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"DESIGN AND OPTIMIZATION OF GASTROPROTECTIVE BEADS OF PANTOPRAZOLE SODIUM AND IMMEDIATE-RELEASE FRACTIONS OF DOMPERIDONE MALEATE FOR ACID REFLUX"

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ABSTRACT

The study aimed to develop duocap comprising rapidly dissolving granules of domperidone maleate (DM) and enteric-coated pantoprazole sodium (PS) beads. The formulated capsules were intended to achieve the simultaneous administration of both drugs, enabling immediate and delayed drug release for the effective management of acid reflux. Pantoprazole sodium-loaded interpenetrating polymer network (IPN) beads were formulated using aluminium chloride as a cross-linking agent, while domperidone maleate granules were prepared by the dry granulation method using lactose and microcrystalline cellulose as excipients. The duocap system consisted of a gelatin capsule shell treated with formalin vapour to impart enteric-coated properties. The treated capsule contained pantoprazole sodium-loaded IPN beads and was enclosed within a larger gelatin capsule that housed fast-dissolving domperidone maleate granules. The formulated IPN beads were evaluated for drug–excipient compatibility, drug content, percentage yield, entrapment efficiency, in vitro drug release, surface morphology, particle size, and swelling index. The domperidone maleate granules were assessed for drug concentration, angle of repose, and bulk density. In vitro drug release studies revealed that the domperidone maleate granules released 88.34 ± 1.56% of the drug within 2h in 0.1N hydrochloric acid, whereas the pantoprazole sodium-loaded IPN beads released 93.45 ± 0.92% of the drug over 7h pH 7.4 phosphate buffer. The study successfully demonstrated the development of a stable and compatible duocap system capable of providing immediate release of domperidone maleate and delayed release of pantoprazole sodium. This delivery approach offers a promising strategy for improving the therapeutic management of acid reflux.

KEYWORDS: IPN Beads; Duocap Technology; Gastroprotective Drug Delivery; Domperidone Maleate; Pantoprazole Sodium.

INTRODUCTION

Gastro-esophageal reflux disease (GERD) is an ongoing gastrointestinal disorder that includes back-flow (reflux) of acidic gastric content and bile into the esophagus, causing irritation of the esophageal mucosa. The condition often follows the intake of a heavy meal especially greasy or junk food and is often made worse by a sedentary lifestyle or lying down soon after eating. Extended exposure of the oesophageal mucosa to gastric acid can result in inflammatory complications, including oesophagitis, mucosal erosion, ulceration, odynophagia, dysphagia, stricture formation, and an increased risk of malignancy.[1] In addition to heartburn, patients with GERD may experience symptoms such as nausea, vomiting, indigestion, and constipation.

The management of GERD typically involves lifestyle modifications in conjunction with pharmacological therapy, including proton pump inhibitors (PPIs), H_2-receptor antagonists, and antacids, used either alone or in combination with alginic acid preparations. However, currently available therapies often fail to provide rapid and sustained symptom control. An ideal therapeutic strategy should therefore deliver immediate symptomatic relief while ensuring prolonged suppression of gastric acid secretion. This goal can be achieved by developing an advanced oral dosage form that incorporates an immediate-release antiemetic agent along with a delayed-release acid-suppressing drug, formulated using microbead-based drug delivery systems.

Microbeads are spherical drug-delivery carriers with micro- or nano-sized dimensions, composed of a polymeric matrix in which the drug may be adsorbed onto the surface or entrapped within the polymer network.[2] These systems are widely employed to achieve controlled and targeted drug delivery.

Polymers used individually often fail to meet the complex requirements of modern drug-delivery systems. Natural polymers are preferred due to their non-toxicity, low cost, biodegradability, and biocompatibility; however, they possess limitations such as susceptibility to microbial contamination, poor hydration rates, and reduced viscosity during storage. Synthetic polymers may not be biocompatible but offer better mechanical strength and stability.[3] Various researchers have used polymer blending or development of interpenetrating polymer networks (IPNs) for modification of polymeric properties to overcome above limitations. The use of IPN technology involving natural-synthetic polymer in drug-delivery systems produces synergistic effects that improve the functional performance of such systems.[4]

A material system consisting of more than one polymers whose networks are entangled at the molecular level is known as an interpenetrating polymer network (IPN). These systems involve the formation or cross-linking of a minimum of a single polymer while the other is present. Nevertheless, the various polymer networks do not establish any molecular connections. Combining the beneficial characteristics of separate polymers into a single, cohesive matrix is the main goal of creating IPNs. In certain cases, the interpenetrated structure exhibits unique characteristics that are not observed when the polymers are used independently. Due to these attributes, IPNs have gained considerable attention in pharmaceutical applications for improving drug bioavailability, enhancing biocompatibility, enabling targeted drug delivery, and maintaining favorable safety profiles. Additionally, IPNs demonstrate desirable physicochemical properties such as controlled porosity, enhanced bioadhesion, elastic behavior, and predictable swelling characteristics. Compared to conventional polymeric systems, IPNs offer superior structural integrity and synergistic functionality while minimizing incompatibility and property loss often associated with polymer blends or copolymers.[5]In the present study, domperidone maleate (DM) and pantoprazole sodium (PS) were selected as model drugs. Oesophageal erosions and ulcerative lesions associated with GERD are frequently viewed with pantoprazole sodium, a long-acting proton pump inhibitor that lowers acidic output.[6] However, pantoprazole sodium is unstable under acidic conditions and may cause gastric irritation, necessitating its formulation in an enteric-coated delivery system. Domperidone maleate is an antiemetic agent with gastroprokinetic activity, commonly employed in the management of upper gastrointestinal motility disorders and gastroparesis. It exerts its pharmacological action by blocking dopamine (D_2) receptors in the chemoreceptor trigger zone located in the area postrema, as well as in the gastric region.[7]In light of these considerations, this research evolved to formulate and assess novel double-releasing oral formulation employing duocap technology, which consists of enteric-coated pantoprazole sodium beads and an instant-releasing part of domperidone maleate. Duocap is an advanced drug-delivery approach in which a single oral dosage form consists of a capsule housed within another capsule. In this system, a smaller prefilled

capsule containing pantoprazole sodium-loaded microbeads is enclosed within a larger outer capsule filled with fast-disintegrating domperidone maleate granules, thereby enabling sequential and site-specific drug release in the gastrointestinal tract.[8]

MATERIALS AND METHODS

Materials: Domperidone maleate and pantoprazole sodium were purchased from Empree Pharma, Belagavi. Sodium carboxymethyl cellulose (SCMC) of medium-viscosity grade was procured from Milton Chemicals, Mumbai, while egg albumin of analytical-reagent grade was obtained from Bombay Research Laboratory. Aluminium chloride (AR grade) and lactose monohydrate (pharmaceutical grade) were sourced from Genuine Chemicals, Mumbai, and LobaChemie, Mumbai, respectively. Microcrystalline cellulose (Avicel® PH 102) was purchased from Rechem Labs Chemicals, Chennai. Methanol of HPLC grade was obtained from HiMediaLaboratories, Dombivli, Mumbai, and polyvinyl pyrrolidone (PVP K-30) was supplied by Oxford Laboratory, Mumbai.

Instruments: Fourier transform infrared (FT-IR) spectroscopy, UV–visible spectrophotometry, particle size analysis (HORIBA SZ-100), scanning electron microscopy (SEM; JEOL JSM-6360, Japan), and a USP-compliant rotating paddle dissolving equipment have been employed for instrumental and analytical evaluations.

Preformulation Tests: To determine the components of the formulation and evaluate the compatibility and purity of the chosen medications, preliminary tests were carried out.

Identification Tests: The melting points of pantoprazole sodium and domperidone maleate were determined using the capillary method. Using this technique, a tiny quantity of each medication was put into individual capillary tubes and fastened to a thermostat. After that, a Bunsen burner was used to progressively heat the setup in a Thiele's tube until it reached the melting point. The melting points of pantoprazole sodium and domperidone maleate were recorded accordingly.[9]

FT-IR Spectroscopy: Infrared absorption spectroscopy was used to analyze the generated samples. To verify their identification and compatibility, the obtained spectra were assessed and compared with standard reference IR spectra of domperidone maleate and pantoprazole sodium. Using a mortar pestle, 0.5–1.0 mg of specimen and 100 mg of potassium bromide (KBr) were combined. After that, the product was compressed to a clear pellet at a pressure of 10,000–15,000 psi. To record the absorption spectrum, this pellet was put in the IR spectrophotometer's sample container and exposed to infrared light.[10]

Compatibility study: The KBr pellet method was used to assess pharmaceutical component suitability using FT-IR spectroscopy. The infrared spectra of pure drugs, excipients, and their physical mixtures were recorded and compared with the standard reference spectra of pantoprazole sodium and domperidone maleate to detect any possible interactions.[11]

Determination of λ_{max}: Phosphate buffer (pH 7.4) and 0.1 N hydrochloric acid were used as solvents to measure the maximum absorption wavelengths (λmax) of pantoprazole sodium and domperidone maleate. A UV–visible spectrophotometer was used to inspect the resulting solutions across a spectrum of 200–400 nm.Pantoprazole sodium and domperidone maleate were subsequently calculated using concurrent analytical method development. Domperidone maleate and pantoprazole sodium were independently calculated utilizing a UV spectrophotometric technique. Method was based on the determination of absorptivity values of pantoprazole sodium and domperidone maleate at 290 nm and 284 nm, respectively, within their respective Beer–Lambert's law concentration ranges.

