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Industrial Manufacture of Enteric Hard Capsules Using Novel Formulations Based on Hypromellose Phthalate/Gelatin and Investigation of Pantoprazole Release

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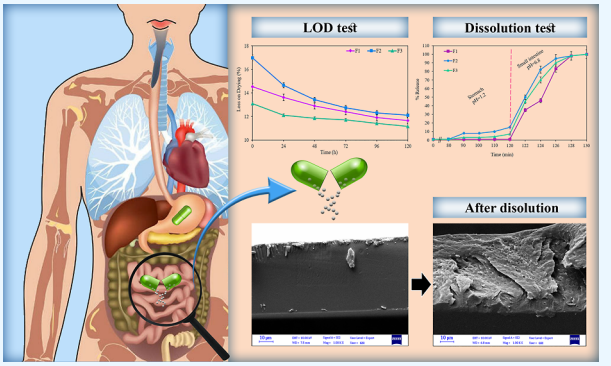
ABSTRACT: Capsules are popular oral dosage forms because of their ease of production. They are widespread pharmaceutical products. Hard capsules are preferred dosage forms for new medicines undergoing clinical tests because they do not require expansive formulation development. Functional capsules with built-in gastro-resistance, aside from the traditional hard-gelatin or cellulose-based vegetarian capsules, would be beneficial. In this research, the effect of polyethylene glycol-4000 (PEG-4000) was investigated on the formulation of uncoated enteric hard capsules based on hypromellose phthalate (HPMCPh) and gelatin. Three different formulations based on HPMCPh, gelatin, and PEG-4000 were tested to achieve the optimal formulation for the industrial production of hard enteric capsules with desired physicochemical and enteric properties. The results reveal that the capsules containing HPMCPh, gelatin, and PEG-4000 (F1) are stable in the stomach environment (pH = 1.2) for 120 min, and during this time, no release happens. The outcomes also demonstrate that PEG-4000 blocks the pores and improves enteric hard capsule formulation. In this research, we present a specific procedure for manufacturing uncoated enteric hard capsules on an industrial scale that does not require an extra coating step for the first time. The industrial-scale validated process can considerably reduce the cost of manufacturing standard enteric-coated dosage forms.



1. INTRODUCTION

One of the most popular solid dosage shapes used for oral administration of active substances is the capsule. The global market for empty capsules was estimated to be worth US$1.4 billion in 2016 and is anticipated to expand at a 7.3% annual rate through 2026.[1] Compared to tablets, which require quality control, take longer to produce, and demand more formulation development, capsules are very straightforward to apply. Additionally, capsules offer a more practical method of delivering nutraceuticals (typically powders) without the requirement for elaborate formulations. Additionally, capsules are frequently used for medications undergoing animal or clinical testing because of their simplicity and quick turnaround in the formulation during the early steps of medication research. Based on the primary aim and scope, hard capsules can be manufactured in various sizes and ingredients. Different types of gelatins (type B and type A) are still utilized to produce the large majority of capsules, although various materials are employed.[2] Further materials were designed to answer the request for non-animal-based capsules that would serve a rising requirement for halal and vegan/vegetarian markets.[3] The most popular substitutes for gelatin are HPMC, pullulan, and starch-based capsules.[4] However, even these materials have drawbacks when used in enteric formulations because none of them exhibit pH-responsive properties.

However, coating tablets with gastroresistant polymers is the most traditional and typical procedure when a gastroresistant formulation is required. The industrial practice of coating gelatin capsules is uncommon,[5] and a more general method is to insert enteric-coated pellets or granules into a traditional hard gelatin capsule. Additionally, this method increases the secondary cost of coating, lengthens the process, and results in deformed capsules in most cases. Consequently, the purportedly less difficult solid dosage form becomes increasingly complicated. Thus, if gastroresistant capsule shells can be fabricated, they can be manufactured in large quantities

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Table 1. Different Formulations of Uncoated Enteric Hard Capsules

	materials (g)							
formulation	HPMCph	gelatin	Na_3PO_4	PEG-4000	SiO_2	SLS	NaOH (0.2 N)	viscosity (cp)
F1	60	40	10	20	10	0.14	340	660
F2	60	40	10		10	0.14	340	600
F3	60		10	20	10	0.14	340	400

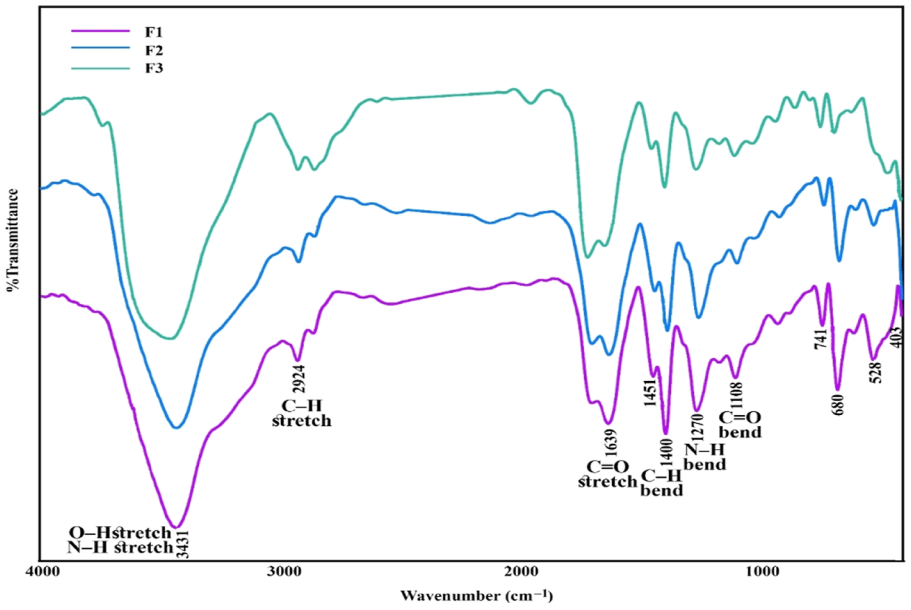

Figure 1. FTIR spectra of F1, F2, and F3 enteric capsules.

utilizing a high-speed capsule filler similar to conventional capsules. The ability to encapsulate nearly any nutraceutical or drug in empty shells for preclinical and clinical assessment without comprehensive formulation evolution will have broad applications in gastrointestinal targeting and drug release control, potentially lowering research and development expenses.

