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Could the Change of Excipient Content Improve the Stability of Gastroresistant Omeprazole Pellets?

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HIGHLIGHTS

- Development of stable omeprazole pellets (OMP).
- Dibasic sodium phosphate dihydrate and hypromellose to protect OMP from degradation.
- Analytical techniques for testing the compatibility and stability of unstable drugs.

Abstract: Omeprazole (OM), a temperature, pH, and moisture-sensitive drug, poses formulation challenges. This study delves into the complex development of OM pellets, focusing on the impact of buffering excipients on stability and release. Addressing the challenges of OM pellet stability requires a comprehensive compatibility and stress study involving key excipients. Binary mixtures of OM with dibasic sodium phosphate dihydrate (DSPD), mannitol, hypromellose (Hyp), and polysorbate underwent scrutiny for possible incompatibilities, subjected to 40°C stress and 75% relative humidity. DSC, TGA, and ATR-FTIR analyses were conducted, with quantitative monitoring of OM by HPLC. Formulations with varied proportions of DSPD and Hyp were also stress-tested. While all excipients exhibited compatibility with OM, thermal analysis suggested a potential incompatibility between OM and mannitol, disproven by HPLC. Stress tests on diverse formulations confirmed their adequacy, maintaining OM content and impurities within acceptable limits. Increased Hyp reduced impurities, and its combination with DSPD further enhanced stability. The study concludes that augmenting DSPD with Hyp offers effective protection for OM pellets, ensuring their stability.

Keywords: Compatibility and stress study; Dihydrate dibasic sodium phosphate; Hypromellose.

INTRODUCTION

The stability of pharmaceutical products refers to the ability of both the drug and formulation to maintain their original characteristics and biological properties over a specific period [1]. This stability is influenced not only by the physicochemical properties of the active pharmaceutical ingredient (API) but also by formulation characteristics and the production process [2].

In the context of formulations, typically comprising an API and pharmacologically inert excipients, it becomes imperative to investigate potential degradation mechanisms [2]. Many degradation reactions involving the interplay between the API and excipients remain poorly understood [3]. However, understanding possible physical and chemical incompatibilities is crucial during the pre-formulation phase for the rational development of pharmaceutical dosage forms [4].

The exposure of drugs and excipients to environmental variations, such as temperature, light, and humidity, aids in identifying potential degradation products and the conditions favoring their formation [5]. These stress factors contribute to investigating drug-excipient compatibility [4]. Pre-formulation studies, based on analytical methodologies like DSC and FT-IR, allow predictions about the formulation's long-term chemical and physical stability [6,7]. While there is no universal protocol for assessing drug-excipient compatibility, researchers often employ analytical techniques alongside stress conditions recommended by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) [8-16]. Although DSC and FT-IR offer immediate results, combining them with classic chromatographic analyses provides more reliable information on the stability of the drug-excipient system [9, 15].

Omeprazole, frequently prescribed for gastrointestinal disorders, acts as a gastric proton pump inhibitor but is highly susceptible to degradation by acid, heat, humidity, light, and organic solvents [18]. The appearance of discoloration ranging from light beige to deep purple necessitates a well-designed pre-formulation study to prevent the formation of degradation products [19].

Enteric coating serves as a strategy for the modified release of drugs in orally administered dosage forms. Its primary objective is to ensure drug stability in harsh stomach conditions and controlled release in the digestive tract. This entails the dissolution of polymers in the intestine, releasing the drug appropriately [20-22]. Pellets, among solid dosage forms, are commonly used to enhance omeprazole stability, providing drug protection and controlled release for improved bioavailability, efficacy, and safety [23]. These drug pellets can be prepared by coating inert pellets with a drug solution/dispersion and various excipients. An insulating polymer layer may further coat the drug core, followed by a polyacrylic derivative [24,25]. Due to potential omeprazole-excipient interactions, a stress study during the pre-formulation phase becomes crucial to predict drug stability in the formulation.

Consequently, this study aimed to investigate the compatibility of omeprazole with specific excipients for the development of gastro-resistant omeprazole pellets. The formulation comprised three coating layers (drug coating, sealing coating, and gastro-resistant coating). The study evaluated the influence of the sodium phosphate buffer amount in the first layer (drug coating) and the presence of hypromellose in the intermediate layer (sealing coat).

MATERIAL AND METHODS

Materials

Omeprazole (purity > 98%; batch no. KOMO75) was procured from the United States Pharmacopeia (USP, North Bethesda, MD, USA). Inert sucrose pellets were obtained from Hanns G. Werner GmbH + Co. KG (Tornesch, Germany). Sodium phosphate dibasic dihydrate and mannitol were sourced from Plury Quimica and Ingredion Brasil (São Paulo, SP, Brazil), respectively. Polysorbate 80 was acquired from M Cassab (Sao Paulo, SP, Brazil). Hypromellose was purchased from IMCD Brasil Farma (Sao Paulo, SP, Brazil). Methacrylic acid copolymer (Eudragit® L-30 D55) was obtained from Evonik (Santos, SP, Brazil). Triethyl citrate was sourced from Vertellus Performance Materials Inc. (Indianapolis, IN, USA), and talc was acquired from Indukern (Maringa, PR, Brazil). All other chemicals were of analytical grade and used without further purification.

Investigation of the compatibility between omeprazole and excipients

The materials utilized for the preparation of omeprazole pellets are detailed in Table 1. Binary mixtures of omeprazole with the excipients Hypromellose 2910 (Hyp), mannitol, dibasic sodium phosphate dehydrate (DSPD), and polysorbate 80 were formulated based on the specified ratio of each component. Excipients not included in direct contact with omeprazole were excluded from testing. Manual stirring and homogenization

were employed to prepare each binary mixture. As for the mixture involving inert pellets, these pellets were initially ground using a mortar and pestle, followed by subsequent mixing with omeprazole.

Table 1. Composition of the pellet formulations containing omeprazole.