The quantitative estimation of pantoprazole sodium and domperidone maleate was carried out utilizing the subsequent formulas:

$$Cx = \frac{(A2 \times ay1) - (A1 \times ay2)}{(ax2 \times ay1) - (ax1 \times ay2)}$$

$$Cy = \frac{(\mathrm{A1} \times \mathrm{ax2}) - (\mathrm{A2} \times \mathrm{ax1})}{(ax2 \times ay1) - (ax1 \times ay2)}$$

here Cx and Cy represent unknown pantoprazole sodium and domperidone maleate concentrations.

A1 is the mixture's absorbency at 290 nm.

A2 is the mixture's absorbance at 284 nm.

ax1 is the pantoprazole sodium absorption spectra around 290 nm.

ax2 is the pantoprazole sodium absorption spectra at 284 nm.

ay1 is the Domperidone maleate's absorptivity at 290 nm.[12]

Formulation Development

Preparation of pantoprazole sodium IPN beads

A magnetic stirrer served to continuously agitate a fluid solution of sodium carboxymethyl cellulose and egg albumin while a measured amount of pantoprazole sodium was evenly distributed. Then, using a 22-gauge hypodermic needle and continuous stirring, the homogenous liquid was agitated

dropwise into an aqueous aluminum chloride solution to create microspheres. To ensure full cross-linking, spheres were left in the aluminum chloride solution for a further fifteen minutes. After that, they were gathered and carefully cleaned with distilled water to get rid of any ions that hadn't reacted. After being rinsed, the strands had the opportunity to air dry for 24 hours at ambient temperature before being dried for 10 hours at 40 ℃ in a hot air oven. Table 1 displays the constituents of the composition.[13]

Table 1: Composition of IPN beads of pantoprazole sodium.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pantoprazole sodium(mg)	500	500	500	500	500	500	500	500	500
Sodium CMC	0.5	1	1.5	0.5	1	1.5	0.5	1	1.5
Egg albumin	1	1	1	1	1	1	1	1	1
$AlCl_3$(%w/v)	4	4	4	5	5	5	6	6	6

Note: All formulations were prepared in a total volume of **50 mL**.**$AlCl_3$ (% w/v)** denotes the concentration of aluminum chloride expressed as **grams per 100 mL of solution**, used as the cross-linking agent.

Optimization of Pantoprazole sodium IPN BEADS

The formulation of pantoprazole sodium interpenetrating polymer network (IPN) beads had been optimized using a triple-level, two-factor factorial design. Nine experimental runs covering every possible combination of the chosen components were produced by studying every separate variable in low, medium, and high levels. Design-Expert® software (Version 11.0; Stat-Ease Inc., USA) was used for the experiment setup and subsequent statistics assessment.

The concentration of sodium carboxymethyl cellulose (SCMC) was chosen to be the first independent factor (X_1), in this investigation, and a concentration of aluminum chloride ($AlCl_3$) was chosen as the second independent variable (X_2). The dependent responses were chosen to be bead size (Y_1) and entrapment efficiency (Y_2).

Bead size was assigned a "minimize" constraint in the optimization criteria to obtain smaller and uniform beads, which are desirable for improved surface area, enhanced flow properties, and predictable drug-release behavior. Reduction in bead size is also advantageous for achieving uniform coating, improved dissolution characteristics, and reproducible in vitro release profiles. To guarantee adequate dosage in polymer matrices, drug entrapment efficiency was simultaneously improved. In all formulations, the amount of pantoprazole sodium was maintained at 500 mg. Table 2 shows the factorial design's composition.

Table 2: Pantoprazole sodium IPN beads were formulated using the 32 factorial design approaches, which included the following independent and dependent variables

Factors	Level used actual (coded) Low (-1)	Medium (0)	High (+1)
Independent variables			
X_1: Sodium Carboxymethyl cellulose	0.5	1	1.5
X_2: Aluminum Chloride	4	5	6
Dependent variables			
Y_1: Bead size(mm)		Minimize	
Y_2: Effectiveness of Entrapment (%)		Maximize	

Note: Bead size (Y_1) was set to **"minimize"** in the optimization criteria to obtain **smaller, uniform beads with improved flow properties and controlled drug release characteristics**.

Preparation of domperidone maleate granules: The wet granulation method was used to create domperidone maleate pellets. Precisely weighed quantities of domperidone maleate (1 g), lactose (3.7 g), and microcrystalline cellulose (0.025 g) were thoroughly blended and then moistened with a sufficient quantity of an aqueous polyvinyl pyrrolidone (PVP) solution to formation of a compact wet substance. Granules of consistent size have been obtained by passing the resultant bulk through the proper sieve. After that, the particles dried out using an oven with hot air until they reached a suitable moisture content.[14]

Formaldehyde treatment to capsule shells: The solubility properties of hard gelatin capsule shells were altered by formaldehyde treatment. Fifty "1"-sized hard gelatin capsules were chosen, and the lids and bodies are carefully separated. Distinct Formaldehyde fumes were produced by adding a small amount of potassium permanganate to 25 mL of formaldehyde solutions at concentrations of 5%, 7%, and 10% (v/v) in desiccators. To guarantee even exposure to the fumes, a grid of wires was inserted into each desiccator, and the empty capsule bodies and caps were laid on the mesh. After that, the desiccators were tightly shut.

In order to maximize the exposure duration, capsules were removed at prearranged intervals and processed in a hot air oven at 50 ˚C for 30 minutes to guarantee that the formaldehyde and gelatin cross-linking process was finished. After being air-dried at room temperature to allow any remaining formaldehyde to evaporate, the treated capsules were sealed in polyethylene bags until needed again.[15]

Characterization of pantoprazole sodium IPN beads

Percentage yield: The total quantity of pantoprazole sodium IPN beads obtained was accurately weighed after formulation. Using the following formula, the % yield determined through the comparison of the actual mass of the beads obtained with the overall theoretical weight of the medication and excipients utilized.:

$$\%\ yield\ = \frac{Actual\ weight\ of\ the\ beads}{Total\ weight\ of\ the\ drug\ and\ excipient} \times 100$$

Drug content: 100 mg of pantoprazole sodium IPN beads were precisely weighed, ground into a fine powder with a mortar and pestle, and precisely transferred into a volumetric flask of 100 mL in order to estimate the drug content. 0.1 N was used to bring the volume up to mark. To make the primary stock solution, use hydrochloric acid. To create the test solution, 1 mL of this solution was taken out and diluted to 100 mL using the same medium. A UV-visible spectrophotometer was used to test the final dilution's absorbance at 290 nm.The drug content was determined using the same method in phosphate buffer (pH 7.4), with the exception that phosphate buffer (pH 7.4) was used as the diluent instead of 0.1 N hydrochloric acid.[16]

Entrapment efficiency: A mortar and pestle were used to finely crush a suitable number of drug-loaded IPN beads after they had been precisely weighed. To guarantee full drug extraction, the crushed beads were distributed in a pH 1.2 buffer solution and allowed to stand for 12 hours. After filtering the resultant suspension, a UV-visible spectrophotometer was used to examine the clear filtrate. To guarantee reproducibility, each formulation was assessed three times. A pH 7.2 phosphate buffer was used to repeat the same experiment. The usual equation was used to determine the drug entrapment efficiency.

$$\%\ EE\ = \frac{Actual\ drug\ content\ in\ the\ beads}{Theoretical\ drug\ content} \times 100$$

Bead size analysis: Using an ocular micrometer and optical microscopy, the size of the drug-loaded beads from each formulation was measured. To guarantee precise bead size measurement, the ocular micrometer was calibrated using a stage micrometer before analysis.

Swelling study: The beadsswelling behavior was assessed at room temperature in phosphate buffer (pH 7.4) and an acidic medium (pH 1.2). To reach equilibrium, the beads were immersed in the appropriate swelling medium and allowed to swell for 24h. Following the swelling period, the beads were carefully taken out and gently blotted with soft tissue paper to remove any extra liquid from the surface without applying pressure. An electronic microbalance was then used to precisely weigh the enlarged beads.

The following formula was used to determine the equilibrium swelling, which was represented as the percentage of water absorption:

$$\%\ Equillibrium\ swelling = \frac{Mass\ of\ swollen\ beads\ -Mass\ of\ dried\ beads}{Mass\ of\ dried\ beads} \times 100$$

Surface topography: A scanning electron microscope (SEM; JEOL JSM-6360, Japan) with a digital camera was used to analyze the beads' surface morphology. Representative micrographs of the bead surfaces were taken for morphological study while the device was running at an accelerating voltage of 18 kV.[17]

Characterization of domperidone maleate granules

Drug content: Using a mortar and pestle, a 100 mg sample of drug-loaded granules was precisely weighed, ground into a fine powder, and put into a 100 mL volumetric flask. To aid in dispersion, a tiny amount of 0.1N hydrochloric acid was added. After careful mixing, the final volume was adjusted to 100 mL using the same medium. One milliliter of this solution was taken out and diluted to one hundred milliliters in a different volumetric flask. A UV-visible spectrophotometer was used to measure the absorbance of the resultant solution at 290 nm. The drug content in phosphate buffer (pH 7.4) was determined using the same method; the only change was to use phosphate buffer (pH 7.4) as the diluent instead of 0.1 N hydrochloric acid.

