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Design and evaluation of pH-sensitive omeprazole enteric-coated pellets IP for sequential release in the gastrointestinal tract

Monika Dadhich[1,*] | Gajendra Singh Tyagi[1] | Ram Garg[1]

[1]Department of Pharmacy, University of Technology, Vatika, Jaipur – 303903, Rajasthan (India)

***Corresponding author:** muskandadhich01@gmail.com

Abstract: Omeprazole, a widely used proton pump inhibitor, is highly unstable under acidic conditions, resulting in degradation in the stomach and reduced therapeutic effectiveness. This study aimed to develop pH-sensitive enteric-coated pellets of omeprazole (7.5% w/w) for sequential drug release within the gastrointestinal tract. The formulation was designed to protect omeprazole from acidic degradation during gastric transit and facilitate controlled release within the intestinal region. Extrusion-spheronization was used to prepare the pellets, followed by coating with an HPMC barrier layer and an enteric coating of Eudragit L100/S100. Three formulation batches with varying polymer concentrations and coating levels were prepared and evaluated to identify the optimal formulation. The prepared formulations were characterized for micromeritic properties, drug content, dissolution behavior, and preliminary accelerated stability. The dissolution studies demonstrated minimal drug release in acidic medium (pH 1.2) for up to 2 hours, followed by controlled drug release exceeding 95% in pH 6.8–7.4 buffer media. Among all formulations, F2 exhibited the most desirable performance, demonstrating effective acid resistance, uniform drug distribution, and controlled drug release in the intestinal medium. Preliminary accelerated stability studies indicated no significant changes in physical appearance or drug release characteristics during the study period. The developed pH-sensitive pellet system successfully achieved sequential drug release and demonstrated satisfactory stability, indicating its potential as a promising oral delivery approach for acid-labile drugs such as omeprazole.

Keywords: Omeprazole, Enteric coating, pH-sensitive pellets, Sequential release, Controlled drug delivery

1. Introduction

The most popular method of medicine administration is oral medication because it is convenient, cost effective, and patients adhere to it. Some of the drugs have, however, faced obstacles like lack of stability within the gastrointestinal milieu, low solubility, and location specificity. One such drug is omeprazole which is a proton pump inhibitor or PPI and a highly unstable drug in acidic conditions and in situations where degradation takes place in the stomach leading to reduced bioavailability and therapeutic effect.

Omeprazole mechanism of action involves irreversible inhibition of the H+/K +-ATPase enzyme system in gastric parietal cells, and thus, prevents gastric acid secretion. It is usually administered in the treatment of GERD, peptic ulcers and other acid-associated diseases.

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Because of its acid-labile nature and absorption only in the upper intestines, it needs to be protected against gastric degradation and, in its delivery to the intestinal region, it requires protection against early degradation in the stomach and targeted delivery to the intestinal region.

To counter such drawbacks, there is an invention of pH-responsive drug delivery systems. Such systems are based on enteric polymers, which are resistant to degradation in low pH and allow release of drugs to the site, in response to increased pH levels. Multi-particulate systems, including pellets, have other benefits including uniformity of distribution in the gastrointestinal tract, reduced chances of dose dumping, and enhanced reproducibility.

The current research entailed the production of pH sensitive enteric coated omeprazole pellets utilizing multi-layered method. It was formulated to sequentially release the drug in which the protection was performed at the gastric conditions but in a way that controlled the release of the drug at the intestinal pH. This plan will aid in protecting the drug from gastric degradation, facilitating targeted intestinal delivery, and providing patients with increased compliance.

2. Literature Review

Omeprazole is highly acid labile, where enteric coating is necessary to ensure the drug release in the intestinal area before its hydrolysis in the lower stomach. For enteric-coated product to perform site-specific drug delivery, they are required to meet certain quality related criteria as described in the USP–NF 42–NF37 including dissolution, acid resistance, and coating integrity. These guidelines for pharmacopeia are the basis for the development and evaluation of preparations of acid-labile substances like omeprazole formulated in a way sensitive to pH.

