

Formulation, Optimization & *In vitro* Evaluation of Pantoprazole Loaded Nanosponges Incorporated Enteric Coated Tablet

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Pantoprazol Yüklü Nanosünger İçeren Enterik Kaplı Tabletlerin Formülasyonu, Optimizasyonu ve *In Vitro* Değerlendirilmesi

SUMMARY

Peptic ulcer disease is a chronic gastrointestinal condition characterized by mucosal erosion and frequent relapse, adversely impacting patient quality of life. Pantoprazole, a proton pump inhibitor commonly employed for gastric acid suppression, faces challenges such as acid-mediated instability. This investigation was focused on enhancing the acid stability of pantoprazole and enabling prolonged intestinal release by formulating nanosponges incorporated into enteric-coated tablets. These nanosponges were prepared via the emulsion solvent diffusion technique and optimized using a factorial design, evaluating the effects of polymer concentration, sonication duration, and stirring speed. The optimized nanosponge formulation (PLN3) demonstrated a yield of $63.0 \pm 2.12\%$, an average particle size of 209.8 ± 0.16 nm, a narrow polydispersity index of 0.0586 ± 0.001 , an entrapment efficiency of $83.0 \pm 4.0\%$, and a zeta potential of -32.5 mV, indicating stable and uniformly dispersed nanosponges suitable for sustained drug delivery. *In vitro* release studies showed limited drug release ($19.2 \pm 0.31\%$) in acidic medium, ensuring protection from gastric degradation, followed by sustained release ($68.2 \pm 0.43\%$) over 12 h in the intestinal pH. Tablets containing the pure drug and the optimized nanosponges, respectively, were prepared and enteric-coated; both demonstrated satisfactory physicochemical properties. Comparative *in vitro* studies revealed that the pure drug enteric-coated tablet released $92.53 \pm 1.2\%$ within 7 h, whereas the nanosponge-based enteric-coated tablet exhibited a controlled release of $83.0 \pm 0.33\%$ over 18 h. This confirms that the nanosponge system provides more effective sustained drug release than the conventional formulation. The developed nanosponge-based enteric-coated tablets of pantoprazole effectively overcame pH instability, and provided prolonged intestinal release, indicating their potential as a novel oral delivery system for improved management of peptic ulcer disease.

Keywords: Nanosponges, peptic ulcer, enteric coating, sustained release, and factorial design

ÖZ

Peptik ülser hastalığı, mukozal erozyon ve sık nüks ile karakterize edilen, hastaların yaşam kalitesini olumsuz etkileyen kronik bir gastrointestinal hastalıktır. Gastrik asit baskılanmasında yaygın olarak kullanılan bir proton pompa inhibitörü olan pantoprazol, asit kaynaklı kararsızlık gibi zorluklarla karşı karşıyadır. Bu çalışma, pantoprazolün asit stabilitesini artırmak ve enterik kaplı tabletlere entegre edilen nanosüngerler aracılığıyla uzatılmış intestinal salım sağlamak amacıyla gerçekleştirilmiştir. Nanosüngerler, emülsiyon çözücü difüzyon tekniği kullanılarak hazırlanmış ve polimer konsantrasyonu, sonikasyon süresi ve karıştırma hızının etkileri değerlendirilerek faktöriyel tasarım yöntemiyle optimize edilmiştir. Optimize edilen nanosünger formülasyonu (PLN3), $63,0 \pm 2,12$ verim, $209,8 \pm 0,16$ nm ortalama parçacık boyutu, $0,0586 \pm 0,001$ dar polidispersite indeksi, $83,0 \pm 4,0$ enkapsülasyon verimi ve $-32,5$ mV zeta potansiyeli göstermiştir. Bu sonuçlar, sürdürülebilir ilaç salımı için uygun, stabil ve homojen şekilde dağılmış nanosüngerleri işaret etmektedir. *In vitro* salım çalışmaları, asidik ortamda sınırlı ilaç salımı ($19,2 \pm 0,31$) göstererek ilacın mide kaynaklı degradasyona karşı korunduğunu ve ardından intestinal pH ortamında 12 saat boyunca uzatılmış salım ($68,2 \pm 0,43$) sağlandığını ortaya koymuştur. Saf ilaç ve optimize edilmiş nanosünger içeren tabletler ayrı ayrı hazırlanmış ve enterik kaplanmıştır; her iki formülasyon da tatmin edici fizikokimyasal özellikler sergilemiştir. Karşılaştırmalı *in vitro* çalışmalar, saf ilaç içeren enterik kaplı tabletin 7 saat içinde $92,53 \pm 1,2$ ilaç salımı sağladığını; nanosünger bazlı enterik kaplı tabletin ise 18 saat boyunca $83,0 \pm 0,33$ oranında kontrollü salım gerçekleştirdiğini göstermiştir. Bu bulgular, nanosünger sisteminin geleneksel formülasyona kıyasla daha etkili sürdürülebilir ilaç salımı sağladığını doğrulamaktadır. Geliştirilen pantoprazol yüklü nanosünger bazlı enterik kaplı tabletler, pH kaynaklı kararsızlık problemini etkili şekilde aşmış ve uzatılmış intestinal salım sağlamıştır. Bu sonuçlar, peptik ülser hastalığının daha etkili yönetimi için yeni bir oral ilaç taşıma sistemi olarak potansiyel taşıdığını göstermektedir.

Anahtar Kelimeler: Nanosüngerler, peptik ülser, enterik kaplama, sürdürülebilir salım ve faktöriyel tasarım

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INTRODUCTION

Peptic ulcer disease (PUD) is a long-lasting gut-related condition marked by mucosal injury in the stomach or duodenum. This damage occurs due to a disruption in the alignment between the stomach's protective defenses and harmful factors like gastric acid, pepsin, bile salts, and infection by *H. pylori*. Globally, PUD affects approximately 5–10% of adults, with a higher incidence in developing nations, and remains a major cause of morbidity due to recurrent episodes and adverse outcomes including hemorrhage, tissue perforation and blockage of the gastric exit (Sung, Kuipers, & El-Serag, 2009).

The development of PUD arises from multiple interacting elements, encompassing microbial agents, chemical irritants, and host susceptibility factors. *Helicobacter pylori* infection stands as the predominant trigger for duodenal ulcers and a major contributor to gastric ulcers, as it compromises epithelial barriers and weakens mucosal protective functions (Malfertheiner et al., 2017). Another significant contributor to ulcers is NSAIDs. They block prostaglandin production, which normally helps protect the stomach. Because of this, the stomach produces less bicarbonate and mucus, and the lining receives less blood, which increases the risk of damage (Lanas & Chan, 2017). Other contributing factors include hypersecretion of gastric acid, stress, alcohol intake, smoking, poor dietary habits, and genetic predisposition. These factors collectively disrupt the mucosal barrier, epithelial injury, and microvascular damage, resulting in chronic ulcer formation (Laine, Takeuchi, & Tarnawski, 2008; Tarnawski & Ahluwalia 2012).

