RESEARCH PAPER

Formulation, Optimization and In Vitro Evaluation of MUPS Capsules Loaded with Esomeprazole DR Pellets as an Adjuvant Therapy for NSAIDs-Induced Gastric Ulcers

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Abstract
Esomeprazole, a proton pump inhibitor, provides gastro protection by inhibiting gastric acid secretion. The present study aimed to develop and optimize delayed release (DR) pellets of esomeprazole magnesium for improved patient compliance and reduced gastrointestinal side effects during long-term NSAIDs therapy. Esomeprazole DR pellets were developed using fluidized bed coating involving drug layering, sub-coating, and enteric coating. A Quality by Design (QbD)-based optimization approach employing response surface methodology was applied to evaluate the effect of key formulation variables on drug release. Esomeprazole optimization considered hydroxypropyl cellulose level, sub-coating percentage, enteric polymer weight gain, and plasticiser ratio. The formulations were systematically characterized for micromeritic properties, drug content, and in-vitro release behavior. Esomeprazole DR pellets demonstrated effective acid resistance for 2 hours in 0.1N HCl, followed by rapid release in phosphate buffer (pH 6.8), confirming reliable gastro protection. Statistical models and response surface plots identified that sub-coating and enteric coating thickness were pivotal for esomeprazole performance.

Keywords: Esomeprazole, Enteric coating, Fluid bed process, Pellets, Quality by Design

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1. Introduction

Esomeprazole is the S-isomer of omeprazole and is a gastric proton pump inhibitor and belongs to the class of organic compounds known as sulfinylbenzimidazoles. These are polycyclic aromatic compounds containing a sulfinyl group attached at position 2 of a benzimidazole moiety. It is available in salt form as magnesium [1]. Esomeprazole is used to manage gastroesophageal reflux disease, to prevent stomach ulcers, and can be used to help treat the effects of an H. pylori infection [2]. Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell, forming the active inhibitor, the achiral sulfenamide. The sulfenamide binds to exposed cysteine residues in the alpha subunit of H+, K+-ATPase to form covalent disulfide bonds, which inhibit the activity of the pump. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity [3].
Esomeprazole is highly soluble in methanol, freely soluble in DMSO and ethanol (143 mg/mL at 25 °C), practically insoluble in heptane, and very slightly soluble in water (0.353 mg/mL at 25 °C) [4]. After oral

administration of esomeprazole magnesium, the peak plasma levels (Cmax) occur at approximately 1.5 hours (Tmax). The Cmax increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. Esomeprazole is extensively metabolised in the liver by the cytochrome P450 (CYP) enzyme system. The plasma elimination half-life of esomeprazole is approximately 1-1.5 hours. Less than 1% of the parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the faeces [5].

Esomeprazole magnesium in acidic and neutral media would be degraded, and in an acidic environment, degradation is particularly rapid. Therefore, the enteric-coated preparation of Esomeprazole is chosen for blocking direct contact between esomeprazole magnesium and gastric juice [6]. The FBD is used for enteric coating of Esomeprazole. Eudragit L100-55 was applied as the enteric coating polymer for esomeprazole to ensure acid resistance. Many studies shows enteric coating by FBD [7]. For instance, P. K. Lakshmi et al., formulated Duloxetine hydrochloride enteric coated pellets using a fluidised bed. Three separate layers, the drug layer, the barrier layer and the enteric layer were coated onto the inert core pellets [8].

Moreover, the stability of Esomeprazole is also affected by the conditions of light, heat and oxygen. DR formulation of Esomeprazole can be used for long-term NSAIDs therapy in osteoarthritis and rheumatoid arthritis with a low risk of mostly observed side effects of dyspepsia or ulcer formation. For the formulation of Esomeprazole magnesium DR pellets, same excipients that are used in the innovator product NEXIUM, 20 mg (Esomeprazole magnesium delayed release capsule) were selected [9]. The formulation shall be compared to existing marketed formulations to prove its safety and efficacy.

2. Materials and Methods

2.1. Material

Esomeprazole Magnesium ($C_{34}H_{36}MgN_6O_6S_2$), Methacrylic acid copolymer dispersion (Eudragit L30 - D55), HPMC Phthalate, Glycerol Monostearate 40-55 (Geleol pellets 40-55), Hydroxypropylcellulose (Klucel LF), Macrogol 6000 (Polyethylene Glycol 6000), Polysorbate 80, EudragitL30D-55, Hypromellose Phthalate (Hydroxypropyl methyl cellulose phthalate HP 55), Crospovidone XL 10 (Polyplasdone XL10), Talc and Light Magnesium oxide, Sugar Spheres USNF (Non-pareil seeds 40-50 mesh), Confectioner's Sugar (Icing sugar with starch). All reagents used for buffer preparation, including potassium dihydrogen phosphate, hydrochloric acid, sodium hydroxide, and acetone, were of analytical grade. Drug, excipients and all chemicals used were obtained as gift samples from Dr. Reddy's Laboratories, Ltd., Hyderabad, India.

2.2. Methods

2.2.1. Compatibility studies of Esomeprazole and formulation components

2.2.1.1. Visual inspection

Esomeprazole magnesium DR pellets prepared using following inactive ingredients: crospovidone, hydroxypropyl cellulose, mannitol, methacrylic acid copolymer type C, sucrose, sugar spheres, talc, titanium dioxide and triethyl citrate [9]. Esomeprazole was mixed with the excipients at a particular ratio. Vials of 1st set were closed with a rubber closure, sealed and kept in an oven at 60±5°C for 4 weeks. Similarly, 2nd set was closed with a rubber closure that is punctured with a needle to make it permeable for external temperature and humidity and kept in ambient environmental conditions for 4 weeks. Samples were checked visually for any colour change by comparing with the control sample of only API and the mixture of all excipients kept in two separate vials under sealed conditions.

2.2.1.2. Fourier transform infrared spectroscopy (FTIR) Study

The infrared (IR) spectrum of any compound gives information about the specific functional groups present in that compound. Apart from visual inspection of the powder, one vial was prepared with API and a mixture of all excipients in a 1:10 ratio and kept in an oven at 60±5°C for 4 weeks. This vial was checked for IR study by taking the powder content after 4 weeks of study.

An IR spectrum was taken using the potassium bromide (KBr) pellets technique using FTIR- 8400S, Shimadzu, Japan. To prepare the pellets, a few milligrams of the sample were ground together in a mortar with about 100 times the quantity of KBr. The finely ground powder was introduced into a stainless-steel die. The powder was then pressed in the die between polished stainless-steel anvils at a pressure of about 9 t/in2. The infrared spectrum of the drug was then taken and compared with the standard.

2.2.3. Formulation of Esomeprazole DR pellets

Esomeprazole DR pellets were prepared (b.size: 3000 units/ capsules) using a fluidized bed coating process in FBE (Make-ACG Pam Pharma, Model GPCG 1.1) involving sequential steps of drug layering, sub-coating, and enteric/delayed release coating with the following formula mentioned in Table 1.

Table 1 Unit Dose formula of Esomeprazole DR pellets

Name of Ingredient	Quantity (mg/capsule)
Stage: Drug Layering	
Esomeprazole magnesium Trihydrate IH (equivalent to	22.264

Esomeprazole 20mg)	
Sugar spheres (Nonpareil seeds 40-50 mesh) Ph. Eur.	20.000
Hydroxypropylcellulose (Klucel LF) Ph. Eur.	10.500
Crospovidone XL 10 (Polyplasdone XL10) Ph. Eur.	5.236
Water, Purified Ph. Eur.	q.s.
Total weight of Drug Layered Pellets	***58.000***
Stage: Sub Coating	
Drug Layered Pellets	58.000
Confectioner's Sugar (Icing sugar with starch) USNF	15.000
Magnesium Oxide Light Ph. Eur.	6.000
Talc Ph. Eur.	2.500
Macrogol 6000 (Polyethylene Glycol 6000) Ph. Eur.	7.500
Water, Purified Ph. Eur.#	q.s.
Total weight of sub-coated pellets	***89.000***
Stage: Enteric Coating (Layer - I)	
Sub Coated Pellets of Layer – IV	89.000
Methacrylic Acid Ethyl Acrylate Copolymer (1:1) Dispersion 30 percent (Eudragit L30 - D55) Ph. Eur.*	54.675
Glycerol Monostearate 40-55 (Geleol pellets 40-55) Ph. Eur.	2.500
Macrogol 400 (Lutrol E 400) Ph. Eur	8.000
Polysorbate 80 (Crillet 4HP) Ph. Eur.	1.500
Water, Purified Ph. Eur.#	q.s.
Total weight -EC Pellets of Layer – I	***155.675***
Stage: Enteric Coating (Layer - II)	
Enteric Coated Pellets of Layer – I	155.675
Hypromellose Phthalate (Hydroxypropyl methyl cellulose phthalate HP 55) Ph. Eur.	39.825
Macrogol 400 (Lutrol E 400) Ph. Eur.	4.500
Acetone Ph. Eur.#	q.s.
Water, Purified Ph. Eur.#	q.s.
Total weight Esomeprazole EC Pellets of Layer – II	***200.000***
Stage: Lubrication	
Esomeprazole Enteric Coated Pellets of Layer II	200.000
Talc	2.000
Total weight of the Lubricated pellet of Esomeprazole EC Pellets	***202.000***
[#] *Does not remain in the final product except in traces and is lost during processing.* **Dry polymer weight considered*	

