AAPS PharmSciTech, Vol. 16, No. 4, August 2015 (© 2015)
DOI: 10.1208/s12249-014-0263-z

Research Article

Solid-State Interactions at the Core-Coat Interface: Physicochemical Characterization of Enteric-Coated Omeprazole Pellets Without a Protective Sub-Coat

Vishnu Dutt Sharma,[1] Suleyman Akocak,[1] Marc A. Ilies,[1,2] and Reza Fassihi[1,2]

Received 13 August 2014; accepted 8 December 2014; published online 17 January 2015

Abstract. Conventionally, scanning electron or transmission microscopy, Raman and near infrared (NIR) spectroscopy, terahertz, florescence, and nuclear magnetic resonance imaging have been used to characterize functional coating structure. This study highlights the use of fluorescence microscopy to investigate the physicochemical stability and coating integrity of the commercially available enteric-coated omeprazole pellets containing a basic excipient and prepared by extrusion and spheronization or drug layering on the nonpareil seed, immediately followed by enteric coating (*i.e.*, absence of protective sub-coat). The nature of coating interface and the likely development of an *in situ* interfacial layer after the application of enteric coating solution was examined using HPLC, NMR, differential scanning calorimetry (DSC), and fluorescent imaging methods. Likewise for the characterization of the solid pellet structure *via* fluorescence microscopy, a new approach based on fracturing technique (to avoid surface contamination) rather than microtome sectioning was used and validated. Analytical data showed that the pellets containing omeprazole remained chemically stable (>99.5% recovered). Control of the microenvironmental pH by the addition of alkalinizing excipient within a core formulation or as part of drug layering on top of nonpareil seed appears to efficiently neutralize the acidic effect of enteric coating dispersion. Fluorescence images further illustrate the absence of any discernable *in situ* layer formation at the coat-core interface.

KEY WORDS: alkalinizing excipient; DSC; enteric coating; florescence microscopy; functional coating layer(s); HPLC; NMR; omeprazole stability.

INTRODUCTION

Omeprazole (5-methyl-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfonyl}-1H-benzimidazole) 1 and its congeners lansoprazole 2, rabeprazole 3, and pantoprazole 4 (Fig. 1) belongs to a substituted benzimidazole class of drugs that are widely used for the treatment of gastroduodenal ulcers and related diseases such as gastroesophageal reflux disease (GERD) (1,2).

In the acidic medium of the parietal cell, omeprazole molecule rearranges forming a pyridinium salt, and in this form, it binds selectively and irreversibly (covalently) to the proton pump H^+/K^+-ATPase at the parietal cell secretory membrane, inhibiting both basal and stimulated acid secretion of these cells, irrespective of the stimulus (Fig. 2) (3,4).

Due to this mechanism of action, omeprazole and its congeners are extremely acid labile and usually degrade very fast in acidic conditions, with a degradation half-life of about 10 min at a pH lower than 4 (5). The degradation is accompanied by a color change to pale and dark yellow, reflecting the different spectral properties of the benzimidazole-pyridinium system formed. The acid-catalyzed degradation rate is much slower as the pH increases. At pH 6.5 and 11, omeprazole has a half-life of 18 h and 300 days, respectively (4,5). Importantly, due to the presence of the acidic NH-proton from benzimidazole moiety, in basic medium, the drug can be converted into its more soluble alkali salts such as omeprazole sodium or magnesium.

For the reasons enumerated above, omeprazole will degrade rapidly in the acidic environment of the stomach upon delivery in an unprotected form. Consequently, many dosage forms are marketed in the form of enteric-coated systems. Enteric-coated (EC) dosage forms (*i.e.*, tablets, capsules, mini-tablets, or pellets) comprise an important group of orally administered dosage forms that usually dissolve in the duodenum (pH >5) or terminal ileum where pH is about 6.8 to 7.5 (6). Examples of drugs given in the form of enteric-coated dosage forms include acid-labile drugs such as omeprazole, erythromycin, pancreatic enzymes, or drugs such as bisacodyl, nonsteroidal anti-inflammatory drugs including diclofenac and aspirin, or drugs for local delivery to the distal intestine and colon such as 5-aminosalicylic acid, budesonide, or prednisone (7).

In general, enteric coating is employed when i) drug substance is destroyed by gastric acid or enzymes and should

[1] Department of Pharmaceutical Sciences, Temple University School of Pharmacy, 3307 North Broad Street, Philadelphia, Pennsylvania 19140, USA.
[2] To whom correspondence should be addressed. (e-mail: mailies@temple.edu; reza.fassihi@temple.edu)

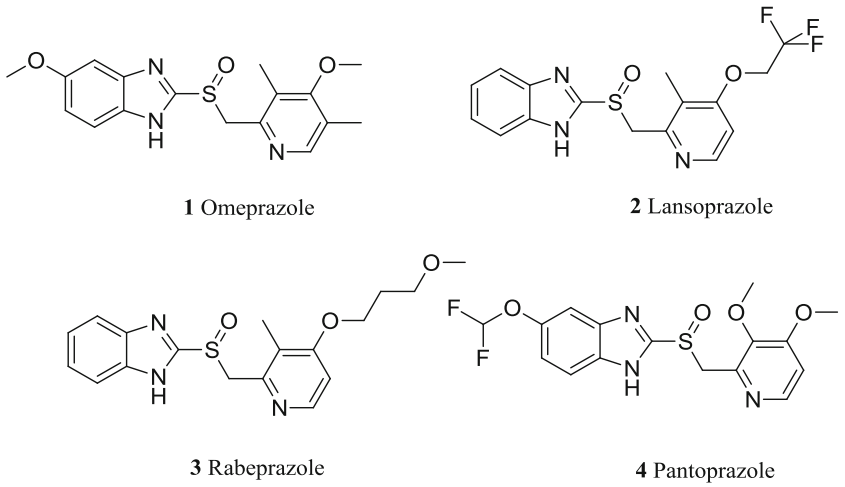

Fig. 1. Chemical structures of omeprazole 1 and some of its congeners used in the treatment of gastroduodenal ulcer and GERD (1,2)

be protected against gastric acid, ii) drug causes irritation to the gastric mucosa and thus improving tolerability is achieved by releasing in the small intestine, iii) absorption and bioavailability is substantially enhanced in the intestine *via* temporal and pH-dependent dissolution and release, iv) it is desirable to deliver drug after a time delay (*i.e.*, controlled onset delivery) particularly as part of controlled release drug delivery, and v) targeting in the GI tract is desirable, especially delivery to the colon, for topical effect or systemic absorption. For example, delayed release in pH ≥7.0 (ileum and colon) for distal GI delivery is particularly advantageous in the treatment of ulcerative colitis and Crohn's disease (*i.e.*, dosage forms containing mesalamine or budesonide) (8).

