RESEARCH PAPER

DEVELOPMENT AND OPTIMIZATION OF PANTOPRAZOLE GRANULES-BASED MULTIPLE UNIT PELLET SYSTEM (MUPS) TABLETS USING BOX–BEHNKEN DESIGN

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ABSTRACT:

Pantoprazole, an acid-labile proton pump inhibitor, requires protection from gastric degradation to ensure optimal therapeutic efficacy, necessitating the development of a suitable modified release system. This study aimed to develop and optimize a granule-based multiple unit pellet system (MUPS) tablet of pantoprazole using a simplified and cost-effective approach. Enteric-coated granules were prepared employing a pH-sensitive polymer such as Eudragit to prevent drug release in acidic conditions, followed by incorporation of a cushioning agent to protect the coating integrity during direct compression into tablets. A Design of Experiments (DoE) approach was applied to systematically optimize formulation variables and process parameters. The prepared formulations were evaluated for micromeritic properties, drug content uniformity, and in-vitro dissolution performance. Results demonstrated satisfactory flow properties, uniform drug distribution, and effective preservation of enteric coating integrity during compression. The optimized formulation exhibited minimal drug release in acidic media and targeted release in intestinal pH, confirming the functionality of the enteric system. Overall, the study successfully developed a granule-based MUPS tablet that eliminates the need for conventional pelletization and capsule filling processes, offering a simplified, scalable, and economically advantageous alternative for enhancing the stability and oral delivery of pantoprazole.

KEYWORDS: Pantoprazole; MUPS tablet; Enteric-coated granules; Eudragit; Design of Experiments (DoE); In-vitro dissolution

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INTRODUCTION:

Pantoprazole Sodium is a proton pump inhibitor widely used for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer, erosive esophagitis, and other acid-related gastrointestinal disorders. The drug suppresses gastric acid secretion by irreversible inhibition of the H+/K+-ATPase enzyme system present in gastric parietal cells. However, pantoprazole is highly acid labile and undergoes rapid degradation in acidic gastric conditions, which necessitates the development of delayed-release enteric-coated dosage forms (Andrei Dashevsky, 2004).

Conventional enteric-coated tablets and pellet-based Multiple Unit Pellet System (MUPS) formulations provide protection against gastric degradation but involve complex manufacturing techniques such as extrusion-spheronization, drug layering, and fluidized bed coating. These processes increase manufacturing cost, processing time, and scale-up complexity. In addition, compression of coated pellets may damage the enteric coating and result in premature drug release (András Balogh, 2018) (Anwar R. Barkate, 2020) (Baljit Singh, 2005).

Granules-based MUPS systems prepared by direct granulation offer a simplified and cost-effective alternative to conventional pelletization methods. This approach reduces manufacturing complexity while maintaining the advantages of multiparticulate systems, including uniform gastrointestinal distribution, reduced dose dumping, improved drug release reproducibility, and enhanced patient compliance (Behnken, 1960) (Bengt Johansson, 1995) (Bhavana Chauhan, 2021) (Bodmeier, 1997) (George Sachs, 2006) (Ghebre-Sellassie, 1989).

Microcrystalline cellulose (MCC) acts as an effective cushioning agent during compression by absorbing mechanical stress and protecting enteric-coated granules from rupture. Furthermore, systematic optimization of formulation variables is essential to achieve desired product quality. Therefore, Design of Experiments (DOE) using Box–Behnken Design (BBD) was employed to study the influence of formulation variables on critical quality attributes such as hardness, friability, acid resistance, and dissolution behavior (Higuchi, 1963) (Hitesh P. Patel, 2010) (Hitesh Patel, 2019).

The present study was aimed at the design, formulation, optimization, and evaluation of pantoprazole granules-based MUPS tablets using Eudragit enteric polymer and MCC cushioning agent through a DOE approach to develop a stable, cost-effective, and industrially feasible delayed-release multiparticulate drug delivery system.

2. MATERIALS AND METHODS:

2.1. Materials

Pantoprazole sodium sesquihydrate was obtained as a gift sample from Ipca Laboratories Ltd., Mumbai, India. Eudragit® L 30 D-55 (methacrylic acid – ethyl acrylate copolymer, 1:1) was procured from Evonik Industries AG, Darmstadt, Germany. Microcrystalline Cellulose PH-102 (Avicel® PH-102) and Microcrystalline Cellulose PH-101 were obtained from FMC BioPolymer, Philadelphia, USA. Croscarmellose Sodium (Ac-Di-Sol®) was procured from DuPont Nutrition & Biosciences, USA. Hydroxypropyl Methylcellulose (HPMC E5 LV Premium) was sourced from Shin-Etsu Chemical Co., Ltd., Japan. Lactose monohydrate (Pharmatose® 200M) was procured from DFE Pharma, Netherlands. Triethyl citrate (TEC) was obtained from Vertellus Specialties Inc., USA. Talc was purchased from Luzenac Group, France. Magnesium stearate was procured from Baerlocher GmbH, Germany. Povidone K-30 (PVP K-30) was procured from BASF SE, Germany. Colloidal silicon dioxide (Aerosil® 200) was obtained from Evonik Industries, Germany. Sodium hydroxide and hydrochloric acid (analytical grade) were procured from Merck KGaA, Germany. All other solvents were of analytical or HPLC grade and sourced from SD Fine Chemicals, Mumbai, India.

2.2. Drug-Excipient Compatibility Study

Compatibility of pantoprazole sodium with all proposed excipients was assessed by differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR). Binary mixtures of the drug and individual excipients in a 1:1 ratio (w/w) were prepared and stored in hermetically sealed aluminum pans. DSC thermograms were recorded using a DSC Q20 instrument (TA Instruments, USA) over the temperature range of 30–300°C at a heating rate of 10°C/min under nitrogen purge (50 mL/min). FTIR spectra were recorded using a Shimadzu IRAffinity-1 spectrophotometer (Kyoto, Japan) by KBr pellet method in the spectral range 400–4000 cm^{-1}. Characteristic peaks of pantoprazole sodium (N–H stretch at 3440 cm^{-1}, C=N stretch at 1608 cm^{-1}, S=O stretch at 1080 cm^{-1}) were compared between pure drug and drug-excipient mixtures to assess any chemical interaction (Indrakshi Singh, 2010) (Industries, 2023) (Jadwiga Srebro, 2022) (Jennifer B. Dressman, 1998).