Angle of repose: The funnel method was used to calculate angle of repose of the granules. A funnel was filled with a certain amount of granules, and its tip was adjusted to just touch the apex of the forming heaps. A conical heap was created by letting the granules fall freely onto a flat surface. The granule cone's diameter was measured, and the relevant equation was used to determine the angle of repose.

$$tan\ \theta = \frac{Height\ of\ the\ granule\ cone}{Radius\ of\ the\ granule\ cone}$$

Bulk density: The ratio of granules' total mass to bulk volume is known as bulk density. A graduated measuring cylinder was filled with a precisely weighed amount of granules, and the initial bulk volume was noted. The standard equation was then used to determine the bulk density in g/mL.

$$Bulk\ density = \frac{Mass\ of\ granules}{Bulk\ volume\ of\ the\ granules}$$

Tapped density: A known weight of granules was transferred into a graduated measuring cylinder to ascertain the tapped density. The final tapped volume was recorded to the closest graduation after the cylinder was tapped 100 times from a height of 14 ± 2 mm. The standard equation was then used to compute the tapped density in g/mL.

$$Tapped\ density = \frac{Mass\ of\ granules}{Tapped\ volume\ of\ granules}$$

Hasusner's ratio: Hasusner's ratio was calculated using the formula [18].

$$Hasuner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Stability Studies: The capacity of a formulation to maintain its physical, chemical, therapeutic, and toxicological characteristics over the course of its shelf life inside a particular container-closure system is known as drug stability. In order to determine suitable storage settings, stability testing is carried out to produce data on how the quality of a therapeutic ingredient or product changes over time under the effect of environmental elements including temperature, humidity,andlight. The International Council for Harmonization (ICH) requirements were followed for conducting accelerated stability assessments of the improved formulation.[19,20]

Dissolution studies: Using a USP Type II (paddle) dissolution equipment running at 50 rpm and 900 mL of dissolution media kept at 37 ± 0.5 ˚C, the in vitro drug release from the duocap system was assessed. To replicate physiological conditions, a two-stage dissolving approach was used. To simulate the gastric environment, the beads were first exposed to 0.1N hydrochloric acid for two hours. Next, they were placed in phosphate buffer (pH 6.8) to simulate intestinal conditions. Throughout the investigation, consistent agitation was maintained and sink conditions were maintained by making sure the drug concentration did not surpass 15% of its saturation solubility. The findings suggested that increasing cross-linking density decreases drug diffusion from the polymeric matrix because beads made with higher concentrations of the cross-linking agent showed slower drug release. Diffusion and polymer relaxation both played a role in the drug release from IPN beads, as evidenced by the non-Fickian transport mechanism.[21]

Drug Release Kinetics and Data Analysis: To ascertain the drug release mechanism and release kinetics of the formulation, the in vitro release data were fitted to a variety of kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Based on the highest correlation coefficient (R^2) value, the best model was chosen.

First-order kinetics show a release rate that is dependent on drug concentration, while zero-order kinetics depict a constant drug release rate that is independent of drug concentration. While the Korsmeyer-Peppas model is frequently used to describe drug release behavior from polymeric delivery systems, the Higuchi model describes drug release from matrix-based systems.[22]

Tests for Formaldehyde Treated Empty Capsules

Physical Tests

Identification characteristics: Size "1" hard gelatin capsules comprised a coloured cap and body with an effective locking mechanism. Prior to formaldehyde treatment, the capsules were free from any detectable odour and exhibited a soft texture with slight stickiness when handled with moist fingers. Following exposure to formaldehyde vapours, no discernible changes in capsule shape, colour, or surface integrity were observed. The treated capsules displayed a non-sticky surface even under damp handling conditions, indicating effective modification of the capsule material.

Visual inspection Out of approximately fifty formaldehyde-treated capsules evaluated, only a few (approximately five) exhibited minor shrinkage or deformation, indicating minimal physical alteration as a result of the treatment process.

Chemical evaluation – qualitative assessment of free formaldehyde: For qualitative comparison, a reference formaldehyde solution of 0.002% (w/v) was employed. In order to ease the extraction of any unreacted formaldehyde, about twenty-five treated capsules were finely crushed, submerged in distilled water, and continuously stirred for one hour. After filtering the resultant extract, the leftover material was carefully cleaned with distilled water. After that, the total volume of the filtrate was adjusted to 50 mL.

Nine milliliters of distilled water were added to an aliquot of one milliliter of this solution. One milliliter of this dilution was added to a test tube along with five milliliters of acetone reagent and four milliliters of distilled water. To enable color development, the

mixture was incubated in a water bath kept at 40 ˚C and left undisturbed for 40 minutes. By looking at the test tubes along their vertical axis, the color intensity of the test solution was visually compared to that of the reference solution made under the same experimental conditions.

The absence of any visible increase in colour intensity compared with the standard indicated

negligible levels of free formaldehyde, confirming effective cross-linking and controlledtreatment conditions. Furthermore, quantitative determination of residual formaldehydeconfirmed that the levels were within the limits specified by ICH guidelines, therebysupporting the safety of the formaldehyde-treated capsule shells.[23]

RESULTS AND DISCUSSION

Preformulation studies: The physical and chemical characteristics of the drug compounds, as well as any possible interactions with excipients, are assessed during preformulation testing. These studies are essential for the development of a formulation that is stable, safe, effective, and pharmaceutically acceptable.

Identification test

Melting point of pantoprazole sodium: The drug sample's integrity was confirmed when the melting point of pantoprazole sodium (PS) was determined to be 135 ˚C, which is similar to the claimed melting point of roughly 140 ˚C.

FT-IR spectroscopy: Before developing a formulation, the identification and structural integrity of pantoprazole sodium and domperidone maleate were verified using Fourier transform infrared (FT-IR) spectroscopy. The presence of all necessary functional groups was demonstrated by the FT-IR spectrum of pantoprazole sodium (Fig. 1), which showed distinctive absorption bands proportional to its molecular structure, such as prominent peaks associated with sulfonyl group (S=O) stretching, imine (C=N) stretching, ether (C–O) stretching, and aromatic ring vibrations.Similar to its reported chemical composition, the FT-IR spectra of domperidone maleate (Fig. 2) showed discrete absorption bands attributable to amide carbonyl (C=O) stretching, N–H bending vibrations, C–N stretching, and aromatic C–H stretching. Peak locations and intensities were found to be in close agreement when the acquired spectra were compared to standard reference data.

Importantly, no significant shifts, reduction in intensity, or appearance of additional peaks were observed in either spectrum, indicating the absence of molecular alteration or degradation. These findings confirm the chemical authenticity, purity, and stability of both pantoprazole sodium and domperidone maleate and support their suitability for further formulation development.