While coating processes have been used for many years, deficiencies in understanding the precise mechanism of film formation, its uniformity, impact of operating parameters, and potential interactions at the coat-core interface remain a challenge. The emphasis in this work is on the characterization of coat-core interface using either sugar sphere-coated pellet or spheronized pellets containing an acid-labile model drug and an alkaline excipient in their formulation composition. Enteric polymers were used by direct application to the core surface in the absence of a protective sub-coat. As a result, it was critical to determine stability and potential degradation levels in the pellets and at the coat-core interface.

Frequently used materials for enteric coating are polymeric acids with free carboxyl groups that confer gastric resistance. They include anionic polymethacrylates (Eudragit-L 100, with a pH value of aqueous dispersion of ~3.05) and cellulose-based polymers (*i.e.*, hypromellose acetate succinate (HPMCAS, with pH about 3.85) or hypromellose phthalate (HPMCP)). Mention must be made that the drug can also be

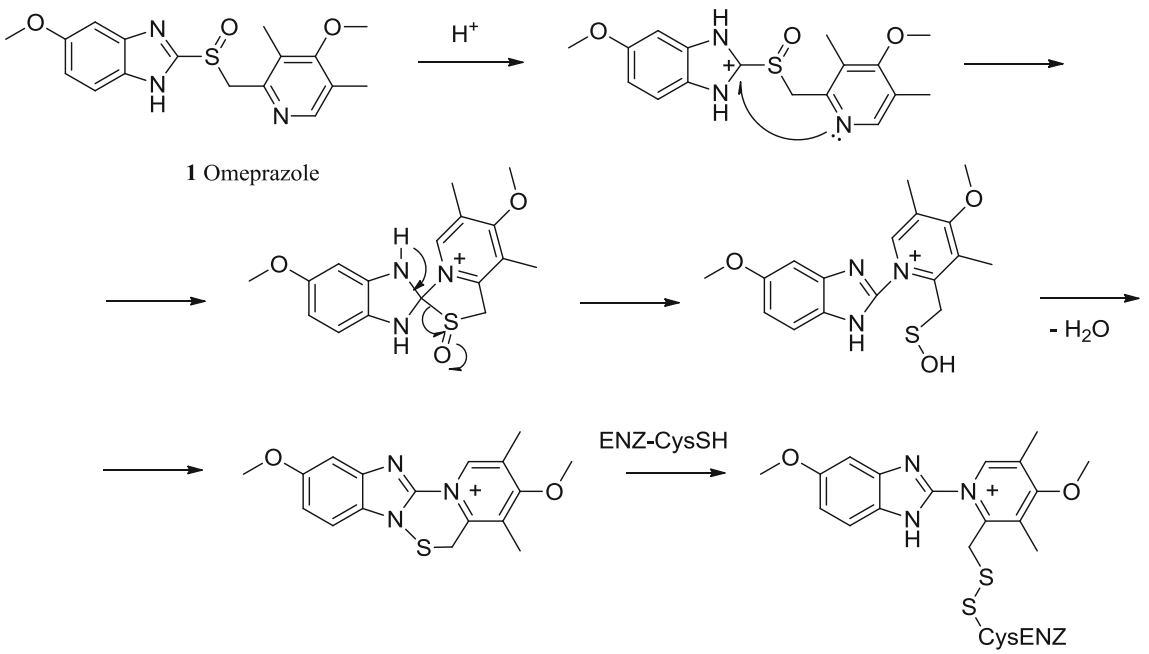

Fig. 2. Activation of omeprazole molecule in acidic medium with formation of a highly reactive benzimidazole-pyridinium intermediates that can covalently bind the Cys residues from active site of H^+/K^+ pump ATPase, inactivating it

degraded as a consequence of contact with the acidic nature of coating polymers during formulation development and manufacturing. Thus, it is essential to protect the drug not only against acid exposure in the acidic environment of the stomach and prevention of its degradation but also have protective measures during formulation development to prevent degradation and also enhance drugs storage stability for predictive bioavailability and therapeutic efficacy after oral administration (9). Multiple methods for manufacturing stable omeprazole products have been reported, including an inert intermediate sub-coat layer (*i.e.*, hydroxypropylcellulose, hydroxymethylcellulose, hypromellose-HPMC, amylopectin, *etc.*) which separates the omeprazole drug layer from acidic enteric coating polymer when spherical nonpareil seed is used as a substrate (10), see Fig. 3.

Other methods include addition of basic excipient (*i.e.*, magnesium hydroxide, MgO, disodium hydrogen phosphate, or organic pH-buffering substances) in the core formulation (*i.e.*, when extrusion and spheronization is used) or drug coating dispersion, to control pH-microenvironment. It is hypothesized that alkaline surfaces exposed to acidic polymers during coating may result in the formation of a putative *in situ* intermediate layer, due to the reaction between the alkaline surface of the core with the acidic groups of the enteric polymer triggering development of water soluble salt which would easily dry or crystallize (11–16).

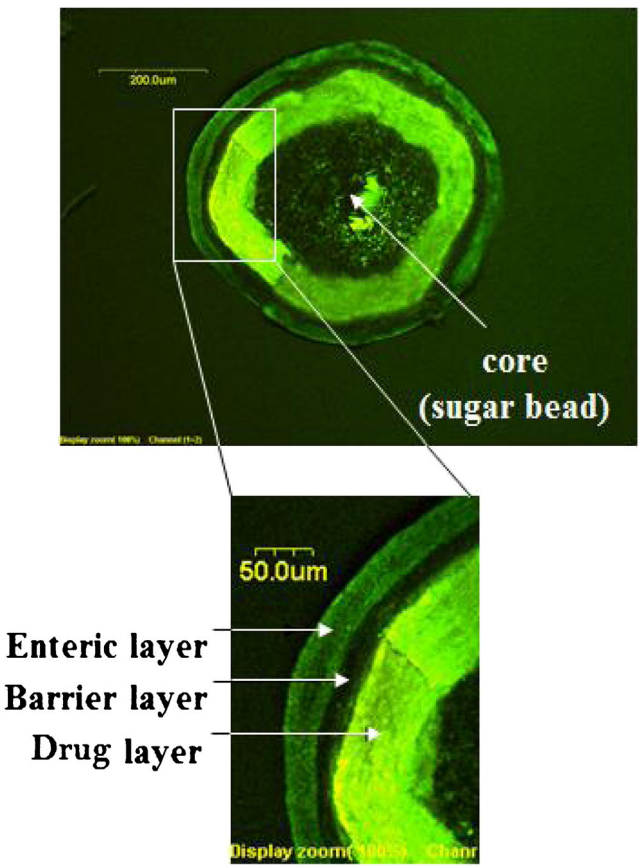

Fig. 3. Fluorescence image of a fractured omeprazole pellet where a spherical nonpareil seed was coated with the omeprazole drug layer followed by application of an inert barrier layer and further coating with an acidic polymer enteric layer on top of the sub-coat or barrier layer (10)

