Formulation and Characterization of Floating Tablet of Esomeprazole Magnesium Trihydrate

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KEYWORDS

Gastroretentive drug delivery systems, Floating tablet, Buoyancy, Esomeprazole, Swelling index etc.

ABSTRACT

Background: Esomeprazole is a protein pump inhibitor (PPI) prescribed to treat acute duodenal ulcers, acute benign gastric ulcers, gastroesophageal reflux disease (GERD), and to prevent duodenal ulcers. It exerts a local effect on the stomach and operates by competitively blocking the H+/K+ ATP enzyme, which is present in gastric parietal cells. **Aim:** The aim is to formulate and evaluate floating tablets of esomeprazole magnesium trihydrate. **Objective:** The current work aims to build a reproducible and robust process for formulating proton pump inhibitors and anti-ulcer drugs. **Method:** The current endeavor to make floating tablets uses the direct compression method. The Esomeprazole Magnesium Trihydrate, sodium bicarbonate, citric acid, Avicel 102, and HPMC K15, Lactose, PVP K30 were sieved through sieve no. 60 and blended uniformly with a mortar and pestle. Using a Rotary tablet punch machine, the powder was compacted into tablets after talc and magnesium stearate were added as lubricants. **Results and Discussion:** The compatibility between drug and excipients was assessed by Fourier transform infrared (FTIR) spectroscopy. The prepared tablets were evaluated for different parameters such as hardness, friability, drug content, floating time, in vitro dissolution, and stability. Optimized batch F9 is further studied for FTIR, DSC, and Stability study as per standard ICH Guidelines.

INTRODUCTION

Oral drug delivery systems have dominated other drug delivery systems used for human administration due to numerous benefits such as ease of administration, formulation flexibility, cost-effectiveness, ease of storage and transport, and high patient compliance. However, oral drug delivery methods confront obstacles such as limited bioavailability due to gastrointestinal heterogeneity, commensal flora pH, gastric retention time of the dose form, surface area, and enzymatic activity [1,2]. Conventional drug delivery systems may fail to address challenges imposed by the gastrointestinal tract (GIT), such as partial drug release, decreased dose efficiency, and repeated dose requirements. As a result, a failure of conventional drug delivery systems to maintain medications in the stomach could lead to the creation of GRDDS [3]. These approaches offer numerous benefits, including extended gastric residence time (GRT) of dosage forms in the stomach of as long as several hours, increased therapeutic efficacy of pharmaceuticals due to better drug absorption, and adaptability for targeted distribution in the stomach [4]. Furthermore, GRDDS are enhancing the controlled delivery of drugs by continuously releasing the drug for an extended duration at the appropriate rate and to the intended absorption location, until the drug is completely released from the dosage form [5].

GRDDS are suitable for medications with minimal absorption in the lower part of the GIT, which are unstable and poorly soluble at alkaline pH, have a short half-life, and have local activity in the upper section of the gut for *Helicobacter pylori* eradication [6]. Several formulation methodologies have been employed to create successful controlled release GRDDS, including superporous hydrogel, bio/mucoadhesive, raft-forming, magnetic, ion-exchange, expandable, and low- and high-density systems. Effervescent floating systems consist of a gas-generating agent and volatile liquids [7]. This approach has been applied to both single and multi-unit systems. In the gas-generating floating system, hydrophilic polymers are coupled with effervescent chemicals such sodium bicarbonate, calcium carbonate, tartaric acid, and citric acid [8]. When this system comes in contact with stomach fluid, the reaction between the effervescent agent and the gastric fluid produces CO_2. The released CO_2 gas is trapped within the hydrocolloid matrix, giving the pill buoyancy and affecting medicine release characteristics. Hydrophilic polymers are frequently used in this technique to control the rate of medicine distribution [9,10].

Esomeprazole is among the latest proton pump inhibitors (PPI) and was developed as the S- isomer of omeprazole which is a mixture of R & S isomers. It suppresses gastric acid secretion by specific inhibition of (H+/K+) ATPase in gastric parietal cell in the luminal surface of stomach [11]. It is considered to have somewhat higher potency in acid inhibition than other PPIs which are the drugs of choice in the treatment of gastroesophageal reflux diseases (GERD) [12]. The superior clinical efficacy of esomeprazole, compared with omeprazole and the R-isomer, is due to its higher systemic bio-availability. This superiority is attributed to the fact that optical isomers of omeprazole undergo significant stereoselective metabolism to the main metabolites, omeprazole sulphone, 5-hydroxy- and 5-O-desmethyl omeprazole, which are all inactive [13].