Drug Layering and Sub-coating

In the drug layering step, a drug suspension was prepared by dissolving hydroxypropyl cellulose in purified water, followed by dispersing of Esomeprazole and Crospovidone to make 40% w/w dispersion. Sugar Spheres (Non pareil seeds 40-50 mesh) was loaded in FBE, and esomeprazole suspension was sprayed on inert pellet cores with hydroxypropyl cellulose serving as the binder using process parameters mentioned in Table 2 to get the desired weight gain of 190.0% ±1%. Drug-loaded pellets were finally dried at 50-60ºC for 30min as a part of curing. This was followed by the application of a protective sub-coating layer by dissolving macrogol in Purified water, followed by dispersing of Talc and Light Magnesium oxide to form 15.8% w/w dispersion. Drug-coated pellets along with Confectioner's Sugar (Icing sugar with starch) was loaded in FBE and subcoating dispersion was sprayed over drug-loaded pellets to get desired weight gain of 53.45% ±1%. Sub-coated pellets were finally dried at 50-60ºC for 30min for curing.

Enteric Coating (EC) Layer-I

Enteric layer was applied in 2 layer i.e. Layer-I using Eudragit L30D55 and layer-II using HPMC Phthalate as an enteric-coated polymers. Enteric coating Layer-I dispersion was prepared by mixing Macrogol, Glyceryl

Monostearate and Polysorbate 80 in Purified water, followed by mixing with Eudragit L30D-55 to obtain an uniform dispersion with a solid content 34% w/w. Enteric coating Layer-I dispersion is sprayed over the sub-coated pellet using the parameters mentioned in Table 2 to obtain 74.9% ±1% weight gain.

Enteric Coating (EC) Layer-II

Enteric coating Layer-II dispersion was prepared by solubilising Hypromellose phthalate in Purified water: Acetone mixture (40:60 ratio), followed by mixing of Macrogol to get a clear solution. Enteric coating Layer-II dispersion was sprayed over the sub-coated to obtain 124.7% ±1% weight gain from the sub-coated pellet. The coating levels of the sub-coating and enteric coating, as well as the plasticiser-to-polymer ratio, were varied according to a statistical design. The prepared multi-unit pellets were encapsulated into hard gelatin capsules as single-unit dosage forms.

Table 2 Machine process parameters used to formulate Esomeprazole delayed release pellets

Machine parameters	Operating range			
	Drug Coating	**Sub coating**	**Enteric coating-1**	**Enteric coating-2**
Number of Gun	1	1	1	1
Filter bag pore size/type	5 µ/ cloth	5 µ /cloth	100µ/ bonnet	100µ/ bonnet
Air distribution plate	C	C	C	C
Inlet Air Temperature (ºC)	45-60	45-60	40-50	40-45
Exhaust Temperature (ºC)	25-50	25-50	25-45	25-42
Product Temperature (ºC)	32-45 (target 38)	32-45 (target 38)	30-36 (Target 33)	30-37 (Target 32)
Inlet Air Flow (CFM)	50-80	50-85	50-85	50-90
Atomization Pressure (bar)	1.0-1.2	1.0-1.2	1.0-1.2	1.0-1.2
Spray Rate (gm/minute)	2-14	2-12	2-10	3-14
Inlet air RH (%)	10-20	10-25	15-25	15-30
Drying temperature(ºC)	50-60	50-60	45-55	45-55
Drying Time (Min.)	30 min or till %LOD achieved	30 min or till %LOD achieved	30 min or till %LOD achieved	30 min or till %LOD achieved
% LOD (at 105°C in 2 minutes).	NMT 3.00%	NMT 3.00%	NMT 3.00%	NMT 3.00%

2.2.4. Dissolution

Esomeprazole Magnesium Delayed-release Capsule is official in the USP. Hence, the dissolution method and specification limit were referred from the USP Monograph [10]. The pellet dissolution was evaluated for acid resistance in 0.1N HCl and intestinal release in phosphate buffer pH 6.8.

The dissolution study was performed according to USP Dissolution Test-1 using 300 mL of 0.1 N hydrochloric acid as the dissolution medium in a USP Apparatus II (paddle) operated at 100 rpm (Lab India, Mumbai, India) with sinker and temperature maintained at 37±0.5°C. The test duration was 2 hours. At the specified dissolution interval, 5 mL of sample was withdrawn, filtered, and diluted to 10 mL with dissolution medium to obtain a final concentration within the range of 10–50 µg/mL. The amount of drug dissolved was quantified by UV spectrophotometry at 301 nm. The acceptance criterion was not more than 10% drug release in 2 hours, as specified in the USP monograph [10].

After 2 h run in the acid stage, dissolution was continued by replacing the media with a pH 6.8 phosphate buffer as follows. The dissolution study was conducted according to USP Dissolution Test-1 using 1000 mL of phosphate buffer (pH 6.8) as the dissolution medium in USP Apparatus II (paddle) operated at 100 rpm (Lab India, Mumbai, India) with sinker and temperature maintained at 37±0.5°C. The dissolution test was performed for 30 minutes. At the specified interval, 5 mL of the sample was withdrawn, filtered, and diluted to 50 mL with dissolution medium to obtain a final concentration within the range of 2–20 µg/mL. Drug release was quantified by UV spectrophotometry at 301 nm. The acceptance criterion was not less than 75% (Q) drug release in 30 minutes, as per the USP monograph [10].

2.2.5. Design of Experiments (DoE) and Optimization Approach

A Quality by Design (QbD)-based optimization strategy was adopted for the development of esomeprazole enteric-coated (EC) pellets [11]. Response surface methodology (RSM) was employed using Design-Expert® software to study the effect of formulation variables on drug release behaviour.

For esomeprazole EC pellets, a central composite design (CCD) was applied with four independent formulation factors: hydroxypropyl cellulose level during drug layering (Factor A), percentage weight gain of the sub-coating (Factor B), percentage weight gain of enteric coating with Eudragit L100-55 (Factor C), and plasticiser-to-polymer ratio (Factor D) (Table 3). The

dependent responses were percentage drug release in 0.1N HCl at 2 hours (R1, acid resistance) and percentage drug release in phosphate buffer pH 6.8 at 30 minutes (R2, intestinal release). The objective was to ensure <2% release in acidic medium and >95% release in buffer within 30 minutes.

Experimental data were fitted to linear, interaction (2FI), and quadratic models. Model adequacy was evaluated using ANOVA, adjusted and predicted R^2 values, and lack-of-fit tests. Perturbation plots and 3D response surface plots were generated to visualize factor influences and interactions. Finally, a numerical optimization based on desirability function was performed to identify the optimal formulation space, ensuring robust performance of EC esomeprazole pellets.

Table 3 Design matrix showing formulation variables (HPC level, sub-coating %, EC coating %, plasticiser ratio) and corresponding experimental runs.

