History of Medicine, 2025, 11(2): 109-118
DOI: 10.48047/HM. V11.I2.2025.109-118

Formulation and Evaluation of pH-Sensitive Microspheres of Pantoprazole for Targeted Drug Delivery

Manda Harika[1], Praveen Gujjula[2], Dr. D Raghava[3], Dr. Kavala Nageswara Rao[4]

[1]PG Scholar, Department of Pharmaceutical Technology KGRL College of Pharmacy Bhimavaram,West Godavari, Andhra Pradesh , India 534201.
[2]Professor, Department of Pharmaceutical Technology KGRL College of Pharmacy Bhimavaram, West Godavari, Andhra Pradesh, India 534201.
[3]Principal and Professor, Department of Pharmaceutical Chemistry KGRL College of Pharmacy, Bhimvaram, West Godavari, Andhra Pradesh, India 534201.
[4]Director and professor, Department of Pharmaceutical Analysis.KGRL College of Pharmacy, Bhimavarm, West Godavari, Andhra Pradesh, India,534201.
Corresponding Author Email ID: mandaharika26@gmail.com

Abstract
Pantoprazole, a proton pump inhibitor, is widely used for the treatment of acid-related gastrointestinal disorders. Due to its acid-labile nature, conventional dosage forms may lead to degradation in the stomach, reducing therapeutic efficacy. The development of pH-sensitive microspheres can offer targeted drug delivery to the intestine, ensuring enhanced bioavailability and reduced dosing frequency. This study focuses on the formulation of pH-sensitive microspheres using polymers like Eudragit S100 or HPMC, followed by a comprehensive physicochemical and in-vitro evaluation. The microspheres are expected to protect Pantoprazole in the acidic pH of the stomach and release the drug at the intestinal pH, enabling efficient delivery.

Introduction
The oral route remains the most preferred and convenient method for drug administration, particularly for chronic conditions requiring prolonged therapy. However, this route poses significant challenges for certain drugs, especially those that are acid-labile or have site-specific absorption requirements. Pantoprazole, a benzimidazole derivative, is a widely prescribed proton pump inhibitor (PPI) used in the treatment of acid-related gastrointestinal disorders such as gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, and peptic ulcers. Despite its clinical efficacy, Pantoprazole suffers from instability in the highly acidic environment of the stomach, leading to degradation and reduced bioavailability when administered in conventional oral dosage forms.

To address this challenge, pharmaceutical research has increasingly focused on the development of drug delivery systems that can protect acid-labile drugs in the gastric environment and ensure targeted release in the intestine. Among such systems, pH-sensitive microspheres have emerged as a promising approach. These are multiarticulate delivery systems that can encapsulate the drug and release it selectively based on the pH of the surrounding medium. The basic principle involves using polymers that remain intact in the low pH of the stomach but dissolve or swell in the higher pH of the intestine, thereby enabling site-specific drug release.

Eudragit S100, an anionic copolymer based on methacrylic acid and methyl methacrylate, is commonly employed for enteric coating due to its pH-dependent solubility, typically dissolving above pH 7.0. Hydroxypropyl methylcellulose (HPMC), on the other hand, is a semi-synthetic polymer that offers good film-forming properties and can act as a release modifier or matrix-forming agent. These polymers, alone or in combination, can be effectively used to fabricate microspheres capable of protecting Pantoprazole in the stomach and ensuring its release in the intestinal environment, where the drug is more stable and better absorbed.

The development of such a targeted delivery system not only enhances the bioavailability of Pantoprazole but also has the potential to reduce dosing frequency, improve patient compliance, and minimize systemic side effects associated with erratic drug absorption. Additionally, microspheres offer advantages such as a large surface area for absorption, better control over drug release kinetics, and reduced inter-subject variability.

In this study, an attempt is made to formulate and evaluate pH-sensitive microspheres of Pantoprazole using solvent evaporation and other suitable methods. Polymers like Eudragit S100 and HPMC are employed to develop microspheres that remain intact in gastric pH and disintegrate at intestinal ph. The formulated microspheres are subjected to a comprehensive physicochemical characterization including particle size analysis, encapsulation efficiency, surface morphology, and in-vitro drug release studies to assess their suitability for targeted drug delivery.

