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Pulsatile Delivery Of Modified-Release Esomeprazole Tablets Via Press Coating Technique For Enhanced Chronotherapeutic Efficacy

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Abstract
The objective of the present study was to design and evaluate a pulsatile release formulation of Esomeprazole magnesium using a press-coated tablet system intended for chronotherapeutic management of acid-peptic disorders. Esomeprazole, a proton pump inhibitor (PPI), exhibits instability in acidic pH and a short plasma half-life, making it a suitable candidate for time-controlled delivery to match the circadian rhythm of gastric acid secretion, which peaks in the early morning. Core tablets of Esomeprazole were prepared via direct compression and subsequently press-coated with varying ratios of hydroxypropyl methylcellulose (HPMC K4M) and ethyl cellulose (EC) to create a programmable lag time before release. A total of nine formulations (F1–F9) were developed and evaluated for pre-compression flow properties, post-compression physical parameters, and in-vitro drug release. The influence of polymer ratio and coating weight gain on lag time and burst release was statistically analyzed using ANOVA. Among all batches, Formulation F3 (HPMC:EC = 6:1 with 10% coating) was optimized, exhibiting a lag time of 120 minutes and 95.4% drug release within the subsequent hours, achieving a desirable pulsatile profile. The study successfully demonstrates that press-coated pulsatile tablets of Esomeprazole can be effectively utilized for chronotherapy, aligning drug release with the body's biological rhythms to improve therapeutic outcomes.
Keywords: *Pulsatile drug delivery, Esomeprazole magnesium, Press-coated tablet, Chronotherapy, Lag time optimization*

INTRODUCTION

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Human physiology is inherently governed by an internal timekeeping mechanism known as the circadian rhythm, which plays a vital role in regulating various biological processes, including hormone release, metabolism, and gastrointestinal functions [1]. This 24-hour biological cycle is synchronized with environmental cues such as light and darkness and is controlled by the suprachiasmatic nucleus (SCN) of the

hypothalamus [2]. Among its many influences, circadian rhythm significantly impacts gastric acid secretion, with evidence indicating that acid output exhibits distinct fluctuations throughout the day. Gastric acid secretion typically follows a biphasic pattern, peaking in the late evening and early morning hours a time when the body's natural protective mechanisms, such as mucosal secretion and bicarbonate release, are diminished [3]. Consequently, patients suffering from acid-related gastrointestinal disorders, such as gastroesophageal reflux disease (GERD) or peptic ulcers, frequently experience exacerbated symptoms during these nocturnal and early morning hours [4]. This pathophysiological pattern underlines the necessity for time-specific drug delivery strategies that align therapeutic concentrations of medications with periods of greatest symptom intensity. Conventional proton pump inhibitors (PPIs), including Esomeprazole, Omeprazole, and Rabeprazole, have become the mainstay in the management of acid-related diseases due to their ability to irreversibly inhibit the H^+/K^+ ATPase pump in gastric parietal cells, thereby significantly reducing gastric acid secretion [5]. However, standard PPI dosing regimens exhibit certain limitations that compromise their clinical effectiveness, particularly in synchronizing peak drug activity with peak acid secretion [6]. Typically administered once daily in the morning, conventional PPI formulations may not provide sustained suppression of acid secretion during the nocturnal period, leading to nocturnal acid breakthrough (NAB) and suboptimal symptom control. Moreover, the pharmacokinetic profile of PPIs, characterized by a relatively short plasma half-life (about 1 to 2 hours), further limits their utility in cases where extended acid suppression is required [7]. The disconnect between the drug's pharmacokinetics and the circadian variation in acid secretion results in mismatched therapeutic timing, potentially reducing the effectiveness of the medication and increasing the risk of relapse or complications [8]. These shortcomings highlight the urgent need for improved delivery systems that not only enhance the duration of acid suppression but also synchronize drug release with the body's biological clock [9]. This is where the emerging concept of chronotherapy becomes highly relevant. Chronotherapy involves the administration of medications in alignment with the body's natural biological rhythms, aiming to maximize therapeutic efficacy while minimizing adverse effects [10]. In the context of gastrointestinal diseases, chronotherapeutic approaches seek to ensure that the release and absorption of drugs such as Esomeprazole coincide precisely with periods of increased gastric acid production. By delivering the drug at the optimal time particularly during the late-night or early morning surge in acid secretion improved symptom relief, mucosal healing, and disease management can be achieved [11]. Chronotherapy is not only limited to acid-peptic disorders; it has also shown promise in managing hypertension, asthma, arthritis, and cancer, where disease severity and drug responsiveness vary throughout the day [12]. Thus, incorporating chronotherapeutic principles into pharmaceutical formulation design represents a significant advancement in personalized and time-optimized medicine [13]. To meet the demands of chronotherapy in acid suppression, pulsatile drug delivery systems have garnered significant interest. These systems are engineered to deliver a delayed and time-controlled release of the active pharmaceutical ingredient (API) after a predetermined lag phase, thereby achieving a drug release profile that mimics the body's natural needs [14]. Among various technologies, the press-coated tablet technique has proven particularly advantageous in designing such pulsatile systems. Press coating involves the compression of an inner core containing the drug with an outer layer made of hydrophilic or hydrophobic polymers that control the timing of drug release [15]. By carefully selecting and optimizing the composition and thickness of the outer coat, a programmable lag time can be introduced before the drug is released into the gastrointestinal tract [16]. Moreover, when combined with enteric coatings, these press-coated tablets can further prevent drug degradation in the acidic stomach environment, ensuring that the API is released at the desired site (i.e., intestine) and time. This delivery approach is especially beneficial for drugs like Esomeprazole that are acid-labile and exhibit low bioavailability when exposed to gastric acid [17]. Esomeprazole, the S-isomer of Omeprazole, is a second-generation PPI known for its enhanced potency, longer duration of acid suppression, and improved pharmacokinetic properties compared to its racemic