Esomeprazole bioavailability was lowered when taken 15 minutes before a high-fat meal compared to fasting. The acid labile nature of esomeprazole may explain its low bioavailability.

Food slows gastric emptying (prolonged t_{max}), and esomeprazole breakdown rises with time in the stomach. Esomeprazole is recommended to be administered at least one hour before meals [14].

Material and methods

Esomeprazole magnesium trihydrate gift sample was obtained from Leben Life Sciences, Analytical grade excipients like HPMC K 15, Avicel 102, polyvinyl pyrrolidone K-30, Carbopol, Lactose, Sodium bicarbonate, Citric acid, Magnesium Stearate, Talc were procured from market

Method

Esomeprazole Magnesium Trihydrate floating tablets were manufactured by direct compression technique. Sodium bicarbonate and citric acid were used for gas generating agent and float tablet was prepared. Esomeprazole and Excipient like HPMC K 15, Avicel 102, Pyrrolidone K-30, Carbopol, Lactose sodium bicarbonate were weighed and sieved using mesh 40# sieve. All other ingredients including drug were properly combined in a glass mortar except for Magnesium stearate and talc. Lubricant and glidant were added in previous mixture and mixed for additional 3-5 minutes. Blend were evaluated by multiple parameter and tablets were compressed by tablet compression machine. Tablets were prepared by different nine formulations and evaluated by various testing parameters.

Formulation Table.

Table 1. Formulation Table

Sr no.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Esomeprazole Magnesium Trihydrate	20	20	20	20	20	20	20	20	20
2	HPMC	45	40	40	35	35	30	30	40	40
3	Carbopol	20	25	20	25	20	20	20	20	20
4	MCC (Avicel 102)	80	80	80	65	60	60	55	50	60
5	Lactose	0	0	0	0	10	10	15	12	10
6	Sodium Bicarbonate	20	15	20	25	25	30	30	30	25
7	Citric acid	10	10	10	12.5	15	15	15	15	12
8	PVP	0	2	5	7.5	5	5	5	3	3
9	Magnesium Stearate	5	3	5	5	5	5	5	5	5
10	Talc	0	5	0	5	5	5	5	5	5
-	Total	200	200	200	200	200	200	200	200	200

Preparation of Calibration Curve

Accurately weighed 100 mg of Esomeprazole magnesium Trihydrate was dissolved in 100 mL of methanol to obtained working standard of 1000 µg/ml. From this 1 ml solution was pipette out and further diluted to 100 ml to prepare 100 µg/ml. this solution was used as stock solution. Pipette 2 ml from 100µg/mL volume make up upto 10 ml gives 20µg/ml. Accurate volume of stock solution was transferred to 10 mL volumetric flask to prepare concentration of 2,4,6,8,10,12,15µg/ml absorbance of the above solution were taken at λmax 237 nm against the blank solution prepared in the same manner without adding the drug.

Evaluation of Pre-Compression study

Bulk Density

Bulk density is the mass of the material particles or powder divided by the bulk volume. The bulk density or apparent density was determined by digital density apparatus. 10 gm of blend powder was poured into a 100 ml calibrated measuring cylinder in density apparatus. The bulk volume and weight of the powder were determined [15]. The bulk density was calculated by using following formula.

Bulk Density (BD) = Weight of Powder / Bulk Volume

Tapped density

Tapped density of a powder is defined as the mass of the material or powder divided by volume occupied by the powder after it has been tapped for a fixed duration of time. Tapped density was calculated by adding the measured quantity of powder into 25ml graduated measuring cylinder. After 100 tapping, the tapped volume was measure [16]. Tapped density of powder or blend was determined by using following formula:

Tapped Density (TD) = Weight of Powder / Tapped Volume

Compressibility Index (Carr's index)

The simplest method of measurement of flow ability of precompressed powder by comparing the bulk density and tapped density of the blend or powder mixture. It is also known as Carr's index. The % Carr's indexor % compressibility index was determined by using the following formula:

Carr's index = [(Tapped Density – Bulk Density)/Tapped Density] x 100

Hausner's ratio

Hausner's ratio is also used to determine the flow properties of powder or blend or mixture. A low Hausner ratio indicates good flow ability and compressibility, meaning the powder flows easily and uniformly into tablets or capsules. Conversely, a higher ratio suggests poorer flow ability [17]. It is determined by using following formula:

Hausner's ratio = Tapped Density / Bulk Density

Angle of Repose

Angle of repose displays the degree of inter-particle friction between individual particles, revealing the flow properties of powders and related materials. The angle of repose was computed using the fixed funnel method. The carefully weighed powder was placed in a funnel. The funnel's height was adjusted such that the tip just touched the apex of the stack of powder. The powder was allowed to flow freely through the passageway and onto the surface. Finally, the diameter of the

powder cone or pile was measured [18]. The angle of repose was calculated using following equation.