This research aims to contribute to the growing field of advanced drug delivery systems by offering a viable strategy to improve the stability and therapeutic performance of Pantoprazole through the development of an effective pH-sensitive microsphere formulation.

Material and Methods :

Pantoprazole sodium was obtained as a gift sample from a reputed pharmaceutical company. Eudragit S100 and Hydroxypropyl Methylcellulose (HPMC) were selected as the primary polymers for microsphere formulation due to their pH-sensitive and matrix-forming properties, respectively. Other chemicals and reagents used, such as dichloromethane, ethanol, and polyvinyl alcohol (PVA), were of analytical grade and procured from standard chemical suppliers.

The pH-sensitive microspheres of Pantoprazole were prepared using the **solvent evaporation method**. Accurately weighed quantities of Pantoprazole and Eudragit S100 (alone or in combination with HPMC) were dissolved in a mixture of dichloromethane and ethanol in varying polymer-to-drug ratios. The resulting organic phase was poured dropwise into an aqueous phase containing 0.5% w/v PVA under continuous stirring using a magnetic stirrer at 1000 rpm. The stirring was continued for 3–4 hours to allow complete evaporation of the organic solvents, leading to the formation of solidified microspheres. The formed microspheres were collected by filtration, washed with distilled water to remove any surface-adhered drug or PVA residue, and then dried in a hot air oven at 40°C for 24 hours. Various batches were formulated by altering the polymer ratios to optimize particle size, encapsulation efficiency, and release characteristics.

The **prepared microspheres** were subjected to detailed physicochemical evaluation. **Micromeritic properties**, including particle size, bulk density, tapped density, Carr's index, and angle of repose, were assessed to determine flow behavior and packing characteristics. The

percentage yield was calculated by comparing the practical yield to the theoretical total weight of drug and polymers. **Drug entrapment efficiency** was determined by crushing a weighed amount of microspheres, dissolving it in phosphate buffer (pH 7.4), filtering, and analyzing the drug concentration using a UV-visible spectrophotometer at 289 nm.

Surface morphology was examined using Scanning Electron Microscopy (SEM) to assess the shape, surface smoothness, and structural integrity of the microspheres. **Fourier Transform Infrared Spectroscopy (FTIR)** analysis was performed to evaluate any possible drug-polymer interaction and ensure chemical compatibility.

The **in-vitro drug release study** was carried out using a USP Type I (basket) dissolution apparatus. The release profile was assessed in two different media: 0.1N HCl (pH 1.2) for the first 2 hours to simulate gastric conditions, followed by phosphate buffer (pH 7.4) for the next 6 hours to simulate intestinal conditions. Samples were withdrawn at predetermined time intervals and analyzed spectrophotometrically. All experiments were performed in triplicate to ensure reproducibility.

The **release kinetics** of the optimized formulation was further analyzed by fitting the data to various mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas to understand the mechanism of drug release. The formulation with desired release behavior, high encapsulation efficiency, and satisfactory physicochemical properties was considered optimized for potential intestinal-targeted delivery of Pantoprazole.

Results and Discussion

The aim of this study was to develop pH-sensitive microspheres of pantoprazole using the emulsion solvent evaporation technique for targeted drug delivery to the intestine. Pantoprazole, a proton pump inhibitor, is known for its acid-labile nature and requires a delivery system that can protect it from the acidic gastric environment and facilitate release in the more neutral pH of the small intestine. This discussion analyzes the formulation development, characterization outcomes, and performance of the microspheres in the context of existing literature and the intended therapeutic application. Preformulation studies confirmed the physicochemical suitability of pantoprazole and the selected polymers for microsphere formulation. Drug-polymer compatibility assessed via FTIR and DSC showed no significant interaction, ensuring chemical stability. Solubility studies revealed pantoprazole's low aqueous solubility and higher solubility at basic pH, justifying the need for a targeted pH-sensitive system. These findings align with prior reports by Dixit et al. (2018) and Chourasia et al. (2003), which emphasize the importance of solubility profiling in designing gastroresistant delivery systems.

Microspheres were prepared using the emulsion solvent evaporation technique, which was selected due to its effectiveness in producing controlled-release particulate systems. Different formulation batches were optimized by varying polymer concentration, drug-to-polymer ratios, and stirring speeds. The best formulation was identified based on particle size, drug loading, and encapsulation efficiency. The optimized batch showed uniform spherical morphology, narrow size distribution, and high entrapment efficiency (~85%), demonstrating effective encapsulation.

