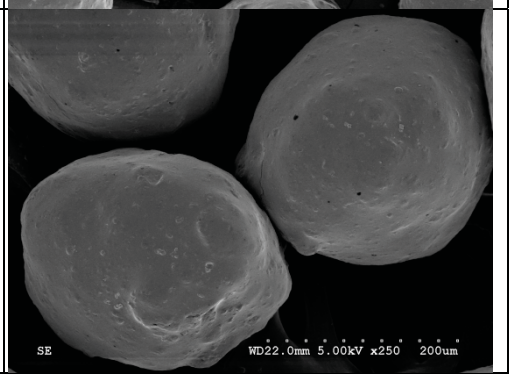
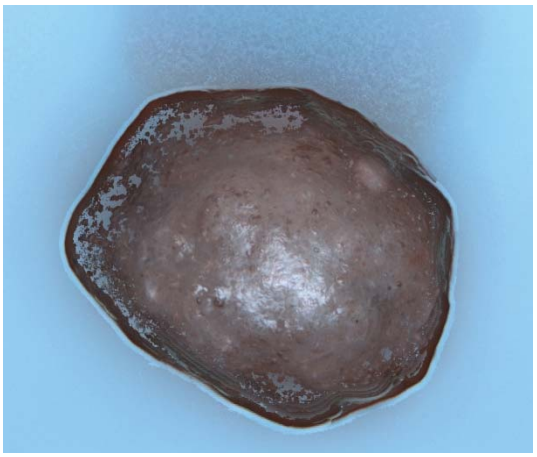
Core	Lansoprazole	Rabeprazole sodium
100% MCC		
45% MCC		
30% MCC		
0% MCC		

Fig. 19 The appearance of drug pellets (SEM)

Lansoprazole (0% MCC)



Rabeprazle sodium (0% MCC)

Fig. 20 The EFI surface of drug pellets

3.1.3.3 SEM of drug layer

A porous lansoprazole layer and a dense rabeprazole layer of all type of cores were revealed (Fig. 21). The interface between the core and the lansoprazole layer were distinguishable and the distinguishability decreased with a decrease in MCC% w/w in the cores. The rabeprazole sodium layer bound to all type of cores tightly, and the interface between the core and the rabeprazole sodium layer fused better with decreasing MCC content of the cores. This demonstrated that solution drug layering led to a dense drug layer and fused border between core and drug layer. The interface between drug layer and subcoat showed similar tendency. Lansoprazole layer and subcoat showed clearer interface than that of rabeprazole layer and subcoat. The "fusing effect" resulted from the rabeprazole sodium layer decreased the effective thickness of the intended subcoat, which implied that a thicker subcoat would be necessary to achieve a similar extent of isolation as for lansoprazole case.

3.1.3.4 PSD of drug pellets

The particle size and PSD of rabeprazole sodium drug pellets (100% MCC cores and 30% MCC cores) were slightly smaller than that of lansoprazole drug pellets from the same cores. Moreover, the particle size and PSD of rabeprazole sodium drug pellets (45% MCC cores and 0% MCC cores) turned out being much smaller than that of lansoprazole drug pellets from the same cores, which confirmed the severe drug loss and core loss in drug layering process (Fig.

22). The dense rabeprazole sodium layer may have also contributed to the smaller particle size of rabeprazole sodium drug pellets than that of lansoprazole drug pellets.

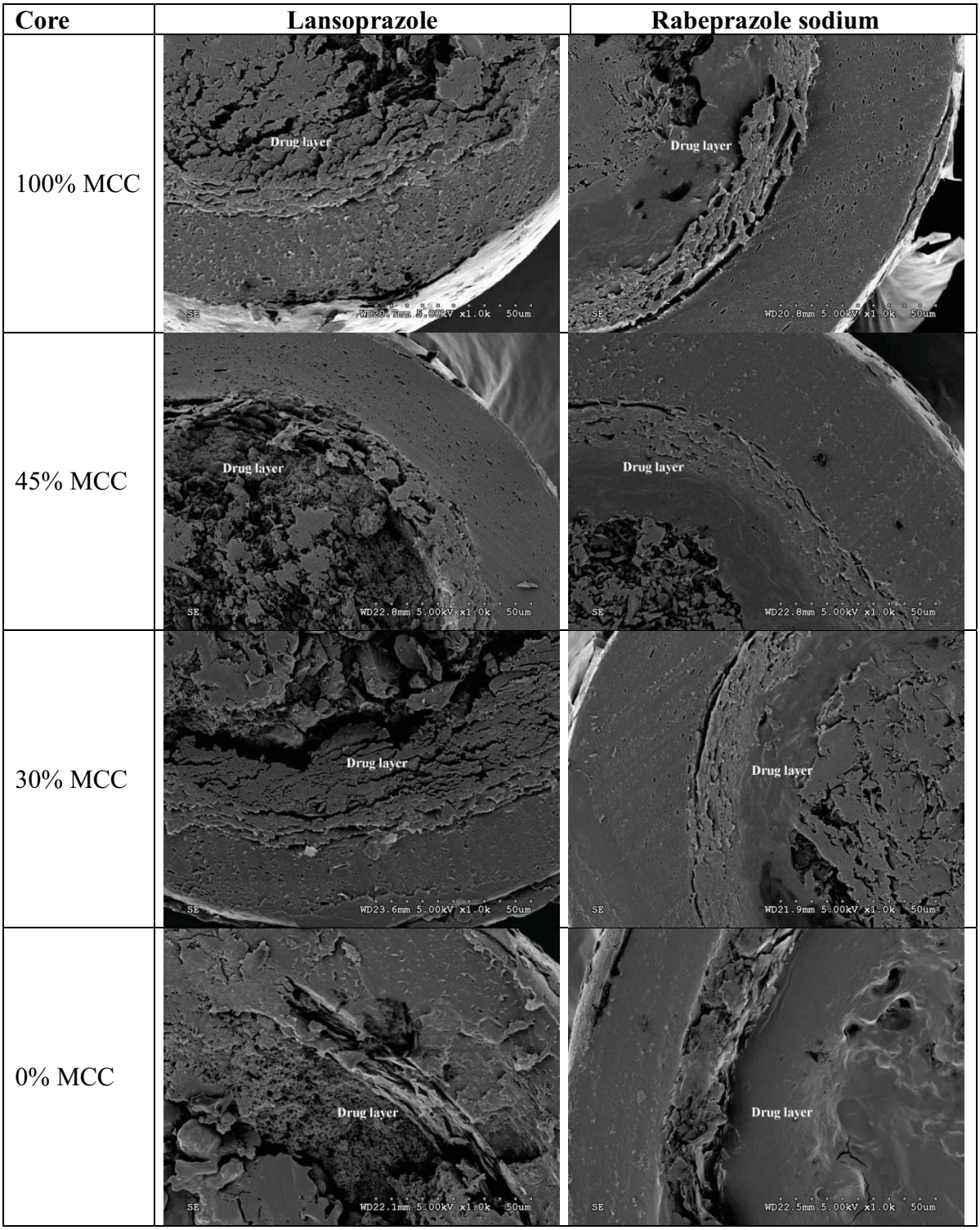


Fig. 21 Lansoprazole and rabeprazole sodium layers (SEM)

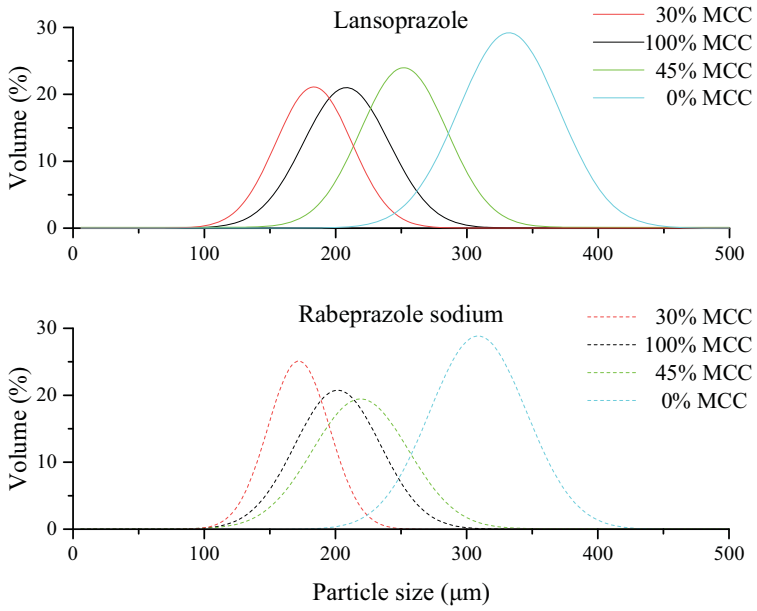


Fig. 22 PSD of drug pellets (laser diffraction)

3.1.4 Performance of lansoprazole and rabeprazole sodium top-coated pellets

3.1.4.1 Lansoprazole and rabeprazole sodium top-coated pellets

Lansoprazole drug pellets and rabeprazole sodium drug pellets from four type of cores were equally mixed by weight for subsequent subcoating, enteric-coating, and top coating. Therefore, the different performances of the top-coated pellets were the result of the differences in drug pellets. The cross section of top-coated pellets was observed under SEM (Fig. 23). Surprisingly, the microscopy images (Fig. 24) provided more information than the SEM images, showing details such as color, transparency, and crystals. The layer structure, thickness, and border from the cross section under microscopy were as distinguishable as under SEM. Compared to the SEM method, microscopy is a very time-effective and cost-effective method that could be used as a fast in-process control method in research and development. The thickness of the drug layer could be estimated from the images. Because the pellets were not perfectly spherical, the cutting position and direction resulted in unpredictable variation. In addition, the sizes of the harvested pellets distributed in a range, and the observed sample was unique and was not able to reflect the general size or thickness

change. The thickness data was informative.

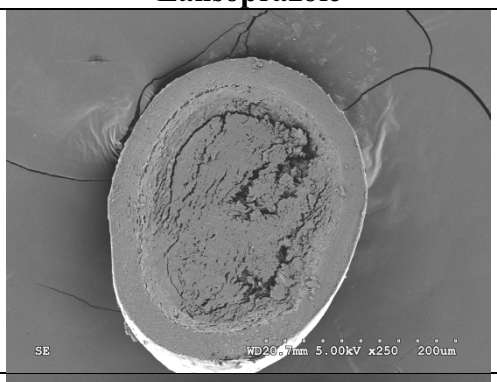
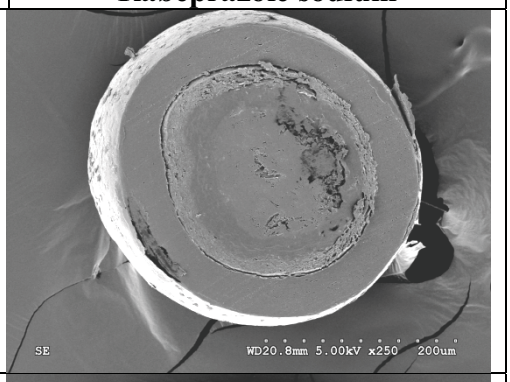
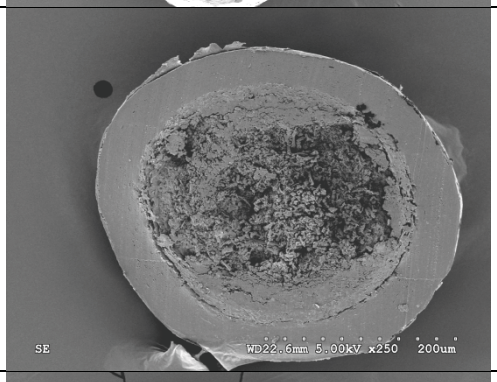
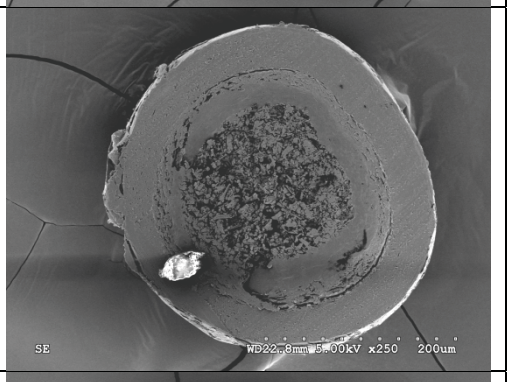
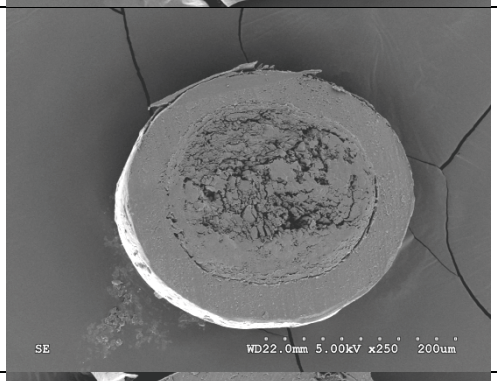
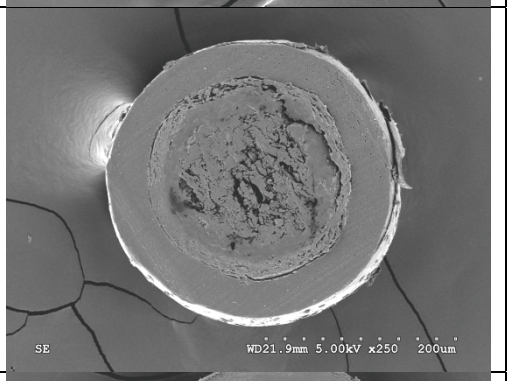
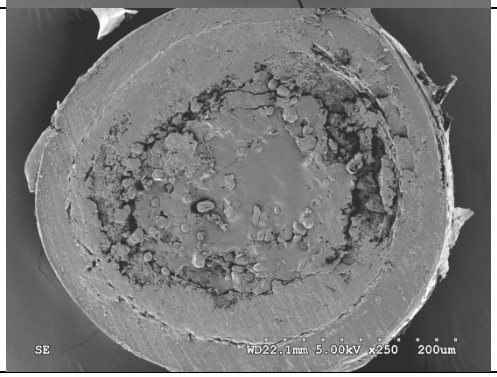
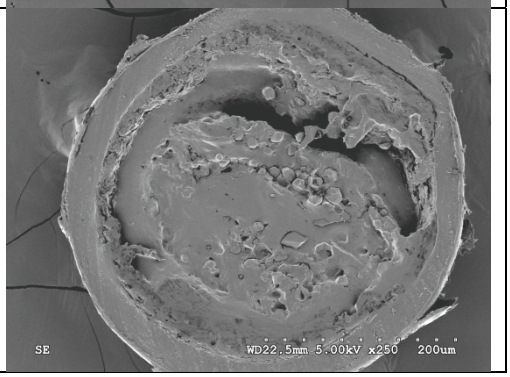
Core	Lansoprazole	Rabeprazole sodium
100% MCC		
45% MCC		
30% MCC		
0% MCC		

Fig. 23 Cross section of top-coated pellets (SEM)

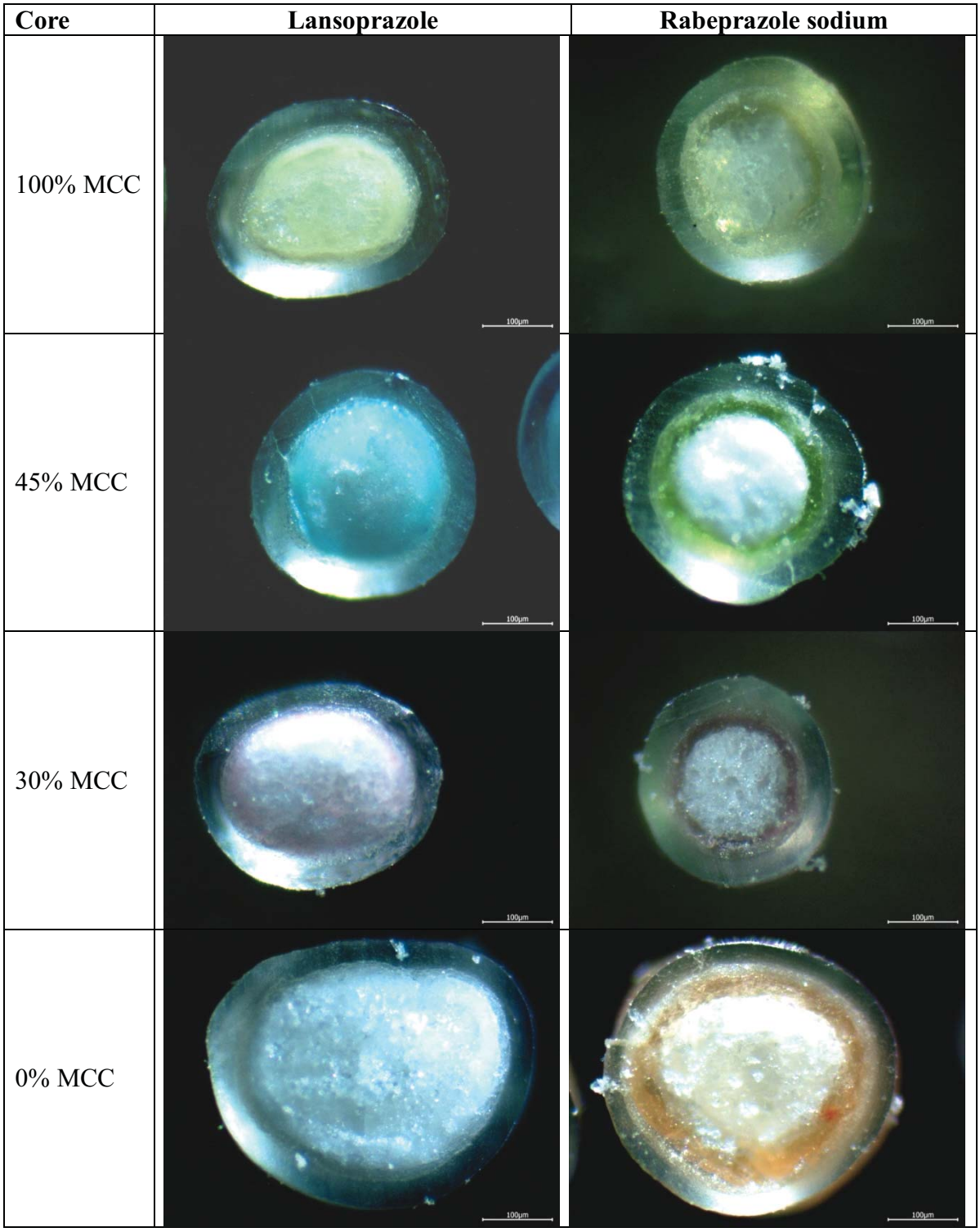


Fig. 24 Cross section of top-coated pellets (microscopy)