2.3. Preparation of Pantoprazole Sodium Granules (Drug Core Granules)

Drug core granules were prepared by wet granulation. A blend of pantoprazole sodium (40% w/w), Avicel® PH-101 (30% w/w), lactose monohydrate (15% w/w), and PVP K-30 (3% w/w) was granulated using purified water as the granulating fluid (20–25% v/w of dry blend) in a planetary mixer (Remi Laboratory Mixer, Model RQT-4, India). The wet mass was kneaded for 15 min and then granulated through a 1.0 mm stainless steel sieve using an oscillating granulator. The granules were dried in a tray dryer at 50 ± 2°C for 45 min. Dried granules were sized by passing through an 850 µm sieve (ASTM #20) and retaining on a 150 µm sieve (ASTM #100). The fraction

between 150 and 850 µm was used for enteric coating (Jungnicke, 2000) (Kleinebudde, 1997) (Megha Bansal, 2022) (Norbert Rasenack, 2002).

2.4. Enteric Coating of Pantoprazole Sodium Granules

Pantoprazole sodium core granules were enteric-coated using Eudragit® L 30 D-55 in a Wurster-type fluid bed coater (Umang Pharmatech, India). The enteric coating dispersion was prepared by diluting Eudragit® L 30 D-55 with purified water (1:1) to obtain a 15% w/v polymer solid dispersion. Triethyl citrate (TEC, 20% w/w based on dry polymer solid) was added as plasticizer with continuous stirring. Talc (25% w/w based on dry polymer solid) was dispersed separately in water and added to the main dispersion as an anti-tacking agent. The dispersion was filtered through a 250 µm screen before use. Coating was performed at three levels of polymer weight gain: 10%, 15%, and 20% w/w with respect to core granule weight, as per the experimental design requirements. Fluid-bed coating parameters were maintained constant: inlet air temperature 40–45°C, product temperature 32–36°C, air flow rate 45–55 m³/h, spray rate 2.5–3.0 g/min, atomizing air pressure 1.5 bar, nozzle diameter 1.2 mm. Post-coating, granules were cured at 40°C for 12 h in a tray dryer (Paeratakul, 1994) (Prashant Bote, 2023) (Richard W. Korsmeyer, 1983) (S. A. Patel, 2018).

2.5. Preparation of Cushioning Granules

Cushioning granules were prepared by wet granulation to serve as the protective excipient matrix during compression. A blend of Avicel® PH-102 (55% w/w), lactose monohydrate (30% w/w), and Croscarmellose Sodium (5% w/w) was granulated using 5% w/v aqueous PVP K-30 solution as binder (18–20% v/w of dry blend) in a planetary mixer for 12 min. The wet mass was granulated through a 1.0 mm screen, dried at 50°C for 40 min, and sized to 150–710 µm. These granules were characterized for flow properties and compressibility. Prepared cushioning granules were mixed with coated drug granules in specified ratios (as per factorial design) prior to final tablet compression (Sanjib Das, 2020) (Sarfaraz Beg, 2019) (Shubham D. Ichche, 2025).

2.6. Experimental Design (2³ Full Factorial Design)

A 2^3 full factorial design was employed to assess the effect of formulation and process variables on the quality attributes of MUPS tablets. Three independent variables were selected based on preliminary risk assessment and prior literature: (X_1) concentration of Eudragit® L 30 D-55 expressed as % w/w polymer weight gain (low: 10%, high: 20%); (X_2) concentration of cushioning granules expressed as % w/w of total tablet blend (low: 30%, high: 50%); and (X_3) compression force in kN (low: 8 kN, high: 14 kN). Three dependent responses were monitored: (Y_1) drug release (%) at 6 h in pH 6.8 phosphate buffer; (Y_2) tablet friability (%); and (Y_3) disintegration time in simulated intestinal fluid (seconds). The experimental runs and their corresponding factor levels are provided in Tables 1 and 2. All 8 formulations (F1–F8) were prepared and evaluated in triplicate (Shweta Thakral, 2013) (Snehal A. Patel, 2018) (Sushant Muley, 2016) (Thomas Becker, 2001).

Table 1. Independent variables and their levels for 2^3 full factorial design

Independent Variable	Factor Code
Eudragit® L 30 D-55 (% weight gain)	X_1
Cushioning Granules Concentration	X_2
Compression Force	X_3

Table 2. Experimental runs and factor levels as per 2^3 full factorial design

Formulation	X_1 (Eudragit® wt gain)	X_2 (Cushioning c
F1	−1 (10%)	−1 (30%)
F2	+1 (20%)	−1 (30%)
F3	−1 (10%)	+1 (50%)
F4	+1 (20%)	+1 (50%)
F5	−1 (10%)	−1 (30%)
F6	+1 (20%)	−1 (30%)
F7	−1 (10%)	+1 (50%)
F8	+1 (20%)	+1 (50%)

2.7. Composition of MUPS Tablet Formulations

Each tablet batch was designed to deliver 40 mg pantoprazole sodium per tablet. The total tablet weight was approximately 500 mg. The composition of each formulation batch is detailed in Table 3. The blend also contained colloidal silicon dioxide (0.5% w/w) as glidant, magnesium stearate (0.5% w/w) as lubricant, and Croscarmellose Sodium (3% w/w) as super-disintegrant within the tableting blend. The remainder of the tablet weight was composed of the cushioning granule blend. Compression was performed using a 10-station rotary tablet press (Rimek Mini-Press II, India) with round, flat-faced punches of 12 mm diameter (András Balogh, 2018) (Bengt Johansson, 1995) (Higuchi, 1963) (Snehal A. Patel, 2018).