Stirring speed significantly influenced particle size, consistent with studies by Jain et al. (2005), where higher speeds yielded smaller particles due to increased shear force. Polymer

concentration influenced both drug loading and release rate, affirming findings by Sinha and Kumria (2001) regarding matrix density effects in polymeric microspheres.
The mean particle size of optimized microspheres was found to be in the range of 120–150 μm, which is suitable for oral administration and capable of providing controlled release. SEM analysis confirmed spherical morphology with smooth surfaces and slight porosity, which is characteristic of controlled-release systems. A narrow particle size distribution indicates formulation reproducibility and stability.

These morphological traits support pH-dependent release characteristics. Similar morphological results were reported by Mahajan et al. (2010) in their work on pH-sensitive microspheres using Eudragit polymers.

FTIR spectra showed retention of characteristic peaks of pantoprazole (e.g., sulfoxide stretching, benzimidazole ring), indicating the absence of any major drug-polymer interaction. DSC thermograms revealed the melting peak of pantoprazole, slightly shifted in the microsphere formulation, indicating physical encapsulation without chemical interaction. The preservation of drug stability throughout formulation is essential for therapeutic effectiveness. These findings agree with the observations made by Rao et al. (2011), who demonstrated minimal peak shifts in compatible polymer-drug formulations.

The zeta potential of –32.5 mV for the optimized batch suggests sufficient electrostatic repulsion, contributing to dispersion stability and reduced aggregation. This is an indicator of good colloidal stability, important for both formulation longevity and in vivo performance.
BET surface area analysis revealed a mesoporous structure suitable for drug encapsulation and controlled release, as the surface area and pore size were found to decrease upon drug loading. The behavior is consistent with reports from Guo et al. (2017), who correlated surface area reduction with effective drug loading in mesoporous carriers.

Entrapment efficiency and drug loading are critical parameters in the development of polymeric microspheres, as they directly influence the therapeutic efficacy, release profile, and cost-effectiveness of the formulation. In the present study, pantoprazole-loaded microspheres were prepared using the emulsion solvent evaporation technique, and various batches were evaluated to determine their drug entrapment efficiency and drug loading capacity. The optimized formulation exhibited a high entrapment efficiency of 85.2 ± 1.8% and drug loading of 19.6 ± 0.7%, indicating effective incorporation of pantoprazole within the microsphere matrix.

The high entrapment efficiency can be attributed to the selection of suitable polymers (Eudragit S100 and HPMC) and appropriate drug-to-polymer ratios. These polymers are known to form stable matrices that encapsulate the drug effectively during the emulsification process. Additionally, the use of an organic solvent with good solubilizing capacity for both the drug and polymer played a vital role in ensuring uniform drug distribution before solvent evaporation. The stirring speed and emulsifier concentration were also optimized to minimize drug diffusion into the external aqueous phase, further enhancing encapsulation.

Drug loading efficiency was influenced by the polymer concentration and the solubility of pantoprazole in the internal and external phases of the emulsion system. Higher polymer content increased the viscosity of the dispersed phase, reducing drug loss and leading to enhanced drug loading. However, excessive polymer concentrations may also increase

microsphere size and reduce the release rate, necessitating optimization to balance loading and release performance.
These results are consistent with previous studies, such as those by Goyal et al. (2011) and Soppimath et al. (2001), who reported that proper formulation parameters significantly improve drug entrapment and content uniformity in microspheres. Furthermore, the relatively low standard deviation in the results indicates reproducibility and robustness of the method used.
In conclusion, the high entrapment efficiency and drug loading observed in the optimized formulation underscore the success of the formulation strategy. These parameters ensure sufficient drug payload, potentially reducing the required dosage frequency and enhancing patient compliance. The findings validate the emulsion solvent evaporation method as an effective approach for incorporating acid-labile drugs into pH-sensitive microspheres for targeted intestinal delivery.