A few researchers have highlighted the need of including pH-responsive polymers to ensure stability and bioavailability of OME. According to Srebro et al. (2022), enteric coating technologies significantly improve the resistance to gastric degradation and provide targeted drug release in the intestine. Cui et al. (2020) also showed, via in vitro–in vivo correlation (IVIVC) studies, that the composition of the polymer, the coating thickness, and the dissolution conditions are key factors to navigate drug release behavior. The results indicate that increasing the knowledge of the coating parameters is essential to ensure predictable drug release profile and pharmacological efficacy of coated dosage forms as per the pH requirements of the body.

Enteric Coated drugs exhibit three different drug release mechanism such as diffusion, dissolution and swelling of polymers. The theoretical fundamentals of controlled release by diffusion-controlled systems were developed by Higuchi (1963), while Korsmeyer et al. (1983) have considered the contribution of polymer swelling and erosion to the drug release kinetic. Costa and Lobo (2001) emphasized that the dissolution profile test and mathematical model are crucial to analyze the release behavior and provide comparison among pharmaceutical formulations. The overall results of the studies gave the theoretical background to explain the release mode of pH-sensitive pellet systems.

Reliable analytical and statistical technique will be necessary for accurate formulation development. Sharma (1981) underlined the application of instrumental analysis in stability testing of pharmaceuticals, studying the stability and course of dissolution behaviour of drugs and coating properties across various pH ranges. In addition, Montgomery (2017) showed that Design of Experiments (DoE) such as factorial design and response surface methodology is a systematic method to optimize the formulation variables and to understand their interactions.

Bolton and Bon (2004) have also emphasized the role of the statistical analysis in the pharmaceutical development to ensure the uniformity of the formulation, statistical reproducibility and product quality.

The enteric-coated dosage forms need to be subjected to stability studies under standard storage conditions. Chauhan et al. (2021) suggest that accelerated and long-term stability testing be conducted to assess the change in the amount of drug substance, its physical changes, integrity of coating and its dissolution performance over the course of the product's shelf life. If formulated in accordance with these guidelines, the formulation is quality, safe, and useful for therapy. While enteric polymers, release mechanisms, analytical characterization and formulation optimization have been previously shown to be important, few studies have tried to elucidate the joint effect of polymer concentration, or enteric coating level, on sequential release behavior of omeprazole pellets obtained by extrusion-spheronization technique. Hence, the present research work was carried out with the aim of developing and screening pH sensitive enteric-coated omeprazole pellets to provide the gastric protective efficacy and controlled release of drug in intestine.

3. Materials and Methods

Materials: Omeprazole IP was purchased, and lactose monohydrate and microcrystalline cellulose (MCC, Avicel PH101) were purchased at Loba Chemie Pvt. Ltd., Mumbai. Hydroxypropyl methylcellulose (HPMC E5) was also supplied by the company (supplier details verified and recorded as per procurement records). Excipients including talc, triethyl citrate, isopropyl alcohol, and purified water were used during formulation development.

Pre-formulation Studies: Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) were used to determine the drug -excipient compatibility. Physical mixtures were stored at 40 +/-2 C, 75 +/-5% RH, 14 days and analyzed on interactions.

Preparation of Pellets: Omeprazole was extruded-spheronized to produce omeprazole in pellet form (7.5% w/w). MCC, lactose was emulsified and moistened with purified water to create a uniform mass. Wet mass was extruded through 1 mm die and was spheronized at 1000 rpm.

Drying: The pellets were dried at 40 +- 2 o C, and sieved to gain homogeneous size.

Coating Process: The coating was made up of a barrier coat of HPMC through the fluidized bed coater. Enteric coating was then done using Eudragit L100 /S100 combined with talc and triethyl citrate to affect a pH dependent release.

Evaluation: Prepared pellets were considered in the following respects: micromeritic properties, drug content and in vitro dissolution using USP Type I apparatus in pH 1.2 and subsequently pH 6.8 buffer.