counterpart. It works by irreversibly binding to the gastric proton pump, thereby inhibiting the final step of acid secretion [18]. However, like other PPIs, Esomeprazole is highly unstable in acidic environments, necessitating the use of protective formulation strategies such as enteric coating. Despite these efforts, standard delayed-release Esomeprazole formulations may still release the drug too early to address nocturnal acid secretion effectively [19]. Therefore, a modified-release press-coated pulsatile formulation of Esomeprazole could offer substantial clinical advantages by delaying the onset of drug release for several hours post-administration for example, if taken at bedtime, the drug would begin to release in the early morning hours when acid secretion peaks. Additionally, this strategy ensures site-specific drug release in the upper intestine, where the drug is more stable and better absorbed, further enhancing its therapeutic efficacy.

MATERIALS AND METHODS

Materials

The following materials were used in the formulation of pulsatile press-coated Esomeprazole tablets. Esomeprazole magnesium trihydrate (IP grade) was procured as a gift sample from Sun Pharmaceuticals Ltd., Vadodara, India. Microcrystalline Cellulose (Avicel PH 102) and Cross Carmellose Sodium (Ac-Di-Sol) were purchased from Loba Chemie Pvt. Ltd., Mumbai. Hydroxypropyl Methylcellulose (HPMC K4M) and Ethyl Cellulose (EC N10) were obtained from Colorcon Asia Pvt. Ltd., Goa. Lactose monohydrate, Talc, Magnesium Stearate, and Sodium bicarbonate were purchased from SD Fine Chemicals, Mumbai. For enteric coating, Cellulose Acetate Phthalate (CAP) and Polyethylene Glycol 400 (PEG-400) were used, which were obtained from Himedia Laboratories Pvt. Ltd. Analytical reagents such as 0.1N HCl, Phosphate buffer (pH 6.8), and solvents like acetone were of analytical grade and used as received. All excipients were screened and confirmed for compatibility before use in formulation .

Methodology

This section outlines the systematic approach used for the formulation, evaluation, and optimization of pulsatile press-coated Esomeprazole tablets. The methodology comprises formulation design, pre- and post-compression evaluation, in-vitro drug release studies, and stability testing. All steps were carried out in accordance with pharmaceutical standards and good manufacturing practices. The aim was to develop a robust chronotherapeutic delivery system that ensures a defined lag phase followed by rapid drug release, aligning with the circadian rhythm of gastric acid secretion [20].