Function	**Component / characteristics**	**Formulation**		
		F1	**F2**	**F3**
Inert core	Sucrose sphere size 20-25 µm (inert pellets)	X	X	X
Omeprazole coating				
Drug	Omeprazole	X	X	X
Buffering	Dibasic sodium phosphate dihydrate	X	X	Increased by 100%
Diluent	Mannitol	X	X	X
Surfactant	Polysorbate 80	X	X	X
Binder/coating polymer	Hypromellose 2910 (first cover)	X	X	X
Sealing coating				
Coating polymer	Hypromellose 2910 (second cover)	X	Increased by 18.5%	Increased by 18.5%
Gastro-resistant coating				
Functional polymer	Methacrylic acid copolymer (Eudragit®L30 D55)	X	X	X
Plasticizer	Triethyl citrate	X	X	X
Glidant	Talc	X	X	X

The mixtures were packed into glass flasks (type III) and assessed at two time points: immediately after packaging (time zero) and after 28 days under specific stress conditions in a climatic chamber (Mecalor model EC/0.75/AR-URC, Sao Paulo, SP, Brazil). The stress conditions included: a) 40 ºC and 75% relative humidity (RH) in open glass flasks; b) 40 ºC and 75% RH in airtight glass flasks. Analysis techniques encompassed visual inspection for color changes (macroscopic analysis), attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR), and thermal analyses (thermogravimetric analysis – TGA and differential scanning calorimetry – DSC). Samples exhibiting potential incompatibilities underwent further assessment using high-performance liquid chromatography (HPLC).

Macroscopic analysis

Macroscopic analysis involved observing the maintenance or alteration of color in omeprazole, mannitol, polysorbate 80, hypromellose, sodium phosphate dibasic dehydrated, inert pellets, and binary mixtures. Results were expressed using a color scale: white, slightly yellowish, yellowish, yellow, more intense yellow, slightly brown, brown, and strongly brown.

Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR)

ATR-FTIR analyses were performed on isolated materials (omeprazole and excipients) and binary mixtures using a Perkin-Elmer spectrometer (Waltham, MA, USA). Scanning ranged from 650 to 4000 cm-1 with a resolution of 4 cm-1, and results were analyzed using Spectrum ES software [26].

Thermal analysis

TGA and DSC analyses were conducted with a Mettler Toledo model I equipment (Columbus, OH, USA). Samples were subjected to a temperature gradient from 30 to 250 °C, with a heating rate of 10 °C/min, under a nitrogen flow of 50 mL/min. Results were analyzed using STAR e software and expressed in terms of onset peak temperatures and enthalpy difference values (ΔH) [14]. A variation of ± 2.0 °C in the onset temperature of omeprazole or excipient melting was considered a systematic error, while any other distinct value suggested possible interaction between components.

HPLC analysis

Content and impurity analyses followed the United States Pharmacopeia (USP) methodology, considering the monographs of pure omeprazole and omeprazole delayed-release capsules for binary mixtures [28]. The HPLC analyses employed a Shimadzu LC 20AT system (Tokyo, Japan) with a Phenomenex® Luna C8 column. The mobile phase comprised solutions A (glycine in water) and B (acetonitrile and methanol). Separation was performed under a gradient elution, and detection wavelength was set at 305 nm. Acceptance criteria for chromatographic analyses included a minimum of 2,000 theoretical plates, tail factor between 0.8 and 2.0, and relative standard deviation (RSD) ≤ 2.0% between injections. Empower® software (Waters®, Milford, MA, USA) facilitated data collection and analysis [27].

The content and impurity analyses adhered to the methodology outlined in the United States Pharmacopeia (USP), taking into account the monographs for pure omeprazole and omeprazole delayed-release capsules within the context of binary mixtures [28]. Following USP guidelines, the specification range considered was 98 to 102% for omeprazole and 90 to 110% for the binary mixtures. In impurity analysis, a maximum impurity value of 2.0% and 0.5% for specific individual impurities was adopted [27]. Only samples exhibiting alterations in prior investigations underwent HPLC analysis for a quantitative assessment of potential impurity presence.

HPLC analyses were conducted using a Shimadzu LC 20AT system (Tokyo, Japan), featuring a photodiode array (PDA) detector (model SPD-20A), an autosampler (model SIL-20A), a pump (model LC-20AT), and a column oven (model CTO-20A). The stationary phase employed was a Phenomenex® Luna C8 column (150 mm x 4.6 mm x 5 µm) sourced from Torrance, USA. The mobile phase consisted of two solutions: i) solution A, comprising 6 g of glycine dissolved in 1500 mL of water, pH = 9.0 (adjusted with a 50% NaOH solution); this solution was then transferred to a 2000 mL volumetric flask, and the volume was made up with ultra-purified water; and ii) solution B, a mixture of acetonitrile and methanol (85:15 v/v). Both solutions underwent filtration through a 0.2 µm filter membrane (Fluoropore PTFE Membrane, Merck, Darmstadt, Germany). Separation was achieved through gradient elution of solutions A and B (0 min 88% A, 20 min 40% A, 21 min 88% A, 21-25 min 88% A) at 25 ºC, with a flow rate of 1.2 mL/min and a detection wavelength of 305 nm [27]. Empower® software (Waters®, Milford, MA, USA) facilitated data collection and analysis. Acceptance criteria for chromatographic analyses included a minimum of 2,000 theoretical plates, a tail factor between 0.8 and 2.0, and a relative standard deviation (RSD) ≤ 2.0% between injections.

Preparation of pellets containing omeprazole

The omeprazole pellets were manufactured at Prati Donaduzzi Industry (Toledo, PR, Brazil) utilizing the fluidized bed coating technique in a three-step process (Figure 1). In the initial phase, the primary layer was established by coating inert pellets with an aqueous dispersion containing omeprazole, hypromellose (binder), sodium phosphate dibasic dihydrate (buffering agent), polysorbate 80 (wetting agent), and mannitol (diluent). Subsequently, the sealing layer (hypromellose intermediate layer 2) was applied in the second stage. Finally, the third step involved the application of the functional polymer coating Eudragit® (gastro-resistant layer). The production process was conducted using the Laboratory Fluid Bed (Unilab, Huttlin GmbH – Syntegon, Schopfheim, Germany), with a spray rate ranging from 5 to 90 g/min and temperature settings of 31 - 39 ºC (layer 1), 39 – 41 ºC (layer 2), and 24 – 26 ºC (layer 3). Three formulations were prepared by adjusting the amount of hypromellose and/or sodium phosphate.