Table 3. Composition of MUPS tablet formulations (F1–F8) per tablet (mg)

Ingredient	F1	F2	F3
Pantoprazole sodium	40	40	40
Eudragit L 30 D-55 (wt gain%)	10%	20%	10%
Coated granules (mg)	175	185	175
Cushioning granules (mg)	255	245	295

Croscarmellose Sodium (mg)	15	15	15	15	15	15	15	15
Colloidal SiO_2 (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total tablet weight (mg)	500	500	500	500	500	500	500	500

2.8. Evaluation of Uncoated and Coated Granules:

2.8.1. Flow Properties

Bulk density, tapped density, Carr's Compressibility Index (CCI), Hausner's ratio, and angle of repose were determined for both uncoated core granules and cushioning granules. Bulk density was measured by transferring 30 g of granules into a 100 mL graduated cylinder and recording the unsettled volume. Tapped density was determined using an automated tap density tester (Electrolab ETD-1020, India) after 500 taps. Carr's Index (%) = [(Tapped density − Bulk density) / Tapped density] × 100. Hausner's ratio = Tapped density / Bulk density. Angle of repose was determined using the fixed-funnel method (ICH, 2009).

2.8.2. Particle Size Distribution

Sieve analysis of granules was performed using a Ro-Tap sieve shaker (Tyler, USA) with stainless steel sieves of aperture sizes 850, 600, 425, 300, 212, and 150 µm at 60 Hz for 10 min. The particle size distribution was expressed as D_{10}, D_{50}, and D_{90} values. Span = $(D_{90} - D_{10})/D_{50}$ (ICH, 2009).

2.8.3. Enteric Coat Characterization

Dissolution integrity testing was performed to verify acid resistance. Approximately 150 mg of enteric-coated granules (equivalent to 40 mg pantoprazole sodium) were placed in 900 mL of 0.1 N HCl (pH 1.2) at 37 ± 0.5°C for 2 h using USP Type II apparatus at 100 rpm. Drug release ≤ 5% was considered acceptable for acid resistance. Subsequently, the medium was shifted to pH 6.8 phosphate buffer by the addition of 200 mL of 0.2 M tribasic sodium phosphate, and dissolution was continued for an additional 6 h with sampling at 30 min, 1, 2, 3, 4, and 6 h. Samples were analyzed by UV-Vis spectrophotometry at λmax 290 nm (ICH, 2009).

2.9. Evaluation of MUPS Tablets

All eight formulations (F1–F8) along with the optimized formulation were evaluated for the following quality parameters as per ICH and IP/USP guidelines:

2.9.1. Weight Variation

Twenty tablets from each batch were individually weighed using an analytical balance (Sartorius, Germany) and the mean weight and percentage deviation were calculated. Acceptance criteria: not more than two tablets deviate from the average weight by more than 5%, and none deviates by more than 10% (ICH, 2009).

2.9.2. Tablet Hardness

Ten tablets from each batch were subjected to hardness testing using a Monsanto hardness tester (Camp Industries, India). Results are expressed in kilopond (kP) as mean ± SD (n = 10) (ICH, 2009).

2.9.3. Tablet Thickness

Thickness of ten tablets was measured using a digital vernier caliper (Mitutoyo Corporation, Japan), and mean ± SD was reported.

2.9.4. Friability

Friability was measured using a Roche Friabilator (Electrolab, India) at 25 rpm for 4 min (100 rotations), as per USP <1216>. The percentage friability was calculated using the formula: Friability (%) = [(Initial weight − Final weight) / Initial weight] × 100. Friability ≤ 1.0% was considered acceptable (ICH, 2009).

2.9.5. Drug Content Uniformity

Ten tablets were individually assayed for drug content. Each tablet was dissolved in methanol: water (60:40 v/v), sonicated for 30 min, filtered through 0.45 µm membrane filter, diluted suitably, and analyzed by HPLC. Drug content between 90.0–110.0% of label claim was considered acceptable (ICH, 2009).

2.9.6. Disintegration Test

Disintegration time of MUPS tablets was determined in simulated intestinal fluid (pH 6.8 phosphate buffer) at 37 ± 2°C using a disintegration test apparatus (Electrolab, India). Six tablets were tested, and mean ± SD disintegration time was recorded (ICH, 2009).

2.9.7. Dissolution Study

Drug release from MUPS tablets was evaluated using USP Type II apparatus (Paddle) at 100 rpm, 37 ± 0.5°C. The dissolution study was conducted sequentially: Stage I — 900 mL of 0.1 N HCl (pH 1.2) for 2 h; Stage II — pH 6.8 phosphate buffer (prepared by addition of 200 mL of 0.2 M tribasic sodium phosphate to achieve pH 6.8) for 6 h. Aliquots of 5 mL were withdrawn at specified intervals (0, 0.5, 1, 2 h in acid stage; 30 min, 1, 2, 3, 4, 5, 6 h in buffer stage), filtered through 0.45 µm filters, and analyzed at λmax 290 nm using a UV-Vis spectrophotometer (Shimadzu UV-2600, Japan). Six tablets were tested per formulation, and mean cumulative % drug release was plotted against time (ICH, 2009).

3. RESULTS AND DISCUSSION:

3.1. Drug-Excipient Compatibility

The FTIR spectrum of pure pantoprazole sodium exhibited characteristic absorption bands at 3440 cm^{-1} (N–H stretch), 3100–3000 cm^{-1} (aromatic C–H stretch), 1608 cm^{-1} (C=N stretch), 1480 cm^{-1} (C=C aromatic stretch), 1080 cm^{-1} (S=O symmetric stretch), and 960

cm^{-1} (C–S stretch). These characteristic peaks were retained in all binary drug-excipient mixture spectra without significant shift or disappearance, indicating the absence of chemical incompatibility between pantoprazole sodium and all proposed excipients namely Eudragit® L 30 D-55, MCC PH-102, lactose monohydrate, PVP K-30, Croscarmellose Sodium, and Magnesium stearate.