Enteric polymers possess properties that vary depending on the pH of their environment due to the presence of acidic functional groups attached to hydrophobic polymer chains.[6] This has been successfully utilized in the past for reducing gastric mucosal injury from nonsteroidal anti-inflammatory drugs and preventing proton pump inhibitor deactivation in stomach acid.[6,7] Additionally, enteric polymers have been used to create pH-responsive carriers for oral solid dosage forms, allowing for greater control over the drug release that can irritate the gastrointestinal tract. Hydroxypropyl methylcellulose phthalate (HPMCPh) is a pH-sensitive polymer that can be used to produce enteric capsules that are resistant to gastric acid and only dissolve in the alkaline environment of the small intestine. This ensures that the active ingredients in the capsule are released at the desired location, thus improving drug delivery and bioavailability.[8] HPMCPh is a nontoxic, biocompatible, and biodegradable polymer, making it safe for use in pharmaceutical formulations. HPMCPh has excellent film-forming properties and can be used to produce thin films with good mechanical strength and flexibility. This makes it suitable for producing capsules with a uniform size and shape. HPMCPh is relatively inexpensive compared to other polymers used for enteric capsule production, making it an economical choice for pharmaceutical companies.[9]

There have been previous reports to make enteric hard capsules, but these depend on a further coating stage or the addition of a gum that would shield acid-sensitive contents by an extended-release mechanism, like DRCaps.[10] These formulations rely on a temporal delay in expectation of timely emptying from the stomach rather than exhibiting a pH-triggered release. Since gastric emptying is actually very unforeseeable,[11] these products are more susceptible to both intra- and intersubject variability in stomach emptying,[12] which has a substantial impact on their potential to be gastroresistant. BioCaps and Capsugel recently created cellulose-based drug delivery technologies (Bio-VXR and enTRinsic, respectively). They declared to offer complete enteric protection without the demand for coatings. However, the whole composition is not announced, and there is also very little proof of clinical efficacy.

In this study, we desired to design enteric hard capsule shells utilizing the most generally employed polymers, including HPMCPh in the pharmaceutical industry, for developing enteric dosage forms. The effect of gelatin and polyethylene glycol-4000 (PEG-4000) was studied on hard enteric capsules by the dissolution test.

2. MATERIALS AND METHODS

2.1. Materials. All raw ingredients from reliable companies were applied as acquired, without additional purification. Hydroxypropyl methylcellulose phthalate HP55 (HPMCPh) was purchased from LOTTE Fine Chemical, South Korea; gelatin type B was acquired from Rousselot (France); Sodium lauryl sulfate (SLS) was acquired from Godrej Industry (India); PEG-4000, trisodium phosphate ($Na_3PO_4{\cdot}12H_2O$), sodium hydroxide (NaOH), and hydrochloric acid 35% (HCl)

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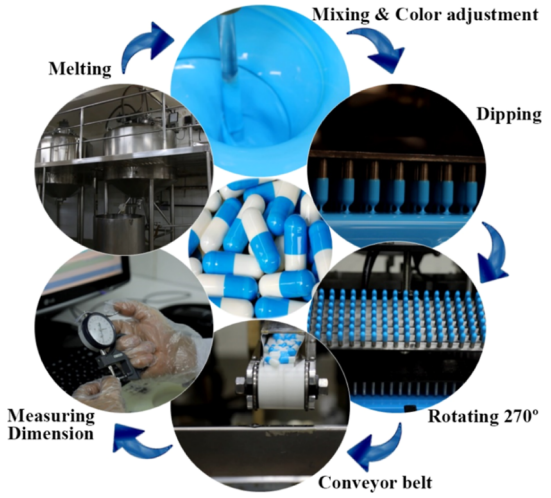
Scheme 1. Schematic Diagram of the Manufacturing Process for the Production of Enteric Hard Capsules without Coating



were purchased from Merck; Colloidal Nano silicon dioxide (SiO_2) was obtained from Evonik (Germany); Propylene glycol (PG) was acquired from Kimyagaran Emrooz Chemical Industries Co. (Iran); propyl paraben and methylparaben were purchased from UENO Fine Chemical Industry (Japan); and zinc sulfate heptahydrate ($ZnSO_4 \cdot 7H_2O$) were purchased from Behansar (Iran). Pantoprazole sodium sesquihydrate was acquired from Sigma-Aldrich.

2.2. Production Procedure. *2.2.1. Fabrication of Enteric Capsules on a Laboratory Scale.* First, the three formulations in Table 1 were prepared on a laboratory scale to ensure that the final formulation was suitable for industrial production. In a typical process, 60 g of HPMCPh was dissolved in 340 mL of NaOH (0.2 N). 10 g of Na_3PO_4 was added to the solution to help dissolve HPMCPh more easily. Then, 40 g of gelatin was added to the above solution under vigorous stirring. Next, 20 g of PEG-4000 was mixed to obtain a homogenous solution. Moreover, 10 of g colloidal SiO_2 and 0.14 g of SLS were combined and blended for 30 min. The final solution was rested in a bain-marie at 55 °C for 5 h. The viscosity of the solution was measured at 660 cp. The solution was transferred into a steel dish with dimensions of 10 × 5 × 7 cm^3. The dipping process was started. The solution begins to form a thin enteric coating or film on the pin bars. The pin bars are indicated in Figure 4b,d,f. After complete drying, the capsules were stripped off the pin and cut to the suitable size. After cutting, the two halves (body and cap) were joined in the prelocked position (Figure 1).

2.2.2. Production Process of Uncoated Enteric Solution on an Industrial Scale. A 160 L feed tank was filled with 85 L of NaOH (0.2 N) to manufacture the uncoated enteric hard capsule. The procedure was carried out inside the feed tank, which had a mechanical stirrer with a propeller blade. At 60 °C, 15 kg of HPMCPh and 2500 g of Na_3PO_4 were added to the feed tank. 5 kg of PEG-4000 was added to the feed tank when HPMCPh had completely dissolved. The feed tank was then filled with 10 kg of gelatin and other additives. After the gelatin had completely melted, the following ingredients were added: 2500 g of SiO_2, 35 g of SLS, 130 g of propylparaben, 20 g of methylparaben, 50 g of PG, and 75 g of $ZnSO_4$. The feed tank was rested at 55 °C for 5 h. The viscosity of the solution was measured at 660 cp. After preparation of enteric solution, the dipping process of enteric solution was started on the metal