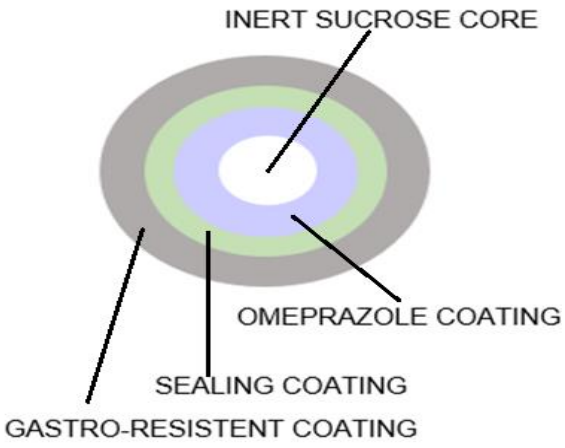

Figure 1. Preparation of pellets containing omeprazole.

Stress test with omeprazole pellets

The omeprazole formulations (F1, F2, and F3) underwent exposure to a temperature of 40 ºC and 75% RH for a duration of 28 days, housed in either open or airtight glass flasks [13]. Subsequently, the formulations were subjected to analysis using the previously described HPLC method for the quantification of drug content and impurities. Specification ranges considered for content were 90 - 110%, 0.5% for specific and nonspecific impurities, and 2.0% for total impurities [27]. To assess the quantitative impact of the excipients hypromellose (intermediate layer) and sodium phosphate dibasic dehydrated (buffering agent) on the stability of omeprazole, variations in their amounts in formulations F2 and F3 were systematically evaluated.

Morphology and size analysis

The morphology of the omeprazole pellets was assessed both before and after the stress test. The formulations, including entire and cross-sectioned pellets, were positioned on a sample holder, coated with gold/palladium, and examined using a scanning electron microscope (SEM; Shimadzu SS550, Tokyo, Japan). SEM micrographs were employed to evaluate the size of the pellets, specifically Feret's diameter, utilizing Image Pro Plus 4 software (Media Cybernetics, Inc., Rockville, MD, USA).

In vitro drug release profile

The drug release studies were conducted using Apparatus 2 (Sotax®, Westborough, USA), following the procedures outlined in Test 1 of the USP monograph [27]. Gastro-resistant hard gelatin capsules containing omeprazole pellets from formulations F1, F2, or F3 were assessed in two phases.

In the initial stage, the capsules (n=12) were introduced into the vessels of the dissolution apparatus, each containing 900 mL of 0.1N hydrochloric acid and stirred with a paddle at 100 rpm for 2 hours. After this period, the capsules and pellets were filtered from the acidic medium, and the omeprazole content was quantified using the previously described HPLC method. No release was anticipated during this acidic medium exposure.

For the second stage, another set of capsules (n=12) was added to 500 mL of the same acidic medium used in the first step, stirred with a paddle at 100 rpm for half an hour. Subsequently, 400 mL of concentrated dibasic sodium phosphate solution (0.235 M) at pH 10.4, pre-heated to 37 ºC, was introduced into the vessel. Following this addition, each vessel was expected to contain 900 mL of a solution at pH 6.8. If pH adjustment was required, 2 N hydrochloric acid or 2 N sodium hydroxide was used. Dissolution analysis continued for an additional 30 minutes with constant paddle stirring. At predefined time intervals (10, 15, 20, 25, and 30 min), 15 mL aliquots of the dissolution medium were withdrawn, filtered, and the omeprazole content determined by the HPLC method [27]. The withdrawn volume was replenished with fresh dissolution medium, and sink conditions were maintained throughout the experiment.

Raman microscopy - Sample preparation

The pellet was bisected to expose a cross-sectional area presenting all layers concentrically. The analysis was conducted on this cross-sectional area, scanning at intervals of 10 µm, creating a matrix of 140 by 140 points and covering an area of 1400 x 1400 µm² [29, 30]. The sample exhibited a diameter (D) of approximately 1300 µm (1.3 mm).

Raman microscopy analysis

The Raman spectra were acquired utilizing a Senterra model Confocal Raman microscope (Bruker Optik GmbH, Ettlingen, Germany) equipped with a 785 nm laser excitation source. The laser operated at a nominal power of 50 mW, focused on the sample using a 20x magnification lens at room temperature. A spectral resolution ranging from 9 to 15 cm^{-1} was applied in the spectral range of 1800 to 200 cm^{-1}. Each spectrum represents an average of 5 spectra obtained at the same point, with an integration time of 0.5 s [28,29].

RESULTS AND DISCUSSION

Macroscopic characteristics

A visual examination of both the drug and excipients was conducted to ascertain whether any color changes occurred following a 28-day exposure to stress conditions. It is noteworthy that the excipients Eudragit®, talc, and triethyl citrate, though present in the formulation, were excluded from this analysis as

they do not come into direct contact with omeprazole. The results for both isolated compounds and binary mixtures, both before and after the stress period, are presented in Table 2.

Table 2. Macroscopic characteristics of omeprazole, pure excipients and their binary mixtures, before and after stress study period (40 ºC and 75% relative humidity), in samples stored in open or closed bottles and after 28 days.

Samples	Before stress	After stress (open flask)	After stress (closed flask)
Isolated compounds	color		
Omeprazole	White	Slightly brown	Slightly brown
Inert pellets	White	White	White
Dibasic sodium phosphate dihydrate	White	White	White
Mannitol	White	White	White
Polysorbate 80	Yellowish	Intense yellow	Yellowish
Hypromellose 2910	White	White	White
Binary mixtures			
Omeprazole +inert pellets	White	Slightly brown	Slightly brown
Omeprazole + dibasic sodium phosphate dihydrate	White	Slightly brown	Slightly brown
Omeprazole +mannitol	White	Slightly brown	Slightly brown
Omeprazole +polysorbate 80	White	Slightly brown[1]	Slightly brown[1]
Omeprazole +hypromellose 2910	White	White	White

[1]Presence of lumps.

Most of the isolated excipients exhibited no discernible color changes after 28 days of stress under both packaging conditions, except for polysorbate 80 stored in the open flask, where a noticeable increase in yellow color intensity was observed. This observation aligns with prior studies suggesting the potential self-oxidation of polysorbate 80 (Jones and coauthors, 2018) [31]. For omeprazole alone, degradation was noted even in the closed flask, albeit with higher intensity in the open flask.