Angle of repose (θ) = tan-1 h/r

Where, 'h' and 'r' are the height and radius of the powder cone/ pile

EVALUATION OF FLOATING TABLET

Post Compression Parameters The floating tablets prepared by above method was evaluated to check quality of tablets by tests such as Diameter and thickness, uniformity of weight, thickness, hardness, % friability, floating studies (buoyancy) i.e. lag time and duration time of floating, in vitro dissolution studies.

Weight Variation Test

Weight variations can occur because to variations in die filling, unequal particle dispersion, and differences in compression force. The weight variation test was done in accordance with IP. 20 tablets from each formulation were ingested, and individual weights of all 20 tablets were taken using the electronic balance, and the average weight was calculated [19]. Following formula was used to calculate percent weight variation:

% Weight variation = (WA-WI) x 100/WA

Where, WA= Average weight of tablet

WI= Individual weight of tablet.

Diameter and Thickness

Three tablets from each formulation are taken in order to measure the floating tablet's thickness and diameter. Diameter and thickness were measured with a vernier calliper. Changes in die fill, packing of the crushed powder mix, particle size distribution, tablet weight, and compression force/pressure can all affect the tablets' thickness and diameter. By making sure the die and punches are the right size and form during the entire compression process, the diameter of the tablets is controlled [20].

Hardness

Hardness is defined as the force or load required to break the tablet. This test is conducted to ensure that the tablet can withstand mechanical shocks during manufacturing, packaging, and shipping. Various types of hardness testers are used to measure the hardness of the tablet like, Monsanto hardness tester, strong cobb tester, Pfizer tester, Dr. Schleuniger tester, etc. The hardness of tablets from all batches were measured by using the Monsanto hardness tester. It was measured in Kg/cm^2 [21].

Friability

Friability is used to ensure that the tablets are sufficiently hard to withstand the mechanical shocks that the tablet is subjected during manufacturing, transportation and handling. Friability generally refers to the loss in weight or materials of tablets in the containers due to removal of small particles from the tablet surface. Method: The Roche friability test apparatus was used to determine the friability of the tablets. In this test tablets with 6.5 g of weights from each batch were taken and weighed then placed in the friabilator, operated for 100 revolutions at 25 rpm for 4 minute and

tablets were removed and recheck the weight of rotated tablets [22]. The % friability was determined by using the following formula:

% Friability = (initial weight-final weight)/(initial weight) × 100

Limit: NMT 1% after 100 revolutions.

Drug Content

Ten tablets are chosen at random from each formulation, weighed, and ground into powder using a glass mortar and pestle. The average weight of ten tablets was then determined using the weight above. To make a concentration of 100 µg/ml, distilled water was added to a 100 ml volumetric flask containing a measured amount of powder equal to 100 mg of medication. The resulting solution was then filtered. A concentration of 10 µg/ml is obtained by pipetting off 1 ml of the aforementioned solution and diluting it with 100 ml of distilled water [23]. Using the UV-Visible spectrophotometer SHIMANDZU 1780, absorbance was measured at 237 nm. Determine the drug's content by repeating the operation and using the absorbance that is obtained.

Buoyancy / Floating Test

It assesses the ability of a tablet to float on a liquid surface. Place the tablet in a 100 ml beaker containing 0.1N hydrochloric acid (HCl). Observe the time it takes for the tablet to rise to the surface and float. This duration is known as the floating lag time or Buoyancy Lag Time. Additionally, note the total duration during which the dosage form remains buoyant or floating is called Total Floating Time (TFT) [24].

Swelling Index

The swelling index of floating tablets is a measure of how much a tablet swells when exposed to a liquid medium The swelling index of a tablet dosage form was determined by checking weight rise or uptake of water (WU) after placing it into an aqueous solution. Formulated tablets were weighed individually and note weights (W0) and placed individually into beaker containing 200ml of distilled water. The tablets were removed from beaker after each hour and continued again upto 8 hours, and reweighed (Wt) [25]. The % swelling index or percentage weight gain was calculated using following formula.

Swelling index (S.I) = [(Wt-W0)/W0] x100

Where, S.I.=swelling index

Wt=Weight of tablet at time t

W0=Weight of tablet before immersion.