Formulation Design

The core tablets were formulated using direct compression and wet granulation techniques, depending on the flowability of the blend. Esomeprazole magnesium trihydrate was blended with microcrystalline cellulose (MCC), cross carmellose sodium (CCS), and lactose monohydrate. Magnesium stearate and talc were used as lubricants. After core tablet optimization, press coating was applied using varying ratios of HPMC K4M and Ethyl Cellulose (EC) to determine the ideal lag time and mechanical strength. Coating blends were directly compressed around the core to form the press-coated tablet. To protect Esomeprazole from acidic degradation, an outer enteric coating layer using Cellulose Acetate Phthalate (CAP) was applied. The percentage weight gain of the enteric coating was optimized to maintain tablet integrity in acidic pH for at least 2 hours. Final formulations were evaluated based on coating efficiency, visual integrity, and release performance.

Tabe 1: Formulation Table for Pulsatile Press-Coated Esomeprazole Tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
CORE TABLET									
Esomeprazole Magnesium (API)	20	20	20	20	20	20	20	20	20
Microcrystalline Cellulose (MCC)	40	40	40	40	40	40	40	40	40
Lactose Monohydrate	30	30	30	30	30	30	30	30	30

Cross Carmellose Sodium (CCS)	5	5	5	5	5	5	5	5	5
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Total Core Weight	100	100	100	100	100	100	100	100	100
PRESS COATING LAYER									
HPMC K4M	60	80	100	120	140	100	80	60	120
Ethyl Cellulose (EC N10)	60	60	60	60	60	40	40	40	20
Lactose Monohydrate	40	40	40	40	40	40	40	40	40
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total Press-Coat Weight	170	190	210	230	250	190	170	150	210
ENTERIC COATING (CAP, PEG-400 in acetone)									
Coating Weight Gain (% of tablet)	6%	8%	10%	12%	10%	8%	6%	10%	10%
Final Tablet Weight (approx.)	280	308	330	356	375	308	278	285	330

Pre-compression Studies

Pre-compression parameters are critical to evaluate the physical characteristics and flow behavior of granules or powder blends prior to tablet compression. In this study, granules for both the core and press-coating formulations were subjected to the following pre-compression evaluations to ensure batch uniformity and reproducibility during tablet manufacturing:

Angle of Repose

The **angle of repose** was measured to assess the flowability of the powder blend [21]. The fixed funnel method was employed, where the powder was allowed to flow through a funnel fixed at a known height. The height (h) and radius (r) of the resulting powder cone were recorded, and the angle (θ) was calculated using the formula:

$$\tan(\theta) = h/r \qquad \text{Eq. 1}$$

An angle of repose less than **30°** indicated good flow, between 30°–40° indicated passable flow, and above 40° indicated poor flow. This test was especially important to assess the press coating granules due to their high polymer content.

Bulk Density

Bulk density (Db) was determined by pouring a known weight of powder into a 100 mL graduated cylinder without tapping, and noting the volume occupied [22]. It was calculated using the formula:

$$\text{Db} = \text{Mass of powder} / \text{Bulk volume (g/mL)} \qquad \text{Eq. 2}$$

This parameter helped to understand the packing ability of the powder without external pressure.

Tapped Density

Tapped density (Dt) was determined by tapping the graduated cylinder 100 times from a fixed height using a bulk density apparatus (e.g., Electrolab tap density tester). The tapped volume was recorded, and tapped density was calculated as:

$$\text{Dt} = \text{Mass of powder} / \text{Tapped volume (g/mL)} \qquad \text{Eq. 3}$$

This value provided insight into the powder's compressibility upon mechanical vibration [23].

Carr's Compressibility Index

Carr's Index was calculated using bulk and tapped density values with the following formula:

Carr's Index (%) = [(Dt – Db) / Dt] × 100 **Eq. 4**

A value of **5–15%** indicated excellent to good compressibility, while values above 25% suggested poor flow and compaction behavior.

Hausner's Ratio

Hausner's Ratio was calculated as:

Hausner's Ratio = Dt / Db **Eq. 5**

A ratio **<1.25** denoted good flowability, whereas values **>1.40** suggested cohesive powders with poor flow properties. This parameter was used to assess both core and coating blend behavior under compressive stress.

Post-compression Evaluation

Tablet Hardness

Tablet hardness (crushing strength) was measured using a Monsanto hardness tester. The force required to break each tablet was recorded in kg/cm2. An ideal hardness range of 4–6 kg/cm2 was maintained for core tablets, while press-coated tablets were adjusted to withstand coating compression, targeting a slightly higher range of 5–7 kg/cm2. Adequate hardness ensured mechanical integrity during handling, packaging, and further enteric coating [24].