Two frequently used techniques to produce pellets that contain drugs include drug layering onto spherical substrates or direct pelletization *via* wet extrusion of drug and excipient mixture followed by spheronization and drying (17). Pellets can be directly enteric coated with pH-sensitive polymers or coated for the controlled release delivery of drug over a prolonged time period. The coating process can be accomplished by using air suspension coating approach where the solution of the polymers or suspension of drug in polymer solution is sprayed *via* nozzle(s) atomization onto the pellets in a fluid bed apparatus under the controlled conditions of air pressure and temperature to achieve percent target weight gain (*i.e.*, desired coat thickness) for specific delivery rate or release location in the GI tract. The core materials could also be a formulated tablet or capsule where pan coating approach is used. Upon the application of coating materials, drug-polymer or core-coating interface interactions can considerably impact the property of the product (18).

Conventionally, scanning electron and transmission microscopy (19), Raman- and near infrared (NIR) spectroscopy (20), and florescence microscopy (21), as well as terahertz, optical coherence tomography (OCT), and nuclear magnetic resonance (NMR) imaging have been used to characterize coating structure and coating interfaces (22). For most of the methods including fluorescence microscopy, sample preparation is often needed, and it is traditionally achieved by preparing thin slices of the coated materials by microtome sectioning. The objective of this study was to investigate the physiochemical stability and coating integrity of the commercially available enteric-coated omeprazole pellets containing a basic excipient and prepared by extrusion and spheronization or drug layering on the nonpareil seed, immediately followed by enteric coating. The nature of coating interface and the likely development of an *in situ* interfacial layer after the application of enteric coating solution were investigated using four analytical methods, HPLC, NMR, differential scanning calorimeter (DSC), and fluorescent imaging. Moreover, for the characterization of the pellet structure *via* fluorescence microscopy, a new approach based on fracturing technique (to avoid surface contamination) rather than microtome sectioning was used and validated.

MATERIALS AND METHODS

Core Composition and Coating

The enteric-coated pellets (two different products, one using nonpareil seed as a substrate for coating and other based on extrusion and spheronization) of omeprazole in capsules were purchased from commercially available sources. According to the manufacturer's method, pellets were produced either by extrusion and spheronization or *via* the drug layering of composition containing an alkalinizing excipient on the nonpareil seeds followed by direct enteric coating. In the former, the core composition comprised mannitol, lactose powder, microcrystalline cellulose, hydroxypropylcellulose, and magnesium hydroxide, all premixed in a V-blender. The mix blend was wet granulated by the addition of an aqueous dispersion of omeprazole, poloxamer surfactant, and disodium hydrogen sulfate followed by extrusion, spheronization, drying, and classification into suitable particle size ranges. When

nonpareil seeds were used, omeprazole dispersion containing poloxamer and disodium hydrogen sulfate was layered onto the substrate. Pellets were finally coated by applying a dispersion of either anionic copolymers based on methacrylic acid and methyl methacrylate (Eudragit-L 100) or hydroxypropylmethylcellulose phthalate as a functional coating, triethylcitrate as a plasticizer, and talc as an anti-tacking agent. The polymer dispersion was directly sprayed on the cores in a fluidized bed apparatus with spray guns placed above the bed. Enteric-coated pellets were dried to a water content of 0.5%, classified, and filled into hard gelatin capsules corresponding to 20 mg of omeprazole.

The stability of drug after storage following ICH guidelines (40°C±2°C/75%±5%; 30 days and 6 months=samples "A" and "B") was determined using NMR, HPLC, DSC, and fluorescent imaging.

NMR Analysis

The NMR spectra were recorded at 300 K, on a Bruker Avance III 400 Plus spectrometer equipped with a 5-mm indirect detection probe, operating at 400 MHz for ^{1}H-NMR and at 100 MHz for ^{13}C-NMR. Chemical shifts are reported as δ values, using TMS as an internal standard for proton spectra and the solvent resonance for carbon spectra, in parts per million (ppm), and the coupling constants (J) are expressed in hertz (Hz). Peak shapes were denoted as follows: s, singlet; d, double; t, triplet; q, quadruplet; m, multiplet; and bs, broad singlet. Assignments were done by means of chemical shifts, peak integration, and COSY experiments. A typical sample was made by dissolving 20 mg material in 600 μL deuterated dimethylsulfoxide (DMSO-d6). COSY spectra: Due to its structure, omeprazole has a rather limited 1H–1H homonuclear correlations, which makes COSY spectra advantageous for the characterization of various formulations.

HPLC Analysis

Drug pellets (40–60 mg) were removed from two to three capsules and were grinded into a clean mortar using a precleaned pestle. Mortar and pestle were cleaned after each use with water and acetone to prevent cross-contamination. For each formulation, 10 mg of freshly grinded powder was dissolved into 0.6 mL dimethylsulfoxide, and 25 μL from each solution were injected into an Agilent 1100 chromatographic system equipped with a quaternary pump, auto sampler, column heater, and UV–Vis detector. Elution was carried out at 25°C on a Zorbax Rx-C18 column (4.6 mm×25 cm, 5 μm) at a flow rate of 1 mL/min, with a mobile phase of phosphate buffer/MeCN 3/1 (v/v) and a detection wavelength of 280 nm.

DSC Analysis

The melting points and/or transition temperatures for omeprazole, excipients, and omeprazole-based formulations were determined by DSC using a using a TA Instruments Q200 MDSC (New Castle, DE) and a heating/cooling rate of 5°C/min. In a typical experiment, about 5 mg of freshly grinded powder was introduced into a *Tzero* pan. The corresponding lid was added on top, and the pan/lid assembly was compacted using a T_0 press to ensure the contact of the material with the bottom of the pan for enhanced sensitivity. The samples were heated/cooled as specified above against an empty pan/lid assembly processed in the same way.