In Vitro Dissolution Studies

Dissolution study was conducted by using USP Dissolution Testing Apparatus II (Paddle method) [26]. 900 ml 0.1N HCl were maintained as dissolution media at 37±0.5oC and 50 rpm was maintained as rotation speed. An Aliquots of 5 ml was withdrawn at specific time intervals for 24 hours and the same volume of the medium was maintained upto 900 ml. Samples were analysed at 237 nm using the UV-Visible spectrophotometer and cumulative percentage (%) drug release was measured using an equation obtained from a standard curve [27-31].

FTIR Study

The FTIR spectroscopy technique used for identification of drug. The medication and excipients were studied using the Fourier transform infrared (FT-IR) technology to examine their physical and chemical interactions [32]. Using the KBr mixing approach, the FT-IR spectra of both the pure drug and the floating tablet were recorded on the institute's central instrument laboratory's FTIR-1700 Shimadzu FT-IR analyzer [33]. Method: KBr powder was grind and passed through 200 mesh size. Dry the KBr to remove any bound water molecules by drying at 110° Celsius. Mix the sample (API & Final Mixture) and KBr: Mix 0.1 to 1% of the sample with 200 to 250 mg of powdered KBr. Put the mixture into a pellet-forming die and apply pressure under vacuum to form a transparent pellet. Place the pellet in a spectrometer to get the spectrum [34].

DSC Study

The physical and chemical interactions between the medication and the excipients were investigated using DSC. On the DSC-60 instrument, which is housed at the institute's core instrument laboratory, the DSC spectra of pure drugs and drug composite mixtures were recorded (DSC-60, Shimadzu) [35].

Stability study

Stability of drug has been defined as the ability of a particular formulation in a specific container to remain within its physical, chemical, therapeutics and toxicological specifications [36]. The stability studies were performed on the tablet formulation trial 9. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influences of a variety of environmental factors such as temperature, humidity and light and enables recommended storage conditions and shelf lives to be established [37].

Short-term stability testing of the optimized F9 batch was carried out at 40°C in a humidity container with 75% relative humidity (RH) to determine the variation in the in vitro dissolution profile and during storage. Optimized batch F9 was selected for accelerated stability study.

RESULT AND DISCUSSION

API Characterization

The Organoleptic properties of API were observed that the organoleptic properties of the API compliance with standards one. This can be used as preliminary identification tool for drug. Physically organoleptic study like Odor, Color, Taste was performed all results gets in between standard characterization range as per IP/USP. Melting point was determined using Thiel’s tube Practically performed melting point of Esomeprazole was found to be 177^0C. the standard melting point of Esomeprazole as per IP is 176 – 178^0C. Hence melting point was successfully done and confirms drug standards as per IP.

Calibration curve

Table 2. Calibration Curve of Esomeprazole UV method

Concentration (µg/ml)	Absorbance(nm) (λ_{max} = 237 nm)
0	0
2	0.154
4	0.233
6	0.380
8	0.461
10	0.552
12	0.694
15	0.857

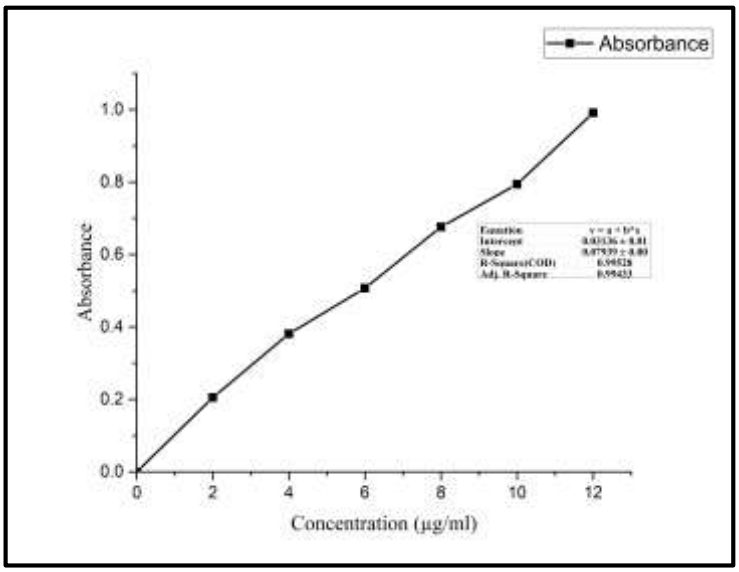

Figure 1. Calibration Curve of Esomeprazole UV method.