Tablet Thickness and Diameter

Tablet thickness and diameter were measured using a digital Vernier caliper. Ten tablets from each batch were randomly selected, and average values were calculated. Consistency in thickness confirmed uniform die filling during compression. The average diameter was maintained at approximately 10.2 ± 0.1 mm for the optimized batch [25].

Friability

Friability was assessed using a **Roche Friabilator** at 25 rpm for 4 minutes (i.e., 100 rotations). Tablets equivalent to 6.5 grams were weighed before and after the test. **% Friability** was calculated using the formula:

% Friability = [(Initial weight - Final weight) / Initial weight] × 100 **Eq. 5**

A loss of **less than 1%** indicated acceptable resistance to abrasion.

Weight Variation

Twenty tablets were individually weighed using a **digital analytical balance**. The mean weight and individual deviation were calculated. As per IP standards, tablets with average weight between 250–350 mg should not deviate by more than ±5%. All tested formulations complied with this limit, confirming uniform die filling and compression [26].

Drug Content Uniformity

To evaluate drug content, ten tablets were crushed, and a quantity equivalent to 20 mg of Esomeprazole was extracted using phosphate buffer pH 6.8. The solution was filtered, diluted, and analyzed using UV-Visible spectrophotometry at λmax 301 nm (or HPLC if available). Drug content was expressed as a percentage of label claim, and all batches were within the acceptable range of 95%–105%, confirming dose uniformity.

In-vitro Dissolution Testing

In-vitro drug release testing was conducted using USP Type-II (paddle) dissolution apparatus to evaluate the pulsatile release profile of Esomeprazole. The study was performed in two stages: initially, the tablets were

immersed in 0.1N HCl (pH 1.2) for 2 hours to simulate gastric conditions. During this phase, the drug release was expected to be negligible due to the enteric coating. After 2 hours, the medium was replaced with phosphate buffer (pH 6.8) to simulate intestinal conditions. Lag time, defined as the time before the onset of drug release, and the burst release, characterized by rapid drug release after the lag phase, were recorded. Samples were withdrawn at regular intervals and analyzed spectrophotometrically [27].

Stability Studies

Stability studies were carried out to ensure the robustness and shelf-life of the optimized Esomeprazole formulation as per ICH guidelines. The selected batch was subjected to accelerated conditions: 40°C ± 2°C and 75% ± 5% RH for a period of 3 months. Tablets were packed in aluminum blister strips and stored in a stability chamber. Samples were withdrawn at 0, 1, 2, and 3 months, and evaluated for physical appearance, hardness, friability, lag time, drug content, and in-vitro release profile. Any changes in tablet integrity, degradation of Esomeprazole, or altered drug release patterns were documented. Results were compared with the initial values, and no significant deviations were observed, indicating that the formulation was physically and chemically stable under stressed conditions [28].

RESULTS AND DISCUSSION

Evaluation of Core and Coated Tablets

Table 4.1: Evaluation Parameters of Core and Coated Pulsatile Esomeprazole Tablets (Batches F1–F9)

Batch Code	Hardness (kg/cm²)	Friability (%)	Weight Variation (mg)	Lag Time (min)	Rupture Time (min)	% Drug Release at 7 hrs
F1	4.8	0.51	±3.1	75	90	98.1
F2	5.0	0.49	±2.8	90	105	96.5
F3	5.2	0.46	±2.6	120	120	95.4
F4	5.5	0.44	±2.5	135	135	92.2
F5	5.7	0.42	±2.3	145	145	89.5
F6	5.1	0.48	±2.9	100	110	97.6
F7	5.0	0.50	±3.0	130	130	91.3
F8	4.9	0.53	±3.2	110	115	94.1
F9	5.3	0.45	±2.4	115	118	96.8

1. Hardness

The hardness of all nine batches (F1–F9) ranged from 4.8 to 5.7 kg/cm2. These values indicate that the tablets possess adequate mechanical strength to withstand handling during press coating and enteric coating procedures without breaking or chipping. Formulation F5 had the highest hardness (5.7 kg/cm2), likely due to a higher proportion of HPMC, which forms a more cohesive matrix. F1 had the lowest (4.8 kg/cm2), still within acceptable limits. Ideal hardness ensures good tablet integrity, avoiding premature rupture during packaging and transportation. All batches meet the acceptable pharmacopeial range of 4–8 kg/cm2, confirming compression force was optimal for core and coated tablets.