Fracturing Procedure of Coated Pellets and Analysis *Via* Fluorescence Microscopy

In a typical experiment, one capsule was randomly removed from each container and placed within a heavy duty aluminum tray made for each sample. The capsule was opened wearing gloves, and the contained pellets were poured onto the aluminum tray. A new razor blade was unsealed and used to fracture individual pellets. The fracturing process was done on top of glass microscope slides that were pre-cleaned with paper wipes and used only once. Each pellet was fractured 2–3 times, and the sectioned pellets were inspected for planarity of both surfaces. Only fractured pellets with most planar surfaces were selected for imaging. The fractured pellets were placed on top of a microscope slide, which was mounted in the microscope dedicated holder for imaging.

The fluorescent imaging experiments were performed on a Leica DM4000B fluorescence microscope (Leica Microsystems, Wetzlar, Germany) equipped with ×5, ×10, ×20, and ×40 Leica PL Fluotar objectives and a Leica DC500 digital camera under the control of Image-Pro Plus 5.1 imaging software (Media Cybernetics Inc, Silver Spring, MD). Focusing was done using normal light, while upon acquiring images, an L5 filter was used in all cases (excitation wavelength 480 nm/40). The work-up of images was done using the Image-Pro software.

RESULTS AND DISCUSSION

The coating of solid substrates in the form of pellets or tablets is one of the most commonly used operation in the pharmaceutical industry for purposes of taste masking, esthetic and trade-marking matters, stability improvement, or for generating functionalized coatings such as enteric or controlled-release (CR) coatings. The functional coating option allows formulators to develop pH-dependent dosage forms of the drug that can resist gastric dissolution or to induce delayed release kinetics as part of modified-release drug delivery systems. A variety of dissolution kinetics can be addressed in this way, together with GI targeting of drug *via* pulsatile release or slow release through permeable or semipermeable coating having one or more orifices. Coating is accomplished by applying a uniform coat on a substrate in a drum/pan coaters or fluidized bed systems by means of liquid spraying, immersion into a liquid or powder deposition by electrostatic forces (23,24). The influence of the acidic enteric coating polymers on the stability of acid-labile drug substances including omeprazole and its congeners has been the subject of many investigations (4,5).

Taking into consideration the degradation mechanism of omeprazole in acidic media and the chemical species that can be formed during the process (Fig. 2), we decided to follow this process *via* ^{1}H-NMR. This technique can distinguish between the pyridine starting material (omeprazole) and the pyridinium intermediates formed in the acidic milieu. In

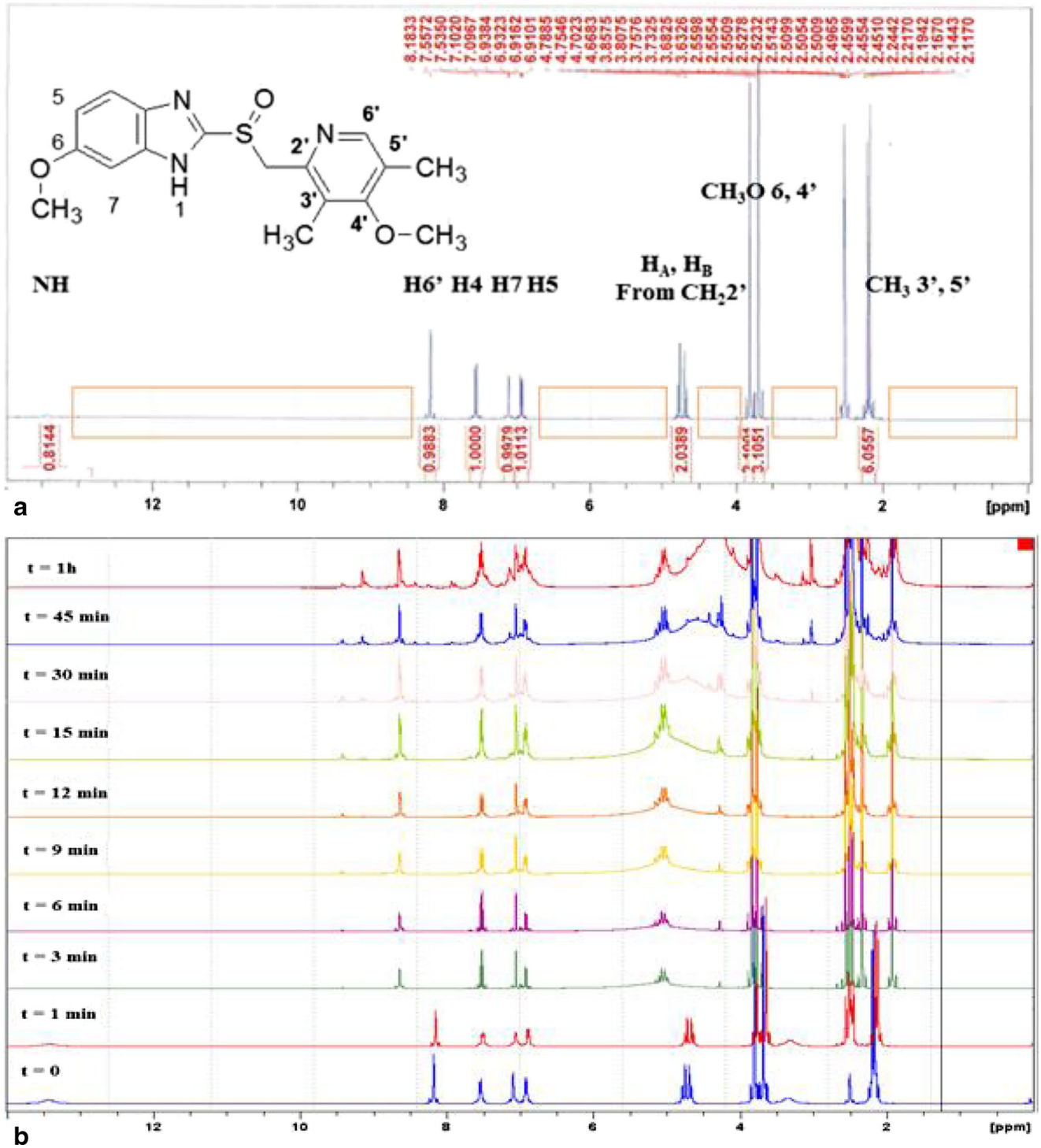

Fig. 4. **a** ^{1}H-NMR spectrum of omeprazole USP, with signal assignments, highlighting the areas that can be used to monitor and quantify drug decomposition through this technique; **b** degradation kinetics of omeprazole at pH=4, in DMSO-d^6, followed by ^{1}H-NMR

general, pyridinium derivatives have aromatic proton resonances at higher fields than their corresponding pyridines (25–27), which allows the qualitative and quantitative analysis of the formulation components. Moreover, the ^{1}H-NMR spectrum of pure omeprazole (Fig. 4a) reveals several regions that can be used for this purpose. Particularly important is the area between 8.5 and 13 ppm, where the pyridinium protons usually appear, and the region between 4.75 and 6.5 ppm where the strongly de-shielded methyl/methylene protons directly attached on the pyridinium ring can be usually found (25–27).