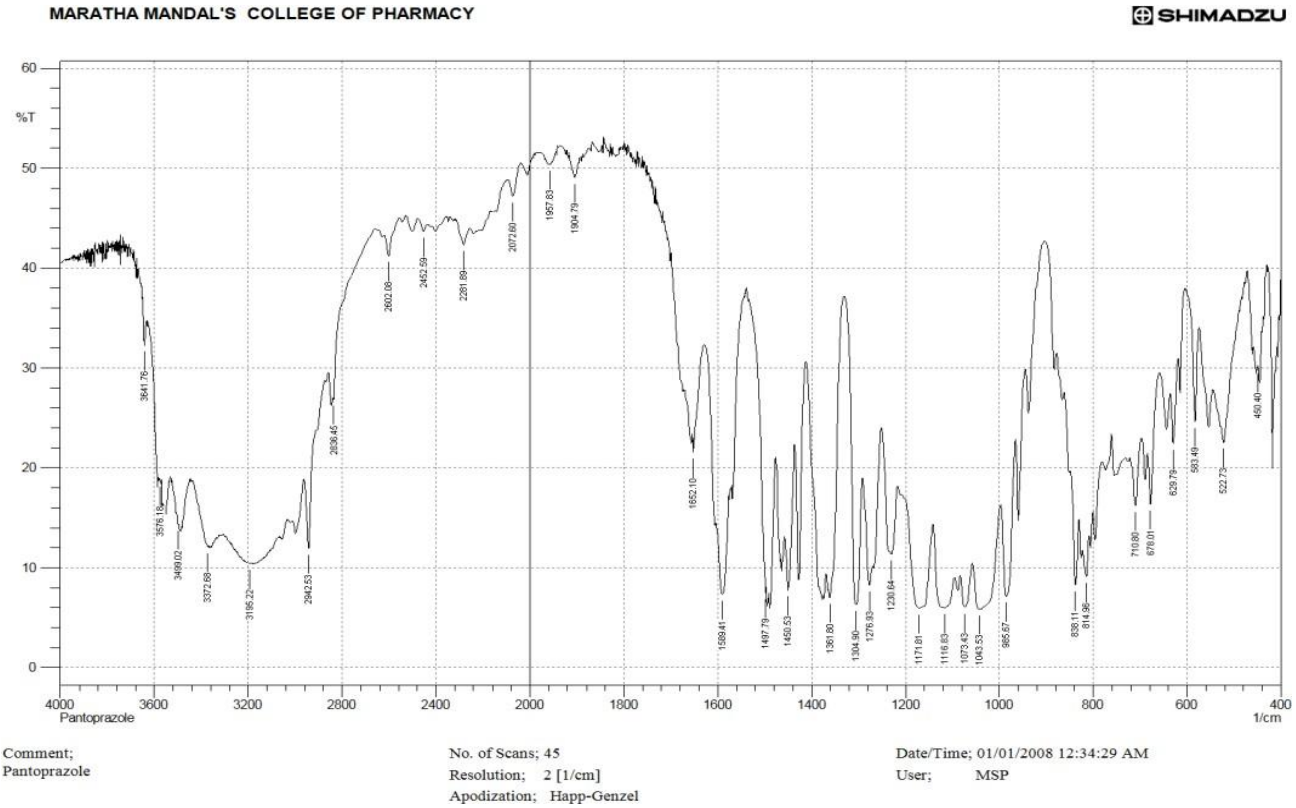

Figure 1: IR spectrum of pantoprazole sodium

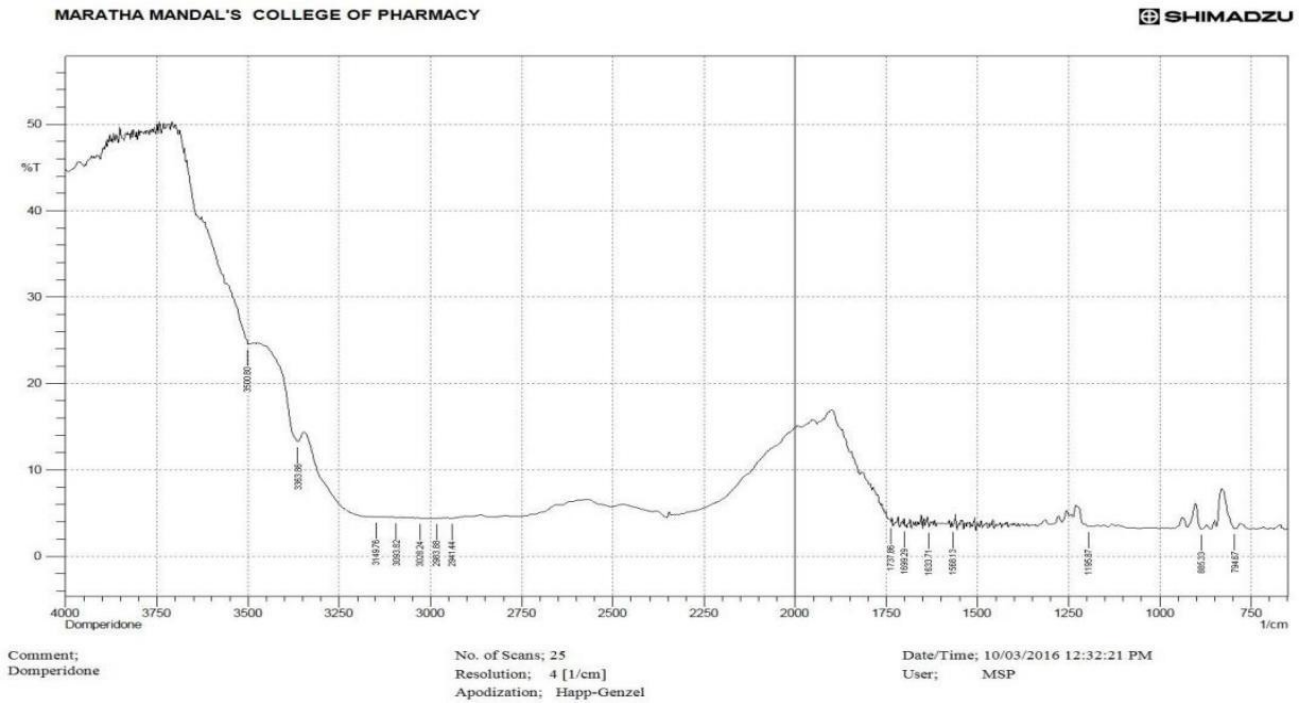

Figure 2: IR spectrum of domperidone maleate

Compatibility studies of drug excipients: A thorough assessment of the drug's and the excipients physical, chemical, and biological characteristics is necessary for the successful creation and preparation of a medication component. The right choice of excipients is crucial for a solid dosage form's stability and efficacy. It is essential that the drug and excipients are compatible to ensure a final product that is safe, efficacious, and stable. The formulation spectra of the current investigation showed the distinctive peaks of pantoprazole sodium at their corresponding wavelengths, suggesting satisfactory drug-excipient compatibility. Figure 2 displays the pantoprazole sodium infrared spectrum.

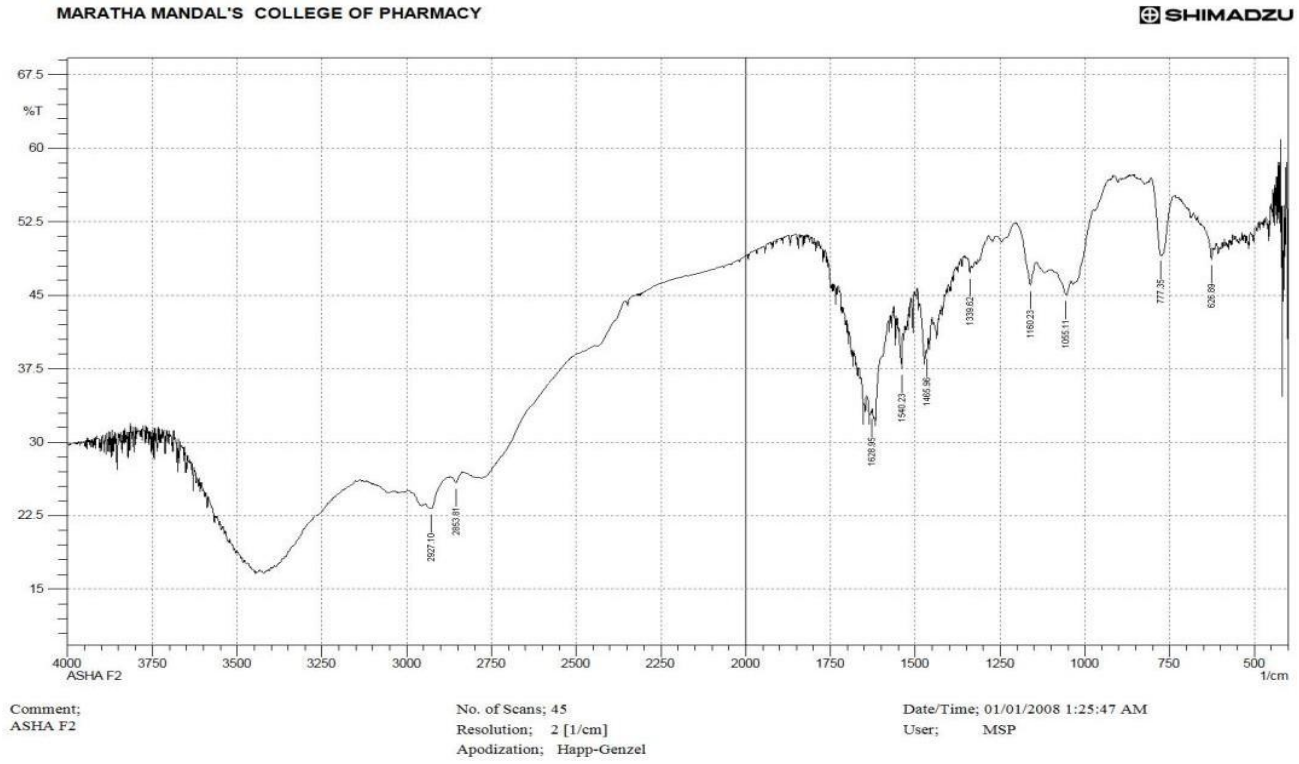

Figure 3: The IR spectrum of pantoprazole sodium with egg albumin and sodium carboxymethyl cellulose

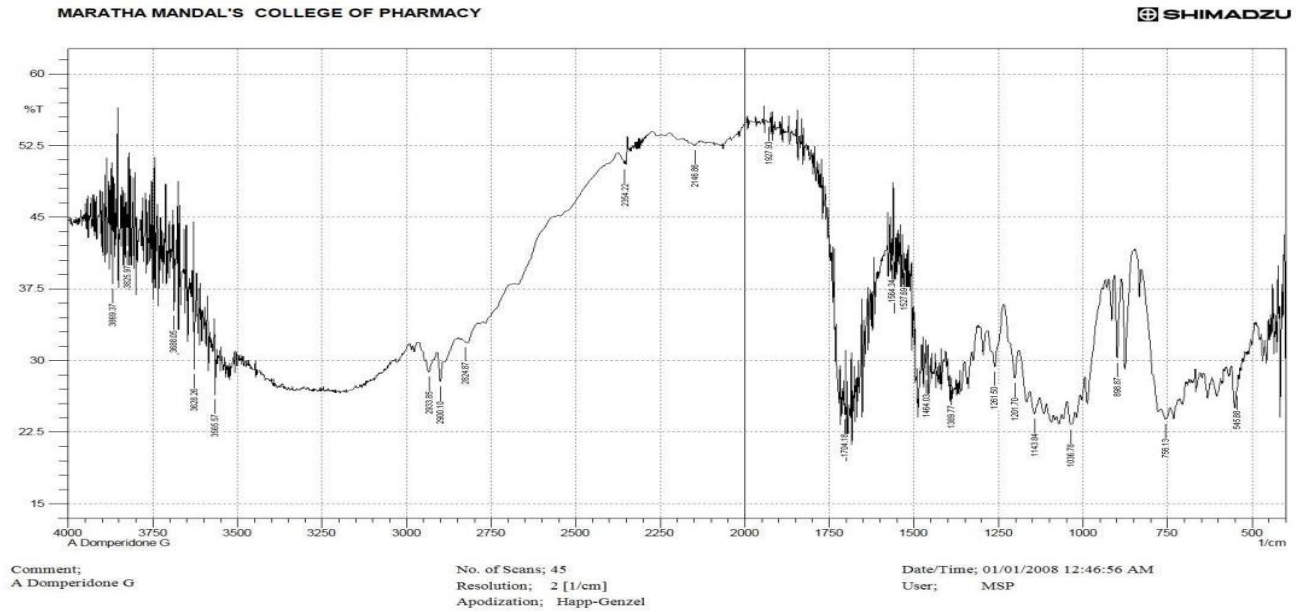

Figure 4: IR spectrum of Domperidone maleate with Lactose, polyvinyl pyrrolidone, and microcrystalline cellulose

Determination of λ_{max}: The samples were scanned over a wavelength range of 200–400 nm to determine the maximum absorption wavelengths (λmax) of pantoprazole sodium and domperidone maleate in 0.1 N hydrochloric acid and phosphate buffer (pH 7.4). In both 0.1 N hydrochloric acid and pH 7.4 phosphate buffer, pantoprazole sodium displayed its peak absorbance at 290 nm, whereas domperidone maleate showed a λmax of 284 nm in the same environment.