Concerning the binary mixtures, color alterations were observed in most cases after the stress period, except for the omeprazole and hypromellose mixture, which maintained its white color. This preservation suggests good compatibility between these components, indicating that hypromellose may contribute to the protection of the drug. In comparison to other samples, and when compared with its respective open flask, the omeprazole and sodium phosphate mixture exhibited a lighter color, implying a potentially less intense degradation behavior of omeprazole in this combination.

Apart from color changes, the binary mixture of omeprazole and polysorbate 80 also exhibited the formation of lumps, likely attributed to increased humidity in the micro-environment of the mixture.

Attenuated total reflectance Fourier transform infrared spectroscopy analysis (ATR-FTIR)

The results of the vibrational analysis of raw substances and their binary mixtures are displayed in Table 3.

The omeprazole stretching vibrations for CCN and SCN bonds were assessed at 1625.7 cm^{-1}, the benzimidazole ring was analyzed at 1204 cm^{-1}, and a resonance band at 1077 cm^{-1} [30]. The characteristic bands of the isolated compounds sodium phosphate dibasic dihydrate, mannitol, hypromellose, polysorbate, and inert pellets (Table 3) were consistent with previous studies [32-36].

Following exposure to stress in open flasks, alterations were observed for hypromellose and sodium phosphate. A new band appeared at 3420 cm^{-1} for hypromellose, and differences in band intensity and new bands emerged for sodium phosphate (Table 3). Some isolated substances, such as omeprazole, mannitol, and inert pellets, did not exhibit vibrational differences. For polysorbate 80 samples in open flasks, an increase in the band at 3500 cm^{-1} was observed, likely related to –OH bonds. While some modifications were evident for the isolated excipients hypromellose, polysorbate 80, and sodium phosphate stored in open flasks, no changes in the characteristic bands of these substances were observed for their respective binary mixtures under any of the packaging conditions. For enhanced visualization, Figure 2 illustrates the ATR-FTIR spectra for pure excipients and in association with omeprazole: (A) hypromellose; (B) polysorbate 80, and (C) sodium phosphate.

Table 3. ATR-FTIR results of each component of pellet formulations and their binary mixture with omeprazole, study period (40 ºC and 75% relative humidity), in samples stored in open or closed bottles and after 28 days.

Sample	Before stress (cm^{-1})	After stress and open flask (cm^{-1})	After stress and closed flask (cm^{-1})	References (cm^{-1})
Isolated compounds				
Omeprazole	1628 / 1204.2 / 1075.8	without changes	without changes	1625.7 / 1204 / 1077 (14)
Inert pellets	3304.58 / 2930.94 / 1149.54	without changes	without changes	3000-3600 / 2931 / 1156 (15)
Dibasic sodium phosphate dehydrate	Bands between 650 -830 and 850-1060 / 1110 / 1200	bands with different intensities in the region of 650 - 1060 / 1119,05 / 1258.18 / 3076.70 / 3371.79	without changes	Bands between 630-830 and 850-1060 / 1100 / 1200 (16)
Mannitol	3277.3 /2939.19 / 1427.89 / 1281.07 / 1076.44 / 1018.4	without changes	without changes	3287 / 2900 / 2980 / 1422 / 1282 / 1082 / 1020 (17)
Polysorbate 80	2856.92 / 1735.07 / 1091.65	New band in 3463.9	without changes	2856 / 1734 / 1091(18)
Hypromellose 2910	1052.18 / 945.56	New band in 3420	without changes	1053 / 944 (19)
Binary mixtures				
Omeprazole + inert pellets	1628 / 1204.2 / 1075.8	without changes	without changes	1625.7 / 1204 / 1077 (14)
Omeprazole + Dibasic sodium phosphate dehydrate				
Omeprazole + mannitol				
Omeprazole + polysorbate 80				
Omeprazole + Hypromellose 2910				