Std	Run	Factor 1 A: Hydroxypropyl cellulose (mg)	Factor 2 B: %wt gain of sub-coating (%)	Factor 3 C: %wt gain of EC Layer 1 (%)	Factor 4 D: Plasticiser, EC Polymer ratio (%)	Response 1 Dissolution in 0.1N HCl (at 2hrs) (%) (n=6) (Mean± SD)	Response 2 Dissolution in 6.8 pH phosphate buffer (at 30 minutes) (%) (n=6) (Mean± SD)
1	1	9	53.45	75	14.6	2.1±1.22	95.8 ±2.79
2	14	12	53.45	75	14.6	2.1±0.60	94.8 ±3.19
3	19	9	63.45	75	14.6	1.9±0.83	96.4 ±2.83
4	6	12	63.45	75	14.6	3.0±0.97	95.9 ±3.85
5	8	10.5	58.45	55	12.6	5.9±0.73	98.8 ±0.75
6	17	10.5	58.45	95	12.6	2.2±0.77	97.0 ±2.46
7	23	10.5	58.45	55	16.6	4.3±0.84	98.0 ±1.76
8	5	10.5	58.45	95	16.6	4.1±1.00	98.8 ±2.67
9	3	9	58.45	75	12.6	3.1±0.83	98.6 ±1.11
10	11	12	58.45	75	12.6	3.9±1.03	95.8 ±1.88
11	24	9	58.45	75	16.6	3.5±0.58	97.2 ±2.44
12	15	12	58.45	75	16.6	3.1±0.92	96.0 ±3.75
13	20	10.5	53.45	55	14.6	3.5±1.23	98.2 ±1.02
14	9	10.5	63.45	55	14.6	4.5±1.47	98.8 ±1.27
15	18	10.5	53.45	95	14.6	2.4±1.36	98.8 ±1.84
16	16	10.5	63.45	95	14.6	1.6±0.79	98.0 ±1.83
17	21	9	58.45	55	14.6	5.1±1.53	97.2 ±3.08
18	4	12	58.45	55	14.6	4.8±1.25	95.7 ±3.71
19	10	9	58.45	95	14.6	2.8±1.11	97.0 ±3.37
20	2	12	58.45	95	14.6	3.5±1.44	97.3 ±1.83
21	25	10.5	53.45	75	12.6	1.6±0.75	99.0 ±1.84
22	27	10.5	63.45	75	12.6	3.2±0.85	99.4 ±1.52
23	7	10.5	53.45	75	16.6	2.6±0.58	98.9 ±1.09
24	26	10.5	63.45	75	16.6	1.8±0.73	98.5 ±0.99
25	12	10.5	58.45	75	14.6	1.1±0.42	100.1 ±2.77
26	13	10.5	58.45	75	14.6	1.0±0.40	101.0 ±2.02
27	22	10.5	58.45	75	14.6	1.0±0.28	100.9 ±1.97

2.2.6. Characterization of Optimized Formulation

2.2.6.1. Infrared Spectroscopy

IR Spectroscopy of Esomeprazole EC Pellets was performed on a Fourier-transformed infrared spectrophotometer (FTIR-8400S, Shimadzu, Japan) to confirm the presence of the drug in drug-resin complex DRC. The DRC and KBr (Potassium bromide) were mixed in a 5:95 ratio and placed on the sample holder. The spectra were scanned over 3000 to 400 cm-1.

2.2.6.2. Micromeritic properties

Weighed accurately 10gm of prepared Esomeprazole EC Pellets was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by drug was measured. Bulk density (ρb) was measured by using formula:

$$\rho b = m / v_b \quad (1)$$

Where, m = mass of the blend, vb = untapped volume

Weighed accurately 10gm of prepared Esomeprazole EC Pellets was taken into a graduated cylinder. Volume

occupied by the drug was noted down. Then the cylinder was subjected to 1250 taps from a height of approx. 3 cm manually and final volume (v t) was measured. Tapped density (ρt) is calculated by the below formula:

$$\rho t = m/v_t \quad (2)$$

Where, vt = tapped volume, m = mass of the blend

The compressibility index measures the pellets flow property. Carr's compressibility index was calculated as follows

$$\text{Carr's index} = [\text{Tapped density} - \text{Bulk density}/\text{Tapped density}] \times 100 \quad (3)$$

3. Results

3.1. Compatibility studies of Esomeprazole and formulation components

3.1.1. Visual inspection

The compatibility of drugs and polymers under experimental conditions is an important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and does not affect the shelf life of the product or any other unwanted effects on the formulation. There is no significant change in physical description found in the drug-excipient mixture stored at 60±5°C for 4 weeks, indicating good compatibility of selected excipient with Esomeprazole, except Methacrylic acid copolymer dispersion (Eudragit L30 - D55) and Hypromellose Phthalate, where brownish black discoloration was observed. This confirms the incompatibility of esomeprazole with Methacrylic acid copolymer dispersion (Eudragit L30 - D55) and Hypromellose Phthalate due to their acidic nature, which causes degradation of Esomeprazole. Because of the acidic degradation of Esomeprazole, the formulation of Esomeprazole was designed as a gastro-resistant dosage form. Methacrylic acid copolymer dispersion (Eudragit L30 - D55) and Hypromellose Phthalate are the polymers used for enteric coating of the formulation. In order to prevent interaction of Esomeprazole with the enteric coating polymer, a protecting coating, i.e. sub-coating with Hypromellose polymer, shall be applied between the drug core and the enteric coating. The outcome of the study is mentioned in Table 5.

Table 5. Drug-excipient compatibility study – Visual observation

Excipients (E)	Drug: Excipient Ratio (binary mixture ratio)	Vial with punctured rubber closure/cap kept at ambient environmental condition			Sealed vial kept at 60°C in oven		
		1 week	2 weeks	4 weeks	1 week	2 weeks	4 weeks
Sugar spheres (non-pareil seeds 40-50 mesh)	1:10	No color change	No color change	No color change	No color change	No color change	No color change
Hydroxypropyl cellulose (Klucel LF)	1:10	No color change	No color change	No color change	No color change	No color change	No color change
Crospovidone XL 10 (Polyplasdone XL10)	1:10	No color change	No color change	No color change	No color change	No color change	No color change
Confectioner's Sugar (Icing sugar with starch)	1:5	No color change	No color change	No color change	No color change	No color change	No color change
Magnesium Oxide Light	1:5	No color change	No color change	No color change	No color change	No color change	No color change
Talc	1:5	No color change	No color change	No color change	No color change	No color change	No color change
Macrogol 6000 (Polyethylene Glycol 6000)	1:5	No color change	No color change	No color change	No color change	No color change	No color change
Methacrylic acid copolymer dispersion (Eudragit L30 - D55)	1:5	Brown colour	Brown colour	Brownish black	Brown colour	Brownish black	Brownish black
Glycerol Monostearate 40-55 (Geleol pellets 40-55)	1:5	No color change	No color change	No color change	No color change	No color change	No color change
Polysorbate 80	1:5*	No color change	No color change	No color change	No color change	No color change	No color change
Hypromellose Phthalate (Hydroxypropyl methyl cellulose phthalate HP 55)	1:5	Brown colour	Brown colour	Brownish black	Brown colour	Brownish black	Brownish black

Gelatin	1:5	No color change	No color change	No color change	No color change	No color change	No color change
Titanium dioxide	1:5	No color change	No color change	No color change	No color change	No color change	No color change
Starch	1:5	No color change	No color change	No color change	No color change	No color change	No color change

* *Initial description: Pale yellow colored powder (All other samples are Creamish colored powder)*

3.2.1. FTIR Study

The physical mixture of the drug & excipients was used for the determination of the infrared spectra [12]. There is no significant change in the characteristic peak of API found in the drug-excipient mixture stored at 60±5°C for 4 weeks, indicating good compatibility of selected excipient with Esomeprazole, except vanishing of peak due to secondary amine (C-N stretch) at 1153.49 as shown in Fig. 1 and Table 6. This was due to the interaction of the basic amine group of esomeprazole with acidic Methacrylic acid copolymer dispersion (Eudragit L30 - D55) and Hypromellose Phthalate, confirming the incompatibility of esomeprazole with enteric coating polymer. In-order to prevent interaction of Esomeprazole with enteric coating polymer, This application of protecting coating i.e. sub-coating with hypromellose polymer over core pellet containing drug shall prevent the shall be applied between drug core and enteric coating shall prevent interaction of Esomeprazole with Eudragit L30 - D55 and Hypromellose Phthalate.

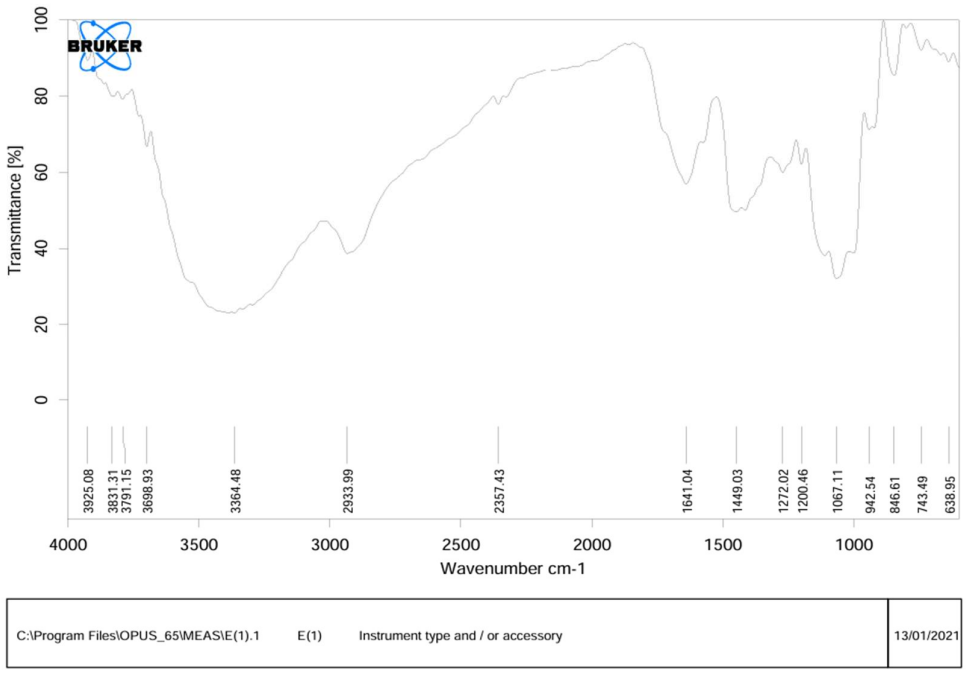


Fig. 1 FT-IR of physical mixture of drug & excipients after 4 weeks of storage at 60±5°C