3.1.4.2 Influence of core type and drug on swelling of top-coated pellets in 0.1N HCl

As shown in Fig. 25 and Fig. 26, before 60 minute soaking in 0.1N HCl, both lansoprazole top-coated pellets and rabeprazole sodium top-coated pellets swelled in a similar manner. After 60 min, rabeprazole sodium top-coated pellets swelled swiftly while lansoprazole top-coated pellets remained generally unchanged. The swelling of rabeprazole sodium pellets accelerated dramatically faster after 90 minute and was inversely correlated with MCC % w/w in the cores in the order of: 100% MCC < 45% MCC < 30% MCC< 0% MCC. This implied that the aqueous medium reached the soluble content in the core and facilitated the swelling. An influence of the core type on the swelling of lansoprazole pellets was not observed, except for the slightly faster swelling of that with 0% MCC cores in 90-120 min, which may because the lansoprazole layer was enriched with insoluble lansoprazole and stabilizer and formed a less permeable barrier. When 0% MCC cores were used, the absorption of a small amount of medium may have increased osmosis and promoted swelling. The high solubility of rabeprazole sodium in top-coated pellets resulted in increasing osmosis at 60 minute and ballooned the corresponding enteric layer, thinned the enteric barrier, and reversely accelerated the seeping of the medium to the drug layer and finally to the core.

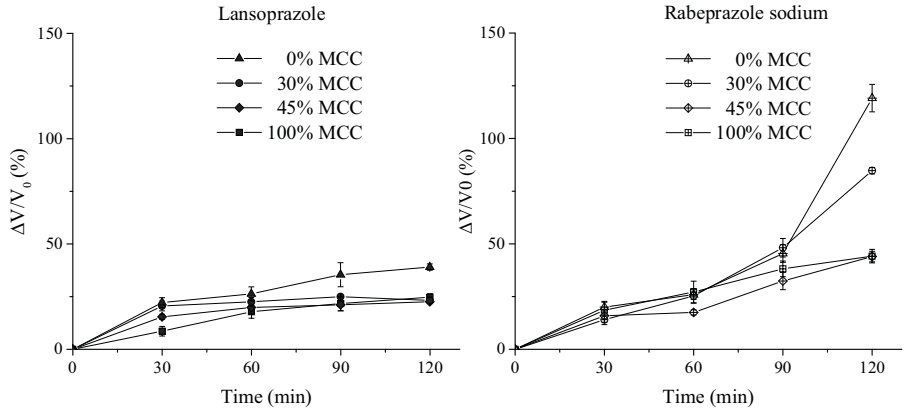
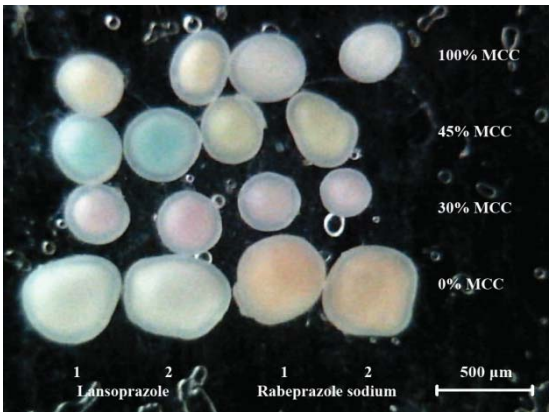
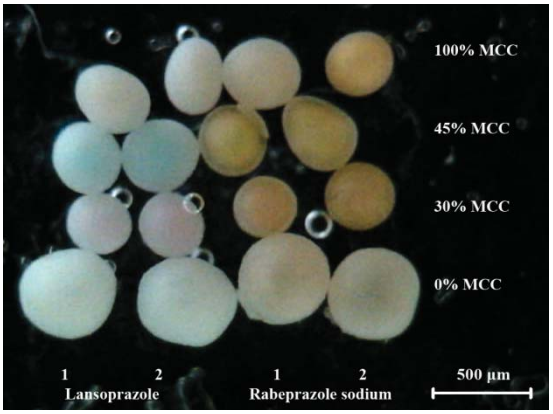


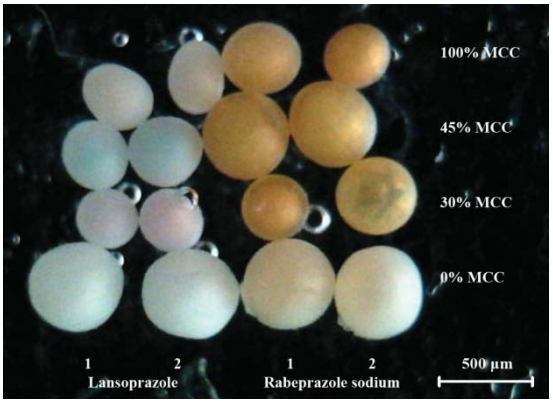
Fig. 25 Impact of core type and drug on swelling of top-coated pellets in 0.1 N HCl



0 min



60 min



90 min

120 min

Fig. 26 Swelling of lansoprazole and rabeprazole top-coated pellets in 0.1N HCl

3.1.4.3 Influence of core type and drug on acid resistance of top-coated pellets

Since rabeprazole sodium is much more susceptible to low pH medium than lansoprazole, the slight permeation of the acidic medium may not destroy the integrity of the enteric-coat but degrade rabeprazole sodium inside the intact pellets to a greater extent than that of lansoprazole. Therefore, a one-hour acid stage was used for the acid resistance test in order to alleviate the interference from the instability of rabeprazole sodium on evaluation of membrane performance.

The acid resistance of lansoprazole top-coated pellets (all cores) was greater than 95% and exhibited slight differences (Fig. 27). The acid resistance of rabeprazole sodium top-coated pellets (all cores) was 15-20% lower than that of lansoprazole. No ruptures or fish eyes were observed for either type of top-coated pellets after the acid stage. No visually detectable coloration was seen in lansoprazole pellets after testing, but rabeprazole sodium pellets developed a brownish color, which also indicated degradation of rabeprazole inside the pellets.

Multiple factors contributed to the unsatisfactory acid resistance of rabeprazole sodium top-coated pellets. The dominant factor was the highly hydroscopic property of the rabeprazole sodium layer, which may have facilitated the permeation of acidic medium towarding the drug layer. Second, rabeprazole sodium was more sensitive to an acidic environment and degraded much faster than lansoprazole. Third, as reported by Dashevsky et al. (2004), smaller coated pellets have a thinner coating at the same weight gain in coating level because of the higher surface area of the smaller pellets. The higher density of the drug layer from solution deposition resulted in a smaller size of the rabeprazole sodium drug pellets in general (Fig. 22), and a thinner subcoat and enteric coat consenqently. Fourth, the fusing effect of the rabeprazole drug layer with the subcoat reduced the effective thickness of the subcoat.

The rabeprazole sodium top-coated pellets, either subcoated 20% more or enteric-coated 8% more, exhibited improved acid resistance. The thicker (20% more) coating of subcoat

resulted in better improvement than that from thicker (8% more) enteric-coat (Fig. 28).

Therefore, less permeable subcoat, and/or thicker subcoat and enteric-coat could be applied to achieve acceptable acid resistance for rabeprazole sodium top-coated pellets. The solubility of the drug played more important role in acid resistance than the core type.

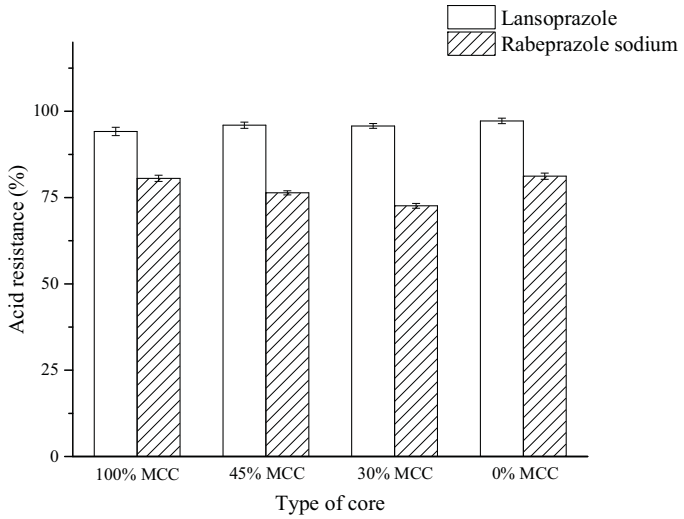


Fig. 27 Acid resistance of lansoprazole and rabeprazole sodium top-coated pellets

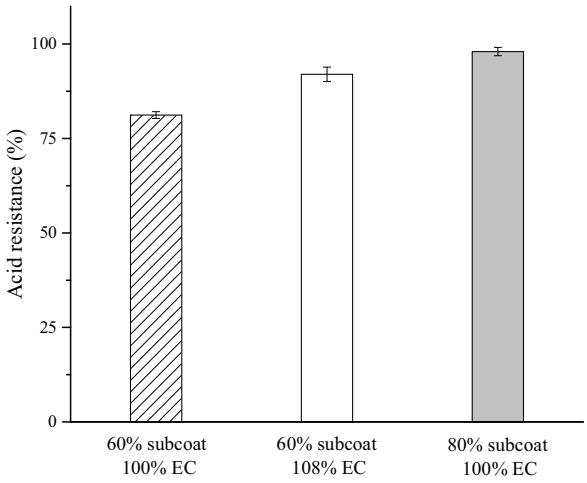


Fig. 28 Acid resistance of rabeprazole sodium top-coated pellets with thicker subcoat or enteric-coat

3.1.4.4 Influence of core type and drug on drug release of top-coated pellets

The degradation rate of lansoprazole and rabeprazole sodium in a PBS pH 6.8 (Eq. 17) is a derivation of the degradation function (Eq. 12). Therefore, the release rate could be calculated with Eq. 18.

$$\frac{\partial\, \mathrm{f(t)_{Degradation}}}{\partial \mathrm{t}} = \mathrm{k}e^{-\mathrm{kt}} \qquad \text{Eq.17}$$

$$\left[\frac{\partial\, \mathrm{f(t)_{Release}}}{\partial \mathrm{t}}\right] = \left[\frac{\partial\, \mathrm{f(t)_{Degradation}}}{\partial \mathrm{t}}\right] + \left[\frac{\partial\, \mathrm{f(t)_{Determined}}}{\partial \mathrm{t}}\right] \qquad \text{Eq.18}$$

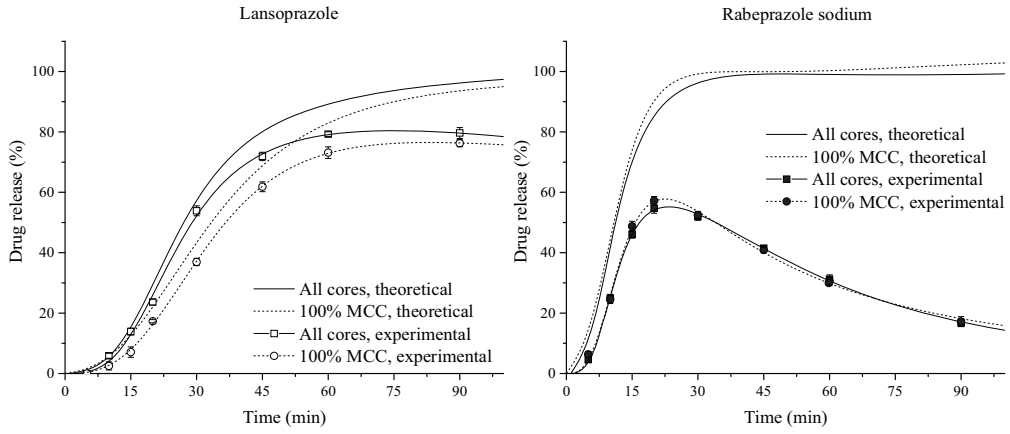


Fig. 29 Drug release of lansoprazole and rabeprazole top-coated pellets in PBS pH 6.8

The release of lansoprazole and rabeprazole sodium in PBS pH 6.8 was integrated from Eq. 18, which revealed a logarithmic pattern (Fig. 29). Rabeprazole top-coated pellets (100% MCC core) achieved 100% release in 30 min, whereas lansoprazole top-coated pellets (100% MCC core) was not completely released at 90 min, as evidenced by the remaining color-indicated cores visible in the dissolution vessel. As both pellets were subcoated, enteric-coated, and top-coated together, the incomplete release of lansoprazole top-coated pellets (100% MCC core) was mainly attributed to the insolubility of lansoprazole, which resulted in slower release rate. The release of rabeprazole top-coated pellets (all cores) was not different from rabeprazole top-coated pellets (100% MCC core), which was attributable to the very high solubility of rabeprazole sodium in aqueous medium. In contrast, the release

of lansoprazole top-coated pellets (all cores) was faster and more complete than that of lansoprazole top-coated pellets (100% MCC core), which illustrated that the incorporation of soluble ingredients into MCC cores, namely 45% MCC core, 30% MCC core, and 0% MCC core in this study, could promote the release of lansoprazole and overcome incomplete release. The osmotic pressure caused by soluble ingredients in the core drove the diffusion of lansoprazole into the release medium. Therefore, the solubility of the drug dominated the release pattern of the top-coated pellets in PBS pH 6.8; incorporation of soluble ingredients into insoluble cores can overcome the incomplete release of insoluble drugs from such top-coated pellets.

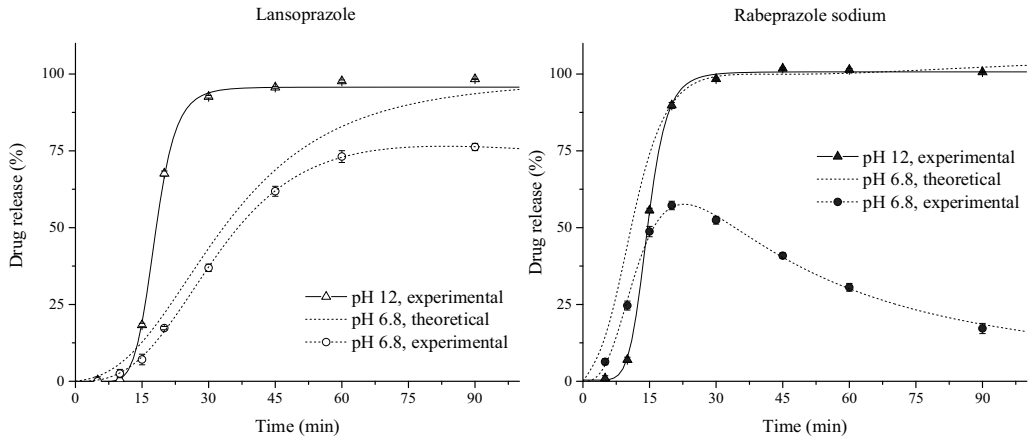


Fig.30 Drug release of top-coated pellets (100% MCC) in PBS pH 6.8 and NaOH pH 12

The solubility of lansoprazole is approximately 100 times higher in pH 12 medium than in pH 6.8 medium (Tabata et al., 1992). Consequently, the release of lansoprazole in an NaOH pH 12 solution was faster and more complete than in PBS pH 6.8 (Fig. 30). The 10-min delayed-release resulted from the lower ionic strength and buffer capacity of the NaOH pH 12 medium on enteric material, as found by Liu et al. (2011) that the rate of proton transfer was increased by the high affinity of water for accepting the proton. These results again confirm that the release pattern is dominated by the drug solubility. Therefore, using the dissolution medium at a higher pH may overcome the instability, which could simplify the dissolution test and drug content determination. However, it may adversely reduce the discriminating power of the method, which was attributed to the solubility change.

Meanwhile, the changes in ionic strength and buffer capacity need to be considered when the release medium is changed.