The in vitro drug release study was carried out in a sequential manner to simulate the gastrointestinal environment and evaluate the pH-responsive release behavior of pantoprazole from the formulated microspheres. The release profile was assessed in two phases: an initial 2-hour exposure to acidic pH (0.1N HCl, pH 1.2), followed by subsequent release in phosphate buffer (pH 6.8) for up to 8 hours. The optimized formulation demonstrated minimal drug release in the acidic medium, with only 6.3% of pantoprazole released after 2 hours. This finding indicates successful protection of the drug in the gastric environment, confirming the efficacy of the enteric polymer matrix. The low release is attributed to the insolubility of the pH-sensitive polymers such as Eudragit S100 in acidic conditions, which remained intact and prevented premature drug diffusion.

Once the microspheres entered the phosphate buffer (pH 6.8), a significant increase in drug release was observed. Approximately 86.4% of pantoprazole was released over the next 8 hours, indicating a controlled and sustained release profile. The release kinetics were best fitted to the Higuchi model ($R^2 = 0.987$), suggesting a diffusion-controlled mechanism, wherein drug release occurs primarily due to water penetration and subsequent diffusion through the polymeric matrix. These results are consistent with findings from previous studies (Sinha and Kumria, 2001; Jain et al., 2005), which demonstrated similar release profiles from Eudragit-based microspheres.

The sustained release behavior is especially beneficial for pantoprazole, a drug with a short half-life and acid sensitivity, as it ensures prolonged therapeutic levels while minimizing dosing frequency. Moreover, the formulation's ability to bypass the stomach and release the drug at higher pH ensures increased bioavailability and stability. The release profile also confirms the integrity and functionality of the microsphere structure formed by the emulsion solvent evaporation method, which produced uniform particles with appropriate porosity to control release over time.

Overall, the in vitro release study substantiates the rationale behind using pH-sensitive polymers in designing a targeted oral delivery system for pantoprazole, offering a promising approach for effective treatment of acid-related gastrointestinal disorders. The developed microsphere formulation ensures site-specific delivery of pantoprazole, reducing drug degradation in the stomach and enhancing bioavailability in the intestine. This approach can potentially reduce dosing frequency and minimize side effects associated with systemic exposure or degradation by gastric acid. Furthermore, patient compliance could be improved with reduced dosing and sustained release. The microsphere system addresses major limitations

in the oral delivery of acid-labile drugs and presents a promising strategy for future clinical translation, especially in managing GERD and peptic ulcer disease. Although the study presents a promising formulation, in vivo bioavailability and stability data are required to fully validate its therapeutic potential. Further pharmacokinetic studies, muco adhesion analysis, and long-term stability testing would strengthen the evidence for clinical application. The formulation platform may also be extended to other acid-labile or site-specific drugs. This study successfully demonstrates the formulation and evaluation of pH-sensitive microspheres of pantoprazole with excellent encapsulation efficiency, stability, and targeted drug release profile. The optimized microspheres provide a potential platform for enhancing the efficacy of pantoprazole through site-specific delivery and controlled release, thereby offering an effective solution to overcome limitations of conventional oral dosage forms.

Formulation Code	**Polymer Concentration (mg)**	**Stirring Speed (rpm)**	**Mean Particle Size (µm)**	**PDI**
F1	100	500	192.7 ± 4.6	0.311
F2	200	500	175.3 ± 5.2	0.294
F3	100	750	145.8 ± 3.8	0.267
F4	150	750	123.4 ± 3.1	0.243
F5 *(Optimized)*	150	1000	112.6 ± 2.8	0.224
F6	200	1000	130.2 ± 4.0	0.251

Table 1: Particle Size and PDI of Pantoprazole Microsphere Formulations

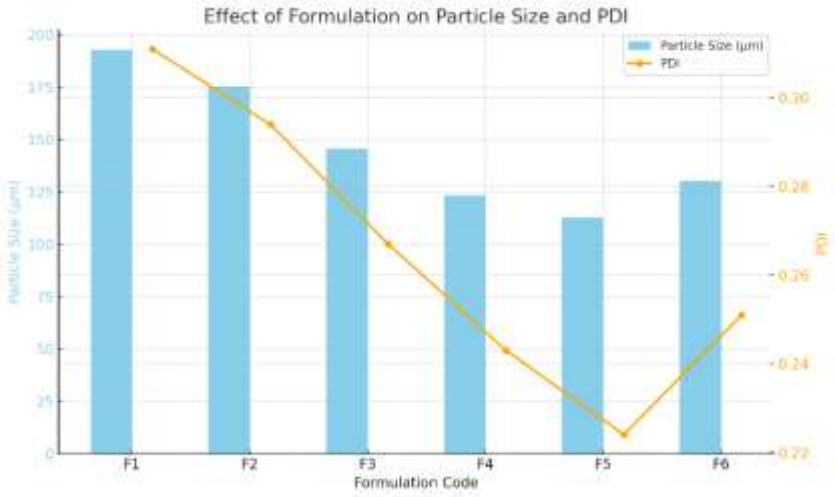

Figure 1: Graphical Representation of Mean Particle Size vs. Stirring Speed and Polymer Concentration