Table 6 Evaluation of FT-IR spectra of Esomeprazole API Vs Esomeprazole-Excipient mixture

S. No.	Wave numbers in API spectra (cm-1)	Characteristic Absorption	Presence of wave number of API in 4 weeks treated drug and excipients mixture (yes/No)
1	634 cm^{-1}	alkyne C-H bend	Yes (638.95)
2	764.57	aromatic C-H out-of-plane bend	Yes (743.49)
3	1076.93	sulphonyl (S=O) group	Yes (1067.11)

4	1153.49	secondary amine (C-N stretch	No*
5	1473.83	methylene (C-H bend at	Yes (1449.02)

3.3. Optimization by Design of Experiment (DOE)

The formulation design of esomeprazole EC pellets was developed using a response surface methodology (RSM) based on a four-factor, three-level Box–Behnken design. The independent formulation factors studied were the concentration of hydroxypropyl cellulose (HPC, Factor A), percentage weight gain of sub-coating (Factor B), percentage weight gain of ethyl cellulose enteric layer (Factor C), and plasticiser-to-polymer ratio (Factor D). The design matrix is presented in Table 3, while the experimental responses were percentage drug release in 0.1N HCl at 2 hours (acid resistance, Response 1) and percentage drug release in phosphate buffer pH 6.8 at 30 minutes (intestinal release, Response 2). The design provided a systematic framework to evaluate both main and interaction effects of the formulation variables.

Response 1: Dissolution in 0.1N HCl at 2 Hours (Acid Resistance)

The dissolution studies in acidic medium revealed that drug release after two hours ranged between 1.0% and 5.9% across different batches, confirming that the prepared pellets possessed strong gastro-resistance. Statistical model fitting indicated that the quadratic model was most appropriate, with an adjusted R^2 of 0.9878 and predicted R^2 of 0.9681, demonstrating excellent predictability (Table 7). The lack-of-fit test was not significant ($p = 0.1280$), further confirming the adequacy of the model (Table 8). Analysis of variance revealed that the percentage weight gain of the EC layer (Factor C) was the most significant determinant of acid resistance ($p < 0.0001$). Hydroxypropyl cellulose content (Factor A) and sub-coating percentage (Factor B) also influenced drug release, although to a lesser extent.

Table 7 Fit summary of different polynomial models for Response 1 (% drug release in 0.1N HCl at 2 hrs)

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	Remarks
Linear	0.1330	0.0021	0.1310	-0.0338	
2FI	0.6976	0.0018	0.0362	-0.4137	
Quadratic	< 0.0001	0.1280	0.9878	0.9681	Suggested
Cubic	0.0151	0.6667	0.9985	0.9887	Aliased

Table 8 ANOVA for quadratic model describing Response 1 (% release in 0.1N HCl at 2 hrs).

Source	Sum of Squares	df	Mean Square	F-value	p-value	Remarks
Model	43.52	14	3.11	151.23	< 0.0001	significant
A-Hydroxypropyl cellulose	0.3008	1	0.3008	14.64	0.0024	
B-%wt gain of subcoating	0.2408	1	0.2408	11.72	0.0051	
C-% wt gain of EC Layer 1	11.02	1	11.02	536.15	< 0.0001	
D-Plasticiser, EC Polymer ratio	0.0208	1	0.0208	1.01	0.3339	
AB	0.3025	1	0.3025	14.72	0.0024	
AC	0.2500	1	0.2500	12.16	0.0045	
AD	0.3600	1	0.3600	17.51	0.0013	
BC	0.8100	1	0.8100	39.41	< 0.0001	
BD	1.44	1	1.44	70.05	< 0.0001	
CD	3.06	1	3.06	148.99	< 0.0001	
A^2	7.10	1	7.10	345.63	< 0.0001	
B^2	0.0334	1	0.0334	1.63	0.2264	
C^2	18.83	1	18.83	916.22	< 0.0001	
D^2	7.73	1	7.73	376.22	< 0.0001	
Residual	0.2467	12	0.0206			
Lack of Fit	0.2400	10	0.0240	7.20	0.1280	not significant
Pure Error	0.0067	2	0.0033			
Cor Total	43.77	26				

The model graphs (Fig. 2) illustrated the dominant role of the enteric polymer layer in minimising drug release under gastric conditions. Response surface plots (Fig. 3) showed clear interaction effects: higher HPC combined with increased coating thickness provided superior acid resistance, while optimised plasticiser levels were critical for maintaining coating flexibility. These findings collectively confirmed that gastro-resistance of esomeprazole was primarily governed by the integrity and thickness of the enteric coat.

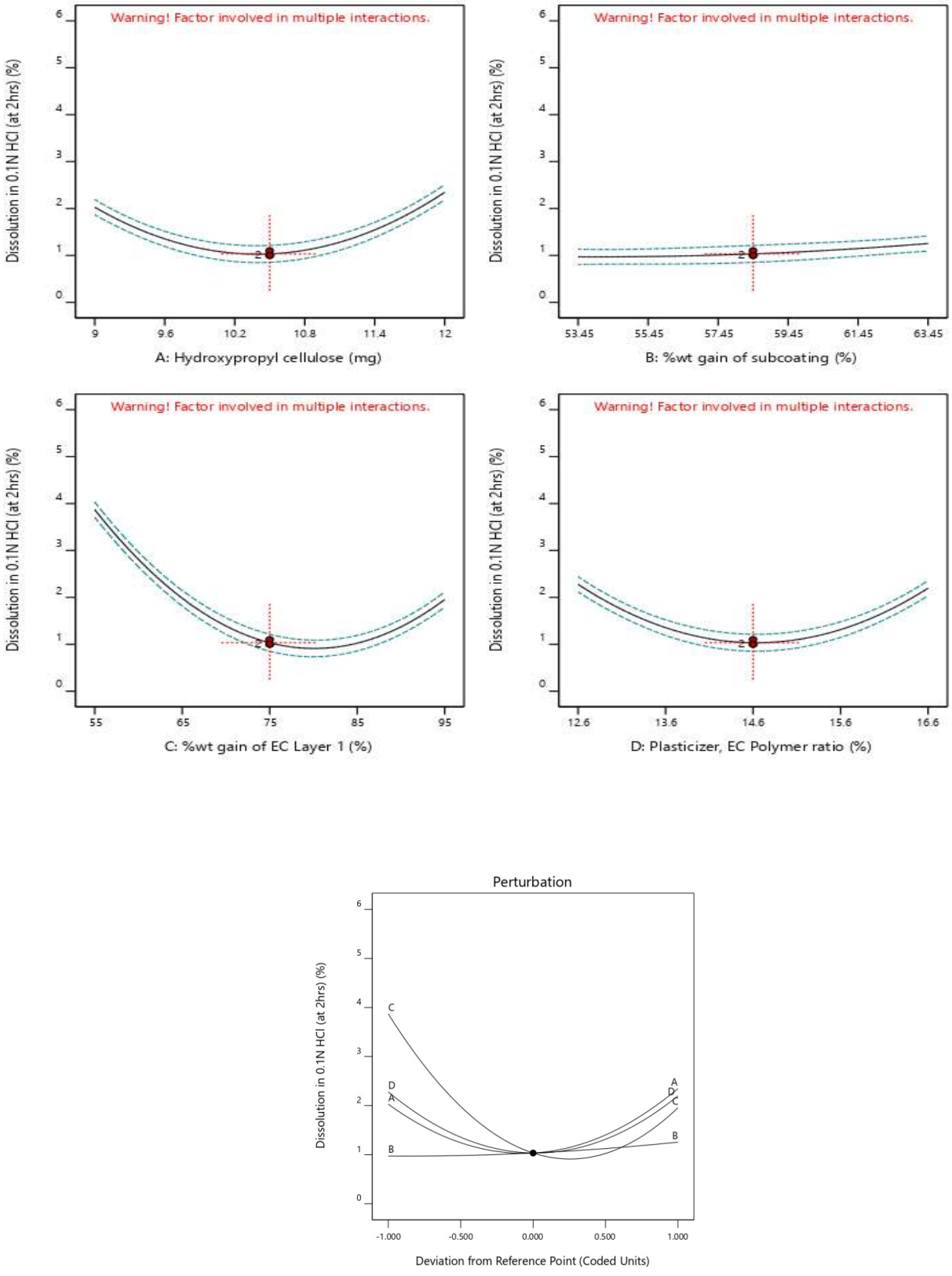


Fig. 2 Model graphs and perturbation plots showing the effect of formulation variables on Response 1 (acid resistance at 2 hrs)