4. Drug and Polymers Profile

Drug Profile: Omeprazole is a type of PPI that has been used to treat acid-related gastrointestinal disorders such GERD, peptic ulcers, and Zollinger-Ellison syndrome. Its molecular weight is 345.42 g/mol, and is a 5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)-methylsulfinyl]-1H-benzimidazole. A white to off-white crystallized powder, which is soluble in organic solvents but is nearly insoluble in water. Omeprazole is acid-labile and it quickly decomposes under acidic conditions, leading to low bioavailability (~30-40%). It works by irreversibly blocking H + K + -ATPase enzyme in the parietal cells of the stomach

thus inhibiting secretion of gastric acid. Its unpredictability in terms of gastric pH and location-specific drug absorption in the intestine necessitate enteric coating and localized effects of the drug on the intestine.

Polymer Profile: Eudragit L100 and S100 are anion copolymers with wide pH-dependent solubility and which are commonly used as enteric coating systems. These dissolve at pH above 5.5-7.0, thus protecting acid-sensitive drugs such as omeprazole in the stomach and release in the intestine. Hydroxypropyl methylcellulose (HPMC) is a hydrophilic polymer which has the ability to act as a binder, release modifier. When it is hydrated it forms a gel layer and with the help of the gel the drug is released in a controlled manner. Ethyl cellulose (EC) is a water insoluble polymer utilized in prolonged discharge through regulation of diffusion of the drugs through a matrix system.

Excipients: Some of the notable excipients that are used during formulation can include microcrystalline cellulose (MCC), talc, magnesium stearate and triethyl citrate. MCC is employed like a filler and it gives the pellets and talc fluidity and prevents aggregation. These are magnesium stearate as a lubricant, triethyl citrate as a plasticizer (to make the coating-film more flexible and stable).

5. Results And Discussion

5.1 Evaluation of Physical Properties of Core Pellets

The prepared batches (F1, F2, and F3) of omeprazole pellets were evaluated for physical parameters, and results are presented in Table 1; data expressed as mean ± SD (n = 3):

Table 1: Micromeritic properties of core pellets

Batch	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio
F1	27.43 ± 0.23	0.42 ± 0.01	0.48 ± 0.01	12.5 ± 0.4	1.14 ± 0.02
F2	26.87 ± 0.19	0.44 ± 0.01	0.49 ± 0.01	10.2 ± 0.3	1.11 ± 0.01
F3	28.12 ± 0.27	0.43 ± 0.01	0.50 ± 0.01	14.0 ± 0.5	1.16 ± 0.02

Interpretation: All batches exhibited excellent to good flow properties.

5.2 Drug Content Estimation

Drug content estimation of the investigated batches is represented in Table 2.

Table 2: Percentage drug content of coated pellets

Batch	Drug Content (%)
F1	98.23 ± 0.52
F2	99.12 ± 0.38
F3	97.87 ± 0.44

Interpretation: All formulations showed drug concentration in the acceptable range of ~97.8–99.1%, indicating uniform drug distribution and process reliability; data expressed as Mean ± SD (n = 3).

5.3 In Vitro Drug Release Study

The in vitro drug release study was carried out to simulate the sequential drug release of Omeprazole in the gastrointestinal tract (GIT), following a pH-sensitive approach. This method ensures drug protection in acidic pH and release in alkaline medium, consistent with

Omeprazole's acid-labile nature. Studied key parameters and their details are represented in Table 3.

Table 3: Test methodology

Parameter	Details
Apparatus	USP Dissolution Apparatus Type I (Basket)
Speed	100 rpm
Temperature	37 ± 0.5°C
Sample Quantity	Pellets equivalent to 20 mg of Omeprazole
Medium (Stage I)	SGF, pH 1.2 (0.1N HCl)
Duration (Stage I)	2 hours (Acid resistance test)
Medium (Stage II)	SIF, pH 6.8 phosphate buffer
Duration (Stage II)	4 hours (Drug release evaluation)
Sampling Intervals	0.5, 1, 2, 2.5, 3, 3.5, 4, 5, and 6 hours
Analysis Method	UV-Visible Spectrophotometry at 301 nm (after suitable dilution and filtration)

Procedure

Acid Stage (0–2 hours):

- Pellets were exposed to 0.1N HCl (pH 1.2) to simulate gastric conditions.
- No significant release was expected due to the enteric coating on pellets.
- Samples were removed at regular intervals, & analyzed to confirm acid resistance.