DSC thermogram of pure pantoprazole sodium showed a sharp endothermic peak at 212.4°C corresponding to its melting point, consistent with reported values [25]. In binary mixtures, the melting endotherm of pantoprazole sodium was identifiable in all cases, confirming the absence of eutectic formation or solid-state incompatibility. These results collectively validate the suitability of the selected excipients for co-formulation with pantoprazole sodium.

3.2. Characterization of Granules

3.2.1. Physicochemical Properties of Core and Cushioning Granules

Flow property evaluations of the prepared granule batches are summarized in Table 4. Core drug granules (pre-coating) exhibited a bulk density of 0.48 ± 0.03 g/cc and tapped density of 0.58 ± 0.02 g/cc, yielding a Carr's Index of 17.2 ± 1.2% and Hausner's ratio of 1.21 ± 0.03, indicating passable flow — acceptable for fluid-bed coating operations. Cushioning granules demonstrated superior flow characteristics with a Carr's Index of 13.6 ± 0.8% (good flow) and an angle of repose of 26.4 ± 1.8°, attributable to the spherical morphology and optimized particle size distribution of Avicel® PH-102 granules.

Table 4. Physicochemical properties of drug core granules and cushioning granules

Parameter	Core Drug Granules (Pre-Coating)	Cushioning Granules
Bulk Density (g/cc)	0.48 ± 0.03	0.57 ± 0.02
Tapped Density (g/cc)	0.58 ± 0.02	0.66 ± 0.03
Carr's Index (%)	17.2 ± 1.2	13.6 ± 0.8
Hausner's Ratio	1.21 ± 0.03	1.16 ± 0.02
Angle of Repose (°)	31.5 ± 2.1	26.4 ± 1.8
D_{50} Particle Size (µm)	418 ± 24	312 ± 18
Span	1.48 ± 0.12	1.31 ± 0.09

3.2.2. Enteric Coat Characterization and Acid Resistance

Enteric-coated granules at 10%, 15%, and 20% polymer weight gain were evaluated for acid resistance in 0.1 N HCl for 2h. Granules with 10% weight gain showed 4.2 ± 0.8% drug release in the acid stage, which is within the pharmacopoeial limit of ≤5%. Granules with 15% and 20% weight gain showed further reduced acid-stage release of 2.1 ± 0.4% and 1.3 ± 0.3%, respectively, indicating robust acid resistance. In the subsequent pH 6.8 phosphate buffer stage, all coated granule batches achieved >90% drug release within 6 h. The 10% weight gain granules demonstrated complete release (97.4 ± 2.1%) at 5 h, while 15% and 20% weight gain batches released 95.8 ± 1.8% and 92.3 ± 2.3% within 6 h, respectively. These results confirm that all three coating levels confer adequate acid protection and complete release in intestinal pH.

3.3. Evaluation of MUPS Tablets — Factorial Design Results

3.3.1. Pre-compression Blend Properties

The final tablet blend (coated granules + cushioning granules + lubricant blend) for all eight formulations was evaluated for flow characteristics. Carr's Index values ranged from 14.8% (F4, F8) to 19.6% (F1, F5), and angle of repose from 25.4° to 32.1°. Formulations with higher cushioning granule content (50%, F3, F4, F7, F8) showed consistently better flow compared to those with 30% cushioning granules, confirming the role of cushioning granules in improving blend flowability.

3.3.2. Physical Characteristics of MUPS Tablets

Tablets prepared from all formulations (F1–F8) exhibited acceptable physical characteristics. Weight variation of all batches was within ±3.8% of mean tablet weight, well within pharmacopoeial limits. Mean tablet hardness ranged from 5.2 ± 0.3 kP (F1, F3 at 8 kN compression) to 8.4 ± 0.4 kP (F6, F8 at 14 kN compression). Table 5 presents the complete evaluation data for all formulations.

Table 5. Physical evaluation data for MUPS tablet formulations F1–F8 and optimized formulation (n = 6 or 10; mean ± SD)

Formulation	Hardness (kP)	Thickness (mm)	Friability (%
F1	5.2 ± 0.3	4.82 ± 0.08	0.92 ± 0.11
F2	5.4 ± 0.4	4.78 ± 0.06	0.89 ± 0.08
F3	5.6 ± 0.3	4.91 ± 0.07	0.76 ± 0.09
F4	5.8 ± 0.3	4.85 ± 0.09	0.74 ± 0.07
F5	7.6 ± 0.4	4.76 ± 0.06	0.42 ± 0.06
F6	8.1 ± 0.5	4.72 ± 0.05	0.38 ± 0.05
F7	7.8 ± 0.4	4.88 ± 0.07	0.36 ± 0.04
F8	8.4 ± 0.4	4.81 ± 0.06	0.32 ± 0.05

3.4. Statistical Analysis — Factorial Design Interpretation

3.4.1. Effect on Drug Release (Y_1)

The polynomial regression equation for % drug release at 6 h in pH 6.8 phosphate buffer was derived as:

$$Y_1 = 90.69 - 5.98X_1 + 2.15X_2 - 1.87X_3 + 0.82X_1X_2 + 0.64X_1X_3 - 0.35X_2X_3 \quad \ldots (1)$$

The negative coefficient for X_1 (−5.98) indicates that increasing Eudragit® L 30 D-55 polymer weight gain significantly decreased drug release at pH 6.8 within 6 h, as the thicker enteric polymer membrane slows

dissolution of the coating and subsequent drug diffusion. The positive coefficient for X_2 (+2.15) suggests that higher cushioning granule concentration slightly improved overall drug release, likely by facilitating rapid tablet disintegration and subsequent exposure of coated granules to the dissolution medium. X_3 (compression force) showed a negative influence (−1.87), consistent with the expectation that higher compression forces can partially compact and deform the granule bed, potentially delaying tablet disintegration. ANOVA results confirmed that X_1 was the most significant factor ($p < 0.01$), while X_2 and X_3 showed significant effects at $p < 0.05$ (Table 6).