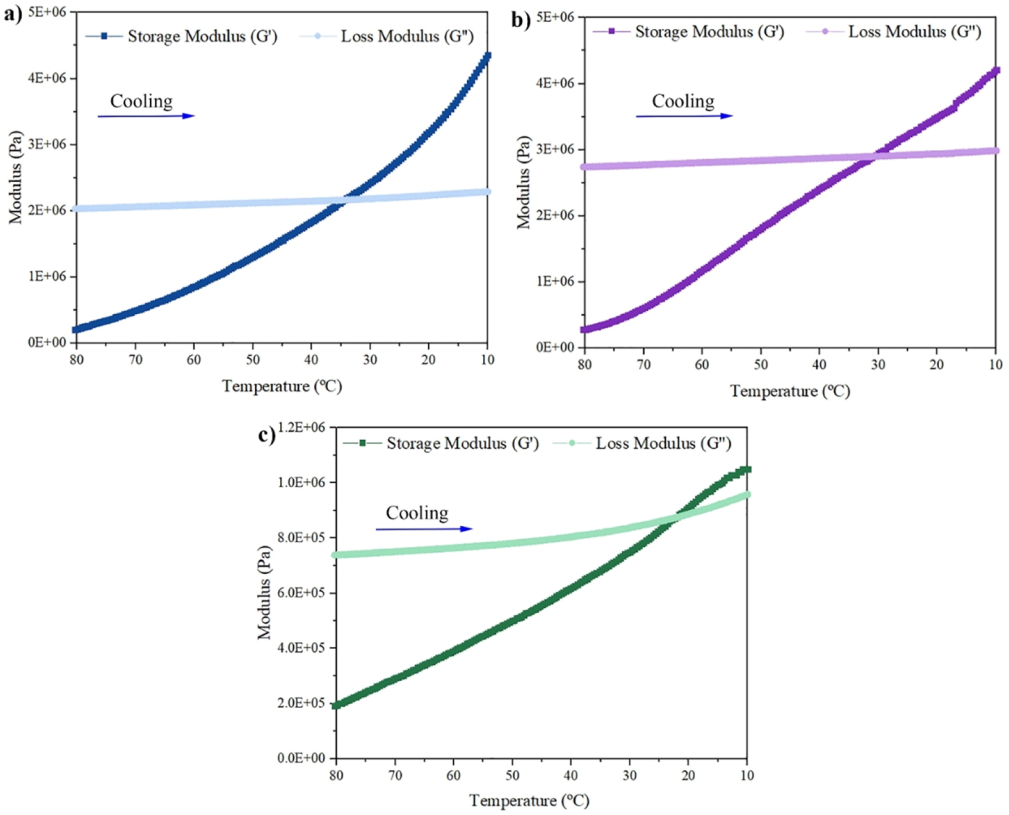


Figure 2. Temperature sweeps of (a) F1, (b) F2, and (c) F3 enteric capsules from 80 to 10 °C.

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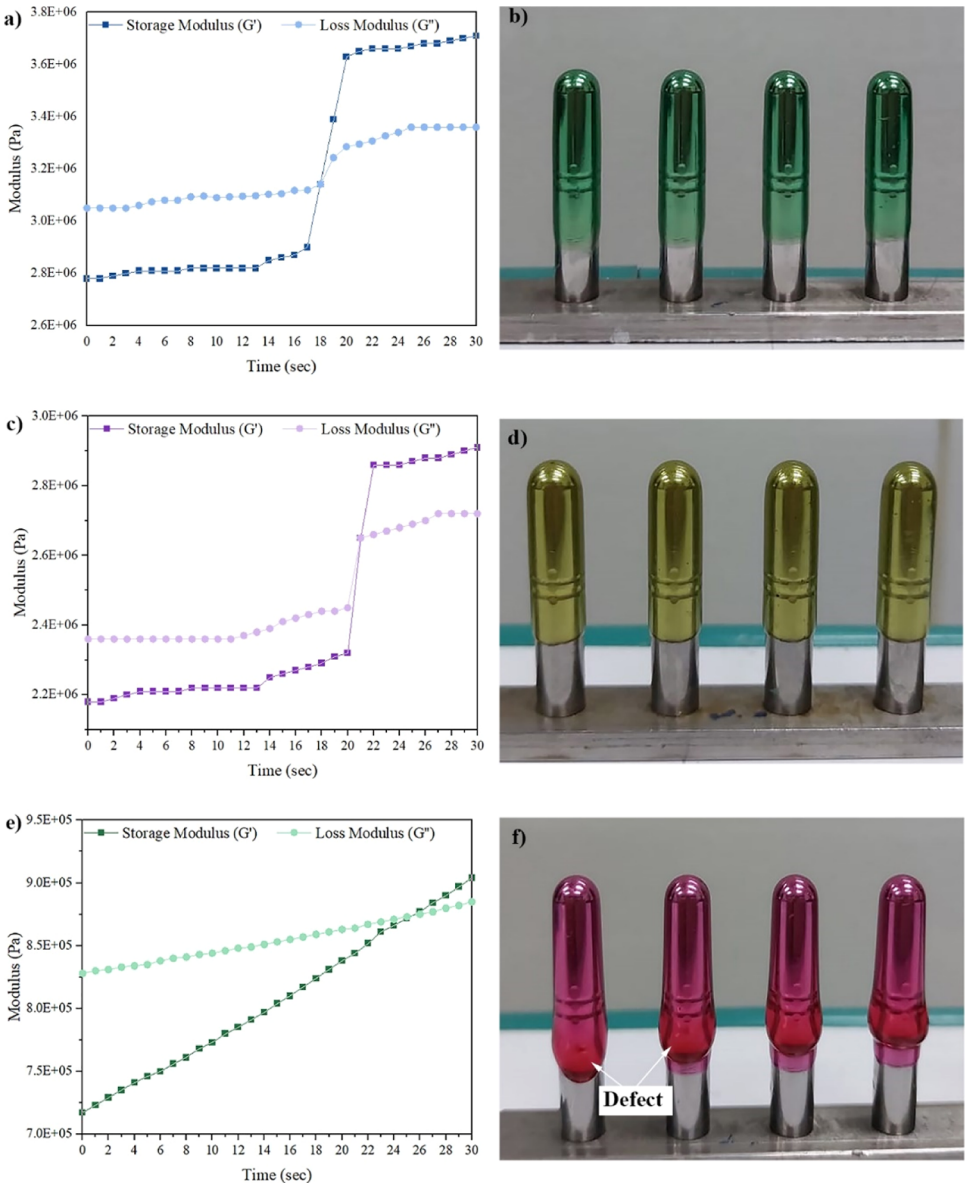

Figure 3. Time sweeps and photograph of the uncoated enteric layer on the pin bars for the different formulations: (a,b) F1, (c,d) F2, and (e,f) F3.