Current therapeutic strategies focus on acid suppression, *H. pylori* eradication, and mucosal protection. Proton pump inhibitors (PPIs) like pantoprazole, omeprazole, and esomeprazole are the mainstay of treatment because of their strong and long-lasting inhibition of gastric acid secretion (Chey et al., 2024; Shin & Kim, 2013). The therapeutic effectiveness of PPIs is hindered by their poor solubility in water,

which affects their absorption and overall clinical performance; their acid-labile nature, short plasma half-life, and low bioavailability, lead to frequent dosing and variable therapeutic outcomes. Furthermore, pantoprazole is a BCS Class III drug with high solubility (~0.495 mg/mL) and moderate oral bioavailability (~77%). However, it is highly acid-labile and undergoes rapid degradation in gastric conditions, necessitating protective formulation strategies. In the present study, Eudragit L100-based nanosponges were developed to enhance acid protection and enable targeted drug release in the intestinal environment (Sharma, Gupta, & Gupta, 2016). Advancements in drug delivery systems based on the nano range have introduced new opportunities to overcome these pharmacokinetic and stability challenges. Nanocarrier systems such as nanoparticles, liposomes, and nanosponges have demonstrated potential for enhancing solubility, stability, and site-specific delivery of drugs.

Among these, nanosponges are three-dimensional, porous polymeric network. offer significant advantages because they can encapsulate various therapeutic molecules, protect drugs that are unstable in acidic conditions, and provide sustained and controlled drug release (AJPRD, Sontakke, Borkar, More, & Shinde, 2025). Unlike classical cyclodextrin-based nanosponges, the present study employs Eudragit L100-based polymeric nanosponges, which offer pH-dependent solubility and are specifically designed for enteric drug delivery. This system provides enhanced protection against gastric degradation and facilitates controlled drug release in the intestinal pH (AJPRD et al., 2025; Moin et al., 2020). The combination of high surface area, controllable porosity, and bio-compatible nature makes them ideal for the oral transport of gastroprotective therapeutics. The purpose of this investigation was to prepare and optimize pantoprazole-loaded nanosponges via the emulsion solvent diffusion technique and integrate them into enteric-coated tablets to provide improved gastric protection and prolonged intestinal drug release for better peptic ulcer management.

MATERIALS AND METHODS

Materials

Pantoprazole sodium was obtained as a gift sample from Pramog Labs (Hyderabad, India). Eudragit L100 was supplied by Evonik Industries AG (Essen, Germany). Polyvinyl alcohol (PVA; analytical grade) and dichloromethane (DCM; $\geq 99\%$ purity) were from Rankem Chemicals Pvt. Ltd. (New Delhi, India). Cellulose acetate phthalate (CAP) was procured from CDH Fine Chemicals Pvt. Ltd. (New Delhi, India), while microcrystalline cellulose (MCC; Avicel PH101) and magnesium stearate were obtained from Valtris Specialty Chemicals Pvt. Ltd. (Mumbai, India). Hydrochloric acid, acetone, and other reagents used were of analytical grade. Double-distilled water was used throughout the study.

Methods

Preformulation studies

Pantoprazole was evaluated for organoleptic properties, melting point, and solubility in different solvents. The absorption maxima ($\lambda_{\max}$) were determined in 0.1 N HCl and phosphate buffer (PB) (pH 6.8) using a UV spectrophotometer within the concentration range of 2–20 $\mu\text{g/mL}$. Drug–polymer compatibility was examined by DSC (Star^c SW) and FTIR (SHIMAZU) to assess potential interactions.

Table 1. Factors and levels used in a 2^3 factorial design

Factor Code	Factor	Low (-1)	High (+1)
A	Eudragit L 100 (mg)	100	600
B	Sonication time (min)	10	20
C	Stirring speed (rpm)	1000	1500

Table 2. Formulation design for preparation of pantoprazole-loaded nanosponges

Formulation Variables	PLN 1	PLN 2	PLN 3	PLN 4	PLN 5	PLN 6	PLN 7	PLN 8
PAN: Eudragit L100	1:1	1:6	1:6	1:6	1:1	1:1	1:6	1:1
PVA (mg)	500	500	500	500	500	500	500	500
DCM (mL)	20	20	20	20	20	20	20	20
Distilled water (mL)	100	100	100	100	100	100	100	100
Sonication time (min)	10	10	10	20	20	10	20	20
Stirring speed (rpm)	1000	1000	1500	1000	1500	1500	1500	1000

Formulation of pantoprazole-loaded nanosponges

Nanosponges were prepared using a 2^3 full factorial design (eight unique formulations) by the emulsion solvent diffusion method. Considering polymer concentration, sonication time, and stirring speed as independent variables (Table 1.), Eudragit L100 and pantoprazole (100 mg) were dissolved in 20 mL dichloromethane (dispersed phase).

The solution was sonicated using a probe sonicator (Magnus MLX, India) at an amplitude of 10% for 10 and 20 min in pulse mode (5sec ON & OFF cycles), while maintaining the temperature at -20°C using an ice bath to prevent degradation. The dispersion was gradually introduced dropwise into 100 mL of 1% w/v PVA aqueous solution (continuous phase) under constant stirring for 2 h at 1000 rpm and 1500 rpm as per the factorial design. The resultant nanosponge dispersion was subjected to filtration to separate the formed nanosponges from the aqueous medium. The formed solution was slowly filtered using a $0.22\ \mu\text{m}$ membrane filter, followed by repeated washing with distilled water to remove residual stabilizer and solvent. The nanosponge particles were retained on the filter surface due to their tendency to form clusters/aggregates during solvent evaporation and PVA stabilization, which prevented them from passing through the membrane. After filtration, the collected nanosponges were dried at room temperature to obtain the nanosponge (Poornima & Priya, 2021).

Characterization of pantoprazole-loaded nanosponges

The formulated nanosponges underwent evaluation of various physicochemical properties to ascertain their potential as carriers for drug delivery.

Percentage yield: The total dried weight of nanosponges obtained was compared with the theoretical yield to calculate production efficiency.

$$1. \text{Percentage yield} = \frac{\text{Weight of product obtained}}{\text{Total weight of drug + Excipients}} \times 100$$

Entrapment efficiency (%EE): Precisely weighed nanosponges, corresponding to 20 mg of pantoprazole, were suspended in PB (pH 6.8) and subjected to centrifugation at 15,000 rpm for 30 minutes at 4 °C. The concentration of the unencapsulated drug in the supernatant was determined using UV spectrophotometry at 288 nm. EE was then calculated by analyzing the theoretical drug load and actual drug content (Moin et al., 2020).

$$2. \% EE = \frac{\text{Actual drug content in nanosponges}}{\text{Theoretical drug content}} \times 100$$

Particle size (PS) and polydispersity index (PDI): The mean PS and its distribution were determined using a Zetasizer (Malvern Zetasizer, UK), diluting the sample with distilled water (1:10). A low PDI indicated a uniform particle distribution.

In vitro drug release studies of pantoprazole-loaded nanosponges: *In vitro* dissolution studies of pantoprazole-loaded nanosponges were carried out using a USP Type II (paddle) dissolution apparatus (Electrolab TDT-08L, India). Nanosponges equivalent to 20 mg of pantoprazole were filled into hard gelatin capsules and subjected to dissolution testing at 37 ± 0.5 °C with a paddle rotation speed of 100 rpm. To simulate gastrointestinal transit conditions, the study was performed in two stages. Initially, the capsules were placed in 900 mL of 0.1 N HCl (pH 1.2) for 2 h to evaluate the acid resistance of the formulation. After completion of the acid stage, the dissolution medium was replaced with freshly prepared phosphate buffer (pH 6.8) pre-equilibrated to 37 ± 0.5 °C, following previously reported sequential pH dissolution methodology

for pH-sensitive oral formulations (Liu, Merchant, Kulkarni, Alkademi, & Basit, 2011). To avoid formulation loss during medium replacement, the dissolution medium was filtered through a 0.22 µm membrane filter, the retained nanosponges were carefully collected, and immediately transferred into the phosphate buffer medium without significant delay. Dissolution testing was then continued under identical conditions of temperature (37 ± 0.5 °C) and paddle rotation speed (100 rpm). This two-stage dissolution approach was adopted to mimic the physiological transition from gastric to intestinal pH and has been reported for the evaluation of nanosponge-based and gastro-resistant drug delivery systems (Abbas et al., 2018; Manyam, Budideti, & Mogili, 2018; Silva et al., 2021).