Buffer Stage (2–6 hours):

- After 2 hours, pH 6.8 phosphate buffer was used in place of the medium, simulating the intestinal environment.
- Samples were collected at predetermined time points to evaluate the release pattern of Omeprazole.
- A plot of the cumulative drug release against time was made.

Expected Release Behavior:

- Stage I (Acid Phase, pH 1.2): Minimal to no drug release due to the pH-sensitive enteric coating, ensuring protection of Omeprazole from degradation.
- Stage II (Buffer Phase, pH 6.8): Rapid or controlled release begins after exposure to alkaline pH, achieving sequential drug release to the upper intestine, where Omeprazole absorption primarily occurs.

Table 4: Dissolution profile of Omeprazole Pellets

Time (hrs)	F1 (%)	F2 (%)	F3 (%)
0	0	0	0
0.5	2	1	3
1	5	4	6
2	10	9	11
3	42	48	39
4	65	72	60
5	83	90	81
6	96	99	95

Outcome Interpretation: The formulation is considered successful if:

- NMT 10% of the medication is released in 0.1N HCl (2 hours), and
- ≥85% of the drug is released within 4 hours in pH 6.8 buffer, indicating effective intestinal drug release.

Dissolution Profile of Omeprazole Pellets has been shown in Table 4 and Fig. 1.

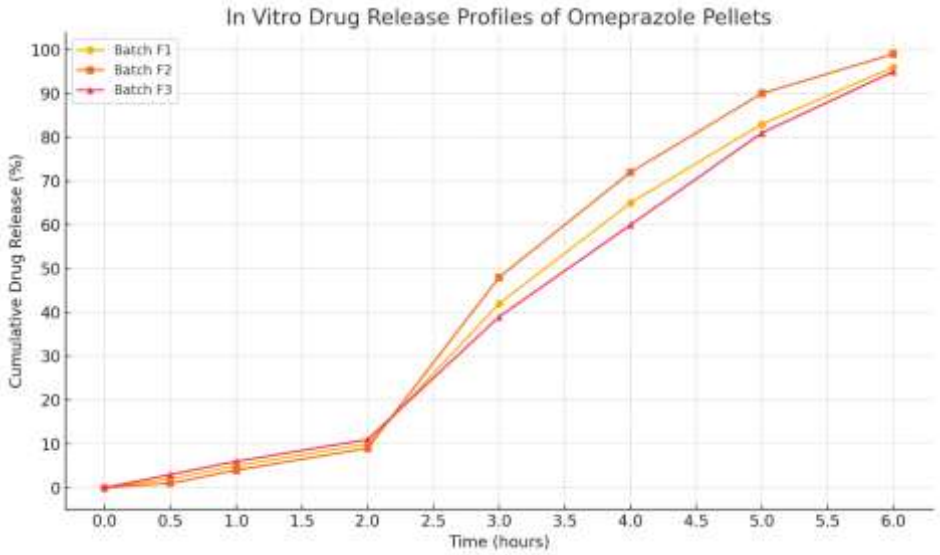

Fig. 1: Dissolution Graph (F1–F3)

Interpretation of Drug Release Profile

- Acid Protection: Minimal release (~10%) was observed in acidic pH, confirming the efficiency of the enteric coating. Batch F2 complied with the NMT 10% release criterion at 2 hours (9%), whereas F3 exhibited 11% release and therefore showed comparatively lower acid resistance.
- Sequential Release: Burst release in pH 6.8 after 2 hrs suggests that the formulation remained intact in the stomach and released drug in the intestinal pH.
- Batch F2 showed the most efficient and controlled release (99% in 6 hrs), suggesting optimal polymer concentration and coating level.