3.2 Subcoat and top-coat influence on delayed-release ilaprazole pellets

3.2.1 Relationship between polymeric structure and subcoat properties

HPC has low Tg (19°C, 20°C, 21°C, Nyamweya et al., 2000; -25°C to 0°C, Picker-Freyer et al., 2007) and HPMC Methocel E5 has rather high Tg (155°C, Hancock et al., 1994). The high level of hydroxypropyl substituents (73.9%) in HPC, which are longer than the major substituent methoxy groups (28.5%) in HPMC, increased the fractional free volume between the chains, and therefore substantially increased chain flexibility (Fig. 3). On the other hand, the methoxy substitutions in the HPMC backbone chain increased the polarity of molecule. Additionally, the remaining unsubstituted hydroxy groups in the HPMC backbone were likely to form hydrogen bonds between neighboring chain segments. Both factors increased the stiffness of the HPMC chain.

The higher ratio of hydroxy groups in HPC may imply its fast and strong water binding ability, which may slow down liquid-solid phase transition in the coating and aid the formation of continuous and dense film, and thus attributed to form lower vapor permeable film than that of HPMC. The density of subcoated ilaprazole pellets (HPC subcoated, bulk density 0.82 g/ml, tapped density 0.90 g/ml; HPMC subcoated, bulk density 0.80 g/ml, tapped density 0.87 g/ml) well supported the concept. Moreover, the subcoating temperature (40±2°C) may have enabled the HPC chains to continue relaxing and curing, which could improve the uniformity of the film and support the combination with the additives. In contrast, the HPMC chains were quickly stiffen as the water evaporated. HPMC and HPC, with vapor transmission rates reported as 1.59 and 0.6 g/100 cm^2/day, respectively, are often combined to exploit the adhesiveness and flexibility of HPC and the high mechanical stability of HPMC films (Warnke, 2012). Films prepared with HPMC and HPC blends in the ratios of 9:1 and 8:2 significantly lowered the moisture permeability, with the maximum adhesion

demonstrated from 8:2 blends (Shin et al., 2015).

3.2.2 Moisture sorption and desorption of subcoated ilaprazole pellets

The subcoat can seal a water-soluble substrate to prevent the migration of the active into the enteric polymer film and prevent the degradation of acid-labile compounds, such as omeprazole (Lovgren et al., 1988). Different moisture absorption capabilities were observed for subcoated ilaprazole pellets at 25°C (RH 93%), but with a similar desorption profile (Fig. 31). The moisture absorption of the three type of subcoated ilaprazole pellets reached equilibration at 360 minute in the following order: HPMC (2.8%) > HPMC-HPC (80:20) (2.7%) > HPC (2.5%) > ilaprazole drug pellets (2.3%). The HPMC subcoat absorbed 0.3% more moisture than the HPC subcoat did. The HPMC-HPC subcoat slowed down the moisture uptake by a smaller magnitude than expected, which may be attributed to the immiscibility of HPMC and HPC, as found by Nyamweya et al. (2000). The time for the subcoated pellets to reach equilibration was in an order of: Ilaprazole drug pellets < HPMC subcoated pellets < HPMC-HPC (80:20) subcoated pellets < HPC subcoated pellets, which indicated that the relative moisture permeability of the subcoat was as follows: HPC < HPMC-HPC (80:20) < HPMC. The similar desorption profile indicated that a similar drying process could be used for the three subcoated pellets.

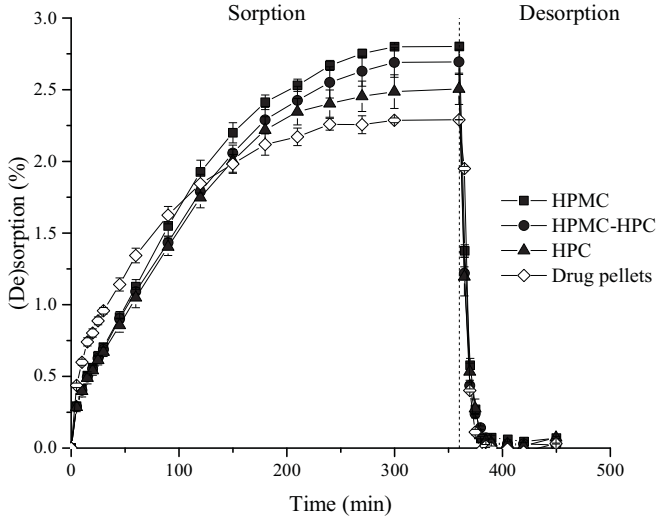


Fig. 31 Moisture absorption/desorption of subcoated ilaprazole pellets

3.2.3 Cloud point of subcoat solutions

The aqueous solubility of HPC and HPMC decreases with increasing temperature due to polymer phase separation (Bergstrand et al., 1999). Cloud point of 34.5°C, 37.5°C and 54°C for HPC, HPMC-HPC (80:20) and HMPC, respetively, was obtained in this study (Fig. 32), which clearly differentiated the solubility of the three subcoats, and its dependence on the temperature. Therefore, in the acid resistance test and swelling study (37°C), HPC subcoat may keep undissoved but HPMC and HPMC-HPC (80:20) dissolved slowly in the permeated medium and produced aqueous pathways. The phase separation of HPC solution at higher than 34.5°C may also implied a slower release of HPC subcoated pellets than HPMC or HPMC-HPC (80:20) subcoated pellets, which turned out to be true (Fig. 34). The cloud point of HPMC-HPC (80:20) is closer to HPC solution, which was caused from the decreasing solubility of HPC, implying that a phase separation between HPMC and HPC existed over the increasing solution temperature.

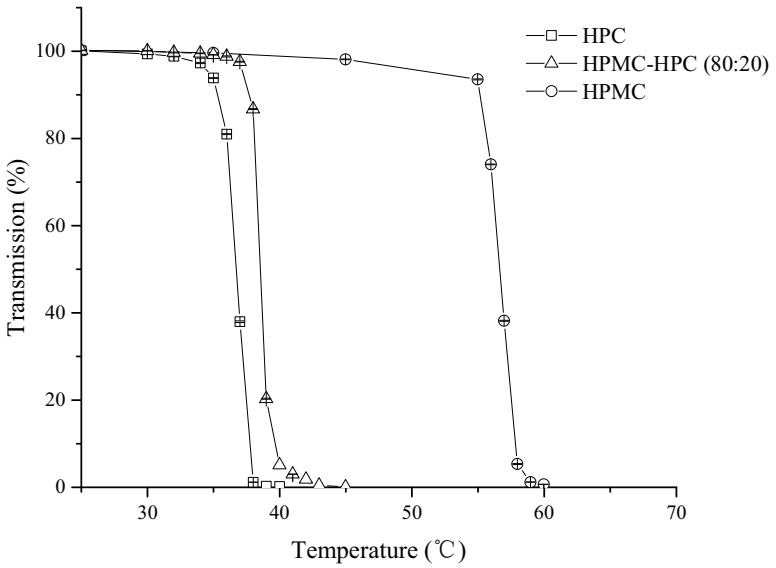


Fig. 32 Cloud points of subcoat solutions

3.2.4 Microstructure of HPMC and HPC subcoat

Coarser surface and looser binding of the granules were revealed on the surface of HPMC subcoat compared with HPC subcoat (Fig. 33). The cross-section of the HPMC subcoat

exhibited fine flakes with sharp edge, which may caused from the rigidness of HPMC. The numerous fine flakes overlapped and produced fine capillary tubes during water evaporation which implied faster medium permeating as confirmed by faster release of ilaprazle from the corresponding subcoated pellets (Fig. 34). In contrast, the cross-section of the HPC subcoat appeared as dense, continuous, and flexible film, which may account for the reduced thickness, higher density of the corresponding subcoated ilaprazole pellets, and less vapor permeation.

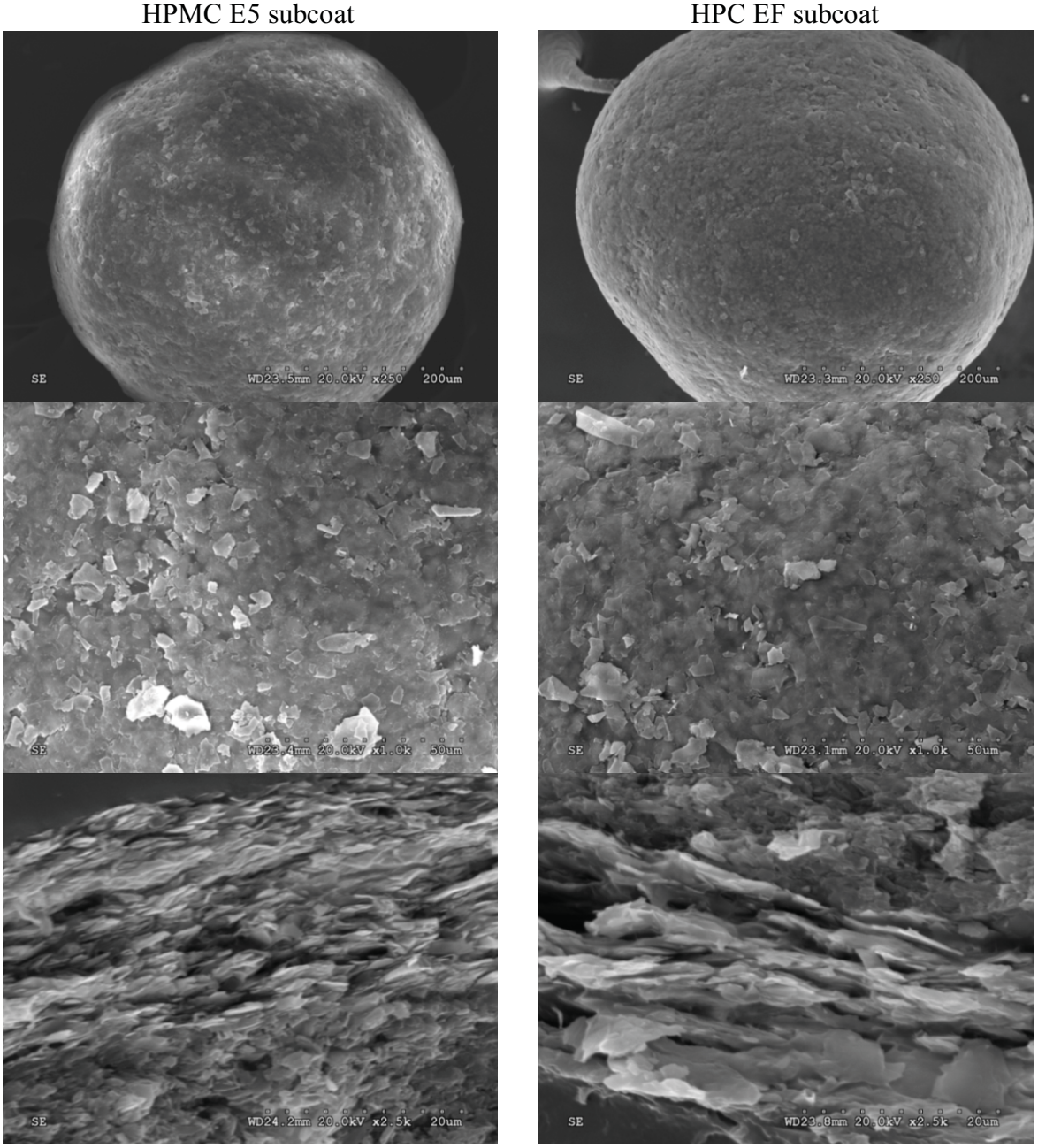


Fig. 33 Surface and cross-sectional microstructure of the HPMC and HPC subcoats (SEM)

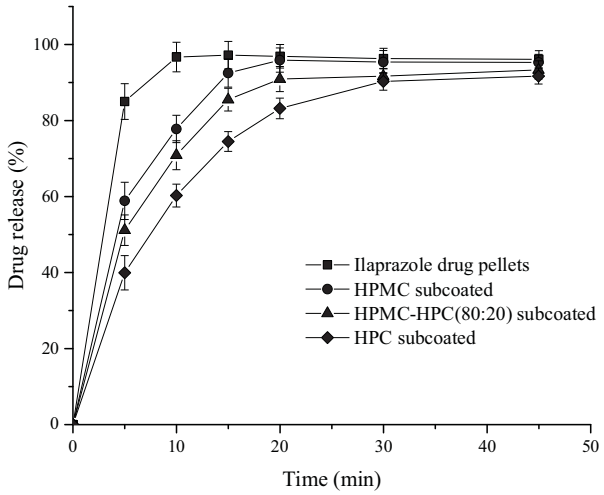


Fig. 34 Drug release of subcoated ilaprazole pellets in PBS pH 6.8/isopropanol (72:28)

3.2.5 Subcoat influence on acidic medium permeation

The top-coated ilaprazole pellets under investigation were prepared from equivalent formulations with different subcoats. Therefore, the different degree of discoloration in the acidic medium permeation reflected the performance of the subcoat on the blocking or hindering of medium permeation and API migration.

Top-coated ilaprazole pellets subcoated with HPC appeared highly dissymmetric shapes at 75 minute (Fig. 35) but remained intact. In contrast, top-coated ilaprazole pellets subcoated with HPMC and HPMC-HPC mixture ruptured at 75 minute from comparably small exits with pellet shape remained. The decreasing solubility of HPC in medium at 45°C, as referred from cloud study, may have reinforced the prevention effect of the medium permeation and API imgration. Moreover, the flexibility of the HPC chain may have distributed the swelling pressure to the entire membrane, and delayed the rupture of the enteric film. In contrast, the higher solubility of HPMC in the medium caused faster medium permeation, and the rigidity of HPMC transformed the minor defects into failure points. The subcoat formed from the HPMC-HPC (80:20) mixture did not ameliorate the formation of defects, which confirmed that the failure resulted from HPMC. However, the HPMC-HPC (80:20) mixture delayed the

degradation, which was evidenced by a smaller brownish area and slower browning compared with HPMC subcoated pellets. The addition of 20% HPC may have significantly prevented the medium permeation, but was still insufficient to form a sucessful barrier. The ruptures were localized, which did not result in instant failure of the whole pellets. The voids formed in subcoat and enteric layer produced bubbles during incubation and shortened the permeation pathway.

Compared to ilaprazole top-coated pellets with 22% w/w HPMC subcoat, that with 30% w/w HPMC subcoat showed less degree of discoloration and less defects at 120 min after soaking (Fig. 36). Therefore, thicker or better subcoat could improve the unsatisfactory acid resistance of the top-coated ilaprazole pellets.

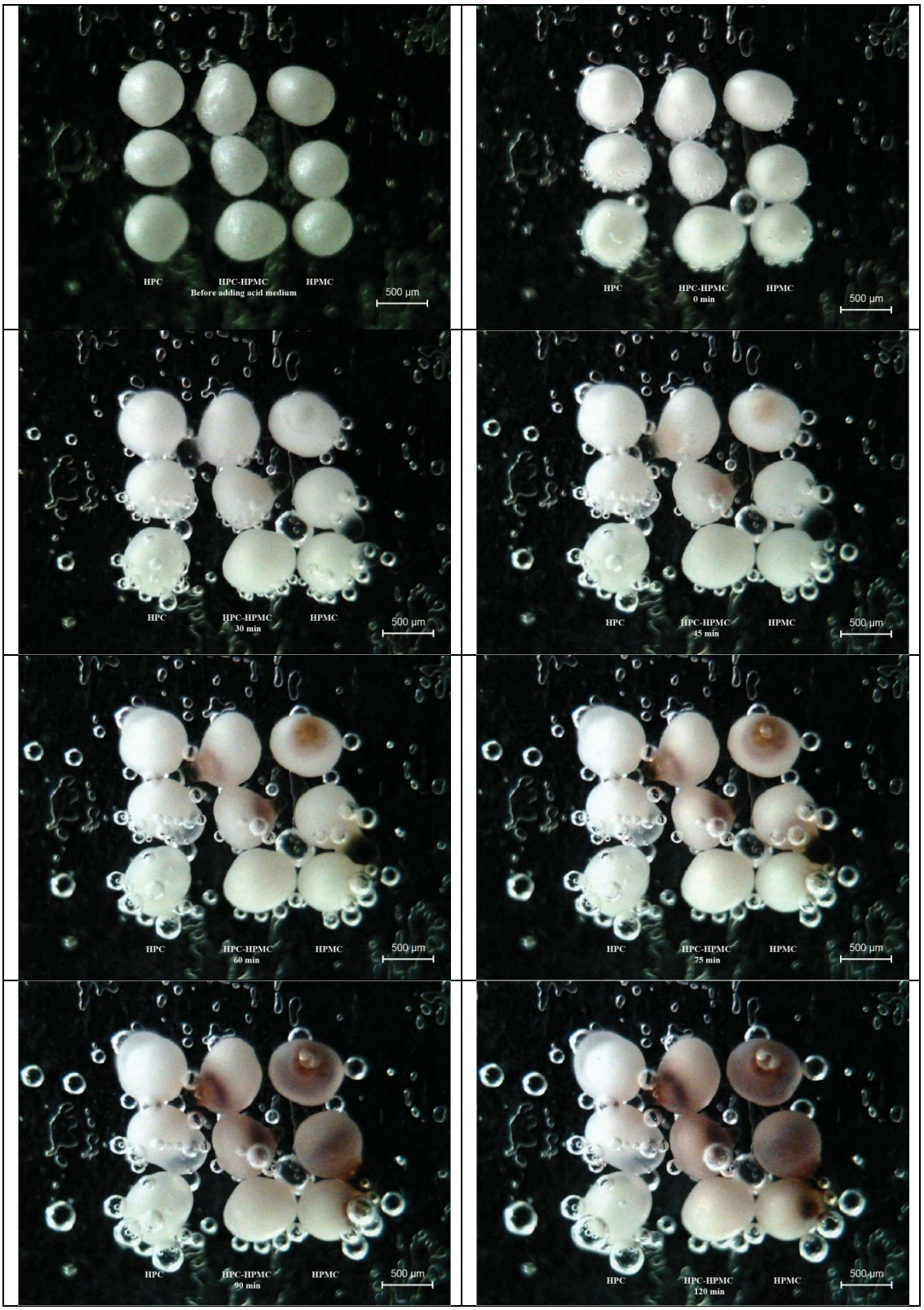


Fig. 35 Swelling of top-coated ilaprazole pellets in 0.1 N HCl

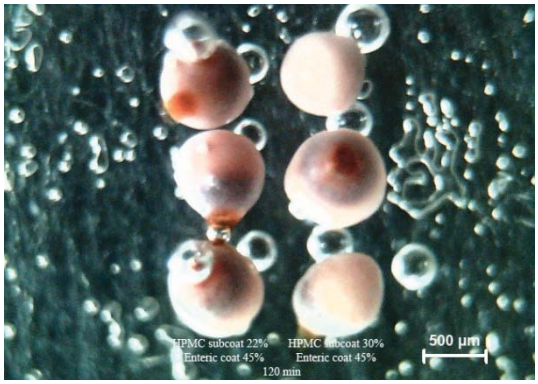


Fig. 36 Swelling of top-coated ilaprazole pellets in 0.1 N HCl: 22% vs. 30% HPMC subcoat

3.2.6 Subcoat influence on pellet compression

The top-coated ilaprazole pellets with HPC subcoat exhibited the best acid resistance before compression and least loss of acid resistance after compression (Fig. 37). Compared with the HPMC subcoated pellets and pellet-tablets, the HPMC-HPC (80:20) subcoat improved the acid resistance of the uncompressed ilaprazole pellets slightly, as well as less loss of acid resistance after compression. After compression, the HPMC subcoat exhibited a large number of fragments; on the contrary, the HPC subcoat was still continuous, but accompanyed with merging layers (Fig. 38), which may have resulted from the compression and resulted in denser subcoat after compression. As shown in Fig. 36, thicker subcoat was needed for the HPMC and HPMC-HPC subcoated ilaprazole top-coated pellets and the corresponding pellet-tablets to achieve pharmacopoeia complianced acid resistance.