At predetermined time intervals, 5 mL samples were withdrawn, filtered, and analyzed spectrophotometrically at 283 nm for 0.1 N HCl (pH 1.2) and 288 nm for phosphate buffer (pH 6.8). Each withdrawn sample was immediately replaced with an equal volume of fresh dissolution medium preheated to 37 ± 0.5 °C to maintain constant dissolution volume and sink conditions throughout the study. All the studies were performed in triplicate (Penjuri, Ravouru, Damineni, Bns, & Poreddy, 2016).

Selection of optimized formulation using a 2³ factorial design

A 2³ factorial design was used to optimize pantoprazole-loaded nanosponge formulations. Three variables-polymer concentration (100, 600 mg), sonication time (10, 20 min), and stirring speed (1000, 1500 rpm) were studied at two levels, generating eight batches. PS and EE were selected as the key responses. Experimental results were analyzed using ANOVA with contour and response surface plots to determine the influence of each factor and their interactions. The formulation showing the smallest PS and higher % entrapment efficiency was considered optimal and subjected to further characterization, including surface morphology and zeta potential analysis to confirm stability.

Characterization of optimized nanosponges

Surface morphology: The morphology and surface features of the optimized formulation were analyzed using scanning electron microscopy (SEM) ZEISS. The samples were subjected to vacuum drying, coated with a thin layer of gold/palladium, and examined at an accelerating voltage of 15 kV.

Zeta potential: The surface charge of the optimized nanosponge formulation was determined using a Zetasizer (Malvern Zetasizer, UK) after diluting the sample with distilled water. Zeta potential values are used to predict colloidal stability.

Evaluation of pantoprazole-loaded nanosponges flow properties

Bulk and tapped densities were measured with the graduated cylinder. Flow properties were evaluated by calculating porosity, Carr's index, Hausner's ratio, and the angle of repose using the fixed funnel method.

Preparation of tablets by the direct compression method

Preparation of powder blend for tablet

The accurately weighed quantities of pantoprazole-loaded nanosponges and MCC were taken into a mortar and pestle, thereby mixed to make a blend. Then the powder blend was passed through sieve (No. 63), and then 1.67% w/w of Mg stearate (lubricant) was mixed thoroughly (Table 3.).

Pre-compression studies of powder blend

The flow characteristics of the powder blend were assessed through the determination of bulk and tapped densities, Carr's index, Hausner's ratio, and the angle of repose.

Compression of tablets

The formulation blend, equivalent to 20 mg of pantoprazole (300 mg total tablet weight), was precisely weighed and directly compressed into tablets using a tablet compression machine.

Evaluation of pantoprazole-loaded nanosponges incorporated tablets

Weight variation: Twenty tablets were weighed individually with a digital analytical balance, and

their weights were documented. The mean weight of tablets was calculated, and the deviation of each tablet from this mean was expressed as a percentage.

Hardness: The tablet's hardness was assessed utilizing the Monsanto hardness tester.

Thickness: The thickness of tablets was measured by using a vernier calliper.

Friability: Tablet friability was assessed using a Roche friabilator. Twenty tablets were weighed and subjected to 100 rotations at 25 rpm, allowing them to tumble freely. After the test, the tablets were removed, dedusted, and reweighed.

Drug assay: Ten tablets were weighed and powdered, after which a portion containing 20 mg of pantoprazole was placed in a 100 mL volumetric flask. The powder was dissolved in a PB at pH 6.8, the volume was adjusted to 100 mL, and the mixture was stirred for a duration of 30 minutes. The solution was carefully diluted, and its absorbance was measured at 288 nm with a UV spectrophotometer to determine the drug content (Indian Pharmacopoeia, 2022).

Enteric coating of pantoprazole-loaded nanosponge tablets

Enteric coating of PLN tablets was prepared by a two-step coating process following the method of Penjuri et al. (2016).

Sub-coating: Tablets were dip-coated with a sub-coating solution prepared by dissolving 66.7% w/v hydroxypropyl methylcellulose (HPMC) and 33.3% w/v polyethylene glycol 400 (PEG 400) in a suitable solvent system (ethanol: water, 5% v/v). The tablets were immersed in the coating solution and dried at room temperature to form a uniform protective layer for subsequent enteric coating (Table 4.).

Enteric coating: The enteric coating solution was formulated by dissolving 2.5% w/v cellulose acetate phthalate (CAP) in acetone under continuous stirring. PEG 400 (1.5% w/v) was added to enhance film flexibility. The solution was filtered to remove any particulates, and its viscosity was adjusted to ensure uniform dip-coating (Table 5.).

***In vitro* drug release studies of pantoprazole-loaded nanospheres incorporated into enteric-coated tablets**

In vitro release studies were conducted using a USP Type II (paddle) apparatus set at 100 rpm. The dissolution process was initiated in 900 mL of 0.1 N HCl for the first 2 hours, after which the medium was replaced with pH 6.8 PB for the remaining time period. The temperature was maintained at 37 ± 0.5 °C. Samples were withdrawn at predetermined time

points; 5 mL samples were withdrawn, replaced with fresh medium to maintain sink conditions, filtered, appropriately diluted, and analyzed spectrophotometrically at 283 nm (0.1 N HCl) and 288 nm (pH 6.8 PB). The cumulative percentage drug release (CDR) was calculated (Poornima & Priya, 2021).

Drug Release Kinetics: The release profile of the optimized tablets was fitted to various kinetic models to determine the release mechanism.

Table 3. Composition for the preparation of tablets

S. No.	Material	% w/w	Quantity for 50 tablets (g)
1	Optimized formulation (PLN3)	80.00%	11.50 g
2	Microcrystalline cellulose (MCC)	18.33%	2.75 g
3	Magnesium stearate	1.67%	0.25 g

Table 4. Composition of sub-coating solution

S. No	Ingredient	Quantity
1	Hydroxypropyl methylcellulose (HPMC)	66.7% w/v
2	Polyethylene glycol 400 (PEG 400)	33.3% w/v
3	Ethanol: Distilled water	5% v/v

Table 5. Composition of enteric coating solution

S. No	Materials	Weight
1	CAP	2.5% w/v
2	PEG 400	1.5% w/v
3	Acetone	q.s.

Preparation and evaluation of pure pantoprazole enteric-coated tablets

Tablets were prepared by direct compression using pure pantoprazole (6.67% w/w), microcrystalline cellulose (83.33% w/w), croscarmellose sodium (6.67% w/w), and magnesium stearate (1.67% w/w) for a batch of 50 tablets (15 g total weight). All ingredients were accurately weighed, blended, and passed through sieve No. 63, followed by lubricant; magnesium stearate. The powder blend was evaluated for its flow properties before compression. The prepared tablets were coated, further evaluated, and subjected to *in vitro* drug release studies following the same procedure as described for pantoprazole-loaded enteric-coated tablets.