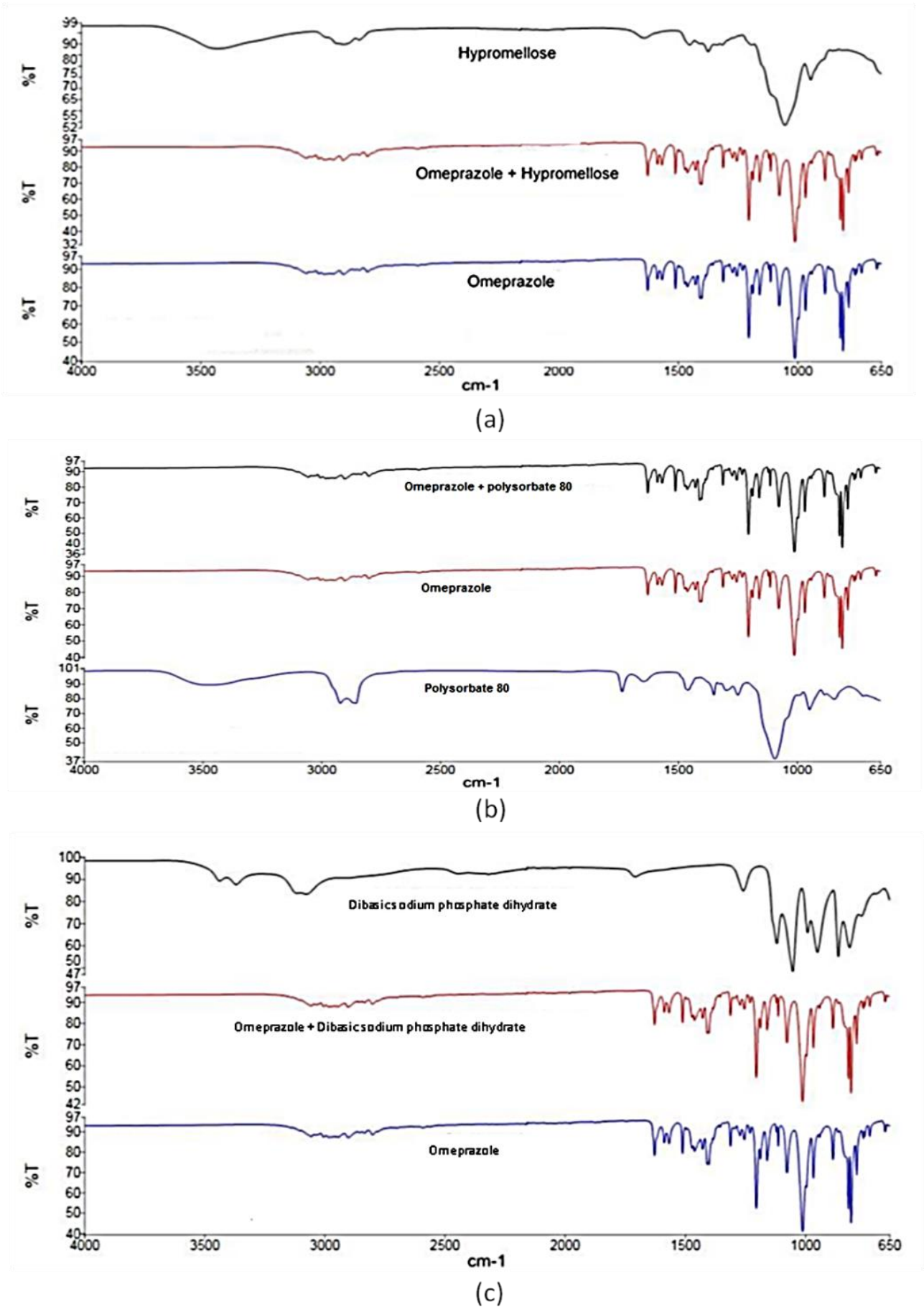

Figure 2. ATR-FTIR spectra for pure excipients and in association with omeprazole: (A) hypromellose; (B) polysorbate 80, and (C) sodium phosphate.

To the best of our knowledge, no incompatibilities between omeprazole and sodium phosphate dibasic dihydrate have been reported thus far; however, it is known that at elevated temperatures, this compound may undergo loss of crystallization water or transform into another hydrated form. The alterations observed in the isolated compound stored in an open flask may indicate sensitivity to higher moisture concentrations, as this compound already contains water molecules in its structure, potentially facilitating degradation or transformation into other hydrated forms.

Regarding changes in the spectra of polysorbate 80 and hypromellose after the stress period in open flasks, this is possibly linked to an increase in the amount of water (75% RH), as the alterations appeared in the region of hydroxyl groups. Nevertheless, in the binary mixtures of omeprazole with these three excipients, no modifications were observed in the characteristic spectrum of the API, even under stress conditions in open flasks (data not shown). Moreover, the same vibrational behavior of omeprazole was found for the other binary mixtures. Thus, the results may indicate compatibility between the drug and the evaluated excipients.

As there were no discernible differences between the two packaging conditions, thermal analyses were solely conducted for the samples stored in closed flasks, simulating conditions for commercialization.

Thermal analysis (TGA/DSC)

The DSC analyses revealed that the binary mixtures did not undergo alterations in the endothermic events after the stress period (Table 4). In contrast to the isolated drug, the omeprazole and mannitol mixture exhibited a modification in the API melting temperature beyond the specified range (± 2.0 °C). Consequently, this sample underwent HPLC analysis to investigate the presence of potential degradation products, identified as impurities, and to assess the drug content. The TGA analysis showed no mass loss, indicating the absence of chemical interactions among the compounds.

Table 4. Onset temperatures obtained by differential scanning calorimetry (DSC) analysis of the isolated components and their binary mixtures, without and after stress, packed in a closed flask.

Sample	Before stress – onset (°C)	After stress – onset (°C)
Isolated compounds		
Omeprazole	155.99	155.77
Inert pellets	175.25	170.32
Dibasic sodium phosphate dihydrate	56.37	59.94
Mannitol	165.19	165.48
Binary mixtures		
Omeprazole +Inert pellets	154.76	154.46
Omeprazole + Dibasic sodium phosphate dehydrate	156.30	156.19
Omeprazole + Mannitol	153.28	153.23
Omeprazole +Polysorbate 80	154.97	154.32
Omeprazole +Hypromellose 2910	155.21	155.76

Note: Polysorbate 80 and Hypromellose 2910 samples did not show endothermic events, and they were not added to this table.

HPLC analysis

The drug content in the binary mixture with mannitol, as well as in isolated omeprazole, was assessed before and after exposure to stress conditions (Table 5). In the case of pure omeprazole, the values before and after the stress period met the predefined acceptance criteria [27].

Furthermore, nonspecific impurities were not quantified. Figure 3 illustrates the chromatograms of mannitol (A), omeprazole (B), and the binary mixture (omeprazole + mannitol) (C), both before (I) and after the stress test (II). Notably, new chromatographic peaks appeared at 2.8, 4.6, and 8.8 minutes (1, 2, and 3) in the chromatograms of isolated omeprazole and the binary mixture after the stress, suggesting the presence of impurities derived from the API. However, neither nonspecific nor total impurities exceeded the established acceptance criteria. Despite the DSC analysis indicating a potential incompatibility between omeprazole and mannitol, this was not quantitatively confirmed by HPLC. Thus, with the absence of incompatibility between

the drug and the excipients, omeprazole pellets were manufactured and characterized, subsequently undergoing a stress study to identify the most stable formulation.