Table 2. Physical Parameters of Produced Uncoated Enteric Capsules (F1) under Stable Conditions

items	cap	body
length (mm)	10.99 ± 0.17	18.94 ± 0.21
wall (μm)	95.77 ± 1.35	91.77 ± 2.76
dome (μm)	163.67 ± 5.36	155.8 ± 6.25
shoulder (μm)	85.77 ± 1.75	86.47 ± 1.52

pins. Under stringent climatic conditions, capsule shells are made by dipping pairs (body and cap) of standardized steel pins arranged in rows on metal bars into the aqueous enteric solution kept at around 45 °C in a jacketed heating dish. Since the pin bars are cooler than the gelation temperature, the solution starts to build a thin enteric layer or film on them. The pin bars are placed in such a way that bodies are formed on one side of the machine, while caps are formed on the opposite side. After molding the solution on the surface of the pins, the pin bars were taken out of the dish and rotated 270° to distribute the solution evenly around the pins. The accurate enteric distribution is essential for a uniform capsule's wall thickness and dome strength. Cool air was applied to set the material on the pin. At this stage, the material was dried, and then the pins moved through several stages of drying to reach the preferred moisture content. After the capsules were dried, they were stripped off the pin and cut to the appropriate size. After cutting, the two halves (body and cap) were joined in the prelocked position (Scheme 1).

2.3. Rheological Measurement. Rheological characteristics, in terms of modulus (G') and loss modulus (G''), were examined using an oscillatory time sweep test at 0.4% amplitude and frequency of 1 Hz for 15 min using a rheometer (Physica MCR 300, Anton Paar Ltd., Austria). The measurement was taken at different temperature for different formulation, including 34 °C for F1, 31 °C for F2, and 22 °C for F3. These characteristics were shown as a time function to calculate the gelling time.[13] The contribution of loss modulus (G'') (liquid form) and storage modulus (G') (gel form) was monitored by a temperature sweep in the range of 80−10 °C at a speed of −2 °C/min.[14]

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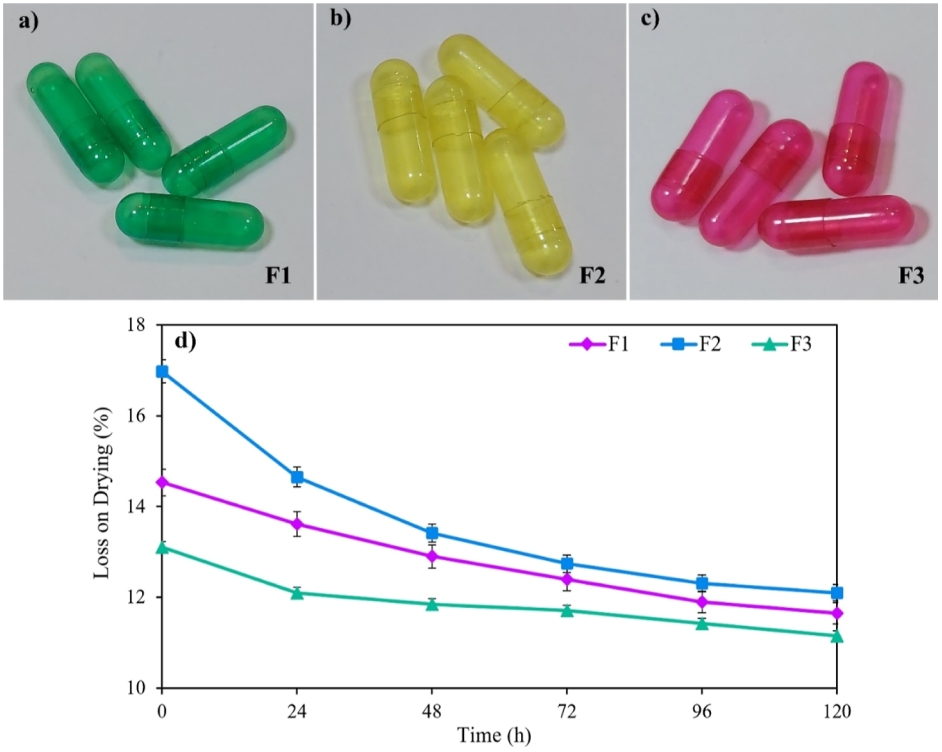

Figure 4. As-prepared enteric hard capsules produced by different formulation, as indicated in Table 1, in a laboratory scale: (a) F1, (b) F2, and (c) F3 capsules; (d) loss on drying (%) of F1, F2, and F3 capsules in different intervals (n = 3).

2.4. Study of Drug Release. The USP dissolution test apparatus ⟨711⟩ was used to study the release of pantoprazole from uncoated enteric capsule formulations, and the study was done in triplicate for all samples. The capsules containing 10 mg of pantoprazole were utilized in each release test by applying the paddle method. The rotational paddle speed was kept constant at 100 rpm, while the medium temperature (900 mL) was kept constant at 37.0 ± 0.5 °C. The drug release was investigated in 900 mL of 0.1 N HCl (pH = 1.2) as a simulated gastric medium for 120 min, followed by the study in phosphate buffer (pH = 6.8) as a simulated intestinal medium for 10 min at 37.0 ± 0.5 °C. HCl (0.1 N) and buffer (pH = 6.8) were prepared based on the USP. 8 mL of the sample was removed from the gastric and intestinal media at certain intervals. After sampling, fresh medium was returned in the vessel.[15] A 0.45 μm nylon filter was used to filter the samples, and the drug released quantity was scrutinized by a UV−visible spectrophotometer (Shimadzu UV-1800) at λ_{max} = 289 nm.[16]

2.4.1. Pantoprazole Calibration. 10 mg of pantoprazole was dissolved in 100 mL of 0.1 N HCl (pH = 1.2) and phosphate buffer (pH = 6.8) to prepare a stock solution of pantoprazole.[17] Appropriate dilutions were made by same solvent in the range of 5−30 μg/mL from the stock solution.[18] Pantoprazole was calibrated in HCl (0.1 N) and phosphate buffer utilizing a UV spectrophotometer (Shimadzu UV-1800) with various dilutions at λ_{max} = 289 nm.

2.5. Physical Instruments. The instruments operated in this study contained a mechanical stirrer with a propeller blade, a manufacturing machine (size 0, HGCM, 03-06 380 V, 50 Hz, SCR 10KA, 200Amps, Technophar, Canada), a homemade feed tank (160 L), quality control gauges (VSX136, Mitutoyo, Japan), a Brookfield Viscosel (VTE model, USA), a hygrometer (MA35M-230N, Sartorius Lab Instrument, Germany), a sorting machine (CI5S, Suzhou Sunny Pharmaceutical Machinery Co. Ltd.), and a fan dryer (GB-121-3, Greenheck Technophar, Canada). A Shimadzu Varian 4300 spectrometer recorded the materials' Fourier transform infrared (FT-IR) spectra between 400 and 4000 cm^{-1} in KBr pellets. The cross-section and surface morphology of capsules were analyzed by field emission scanning electron microscopy (FESEM) (ZEISS GeminiSEM 560). Thermogravimetric analysis and differential thermal analysis (DTA) were used to study the thermal behavior of capsules by TG-DTA (STA 503, BAHR, Germany), and differential scanning calorimetry (DSC) was conducted by DSC 404 F3 Pegasus—NETZSCH (Germany).