RESULTS AND DISCUSSION

Physicochemical characteristics

Pantoprazole (PAN) appeared as a white, odourless, smooth-textured powder. The melting point (139 °C) matched the reported pharmacopeial range (139–140 °C), confirming purity. These findings ensured the suitability of PAN for further formulation development.

Solubility studies

PAN exhibited solubility of 0.560 ± 0.248 mg/mL in distilled water, 0.461 ± 0.222 mg/mL in 0.1 N HCl, 0.444 ± 0.354 mg/mL in methanol, 0.401 ± 0.363 mg/mL in dichloromethane, and 0.518 ± 0.284 mg/mL in phosphate buffer (pH 6.8). The relatively higher sol-

ubility in organic solvents compared to aqueous media supports its potential for encapsulation in nano-sponge systems.

UV spectroscopic analysis

The $\lambda_{\max}$ values of PAN were identified at 283 nm (0.1 N HCl) and 288 nm (pH 6.8 buffer). Calibration curves followed Beer's law within the range of 2–20 $\mu\text{g/mL}$, with excellent linearity ($R^2 = 0.9918$ in acidic medium and $R^2 = 0.9946$ in pH 6.8 buffer). These data confirmed UV spectrophotometry as a reliable method for drug quantification during further studies.

Drug–excipient compatibility

DSC thermograms of PAN and Eudragit L100 retained their individual peaks in physical mixtures (Figures 1 (a), (b), (c), & (d)). These results indicate that no significant drug–polymer interaction occurred. Similar compatibility has been reported for pantoprazole with other polymers, ensuring stability during nanosponge formulation (Ghortale & Ali,

2024). The absence of the drug's sharp melting peak in the optimized formulation (PLN3) compared to the pure drug suggests successful encapsulation of the drug within the polymer matrix, indicating conversion to amorphous state. While FTIR spectra confirmed the presence of characteristic functional groups without major shifts (Figures 2 (a), (b), & (c)). Pantoprazole showed characteristic peaks at 3410.38 cm^{-1} (N–H/O–H stretching), 2919.83 cm^{-1} (aliphatic C–H stretching), 1611.73 cm^{-1} (C=N stretching), 1460.16 cm^{-1} (C–H bending/C–N stretching), 1223.00 cm^{-1} (S=O stretching), and 1037.39 cm^{-1} (C–O–C stretching). Eudragit L100 exhibited peaks at 3484.92 cm^{-1} (O–H stretching), 2954.84 cm^{-1} (C–H stretching), 1731.33 cm^{-1} (ester C=O stretching), 1462.09 cm^{-1} (C–H bending), and 1193.84 cm^{-1} (C–O–C stretching). In the physical mixture, all major peaks were retained, indicating no significant interaction between the drug and polymer.

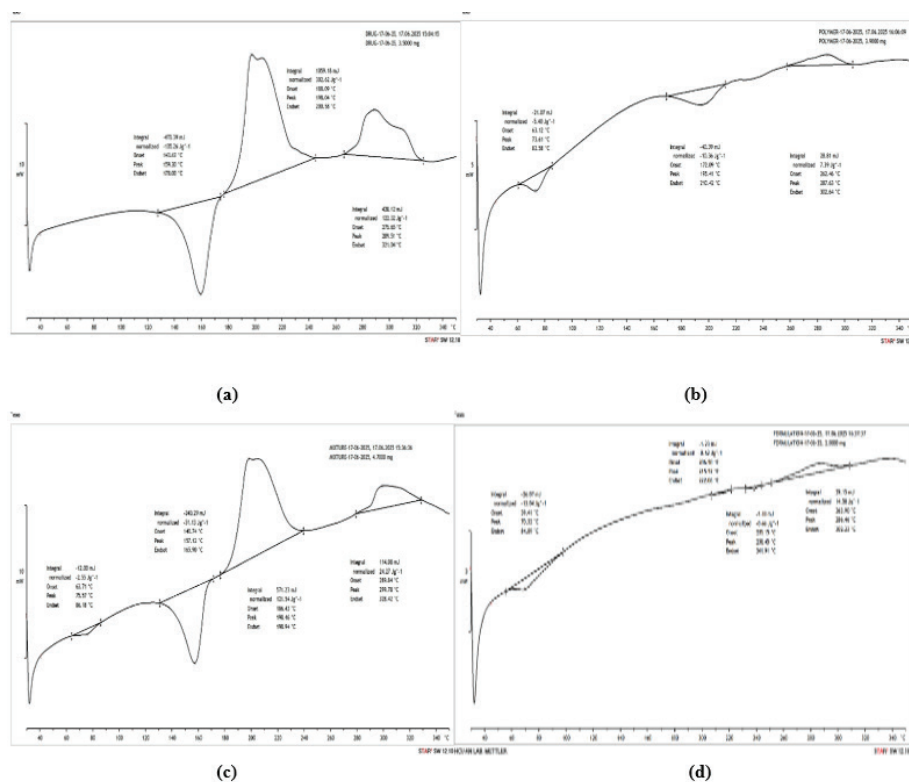


Figure 1. DSC thermograms(a) Drug (b) Polymer (c) Physical mixture (d) PLN3

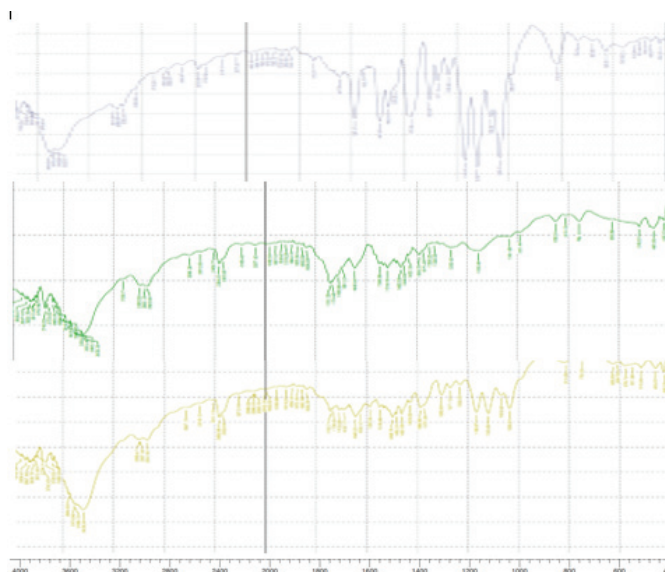


Figure 2. FI-TR spectrum (a) Drug (b) Polymer (c) Physical mixture

PAN-loaded nanosponges were successfully formulated (Figure 3.) using the emulsion solvent diffusion technique.

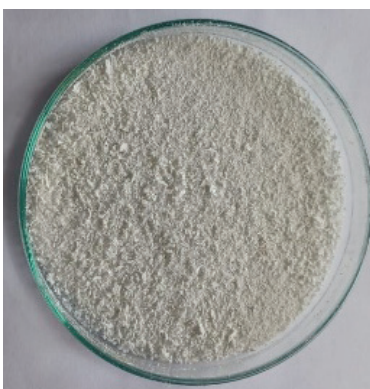


Figure 3. Dried pantoprazole-loaded nanosponges

Percentage yield

The percentage yield varied between $10.05 \pm 1.2\%$ and $63.09 \pm 4.1\%$ (Table 6.). The optimized batch (PLN3) exhibited the highest yield, suggesting effective recovery and minimal aggregation.