These expectations were confirmed when the degradation kinetic of omeprazole at pH 4 was followed by ^{1}H-NMR (Fig. 4b). One may observe the up-field shift of the H6′ of the pyridine in omeprazole from 8.20 to 8.7 ppm in the pyridinium and the similar shift up-field from 4.75 to 5.1 ppm for the 2′-CH_2 of

the same heterocycle(s). Other signals appeared between 9 and 10 ppm, probably due to the aromatic protons of several other heterocyclic species involved in the degradation process, some highlighted in Fig. 2. In the low field part, one can also observe characteristic signals of these newly formed compounds at 4.3 and 2.9 ppm, in good agreement with the chemical shift of the aliphatic groups substituting pyridinium species (25–27). The ^{1}H-NMR analysis also confirmed the very short half-life of the drug at pH lower than 4.

The detailed knowledge of the degradation products of omeprazole and of the chemical shifts that they display allowed us to proceed toward the analysis of omeprazole formulations in order to evaluate their stability and potential degradation. We have also recorded the ^{1}H-NMR spectra of all formulation components in order to distinguish between the signals introduced by these chemical entities and the signals of the degradation products of the drug (Fig. 5).

A thorough analysis of all these spectra allowed us to define two areas where ^{1}H-NMR allows the selective monitoring of omeprazole decomposition in the developed pharmaceutical composition—a narrow low field area between 1.5 and 2 ppm and a wide high field area between 8.3 and 13 ppm. In these two areas, no signals of drug or excipients can be normally found thus allowing the qualitative and quantitative evaluation of drug decomposition within the formulation.

Focusing on these two specific areas, we further analyzed the purity of the drug in two formulations, and we concluded that the large majority of the drug was intact, with degradation products present in an amount lower than 1% of the drug in both cases (samples A and B, Fig. 5).

Since this low amount of degradation products is bordering the detection limit of the NMR method, we analyzed the formulations *via* HPLC, using the US Pharmacopeia method for omeprazole quantitative analysis and a RP-C18 column (28). This very hydrophobic column, in tandem with the phosphate buffer/acetonitrile isocratic elution, allowed the efficient separation of various components of the formulation and optimum detection of the drug and its degradation products *via* UV absorption at 280 nm (Fig. 6). An analysis of the HPLC chromatograms for the samples A and B revealed an omeprazole purity of 99.6% in the first formulation and of 99.5% in the second formulation, in agreement with the NMR data. The HPLC method also allowed us to identify five drug degradation products in the first sample and nine degradation products in the second sample analyzed, showing that some degradation of the drug do exist in both formulations lacking the protective sub-coat, but it is rather minor. This set of data proved that direct application of acidic enteric coating polymeric solution to the substrate containing alkalinizing excipient in the absence of protective layer has no serious detrimental effect on omeprazole and that the optimized formulation process successfully avoided drug decomposition (Fig. 6).

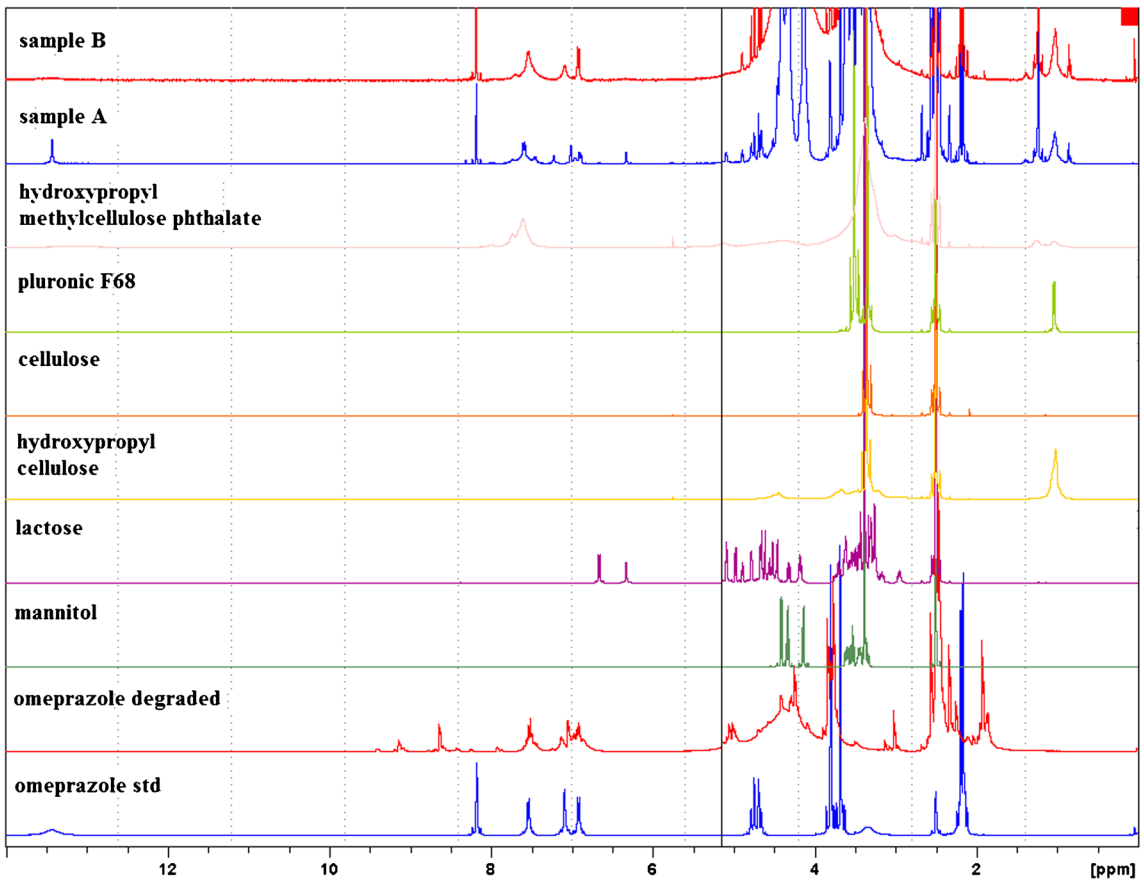

Fig. 5. ^{1}H-NMR analysis of omeprazole formulation individual components (reference spectra) and two representative samples; no drug decomposition was observed as one can compare the spectrum of the two samples analyzed with the degraded omeprazole reference spectrum also included