3. RESULTS AND DISCUSSION

3.1. Laboratory Scale. *3.1.1. FTIR Data.* FTIR spectra of three different formulations of enteric capsules are illustrated in Figure 1. As observed in these spectra, a sharp absorption peak at 3431 cm^{-1} is allocated to O−H and N−H stretching vibration mode belonging to HPMCPh and gelatin, respectively.[19] The peak at 3431 cm^{-1} is also related to PEG-4000 due to the primary alcohol.[20] The characteristic peaks at 1639 and 1108 cm^{-1} are attributed to the stretching and bending modes of C═O.[21] The bending vibration of N−H belonging to gelatin is located at 1270 cm^{-1}.[22] The bands around 2924 and 1400 cm^{-1} are due to the stretching and bending modes of C−H. As can be seen, the FTIR spectra of the three formulations are similar, and the presence or absence of gelatin or PEG−4000 did not change the spectrum due to the same functional groups.

3.1.2. Rheology Results. The rheological properties of as-produced hard uncoated enteric capsules with different formulations were assessed by evaluating the storage modulus (G') and loss modulus (G''), which represent the elasticity and viscosity of capsules, respectively.[23] The enteric solutions

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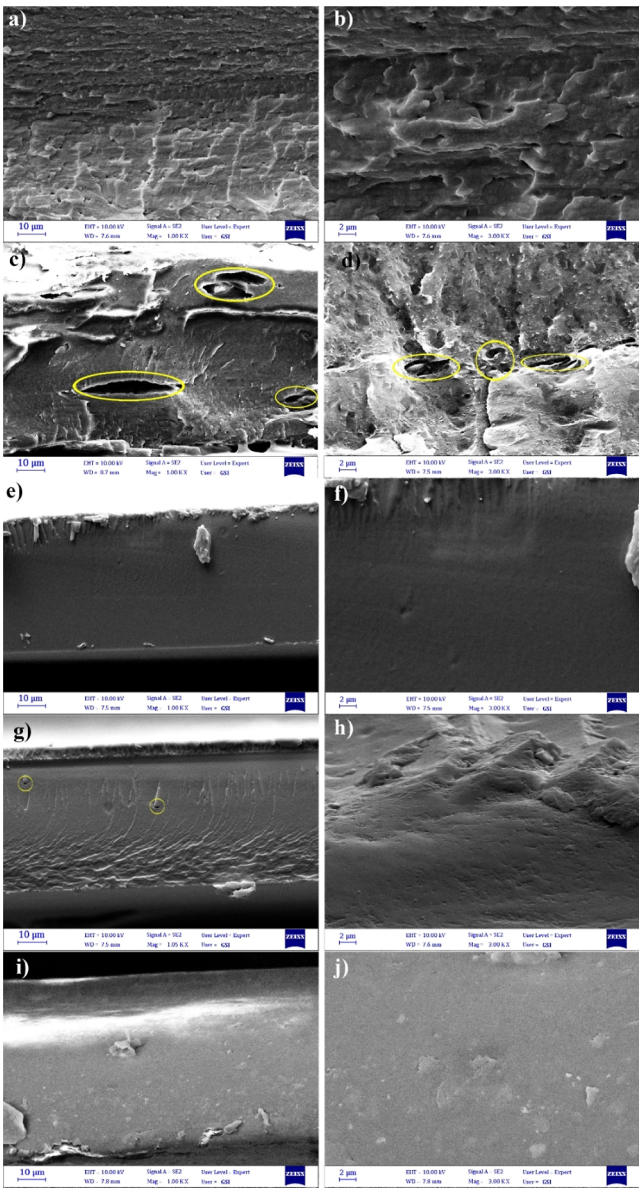

Figure 5. Cross-sectional and surface images of (a,b) pure HPMCPh, (c,d) pure gelatin, (e,f) F1 capsule, (g,h) F2 capsule, and (i,j) F3 capsule.

behave more like liquids, with a low G'. While the gelation is taking place, the G' will increase. The temperature at which the capsule changes from a liquid to a gel is known as the gelation temperature because it is the point at which G'' equals G'.[24] G'' and G' as a function of temperature followed the viscoelastic behavior of the uncoated enteric capsules (Figure 2). The temperature was reduced (cooling) from 80 to 10 °C at a rate of −2 °C/min. There appears to be a gelation temperature where G' equals G'' for all of the capsules examined. The gelation temperature implies the capsules' thermosensitivity. G' is less than G'' when the temperature is higher than the gelation temperature. Near this temperature, particularly at the gelation temperature, G' rises sharply. Figure 2a shows that the temperature at which gelation occurs is 34 °C for F1. In addition, the gelation of F2 and F3 occurs at 31 and 22 °C, respectively (Figure 2b,c). The results imply that F1 is more suitable for the production of capsules, since reducing the temperature of the solution (dish temperature) to less than 32 °C is not possible in the production process.

The setting time is one of the essential properties of hard capsules to prevent them from defecting. The time sweep of the different formulations was conducted to study the gelation procedure at 34 °C for F1, 31 °C for F2, and 22 °C for F3, as shown in Figure 3a,c,e, respectively. When gelation begins, the G' is smaller than the G'', implying a liquid behavior and the predominating viscous features. G' advances more quickly than G'' by lengthening the time. It signifies that the solution has shifted into an elastic jelly phase. The gelation times of F1, F2, and F3 are 18 s, 21 s, and 25 s, respectively, which is adequate for working in capsule production lines. A long gelation time will worsen the capsule defect and result in a capsule with an improper wall, dome, and shoulder that is outside of the specified range. As a result, the ideal gelation time for industrial capsule production is less than 20 s.

3.1.3. Physical Properties of Hard Capsules. Three different formulations were tested to attain the desired gastroresistant capsules. Table 1 outlines the formulations that produced a capsule with a suitable wall, dome, smoothness, shoulder, and gastroresistance. Defective capsules produced without gelatin as a gelling agent (F3) were damaged when taken out of the pins. F3 capsules had a weak and thin wall, dome, and shoulder. The capsules were cut to "0" size length,[25] and quality control gauges were used to measure their wall, dome, shoulder, and length (Table 2). Figure 4a−c display the capsules that were produced on a laboratory scale.