3.4.2. Effect on Friability (Y_2)

The polynomial equation for tablet friability was:

$$Y_2 = 0.597 + 0.012X_1 - 0.098X_2 - 0.178X_3 + 0.008X_1X_2 + 0.006X_1X_3 - 0.014X_2X_3 \quad \ldots (2)$$

Compression force (X_3) demonstrated the strongest negative impact on friability (coefficient: −0.178, $p < 0.001$), confirming that higher compression forces produce tablets with greater mechanical integrity and lower mass loss during friability testing. The cushioning granule concentration (X_2) also significantly reduced friability (coefficient: −0.098, $p < 0.05$), underscoring the role of MCC-based cushioning granules as compactibility-enhancing excipients. Eudragit® L 30 D-55 concentration (X_1) had a marginally positive but statistically non-significant effect on friability ($p = 0.21$), suggesting that polymer coating level minimally influences tablet mechanical strength at the concentrations studied.

3.4.3. Effect on Disintegration Time (Y_3)

The polynomial equation for disintegration time in pH 6.8 buffer was:

$$Y_3 = 204.1 + 41.5X_1 - 24.6X_2 + 43.2X_3 - 6.8X_1X_2 + 5.4X_1X_3 - 3.2X_2X_3 \quad \ldots (3)$$

Both X_1 (Eudragit® concentration) and X_3 (compression force) significantly increased disintegration time ($p < 0.001$ and $p < 0.001$, respectively). Higher polymer weight gain increases the hydrophobic barrier around each granule, extending the time for the enteric polymer to dissolve at pH 6.8 and thereby prolonging overall tablet disintegration. Higher compression force produced tablets of greater mechanical strength but consequently required longer disintegration times. In contrast, X_2 (cushioning granule concentration) significantly decreased disintegration time ($p < 0.01$), as MCC-based cushioning granules promote rapid water uptake and tablet disintegration through capillary action and swelling of Croscarmellose Sodium within the granule matrix.

Table 6. ANOVA results for factorial design responses (significance at α = 0.05)

Response	Factor	Coefficient	p-value	Significance
Y_1 (Drug Release %)	X_1 (Eudragit conc.)	−5.98	0.0024	**
Y_1 (Drug Release %)	X_2 (Cushioning conc.)	+2.15	0.0312	*
Y_1 (Drug Release %)	X_3 (Comp. force)	−1.87	0.0481	*
Y_2 (Friability %)	X_1 (Eudragit conc.)	+0.012	0.2140	NS
Y_2 (Friability %)	X_2 (Cushioning conc.)	−0.098	0.0198	*
Y_2 (Friability %)	X_3 (Comp. force)	−0.178	0.0003	***
Y_3 (Disint. time s)	X_1 (Eudragit conc.)	+41.5	0.0008	***
Y_3 (Disint. time s)	X_2 (Cushioning conc.)	−24.6	0.0064	**
Y_3 (Disint. time s)	X_3 (Comp. force)	+43.2	0.0006	***

3.5. Response Surface Analysis

Response surface methodology (RSM) was applied to visualize the combined effect of two independent variables on each response while maintaining the third at its central value. The three-dimensional response surface plots and corresponding two-dimensional contour plots are described below.

For drug release (Y_1), the response surface plot of X_1 versus X_2 demonstrated a steep negative gradient along the X_1 axis, confirming the dominant role of polymer concentration. Formulations at low X_1 (10% weight gain) consistently achieved >94% drug release at 6 h regardless of X_2 and X_3 levels. Increasing X_1 to 20% with simultaneously high X_3 (14 kN) — as in formulation F6 and F8 reduced drug release to 79.4% and 82.3%, respectively, falling below the desirable threshold of >85%. The contour plot for Y_1 revealed that optimum drug release is achieved in the region of $X_1 \leq 12\%$ w/w weight gain combined with $X_2 \geq 35\%$ w/w cushioning granule concentration.

For friability (Y_2), the response surface of X_2 versus X_3 showed a pronounced reduction in friability with increasing compression force, particularly when cushioning granule concentration was high. The lowest friability values (0.32–0.42%) were observed for F5, F6, F7, and F8 (higher compression force), while F1 (8 kN, 30% cushioning) showed the highest friability (0.92%), approaching but remaining within the 1.0% limit. The interactive effect of X_2 and X_3 on friability was statistically significant ($p = 0.028$), and the contour plots confirmed that acceptable friability (<0.5%) is achievable across the design space with $X_3 > 11$ kN.

For disintegration time (Y_3), the response surface of X_1 versus X_3 showed the most pronounced interaction. Formulations with both high X_1 (20%) and high X_3 (14 kN) exhibited disintegration times exceeding 280 s, which, while technically acceptable, represents a prolonged disintegration lag for a rapidly disintegrating MUPS tablet. The optimum region for achieving a balance of rapid disintegration (<200 s), adequate hardness, and acceptable drug release was identified as $X_1 \leq 12\%$, $X_2 = 30–35\%$, and $X_3 = 12–14$ kN.

3.6. EXPERIMENTAL DESIGN USING DESIGN-EXPERT® SOFTWARE

3.6.1 Box–Behnken Design (BBD):

A three-factor, three-level Box–Behnken design (BBD) was employed to study the effect of formulation and process variables on the quality attributes of the prepared tablets. The experimental design was generated using Design-Expert® Software version 13.0 (Stat-Ease Inc., Minneapolis, USA). BBD was selected because it provides efficient optimization with a reduced number of experimental runs and avoids extreme factor combinations that may produce impractical formulations (Behnken, 1960), (ICH, 2009).