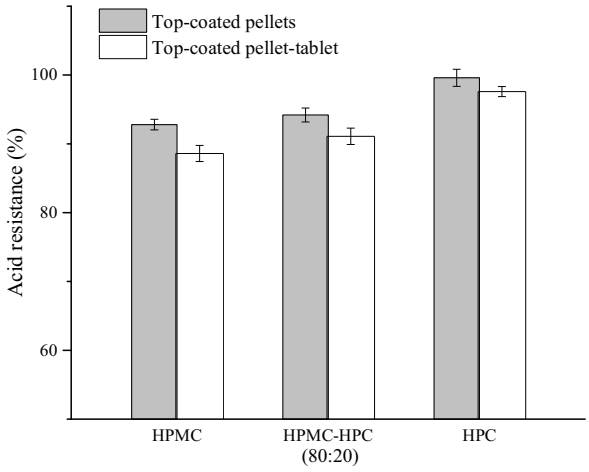
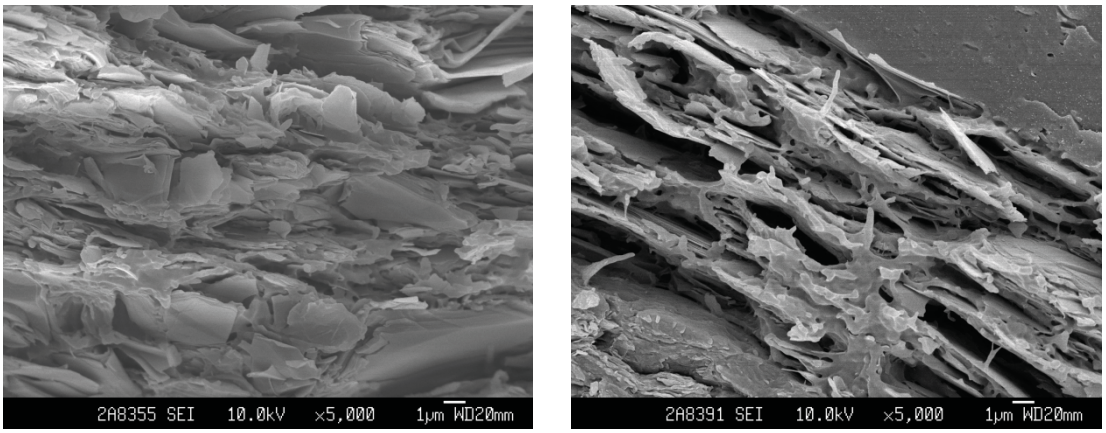


Fig. 37 Acid resistance of top-coated ilaprazole pellets and pellet-tablets



HPMC HPC

Fig. 38 HPMC and HPC subcoat after compression (SEM)

3.2.7 Top-coat influence on pellet compression

Either compressed with or without sodium hyaluronate-xanthan gum granules, applying 10% w/w HPMC as top-coat based the weight of enteric-coated ilaprazole pellets helped the enteric-coated pellets withstand compression better (Fig. 39), which was more pronunced in HPMC subcoated pellets than in HPC subcoated pellets. 10% w/w top-coat had markedly buffered the compression force and reduced the damage to the enteric-coat and subcoat, which could be attributed to the good mechenical resistance of HPMC and the good cusion effect from the overlapped HPMC flakes abundant with fine gaps. The difference of acid resistance between the enteric-coated pellet-tablets and top-coated pellet-tablets from HPC subcoated pellets was smaller than that from HPMC subcoated pellets, which confirmed that the flexible subcoat could dissipate the compression force more efficiently.

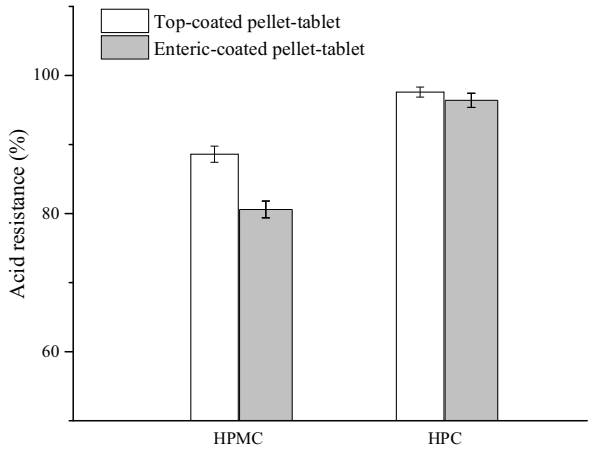


Fig. 39 Acid resistance of enteric-coated and top-coated ilaprazole pellet-tablets (tablets compressed with sodium hyaluronate-xanthan gum granules)

3.2.8 Drug release of top-coated ilaprazole pellets and pellet-tablets

Rotary tableting machines can mimic the work conditions encountered in the pharmaceutical industry (Ghanam et al., 2010). The MUPS tablet produced with the setup in this study achieved USP acceptable content uniformity and weight variation. A smaller acceleration of drug release from HPC subcoated ilaprazole pellet-tablets was observed when compared to that from HPMC subcoated pellet-tablets (Fig. 40).

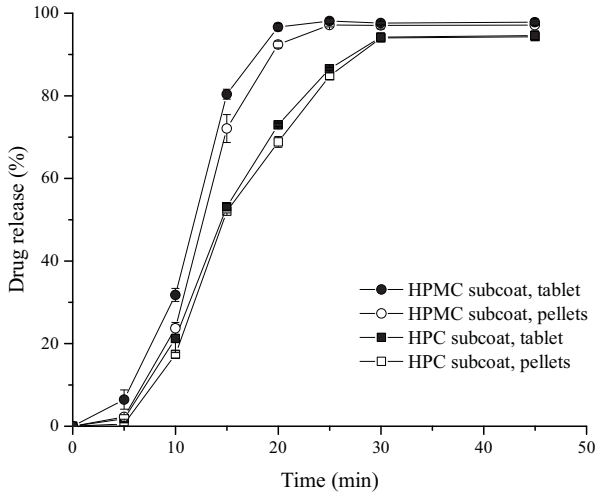


Fig. 40 Drug release of ilaprazole pellet-tablets in PBS pH 6.8/isopropanol (72:28)

3.3 Lansoprazole and rabeprazole sodium pellet-tablets

The process parameters and critical attributes of pellet-tablets preparation were summarized in Table 14.

3.3.1 MUPS tablets by pellet compression

One major issue with compressing pellets into a tablet is the segregation phenomenon. As shown in Fig. 41, eight type of lansoprazole and rabeprazole sodium pellets were uniformly scattered on the surface and cross-section. The content uniformity of both drugs in the compressed tablets and the weight variation of the tablets were well within USP acceptance criteria (Table 14). Therefore, segregation-free tablets were successfully compressed in this study with a rotary tableting machine, which may be attributable to the small size of top-coated pellets used for compression.

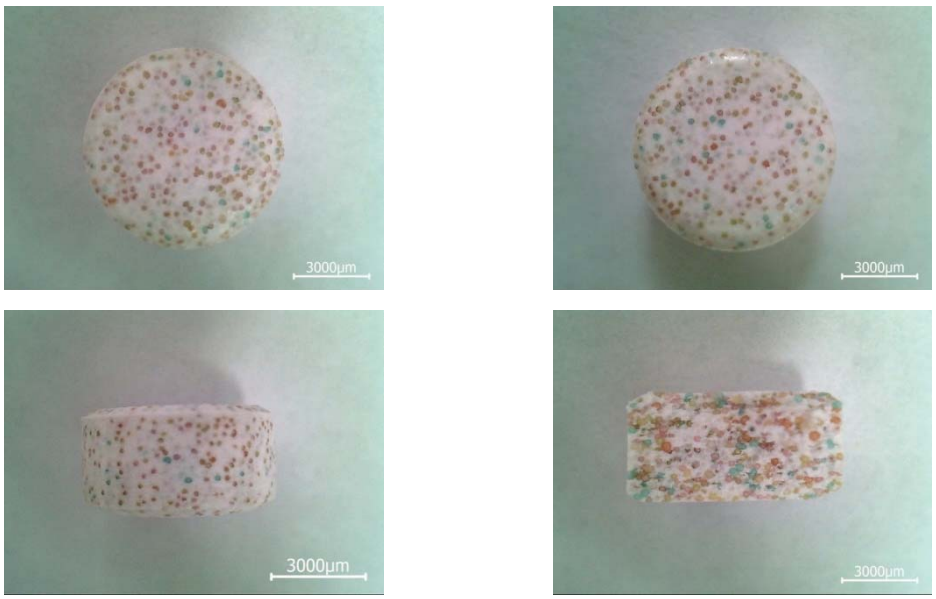


Fig. 41 Appearance of lansoprazole and rabeprazole sodium pellet-tablet

Table 14 Compression/freeze-drying parameters and MUPS tablet attributes

	Compressed without sodium hyaluronate-xanthan gum	Compressed with sodium hyaluronate-xanthan gum	Freeze-dried
Die diameter, mm	8.5	8.5	11.5
Feeding speed, rpm	15	15	-
Turret speed, rpm	10	10	-
Filling depth, mm	8.5-8.7	8.4-8.6	-
Compression pressure, kN	4.5-4.8	9.0-12.0	-
Hardness, N	36-42	20-30	6-7
Weight of tablet, mg	303.1±5.0	303.1±5.0	182.2±3.0
Pellets loading, w/w%	41.7	41.7	69.4
Weight uniformity	Confirm to USP	Confirm to USP	Confirm to USP
Content uniformity, lansoprazole	Confirm to USP	Confirm to USP	Confirm to USP
Content uniformity, rabeprazole sodium	Confirm to USP	Confirm to USP	Confirm to USP
Disintegration, s	56±2	>300	12±2

3.3.2 MUPS tablets by freeze-drying

The top-coated pellets of lansoprazole and rabeprazole sodium (all cores) were freeze-dried into MUPS tablets containing 5 mg lansoprazole and 5 mg rabeprazole sodium (Fig. 42). To ensure content uniformity of the freeze-dried pellet tablets, the pellet suspensions must remain homogeneous during gel dispensing. The content uniformity of lansoprazole and rabeprazole sodium of the freeze-dried pellet-tablets was well within USP acceptance criteria (Table 14). Therefore, the dispensing process was considered segregation free.

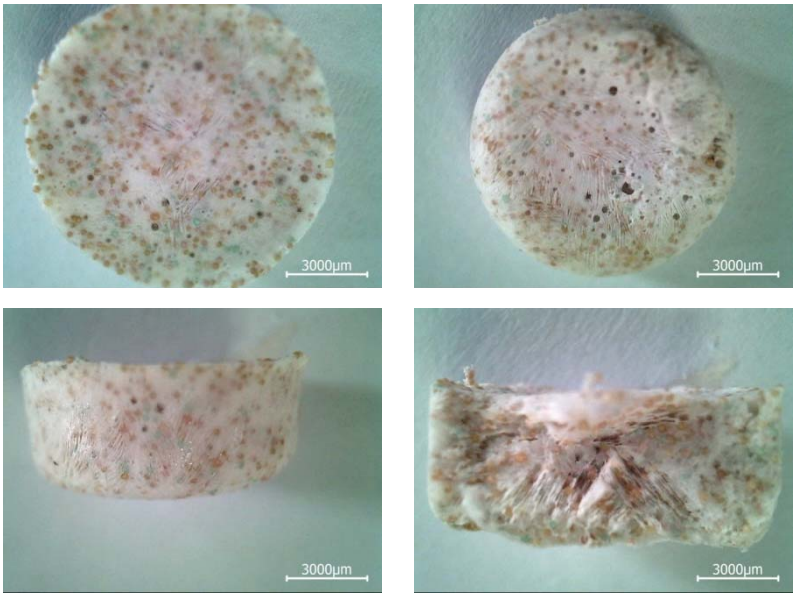


Fig. 42 Appearance of freeze-dried pellet-tablet of lansoprazole and rabeprazole sodium

3.3.3 Disintegration of MUPS tablets

FDA CDER (2008) proposed an *in vitro* disintegration time of approximately 30 s or less for ODTs. Based on NG feeding experiences, we considered 180 s as an acceptable thickening time and 10 s as feeding time. Accordingly, the compressed pellet-tablets without sodium hyaluronate-xanthan gum granules considered to be potential candidates for enteral tube feeding, but not ideal for oral administration in ingestion problematic population (Table 14). Further, the compressed pellet-tablets with sodium hyaluronate- xanthan gum granules totally failed the disintegration tests due to the strong binding of the polymers. The freeze-dried pellet-tablets was most promising for oral administration to ingestion problematic population or pediatric population.

Hand shaking of a syringe containing 5 mL water dissolved the pellet-tablets to a greater extent than that of the compendia disintegrator device. As shown in Table 15 and Fig. 43, the compressed pellet-tablets without sodium hyaluronate-xanthan gum dissolved within 5 s in a catheter tipped syringe, but settled completely within 2 s. The compressed pellet-tablets containing sodium hyaluronate-xanthan gum granules dissolved at approximately 145 s in catheter tipped syringes and remained stable for more than 10 minute. Freeze-dried

pellet-tablets dissolved in approximately 5 s in catheter tipped syringes and also remained in stable suspension for longer than 10 minutes (Fig. 43).

Table 15 Thickening and sedimentation of pellet suspension in catheter tipped syringes

Parameters / Samples		Thickening time s	Settle time s
(a)	Compressed tablet without sodium hyaluronate-xanthan gum	5±1	2±1
(b)	Compressed tablet with sodium hyaluronate-xanthan gum	145±3	> 300
(c)	Pellet mixture with sodium hyaluronate-xanthan gum	3±1	> 300
(d)	Freeze-dried pellet-tablet	5±1	> 300

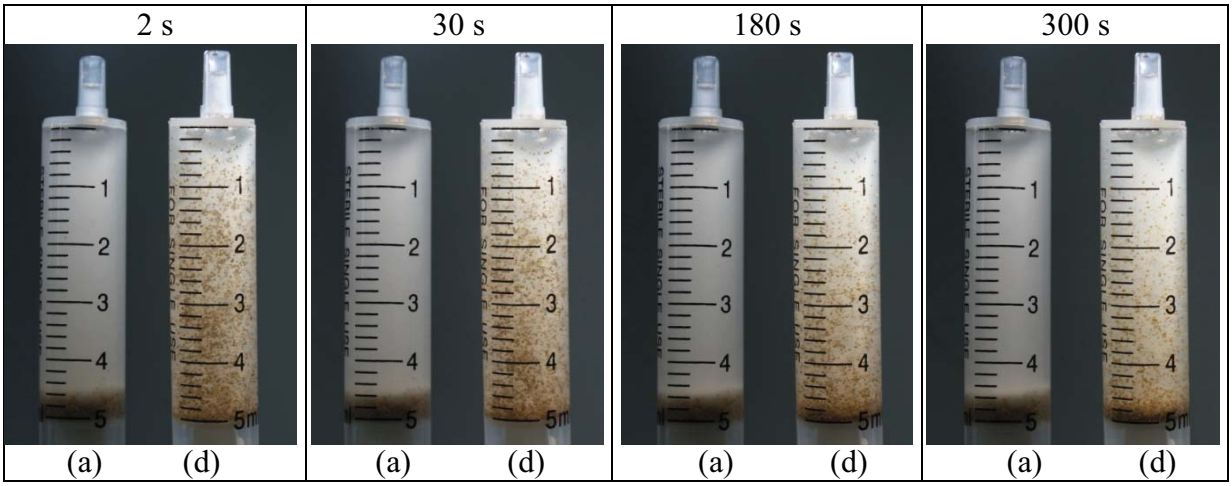


Fig. 43 Sedimentation of pellet suspensions

3.3.4 Drug influence on acid resistance loss after compression

The acid resistance of compressed lansoprazole and rabeprazole sodium pellet-tablets without suspending agent and freeze-dried pellet-tablets was compared to that of top-coated pellets (Fig. 44).