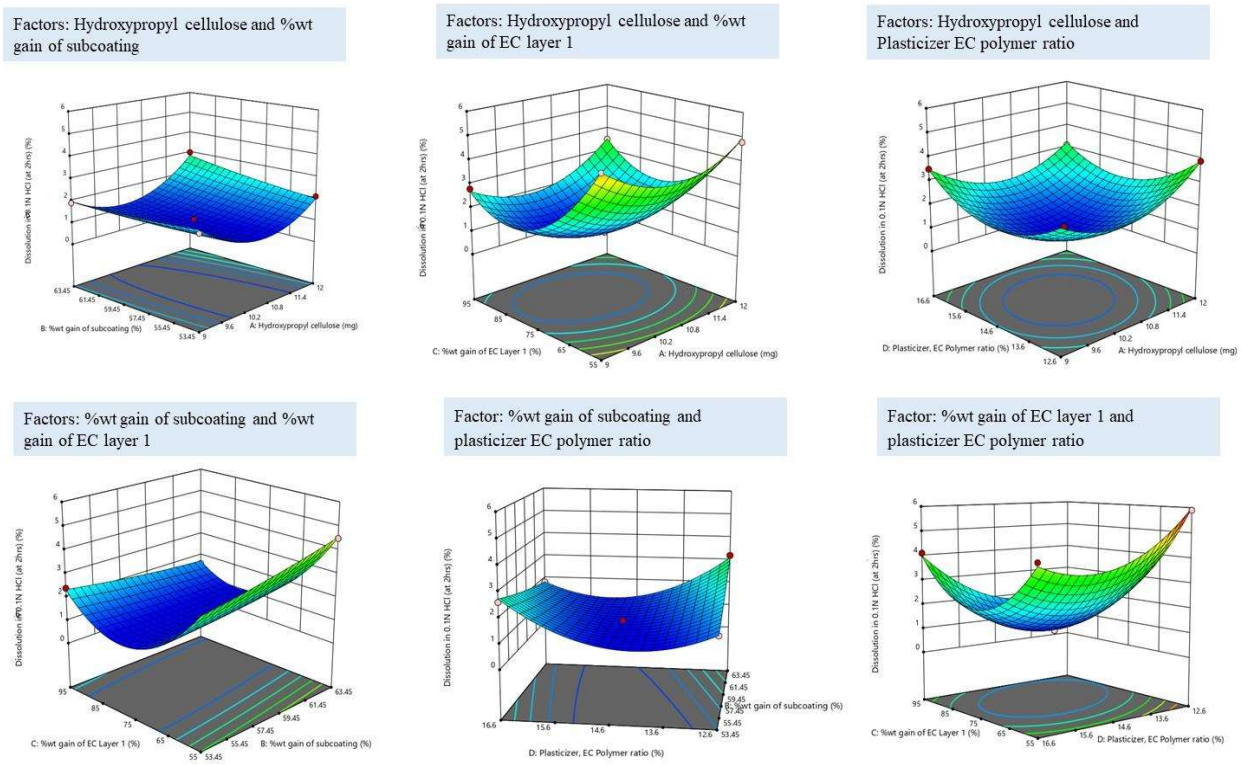


Fig. 3 3D surface response plots depicting the influence of formulation factors on % release in 0.1N HCl at 2 hrs.

Response 2: Dissolution in Phosphate Buffer (pH 6.8) at 30 Minutes (Intestinal Release)

Drug release in phosphate buffer pH 6.8 after 30 minutes ranged from 94.8% to 101%, indicating rapid and complete dissolution of esomeprazole under intestinal conditions. Statistical evaluation (Table 9) confirmed that the quadratic model provided the best fit, with adjusted R^2 and predicted R^2 values of 0.8028 and 0.5009, respectively (Table 10).

Table 9 Fit summary of different polynomial models for Response 2 (% release in phosphate buffer pH 6.8 at 30 min).

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	Remarks
Linear	0.9237	0.0722	-0.1361	-0.3312	
2FI	0.9887	0.0537	-0.4846	-1.2187	
Quadratic	< 0.0001	0.3368	0.8028	0.5009	Suggested
Cubic	0.9505	0.1198	0.6105	-6.6108	Aliased

Table 10 ANOVA for quadratic model describing Response 2 (% release in phosphate buffer pH 6.8 at 30 min).

Source	Sum of Squares	df	Mean Square	F-value	p-value	Remarks
Model	61.63	14	4.40	8.56	0.0003	significant
A-Hydroxypropyl cellulose	2.43	1	2.43	4.73	0.0504	
B-%wt gain of subcoating	0.1875	1	0.1875	0.3646	0.5572	
C-%wt gain of EC Layer 1	0.0033	1	0.0033	0.0065	0.9372	
D-Plasticiser, EC Polymer ratio	0.0008	1	0.0008	0.0016	0.9686	
AB	0.0625	1	0.0625	0.1215	0.7334	
AC	0.8100	1	0.8100	1.58	0.2334	
AD	0.0225	1	0.0225	0.0438	0.8378	
BC	0.4900	1	0.4900	0.9529	0.3483	
BD	0.1600	1	0.1600	0.3111	0.5872	
CD	1.69	1	1.69	3.29	0.0949	
A^2	55.47	1	55.47	107.87	< 0.0001	

B^2	7.84	1	7.84	15.25	0.0021	
C^2	6.16	1	6.16	11.99	0.0047	
D^2	4.69	1	4.69	9.12	0.0107	
Residual	6.17	12	0.5142			
Lack of Fit	5.68	10	0.5684	2.34	0.3368	not significant
Pure Error	0.4867	2	0.2433			
Cor Total	67.80	26				

The results highlighted that the enteric coating thickness (Factor C) exerted the strongest effect on drug release in buffer. Excessively thick coatings delayed drug release, while thinner coatings ensured rapid availability. Hydroxypropyl cellulose (Factor A) and the sub-coating percentage (Factor B) contributed indirectly by ensuring coating uniformity and stability. The plasticiser-to-polymer ratio (Factor D) modulated the disintegration and dissolution behavior, with an optimal level required to balance flexibility and solubility.

Perturbation plots (Fig. 4) and three-dimensional surface plots (Fig. 5) confirmed that achieving rapid dissolution required controlling both the enteric coating thickness and the plasticiser ratio. Significant interactions (particularly between Factors A and C, and between Factors B and D) emphasized the importance of balancing coating thickness, binder concentration, and film flexibility to achieve the desired dissolution performance.