3.1.4. Humidity of As-manufactured Uncoated Enteric Capsules. Loss on drying is one of the most important physical parameters in uncoated enteric capsules. The moisture content of the capsules must be sufficient and appropriate. It should not be so low that it becomes brittle, nor should it be so high that the active pharmaceutical ingredient (API) adheres to the capsule's wall.[26] Figure 4d shows that the presence of gelatin in the formulations causes the initial moisture of the capsules to be higher at the moment of production and that the rate of moisture loss is also higher. The graphs have a steep slope from 0 to 24 h. The presence of PEG-4000 as a filler reduces the moisture content of the capsules. After 48 h, the rate of moisture loss in enteric capsules is almost constant without significant changes. Empty gelatin capsules have a moisture content of 13 to 16%. As mentioned above, if the moisture content goes below this level, they will become brittle, and if it rises over it, they will soften. The moisture content of empty HPMC capsules ranges from 6 to 7%. This variability, regardless of the material used, can lead to some degree of impaired capsule strength and overall quality; thus, it must be considered from the start of production. Among the prepared capsules (F1, F2, and F3), F1 capsules, which have been selected as an acceptable formulation for industrial production, are approved in terms of moisture content. Therefore, the moisture content of F1 is the most suitable that that two other formulations.

3.1.5. Morphology Study. SEM images of the surface and cross sections of pure HPMCPh, pure gelatin, F1, F2, and F3 samples were taken to examine the morphology and porosity of the prepared capsules (Figure 5). As shown in Figure 5, pure HPMCPh capsules have a relatively uniform surface, and no porosity can be observed on that surface or its cross-section (Figure 5a,b). On the other hand, pure gelatin capsules have a completely rough surface, where relatively large holes can be seen in their cross-section (Figure 5c,d). Adding gelatin to the

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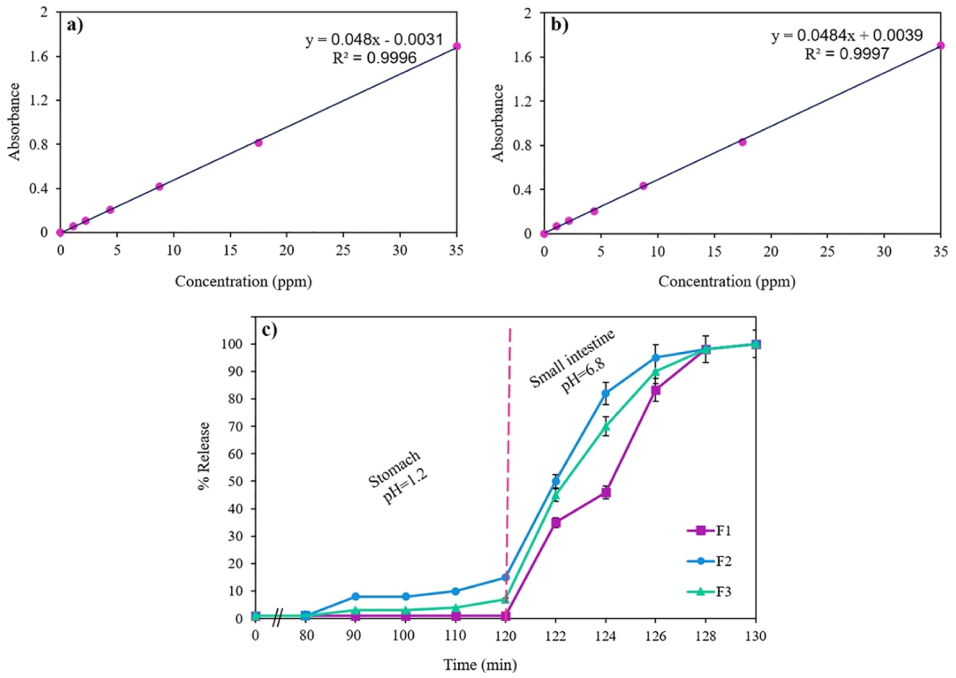

Figure 6. Pantoprazole calibration in (a) HCl 0.1 N (pH = 1.2), (b) phosphate buffer (pH = 6.8), and (c) pantoprazole release diagram.

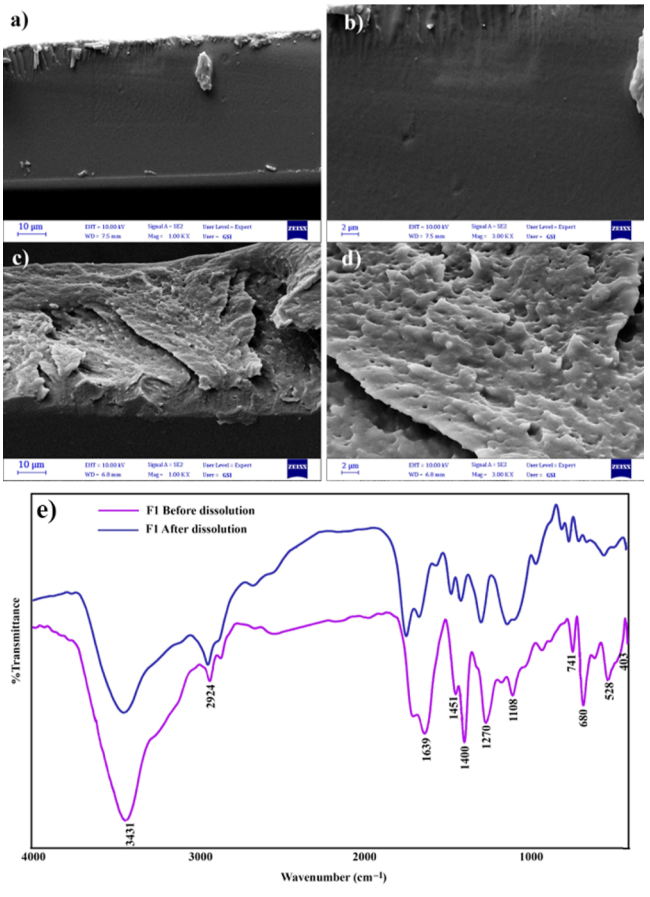

Figure 7. FESEM images of the cross-section and surface of F1 capsules (a,b) before dissolution and (c,d) after dissolution, and (e) FTIR spectra of F1 capsules before and after dissolution.

formulation can cause porosity in the capsules, which can jeopardize the stability of the capsules in the stomach and drug release. On the other hand, the presence of gelatin is necessary to create gelation. The porosity brought on by the presence of gelatin in the F1 capsule formulation has been eliminated by adding PEG-4000 as a filler, making the capsule stable in the stomach environment (Figure 5e,f). The presence of gelatin without PEG-4000 caused some small holes in the surface and cross-section of F2 capsules (Figure 5g,h), resulting in drug release in the stomach. The lack of gelatin and the presence of PEG-4000 have resulted in a completely uniform surface and cross-section with no porosity (Figure 5i,j). Therefore, the best morphology in terms of smoother surface and cross section belongs to the F1 capsule.