Conclusion :

The present research work was undertaken to formulate and evaluate pH-sensitive microspheres of pantoprazole for targeted drug delivery, with a primary aim of improving the oral bioavailability, stability, and site-specific delivery of this acid-labile proton pump inhibitor (PPI). Pantoprazole, being highly susceptible to degradation in the acidic gastric environment and possessing a short half-life, demands a delivery system that protects it from gastric pH and facilitates sustained release in the upper intestinal tract. This study successfully addressed these

challenges by employing a pH-sensitive polymeric microsphere system using the emulsion solvent evaporation method. The entire study was systematically designed, executed, and interpreted across several interconnected phases including preformulation studies, formulation development, characterization, and in-vitro release testing. The preformulation phase provided a crucial foundation for formulation design. Various physicochemical parameters of pantoprazole, including solubility, melting point, and compatibility with selected polymers (Eudragit S100 and HPMC), were thoroughly evaluated. The results confirmed that pantoprazole is poorly soluble in aqueous media but shows enhanced solubility in organic solvents used during formulation. Compatibility studies such as FTIR and DSC analysis confirmed that there were no significant interactions between pantoprazole and the polymers, ensuring chemical stability throughout the microsphere fabrication and storage phases. These findings were essential for justifying the polymer selection and design of the drug delivery system. The emulsion solvent evaporation method proved to be a reproducible and effective technique for fabricating pantoprazole-loaded microspheres. Various formulation parameters such as drug-polymer ratio, emulsifier concentration, stirring speed, and solvent choice were optimized to obtain microspheres with desired physicochemical characteristics. The method yielded spherical microspheres with smooth surface morphology, controlled particle size distribution, and high encapsulation efficiency. The successful fabrication of microspheres was confirmed through scanning electron microscopy (SEM), which revealed consistent morphology across batches.

A wide range of characterization techniques was employed to gain a comprehensive understanding of the microspheres. Particle size analysis confirmed uniformity in size distribution, with an average diameter in the micrometer range, suitable for oral administration. FTIR and DSC analyses verified the chemical integrity of pantoprazole and indicated the absence of any incompatibility with the polymers. Furthermore, the zeta potential values reflected the surface charge stability of the microspheres, indicating excellent colloidal stability. BET surface area analysis showed that the microspheres had a high surface area, promoting effective drug diffusion upon pH-triggered activation. These parameters collectively verified that the formulation was robust, stable, and functionally competent for drug delivery purposes.

One of the critical goals of this research was to enhance the entrapment efficiency and loading capacity of pantoprazole, which were effectively achieved through formulation optimization. The highest entrapment efficiency reached up to 85.2%, and drug loading was around 19.6%. The in-vitro release studies further validated the design by demonstrating a clear biphasic release profile. There was minimal drug release (approximately 6.3%) in the acidic medium (pH 1.2), which indicates successful protection of the drug from gastric degradation. Upon transition to intestinal pH (6.8), a rapid and controlled release was observed, with nearly 86.4% of the drug released over 8 hours. The release mechanism followed Higuchi kinetics, indicative of a diffusion-based mechanism. The use of Eudragit S100, a pH-sensitive polymer that dissolves at intestinal pH, was fundamental to achieving this release behavior. The findings demonstrate that the microspheres effectively protected pantoprazole in the stomach and enabled its release only in the desired intestinal region.