Pantoprazole sodium and domperidone maleate estimation simultaneously

Using a UV-visible spectrophotometer and the simultaneous equation approach (Vierordt's method), a technique for the simultaneous estimation of pantoprazole sodium and domperidone maleate was created. Using this method, the absorbance of pantoprazole sodium and domperidone maleate is measured over their respective Beer's law concentration ranges at wavelengths of 290 nm and 284 nm. Table 3 displays the absorptivity data in phosphate buffer (pH 7.4) and 0.1 N hydrochloric acid**.**

Table 3: Absorptivity of drugs in 0.1 N HCl and phosphate buffer (pH 7.4)

Drugs	Absorptivity in 0.1 N HCl		Absorptivity in phosphate buffer pH 7.4	
	290nm	284nm	290nm	294nm
Pantoprazole sodium	0.0202(ax_1)	0.0197(ax_2)	0.03228($ax_{1)}$	0.03128($ax_{2)}$
Domperidone maleate	0.0159(ay_1)	0.0222(ay_2)	0.01506($ay_{1)}$	0.0209($ay_{2)}$

Formulation design

The goal of the current study was to use duocap technology to create immediate-release domperidone maleate granules and pantoprazole sodium interpenetrating polymer network (IPN) beads. In this approach, a prefilled inner capsule containing IPN beads was enclosed within an outer capsule filled with fast-release granules.

A two-factor, triple-level factorial design created with Design-Expert® software was used to optimize the pantoprazole sodium IPN bead formulation. Sodium carboxymethyl cellulose (X_1) and aluminium chloride (X_2) were selected as critical formulation variables based on their influence on polymer network formation, cross-linking density, bead integrity, and drug entrapment.

Exploratory experimental trials that found concentration ranges producing mechanically stable beads with uniform size and sufficient entrapment efficiency were used to determine the low, medium, and high levels of these parameters. To assess the impact of the chosen factors on bead size (Y_1) and % entrapment efficiency (Y_2), nine experimental runs were carried out using the factorial design (Table 8).

Analysis of variance (ANOVA), with p-values less than 0.05 deemed significant, was used to statistically validate the model. Response surface plots, contour plots, and perturbation plots were used to interpret the relationship between formulation factors and

responses. A high coefficient of determination (R^2 > 0.90) and strong agreement between the anticipated and modified R^2 values demonstrated adequate model fit (Table 4).

Table 4: Factor and response of factorial design

Formulation code	NA-CMC (X_1) (mg)	Aluminum Chloride (X_2) (mg)	Bead Size (mm) (mean ± SD, n=3)	Entrapment Efficiency (%) (mean ± SD, n=3)
F1	0.5	4	1.16 ±0.02	92.77 ±0.07
F2	1.0	4	1.20 ±0.02	97.06 ±0.02
F3	1.5	4	1.25 ±0.02	96.14 ±0.02
F4	0.5	5	1.00 ±0.02	91.45 ±0.05
F5	1.0	5	1.04 ±0.01	94.69 ±0.06
F6	1.5	5	1.08 ±0.01	93.16 ±0.01
F7	0.5	6	0.96 ±0.02	87.71 ±0.04
F8	1.0	6	0.99 ±0.02	90.73 ±0.04
F9	1.5	6	0.89 ±0.03	89.57±0.76

Note: All values are expressed as **mean ± standard deviation (SD), n = 3**.

Fitting information into the model: In order to determine which mathematical model best described bead size, the experimental data from the nine formulations were statistically examined using Design-Expert® software and fitted to several models, such as linear, two-factor interaction (2FI), and quadratic models. Instead of depending only on the coefficient of determination (R2), a thorough analysis of statistical characteristics was used to pick the model.

Although higher-order models exhibited comparatively increased R^2 values, these improvements were not considered sufficient to justify their selection. The factorial design employed in this study involved a limited number of experimental runs, which restricts accurate estimation of interaction and quadratic terms and increases the possibility of overfitting. Additionally, the higher-order terms did not demonstrate statistical significance, and the increase in R^2 was not accompanied by a corresponding improvement in predictive performance. As evidenced by a reduced standard deviation and anticipated residual sum of squares, as well as a tighter agreement between adjusted and predicted R2 values, the linear model,on the other hand, demonstrated superior consistency between predicted and experimental results. The adequate precision value for the linear model was well above the acceptable threshold, indicating a reliable signal for interpreting the effects of formulation variables.

Considering these factors and the principle of selecting the simplest statistically valid model, the linear model was identified as the most appropriate for representing the bead size response and was therefore selected for further analysis (Table 5).

Table 5: Summary of result of regression analysis for response Y1(Bead size), Y2(%Entrapment efficiency)

Models	SD	R^2	Adjusted R^2	Predicted R^2	PRESS	Remark
Response 1						
Linear	0.0471	0.8830	0.8440	0.6916	0.0351	
2FI	0.0372	0.9392	0.9028	0.8016	0.0226	Suggested
Quadratic	0.0350	0.9678	0.9141	0.6239	0.0428	
Cubic	0.0200	0.9965	0.9719	0.3594	0.0729	
Response 2						
Linear	1.55	0.8139	0.7518	0.5882	32.02	
2FI	1.68	0.8191	0.7105	0.0968	70.22	Suggested
Quadratic	0.3913	0.9941	0.9842	0.9280	5.60	
Cubic	0.0317	1.0000	0.9999	0.9976	0.1828	

SD: standard deviation, R2: multiple correlation coefficient, 2FI: two factor interaction, PRESS: predicted residual sum of square.

Impact of independent variables on Pantoprazole IPN Bead Size (Y1):

Table VIII displays the diameters of the pantoprazole IPN bead formulations, which range from 0.89 to 1.25 mm. The following formula can be used to express how the independent factors affect bead size: $Y1=+1.06 + 0.0167X1-0.1283X2Y_1 = +1.06 + 0.0167X_1 - 0.1283X_2Y1=+1.06+0.0167X1-0.1283X2$

In this study, Y_1 represents bead size, X_1 corresponds to the amount of sodium carboxymethyl cellulose (Na-CMC), and X_2 represents the quantity of aluminium chloride ($AlCl_3$). According to the equation, adding more Na-CMC has a beneficial impact on bead measurement, leading to larger IPN beads. On the other hand, aluminum chloride has a detrimental effect on bead size.

Table VI summarizes the findings of the ANOVA for bead size. There is only a 1.6% probability that the model's F-value of 22.64 may be the result of random variation, indicating model significance. Prob > F values less than 0.0500 are regarded as important model terms, and both X_1 and X_2 satisfy this requirement.

The modified R^2 value of 0.8440 and the expected R^2 value of 0.6916 accord fairly well indicating consistency between predicted and observed responses. Additionally, the adequate precision ratio of 10.66 reflects a strong signal-to-noise ratio. Overall, these results confirm that the linear model is appropriate for exploring the design space.

Three-dimensional response surface plots (Fig. 12A) and matching two-dimensional contour plots (Fig. 12B) are used to show how the independent variables affect bead size. These results are further supported by the bead size perturbation plot (Fig. 12C).

Table 6: ANOVA results for various responses of pantoprazole sodium IPN beads

Source	Responses					
	Y_1 (Size)			Y_2 (% entrapment efficiency)		
	F-value	p-value Prob> F	Adequacy Precision	F-value	p-value Prob> F	Adequacy Precision
Model	22.64	0.016	10.66	100.93	0.0015	29.22
X_1	0.7509	0.4195		54.25	0.0052	
X_2	44.52	0.0005		358.92	0.0003	

X1and X2 are coded terms for independent variables.

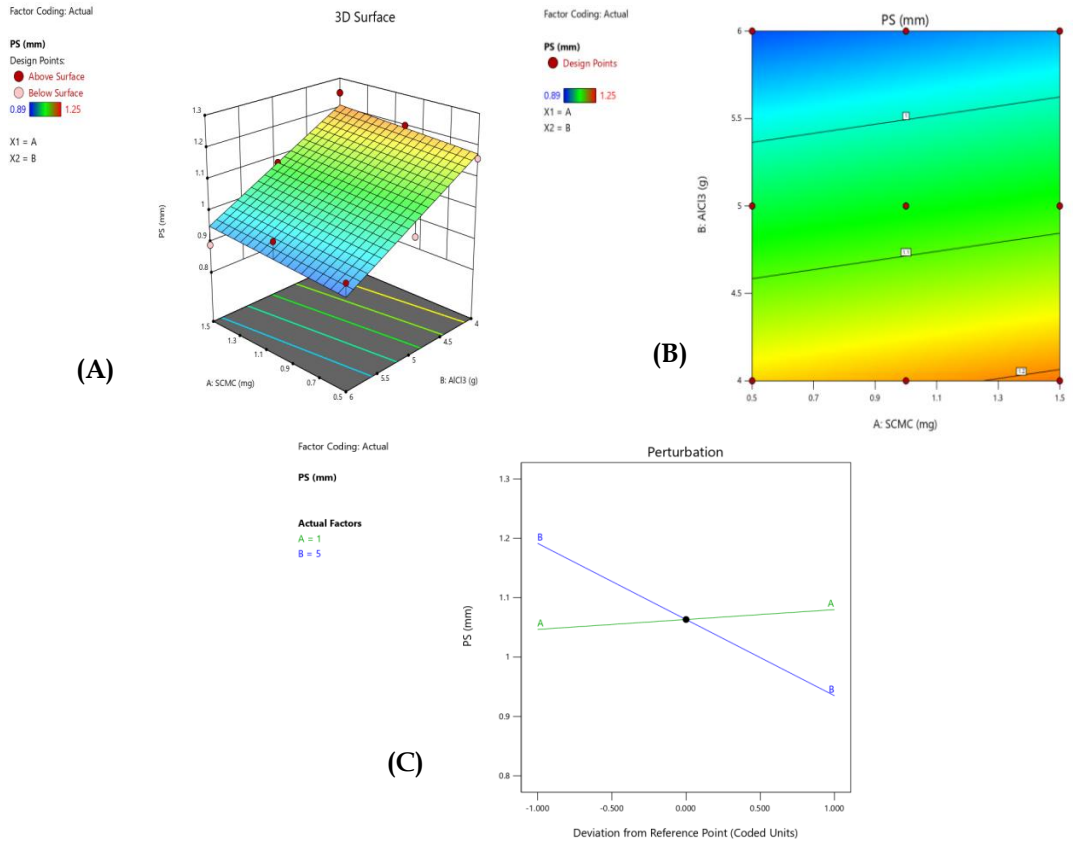

Figure 5:(A) Three-dimensional response surface representation, (B) contour plot, and (C) perturbation plot showing the effect of sodium carboxymethyl cellulose and aluminum chloride levels on bead size