Statistical Optimization Using DoE

Three formulation batches with varying polymer concentrations and coating levels were prepared and evaluated to assess their influence on drug release behaviour (Table 5). A complete factorial design (Fig. 2) was utilized to maximize two critical variables:

- X_1 = Polymer concentration (%)
- X_2 = Coating level (%)
- Y = Cumulative Drug Release at 6 hours (%)

Table 5: Formulation variables and observed drug release

Batch	X_1: Polymer (%)	X_2: Coating (%)	Y: Drug Release (%)
F1	10	25	92
F2	12	30	95
F3	14	35	94

Effect Analysis

- Increasing polymer concentration from 10% to 14% resulted in more sustained release due to tighter matrix structure.
- Increasing coating level from 25% to 35% provided enhanced protection in acidic pH and prolonged release in the intestinal pH.

The optimized Batch (F2) was found at 12% polymer and 30% coating, providing ~95% drug Batch F2 was selected as the optimized formulation because it exhibited the lowest drug release in acidic medium (9% at 2 hours), satisfactory intestinal drug release (99% at 6 hours), and acceptable formulation characteristics.

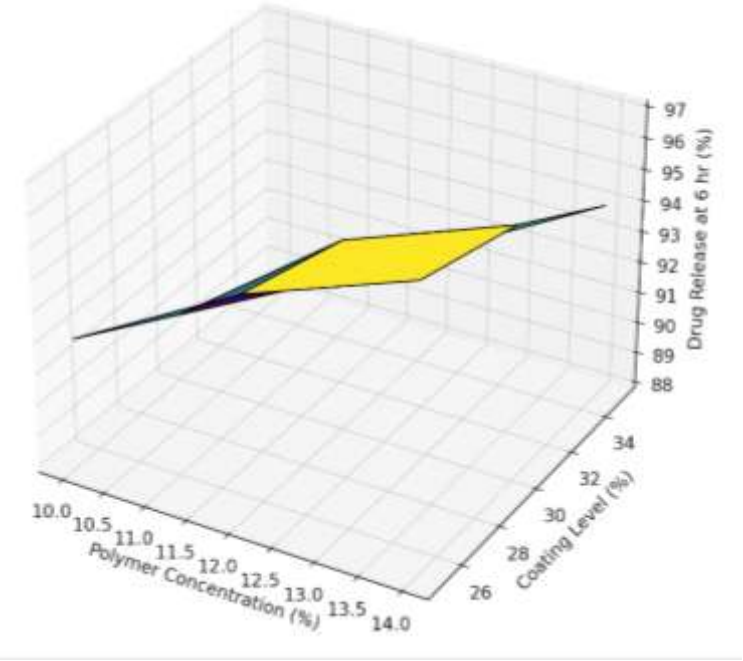

Fig. 2: Response Surface: Effect of Coating and Polymer Concentration

Stability Study

A preliminary accelerated stability study was conducted on the optimized batch (F2) under accelerated storage conditions (Table 6).

Conditions:

- Temperature: 40 ± 2 °C
- Relative Humidity: 75 ± 5% RH
- Duration: 1 month
- Container: HDPE bottles sealed with desiccant under nitrogen atmosphere

Table 6: Stability Study Results for Batch F2

Test Parameter	Initial (0 Day)	15 Days	30 Days
Physical Appearance	Off-white pellets	No change	No change
Assay (% of label claim)	101.5%	100.8%	99.7%
Moisture Content (%)	1.1	1.2	1.3
Cumulative Drug Release (%)	95.2%	94.7%	93.8%
Enteric Coating Integrity	Intact	Intact	Intact

No appreciable changes in physical appearance, assay, or drug release profile were observed during the 30-day study period. The pellets retained enteric coating integrity under the tested conditions. However, extended stability studies are required to establish long-term stability in accordance with ICH guidelines.