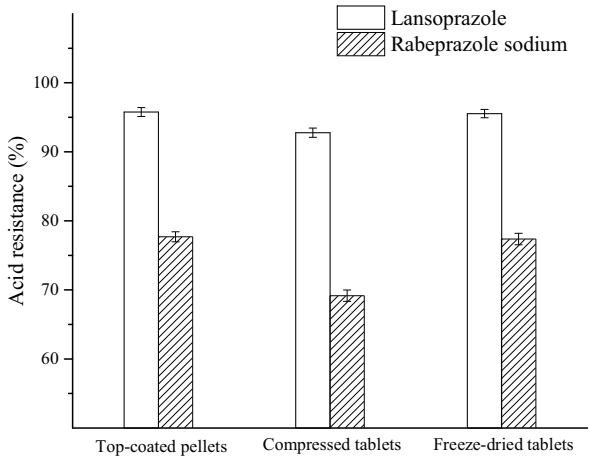


Fig. 44 Acid resistance of lansoprazole and rabeprazole sodium pellet-tablets

Compression dramatically decreases the acid resistance of rabeprazole sodium pellets, but only slightly affected the acid resistance of lansoprazole pellets. Despite being coated with the same formula and process, rabeprazole sodium had a denser and higher hydroscopic drug layer, thinner effective subcoat, and increased instability than lansoprazole pellets, resulting in a marked decrease in acid resistance after compression. These results may also imply that thicker and less permeable subcoat and function layer are needed for soluble drugs to achieve similar controlled release or sustained release properties as those of insoluble drugs.

Freeze-drying of pellets into tablets in this study did not cause a loss in acid resistance.

Therefore, compression of eight type of pellets into one tablet with minimal loss of function is possible; multiparticulate combinations could be compressed or freeze-dried into one tablet.

3.3.5 Drug influence on drug release of MUPS tablets

Drug release of compressed pellet-tablets without a suspending agent and freeze-dried pellet-tablets was compared to that of top-coated pellets in PBS pH 6.8 (Fig. 45). After compression, a slight acceleration in the release of lansoprazole from compressed MUPs tablets was observed. Based on the loss of acid resistance, the rabeprazole sodium pellet coatings were assumed to have been deteriorated to a greater extent than that of lansoprazole

pellets, and the accelerated release of rabeprazole sodium was expected to be greater than that of lansoprazole. However, due to the fast release of rabeprazole sodium in PBS pH 6.8, the method may have failed to discriminate the difference.

Freeze-drying of pellets into tablets in this study did not alter the release of both drugs.

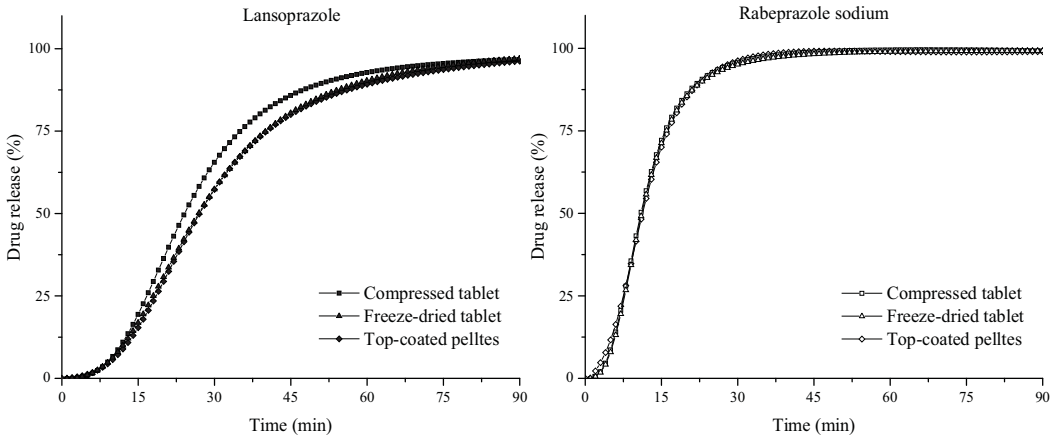


Fig. 45 Drug release (theoretical) of lansoprazole and rabeprazole sodium pellet-tablets (all cores) in PBS pH 6.8

3.3.6 Sedimentation of the pellet suspension

3.3.6.1 Suspending ability

A stable pellet suspension is ideal for oral taking and EFT feeding. The pellet suspensions that settle very fast require repeated shaking of the syringe before feeding or turning of the syringe during the feeding to reduce the sedimentation, which often results in incomplete feeding or blockage. Based on the feeding experiences in this study, we considered 10 s as feeding time. The settle time was recorded when the solid mass settled to less than half of the syringe's height.

The formulations with sodium hyaluronate-xanthan gum were with excellent suspending ability in catheter tipped syringe (Table 15), attributable to the thickening properties of sodium hyaluronate and xanthan gum, which effectively prevented settling and agglomeration of the pellets; further, the pellets were prevented from sticking to the syringe

and tube walls when in standing and during the feeding process; therefore, blockages and incomplete feeding were avoided. When the pellet mixtures were charged into 5-mL syringe very cautiously; the solid powder collected at the catheter tip and then gelled *in-situ* when distilled water was drawn into the syringe. Therefore, the gel had to be drawn back into the syringe by repeated drawing-pushing effort. Considering together with the thickening time, freeze-dried pellet-tablets are optimal for orally administration intact or via oral syringe to pediatric populations.

3.3.6.2 Minimum viscosity of the suspension

Martin (2006) suggested that Stokes' law is valid for diluted pharmaceutical suspensions that are composed of no more than 2% solids. The volume fraction of the pellets in the target suspension in this study was 2.3%. Stokes' law was used to estimate the minimum viscosity required to suspend the top-coated pellets in a 5-mL catheter tipped syringe for 10 s, maintaining the suspended pellets at over half the height of the suspension. Stokes' law was therefore modified to:

$$V = \frac{d^2(\rho_1 - \rho_2)g}{18\eta_0} = \frac{H}{2t} \qquad \text{Eq. 19}$$

the minimum viscosity was calculated according to:

$$\eta_0 = \frac{d^2(\rho_1 - \rho_2)g}{9} \times \frac{t}{H} \qquad \text{Eq. 20}$$

where, η_0 is the viscosity of the medium; V is the terminal velocity of sedimentation (cm/s); d is the diameter of the pellets, d_{50} is 0.04 cm; ρ_1 is the density of the pellets, 1.12 g/cm^3; ρ_2 is the density of the medium, 1.01 g/cm^3; and H is 5 cm.

Therefore, the minimum viscosity to keep suspension stable could be calculated with Eq. 21:

$$\eta_0 = 0.38\, t\ (mPa \cdot s) \qquad \text{Eq. 21}$$

The suspending solution consisting of 0.1% HA and 0.1% xanthan gum in this study showed zero shear viscosity at 261.5 mPa.s (Fig. 48), could theoretically keep the pellet suspensions stable for more than 10 minutes and proved to be correct.

3.4 *In-vitro* NG tube feeding

3.4.1 Rheology of thickening solution

Mueller et al. (2010) used a three parameter Herschel-Bulkley model (Herschel et al.,1926) to fit a non-Newtonian system:

$$\tau = \tau_0 + K\gamma^n \qquad \text{Eq. 22}$$

where, τ_0 is the yield stress below which there is no flow; K is the consistency (which takes the same value as η evaluated at γ=1); and n is the flow index, which defines the degree of non-Newtonian behavior (shear thickening for n>1, and shear-thinning for n <1).

Sodium hyaluronate (0.1%), xanthan gum (0.1%), and sodium hyaluronate-xanthan gum (0.1%-0.1%) were all non-Newtonian fluids (Fig. 46); however, sodium hyaluronate (0.1%) was very Newtonian-like, with almost constant viscosity. The shear-thinning ability in ascending order was as follows: xanthan gum (0.1%) > sodium hyaluronate-xanthan gum (0.1%-0.1%) > sodium hyaluronate (0.1%). The sodium hyaluronate-xanthan gum (0.1%-0.1%) solution had a smaller shear stress than that of xanthan gum (0.1%) (Fig. 47); this may be attributable to the lubrication effects of sodium hyaluronate resulting from its ability to disentangle from the linear molecular structure.

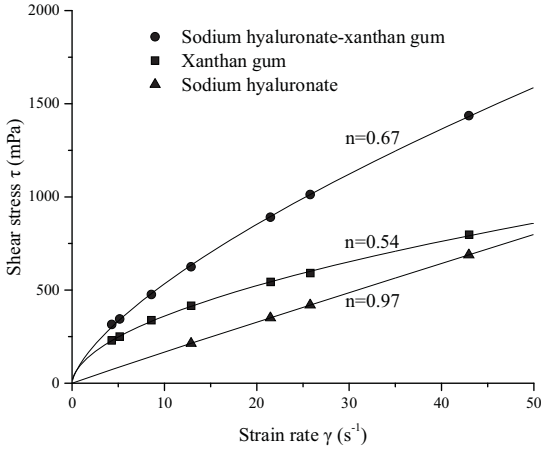


Fig. 46 τ (γ) curves of sodium hyaluronate (0.1%), xanthan gum (0.1%), and sodium hyaluronate-xanthan gum (0.1%-0.1%) solutions

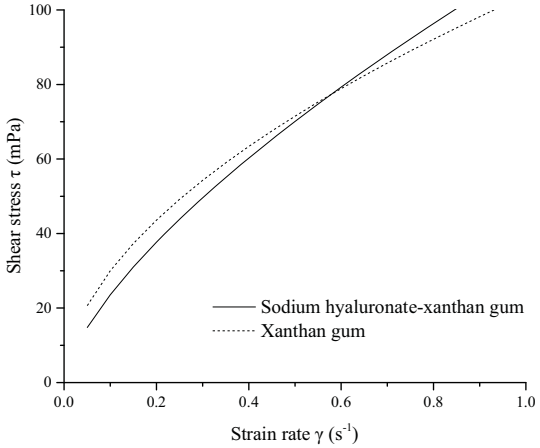


Fig. 47 τ (γ) curves of xanthan gum (0.1%) and sodium hyaluronate-xanthan gum (0.1%-0.1%) at low strain rates

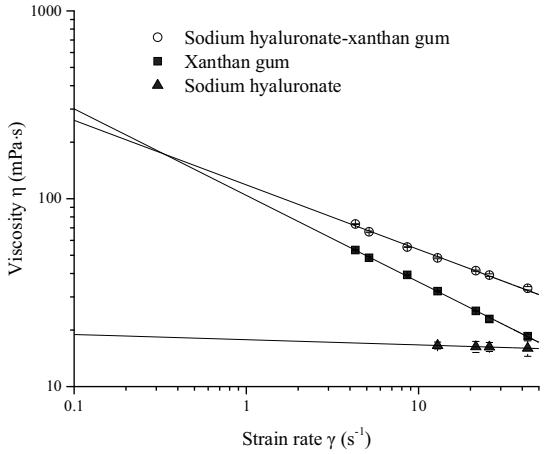


Fig. 48 η (γ) curves of sodium hyaluronate (0.1%), xanthan gum (0.1%), and sodium hyaluronate-xanthan gum (0.1%-0.1%) solutions

Zero shear viscosities of 18.9 mPa.s, 261.6 mPa.s, and 300.8 mPa.s for sodium hyaluronate (0.1%), sodium hyaluronate-xanthan gum (0.1%-0.1%), and xanthan gum (0.1%), respectively, were extrapolated from the η(γ) curves (Fig. 48). The addition of 0.1% sodium hyaluronate to a 0.1% xanthan gum solution lowered its zero shear viscosity, which implied the improved instant shear-thinning effect with less force required for starting injection. Based on Eq. 21, the zero shear viscosity of sodium hyaluronate-xanthan gum could keep the target suspension system stable for more than 10 minutes. When the shear rate was increased to 50 s^{-1}, the viscosity quickly decreased to 20 mPa.s, which allowed for easy handling of the solution.

3.4.2 Rheology of pellet suspension

The sodium hyaluronate-xanthan gum (0.1%-0.1%) solution and pellet suspension were both non-Newtonian fluids (Fig. 49 and Fig. 50). The pellet suspension had higher viscosity than that of the suspending solution, exhibiting a stronger shear-thinning effect.

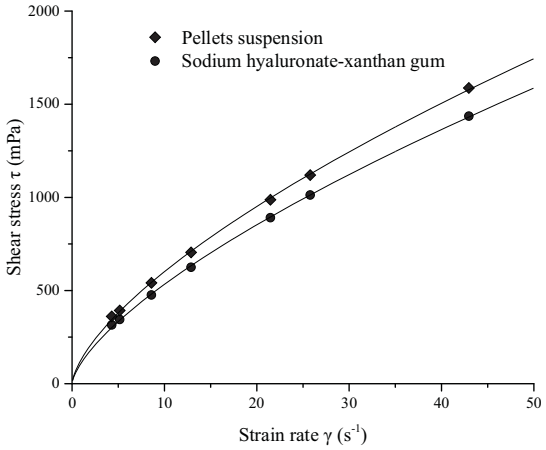


Fig. 49 τ (γ) curves of sodium hyaluronate-xanthan gum (0.1%-0.1%) solution and pellets suspension

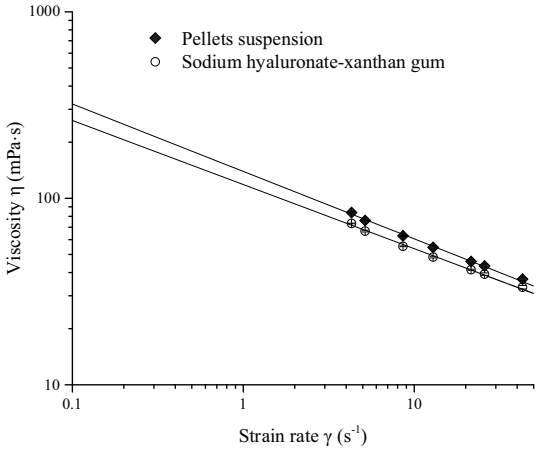


Fig. 50 η (γ) curves of sodium hyaluronate-xanthan gum solution and pellets suspension

The volume fraction (ϕ) of the pellets in the suspension for NG tube feeding in this study was 2.3%, which was deemed as a diluted particle solution. According to Einstein equation:

$$\frac{\eta}{\eta_0} = 1 + \mathrm{B}\phi \qquad \text{Eq. 23}$$

when the system strictly follows Einstein assumptions, the coefficient B is 2.5.

In this study, B (γ) curve was plotted based on Eq. 24:

$$B = (\frac{\eta}{\eta_0} - 1)/\phi \qquad \text{Eq. 24}$$

Coefficient B led to a constant at high strain rates, attributable to Newtonian-like behavior with a constant of 4.6 (Fig. 51), which fell into the favorable range of 1.5<B<5, as reported by other researchers (Mueller et al., 2010).

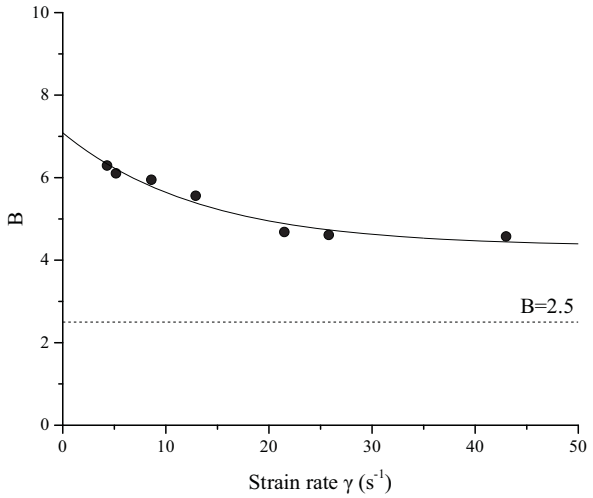


Fig. 51 B (γ) curve of pellets suspension

3.4.3 *In-vitro* NG tube feeding

Broderick et al. (2014) found that wide bore tubes were never blocked and never needed to be replaced for blockage; however, patients found them more uncomfortable. Narrow bore tubes were frequently blocked, with increased time demands on nurses and the team to unblock and replace the tubes, causing increased radiographical exposure. But for small children, narrow bore tubes with no or minimal blockage are needed. The 8-Fr NG tubes (Fig. 6) comprised of three sharp bends (position 40, 30, and 5) and one narrow-down connection, which were susceptible for pellets agglomeration. Suspension of compressed lansoprazole and rabeprazole sodium pellet-tablets without suspending agents blocked the feeding entrance completely (Fig. 52); the pellets immediately settled and clumped at the narrowing cannula. Rinsing with water did not eradicate the blockage. The first downward bent position (45-40) and upward bent position (30-25) showed pellet accumulation. The freeze-dried

pellet-tablets needed the least force to feed the suspension and no pellets remained in the syringe and tube. The non-Newtonian and viscoelastic properties of the sodium hyaluronate-xanthan gum solution may have induced an excellent isolation and lubrication effect for the pellets. Further, the excellent suspending ability of the sodium hyaluronate-xanthan gum solution prevented sedimentation and agglomeration of the pellets during standing and feeding process. Sodium hyaluronate is also a natural super lubricant that may have helped lubricate the inner wall of the syringe and NG tube. Complete recoveries were achieved in these cases.