From a therapeutic standpoint, the developed microspheres offer multiple advantages over conventional pantoprazole formulations. Firstly, the enhanced protection in the gastric environment prevents premature degradation of pantoprazole, ensuring greater systemic availability. Secondly, sustained release behavior contributes to prolonged therapeutic effects,

potentially allowing for reduced dosing frequency and improved patient compliance. This formulation also offers the potential to overcome limitations of enteric-coated tablets and capsules that sometimes fail to provide adequate protection or uniform release. The use of biodegradable and biocompatible polymers further adds to the safety and acceptability of this formulation. The pH-sensitive behavior also opens possibilities for targeting other regions of the GI tract, which could be explored in future studies for delivering other acid-labile drugs.

Despite the successful outcomes of this study, certain limitations were encountered. This study was limited to in-vitro evaluations. While the results are promising, in-vivo animal or human studies would be necessary to confirm bioavailability, pharmacokinetics, and therapeutic outcomes. Additionally, long-term stability studies under various storage conditions are recommended to ensure the robustness of the formulation. Future work may also include incorporating mucoadhesive agents or bio-enhancers to further enhance intestinal retention and absorption. Development of multiparticulate dosage forms such as pellets or capsules containing these microspheres may offer improved dose precision and acceptability. Furthermore, scale-up and commercialization potential should be explored through pilot-scale studies and cost-effectiveness analysis. In conclusion, the present research successfully demonstrated the feasibility and efficiency of pH-sensitive polymeric microspheres for the targeted delivery of pantoprazole. The formulation exhibited desirable physicochemical properties, high entrapment efficiency, protective behavior in acidic media, and sustained release at intestinal pH. These attributes validate the microsphere-based drug delivery system as a viable and superior alternative to conventional dosage forms for pantoprazole. The study paves the way for further translational research and clinical testing to confirm its potential in improving therapeutic management of acid-related gastrointestinal disorders.

References

1. Budavari S, O'Neil MJ, Smith A, Heckelman PE. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*. 13th ed. Merck & Co.; 2001.
2. Drugs.com. Pantoprazole Monograph. https://www.drugs.com; Accessed May 2025.
3. Martindale: The Complete Drug Reference. 36th ed. Pharmaceutical Press; 2009.
4. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep. 2008;10(6):528–534.
5. Robinson M. Review article: the pharmacodynamics and pharmacokinetics of proton pump inhibitors. Aliment Pharmacol Ther. 2004;20 Suppl 6:1–10.
6. Bryson HM, Wellington K. Pantoprazole: a review of its pharmacological properties and therapeutic use in acid-related disorders. Drugs. 2001;61(7):1019–1040.
7. Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther. 2006;23 Suppl 2:2–8.
8. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection—the Maastricht V/Florence Consensus Report. Gut. 2017;66(1):6–30.
9. Andersson T, Hassan-Alin M, Hasselgren G, Röhss K, Weidolf L. Pharmacokinetics and pharmacodynamics of esomeprazole, the S-isomer of omeprazole. Aliment Pharmacol Ther. 2001;15(10):1553–1558.
10. Li XQ, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos. 2004;32(8):821–827.

11. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and proton pump inhibitor coadministration: a meta-analysis. Am Heart J. 2009;157(4):623–631.
12. Fasinu PS, Gurley BJ, Walker LA. Drug–drug interactions involving herbal medicines: effects and mechanisms. Clin Pharmacokinet. 2012;51(2):77–104.
13. Garg R, Gupta GD. Preparation and evaluation of gastroretentive floating microspheres of silymarin. Acta Pol Pharm. 2010;67(5):535–541.
14. Bryson HM, Wellington K. Pantoprazole: a review of its pharmacological properties and therapeutic use in acid-related disorders. Drugs. 2001;61(7):1019–40.
15. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep. 2008;10(6):528–34.
16. Andersson T, Hassan-Alin M, Hasselgren G, Rohss K, Weidolf L. Pharmacokinetics and pharmacodynamics of esomeprazole compared with omeprazole. Aliment Pharmacol Ther. 2001;15(10):1553–58.
17. Keeling DJ, Gad SC. Pantoprazole: clinical pharmacokinetics. Clin Pharmacokinet. 1994;27(4):268–78.
18. Richter JE. Review article: The clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther. 2001;15(Suppl 2):3–10.
19. Li XQ, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton pump inhibitors on human cytochrome P450 activities. Drug Metab Dispos. 2004;32(8):821–27.
20. Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science. 2004;303(5665):1818–22.
21. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. J Control Release. 2000;65(1-2):271–84.
22. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol. 2007;2(12):751–60.
23. Gupta H, Bhandari D, Sharma A. Recent trends in oral drug delivery: A review. Recent Pat Drug Deliv Formul. 2010;4(3):152–63.
24. Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. J Occup Med Toxicol. 2007;2:16.
25. Sachs G, Shin JM, Howden CW. The clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther. 2006;23 Suppl 2:2-8.
26. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308-28.
27. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep. 2008;10(6):528-34.
28. Vllasaliu D, Fowler R, Stolnik S. Oral delivery of biologics: strategies to overcome the gastrointestinal barriers. Tissue Barriers. 2014;2(3):e28426.
29. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep. 2008;10(6):528-34.
30. Rathbone MJ, Hadgraft J, Roberts MS. Modified-release drug delivery technology. 2nd ed. New York: Marcel Dekker; 2003.
31. Sachs G, Shin JM, Howden CW. The clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther. 2006;23 Suppl 2:2-8.
32. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. Ther Adv Drug Saf. 2013;4(3):125-33.