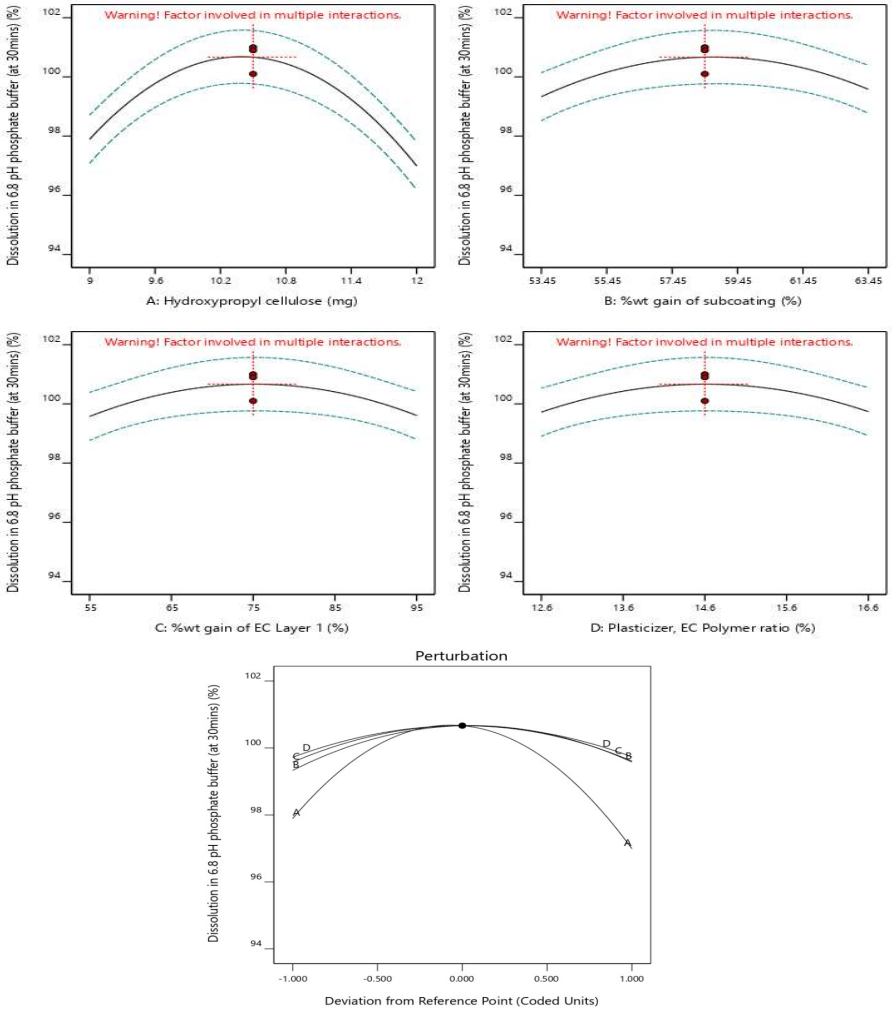


Fig. 4 Model graphs and perturbation plots showing the effect of formulation variables on Response 2 (intestinal release at 30 min).

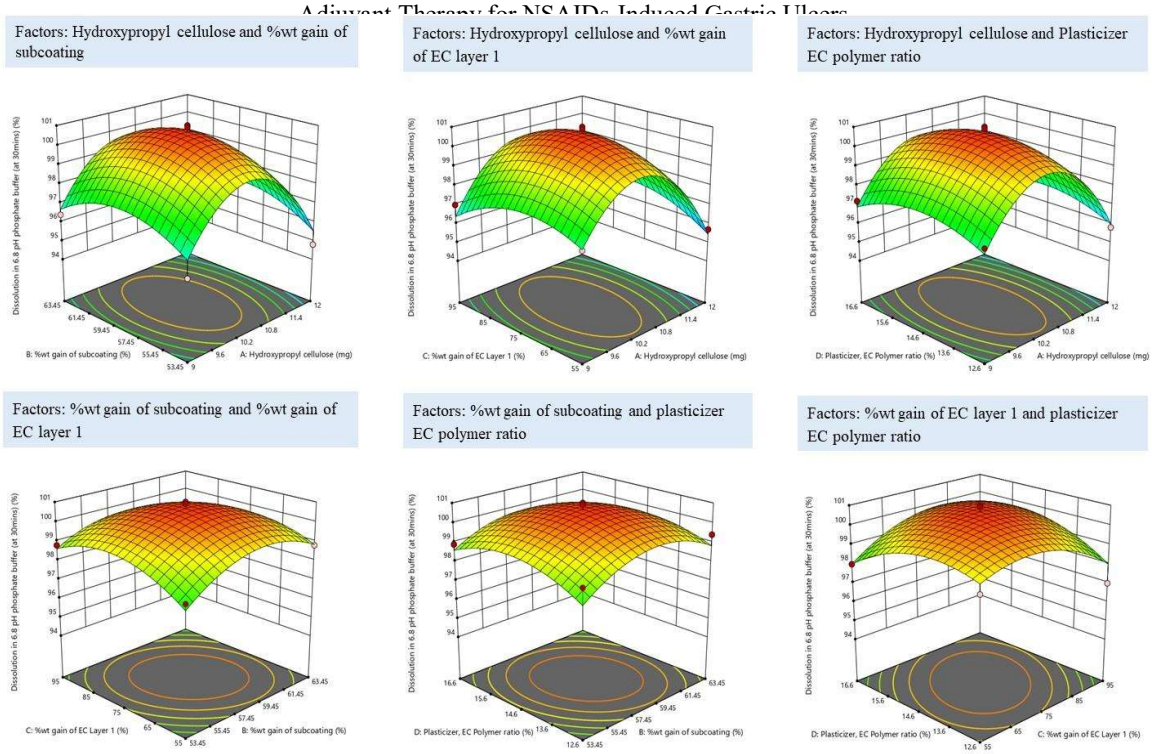


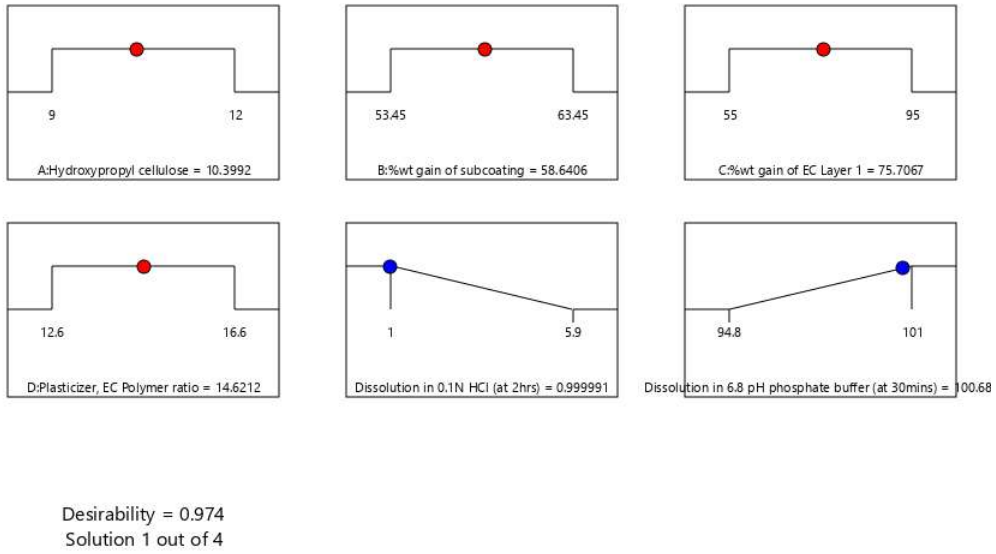
Fig. 5 3D surface response plots illustrating the combined effect of formulation factors on % release in phosphate buffer pH 6.8 at 30 min.

3.3.1. Optimization of Esomeprazole EC Pellets

Numerical optimization was performed using a desirability function approach, targeting less than 2% drug release in 0.1N HCl at 2 hours and more than 98% release in phosphate buffer within 30 minutes. The overlay plot (Fig. 6) defined the design space where both responses were simultaneously optimised. The optimization yielded a desirability value of 0.974, demonstrating high reliability of the model in predicting formulation performance.

The optimised formulation corresponded to hydroxypropyl cellulose concentration of 10.39 mg, sub-coating weight gain of 58.64%, enteric coating weight gain of 75.70%, and a plasticiser-to-polymer ratio of 14.62%. When evaluated, this optimised formulation showed 0.99% drug release in 0.1N HCl at 2 hours and 100.6% drug release in phosphate buffer at 30 minutes, fully meeting pharmacopeial requirements.

These findings confirm that the enteric-coated pellets provided effective acid resistance while ensuring rapid drug release in intestinal conditions. The systematic application of response surface methodology allowed clear identification of critical formulation parameters and successful optimization of the esomeprazole EC pellet formulation.



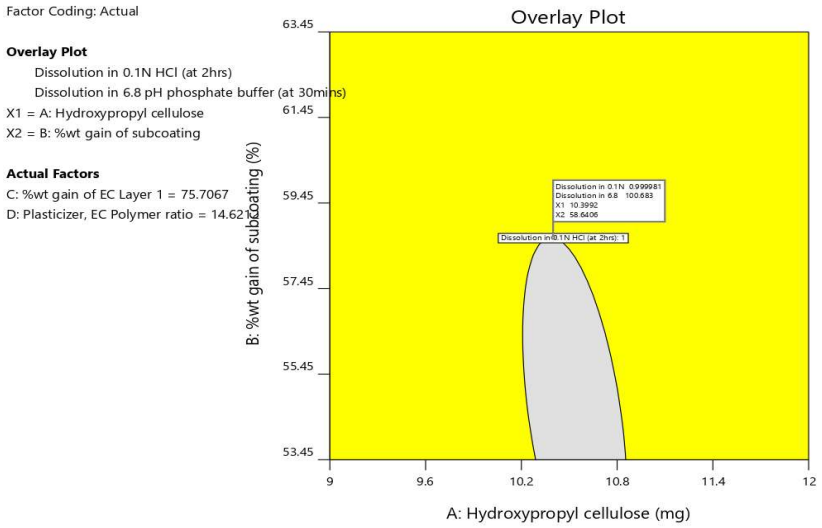


Fig. 6 Graphical optimization (overlay plot) showing the design space for esomeprazole EC pellets with target constraints for both responses.