Impact of independent variables on pantoprazole IPN beads' entrapment efficiency(Y2)

Table VIII displays the gastroprotective bead formulations' percentage entrapment efficiency, which ranges from 91.65% to 97.11%. The following linear equation can be used to explain how the independent variables affect entrapment efficiency:

$Y2=+94.88+1.18X1+3.03X2Y_2= +94.88 + 1.18X_1 + 3.03X_2Y2=+94.88+1.18X1+3.03X2$

In this study, Y_2 represents the percentage entrapment efficiency, X_1 denotes the amount of sodium carboxymethyl cellulose (SCMC), and X_2 represents the volume of aluminium chloride. The equation shows that increasing the amount of SCMC

positively influences percentage entrapment efficiency, indicating enhanced drug entrapment within the IPN beads.

Table VI provides a summary of the % entrapment efficiency ANOVA results. There is only a 1.5% chance that the model's F-value of 100.93 might be the product of random variation, indicating statistical significance. Both X_1 and X_2 meet the requirement that model terms with Prob>Fvalues less than 0.0500 be deemed significant.

The modified R2 value of 0.9842 and the expected R2 value of 0.9280 agree quite well. A significant signal-to-noise ratio (Table VI) is further confirmed by the sufficient precision ratio of 29.22, which supports the linear model's viability for design space exploration.

Three-dimensional response surface plots (Fig. 6A) and matching contour plots (Fig. 6B) are used to show how the independent factors affect the percentage entrapment efficiency. The perturbation plot (Fig. 6C) provides additional confirmation of the observed trends.

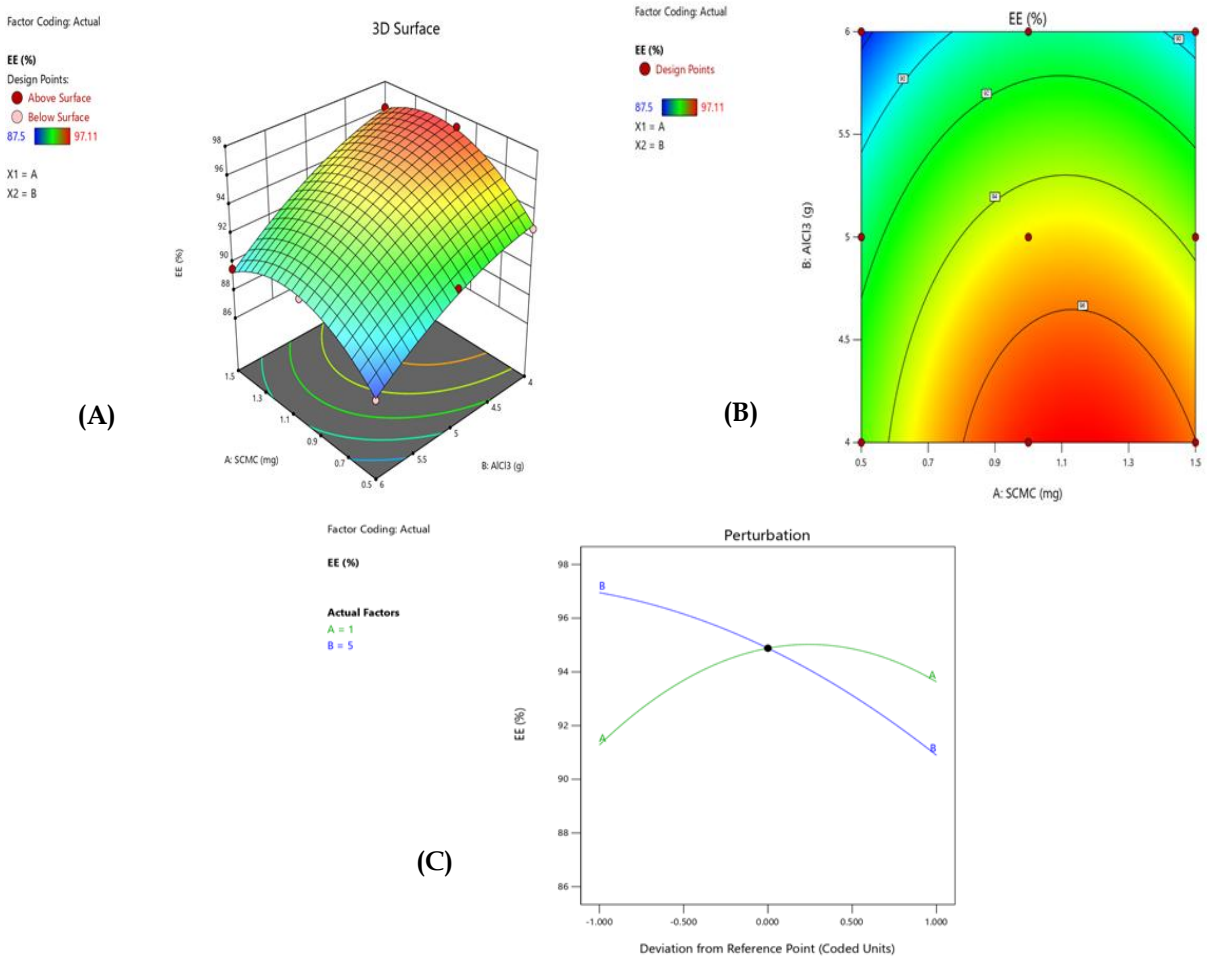

Figure 6. (A) Three-dimensional response surface plot, (B) contour plot, and (C) perturbation plot showing the effect of sodium carboxymethyl cellulose and aluminum chloride on the percentage entrapment efficiency

A numerical optimization procedure was carried out by adding constraints to the independent variables in order to find the optimal formulation within the design space. The goal of this method was to maximize % entrapment efficiency while maintaining bead size within a given range. The software recommended an optimum formulation with a desire value of 1.00 that contained 4.05 mg of $AlCl_3$ and 1.13 mg of Na-CMC. Fig. 14 displays the overlay plot that shows the optimized formulation and its expected response values. After that, the optimized IPN beads were made and tested for the chosen response parameters. Table VII summarizes the experimentally observed and projected values as well as the % prediction error.

The strong agreement between anticipated and observed values, with percentage prediction errors ranging from 0.05% to 1.6%, shows that the Quality-by-Design (QbD) approach was successfully applied to optimize the IPN bead composition and validates the experimental design's dependability.

Table 7: Validation of optimized formulation

Response	Predicted value	Observed value	Prediction error (%)
Size	97.113	97.11	0.05
%Entrapment efficiency	1.18	1.2	1.6

$$\% = \frac{\boldsymbol{Predicted\ value - Observed\ value}}{\boldsymbol{Predicted\ value}} \times \mathbf{100}$$

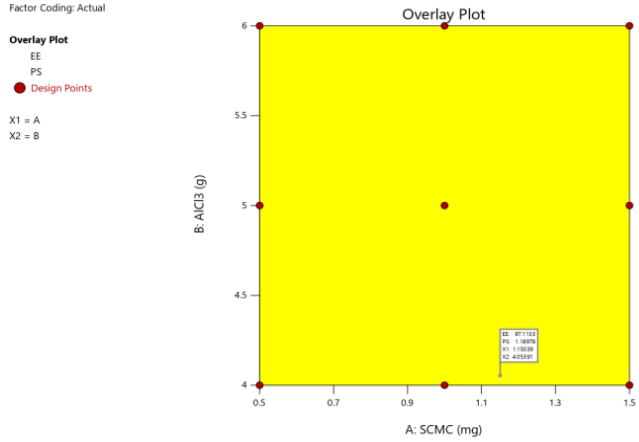

Figure 7: overlay plot illustrating the combined effect of sodium carboxymethyl cellulose and aluminum chloride on bead size and entrapment efficiency

EVALUATION STUDIES

Characterization of pantoprazole IPN beads

Percentage yield: The obtained percentage yield for all formulated beads ranged from 82.40% to 98.86%. The variation in percentage yield is attributed to material loss during the bead preparation process. Such losses can occur due to factors related to process parameters, such as drying or cross-linking.

Drug content: To guarantee consistency in the quantity of drug contained in the IPN beads, drug content uniformity was assessed. The percentage of theoretical drug content for pantoprazole sodium was determined to be between 70.33 ± 0.52% and 78.91 ± 0.44% in 0.1 N hydrochloric acid and 70.43 ± 0.23% and 79.45 ± 0.45% in phosphate buffer (pH 7.4). While homogeneity among formulations shows consistent drug distribution, the relatively lower values could be explained by partial drug loss during the bead production and washing stages.