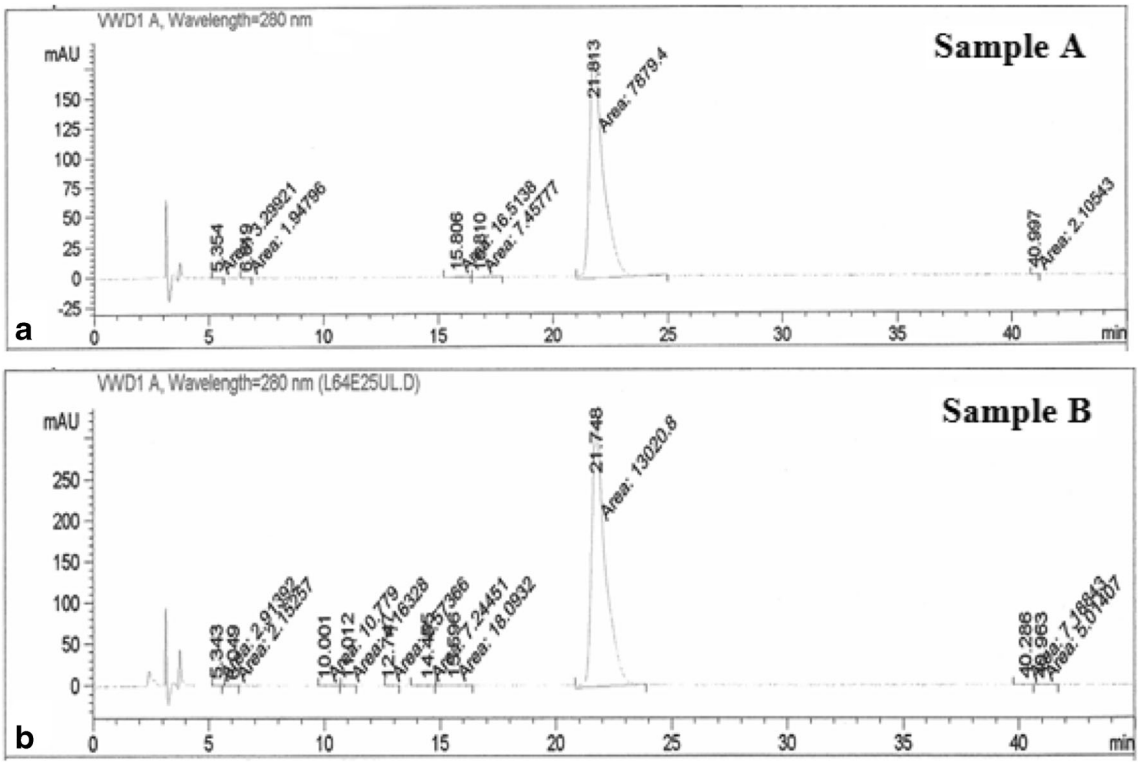

Fig. 6. Omeprazole content in two formulations lacking a protective sub-coat, referred to as samples "A" and "B," (**a** and **b**, respectively); both samples displayed drug content (*i.e.*, purities) higher than 99.5% of the labeled claim

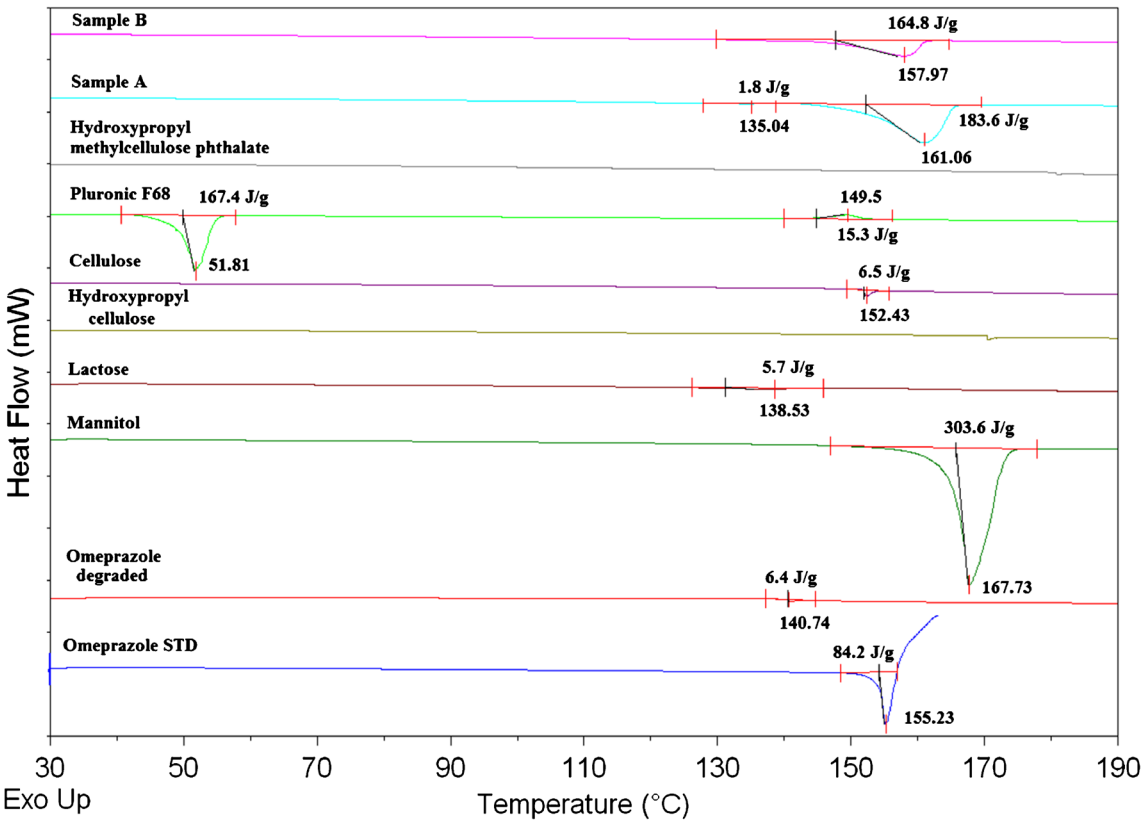

Fig. 7. Comparative DSC analysis of omeprazole formulations: thermograms (first heating) of samples "A" and "B" against omeprazole (pure and degraded) and against different core components used in the formulations, at a constant heating rate of 5°C/min. Transition temperatures (°C) and associated enthalpies (J/g) are shown in each case