3.4. Final Optimized formulation of Esomeprazole EC Pellets (For Design Space Verification)

3.4.1. Binder optimization in Drug Loading

Drug-loaded pellets manufactured with 12 mg/capsule of the binder were found to have retarded dissolution at 5 min. Fines were found to be more with the drug-loaded pellets manufactured with 9 mg/capsule as compared to those of 10mg/capsule and 12 mg/capsule. Hence, a binder quantity of 10 mg/capsule is selected as the optimized concentration (Table 9).

Table 9 Formulation with different concentrations of Binder in drug-loaded pellet

Name of Ingredient	Quantity (mg/capsule)	Quantity (mg/capsule)	Quantity (mg/capsule)
	DLP1	DLP2	DLP3
Hydroxypropyl cellulose (Klucel LF) Ph. Eur.	9.000	10.500	12.000
Dissolution: pH 6.8 phosphate buffer, 1000 ml, USP II (Paddle) with sinker, 100 rpm (n=6)			
Batch No.	DLP1	DLP2	DLP3
	%Release (Mean ±SD)		
5 min	94.4±2.76	86.5±3.56	58.8±4.04
10 min	97.2±1.56	90.0±2.21	91.3±1.74
15 min	96.8±1.20	90.7±2.75	93.3±3.23

3.4.2. Wait Gain optimization during Sub-coating

Three batches were manufactured with different weight gains of the sub-coating layer, i.e. 53.45%, 58.45% and 63.45% w/w (Table 10). There is no significant difference in dissolution observed. However, for the safer side and based upon the DOE study, 58.45% w/w is selected as the optimum weight gain.

Table 10 Formulation with different weight gain in sub-coating

Batch No.	SCP1	SCP2	SCP3
% weight gain of sub-coating	53.45	58.45	63.45
Dissolution: pH 6.8 phosphate buffer, 1000 ml, USP II (Paddle) with sinker, 100 rpm (n=6)			
	%Release (Mean ±SD)		
10 min	93.5±1.08	89.0±2.78	94.5±3.02
20 min	100.0±1.25	97.5±2.34	97.0±1.81

30 min	100.0±2.11	99.5±1.87	99.0±2.33

3.4.3. Wait Gain optimization during Enteric coating

Three batches were manufactured with different weight gain of the enteric layer, i.e. 55%, 75% and 95% w/w (Table 11). With 55% weight gain release in acid media found to be comparatively higher with respect to other formulations and also in marketed formulation. There is no significant difference in dissolution observed between 75% and 95% weight gain, both resembling the drug release profile of the marketed product. However, for cost effectiveness point of view and based on the DOE study, 75% w/w is selected as the optimum weight gain.

Table 11 Formulation with different weight gain in the enteric coating

Batch No.	EC1	EC2	EC3	Market Formulation
% weight gain of EC layer 1	55 % w/w	75 % w/w	95% w/w	
Dissolution: 0.1N HCL, 300 ml: Apparatus: USP II (Paddle) with sinker, RPM: 100. Temperature: 37°±0.5°C (n=6)				
	%Release	%Release (Mean ±SD)		
2 Hrs	6.5±0.84	0.5±0.30	0.5±0.16	6.8±1.01
Limit: NMT 10% in 2hrs				
Dissolution: pH 6.8 phosphate buffer, 1000 ml, USP II (Paddle) with sinker, 100 rpm (n=6)				
	%Release	%Release	%Release	%Release
10 min	89.0±2.70	85.0±1.83	84.0±2.05	80.0±1.89
20 min	94.0±1.90	91.0±1.94	93.0±1.83	89.0±1.67
30 min	98.0±1.32	98.0±0.96	99.0±0.86	92.0±1.13
Limit: NLT 75% Q in 30 min				

3.4.4. Optimization % plasticizer against EC-1 Polymer during Enteric coating

Three batches were manufactured with different weight percentages of plasticiser against EC-1 polymer, i.e. 12.6%, 14.6% and 16.6% w/w (Table 12). Pellets are found to have a rough surface, and fines were found to be more with the EC pellets manufactured with plasticiser percentage of 12.6% as compared to that of 14.6% and 16.6%. However, there is no significant difference in dissolution profile observed in all three formulations and found to be comparable with the marketed product. Hence, the plasticiser percentage of 14.6% is found to be the optimum concentration.

Table 12 Formulation with different plasticiser percentages

Batch No.	EC1	EC2	EC3	Marketed Formulation
% of plasticizer against EC-1 polymer content	12.6	14.6	16.6	
Dissolution: 0.1N HCL, 300 ml: Apparatus: USP II (Paddle) with sinker, RPM: 100. Temperature: 37°±0.5°C (n=6)				
	%Release (Mean ± SD)			
2 Hrs	1.0±0.36	1.1±0.26	1.5±0.43	6.8±2.16
Limit: NMT 10% in 2hrs				
Dissolution: pH 6.8 phosphate buffer, 1000 ml, USP II (Paddle) with sinker, 100 rpm (n=6)				
	%Release (Mean ± SD)			
10 min	88.0±1.79	89.0±1.70	87.0±2.16	80.0±1.89
20 min	94.0±1.40	94.0±1.05	98.0±1.09	89.0±1.67
30 min	100.0±1.44	101.0±2.32	98.0±1.47	92.0±1.13

3.5. Final Optimized formulation and its Characterization

Based upon the above outcome of formulation optimization, the following composition is finalized for the subject formulation (Table 13).

The optimized formulation of Esomeprazole DR capsule corresponded to hydroxypropyl cellulose concentration of 10.39 mg, sub-coating weight gain of 58.64%, enteric coating weight gain of 75.70%, and a plasticiser-to-polymer ratio of 14.62%. When evaluated, this optimized formulation showed 0.99% drug release in 0.1N HCl at 2

hours and 100.6% drug release in phosphate buffer at 30 minutes, fully meeting pharmacopeial requirements.

Table 13 Final formula of Esomeprazole EC Pellets

Esomeprazole EC Pellets	
Name of Ingredient	**Quantity (mg/capsule)**
Stage: Drug Layering	
Esomeprazole magnesium Trihydrate	22.264
Sugar spheres (Non-pareil seeds 40-50 mesh)	20.000
Hydroxypropyl cellulose (Klucel LF)	10.500
Crospovidone XL 10	5.236
Water, Purified	q.s.
Total weight	58.000
Stage: Sub Coating	
Drug Layered Pellets	58.000
Confectioner's Sugar (Icing sugar with starch)	15.000
Magnesium Oxide Light	6.000
Talc	2.500
Macrogol 6000 (Polyethylene Glycol 6000)	7.500
Water, Purified Ph. Eur.	q.s.
Total weight of sub-coated pellets	89.000
Stage: Enteric Coating (Layer - I)	
Sub Coated Pellets	89.000
Methacrylic Acid Ethyl Acrylate Copolymer(Eudragit L30 - D55)	54.675
Glycerol Monostearate 40-55 (Geleol pellets 40-55)	2.500
Macrogol 400 (Lutrol E 400)	8.000
Polysorbate 80 (Crillet 4HP)	1.500
Water, Purified Ph. Eur.	q.s.
Total weight	155.675
Stage: Enteric Coating (Layer - II)	
EC Pellets of Layer – I	155.675
Hypromellose Phthalate (HPMC phthalate HP 55)	39.825
Macrogol 400 (Lutrol E 400)	4.500
Acetone	q.s.
Water, Purified	q.s.
Total weight	200.000
Stage: Lubrication	
Esomeprazole Enteric Coated Pellets	200.000
Talc	2.000
Lubricated Esomeprazole EC Pellets	202.000

3.5.1. Infrared Spectroscopy

FTIR spectrum of API and the formulation of Esomeprazole pellets were found to be comparable. Presence of wave number of Secondary amine (C-N stretch) indicates an effective barrier of sub-coating to protect the API in the core from acidic enteric coating layer. IR Spectroscopy of Esomeprazole EC Pellets was presented below in Fig. 7 and Table 14.