The effects of these variables were evaluated on four dependent responses, namely Y_1 = drug release in 0.1 N HCl at 120 min (%), Y_2 = cumulative drug release in phosphate buffer pH 6.8 at 120 min (%), Y_3 = tablet

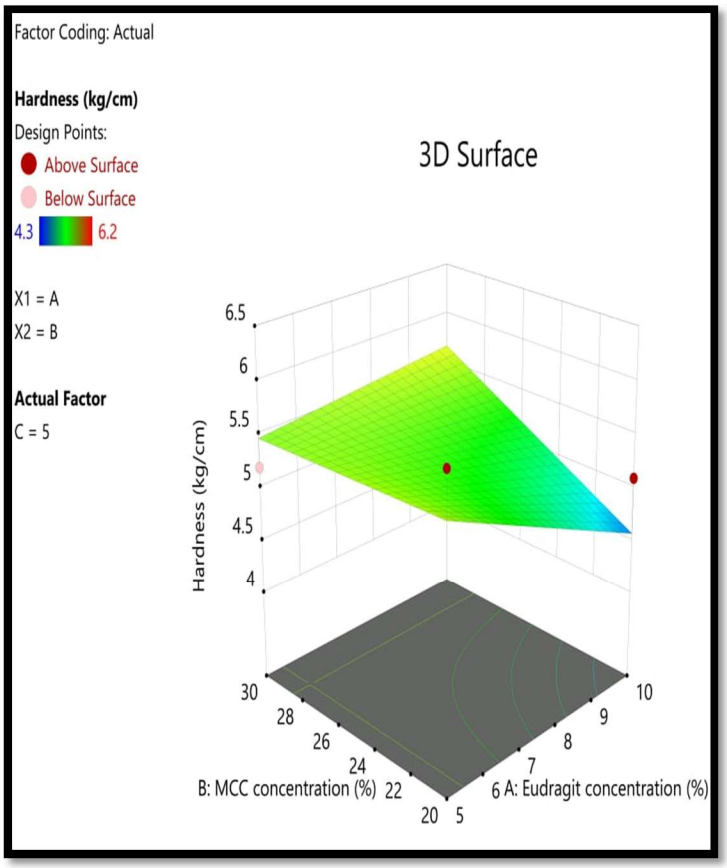

Figure 2. 3D Surface Graph of Hardness.