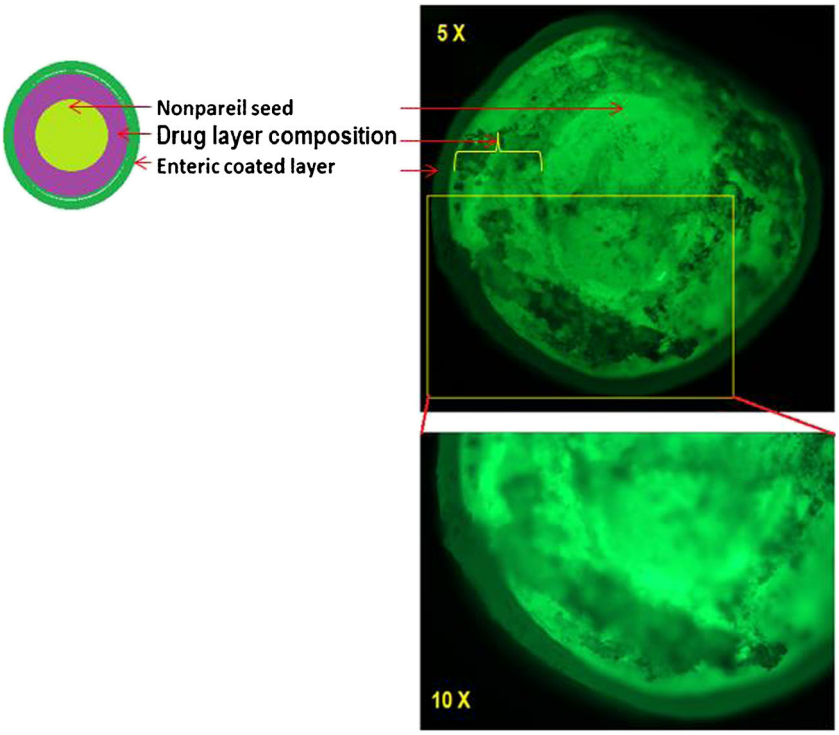

Fig. 8. Fluorescence images of fractured pellet at two different magnifications showing the nonpareil seed, a thick drug layer with alkaline excipient present and a uniform enteric coat layer. Note the absence of any visible sub-coat

In order to further validate these findings and to gain further insights regarding the effect of formulation process on the drug integrity, we have also performed a DSC analysis of the same omeprazole formulations previously analyzed *via* NMR and HPLC. DSC was frequently used to characterize the impact of various excipients used in the pellet coat-core formulations. Thus, we performed a comparative analysis of the DSC thermograms corresponding to samples "A" and "B" against pure drug, degraded drug, and individual formulation components (Fig. 7).

The different thermal properties of the materials used in omeprazole formulations, analyzed in the range 30–190°C, became obvious upon the analysis of data from Fig. 7. Thus, pure omeprazole melts around 155°C and subsequently decomposes exothermically. In contrast, the mixture of omeprazole degradation products exhibits only a modest thermal transition around 141°C, in agreement with the increased thermodynamic stability of pyridinium salts as compared with the corresponding pyridines. A similar behavior can be observed for the lactose, hydroxypropyl cellulose, and hydroxypropylmethylcellulose

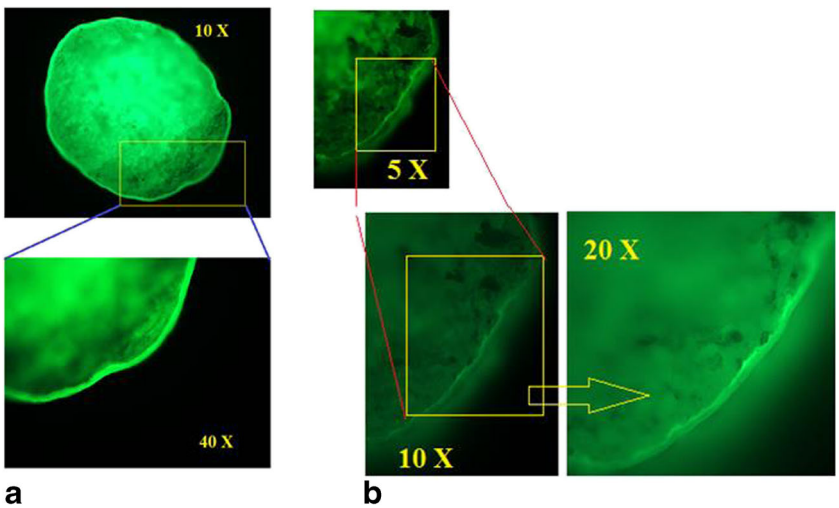

Fig. 9. Fluorescence images of two different batches (**a** and **b**) of fractured pellets produced by extrusion and spheronization followed by direct application of enteric coating viewed under different magnifications. Note the absence of any visible sub-coat

phthalate, which do not have any transition temperature or display only very small thermal transitions in the working range of temperatures due to lack of crystallinity or due to a much higher melting temperature. Significant thermal transitions are displayed by mannitol, which melts around 168°C, and by the poloxamer Pluronic F68 that has a rather low transition temperature, with an endothermic peak around 52°C. This polymer displays another exothermic transition at around 149°C, which is in the immediate vicinity of the omeprazole melting temperature. However, we expected a rather small influence of this excipient on the overall thermal behavior of omeprazole formulations since the amount used in the formulation is rather limited.

An analysis of the DSC thermograms for samples A and B revealed a single broad endothermic peak around 160°C corresponding to the melting of the drug and some of the excipient. In the case of sample A, one can observe a small transition temperature at 135°C, which is probably due to the presence of lactose. Importantly, both omeprazole formulations A and B were stable at temperatures higher than 165°C, while the pure drug was not, thus revealing the combined stabilizing effect of the excipients on the active compound.

Fluorescence images of fractured pellets having different composition and coating thicknesses (*i.e.*, typically 5 to 100 μm ranges) without a protective sub-coat are shown in Figs. 8 and 9. In Fig. 8, drug layer containing an alkaline excipient was applied onto a nonpareil seed followed by enteric coating. As shown, the nonpareil seed (*i.e.*, core), drug layer, and enteric coat layer can be easily differentiated from each other. It appears that there is no visible *in situ* layer formation at the enteric coat and drug layer interface at this level of magnification. The presence of a sub-coat or a protective coat can be easily identified using fluorescence microscopy as previously shown (see Fig. 3).