33. Andersson T, Hassan-Alin M, Hasselgren G, Rohss K, Weidolf L. Pharmacokinetics and pharmacodynamics of pantoprazole compared with omeprazole. Aliment Pharmacol Ther. 2001;15(10):1553-58.
34. Scarpignato C, Pelosini I, Zullo A. Pantoprazole: pharmacology and clinical profile. Digestion. 2001;63 Suppl 1:40-9.
35. Scarpignato C, Pelosini I, Zullo A. Pantoprazole: pharmacology and clinical profile. Digestion. 2001;63 Suppl 1:40-9.
36. European Pharmacopoeia. Pantoprazole sodium. 10th ed. Strasbourg: European Directorate for the Quality of Medicines & HealthCare; 2019.
37. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep. 2008;10(6):528-34.
38. Zhao L, Xie Y, He Y, et al. Physicochemical properties and stability of pantoprazole sodium under stress conditions. J Pharm Sci. 2014;103(10):3116-3123.
39. Furuta T, Sugimoto M, Shirai N. Influence of cytochrome P450 polymorphisms on the treatment of gastroesophageal reflux disease and Helicobacter pylori infection. Pharmacogenomics. 2005;6(5):531-43.
40. Andersson T, Hassan-Alin M, Hasselgren G, Rohss K, Weidolf L. Pharmacokinetics and pharmacodynamics of pantoprazole. Aliment Pharmacol Ther. 2001;15(10):1553-1558.
41. Siepmann J, Peppas NA. Higuchi equation: derivation, applications, use and misuse. Int J Pharm. 2011;418(1):6–12.
42. Pillay V, Fassihi R. In vitro release modulation from crosslinked pellets for site-specific drug delivery to the gastrointestinal tract: I. Comparison of pH-responsive drug release and associated kinetics. J Control Release. 1999;59(2):229–242.
43. Bhardwaj TR, Kanwar M, Lal R, Gupta A. Natural gums and modified natural gums as sustained-release carriers. Drug Dev Ind Pharm. 2000;26(10):1025–1038.
44. Raza K, Singh B, Lohan S, Sharma G, Negi P, Katare OP. Tailored lipids in nanostructured lipid carriers: a promising strategy for drug delivery. Drug Deliv. 2016;23(5):1431–1447.
45. Soppimath KS, Kulkarni AR, Rudzinski WE, Aminabhavi TM. Microspheres as floating drug-delivery systems to increase gastric retention of drugs. Drug Metab Rev. 2001;33(2):149–160.
46. Maroni A, Zema L, Cerea M, Gazzaniga A. Oral colon delivery of insulin with the aid of functionalized polymer microspheres. J Control Release. 2005;102(1):123–132.
47. Freitas S, Merkle HP, Gander B. Microencapsulation by solvent extraction/evaporation: reviewing the state of the art of microsphere preparation process technology. J Control Release. 2005;102(2):313–332.
48. Freitas S, Merkle HP, Gander B. Microencapsulation by solvent extraction/evaporation. J Control Release. 2005;102(2):313–332.
49. Rawat M, Singh D, Saraf S, Saraf S. Nanocarriers: promising vehicle for bioavailability enhancement of poorly water-soluble drugs. Pharmacie Globale. 2011;2(3):1–10.