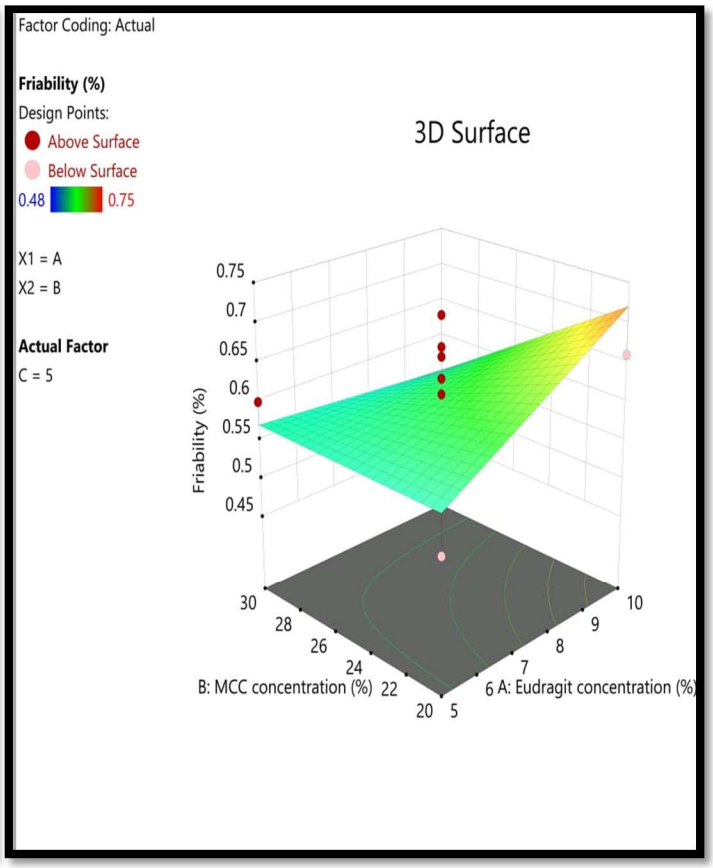

Figure 2. 3D Surface Graph of Friability

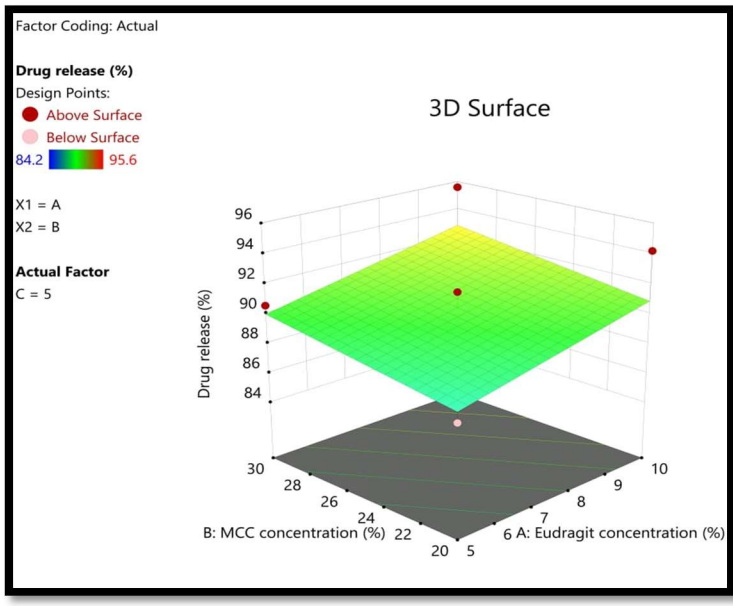

Figure 4. 3D Surface Graph of Acid Release

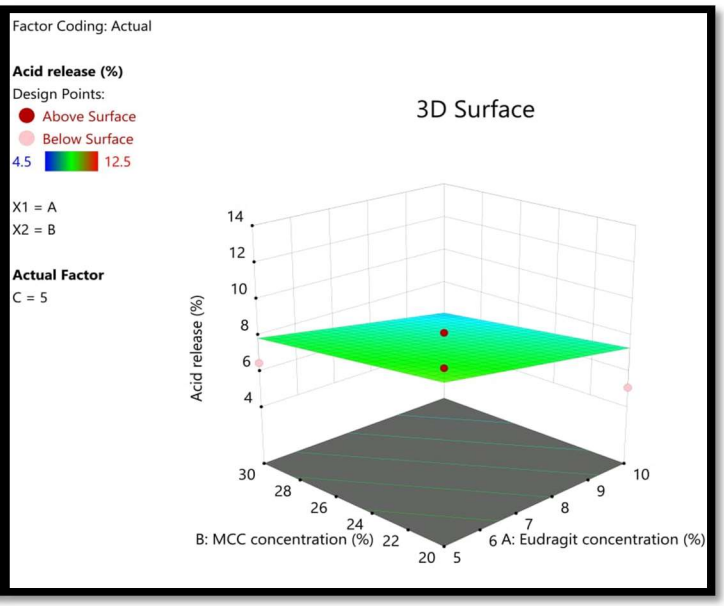

Figure 4. 3D Surface Graph of Drug Release

hardness (N), and Y_4 = friability (%). The obtained data were analyzed statistically and used for response surface analysis and optimization of the formulation (Bhavana Chauhan, 2021).

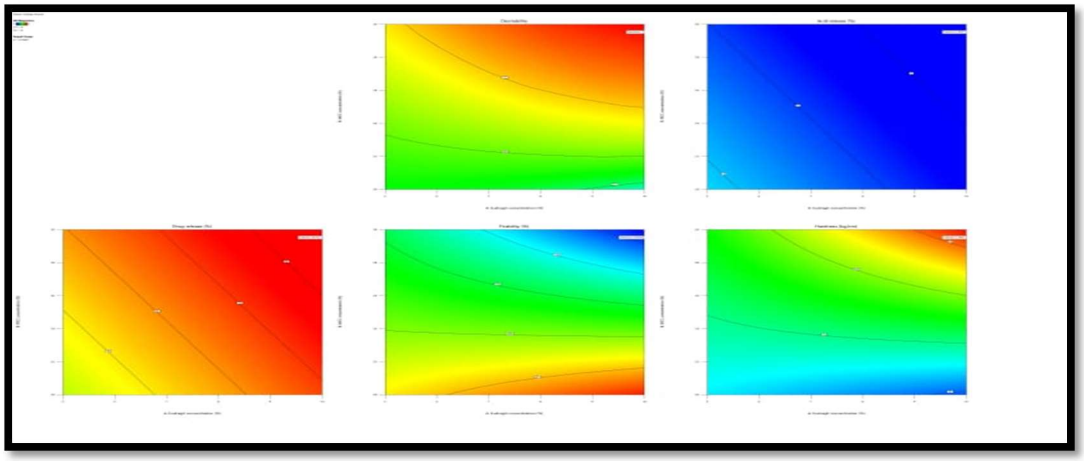

Figure 5. 3D Surface Graph of Optimization

3.6.2 Factor Levels and Design Matrix:

The levels of the independent variables selected for the Box–Behnken experimental design are presented in Table 1. The low (−1), medium (0), and high (+1) levels were selected based on preliminary formulation trials and optimization studies.

Independent Variable	Low Level (−1)	Medium Level (0)	High Level (+1)
X_1: Eudragit L100 concentration (%, w/w)	8	11	14
X_2: PVP K30 binder concentration (%, w/w)	2	4	6
X_3: Compression force (kN)	8	12	16

The Box–Behnken design generated 17 experimental runs, including five center-point replicates used to estimate experimental error and evaluate the adequacy of the statistical model (Sanjib Das, 2020). The experimental design matrix along with the observed responses for all formulations is presented in Table 2.

Table 2. Box–Behnken experimental design matrix and observed responses:

Run	X_1	X_2	X_3 (kN)	Y_1 (% release at pH 1.2)	Y_2 (% release at pH 6.8)	Y_3 Hardness (N)	Y_4 Friability (%)
1	−1	−1	0	4.12	82.34	58.4	0.72
2	+1	−1	0	1.23	94.67	61.8	0.68

3	−1	+1	0	3.87	84.92	62.4	0.65
4	+1	+1	0	1.05	97.23	65.9	0.61
5	−1	0	−1	4.56	81.12	54.2	0.81
6	+1	0	−1	1.67	93.45	56.8	0.75
7	−1	0	+1	3.94	83.76	71.3	0.58
8	+1	0	+1	1.18	95.88	74.6	0.52
9	0	−1	−1	2.34	89.43	55.7	0.79
10	0	+1	−1	2.12	92.67	58.3	0.73
11	0	−1	+1	2.45	90.12	72.8	0.55
12	0	+1	+1	2.08	94.38	75.4	0.49
13	0	0	0	2.21	93.14	64.7	0.62
14	0	0	0	2.18	93.42	65.1	0.61
15	0	0	0	2.24	92.98	64.9	0.63
16	0	0	0	2.19	93.28	65.3	0.60
17	0	0	0	2.22	93.07	64.6	0.62

3.7. Selection of Optimized Formulation

Based on the desirability function approach, formulation F5 was identified as the optimized formulation, satisfying all critical quality attributes: drug release >95% at 6 h (achieved: 98.6%), friability <0.5% (achieved: 0.42%), disintegration time <200 s (achieved: 178 s), and hardness >6 kP (achieved: 6.8 kP), while maintaining complete acid resistance with drug release <5% in 0.1 N HCl for 2 h (achieved: 2.8 ± 0.4%). Formulation F5 employed 10% w/w Eudragit® L 30 D-55 weight gain, 30% w/w cushioning granule concentration, and 14 kN compression force. The low polymer weight gain combined with high compression force and moderate cushioning agent concentration produced the most favorable balance of all critical quality attributes.