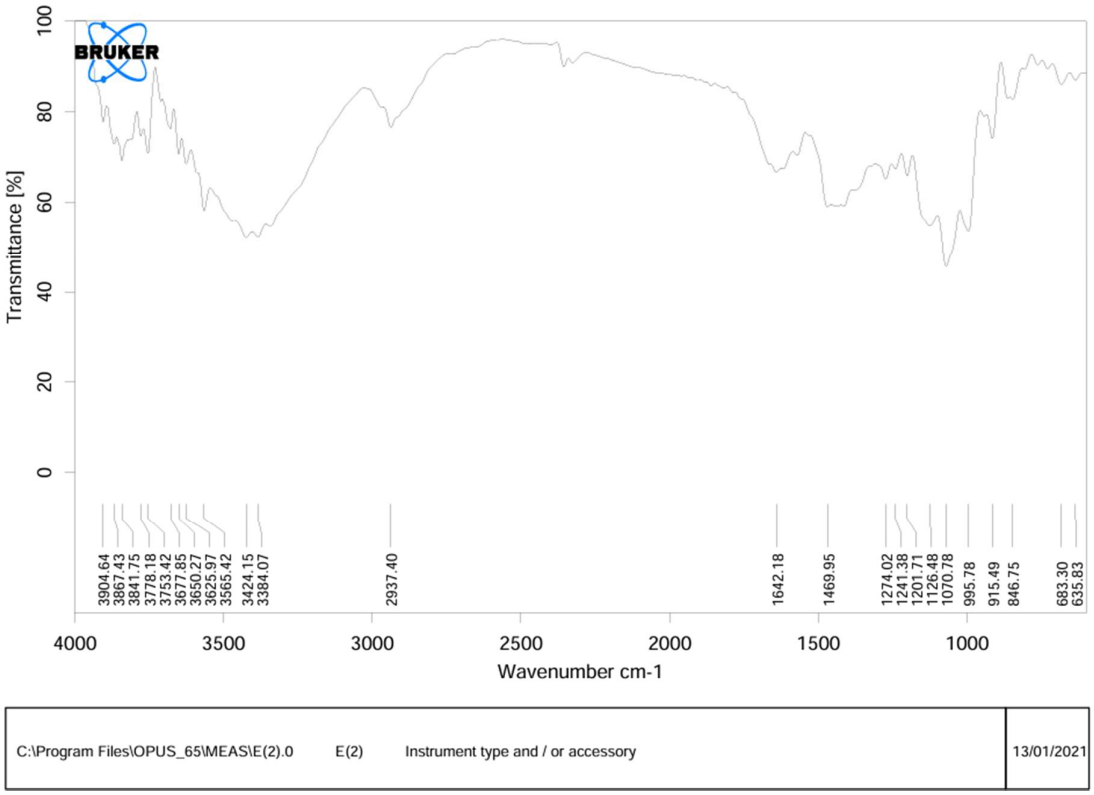


Fig. 7 FT-IR spectra of Esomeprazole Pellets

Table 14 Evaluation of FT-IR spectra of Esomeprazole Pellets

S. No.	Wave numbers in API spectra (cm-1)	Characteristic Absorption	Presence of wave number in Esomeprazole Pellets (Yes/No)
1	634.00	Alkyne C-H bend	Yes (635.83)
2	764.57	Aromatic C-H out-of-plane bend	Yes (683.30)
3	1076.93	Sulphonyl (S=O) group	Yes (1070.78)
4	1153.49	Secondary amine (C-N stretch)	Yes (1126.48)
5	1473.83	Methylene (C-H bend)	Yes (1469.95)

3.5.2. Micromeritic properties

Bulk, Tapped Density, and Carr's Index of Esomeprazole EC pellets are mentioned in Table 15 and found to be comparable with the pellets of the marketed product. Moreover, the characteristics of both pellets (i.e. Carr's Index) were found to be excellent, i.e. < 15.

Table 15 Evaluation of Micromeritic properties of Esomeprazole API

Parameters	Esomeprazole EC Pellets	
	Test Product	Marketed product
Bulk Density(gm/ml)	0.69	0.71
Tap Density (gm/ml)	0.77	0.82
Carr's Index	10	13

3.5.3. Dissolution profile and comparison with marketed formulation.

Dissolution profile of optimized formulation of Esomeprazole EC pellets filled into hard gelatin capsule was evaluated and compared against marketed products and found to be similar (i.e. f2>50%). This provide an assurance that the prepared formulation may be equally effective as the marketed formulation (Table 16).

Table 16 Dissolution profile of optimized final formulation and marketed product

Dissolution-Esomeprazole EC Pellets	Test Product	Marketed Product
Dissolution: 0.1N HCL, 300 ml: USP II (Paddle), Limit: NMT 10% in 2hrs (n=6)		
	%Release %Release (Mean ± SD)	
2 Hrs	0.9±0.32	4.8±1.6
Dissolution: pH 6.8 phosphate buffer, 1000 ml, USP II (Paddle), Limit NMT 75% (Q) / (n=6)		
10 min	89.0±2.03	85.0±1.82
15min	93.0±1.52	89.0±2.45
20 min	94.0±1.98	92.0±1.55
30 min	101.0±2.48	97.0±2.40
F2 (Similarty Factor) (Limit >50%)	Remarks: Since more than 85% drug released in 15min, hence f2 calculation is not applicable.	

4. Conclusion

The present research successfully demonstrated the formulation and optimization of enteric-coated esomeprazole magnesium. The use of fluidized bed coating process used to prepare esomeprazole EC pellets enabled precise control over release kinetics. Application of a QbD-based optimization strategy provided robust models to identify critical formulation parameters and their interactions. Among the studied factors, sub-coating and enteric coating levels played the most significant role in governing esomeprazole stability in acidic condition and release at alkaline pH environment in small intestine. This not only enhances patient compliance by reducing dosing frequency but also minimizes the risk of NSAIDs-induced gastric complications. The findings confirm that a scientifically optimized combination formulation can serve as a promising alternative to conventional therapy requiring separate administration of PPI. Future studies may include in vivo pharmacokinetic evaluation and stability testing under ICH guidelines to further establish clinical relevance and commercial viability.

References

1. Neishi M, Hamano H, Niimura T, Denda M, Yagi K, Miyata K, et al. Structural characterization of the optical isomers esomeprazole and omeprazole using the JADER and FAERS databases. Toxicology and Applied Pharmacology. 2023;475:116632. https://doi.org/10.1016/j.taap.2023.116632
2. Sugimoto M, Furuta T. Efficacy of esomeprazole in treating acid-related diseases in Japanese populations. CEG. 2012;49. https://doi.org/10.2147/CEG.S23926
3. Bi H, Chen X, Chen Y, Zhao X, Wang S, Wang J, et al. Efficacy and safety of high-dose esomeprazole–amoxicillin dual therapy for Helicobacter pylori rescue treatment: a multicenter, prospective, randomized, controlled trial. Chinese Medical Journal. 2022;135:1707–15. https://doi.org/10.1097/CM9.0000000000002289
4. Esomeprazole Magnesium Trihydrate Monograph | PDF | Chromatography | Phosphoric Acid [Internet]. [cited 2026 Apr 13]. https://www.scribd.com/document/323322610/Esomeprazole-Magnesium-Trihydrate. Accessed 13 Apr 2026
5. Hadrich S, Lamti F, Trabelsi I, Dhaoui R, Ben Abdewahed M, Sekma A, et al. Randomized trial of the effect of esomeprazole on functional dyspepsia during Ramadan fasting. Sci Rep. 2025;15:36535. https://doi.org/10.1038/s41598-025-17532-x
6. Shan R, Feng R, Huang Y, Huang G. Preparation and Evaluation of Dual–release Esomeprazole Magnesium Pulsed Capsules Filled with Two Kinds of Enteric-coated Pellets. J Pharm Innov. 2023;18:851–60. https://doi.org/10.1007/s12247-022-09683-5
7. Formulation Design, Optimization, Characterization and In Vivo Ph...: Ingenta Connect [Internet]. [cited 2026 Apr 13]. https://www.ingentaconnect.com/content/ben/ddl/2015/00000005/00000002/art00004. Accessed 13 Apr 2026
8. Kuang C, Sun Y, Li B, Fan R, Zhang J, Yao Y, et al. Preparation and evaluation of duloxetine hydrochloride enteric-coated pellets with different enteric polymers. Asian J Pharm Sci. 2017;12:216–26. https://doi.org/10.1016/j.ajps.2016.08.007
9. NEXIUM® (esomeprazole magnesium) delayed-release capsules, [Internet]. [cited 2026 Apr 13]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021153s056,021957s023,022101s020lbl.pdf. Accessed 13 Apr 2026
10. Esomeprazole Magnesium Delayed-Release Capsules. 2019;
11. Kan S, Lu J, Liu J, Wang J, Zhao Y. A quality by design (QbD) case study on enteric-coated pellets: Screening of critical variables and establishment of design space at laboratory scale. Asian Journal of Pharmaceutical Sciences. 2014;9:268–78. https://doi.org/10.1016/j.ajps.2014.07.005

12. Full article: Fourier transform infrared spectroscopy used in drug excipients compatibility studies [Internet]. [cited 2026 Apr 13]. https://www.tandfonline.com/doi/full/10.1080/05704928.2024.2438747. Accessed 13 Apr 2026.