6. Formulation and Development

Objective: The purpose of this project was to develop and optimise pH-sensitive omeprazole pellets (7.5% API) for sequential drug release in the gastrointestinal tract, ensuring gastric protection and targeted intestinal delivery.

Rationale for Formulation Design: Omeprazole is an acid-labile drug that degrades in gastric conditions. Therefore, a multi-layered pellet system was designed consisting of a drug-loaded core, a protective seal coat, and a pH-sensitive enteric coating to enable controlled and site-specific drug release.

Materials and Equipment: Omeprazole, microcrystalline cellulose (MCC), lactose monohydrate, HPMC, Eudragit L100/S100, talc, and triethyl citrate were used. Equipment included a fluidized bed processor, sieve shaker, drying oven, extruder, and spheronizer.

Formulation Strategy: Drug-loaded pellets were prepared by extrusion-spheronization. MCC and lactose were blended with omeprazole and processed to obtain uniform pellets. A barrier coat of HPMC was applied to prevent drug degradation, followed by enteric coating using Eudragit L100/S100 to achieve pH-dependent drug release above pH 6.8. The coated pellets were subsequently dried and stored.

Formulation Trials and Evaluation: Three batches (F1–F3) were prepared with varying coating levels. Pellets were evaluated for size, drug content, and dissolution. Batch F2 showed acceptable acid resistance and the highest cumulative drug release in the intestinal medium.

Optimization Outcome: Batch F2 was selected as the optimized formulation because it demonstrated acceptable acid resistance (9% release at 2 hours), controlled intestinal drug release (99% release at 6 hours), and satisfactory stability characteristics.

7. Discussion

The current research was able to prove the design of pH-sensitive enteric coated omeprazole with controlled sequential release in the gastrointestinal tract. The suitability of pellets in further processing and coating was observed in the micromeritic properties of all batches that were found to have good flowability and compressibility. Analysis of drug content revealed that there is uniformity in dispersion of the active pharmaceutical component which indicates consistency formulation process.

In vitro dissolution experiments found that the enteric coating was effective in preventing drug release in acidic environments (pH 1.2), & thus in preventing degradation of the omeprazole. When the polymers of the coating material switched to intestinal pH (6.8), a substantial pH-dependent enhancement in the release of drugs was also observed, as a validation of the pH-dependent nature of the polymers used. Among the tested formulations, batch F2 exhibited the most desirable performance, showing acceptable acid resistance and controlled drug release in the intestinal medium.

The results further demonstrated that polymer concentration and coating level influenced the drug release behaviour of the pellets. Increasing the coating level enhanced protection in acidic conditions, while appropriate polymer concentration contributed to controlled release in the

intestinal environment. Preliminary accelerated stability studies indicated minimal changes in drug content and release characteristics during the study period, suggesting satisfactory formulation stability under the tested conditions.

In sum, the research results confirm that the multi-layered pellet system is an efficient method of attaining controlled and targeted drug delivery.

8. Conclusion

The current study has been able to develop and optimize pH sensitive enteric coated omeprazole pellets capable of sequential discharge of the medication in the gastrointestinal tract. Formulation was effective in solving the major limitation with omeprazole whose major limitation is the lack of acid stability and thus its lack of acid stability can be exploited to only release the active ingredient in the intestinal location. The optimized batch (F2) had shown good physicochemical qualities, uniform drug content, and good release properties. The in vitro dissolution investigations confirmed the little drug release in gastrointestinal pH and the constant drug release in enteric pH. Zero-order release kinetics was also observed in the formulation, which at least guaranteed drug release nature over the course of time. The preliminary accelerated stability study indicated that the developed pellets retained their physical integrity, drug content, and release characteristics during the study period. Multi-layered pellet system was a more efficient way of controlling and site-specific drug delivery.

To sum up, the available formulation has a possible remedy for the issue of increasing bioavailability & therapeutic effect of acid-labile drugs such as omeprazole. Further studies are required to establish long-term stability and evaluate in vivo performance.

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