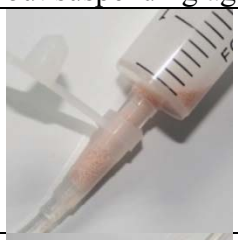
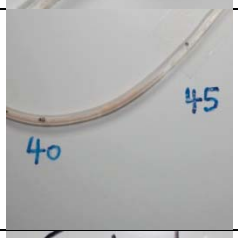
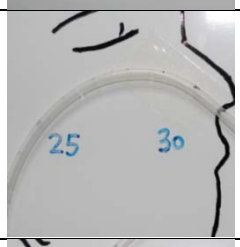
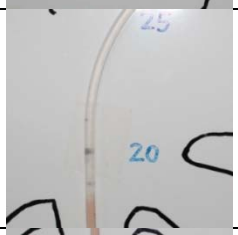
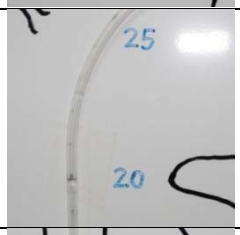
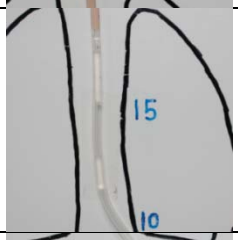
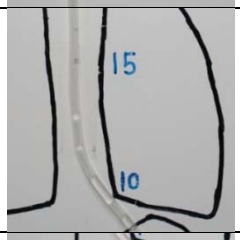
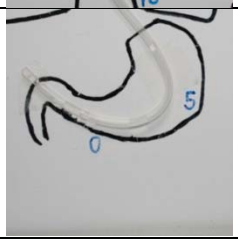
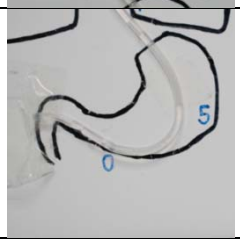
Position	Compressed pellet-tablet without suspending agents	Freeze-dried pellet-tablet with suspending agents
Feeding part after flush-through		
45-40		
30-25		
25-20		
15-10		
5-0		
Recovery (%)		
Lansoprazole	47.3, 0	99.3, 99.7
Rabeprazole sodium	45.2, 0	99.2, 99.5

Fig. 52 NG tube feeding of lansoprazole and rabeprazole sodium pellet-tablets

4. Summary

Acid-labile drugs are easily degraded in acidic medium, which have been mainly formulated as enteric-coated dosage forms for oral administration. The objective of this study was to prepare oral multiparticulate formulations of acid-labile drugs, using ilaprazole, lansoprazole and rabeprazole sodium as model drugs. The influence of drug solubility and core type on drug layering, swelling, acid resistance, and drug release of the delayed-release pellets and pellet-tablets was investigated using lansoprazole and rabeprazole sodium as drug pair. The influence of subcoat on water vapor sorption, acidic medium seeping, acid resistance of the delayed-release pellets and pellet-tablets, as well as the influence of top-coat on pellet compression were investigated using ilaprazole as the model drug.

Three commercially-available cores (CP-102, Nonpareil-105, and PF 053) and one laboratory made cores were used in the study with MCC% w/w in the cores in descending order of CP-102 (100% MCC) > laboratory made cores (45% MCC) > Nonpareil-105 (30% MCC) > PF 053 (0% MCC). Rabeprazole sodium was more influenced by a decreasing pH of the medium than lansoprazole. Rabeprazole sodium was dissolved in the binder solution with higher dissolved content (15.67%) and viscosity (92.05 mPa.s), compared with lansoprazole, which was insoluble in the drug suspension with 4.86% of dissolved content and viscosity of 80.24 mPa.s. The coating levels of rabeprazole sodium drug pellets with 45% MCC cores and 0% MCC cores were lower than those of lansoprazole drug pellets made in the same cores, and much lower than those of both drug pellets from 100% MCC cores and 30% MCC cores, which implied that the 45% MCC cores had the least mechanical strength, and that 0% MCC cores were strong enough for layering of lansoprazole, but not strong enough for layering rabeprazole sodium. When the core loss dominated, the coating level by weight decreased while the actual coating level increased. When drug loss dominated, the coating level by weight decreased and actual coating level also decreased. The decrease in coating level / actual coating level reflected an increase in core loss. The visible dents, broken parts, and cracks on the surface of rabeprazole sodium drug pellets layered from 0% MCC cores and 45% MCC cores provided sufficient evidence for core crumbling or

breakage.

Equal weight of lansoprazole drug pellets and rabeprazole sodium drug pellets from four type of cores were mixed for subsequent subcoating, enteric-coating, and top-coating. A porous lansoprazole layer and a dense rabeprazole layer of all type of cores were revealed. The interface between the core and the lansoprazole layer was distinguishable and the distinguishability decreased with a decrease in MCC% w/w in the cores. The rabeprazole sodium layer bound to all type of cores tightly, and the interface between the core and the rabeprazole sodium layer fused better with a decrease in MCC % w/w in the cores. This demonstrated that a higher percentage of soluble content in drug suspension led to a denser drug layer and a less distinguishable border between core and drug layer. The interface between drug layer and subcoat showed similar tendency. Lansoprazole layer and subcoat showed clearer interface than that of rabeprazole layer and subcoat. The "fusing effect" resulted from the rabeprazole sodium layer decreased the effective thickness of the intended subcoat, which implied that a thicker subcoat woud be necessary to achieve a similar extent of isolation as for lansoprazole.

In the swelling study conducted in 0.1N HCl solution, the rabeprazole sodium top-coated pellets swelled swiftly after 60 min, while the lansoprazole pellets top-coated remained unchanged. The swelling of rabeprazole sodium pellets became dramatically faster after 90 minute and was inversely correlated with MCC% w/w in the cores in an order of 100% MCC < 45% MCC < 30% MCC < 0% MCC. The cores did not influence the swelling of lansoprazole pellets, which may due to the less permeable drug layer that enriched with insoluble lansoprazole and stabilizer. When 0% MCC cores were used, the absorption of a small amount of medium may have resulted in an increase in osmosis and promoted swelling. Therefore, compared to lansoprazole, the rabeprazole sodium drug pellets may need a thicker or more medium-resistant subcoat, or a thicker enteric layer or better acid-resistant material to hinder the permeation of acidic medium into the drug layer.

The acid resistance of the four type of rabeprazole sodium top-coated pellets was 15-20% lower than that of lansoprazole. The unsatisfactory acid resistance of the rabeprazole sodium

pellets was attributed to 1) the highly hydroscopic property of the rabeprazole sodium layer, which may have facilitated the permeation of acidic medium towarding the drug layer.; 2) rabeprazole sodium was more sensitive to an acidic environment and degraded much faster than lansoprazole; 3) the higher density of the drug layer from solution deposition resulted in a smaller size of the rabeprazole sodium drug pellets in general, and a thinner subcoat and enteric layer consenqently; and 4) the fusing effect of the rabeprazole drug layer with the subcoat reduced the effective thickness of the subcoat. When thicker subcoat or enteric-coat was applied, the acid resistance of rabeprazole sodium top-coated pellets (0% MCC cores) was improved.

The incorporation of soluble ingredients into MCC cores promoted the release of lansoprazole and overcame incomplete release. The osmotic pressure caused by soluble ingredients in the core drove the diffusion of lansoprazole into the release medium. The release of lansoprazole from the top-coated pellets with insoluble cores in NaOH solution (pH 12) was faster and more complete than in PBS pH 6.8, which confirmed that the release pattern was dominated by the solubility of the drug.

A high level of hydroxypropyl substituents in HPC substantially increases chain flexibility, and implies a faster water-binding ability than that of HPMC. The excellent water binding ability of HPC also slows down the liquid-solid phase transition in the coating and helps to form a continuous and dense film. The extent and rate of the moisture absorption of subcoated ilaprazole pellets decreased in an order of: HPMC > HPMC-HPC (80:20) > HPC > ilaprazole drug pellets. The surface and cross-sectional microstructure of the subcoated ilaprazole pellets demonstrated that the HPMC subcoat had more loosely bound granules, finer pores, and increased brittleness compared with the HPC subcoat, which was dense, continuous, and flexible. The top-coated ilaprazole pellets with HPC subcoat exhibited the best acid resistance before compression and least loss of acid resistance after compression. After compression, the HPMC subcoat exhibited a large number of fragments; while the HPC subcoat kept continuous and accompanyed with merging layers.

Applying 10% w/w HPMC as top-coat helped the enteric-coated pellets withstand

compression better, which was more pronunced in HPMC subcoated pellets than in HPC subcoated pellets. A smaller acceleration of drug release from HPC subcoated ilaprazole pellet-tablets was observed when compared to that from HPMC subcoat.

The compression dramatically decreased the acid resistance of rabeprazole sodium pellets, but only slightly affected the acid resistance of lansoprazole pellets. Despite using the same formula and process for coating, rabeprazole sodium had a more hygroscopic drug layer, thinner effective subcoat, and greater instability than lansoprazole pellets, which resulted in the observed decrease in acid resistance after compression. This also suggested that a thicker and less permeable subcoat and functional layer are required for soluble drugs to achieve similar controlled or sustained release properties to insoluble drugs. The freeze-drying of pellets into tablets did not cause a loss in acid resistance or changes in the drug release in this study.

Freeze-dried pellet-tablets dissolved in approximately 5 s in catheter tipped syringes and remained in suspension for longer than 10 minutes. The thickening properties of sodium hyaluronate and xanthan gum effectively prevented the settling and agglomeration of the pellets; furthermore, the pellets were prevented from sticking to the syringe and tube wall either in standing or during feeding; therefore, blockages and incomplete feeding were avoided. Stokes' law was used to predict the suspending ability and proved to be suitable.

The pellet suspension had a higher viscosity than that of the suspending solution (0.1%-0.1% sodium hyaluronate-xanthan gum) and exhibited a stronger shear-thinning effect. The coefficient B led to a constant viscosity at high strain rates with a constant of 4.6, which fell into the favorable range of $1.5<B<5$, as reported by other researchers.

In conclusion, oral multiparticulate formulations of acid-labile drugs were prepared, which could be also an ideal formulation for small children and patient populations with sucking and swallowing problems.

5. Zusammenfassung

Säure-labile Medikamente werden leicht in saurem Medium abgebaut, welche hauptsächlich als enterisch beschichtete Dosierungsformen für die orale Verabreichung formuliert wurden. Das Ziel dieser Studie war es, orale multipartikuläre Formulierungen von säure-labilen Medikamenten, mit Ilaprazol, Lansoprazol und Rabeprazol Natrium als Modellarzneistoffe vorzubereiten. Der Einfluss der Wirkstofflöslichkeit von Lansoprazol und Rabeprazol Natrium und des Kerntyps, wurde auf das Überziehen mit Wirkstoff, sowie das Aufquellen, die Säureresistenz und die Wirkstofffreisetzung der Pellets und Pellettabletten untersucht. Der Einfluss einer Unterschicht auf die Wasserdampfdurchlässigkeit, die Perkolation des sauren Mediums, Säureresistenz der wirkstoffverzögerten Pellets und Pellettabletten, sowie der Einfluss des abschließenden Überzuges auf die Verpressbarkeit der Pellets, wurden mit Hilfe des Modellwirkstoffes Ilaprazol untersucht. Drei im Handel erhältliche Kerne (CP-102, Nonpareille-105 und PF 053), sowie ein im Labor hergestellter Kern wurden in dieser Studie mit folgenden sinkenden MCC-Anteilen (% m/m) verwendet: CP-102 (100% MCC > Labor hergestellter Kern (45% MCC) > Nonpareil-105 (30% MCC) > PF 053 (0% MCC). Wenn dieselbe Formulierung für das Überziehen der Pellets genutzt wurde, führte die unterschiedliche Löslichkeit der Modellwirkstoffe im wässrigen Medium zu sehr unterschiedlichen Verhältnissen gelöster Masse in der Wirkstoffsuspension für Lansoprazol und Rabeprazol-Natrium (jeweils 4.86 % und 15.67 %), was zu einer höheren Viskosität der Rabeprazol-Natrium-Suspension (92,05 mPa*s) gegenüber der Lansoprazol-Suspension (80,24 mPa*s) führte. Die Überzugsdicken von Rabeprazol-Natrium-Wirkstoffpellets auf 45% MCC-Kernen und 0% MCC-Kernen, waren geringer als diejenigen von Lansoprazol-Wirkstoffpellets auf denselben Kernen, und viel geringer als die Überzugsdicken beider Wirkstoffpellets auf 0% MCC-Kernen und 30% MCC-Kernen. Diese Ergebnisse implizierten, dass der 45% MCC-Kernen die geringste mechanische Stärke hat und 0% MCC-Kernen für die Wirkstoffbeschichtung von Lansoprazol zwar stark genug, jedoch nicht stark genug für die Beschichtung von Rabeprazol sein könnte. Wenn der Kernverlust dominierte, ging die

Überzugsdicke nach Gewicht zurück, während die tatsächliche Überzugsdicke anstieg. Wenn der Wirkstoffverlust dominierte, ging die Überzugsdicke nach Gewicht genauso wie die tatsächliche Überzugsdicke zurück. Der Rückgang der Überzugsdicke/tatsächliche Überzugsdicke spiegelte eine Zunahme des Kernverlusts wieder. Die sichtbaren Zacken, abgebrochenen Teile und Risse auf der Oberfläche der mit Rabeprazol-Natrium beschichteten 0% MCC-Kernen und 45% MCC-Kernen, lieferten ausreichende Nachweise für eine Zerbröckelung oder einen Bruch des Kerns.

Gleiche Gewichtsanteile der Lansoprazol- und Rabeprazol-Natrium-Wirkstoff-Pellets aus vier Kerntypen, wurden für das nachfolgende Aufbringen der Unterschicht, des enterischen Überzugs und des abschließenden Überzugs gemischt. Für alle vier Kerntypen wurde eine poröse Lansoprazol- und eine dichte Rabeprazolschicht entdeckt. Die Grenzfläche zwischen den Kernen und der Lansoprazolschicht war erkennbar, wobei sie mit abnehmendem MCC-Anteil in % (m/m) schwerer zu erkennen war. Die Rabeprazol-Natrium-Schicht verschmolz mit allen Kerntypen und der Zusammenschluss verbesserte sich mit abnehmendem MCC-Anteil in % (m/m). Ein höherer Prozentanteil der löslichen Inhaltsstoffe, führte zu einer dichteren Struktur der Wirkstoffschicht und weniger gut unterscheidbaren Grenzen. Der Zusammenschluss der Rabeprazol-Natrium-Wirkstoffschicht, verringerte die effektive Dicke der geplanten Unterschicht, was bedeutet, dass eine dickere Unterschicht notwendig war, um die erwartete Isolationswirkung für Rabeprazol-Natrium-haltige Pellets zu erreichen.

In der Quellungsstudie, die in 0,1 N HCl-Lösung durchgeführt wurde, quollen die überzogenen Rabeprazol-Natrium-Pellets nach 60 Minuten rasch auf, während die überzogenen Lansoprazol-Pellets unverändert blieben. Das Aufquellen der Rabeprazol-Natrium-Pellets beschleunigte sich nach 90 Minuten drastisch und korrelierte in folgender Reihenfolge umgekehrt mit dem MCC-Anteil in % (m/m) in den Kernen: 100% MCC < 45% MCC < 30% MCC < 0% MCC. Die Kerne beeinflussten das Aufquellen von Lansoprazol-Pellets nicht, was sich möglicherweise auf die Anreicherung der

Wirkstoffschicht mit unlöslichem Lansoprazol und Stabilisator und somit auf die Entstehung einer weniger permeablen Barriere zurückführen lässt. Wenn 0% MCC-Kernen verwendet wurde, verstärkte die Aufnahme einer winzigen Menge des Mediums möglicherweise die osmotische Wirkung und förderte das Aufquellen. Daher ist für die Rabeprazol-Natrium -Wirkstoff-Pellets möglicherweise im Vergleich zu Lansoprazol eine dickere oder medium-resistente Unterschicht, ein dickerer enterischer Überzug oder ein Material mit besserer Säureresistenz notwendig, um die Permeation von saurem Medium in die Wirkstoffschicht zu verhindern.