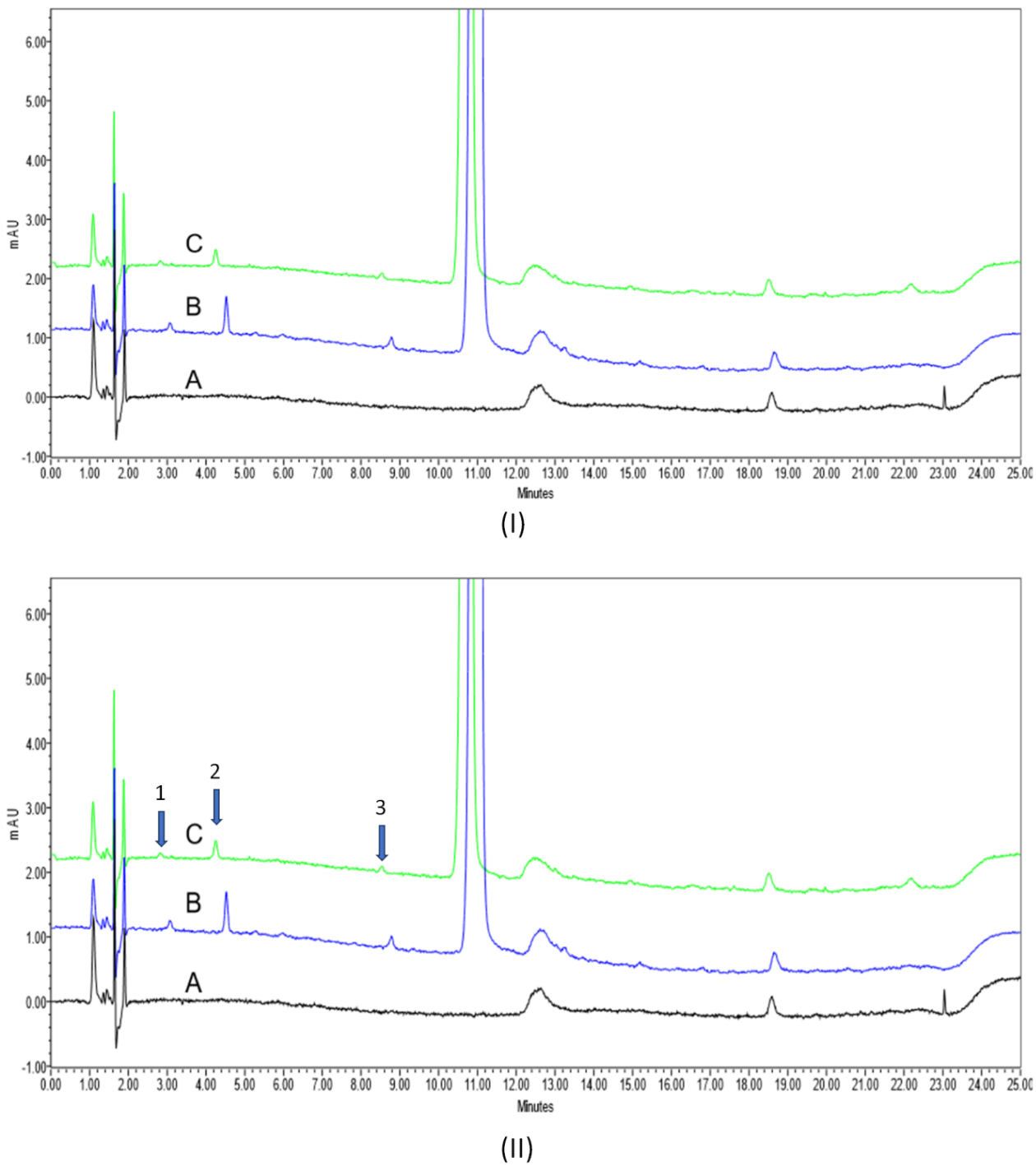

Figure 3. HPLC Analysis. Chromatograms of mannitol (A), omeprazole (B), and the binary mixture (omeprazole + mannitol) (C), before (I) and after the stress test (II). Presence of new chromatographic peaks (impurities) in 2.8, 4.6 and 8.8 minutes (1,2 and 3).

Omeprazole pellets

In pursuit of stabilizing the drug lansoprazole, a study was undertaken to assess various alkalinizing excipients, aiming to determine the optimal pH for effective drug solubilization without inducing degradation [38]. Another investigation involving two commercially available products comprising omeprazole pellets, incorporating hydroxypropyl cellulose in the intermediate layer and magnesium oxide as an alkalinizing excipient, concluded that the use of an alkaline excipient created a favorable pH environment to uphold drug stability within the pellet, counteracting the acidic degradation effects [38]. Therefore, in our study, sodium phosphate dibasic dihydrate and hypromellose were chosen to achieve optimal drug stability in the pellet.

Typically, hypromellose is employed as a film-coating for tablets at concentrations ranging from 2 to 20% (w/w), depending on the viscosity grade. Lower viscosity grades, such as Methocel E6 premium LV 2910 [39], are utilized in aqueous film-coating solutions and were employed in the intermediate layer in this study. Sodium phosphate dibasic dehydrated served as both a stabilizing agent and an alternative to magnesium oxide. Notably, sodium phosphate exhibits high solubility in water compared to the poor solubility of magnesium oxide [39]. This hydrophilic characteristic is crucial for certain drugs produced in pellet form, where the drug is often dispersed in the polymer using an aqueous suspension.

Three pellet formulations containing omeprazole were prepared, and the HPLC analyses of formulations F1, F2, and F3, both before and after the stress test, are presented in Table 5. Following the stress period, several impurities were observed in all three formulations. However, the results for drug content and impurities remained within the acceptance criteria. Formulation F2, with an increased amount of hypromellose compared to F1, demonstrated a qualitative and quantitative reduction in impurity appearance after the stress period. Furthermore, the higher quantities of both hypromellose and sodium phosphate in formulation F3 yielded improved results, revealing a reduction in the number and quantity of impurities when compared to F1 and F2.

Morphology and size

As depicted in the micrographs shown in Figure 4, the pellets exhibited a spherical shape, and the surface appeared relatively smooth. The cross-section of the pellets allowed for the observation of distinct layers within the internal structure. Notably, the appearance of the pellets remained unaltered even after the stress period, indicating robust stability of the formulations. The formulations maintained a consistent and uniform size, with pellet dimensions ranging between 1.2 and 1.4 mm.