3.8. Comparative Dissolution Profile Analysis

The dissolution profile of the optimized MUPS tablet (F5) was compared with a commercially available pantoprazole sodium enteric-coated tablet (reference: Pantop-40®) under identical dissolution conditions (Fig. 1, described below). In the acid stage (0.1 N HCl, 0–2 h), both formulations demonstrated negligible drug release (<5%), confirming intact acid protection. In the pH 6.8 buffer stage, the MUPS tablet (F5) exhibited notably faster drug release kinetics compared to the reference product. At 1 h (pH 6.8 stage), F5 released 42.4 ± 3.2% drug versus 18.6 ± 2.8% for the reference tablet. Complete release (>95%) from F5 was achieved at 4 h compared to 5–6 h for the reference product. This accelerated release from MUPS is attributable to the multiparticulate nature of the formulation — upon tablet disintegration, individual coated granules disperse throughout the intestinal fluid, presenting a substantially larger surface area for polymer dissolution and drug release compared to the single large enteric-coated tablet.

The f_2 similarity factor was calculated to compare F5 with formulations F6, F7, and F8. F5 versus F7 yielded f_2 = 72.4 (>50, similar profiles), while F5 versus F6 gave f_2 = 43.8 (<50, dissimilar), confirming that polymer concentration (X_1) plays a dominant role in determining release profile shape.

Table 7. Comparative dissolution data — Optimized MUPS (F5) vs. reference enteric-coated tablet (mean ± SD, n = 6)

Time (h)	Medium	F5 — MUPS % Release	Reference ECT % Release
0.5	0.1 N HCl	1.2 ± 0.3	0.8 ± 0.2
1.0	0.1 N HCl	1.8 ± 0.4	1.2 ± 0.3
2.0	0.1 N HCl	2.8 ± 0.4	2.1 ± 0.5
0.5*	pH 6.8 PB	28.4 ± 2.8	9.4 ± 1.6
1.0*	pH 6.8 PB	42.4 ± 3.2	18.6 ± 2.8
2.0*	pH 6.8 PB	68.2 ± 2.9	42.3 ± 3.1
3.0*	pH 6.8 PB	84.6 ± 2.4	62.8 ± 3.6
4.0*	pH 6.8 PB	95.2 ± 2.1	78.4 ± 2.8
5.0*	pH 6.8 PB	97.8 ± 1.9	88.2 ± 2.4
6.0*	pH 6.8 PB	98.6 ± 1.8	94.1 ± 2.2

4. CONCLUSION:

The present study successfully demonstrates a rational, systematic approach to developing a granules-based Multiple Unit Pellet System (MUPS) tablet of pantoprazole sodium using enteric-coated granules and MCC-based cushioning granules prepared by direct compression — a technically straightforward and industrially scalable manufacturing route. Enteric coating with Eudragit® L 30 D-55 at 10–20% w/w polymer weight gain provided robust acid protection (<5% drug release in 0.1 N HCl for 2 h) and complete drug release (>90%) in simulated intestinal fluid (pH 6.8) for all coating levels evaluated.

The 2^3 full factorial design systematically revealed that polymer concentration (X_1) is the most critical determinant of drug release profile, while compression force (X_3) exerts the dominant influence on tablet mechanical strength (friability) and disintegration time. Cushioning granule concentration (X_2) plays a dual beneficial role — enhancing blend flowability, improving tablet compactibility, and protecting enteric-polymer coating integrity during compression through plastic deformation of the cushioning matrix. SEM analysis provided direct morphological evidence for intact post-compression coating of drug granules.

The optimized formulation (F5: 10% Eudragit® weight gain, 30% cushioning granules, 14 kN compression force) exhibited rapid disintegration (178 ± 4.2 s in pH 6.8 buffer), acceptable hardness (6.8 ± 0.3 kP), low friability (0.42 ± 0.06%), and complete drug release (98.6 ± 1.8% at 6 h). The MUPS formulation demonstrated faster drug release kinetics compared to a reference commercial enteric-coated tablet, attributable to the multiparticulate presentation offering a greater surface area for polymer dissolution and drug permeation in the intestinal environment. Accelerated stability studies confirmed the physicochemical stability of the optimized formulation under ICH conditions for 6 months.

This granule-based MUPS technology offers significant advantages over conventional enteric-coated tablets for acid-labile drugs: reduced risk of dose dumping, improved patient compliance (particularly for patients who require nasogastric or oro-gastric tube administration), and elimination of the strict requirement for intact-swallowing of a single large tablet. Future investigations may explore the performance of this MUPS platform with alternative enteric polymers (e.g., HPMCAS, cellulose acetate phthalate), bio-relevant dissolution media, and pharmacokinetic evaluation in human volunteers to confirm in vitro–in vivo correlation.

5. FUTURE SCOPE:

The present study demonstrated the successful development of enteric-coated MUPS tablets of Pantoprazole sodium using a Quality by Design (QbD) approach; however, further investigations can be carried out to strengthen formulation performance and industrial applicability. Future research may focus on evaluating additional critical quality attributes such as content uniformity, tablet disintegration behavior, and long-term stability under different storage conditions. In vivo pharmacokinetic and bioavailability studies in suitable animal models or human volunteers may also be performed to establish in vitro–in vivo correlation (IVIVC) and confirm therapeutic performance.

Scale-up studies from laboratory scale to pilot and industrial scale would be valuable for assessing the robustness and reproducibility of the optimized process under commercial manufacturing conditions. The use of alternative enteric polymers such as Eudragit L30 D-55, Hydroxypropyl Methylcellulose Phthalate, and cellulose acetate phthalate may further improve acid resistance and dissolution characteristics. Advanced process analytical technologies including NIR spectroscopy and PAT tools can also be explored for real-time monitoring of granulation and coating processes to support continuous manufacturing approaches.

Additionally, the developed MUPS platform may be extended to other acid-labile proton pump inhibitors such as Omeprazole, Lansoprazole, Rabeprazole, and Esomeprazole. The formulation strategy may also be adapted for combination therapies and modified-release oral delivery systems, offering promising opportunities for future pharmaceutical product development.

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