Die Säureresistenz der vier Typen von Rabeprazol-Natrium-Pellets, war um 15-20 % niedriger als die der entsprechenden Lansoprazol-Pellets. Die unzureichende Säureresistenz der Rabeprazol-Natrium-Pellets, wurde 1) den stark hygroskopischen Eigenschaften der Rabeprazol-Natrium-Schicht zugeschrieben, die möglicherweise die Permeation des sauren Mediums in die Wirkstoffschicht ermöglichten; 2) der geringeren Stabilität von Rabeprazol-Natrium zugeschrieben, die zu dessen schnellerem Zerfall gegenüber Lansoprazol führte; 3) einer höheren Dichte der Wirkstoffschicht durch Auftragen aus der Lösung zugeschrieben, was zu einer geringeren Größe der Rabeprazol-Natrium-Wirkstoff-Pellets und einer folglich dünneren Unterschicht, so wie einem dünneren enterischen Überzug führte; und 4) dem Zusammenschluss der Rabeprazol-Natrium-Wirkstoffschicht mit der Unterschicht zugeschrieben, die zu einer Reduktion der effektiven Dicke der Unterschicht führte. Wenn eine dickere Unterschicht oder ein dickerer enterischer Überzug aufgebracht wurde, wurde die Säurebeständigkeit von Rabeprazol-Natrium-Top-beschichteten Pellets (0% MCC-Kerne) verbessert.

Die Einarbeitung von löslichen Bestandteilen in die MCC-Kerne, förderte die Freisetzung von Lansoprazol und ermöglichte eine vollständige Freisetzung. Der durch die löslichen Bestandteile im Kern hervorgerufene osmotische Druck, schob die Diffusion von Lansoprazol in das Freisetzungsmedium an. Die Freisetzung von Lansoprazol aus den überzogenen Pellets mit unlöslichen Kernen in eine NaOH-Lösung (pH 12), erfolgte schneller als in PBS mit

pH 6,8 und vollständig. Damit bestätigte sich, dass die Löslichkeit des Wirkstoffs das Freisetzungsprofil bestimmt.

Eine höhere Anzahl von Hydroxypropyl-Substituenten im HPC, erhöht die Flexibilität der Polymerketten und ermöglicht eine raschere Wasserbindungsfähigkeit gegenüber HPMC . Die ausgezeichnete Wasserbindungsfähigkeit verlangsamt ebenfalls beim Überziehen den Übergang vom flüssigen in den festen Zustand und unterstützt die Bildung eines durchgängigen, dichten Films. Das Ausmaß und die Rate der Feuchtigkeitsaufnahme von mit einer Unterschicht versehenen Ilaprazol-Pellets, nahm in der folgenden Reihenfolge ab: HPMC > HPMC-HPC (80:20) > HPC > Ilaprazol-Wirkstoff-Pellets. Die Oberflächen- und Querschnittmikrostruktur der Ilaprazol-Pellets bewiesen, dass die HPMC-Unterschicht im Vergleich zur dichten, durchgängigen und wachsigen HPC-Unterschicht über mehr lose gebundene Körnchen, feinere Poren und eine ausgeprägtere Brüchigkeit verfügt. Die überzogenen Ilaprazolpellets mit einer HPC-Unterschicht, zeigten die beste Säureresistenz vor deren Verpressung und auch den gerinsten Verlust an Säureresistenz nach der Verpressung. Die HPMC-Unterschicht zeigte eine große Anzahl von Bruchstücken, wohin gegen die HPC-Unterschicht nach der Verpressung durchgehend und mit der anderen Schicht verbunden war. Ein abschließender Überzug aus 10% (m/m) HPMC, half den enterisch überzogenen Pellets die Kompressionskräfte besser zu überstehen, wobei dies bei den Pellets mit HPMC-Unterschicht ausgeprägter war, als bei denen mit HPC-Unterschicht.

Die Kompression verringerte die Säureresistenz der Rabeprazol-Natrium-Pellets dramatisch, beeinträchtigte jedoch die Säureresistenz der Lansoprazol-Pellets nur geringfügig. Trotz derselben Formulierung und desselben Beschichtungsprozesses, wies die Rabeprazol-Natrium-Schicht ausgeprägtere hygroskopische Eigenschaften, eine dünnere, effektive Unterschicht und eine größere Wirkstoffinstabilität als die Lansoprazol-Pellets auf. Dies führte sowohl vor, als auch nach der Kompression zur beobachteten Verringerung der Säureresistenz. Dies legte auch nahe, dass für lösliche Wirkstoffe eine dickere Unterschicht mit geringerer Permeabilität und ein funktioneller Überzug erforderlich sind, um für lösliche

Wirkstoffe ähnliche, kontrollierte oder verzögerteFreisetzungseigenschaften zu erhalten, wie für unlösliche Wirkstoffe. Die Gefriertrocknung von Pellets in Tabletten, führte nicht zum Verlust der Säureresistenz oder Veränderungen der Wirkstofffreisetzung.

Gefriergetrocknete Pellet-Tabletten lösten sich in etwa 5 s in mit einer Sonde versehenen Spritzen auf und verblieben länger als 10 Minuten. in Suspension. Die Verdickungseigenschaften von Natriumhyaluronat und Xanthangummi, verhinderten effektiv das Absetzen und die Agglomeration der Pellets; desweiteren wurde damit verhindert, dass die Pellets sich an die Spritze und die Sondenwände hafteten sowohl als Suspension, als auch während des Verabreichungsprozesses; somit ließen sich Sondenblockaden und eine unvollständige Verabreichung vermeiden. Zur Vorhersage der Suspendierbarkeit, wurde die Stokessche Gleichung angewendet, deren Ergebnis sich als richtig erwies.

Die Pellet-Suspension verfügte über eine höhere Viskosität als die der Suspensionslösung (0,1 %-0,1 % sodium hyaluronate-xanthan gum) und demonstrierte eine stärkere strukturviskose Wirkung. Der Koeffizient B führte zu einer konstanten Viskosität bei hohen Belastungsraten, mit einer Konstanten von 4,6, die, wie von anderen Forschern berichtet, in den günstigen Bereich von $1,5<B<5$ fällt.

Abschließend wurden orale multipartikuläre Formulierungen von säurelabilen Arzneimitteln hergestellt. Diese Formulierungen sind ideal bei Säuglingen und Patientenpopulation mit Saug- und Schluckproblemen.

6. References

A

Abbott Laboratories, 2014. ^{Pr}Abbott-Rabeprazole. Product monograph.

Abdul, S., Chandewar, A. V., Jaiswal, S.B., 2010. A flexible technology for modified-release drugs: Multiple-unit pellet system (MUPS). J. Control. Release. 147, 2 -16.

Actavis, 2014. Kadian (morphine sulfate) extended-release capsules. FDA, Reference ID: 3490190.

Actavis, 2014. Rabeprazole Actavis 20. Product information.

Alhusban, F., Perrie, Y., Mohammed, A.R., 2011. Formulation of multiparticulate systems as lyophilised orally disintegrating tablets. Eur. J. Pharm. Biopharm. 79, 627-634.

American Gastroenterological Association, 1995. American gastroenterological association technical review on tube feeding for enteral nutrition. Gastroenterology, 108 (4), 1282-1301.

Ashland, 2012. Klucel^{TM} hydroxypropylcellulose physical and chemical properties. www.ashland.com (accessed 05.12.2016).

AstraZeneca, 2014. Label of Nexium (esomeprazole magnesium). US FDA, reference ID: 3675799.

AstraZeneca, 2016. Prilosec omeprazole magnesium for delayed release oral suspension. FDA, Reference ID: 3882463.

Axon, A. T., 1995. The potential value of lansoprazole in helicobacter pylori eradication. J. Clin. Gastroenterol. 20 Suppl (1), S43-47.

B

Badgujar, B. P., Mundada, A. S., 2011. The technologies used for developing orally disintegrating tablets: a review. Acta Pharm. 61 (2), 117-139.

Balazs, E. A., 2004. Chapter 20 Viscoelastic Properties of Hyaluronan and Its Therapeutic Use,

in: Garg, H. G., Hales, C.A.(Eds.), Chemistry and Biology of Hyaluronan, Elsevier Ltd., London, pp.415-455.

Bashaiwoldu, A. B., Podczeck, F., Newton, J. M., 2011. Compaction of and drug release from coated pellets of different mechanical properties. Adv. Powder Technol. 22, 340-353.

Bergstrand, P., Wang, P., 1999. Pharmaceutical formulation comprising omeprazole. US 6,428,810 B1.

Besancon, M., Simon, A., Sachs, G., Shin, J. M., 1997. Sites of reaction of the gastric H,K-ATPase with extracytoplasmic thiol reagents. J. Biol. Chem. 272 (36), 22438-22446.

Bladh, N., Blychert, E., Johansson, K., Backlund, A., Lundin, C., Niazi, M., Pettersson, G., Fjellman, M., 2007. A new esomeprazole packet (sachet) formulation for suspension: in vitro characteristics and comparative pharmacokinetics versus intact capsules/tablets in healthy volunteers. Clin. Ther., 29 (4), 640-649.

Bley, O., Siepmann. J., Bodmeier, R., 2009. Characterization of moisture-protective polymer coatings using differential scanning calorimetry and dynamic vapor sorption. J. Pharm. Sci., 98 (2), 651-664.

Bley, O., Siepmann. J., Bodmeier, R., 2009. Importance of glassy-to-rubbery state transitions in moisture-protective polymer coatings. Eur. J. Pharm. Biopharm., 73 (1), 146-153.

Bodmeier., R., 1997. Tabletting of coated pellets. Eur. J. Pharm. Biopharm. 43, 1-8.

Bortoli, N., Martinucci, I., Giacchino, M., Blandizzi, C., Marchi, S., Savarino, V., Savarino, E., 2013. The pharmacokinetics of ilaprazole for gastro-esophageal reflux treatment. Expert Opin. Drug Metab. Toxicol., 9 (10), 1361-1369.

Bothner, H., Wik, O., 1987. Rheology of hyaluronate. Acta Otolaryngol Suppl. 442, 25-30.

Bowles, A., Keane, J., Ernest, T., Clapham, D., Tuleu, C., 2010. Specific aspects of gastro-intestinal transit in children for drug delivery design. Int. J. Pharma. 395, 37-43

Broderick, D., Stassen, L. F. A., Ekanayake, K., 2014. A study to compare the use of wide bore nasogastric feeding tubes compared to fine bore nasogastric feeding tubes for the purpose of feeding and medication administration inserted peri- operatively for head and neck oncological resections. Br. J. Oral Maxillofac. Surg., 52 (8), e85.

Bruce, L. D., Koleng, J. J., McGinity, J. W., 2003. The influence of polymeric subcoats and pellet formulation on the release of chlorpheniramine maleate from enteric coated pellets. Drug Dev. Ind. Pharm. 29 (8), 909-924.

Bruce, L.D., McGinity, J. W., 2008. Polymer Interactions with Drugs and Excipients, in: McGinity, J. W., Felton, L. A. (Eds.), Aqueous polymeric coatings for pharmaceutical dosage forms. Informa Healthcare USA, Inc., New York, pp. 369-408.

Bruce, L. D., Petereit, H. U., Beckert, T., McGinity, J. W., 2003. Properties of enteric coated sodium valproate pellets. Int. J. Pharm., 264 (1-2), 85-96.

C

Chan, L. W., Kou, X., Heng, P. W. S., 2010. Drug substance and excipient characterization. in: Parikh, D.M. (Ed.), Pharmaceutical granulation technology. Informa Healthcare USA. 978-1-4398-0789-7, pp. 59-71.

Children's Hospital of University of Iowa, 2016. Equipment sizing chart. http://www.uichildrens.org/childrens-content.aspx?id=239585 (accessed 28.04.2016).

Chinese Pharmacopoeia Commission, 2015. Monograph, rabeprazole sodium. Chinese Pharmacopoeia 2015, 1478-1479.

Chun, A. H., Shi, H. H., Achari, R., Dennis, S., Cavanaugh, J. H., 1996. Lansoprazole: administration of the contents of a capsule dosage formulation through a nasogastric tube. Clin. Ther. 18, 833-842.

Cui, M. L, 2014. Bioequivalence of oral generic product with an alternate administration. http://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm427466.pdf

(accessed 19.09.2016).

D

Dandeles, L. M., Lodolce, A. E., 2011. Efficacy of agents to prevent and treat enteral feeding tube clogs. Ann. Pharmacother. 45, 676-680.

Dashevsky, A., Kolter, K., Bodmeier, R., 2004. Compression of pellets coated with various aqueous polymer dispersions. Int. J. Pharm. 279, 19–26.

Dunn, A., White, C. M., Reddy, P., Quercia, R. A., Chow, M. S., 1999. Delivery of omeprazole and lansoprazole granules through a nasogastric tube in vitro. Am. J. Health-Syst. Pharm. 56, 2327-2330.

E

EDQM (European Directorate for the Quality of Medicines), 2016. Monograph: lansoprazole. European Pharmacopoeia 8.0, 2592-2594.

Einstein, A., 1906. Eine neue Bestimmung der Moleküldimensionen. Ann. Phys., 19, 289–306.

Einstein, A., 1911. Berichtigung zu meiner Arbeit: eine neue Bestimmung der Moleküldimensionen. Ann. Phys., 34, 591–592.

Eisai, 2014. ACIPHEX Sprinkle-FDA Label.

F

Falcone, S. J., Palmeri, D. M., Berg, R. A., 2006. Rheological and cohesive properties of hyaluronic acid. J. Biomed. Mater. Res. A. 76 (4), 721-728.

Fang, Y., Wang, G., Zhang, R., Liu, Z., Liu, Z., Wu, X., Cao, D., 2014. Eudragit L/HPMCAS blend enteric-coated lansoprazole pellets: enhanced drug stability and oral bioavailability. AAPS PharmSciTech. 15 (3), 513-521.

FDA CDER, 2008. Guidance for industry orally disintegrating tablets.

http://www.fda.gov/cder/guidance/index.htm (accessed 01.05.2016).

Florjancic, U., Zupancic, A., Zumer, M., 2002. Rheological characterization of aqueous polysaccharide mixtures undergoing shear. Chem. Biochem. Eng. Q. 16 (3), 105-118.

Ford, J. L., 2014. Design and evaluation of hydroxypropyl methylcellulose matrix tablets for oral controlled release: a historical perspective. in: Timmins, P., Pygall, S. R., Melia, C. D. (Eds.), Hydrophilic matrix tablets for oral controlled release. ISBN 978-1-4939-1519-4 (eBook), pp.17-51.

Frelinger, A. L. 3rd, Lee, R. D., Mulford, D. J., Wu, J., Nudurupati, S., Nigam, A., Brooks, J. K., Bhatt, D. L., Michelson, A. D., 2012. A randomized, 2-period, crossover design study to assess the effects of dexlansoprazole, lansoprazole, esomeprazole, and omeprazole on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. J. Am. Coll Cardiol. 59 (14), 1304-1311.

Freston, J. W., Kukulka, M. J., Lloyd, E., Lee, C., 2004. A novel option in proton pump inhibitor dosing: lansoprazole orally disintegrating tablet dispersed in water and administered via nasogastric tube. Aliment. Pharmacol. Ther. 20, 407-411.

FREUND corporation, 2016. NONPAREIL®.
http://www.freund.co.jp/english/chemical/additive/nonparell.html (accessed 30.06.2016).

G

Garcia, C. V., Paim, C. S., Steppe, M., Schapoval, E. E., 2006. Development and validation of a dissolution test for rabeprazole sodium in coated tablets. J. Pharm. Biomed. Anal. 41, 833–837.

Gatej, I., Popa, M., Rinaudo, M., 2005. Role of the pH on hyaluronan behavior in aqueous solution. Biomacromolecules. 6 (1), 61–67.

Ghanam, D., Hassan, I., Kleinebudde, P., 2010. Compression behaviour of k-carrageenan pellets. Int. J. Pharm. 390,117-127.

Ghebre-Sellassie, I., 1994. Multiparticulate oral drug delivery. CRC Press Taylor & Francis Group, Florida.

Gryczová, E., Rabisková, M., Vetchý, D., Krejcová, K., 2008. Pellet starters in layering technique using concentrated drug solution. Drug Dev. Ind. Pharm. 34, 1381–1387.

H

Hancock, B. C., Zografi, G., 1994. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm. Res. 11 (4), 471-477.

Haxaire, K., Braccini, I., Milas, M., Rinaudo, M., Pérez, S., 2000. Conformational behavior of hyaluronan in relation to its physical properties as probed by molecular modeling. Glycobiology. 10 (6): 587-594.

He, W., Yang, M., Fan, J. H., Feng, C. X., Zhang, S. J., Wang, J. X., Guan, P. P., Wu, W., 2010. Influences of sodium carbonate on physicochemical properties of lansoprazole in designed multiple coating pellets. AAPS PharmSciTech. 11 (3), 1287-1293.

Herschel, W. H., Bulkley, R., 1926. Konsistenzmessungen von Gummi-Benzollö ungen. Kolloid-Zeitschrift, 39, 291-300.

Higashide, T., Sugiyama, K., 2008. Use of viscoelastic substance in ophthalmic surgery – focus on sodium hyaluronate. Clinical Ophthalmology, 2 (1), 21–30.

Hoang Thi, T. H., Lhafidi, S., Carneiro, S. P., Flament, M. P., 2015. Feasability of a new process to produce fast disintegrating pellets as novel multiparticulate dosage form for pediatric use. Int. J. Pharm. 496, 842–849.