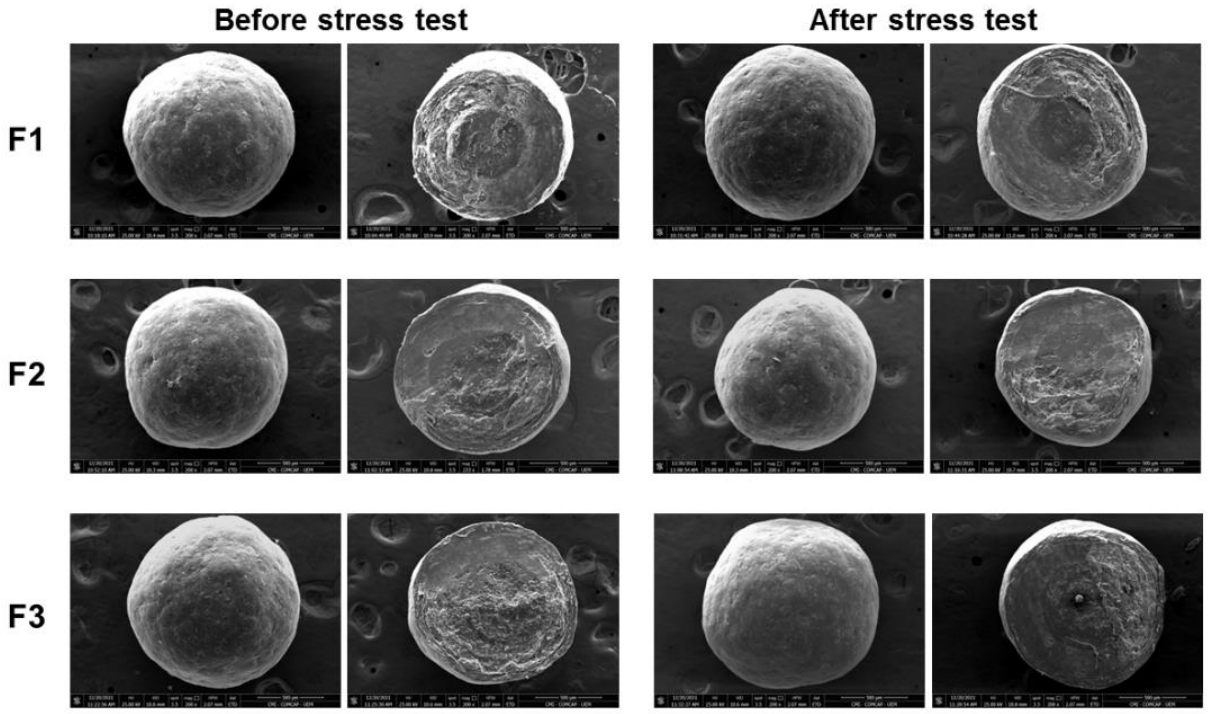

Figure 4. Morphology analysis (MEV) of F1, F2 and F3 (omeprazole formulations).

Table 5. Nonspecific and total content and impurities in the three different formulations (F1, F2 and F3) of omeprazole pellets, before and after the 28-day stress test.

Sample	Omeprazole content (%, w/w)		Nonspecific impurities (%, w/w)				Total impurities (%, w/w)	
	Before stress	After stress	Peak 1*	Peak 2*	Peak 3*	Peak 4*	Before stress	After stress
F1	96.73±0.84	97.91±1.63	0.40±0.02	0.27±0.02	0.32±0.02	0.12±0.01	0.00±0.00	1.06±0.05
F2	98.23 ±0.25	99.43±1.44	0.29±0.02	0.28±0.02	0.16±0.05	-	0.00±0.00	0.78±0.05
F3	101.46±1.48	105.71±1.92	0.18±0.01	0.13±0.01	-	-	0.00±0.00	0.30±0.01

*Peak 1: RT= 4.6 min; peak 2: RT:=5.2 min; peak 3, RT=9.8 min; peak 4: RT=10.2 min.

In vitro drug release profile

The drug release profiles for formulations F1, F2, and F3 are illustrated in Figure 5. A rapid release was observed across all formulations, with more than 70% of omeprazole released within the first 10 minutes. Formulations F2 and F3 exhibited a higher omeprazole release up to 20 minutes compared to formulation F1. Furthermore, both formulations F2 and F3 achieved a release exceeding 90%, while formulation F1 demonstrated a maximum release of 87% at 30 minutes. This disparity is likely attributed to the increased amount of hypromellose in the second layer of formulations F2 and F3.

Hypromellose, as a hydrophilic excipient with dispersing, emulsifying, and dissolution-enhancing properties [39], plays a crucial role in these formulations. Given that the functional layer composed of Eudragit® is semi-permeable, the presence of the second layer of hypromellose serves to protect omeprazole from degradation as small amounts of gastric fluids begin to enter the pellets. This is vital for maintaining the structure of the pellet and ensuring the stability of omeprazole in solution. Notably, formulation F3 contains a higher quantity of sodium phosphate than F2, potentially offering additional protection for the drug during dissolution in an acidic medium. Consequently, there is a clear imperative to devise a sealant coating for enteric-coated granules to govern the system and enhance the stability of omeprazole preparations.

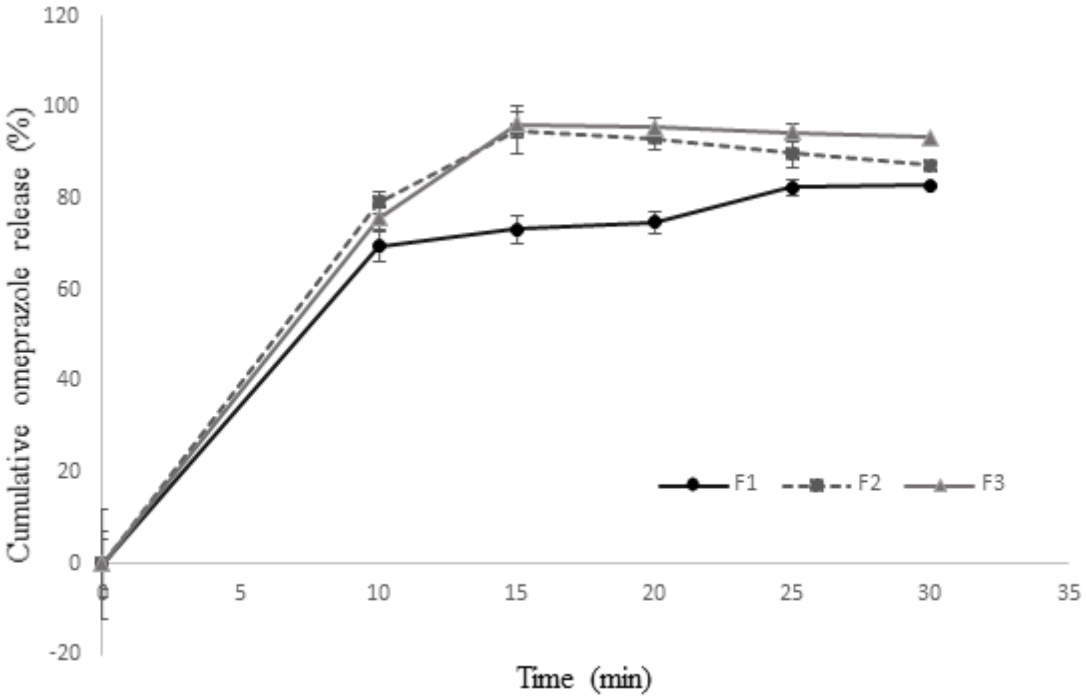

Figure 5. In vitro release drug profile of F1, F2 and F3 (omeprazole formulations).