3.1.6. Dissolution Tests. The calibration of pantoprazole in HCl (0.1 N) and phosphate buffer is depicted in Figure 6a,b, respectively. As shown in the figure, the linear R^2 values for HCl (pH = 1.2) and phosphate buffer (pH = 6.8) are 0.9996 and 0.9997, respectively. The uncoated enteric capsules were placed in the dissolution apparatus to test the stability of the prepared capsules (Figure 6c).[27] The findings revealed that F2 capsules containing gelatin and HPMCPh began to release within 80 min, owing to the porosity in the capsule caused by the presence of gelatin (Figure 6g,h). F2 capsules had about 15% release during 120 min of being in the stomach environment, which is unacceptable according to the definition of enteric capsules. F3 capsules were also stable in the stomach medium for only 90 min before the release began, with approximately 7% of pantoprazole released within 120 min. Due to the presence of PEG-4000 and the blocking of pores, F1 capsules can be stable in the stomach medium (pH = 1.2) for 120 min. After transferring to the small intestinal medium (pH = 6.8), pantoprazole was gradually released. A complete release occurred within 8 min. In fact, when HPMCPh is exposed to a pH greater than 6, it begins to dissolve, and the drug is released.

3.1.7. Stability of Uncoated Enteric Capsules. Figure 7 depicts the FESEM images of the cross-section and surface of F1 capsules before and after the dissolution test. Before dissolution, the surface and cross-section of F1 are smooth,

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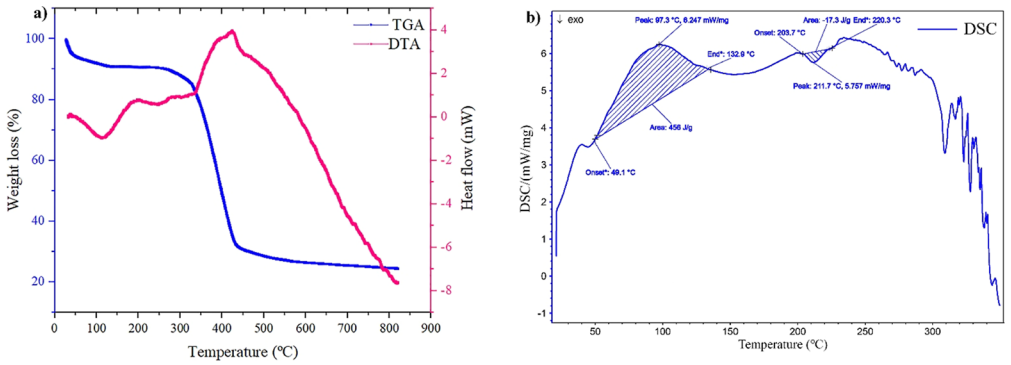

Figure 8. (a) TG-DTA and (b) DSC of F1 capsules.

Table 3. Manufacturing Machine Parameters for Producing Uncoated Enteric Hard Capsules on an Industrial Scale

manufacturing machine parameters		enteric capsules (F1)	
		cap	body
air conditioner pressure (Pa)	Kiln 1	43	19
	Kiln 2	95	113
	Kiln 3	68	112
	Kiln 4	65	70
	Kiln 5	70	65
temperature of kilns (°C)	Kiln 1	22	23
	Kiln 2	26	25.5
	Kiln 3	27	26.5
	Kiln 4	27.3	27.4
	Kiln 5	23	22
temperature of the solution (°C)	45	45	
temperature of the air conditioner (°C)	23		
humidity (%)	30.6		
speed of the machine (pin bar/min)	29		

and no roughness or porosity exist (Figure 7a,b). The FESEM images of F1 capsules after being 120 min in stomach medium are indicated in Figure 7c,d. The surface is rough, and roughness can be seen on the surface and in the cross-section due to being in an acidic environment, but the interesting part is the lack of holes, which proves that the drug does not leak into the stomach environment. Figure 7e shows the FTIR spectra of F1 before and after dissolution in HCl (pH = 1.2). As can be observed, the FTIR spectrum of F1 did not change after exposure to stomach medium, indicating the stability of enteric capsules in acidic media. All absorption peaks mentioned in Section 3.1.1 exist in the FTIR spectrum of F1 after dissolution.

3.1.8. Thermal Analysis. The TG-DTA diagram of F1 capsules is demonstrated in Figure 8a. Dehydration caused the first event in the temperature range of 66 to 130 °C, with a weight loss of 10.0%. The second endothermic event, which is the most important, occurs between 280 and 450 °C, with a weight loss of approximately 65% due to polymer decomposition. The DSC thermogram of F1 capsules analyzed in the range of 10−300 °C is revealed in Figure 8b. The DSC thermogram of F1 shows an exothermic peak at 97 °C due to dehydration.[28] This formulation also depicts an endothermic peak at about 211 °C, corresponding to the melting (T_m) of additives, especially gelatin.[29] The glass transition temperature (T_g) of HPMCPh was recorded at 133 °C.[28]

3.2. Industrial Scale. Several different formulations were tested to achieve an uncoated, hard enteric capsule. In these formulations, many parameters were changed, including the amount of salt, the gelatin content, the type of solvent, the type of pH-sensitive polymer, the presence or absence of PEG-4000, etc. In some formulations, capsules with suitable walls and domes were not produced, or if they were manufactured, they could not be industrialized and produced in capsule production machines. On the other hand, some formulations could be industrialized but did not pass the dissolution test. Therefore, uncoated enteric hard capsules (F1), size 0, were manufactured by adjusting the parameters of the manufacturing machine (Table 3) and the enteric solution. The quality control unit evaluated capsules produced on an industrial scale. The length, shoulder, dome, and wall of the as-produced capsules were measured (Figure 9). These manufactured capsules are found to be in good physical agreement with the specifications of the typical capsule range. The capsule dimension shows that they are produced within the international standard range.

3.2.1. Moisture Content. To pack the hard capsules with appropriate humidity, the humidity is assessed multiple times during the industrial production process. The humidity of uncoated enteric capsules was checked at four different steps, including as-produced, after the fan dryer, after sorting, and after packaging (Figure 10a). The results showed that the produced capsules have an initial moisture content of 14.53% and lose about 1% of their moisture after being placed on a fan dryer. Considering that the sorting process is done immediately after being placed on the fan dryer, the moisture is almost constant at this stage. After the packaging process (12 h after production), the humidity of F1 capsules is 13.62%, which is suitable for enteric capsules and the process of filling capsules with API.