Horn, J., 2000. The proton-pump inhibitors: similarities and differences. Clin. Ther. 22 (3): 266-280.

Hosseini, A., Körber, M., Bodmeier, R., 2013. Direct compression of cushion-layered ethyl cellulose-coated extended release pellets into rapidly disintegrating tablets without changes in the release profile. Int. J. Pharm. 457, 503-509.

Huber, R., Kohl, B., Sachs, G., Senn-Bilfinger, J., Simon, W. A., Sturm, E., 1995. Review article: the continuing development of proton pump inhibitors with particular reference to pantoprazole. Aliment Pharmacol. Ther. 9, 363-378.

J

Jain, K. S., Shah, A. K., Bariwal, J., Shelke, S. M., Kale, A. P., Jagtap, J. R., Bhosale, A. V., 2007. Recent advances in proton pump inhibitors and management of acid-peptic disorders. Bioorg. Med. Chem. 15 (3), 1181-1205.

Ji, X. Q., Du, J. F., Chen, Ga., Chen, Gu., Yu, B., 2014. Efficacy of ilaprazole in the treatment of duodenal ulcers: a meta-analysis. World J. Gastroenterol. 20 (17), 5119-5123.

Johansson, B., Alderborn, G., 1996. Degree of pellet deformation during compaction and its relationship to the tensile strength of tablets formed of microcrystalline cellulose pellets. Int. J. Pharm. 132, 207-220.

Johansson, B., Nicklasson, F., Alderborn, G., 1998. Effect of pellet size on degree of deformation and densification during compression and on compactability of microcrystalline cellulose pellets. Int. J. Pharm. 163, 35-48.

Johansson, B., Wikberg, M., Ek, R., Alderborn, G., 1995. Compression behaviour and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties. Int. J. Pharm. 117, 57-73.

K

Kállai, N., Luhn, O., Dredán, J., Kovács, K., Lengyel, M., Antal, I., 2010. Evaluation of drug release from coated pellets based on isomalt, sugar, and microcrystalline cellulose inert cores. AAPS PharmSciTech. 11 (1), 383-391.

Kállai-Szabó, N., Luhn, O., Bernard, J., Kállai-Szabó, B., Zelkó, R., Antal, I., 2014. Comparative dissolution study of drug and inert isomalt based core material from layered pellets. J. Pharm. Biomed. Anal. 98, 339-344.

Kristl, A., 2009. Acido-Basic Properties of Proton Pump Inhibitors in Aqueous Solutions, Drug Dev. Ind. Pharm. 35 (1), 114-117.

Kristl, A., Vrecˇer, F., 2000. Preformulation investigation of the novel proton pump inhibitor lansoprazole. Drug Dev. Ind. Pharm. 26 (7), 781–783.

Kromer, W., Krüger, U., Huber, R., Hartmann, M., Steinijans, V. W. , 1998. Differences in pH-dependent activation rates of substituted benzimidazoles and biological in vitro correlates. Pharmacology. 56, 57–70.

Kulkarni, V. S., Shaw, C., 2016. Chapter 5 - Use of polymers and thickeners in semisolid and liquid formulations. Essential chemistry for formulators of semisolid and liquid dosages (e-book), 43-69.

Kulshreshtha, A. K., Singh, O. N., Wall, G. M. (Eds.), 2010. Pharmaceutical suspensions-from formulation development to manufacturing. AAPS, Springer, London.

Kupská, I., Lapcík, L., Lapcíková, B., Záková, K., Juríková, J., 2014. The viscometric behaviour of sodium hyaluronate in aqueous and KCl solutions. Colloids and Surfaces A: Physicochem. Eng. Aspects. 454, 32-37.

Kwon, D., Chae, J. B., Park, C. W., Kim, Y. S., Lee, S. M., Kim, E. J., Huh, I. H., Kim, D. Y., Cho, K. D., 2001. Effects of IY-81149, a newly developed proton pump inhibitor, on fastric acid secretion in vitro and in vivo. Arzneim.-Forsch./Drug Res. 51 (I), 204−213.

L

Larson, C., Cavuto, N. J., Flockhart, D. A., Weinberg, R. B., 1996. Bioavailability and efficacy of omeprazole given orally and by nasogastric tube. Dig. Dis. Sci. 41, 475-479.

Li, R. S., Feke, D. L., 2015. Rheological and kinetic study of the ultrasonic degradation of xanthan gum in aqueous solutions. Food Chemistry, 172, 808-813.

Liu, F., Merchant, H. A., Kulkarni, R. P., Alkademi, M., Basit, A. W., 2011. Evolution of a physiological pH 6.8 bicarbonate buffer system: application to the dissolution testing of

enteric coated products. Eur. J. Pharm. Biopharm. 78 (1),151-157.

Lovgren, K. I., Pilbrant, A. G., Yasumura, M., Morigaki, S., Oda, M., Ohishi, N., 1988. Pharmaceutical preparation for oral use. US Patent 4,786,505.

Luhn, O., Kállai, N., Nagy, Z. K., Kovács, K., Fritzsching, B., Klebovich, I., Antal, I., 2012. Dissolution profile of novel composite pellet cores based on different ratios of microcrystalline cellulose and isomalt. J. Pharm. Sci. 101 (8), 2675-2680.

M

Maganti, L., Celik, M., 1993. Compaction studies on pellets I. Uncoated pellets. Int. J. Pharm. 95, 29-42.

Malvern, 2016. Webinar, Laser Diffraction. http://www.malvern.com/en/support/resource-center/ (assessed 01.04.2016)

Martin, A. N., 2006. Coarse dispersions, in: Sinko, P. J. (Ed.), Martin's Physical Pharmacy and Pharmaceutical Sciences, 5th ed., Lippincott Williams & Wilkins, Philadelphia, PA, pp 499-530.

Mathews, M. B., Decker, L., 1977. Conformation of hyaluronate in neutral and alkaline solutions. Biochimica et Biophysica Acta, 498, 259-263.

McConnell, E. L., Macfarlane, C. B., Basit, A. W., 2009. An observational study on the influence of solvent composition on the architecture of drug-layered pellets. Int. J. Pharm. 380 (1-2), 67-71.

MHLW (Ministry of Health, Labour and Welfare), 2015. Official Monograph: Rabeprazole Sodium. JP XVI, 1332-1333.

Miller, R. A., Leung, E. M., Oates, R. J., 1999. The compression of spheres coated with an aqueous ethylcellulose dispersion. Drug Dev. Ind. Pharm. 25 (4), 503-511.

Mitchell, K., Ford, J. L., Armstrong, D. J., Elliott, P. N. C., Hogan, J. E., Rostron, C., 1993.

The influence of substitution type on the performance of methylcellulose and hydroxypropyl methylcellulose. Int. J. Pharm. 100, 143–154.

Mueller, S., Llewellin, E. W., Mader, H. M., 2010. The rheology of suspensions of solid particles. Proc. R. Soc. A. 466, 1201-1228.

N

Necas, J., Bartosikova, L., Brauner, P., Kolar, J., 2008. Hyaluronic acid (hyaluronan): a review. Veterinarni Medicina, 53 (8), 397-411.

Nicklasson, F., Johansson, B., Alderborn, G., 1999. Tabletting behaviour of pellets of a series of porosities - a comparison between pellets of two different compositions. Eur. J. Pharm. Sci. 8, 11-17.

Nagarsenker, M. S., Hegde, D. D., 1999. Optimization of the mechanical properties and water-vapor transmission properties of free films of hydroxypropylmethylcellulose. Drug Dev. Ind. Pharm. 25 (1), 95-98.

Nyamweya, N., Hoag, S. W., 2000. Assessment of polymer-polymer interactions in blends of HPMC and film forming polymers by modulated temperature differential scanning calorimetry. Pharm. Res.17 (5), 625-631.

Newton, J. M., 2010. Gastric emptying of multi-particulate dosage forms. Int. J. Pharm. 16, 395 (1-2), 2-8.

O

Olbe, L., 1999. Proton pump inhibitors. Springer Basel AG, Switzeriand.

Olbe, L., Carlsson, E., Lindberg, P., 2003. A proton-pump inhibitor expedition: the case histories of omeprazole and esomeprazole. Nat. Rev. Drug Discov. 2 (2), 132-139.

P

Pabst, W., 2004. Fundamental considerations on suspension rheology. Ceramics - Silikáty, 48

(1), 6-13.

Pantoflickova, D., Dorta, G., Ravic, M., Jornod, P., Blum, A. L., 2003. Acid inhibition on the first day of dosing: comparison of four proton pump inhibitors. Aliment Pharmacol. Ther. 17, 1507-1514.

Pašić, M., 2008. Study to design stable lansoprazole pellets. PhD Thesis, University of Basel, Faculty of Science.

Pearce, C. B., Duncan, H. D., 2002. Enteral feeding. Nasogastric, nasojejunal, percutaneous endoscopic gastrostomy, or jejunostomy: its indications and limitations. Postgrad. Med. J. 78, 198-204.

Picker-Freyer, K. M., Dürig, T., 2007. Physical mechanical and tablet formation properties of hydroxypropylcellulose: In pure form and in mixtures. AAPS PharmSciTech., 8 (4), 82.

Pluta, P. L., Poska, R., 2010. GMP yield-considerations beyond percent theoretical yield. Global Regulatory Viewpoint. 14 (3), 76-83.

Ponrouch, M. P., Sautou-Miranda, V., Boyer, A., Bourdeaux, D., Montagner, A., Chopineau, J., 2010. Proton pump inhibitor administration via nasogastric tube in pediatric practice: comparative analysis with protocol optimization. Int. J. Pharm. 390, 160-164.

R

Remuñán-lópez, C., Bodmeier, R., 1996. Mechanical and water vapor transmission properties of polysaccharide films. Drug Dev. Ind. Pharm. 22 (12), 1201-1209.

Richter, J. E., Kahrilas, P. J., Sontag, S. J., Kovacs, T. O., Huang, B., Pencyla, J. L., 2001. Comparing lansoprazole and omeprazole in onset of heartburn relief: results of a randomized, controlled trial in erosive esophagitis patients. Am. J. Gastroenterol. 96 (11), 3089-3098.

Rowe, R. C., Sheskey, P. J., Owen, S. C., 2006. American Pharmacists Association. Handbook of pharmaceutical excipients, sixth ed. Pharmaceutical Press, London.

S

Safari, A., Cervantes, M. J., Emami, N., 2016. Viscoelastic behaviour effect of hyaluronic acid on reciprocating flow inside mini-channel. Lubrication Science. Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ls.1344.

Samuels, R. J., 1969. Solid-state characterization of the structure and deformation behavior of water-soluble hydroxypropyl cellulose. J. Polym. Sci., Polym. A-2. 7, 1197–1258.

Santarus, 2014. Zegerid omeprazol sodium bicarbonate powder for oral suspension. Label. FDA, Reference ID: 3675798.

Schirm, E., Tobi, H., de Vries, T. W., Choonara, I., De Jong-van den Berg, L. T., 2003. Lack of appropriate formulations of medicines for children in the community. Acta Pædiatr. 92, 1486-1489.

Shah, S. A., Sander, S., Coleman, C. I., White, C. M., 2006. Delivery of esomeprazole magnesium through nasogastric and gastrostomy tubes using an oral liquid vehicle as a suspending agent in vitro. Am. J. Health-Syst. Pharm. 63, 1882-1887.

Shin, K. I., Ahn, J. H., Lee, S. Y., 2015. The exceptional combination method of hypromellose (HPMC) and hydroxypropyl cellulose (HPC) film coating. Poster submissions. http://abstracts.aaps.org/Verify/AAPS2015/PosterSubmissions/T2028.pdf (accessed 08.12. 2016).

Standing, J. F., Tuleu, C., 2005. Paediatric formulations- getting to the heart of the problem. Int. J. Pharma. 300, 56-66.

Stange, U., Führling, C., Gieseler, H., 2015. Freeze drying of orally disintegrating tablets containing taste masked naproxen sodium granules in blisters. Pharm. Dev. Technol. 20 (8), 1018-1024.

Stedman, C. A., Barclay, M. L., 2000. Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. Aliment Pharmacol. Ther. 14 (8),

963-978.

T

Tabata, T., Makino, T., Kashihara, T., Hirai, S. Kitamori, N., Toguchi, H., 1992. Stabilization of a new antiulcer drug (Lansoprazole) in the solid dosage forms. Drug Dev. Ind. Pharm. 18 (13), 1437-1447.

Takeda, 2016. Dexilant dexlansoprazole delayed-release capsules. FDA, Reference ID: DEX006 R25.

Takeda, 2016. Prevacid SoluTab Label. Takeda Pharmaceuticals America, Inc.. FDA, Reference ID: 3861509.

Teng, Y., Qiu, Z. H., 2010. Chapter 8. Fluid Bed Coating and Granulation for CR Delivery, in: Wen, H., Park, K. (Eds.), Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice. John Wiley & Sons, Inc. New Jersey.

The Dow Chemical Company, 2002. Methocel cellulose ethers in aqueous systems for tablet coating. www.methocel.com (accessed 01.12.2016)

The Dow Chemical Company. Tablet Coating. A Technical Review. www.dowwolff.com (accessed 30.12.2016)

The United States Pharmacopeial Convention, 2012. USP Monographs, in-process revision: rabeprazole sodium delayed-release tablets. Pharmacopeial Forum online, 38 (2) (accessed 01.09.2016).

The United States Pharmacopeial Convention, 2016. NF 34 Xanthan Gum. USP online (accessed 01.09.2016).

The United States Pharmacopeial Convention, 2016. USP 38 <616> Measures of powder compressibility. USP online (accessed 01.02.2016).

The United States Pharmacopeial Convention, 2016. USP 39 <1151> Pharmaceutical dosage

forms. USP online (accessed 01.09.2016).

The United States Pharmacopeial Convention, 2016. USP 39 <711> Dissolution. USP online (accessed 01.09.2016).

The United States Pharmacopeial Convention, 2016. USP Monographs, lansoprazole delayed-release capsules. USP online (accessed 01.09.2016).

The United States Pharmacopeial Convention,2016. Official Monographs / Hypromellose. USP 39-NF 34,8678-8680.

Thomas Reuter, 2014. Cortellis™ lansoprazole. Online database (accessed 30.01.2016).

Thomas Reuter, 2014. Cortellis™ rabeprazole. Online database (accessed 30.01.2016).

Thomas Reuter, 2016. Cortellis™ ilaprazole. Online database (accessed 16.01.2017).

Tripathi, A., Joshi, B.S., Joshi, J., 2010. Polymorphism in rabeprazole sodium. Rasayan J. Chem. 3 (4), 736-744.

Troy, D. B., 2005. Remington: The Science and Practice of Pharmacy. 21st ed. Lippincott Williams & Wilkins, London.

V

Verband Forschender Arzneimittelhersteller e.V., 2016. Zulassungen und Zulassungserweiterungen für Arzneimittel oder Applikationshilfen für Kinder und Jugendliche seit 2001, http://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/amzulassungen-kinder.html/arzneimittelzulassungen-fuer-kinder.pdf (accessed 25.01.2016).

Vogeleer, J., 2014. Solving segregation challenges in MUPS production. GEA Kundenberichte. http://www.gea.com/de/de/stories/mups-production.jsp (accessed 21.09. 2016).

W

Wang, L., Zhou, L., Hu, H., Lin, S., Xia, J., 2012. Ilaprazole for the treatment of duodenal ulcer: a randomized, double-blind and controlled phase III trial, Current Medical Research and Opinion, 28 (1), 101-109.

Warnke, G., 2012. Pharmaceutical Coatings. Encyclopedia of industrial chemistry, 26, 407-417.

Wensel, T. M., 2009. Administration of proton pump inhibitors in patients requiring enteral nutrition. Pharmacy and Therapeutics. 34 (3), 143-160.

White, C. M., Kalus, J. S., Quercia, R., Fortier, C., Piotrowski, A., Roach, A., Sostek, M. B., 2002. Delivery of esomeprazole magnesium enteric-coated pellets through small caliber and standard nasogastric tubes and gastrostomy tubes in vitro. Am. J. Health Syst. Pharm. 59, 2085-2088.

White, R., Bradnam, V, 2007. Handbook of Drug Administration via Enteral Feeding Tubes. Pharmaceutical Press, London, UK.

Williams, M. P., Sercombe, J., Hamilton, M. I., Pounder, R. E., 1998. A placebo-controlled trial to assess the effects of 8 days of dosing with rebeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in young healthy male subjects. Aliment Pharmacol. Ther. 12, 1079-1089.

Williams, N. T., 2008. Medication administration through enteral feeding tubes. Am. J. Health-Syst. Pharm. 65, 2347-2357.

Wyethpharms, 2014. Protonix pantoprazole sodium for delayed-release oral suspension. FDA, Reference ID: 3675795.

Z

Zhong, L., Oostrom, M., Truex, M. J. , Vermeul, V. R., Szecsody, J. E., 2013. Rheological behavior of xanthan gum solution related to shear thinning fluid delivery for subsurface remediation. J. Hazard Mater. 244-245, 160-170.

7. Publications

Huang, F., Bodmeier, R., 2017. Preparation and evaluation of oral multiparticulate formulations of acid-labile drugs. In preparation.

Huang, F., Bodmeier, R., 2017. Preparation and evaluation of oral multiparticulate ilaprazole tablet. In preparation.

8. Curriculum Vitae

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.