Raman microscopy

In Figure 6 (A, E, and I), the Raman spectra of the raw materials utilized in the preparation of the pellets (formulations F1, F2 and F3) are presented. Specific Raman bands for each raw material were carefully chosen to enable their identification within the pellet. The selected bands were as follows: from 865 to 810 cm^{-1} for inert pellets; from 1290 to 1260 cm^{-1} for omeprazole; and from 590 to 533 cm^{-1} for Eudragit®. Subsequently, the Raman band areas were calculated by integration, highlighted in the spectra. The spatial distribution of each raw material in the formulations F1, F2 and F3 was determined by means of Raman bands areas maps, using the OPUS® software. The presence of the raw materials might be identified by the color intensity bars on the side of the maps: pink higher intensity and blue lower intensity. In all formulations is noted the inert material in the central region (Figures 6B, C and D), omeprazole in the intermediate layer (Figures 6F, G and H), and Eudragit® in the external layer (Figures 6J, K and L). The diameter of the central region (i.e., the inert material) is approximately 750 µm, and the omeprazole layer width is about 223 µm.

Unfortunately, the hypromellose layer could not be identified using this analysis. The hypothesis is that cutting the pellet may have removed the layer [27, 29]. Despite not being visible in the image due to the limitations of the technique, the use of hypromellose was instrumental in maintaining the stability of the pellet.

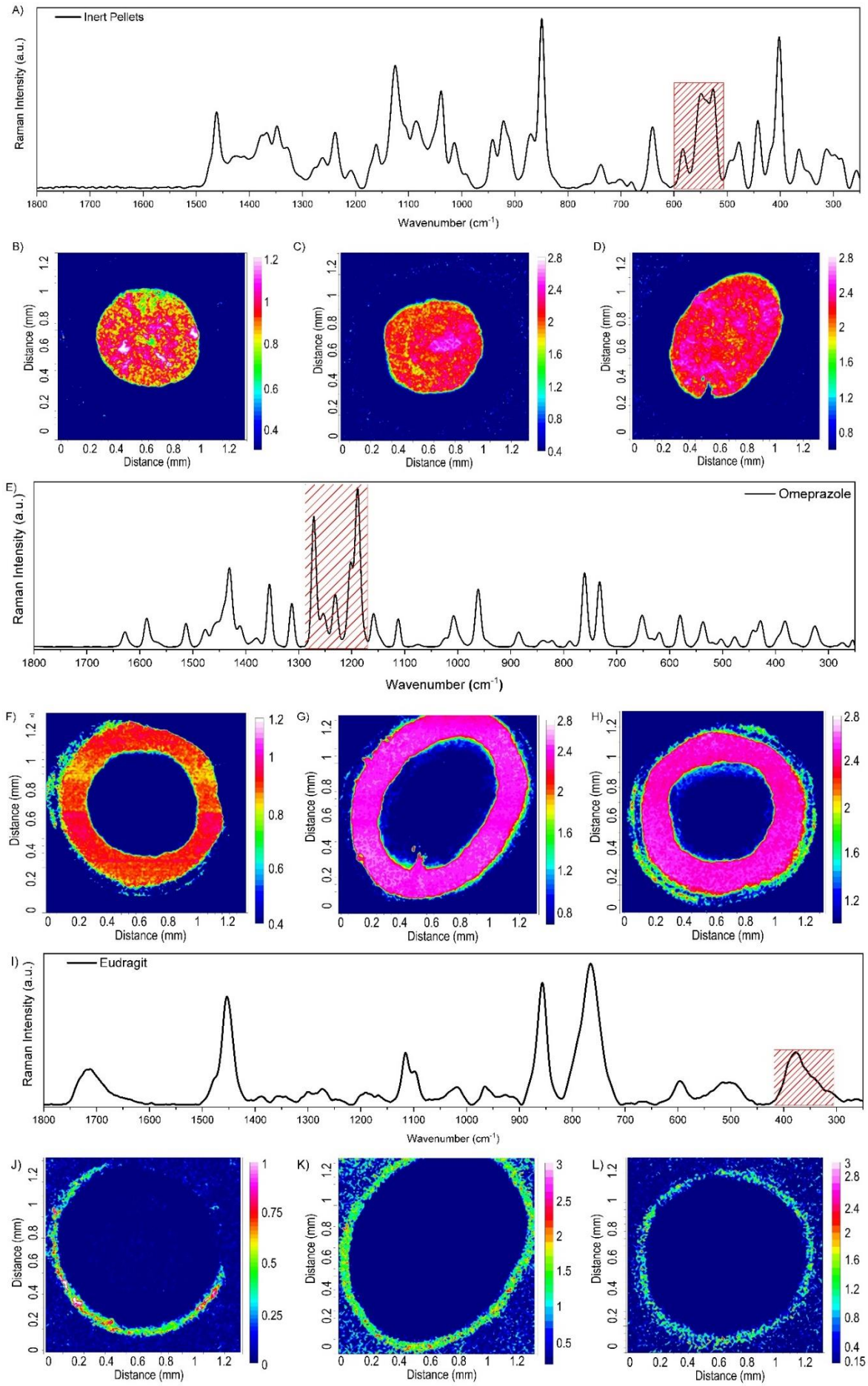

Figure 6. Raman spectra of raw materials: A) inert pellet, B) omeoprazole and I) Eudragit. Omeoprazole formulations Raman maps: B), F) and J) F1; C), G) and K) F2; D), H) and L) F3.

Omeprazole exhibited compatibility with the studied excipients, namely, inert pellets, sodium phosphate dibasic dihydrate, mannitol, polysorbate 80, and hypromellose. This compatibility enabled the formulation of three pellet formulations. The augmentation of hypromellose content in the intermediate layer led to improved drug stability, as evidenced by the reduced formation of impurities. Additionally, the impact of sodium phosphate on the stability of omeprazole in the formulation was evident. Both excipients proved to be beneficial for drug protection and the optimization of the drug delivery system.

CONCLUSION

The technological approach employed for omeprazole pellet preparation holds potential for enhancing the stability of other unstable drugs and ensuring the quality of the final product, particularly in pellet formulations. These findings underscore the importance of developing effective sealing coatings for enteric-coated pellets. Additionally, they highlight key technical considerations for controlling the stability of omeprazole preparations.

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