PS and PDI

Particle size (89.9 ± 0.42 - 411 ± 0.21 nm) and PDI (0.0586 ± 0.001 - 0.935 ± 0.07) significantly influenced nanosponge performance, with PLN3 has showed the

lowest PDI and highest uniformity. Nanoscale size (<200 nm) in PLN3 enhances dissolution due to increased surface area, consistent with (Moin et al., 2020; Torne, Ansari, Vavia, Trotta, & Cavalli, 2010). Higher PS and PDI (PLN2, PLN5) indicate aggregation and poor stability, aligning with Penjuri et al. (2016). Low PDI (<0.3) in PLN3 confirms monodispersity and predictable drug release, supported by (Poornima & Priya, 2021). Thus, PLN3 is the optimized formulation for enteric-coated delivery of pantoprazole.

Entrapment efficiency (EE)

Entrapment efficiency ranged from $15.05 \pm 2\%$ (PLN6) to $83.02 \pm 4\%$ (PLN3), indicating a strong influence of formulation variables. Higher % EE in PLN3 reflects optimal polymer concentration and stirring conditions, promoting effective drug encapsulation. In contrast, excessive stirring or improper polymer ratios led to drug leakage and reduced % EE. This trend is consistent with findings by Moin et al. (2020) and Penjuri et al., (2016). Overall, optimized formulation parameters are crucial for maximizing entrapment efficiency and nanosponge performance.

In Vitro drug release studies of pantoprazole-loaded nanosponges

The release profile showed that PLN3 achieved sustained drug release, with 19.2% at 2 hours (pH

1.2) and 68.2% at 12 hours (pH 6.8) (Figure 4.). The minimal release (less than 10% to 20 %) in acidic medium indicated effective protection of PAN from gastric degradation (Indian Pharmacopoeia, 2022). In contrast, PLN1 and PLN8 released more than 30% at 2 hours, suggesting inadequate encapsulation. The sustained release behavior observed in the optimized formulation (PLN3) can be attributed to the porous structure of the Eudragit-based nanosponges, which regulates drug diffusion. Similar findings have been reported in polymeric nanosponge systems, where controlled release is governed by matrix diffusion and polymer relaxation mechanisms (Moin et al., 2020). The reduced drug release in acidic medium confirms the protective role of Eudragit L100, which remains insoluble at low pH and dissolves at intestinal pH, thereby preventing premature drug degradation.

Table 6. Physicochemical characteristics of different nanosponge formulations

Formulation Code	Percentage yield (%) Am $\pm$ SD*	Particle size (nm) Am $\pm$ SD*	PDI Am $\pm$ SD*	%Entrapment efficiency Am $\pm$ SD*
PLN 1	15.02 $\pm$ 1.5	209.0 $\pm$ 0.15	0.685 $\pm$ 0.02	19.02 $\pm$ 2.5
PLN 2	41.06 $\pm$ 3.0	411.0 $\pm$ 0.21	0.893 $\pm$ 0.06	43.01 $\pm$ 3.5
PLN 3	63.09 $\pm$ 4.0	209.8 $\pm$ 0.16	0.0586 $\pm$ 0.001	83.02 $\pm$ 4.0
PLN 4	36.04 $\pm$ 2.5	89.9 $\pm$ 0.42	0.439 $\pm$ 0.017	45.09 $\pm$ 3.0
PLN 5	28.05 $\pm$ 2.0	178.7 $\pm$ 0.64	0.935 $\pm$ 0.07	17.02 $\pm$ 2.0
PLN 6	10.05 $\pm$ 1.0	120.3 $\pm$ 0.33	0.522 $\pm$ 0.04	15.05 $\pm$ 2.0
PLN 7	35.04 $\pm$ 2.5	95.0 $\pm$ 0.75	0.583 $\pm$ 0.03	67.05 $\pm$ 3.5
PLN 8	25.02 $\pm$ 2.0	110.3 $\pm$ 0.25	0.377 $\pm$ 0.02	17.02 $\pm$ 2.0

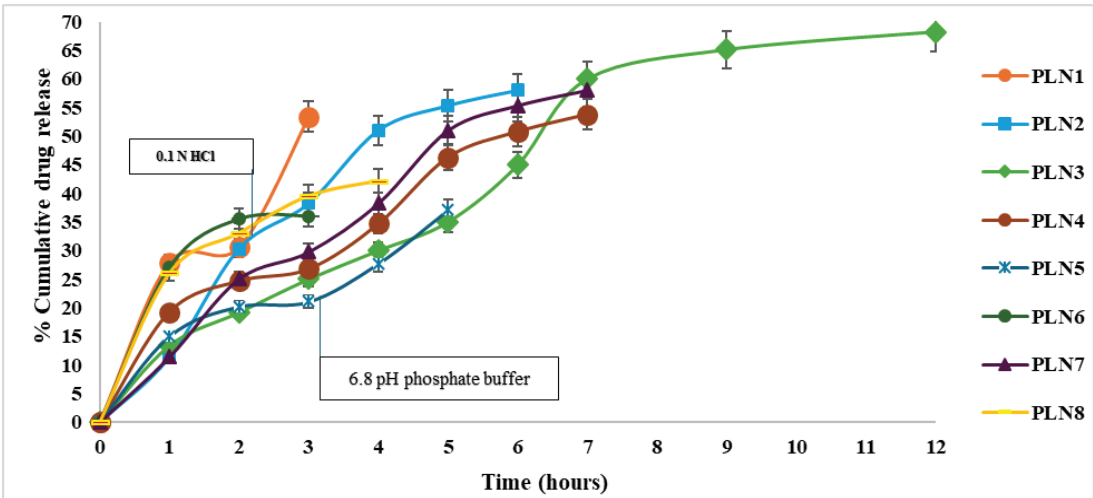


Figure 4. % Cumulative drug release of pantoprazole-loaded nanosponges

Selection of optimized formulation using 2³ factorial designs

A 2³ factorial design was applied using Stat-Ease software (Version 25.0.2, 64-bit) to assess how three independent factors, polymer concentration (A), sonication time (B), and stirring speed (C), affect the response variables, PS (Y₁) and EE (Y₂). Eight experimental runs (PLN1–PLN8) were generated, ensuring a systematic assessment of main effects and their interactions.

Statistical analysis (ANOVA) confirmed the significance of the models ($p < 0.05$), with high predictive reliability ($R^2 = 0.9510$ for PS; $R^2 = 0.9958$ for EE).

Analysis of response: particle size and percentage entrapment efficiency

Effect on particle size

Interaction plots indicated that particle size increased with higher polymer concentration when sonication time was short (10 min), but reduced substantially with longer sonication (20 min), suggesting that extended sonication mitigates the viscosity effect of polymer (Table 8.). Similarly, the combined effect of stirring speed and sonication time demonstrated that particle size decreased at high stirring speeds, particularly during prolonged sonication (10 min & 20 min) due to improved energy transfer and dispersion. Contour and 3D plots confirmed that minimum particle size (90–150 nm) was achieved under high sonication and high stirring conditions, whereas larger particles formed under high polymer with short sonication.