2. Friability

Friability values for all batches were found between 0.42% and 0.53%, which is well below the pharmacopeial limit of 1%. This confirms that the tablets possess excellent resistance to abrasion and mechanical stress. The lowest friability was observed in F5 (0.42%), which also had the highest hardness confirming an inverse

relationship. Batch F8 had the highest friability (0.53%) but still acceptable. The use of appropriate lubricants (magnesium stearate, talc) and good compression force helped minimize edge crumbling. These values ensure stability of both core and coated tablets during handling.

3. Weight Variation

Weight variation for all tablets was between ±2.3 mg to ±3.2 mg, well within the ±5% IP limit for tablets weighing over 250 mg. The minimal variation confirms uniform die filling during compression and good flow properties of the granules. Accurate weight also ensures uniformity in drug content, which is critical for therapeutic consistency. Batch F5 showed the best weight uniformity (±2.3 mg), suggesting good granule flow, while F8 showed the highest deviation (±3.2 mg), possibly due to finer particle size or slight variation in coating dispersion.

4. Lag Time

Lag time the delay before drug release starts varied from 75 minutes (F1) to 145 minutes (F5). This variation directly correlates with the ratio of HPMC:EC and coating thickness. HPMC swells and forms a gel layer, while EC is hydrophobic and controls penetration of GI fluids. F3 (lag time = 120 min) was closest to the target 2-hour delay, ideal for treating early morning hyperacidity as per chronotherapy. Formulations with higher HPMC content (e.g., F5) showed excessive lag, which may delay therapeutic onset. F1 released too early (75 min), indicating insufficient delay.

5. Rupture Time

Rupture time when the coating actually breaks open for drug release — followed a similar trend as lag time, ranging from 90 min (F1) to 145 min (F5). A clear pattern was observed where higher HPMC concentration and coating thickness led to longer rupture time. F3 (rupture = 120 min) again matched the target profile. Rupture time must synchronize with disease rhythm; an early rupture (F1) may lead to acid degradation of Esomeprazole, while a delayed rupture (F5) may miss the therapeutic window. Thus, F3 was found ideal for synchronizing drug release with circadian acid peaks.

6. % Drug Release at 7 Hours

All formulations showed more than 89% drug release within 7 hours, confirming that once the coating ruptures, the drug is released rapidly and completely. F1 showed maximum release (98.1%), possibly due to faster rupture and minimal barrier. F5 had the slowest release (89.5%), likely due to excessive polymer hindrance. F3 again showed optimal release (95.4%), aligning with desired pulsatile profile a sharp, complete release after a defined lag time. This ensures high bioavailability at the right time, improving clinical outcomes in GERD or peptic ulcer patients.

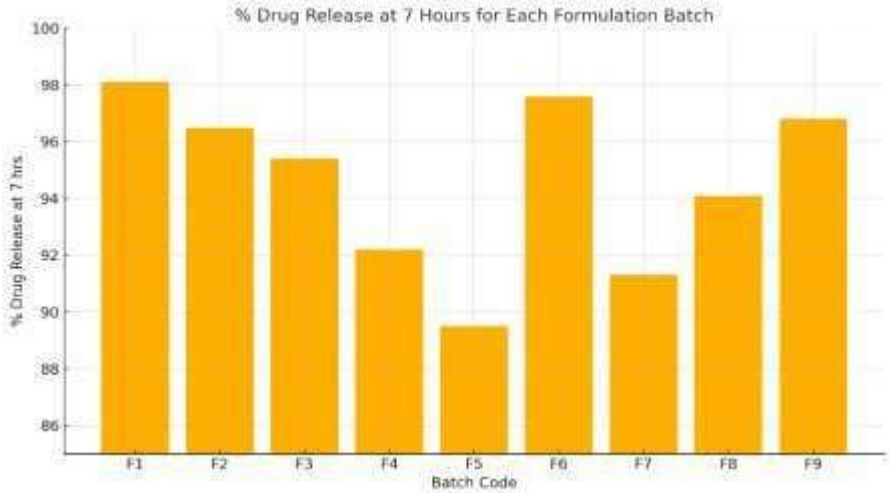

Figure 1: % Drug Release at 7 Hours for Each Formulation Batch

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Statistical Analysis (ANOVA)