Entrapment efficiency: Beads were shown to have a drug entrapment efficiency of 87.50 ± 0.20% to 97.11 ± 0.07% in 0.1 N hydrochloric acid and 88.71 ± 0.04% to 96.06 ± 0.02% in phosphate buffer (pH 7.4). Pantoprazole sodium entrapment was highest in formulation F2 (97.11 ± 0.07% and 96.06 ± 0.02%), and lowest in formulation F7 (87.50 ± 0.20% and 88.71 ± 0.04%) in phosphate buffer (pH 7.4). Therefore, the results show that as the concentration of the cross-linking agent increases, the entrapment effectiveness of the beads falls.

Bead size analysis: Bead size determination was conducted for all formulations using an optical microscopic method. For every composition, the beads ranged in size from 0.89 to 1.25 mm. The findings showed that the concentration of the cross-linking agent $AlCl_3$ and the concentration of polymers both affected particle size. A drop in particle size was connected with a rise in $AlCl_3$ concentration, indicating that the cross-linking agent selection and concentration have a major influence on the beads' physical properties.

Equilibrium swelling: To determine the impact of pH on water absorption, the swelling characteristics of the optimized IPN beads were assessed in both an acidic media (0.1 N HCl) and a neutral medium (phosphate buffer, pH 7.4). To establish a comprehensive kinetic profile, swelling measures were made at multiple time intervals: 30, 60, 120, 180, 240, 300, and 360 minutes. The beads displayed rapid swelling during the initial two hours, followed by a gradual approach to equilibrium. Swelling in the neutral medium was consistently greater than in acidic conditions, demonstrating the pH-responsive nature of the polymer network. These findings suggest that the degree of cross-linking and polymer concentration have a significant impact on equilibrium swelling and water uptake. By considering the results of percentage yield, percentage entrapment efficiency, and release studies, formulation F2 emerged as the best formulation, and the results of percentage yield, percentage drug content, percentage entrapment efficiency, percentage equilibrium swelling, and practical size are presented in Table 8.

Table 8: Results of Percentage yield, % drug content, % Entrapment efficiency, %Equilibrium swelling and practical size.

Code	% yield	Drug Content (%)		% Entrapment efficiency		Equilibrium swelling (%)		Particle Size (mm) (mean ± SD)
		(0.1 N HCl) (mean ± SD)	(pH 7.4) (mean ± SD)	(0.1 N HCl) (mean ± SD)	(pH 7.4) (mean ± SD)	0.1N HCL	pH 7.4	
F_1	82.40±0.31	71.34±0.31	72.38±0.37	92.92±0.44	92.77 ±0.07	210±0.02	540±0.02	1.16 ±0.02
F_2	88.66±0.05	78.91 ±0.44	79.45 ±0.45	97.11 ±0.07	96.06 ±0.02	240±0.02	660±0.02	1.20 ±0.02
F_3	84.45±0.09	73.33 ±0.64	72.25 ±0.70	96.12 ± 0.05	95.14 ±0.02	230±0.03	580±0.02	1.25 ±0.02
F_4	88.80±0.14	71.55 ±0.67	71.92 ±0.59	91.65 ± 0.09	91.45 ±0.05	180±0.03	520±0.03	1.00 ±0.02
F5	95.26±0.20	75.10 ±0.72	76.05 ±0.96	94.86 ± 0.11	94.69 ±0.06	160±0.02	500±0.03	1.04 ±0.01
F6	91.14±0.25	70.33 ±0.52	70.43 ±0.23	93.28 ± 0.14	93.16 ±0.01	140±0.02	480±0.02	1.08 ±0.01
F7	93.36±0.44	72.43 ±0.35	72.82 ±0.15	87.50 ± 0.20	88.71 ±0.04	110±0.03	410±0.01	0.96 ±0.02
F8	98.86±0.04	74.38 ±0.24	75.82 ±0.25	90.76 ± 0.06	90.73 ±0.04	130±0.03	460±0.03	0.99 ±0.02
F9	90.97±0.11	72.92 ±0.69	73.23±0.30	89.58±0.09	89.02 ±0.04	120±0.04	440±0.02	0.89 ±0.03

Note: The values presented are expressed as arithmetic mean ± standard deviation (SD) of three independent determinations (n = 3). % Drug content represents the percentage of pantoprazole sodium recovered relative to the theoretical amount added during formulation

Surface topography: Scanning electron microscopy was used to analyze the surface properties of the improved formulation (F2) at a magnification of 200× and an accelerating voltage of 5 kV. The micrograph (Fig. 8) reveals that the IPN beads possess a predominantly spherical to slightly irregular morphology with a uniform and smooth outer surface. The absence of visible cracks, fractures, or surface erosion indicates effective polymer cross-linking and structural stability of the beads. The relatively smooth surface is expected to contribute to controlled drug diffusion and sustained release behaviour from the IPN matrix.

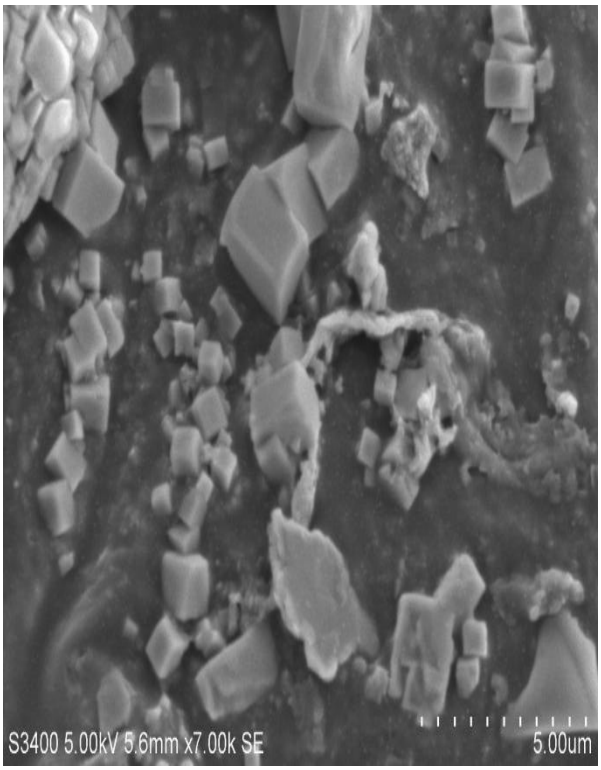

Figure 8: Scanning electron microscopy of pantoprazole sodium beads (F2 formulation)

Characterization of Domperidone maleate granules

Drug content: Domperidone maleate granules were found to have a drug concentration of 89.06 ± 0.23% in 0.1 N hydrochloric acid and 87.17 ± 0.23% in phosphate buffer (pH 7.4).

Angle of repose (θ): Domperidone maleate granules were found to have an angle of repose of 28.47 ± 0.30°. The granules had good flow characteristics because the angle of repose for each formulation was less than 30°.

Untapped bulk density and tapped bulk density: The untapped bulk density (UBD) and tapped bulk

density (TBD) of the domperidone maleate granules were assessed. The results showed that the tapped density was 0.79 ± 0.008 g/mL and the untapped bulk density was 0.41 ± 0.02 g/mL.

Hausner's ratio: Domperidone maleate granules have a Hausner's ratio of 1.89 ± 0.12, which indicates strong flow ability.

***In-vitro* drug release studies:**

Using a USP type XXIV dissolution apparatus, the in vitro drug release study was carried out under the following conditions: paddle rotation at 50 rpm, dissolution medium volume of 900 mL, 0.1 N hydrochloric acid for the first two hours and phosphate buffer (pH 7.4) for the remaining time, and temperature maintained at 37 ± 0.5 °C. As Table 9 illustrates, the results showed that beads made with larger concentrations of the cross-linking agent exhibited slower drug release rates, indicating that increasing the amount of cross-linker decreases drug release. Furthermore, as Table 9 illustrates, drug release was discovered to follow a non-Fickian transport mechanism.

Table 9: In-vitro drug release of domperidone maleate and pantoprazole sodium

Formulation code	Cumulative % Drug Release of Domperidone Maleate at 120 min (mean ± SD)	Cumulative % Drug Release of Pantoprazole Sodium at 540 min (mean ± SD)
F1	86.34±1.5	91.07±0.53
F2	88.34±1.56	93.45±0.92
F3	85.44±1.56	92.53±0.92
F4	81.38±2.71	89.43±0.53
F5	84.26±0.03	90.67±0.92
F6	85.23±1.64	87.38±0.53
F7	86.94±1.52	83.54±0.53
F8	88.16±1.56	88.03±0.92
F9	86.36±1.5	85.40±0.53

Note: All values are expressed as mean ± standard deviation (SD), n = 3

Release kinetic data: Zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models were used to examine the in vitro release data of pantoprazole sodium IPN beads and domperidone maleate granules. Table 10 summarizes the relevant regression coefficients (R^2). The first-order model exhibited the highest R^2 values among the traditional kinetic models, suggesting that the drug release rate was influenced by the amount of drug still present in the dose form. The Korsmeyer–Peppas model was used to further clarify the releasing mechanism. Drug release followed a non-Fickian (anomalous) diffusion process, as confirmed by the model's relatively high R2 values and release exponent (n) values between 0.5 and 1.0. This suggests that diffusion and polymer matrix relaxation worked together to control drug release. Fig. 9 displays the release profiles that demonstrate this phenomenon.

Such non-Fickian release behavior is advantageous for controlled and gastroprotective drug delivery systems, as it ensures sustained drug release without an initial burst effect. In the present formulation, this mechanism supports prolonged availability of pantoprazole sodium for effective acid suppression while maintaining controlled release characteristics of domperidone maleate, thereby contributing to improved therapeutic efficacy and patient compliance.