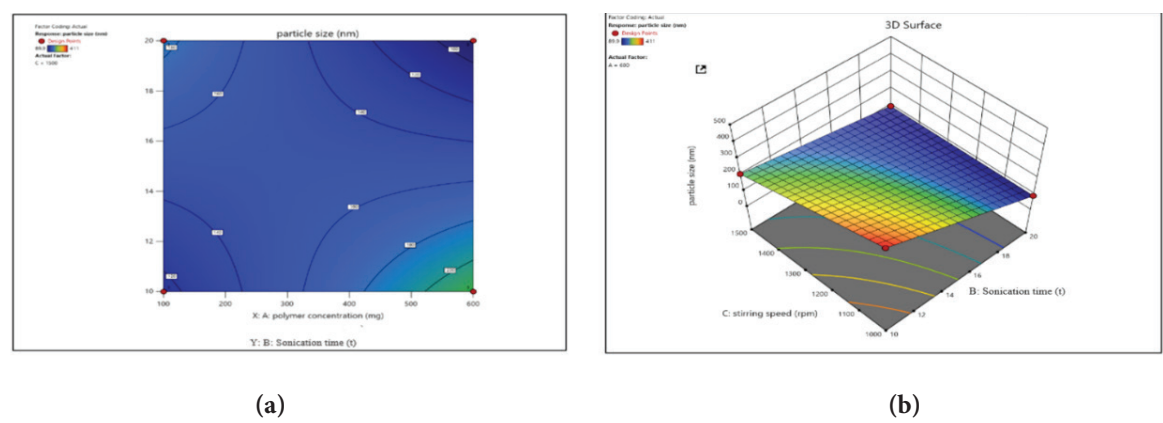


Figure 5. (a) Predicted vs actual (b) Interaction plot of particle size

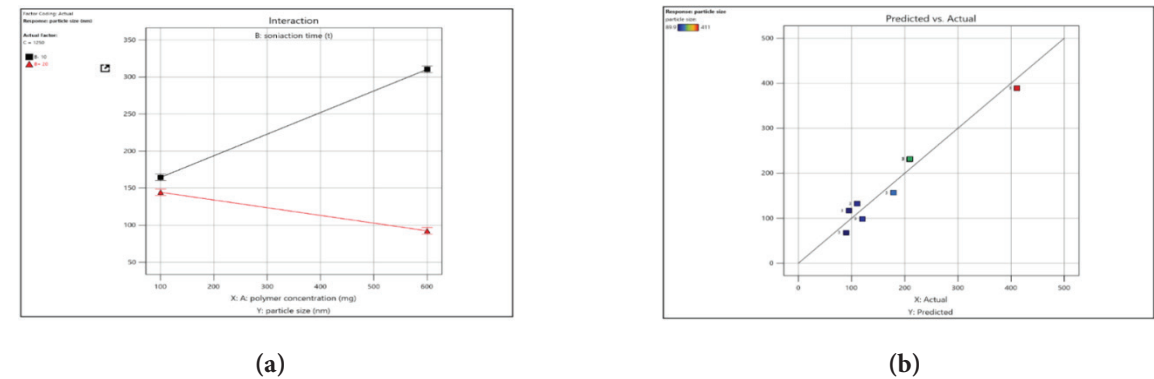


Figure 6. (a) Contour plot (b) 3D surface plot of particle size

Table 7. Fit statistics of particle size

Std. Dev.	26.11	R²	0.9510
Mean	178.00	Adjusted R²	0.9510
C.V. %	14.67	Predicted R²	0.9023
		Adeq Precision	22.7712

Table 8. ANOVA of factorial model response PS

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2.249E+05	6	37480.86	54.98	< 0.0001	significant
A-polymer concentration	13169.54	1	13169.54	19.32	0.0004	
B-sonication time	85037.42	1	85037.42	124.74	< 0.0001	
C-stirring speed	17560.86	1	17560.86	25.76	< 0.0001	
AB	58687.26	1	58687.26	86.08	< 0.0001	
BC	49522.34	1	49522.34	72.64	< 0.0001	
ABC	907.74	1	907.74	1.33	0.2645	
Residual	11589.61	17	681.74			
Lack of Fit	11589.61	1	11589.61			
Pure Error	0.0000	16	0.0000			
Cor Total	2.365E+05	23				

Table 9. Effect of variables on particle size (from interaction, contour & 3D surface plots)

Plot Type	Variables Studied	Key Observations	Interpretation
Interaction Plot (AB)	Polymer concentration vs Sonication time	Particle size increased with higher polymer at short sonication (10 min) but reduced at long sonication (20 min).	Prolonged sonication reduces viscosity effects, yielding smaller particles.
Interaction Plot (BC)	Sonication time vs Stirring speed	Stirring speed impact was stronger at long sonication, producing finer particles.	Combined high sonication along with high stirring enhances dispersion, reducing size.
Contour Plot	Polymer concentration vs Sonication time	Smallest particles (90–150 nm) at high sonication with low polymer concentration.	The balance of polymer load and energy input is essential for size control.
3D Surface Plot	Polymer concentration vs Stirring speed	High stirring reduced size, even with high polymer load.	Strong shear compensates for polymer-induced particle growth.

Effect on EE: EE was mainly governed by the levels of polymer and the stirring speed used (Table 11.). Interaction plots revealed that higher polymer concentration significantly improved EE, as it provided sufficient matrix for drug encapsulation. However, extended sonication in combination with high stirring

caused a slight reduction in EE, possibly due to drug leakage from the polymeric network. Contour and 3D surface plots further illustrated that maximum EE (>80%) was obtained at high polymer load with moderate stirring, while prolonged sonication slightly reduced encapsulation efficiency.