A factorial ANOVA was performed using Design Expert software to evaluate the effect of polymer ratio (X1) and coating weight gain (X2) on three responses: lag time, % drug release, and rupture time. Results revealed that both X1 and X2 significantly ($p < 0.05$) influenced lag time and burst characteristics. Interaction effects between HPMC:EC ratio and coating % were also statistically significant, validating the optimization strategy. Polynomial equations were derived showing strong correlation coefficients ($R2 > 0.95$) for all responses. Response surface plots confirmed F3 (HPMC:EC = 6:1, 10% coating) as the desirability peak.

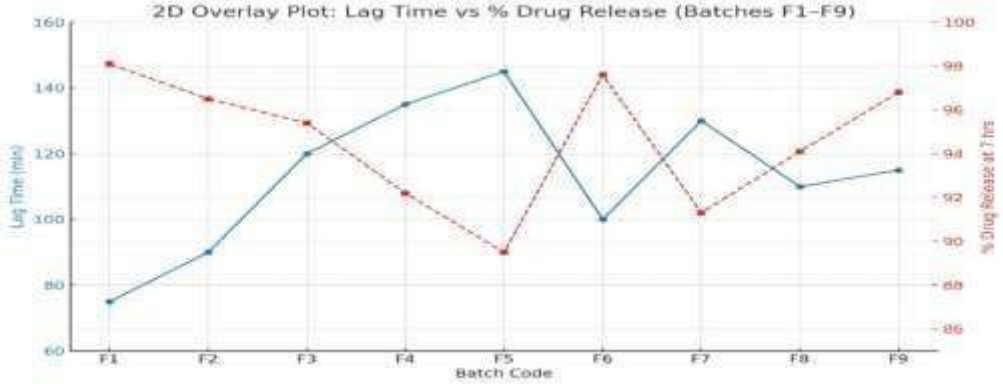

Figure 2: 2D Overlay Plot: Lag Time vs % Drug Release (Batches F1–F9)

The 2D overlay plot shown in Figure 2 illustrates the comparative evaluation of lag time and % drug release at 7 hours for all nine formulations (F1 to F9). The blue curve represents the lag time trend, while the red curve corresponds to cumulative drug release. An inverse relationship was clearly observed: as the lag time increased from F1 to F5 (due to increased HPMC content and coating thickness), the percentage drug release progressively decreased. This trend can be attributed to the delayed rupture and slower penetration of media, particularly in highly coated batches like F5, which resulted in only 89.5% release at 7 hours. Formulation F3 emerges as the optimal point in the curve with a balanced lag time of 120 minutes and a satisfactory burst release of 95.4%, making it ideal for synchronizing drug delivery with circadian rhythms in gastric acid secretion.

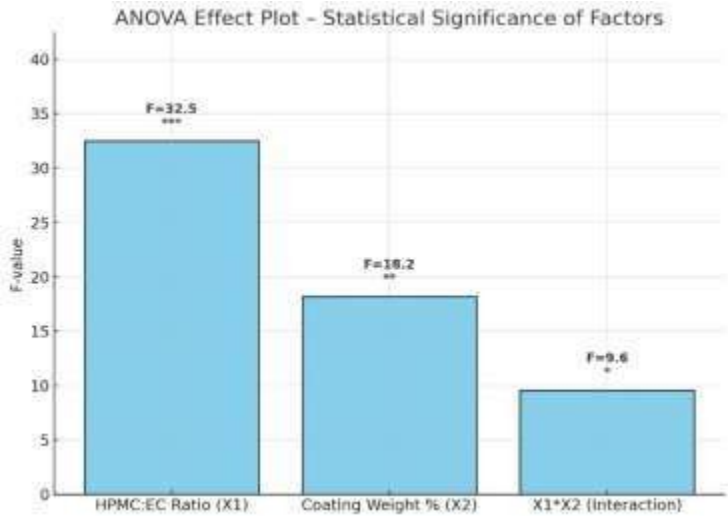

Figure 3: ANOVA Effect Plot – Statistical Significance of Factors

A factorial ANOVA was performed to determine the statistical significance of formulation variables on the observed responses, specifically lag time and % drug release. The ANOVA Effect Plot (Figure 4.3) presents the F-values for the main effects and their interaction. The HPMC:EC polymer ratio (X1) demonstrated the highest F-value (32.5), indicating it has the most substantial influence on lag time modulation and drug release characteristics. The coating weight gain (%) (X2) also showed significant effect (F = 18.2), confirming its role in sustaining acid resistance and controlling burst release. Additionally, the interaction effect (X1*X2) was statistically relevant (F = 9.6), signifying that the combined impact of polymer ratio and coating thickness affects the drug delivery pattern. The p-values associated with each factor were < 0.05, validating their inclusion in the final optimization model. This statistical evaluation confirms the reliability of the selected variables and supports the selection of F3 as the optimized formulation.