Table 10: Release kinetics data of preliminary formulations of pantoprazole sodium and domperidone maleate

Formulation Code	Mathematical models(kinetics)									
	Zero order (R)		First order (R)		Higuchi (R)		Korsmeyer-Peppas			
							Pantoprazole sodium		Domperidone maleate	
	PS	DM	PS	DM	PS	DM	(N)	(R)	(N)	(R)
F_1	0.965	0.681	0.989	0.989	0.882	0.915	0.912	0.895	0.901	0.844
F_2	0.964	0.719	0.989	0.949	0.880	0.929	0.929	0.906	0.889	0.855
F_3	0.971	0.649	0.990	0.929	0.870	0.894	0.938	0.931	0.894	0.852
F_4	0.969	0.734	0.990	0.946	0.878	0.945	0.914	0.904	0.901	0.884
F5	0.970	0.792	0.979	0.944	0.872	0.952	0.927	0.917	0.869	0.858
F6	0.970	0.751	0.991	0.941	0.879	0.955	0.914	0.909	0.907	0.877
F7	0.969	0.762	0.980	0.961	0.864	0.955	0.914	0.909	0.916	0.891
F8	0.972	0.787	0.978	0.986	0.862	0.968	0.914	0.909	0.906	0.884
F9	0.969	0.710	0.974	0.945	0.857	0.932	0.899	0.931	0.907	0.869

Note: The values presented are arithmetic mean ± SD's of 3trials, n=0.899 & n=0.869

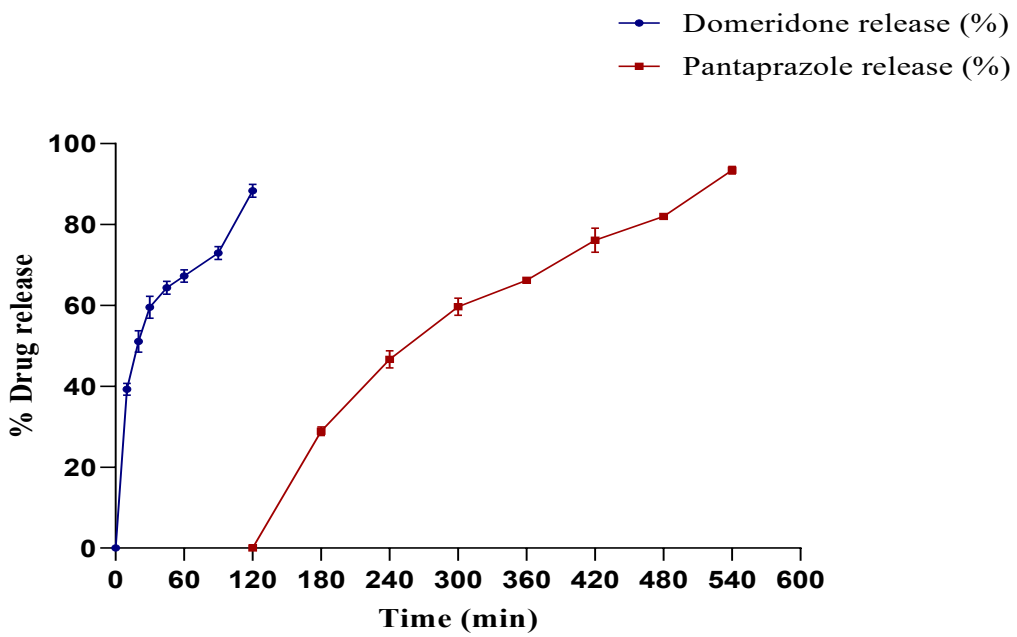

Figure 9: In-vitro release patterns of Domperidone maleate granules and Pantoprazole sodium IPN beads, illustrating rapid drug release from Domperidone and delayed release from Pantoprazole formulations.

Formaldehyde concentration and exposure duration are optimized for crosslinking:

By altering the formaldehyde content (% v/v) and exposing the capsules for variousdurations, the solubility of the cross-linked capsule shells was investigated. The following outcomes were obtained from observing the capsules' behavior in dissolution media that contained phosphate buffer(pH7.4)and0.1NHCl. After four hours of exposure to a 5% formaldehyde concentration, the capsule shells softened in two hours in both phosphate buffer (pH 7.4) and 0.1 N HCl. The capsule shells softened in three hours in both phosphate buffer (pH 7.4) and 0.1 N HCl following two hours of exposure to a 7% formaldehyde concentration. After two hours of exposure to a 10% formaldehyde concentration, the capsule shells required nine hours to soften in phosphate buffer (pH 7.4) and 0.1 N HCl.The capsule shells' solubility was assessed, and it was found that treating them with 5% v/v formaldehyde for four hours was the best course of action because the capsule bodies held together for up to two hours in every tested medium. For the purpose of cross-linking the capsule shells, these conditions were chosen.

Stability study: The improved formulation (F2) underwent accelerated stability testing in compliance with ICH recommendations to evaluate its chemical and physical stability under stressful storage circumstances. Evaluations were carried out at 30, 60, and 90 days after the formulation was sealed in airtight containers and kept in an ICH-compliant stability chamber at 40 ℃ ± 2 ℃ and 75% RH ± 5% RH. The formulation's physical appearance, flow properties, drug content, and in vitro drug release pattern were assessed at each sampling interval. No noticeable alterations in color, texture, or flow properties were observed throughout the study period. Drug content values remained within acceptable limits, and dissolution profiles showed no significant deviation from the initial release pattern, indicating preservation of release characteristics. Furthermore, the formulation did not exhibit any signs of microbial or fungal growth, nor did it develop an objectionable odor. These findings confirm that the optimized formulation F2 possesses adequate stability under accelerated conditions, suggesting its suitability for long-term storage under normal conditions.

DISCUSSION

In the present study, duocap capsules containing immediate-release domperidone maleate granules and enteric-coated pantoprazole sodium IPN beads were successfully developed to achieve sequential drug delivery for the effective management of acid reflux. The combined use of a proton pump inhibitor and a prokinetic agent has been previously reported to enhance therapeutic outcomes in acid-related disorders by providing rapid symptom relief along with sustained acid suppression [6,7]. However, earlier approaches primarily focused on conventional tablets or matrix systems, whereas the present work employs a duocap-based

multiparticulate strategy, offering greater flexibility in release modulation and improved patient compliance.FT-IR studies confirmed the retention of characteristic functional group peaks of pantoprazole sodium and domperidone maleate, indicating the absence of drug–excipient interactions. Similar observations have been reported in earlier pharmaceutics and polymer-based drug delivery studies, where FT-IR analysis established compatibility and chemical stability of drugs within polymeric systems [10–12]. The unchanged λmax values of both drugs in acidic and buffer media further support their stability, consistent with standard analytical reports for these drugs and pharmacopeial guidelines [9,12].Optimization of pantoprazole sodium IPN beads using a QbD-based approach demonstrated that sodium carboxymethyl cellulose (SCMC) significantly increased bead size and entrapment efficiency, while aluminium chloride reduced bead size due to increased cross-link density. The results obtained are consistent with earlier studies on ionotropically cross-linked bead systems and interpenetrating polymer networks, where higher cross-linker concentrations produced compact structures with decreased drug diffusion, while higher polymer concentrations increased swelling and particle size [2–5,13]. The high entrapment efficiency achieved in the present study correlates well with earlier IPN-based formulations reported for controlled and gastroprotective drug delivery [3–5,13]. According to in vitro drug release experiments, the desired sequential release design was fulfilled by the immediate release of domperidone maleate and the sustained release of pantoprazole sodium. Comparable biphasic and pulsatile delivery systems have been reported to improve therapeutic efficacy and reduce dosing frequency in chronic conditions such as GERD and rheumatoid arthritis [15,23]. Drug release was controlled by a combination of diffusion and polymer relaxation mechanisms, according to the release kinetics, which followed a first-order model with non-Fickian transport behavior. These results are consistent with the classical release behavior described by Peppas and other researchers for hydrogel and IPN-based systems [22].The optimized formaldehyde cross-linking condition (5% for 4 h) produced gastro-resistant capsule shells capable of maintaining integrity in acidic and buffer media for up to 2 h. Similar formaldehyde-treated capsule shells have been previously reported for delayed and site-specific drug delivery applications, supporting the suitability of this approach for gastro-resistant formulations [14,15]. Accelerated stability studies further demonstrated that the optimized formulation remained stable under ICH conditions, aligning with previously reported stability data for polymer-based and poorly water-soluble drug formulations [16,19,20].Overall, when compared with earlier reports on IPN systems, sustained-release formulations, and sequential drug delivery approaches [3–5,7,13], the present study demonstrates improved control over drug release, high encapsulation efficiency, and formulation stability using a simple and scalable duocap-based design. The integration of IPN technology with QbD optimization highlights the novelty and pharmaceutical relevance of this work for the effective management of acid reflux.

CONCLUSION

The study successfully developed and optimized a Duocap drug delivery system combining immediate-release Domperidone maleate granules with enteric-coated Pantoprazole sodium IPN beads for the management of acid reflux. A QbD-based optimization approach confirmed the significant influence of polymer and cross-linker concentrations on bead size and entrapment efficiency, with the optimized formulation exhibiting high drug loading, suitable bead size, and good desirability. Analytical studies established drug integrity and compatibility, while in-vitro release demonstrated immediate release of Domperidone and delayed release of Pantoprazole following first-order, non-Fickian kinetics. Formaldehyde-treated capsule shells provided adequate gastro-resistance, and stability studies confirmed formulation stability under ICH conditions. Overall, the developed Duocap system represents a stable and effective approach for sequential drug delivery with improved therapeutic performance and patient compliance.

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Conflicts of Interest

The authors declare that there are no financial or other conflicts of interest associated with this work.

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