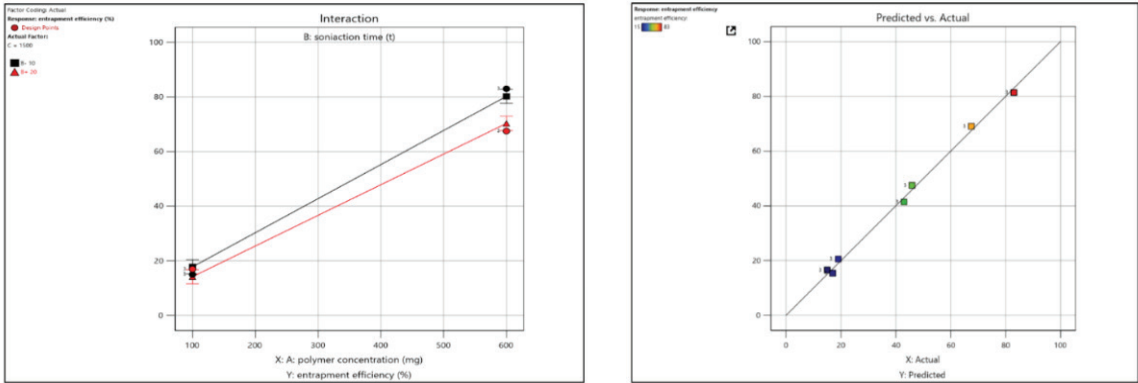


Figure 7. (a) Predicted vs actual (b) Interaction plot of EE

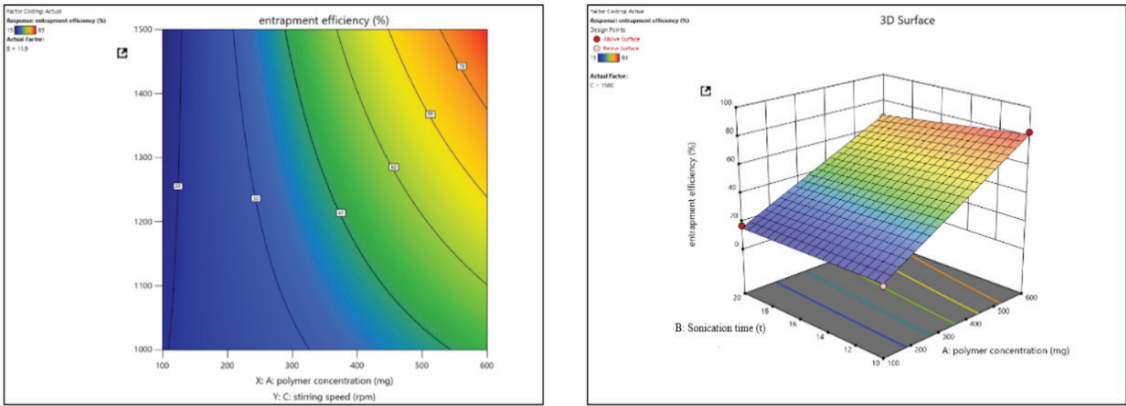


Figure 8. (a) Contour plot (b) 3D- surface plot of PS

Table 10. Fit Statistics of entrapment efficiency

Std. Dev.	1.87	R ²	0.9958
Mean	38.42	Adjusted R ²	0.9944
C.V. %	4.87	Predicted R ²	0.9917
		Adeq Precision	65.3039

Table 11. ANOVA for factorial model response %EE

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	14200.11	6	2366.68	675.80	< 0.0001	significant
A-polymer concentration	11016.73	1	11016.73	3145.79	< 0.0001	
B-sonication time 59.53		1	59.53	17.00	0.0007	
C-stirring speed	1244.16	1	1244.16	355.27	< 0.0001	
AC	1613.76	1	1613.76	460.80	< 0.0001	
BC	77.76	1	77.76	22.20	0.0002	
ABC	188.16	1	188.16	53.73	< 0.0001	
Residual	59.53	17	3.50			
Lack of Fit	59.53	1	59.53			
Pure Error	0.0000	16	0.0000			
Cor Total	14259.65	23				

Table 12. Effect of variables on entrapment efficiency (from interaction, contour, and 3D surface plots)

Plot Type	Variables Studied	Key Observations	Interpretation
Interaction Plot (AC)	Polymer concentration vs Stirring speed	Entrapment efficiency improved at high polymer and high stirring.	Higher polymer provides the matrix; stirring aids encapsulation.
Interaction Plot (BC)	Sonication time vs Stirring speed	Prolonged sonication with high stirring slightly reduced EE.	Excess energy may cause drug leakage from the matrix.
Contour Plot	Polymer concentration vs Stirring speed	EE >80% observed at high polymer with moderate stirring.	Adequate polymer is crucial for maximum drug loading.
3D Surface Plot	Polymer concentration vs Sonication time	EE increased with polymer concentration, but slightly declined at long sonication.	Polymer promotes encapsulation; extended sonication can disrupt drug retention.

Numerical optimization

Numerical optimization was performed to minimize particle size while maximizing EE. The optimized formulation was obtained at 600 mg polymer, 10 min sonication, and 1500 rpm stirring speed, with a desirability value of 0.892. Predicted values (PS: 231.78 nm, EE: 81.43%) were in close agreement with experimental results (PS: 209.5 nm, EE: 83%), confirming model validity. The optimized batch (PLN3) exhibited porous nanosponge morphology, stable zeta potential (−32.5 mV), high entrapment efficiency, and sustained drug release, establishing it as the most suitable formulation for further development.

The predicted versus actual data showed closeness between model predictions and experimental data, with minimal deviations (EE: 81.43% vs. 83%; particle size: 231.78 nm vs. 209.5 nm). Percentage predicted error of EE & particle size is -1.89 % and 10.63 % respectively, confirming the model’s accuracy and reliability.

Surface morphology using SEM

The SEM image of PLN3 showed a porous and sponge-like rough surface, confirming successful nanosponge formation as shown in Figure 9. Such morphology supports efficient drug entrapment and sustained release behavior.

3. Percentage predicted error = $\frac{\text{Predicted value} - \text{actual value}}{\text{actual value}} \times 100$

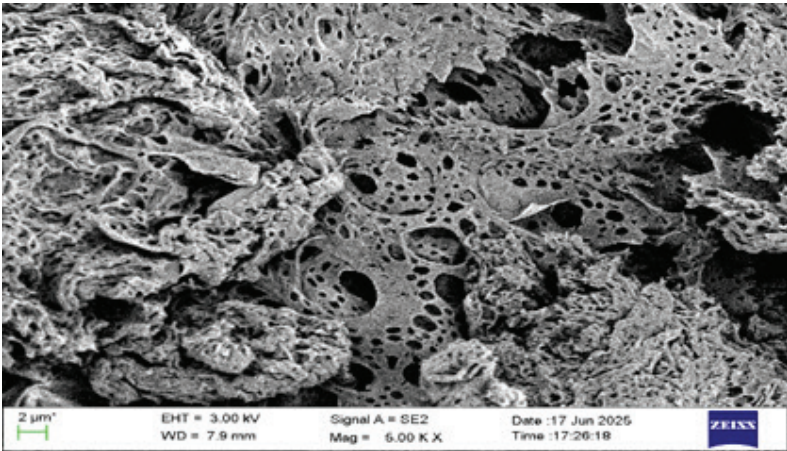


Figure 9. SEM image of optimized formulation (PLN 3) at 5000× magnification

Zeta potential

Zeta potential value of -32.5 mV as mentioned in the Figure 10 and Table 13; signifies that the nano-

sponge formulation is stable, with a negatively charged surface and adequate repulsive forces between particles. This is favorable for maintaining a uniform dispersion and preventing aggregation during storage.

Table 13. Zeta potential of optimized formulation (PLN 3)

Peak No.	Zeta Potential (mV)	Electrophoretic Mobility (cm ² /V·s)
1	-32.5	-0.000251
2	---	---
3	---	---
Mean	-32.5	-0.000251

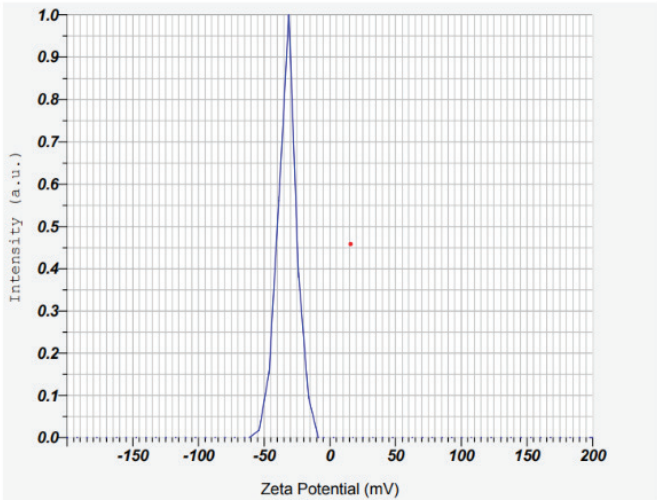


Figure 10. Zeta-potential distribution of optimized formulation (PLN 3)

Evaluation of pantoprazole-loaded nanosponges flow properties

PLN3 nanosponges showed low porosity (5.26%)

and a passable angle of repose (42°), indicating acceptable but not excellent flow, suitable for the tablet formulation with excipient support.