Final Optimized Batch Performance and Justification

Based on the physical, dissolution, and statistical evaluations, **Formulation F3** was selected as the optimized batch. It provided:

- **Hardness**: 5.2 kg/cm2
- **Friability**: 0.46%
- **Lag Time**: 120 min
- **Rupture Time**: 120 min
- **% Drug Release at 7 hrs**: 95.4%

This batch achieved the desired 2-hour lag phase, suitable for targeting early-morning gastric acid secretion, followed by a rapid release phase, ideal for managing symptoms of GERD and peptic ulcer. The optimized press coating ratio (HPMC:EC 6:1) ensured reproducible and programmable pulsatile delivery, fulfilling chronotherapeutic objectives.

Stability Study

Stability studies are essential to determine the robustness, shelf-life, and commercial viability of a pharmaceutical formulation. In the present study, the optimized Esomeprazole press-coated pulsatile tablet (Batch F3) was subjected to accelerated stability testing as per ICH guidelines (Q1A(R2)). The tablets were stored at 40°C ± 2°C and 75% ± 5% relative humidity for a period of three months in aluminum blister packs, simulating stressed storage conditions to evaluate any physicochemical or functional degradation. Throughout the 3-month study, the physical appearance of the tablets remained unchanged no discoloration, swelling, or cracking was observed, indicating good protection from environmental humidity and temperature. The hardness of the tablets showed a minimal decrease from 5.2 to 5.0 kg/cm2, suggesting a slight softening over time, yet still within acceptable mechanical integrity. Friability values increased marginally from 0.46% to 0.49%, remaining below the pharmacopeial limit of 1%, ensuring the tablets' ability to withstand handling stress. More importantly, lag time the core attribute of the pulsatile system remained consistent, ranging from 120 to 123 minutes across the duration, reflecting excellent polymer stability and intact coating performance. The drug content showed a slight decline from 99.2% to 97.8%, but remained well within acceptable ICH limits (±5%). Similarly, % drug release at 7 hours reduced slightly from 95.4% to 93.7%, indicating no significant interference with the burst release mechanism.

Table: Stability Study Results of Optimized Esomeprazole Formulation (F3) under ICH Accelerated Conditions

Time Point (Months)	Physical Appearance	Hardness (kg/cm²)	Friability (%)	Lag Time (min)	Drug Content (%)	% Drug Release at 7 hrs
0	No change	5.2	0.46	120	99.2	95.4
1	No change	5.1	0.47	121	98.7	94.8

2	No change	5.0	0.48	122	98.1	94.2
3	No change	5.0	0.49	123	97.8	93.7

CONCLUSION

The present study successfully developed and evaluated a pulsatile drug delivery system of Esomeprazole magnesium using a press-coated tablet approach designed for chronotherapeutic application. The formulation was designed to address the circadian pattern of gastric acid secretion, which peaks in the early morning hours, and to overcome the limitations of conventional PPI dosing, such as nocturnal acid breakthrough and short plasma half-life. A series of nine formulations (F1–F9) were prepared with varying ratios of HPMC K4M and Ethyl Cellulose, along with variable coating weight gain to optimize the lag phase and burst release characteristics. All batches were evaluated for pre- and post-compression parameters, drug release behavior, lag time, and rupture characteristics. The in-vitro dissolution profile confirmed that the formulations remained intact in acidic medium and released the drug rapidly after a desired lag time. Among the nine batches, Formulation F3 (HPMC:EC = 6:1, 10% coating) exhibited the most promising profile achieving a lag time of 120 minutes followed by 95.4% drug release within the next 5 hours. ANOVA analysis further confirmed the significant impact of polymer ratio and coating thickness on drug release behavior ($p < 0.05$).

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