Similar observations was also apparent in two other batches produced in a similar manner as described above *via* extrusion and spheronization procedures, followed by the direct application of enteric coating as shown in Fig. 9a, b.

CONCLUSIONS AND SUMMARY

Analytical data showed that the pellets containing omeprazole remained chemically stable with a drug content of greater than 99.5% of the label claim recovered. The control of the microenvironmental pH by the addition of alkalinizing excipient within core formulation or as part of drug layering on top of nonpareil seed appears to efficiently neutralize the acidic effect of enteric coating dispersion. At the coat-core interface, immediately upon impingement of the atomized droplets of enteric dispersion on to the substrate surface, the alkalizing excipient appears to preferentially dissolve and create a favorable alkaline pH condition that supports drug stabilization as was confirmed by NMR, HPLC, and DSC data. In addition, fluorescence imaging microscopy appears to be a powerful and easy to operate tool, capable of easily differentiating between different layers. Acquired images following our artifact-free fracturing technique (*i.e.*, absence of surface contamination that easily occurs when microtoming hard solid materials) clearly show the presence of an enteric-coated layer of significant thickness and the existence of omeprazole throughout the core or within the drug-layering composition based on the fluorescing color. Images further illustrate the absence of any discernable *in situ* layer formation at the coat-core interface. Therefore, the hypothesized theory describing the potential formation of an *in situ* layer at the coat-core interface based on the observed images for omeprazole batches investigated in this work appears to be unsound. Additional investigation using CLSM and terahertz imaging is underway to further ratify these observations.

REFERENCES

1. Robinson M. Proton pump inhibitors: update on their role in acid-related gastrointestinal diseases. Int J Clin Pract. 2005;59:709–15.
2. Hershcovici T, Fass R. Pharmacological management of GERD: where does it stand now? Trends Pharmacol Sci. 2011;32:258–64.
3. Lindberg P, Brandstrom A, Wallmark B. Structure-activity-relationships of omeprazole analogs and their mechanism of action. Trends Pharmacol Sci. 1987;8:399–402.
4. Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole-a gastric proton pump inhibitor-on pentagastrin stimulated acid secretion in man. Gut. 1983;24:270–6.
5. Pilbrant A, Cederberg C. Development of an oral formulation of omeprazole. Scand J Gastroenterol. 1985;20:113–20.
6. Thoma K, Bechtold K. Enteric coated hard gelatin capsules. Capsugel Libr. 2000;145:1–17.
7. Pillay V, Fassihi R. In vitro release modulation from crosslinked pellets for site-specific drug delivery to the gastrointestinal tract. I. Comparison of pH-responsive drug release and associated kinetics. J Control Release. 1999;59:229–42.
8. Kolte BP, Tele KV, Mundhe VS, Lahoti SS. Colon targeted drug delivery system—a novel perspective. Asian J Biomed Pharm Sci. 2012;2:21–8.
9. Mathew M, Das Gupta V, Bailey RE. Stability of omeprazole solutions at various pH values as determined by HPLC. Drug Dev Ind Pharm. 1995;21:965–71.
10. Missaghi S. Formulation design and approaches to enteric coating delivery via compression coating or encapsulation of acid-labile compounds using omeprazole as a model drug. PhD dissertation, Temple University, School of Pharmacy; Philadelphia, 2006. Chapter 4.
11. Erickson M, Josefson L. Pharmaceutical formulation of omeprazole. 1988. US Patent 6090827.
12. Chen CM, Chou J, Weng T. Omeprazole formulation. 1999. US Patent 6077541.
13. Chen CM, Chou J, Weng T. Omeprazole formulation. 1999. US Patent 6096340.
14. Stroyer A, McGinity JW, Leopold CS. Solid state interactions between the proton pump inhibitor omeprazole and various enteric coating polymers. J Pharm Sci. 2006;95:1342–53.
15. Lundberg PJ, Lovgren K. New pharmaceutical formulation and process. 1996. WO96/24338.
16. Lee FY, Chen SC, Kuo HC. Orally administered pharmaceutical formulations of benzimidazole derivatives and method of preparing the same. 2000. US Patent 6228400B1.
17. Jantzen GM, Robinson GR. Sustained-and controlled-release drug-delivery systems. In: Banker GS, Rhodes CT, editors. Modern pharmaceutics. 4th ed. New York: Marcel Dekker; 2002. p. 501–28.
18. Porter SC. Coating of pharmaceutical dosage forms. In: Gennaro AR, editor. Remington, the science and practice of pharmacy, 20th Edition: Lippincott Williams and Wilkins; 2000. p. 894–902.
19. Munday DL, Fassihi AR. Controlled release delivery: effect of coating composition on release characteristics of mini-tablets. Int J Pharm. 1989;52:109–14.
20. Coutts-Lendon CA, Wright NA, Mieso EV. The use of FT-IR imaging as an analytical tool for characterization of drug delivery systems. J Control Release. 2003;93:223–48.
21. Missaghi S, Fassihi AR. A novel approach in the assessment of polymeric film formation and film adhesion on different pharmaceutical solid substrates. AAPS Pharm Sci Tech. 2004;5(2):1–8.

22. Merrett K, Cornelius RM, McClung WG, Unsworth LD, Sheardown H. Surface analysis methods for characterizing polymeric biomaterials. J Biomater Sci Polym Ed. 2002;13:593–621.
23. Munday DL, Fassihi AR, De Villiers C. Bioavailability study of a theophylline oral controlled release capsule containing film coated mini-tablets in beagle dogs. Int J Pharm. 1991;69:123–7.
24. Munday DL, Fassihi AR. Changes in drug release rate: effect of stress storage conditions on film coated mini-tablets. Drug Dev Ind Pharm. 1991;17:2135–43.
25. Dave K, Scozzafava A, Vullo D, Supuran CT, Ilies MA. Pyridinium derivatives of histamine are potent activators of cytosolic carbonic anhydrase isoforms I, II and VII. Org Biomol Chem. 2011;9:2790–800.
26. Savarala S, Brailoiu E, Wunder SL, Ilies MA. Tuning the self-assembling of pyridinium cationic lipids for efficient gene delivery into neuronal cells. Biomacromolecules. 2013;14(8):2750–64.
27. Sharma VD, Aifuwa EO, Heiney PA, Ilies MA. Interfacial engineering of pyridinium gemini surfactants for the generation of synthetic transfection systems. Biomaterials. 2013;34(28):6906–21.
28. US Pharmacopeia, 25th Edition: USP Convention Inc; 2002. p. 1265–6.