Pre-compression studies of powder blend

According to pharmacopeial standards, the blend showed favorable flow behavior (Table 14.). The lower

densities and slightly higher flow indices in PLN3 are attributed to nanosponge incorporation and increased surface area. All parameters were within acceptable limits, confirming suitability for direct compression.

Table 14. Pre-compression evaluation data of powder blend

Test	Result (PLN3 tablets powder blend) Am ± SD*, n=3	Result (Pure PAN powder blend)	Inference
Tapped Density (g/mL)	2.10 ± 0.05	3.60 ± 0.05	-
Bulk Density (g/mL)	1.826 ± 0.04	1.966 ± 0.04	-
Hausner Ratio	1.150 ± 0.02	1.040 ± 0.02	Good
Carr's Compressibility Index (%)	13.04 ± 1.0	11.04 ± 1.0	Good
Angle of Repose (°)	34.0 ± 1.5	32.0 ± 1.5	Good flow

Evaluation of pantoprazole-loaded nanosponges incorporated tablets and pure pantoprazole tablets

The formulated pantoprazole-loaded nanosponges incorporated tablets and pure pantoprazole tablets demonstrated satisfactory after-compression parameters, with weight variation ranging from $1.02 \pm 0.2\%$ to $4.44 \pm 0.4\%$ and $1.50 \pm 0.3\%$ to $4.80 \pm 0.5\%$, confirming batch uniformity. The hardness was found to be $5 \pm 0.30 \text{ kg/cm}^2$ and $4.5 \pm 0.25 \text{ kg/cm}^2$, respectively, ensuring adequate mechanical strength, while the consistent thickness was $1.2 \pm 0.05 \text{ mm}$ and $1.18 \pm 0.04 \text{ mm}$, indicating uniform compression. Friability was $0.20 \pm 0.05\%$ and $0.35 \pm 0.06\%$, well below the 1 % limit, confirming resistance to breakage, and the drug assay was $92.53 \pm 0.50\%$ and $90.20 \pm 0.60\%$, respectively, for PLN incorporated tablets and pure pantoprazole tablets, ensuring uniform drug content and reliable therapeutic performance; all fell within the pharmacopeial limits.

In vitro drug release studies of pantoprazole-loaded nanosponges incorporated in enteric-coated tablets

Drug release experiments were conducted *in vitro* utilizing 0.1 N HCl for a duration of 2 hours, followed by pH 6.8 PB for eighteen hours. The absence of drug release during the first two hours in 0.1 N HCl suggests that PAN was shielded from acid destruction. Later, the tablet in the pH 6.8 PB, an increase in drug release was noted. This was subsequently followed by a phase of steady drug release. As seen in the Figure 11., the CDR at 18 hours was 83.00 ± 0.33 percent.

Drug release kinetic studies of pantoprazole-loaded nanosponges incorporated in enteric-coated tablets

The release rate exponent ($n = 0.62$) suggests anomalous (non-Fickian) kinetics as described in Table 15. As a result, the *in vitro* drug release profile fit a First-order model with a Korsmeyer-Peppas exponent value ($n > 0.5$), showing that both diffusion and erosion mechanisms regulated the release.

Table 15. Drug release kinetics of enteric-coated tablet

Release Kinetic Model	R ² Value	Interpretation
Zero-order	0.7895	Poor fit
First-order	0.932	Better correlation than zero-order
Higuchi model	0.9512	Indicates diffusion-controlled release
Korsmeyer-Peppas	0.954	Best fit; most appropriate release model

Comparative *in vitro* drug release study of enteric-coated pantoprazole nanosponge (PLN) tablet and pure drug tablet

The *in vitro* drug release of enteric-coated pantoprazole nanosponge (PLN) tablet and pure drug tablet did not show drug release for 2 h in acidic medium (pH 1.2), confirming effective enteric protection. At pH 6.8, the pure drug tablet exhibited rapid release

with $45.32 \pm 1.2\%$ (3 h) and $92.53 \pm 1.2\%$ (7 h). In contrast, the PLN tablet showed sustained release with $36.00 \pm 1.1\%$ (3 h) and $83.00 \pm 1.3\%$ (18 h) as seen in Figure 11. The prolonged release from the PLN tablet is attributed to the nanosponge matrix controlling drug diffusion, with non-Fickian release behavior compared to the immediate release pattern of the pure drug tablet.

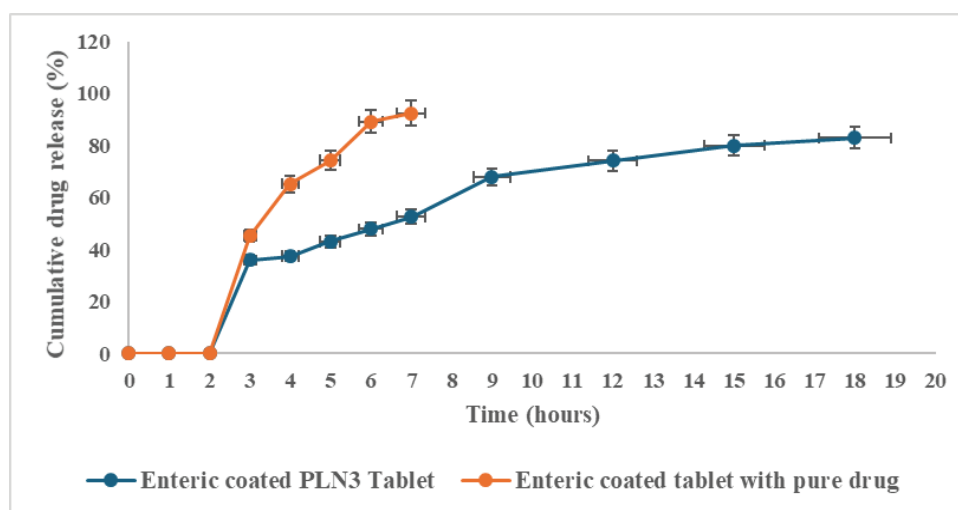


Figure 11. % Cumulative drug release profile of enteric-coated PLN tablet and enteric-coated tablet with pure pantoprazole

CONCLUSION

Pantoprazole-loaded nanosponge-based enteric-coated tablets were successfully developed and optimized using a 2^3 factorial design. The optimized formulation (PLN 3) has showed favorable particle size, high entrapment efficiency, stability, and sustained release characteristics. Tablets showed acceptable pre and post-compression parameters and sustained release up to 18 h, following anomalous (non-Fickian) kinetics. Comparative *in vitro* release studies demonstrated that the pure drug enteric-coated tablet showed rapid drug release reaching $92.53 \pm 1.2\%$ within 7 h; the optimized PLN enteric-coated tablet exhibited sustained drug release of up to $83.00 \pm 1.3\%$ over 18 h following non-Fickian kinetics. These findings confirm the superior release-retarding ability of the nanosponge-based system compared to the conventional formulation. This delivery system enhances

drug stability, provides acid protection, and sustained release, offering a promising strategy for improved management of peptic ulcer disease.

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AUTHOR CONTRIBUTION STATEMENT

M. K.: Provided conceptualization, supervision, research planning, and critical revision of the manuscript. The author approved the final version of the manuscript. L. D. A.: The author performed the experimental work, data collection, formulation and evaluation studies, data analysis, and drafting and editing of the manuscript. B. M.: Reviewed and checked the

final manuscript. G. S. A.: Reviewed and checked the final manuscript. P. V. B.: Reviewed and checked the final manuscript. P. B.: Reviewed and checked the final manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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