3.2.2. Drug Release. The drug release of industrial enteric capsules (F1) was tested through the dissolution test to confirm that the additives of the formulation, including parabens, zinc sulfate, and PG, do not compromise the drug release. As shown in Figure 10b, the manufactured enteric capsules are stable in stomach medium for 120 min, and the release ratio is 0%. After being in the small intestine medium (pH = 6.8), the pantoprazole is gradually released and totally released within 10 min.

4. CONCLUSIONS

One of the primary objectives of this study was the design and development of the uncoated enteric capsules. Following laboratory analysis and preliminary testing, the research

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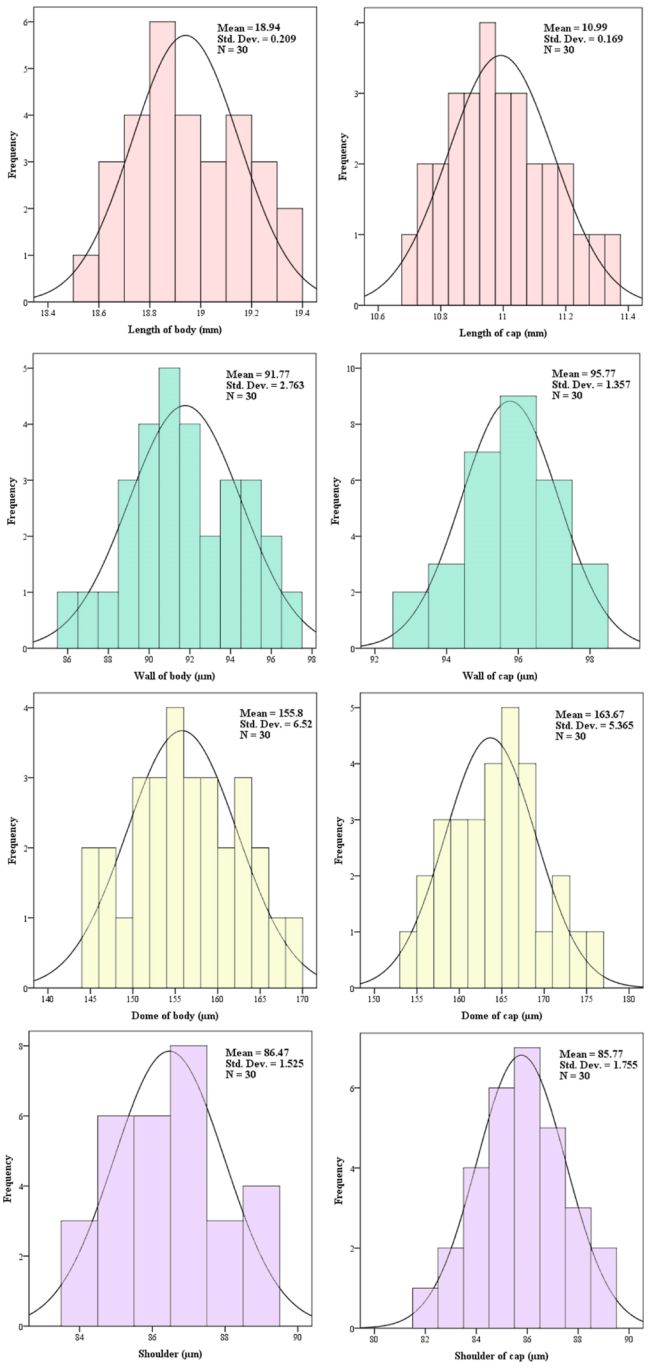

Figure 9. Normal graph distribution of as-produced enteric capsules (size 0).

outcomes have moved into the industrial and production phases. All tests revealed that using PEG-4000 as a filler exhibited the best features in the enteric capsule formulation. The rheology results showed that the gelation temperature and time of the optimum enteric capsule were achieved at 34 °C and 19 s, respectively. The dissolution study revealed that F1 capsules containing HPMCPh, gelatin, and PEG-4000 were stable in the stomach medium (pH = 1.2) for 120 min without releasing any pantoprazole as a drug model. The morphology study of the surface and cross-section of capsules depicted that PEG-4000 blocked the pores and prevented drug release in an acidic environment. This is the first time that uncoated enteric

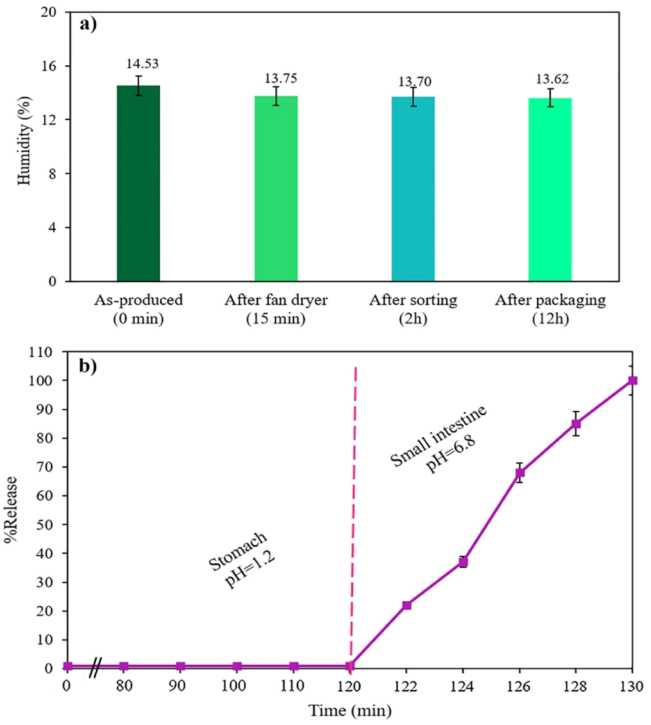

Figure 10. (a) moisture content of manufactured F1 capsules in different steps and (b) dissolution test of manufactured F1 capsules.

hard capsules have been manufactured on an industrial scale without going through a separate coating process.

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Author Contributions

CRediT authorship contribution statement: **Ramin Ramezani Kalmer**: conceptualization, supervision, project administration, and visualization, **Mohsen Mohammadi Haddadan:** investigation, formal analysis, methodology, and software, **Maryam Azizi:** investigation, formal analysis, and writing—review and editing, software. **Mojgan Ghanbari:** writing—review and editing, validation, resources, and data curation. **Atefeh Sadjadinia:** investigation and formal analysis, **Dariush Samandarian**: methodology. **Hamed Ramezanalizadeh:** data curation, validation, and resources. **Afzal Karimi:** data curation and validation. **Mortaza Golizadeh:** methodology.

Notes

The authors declare no competing financial interest.

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