Table 3. Preformulation Parameter of Powder blend

All values are expressed as mean± SD (n=3).

Table 4. Post-formulation Parameter of All formulation

Formulations	Thickness (mm)	Diameter (mm)	Weight variation	Hardness (kg/cm2)	Friability (1%)	Drug Content (%)	Floating lag time (Sec)	Total floating time (Hrs)
F1	4.08±0.06	8.12±0.10	189±1.98	4.24±0.36	0.76	98.20	17±0.23	>11±0.56
F2	4.10±0.04	8.13±0.06	192±2.02	4.36±0.22	0.56	96.32	15±0.18	>10±0.37
F3	4.09±0.04	8.16±0.07	192±2.06	4.28±0.32	0.52	94.20	15±0.36	>10±0.26
F4	4.08±0.03	8.12±0.04	196±1.97	4.86±0.12	0.68	93.66	14±0.52	>10±0.14
F5	4.08±0.04	8.14±0.04	194±1.96	4.56±0.22	0.58	95.12	15±0.27	>10±0.49
F6	4.09±0.03	8.12±0.02	197±1.86	4.96±0.20	0.52	96.45	16±0.25	>10±0.36
F7	4.10±0.05	8.12±0.02	195±1.99	5.02±0.16	0.55	98.08	14±0.36	>10±0.47
F8	4.10±0.04	8.12±0.02	196±1.92	4.36±0.60	0.52	97.72	14±0.32	>10±0.29
F9	4.10±0.04	8.12±0.02	197±1.94	4.62±0.12	0.54	99.12	14±0.31	>10±0.22

Formulations	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	Carr's index	Hausner's ratio	Angle of Repose
F1	0.512±0.049	0.628±0.022	18.47±0.028	1.22±0.036	24.47 ± 0.23
F2	0.539±0.036	0.639±0.019	15.65±0.022	1.18±0.021	26.12 ± 0.35
F3	0.518±0.039	0.632±0.015	18.04±0.042	1.22±0.028	27.47 ± 0.22
F4	0.542±0.053	0.656±0.045	17.38±0.026	1.21±0.038	25.31 ± 0.68
F5	0.563±0.018	0.698±0.026	19.34±0.039	1.24±0.021	24.78 ± 0.23
F6	0.502±0.038	0.632±0.042	20.57±0.017	1.25±0.029	25.51 ± 0.40
F7	0.548±0.034	0.678±0.056	19.17±0.032	1.24±0.036	26.11 ± 0.61
F8	0.521±0.018	0.628±0.031	17.04±0.012	1.20±0.019	25.52 ± 0.71
F9	0.568±0.051	0.621±0.042	8.53±0.021	1.09±0.012	27.68 ± 0.88

All values are expressed as mean± SD (n=3).

Table 5. Swelling index of All formulation

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	10.32	9.56	10.20	10.02	8.66	10.20	10.36	11.20	11.26
2	16.14	15.20	17.32	15.36	13.88	17.22	16.39	19.36	19.89
3	22.69	23.11	24.06	21.96	20.63	26.41	25.96	28.46	30.45
4	34.56	32.06	31.02	31.20	26.36	34.69	35.26	36.52	38.11
5	41.63	42.30	39.56	39.45	38.12	40.12	41.20	44.96	45.20
6	48.32	51.88	44.98	50.20	46.03	49.20	49.36	56.20	57.02
7	55.12	59.20	53.20	59.47	52.96	59.66	61.24	69.46	70.11
8	64.63	67.36	64.66	66.30	61.88	71.20	73.96	77.31	78.20
9	71.32	73.89	73.09	78.20	70.96	83.36	84.96	85.77	85.32
10	85.20	86.28	84.21	83.33	78.20	90.96	91.56	94.63	95.33
11	90.11	94.20	91.88	89.36	86.56	96.89	101.20	103.69	104.89
12	99.11	105.02	101.02	99.45	98.20	106.20	109.63	111.96	114.63

All values are expressed as mean± SD (n=3).

Table 6. % cumulative drug release of F1-F9 batch

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	12.11	11.20	9.30	9.89	10.36	9.25	11.36	10.10	10.25
1	21.36	19.12	15.36	18.20	16.85	14.36	16.58	15.20	17.20
2	35.09	27.33	22.36	24.63	21.36	20.22	23.36	21.36	26.89
3	42.36	36.77	32.45	31.02	32.69	31.25	32.40	35.20	37.31

4	52.63	45.20	39.65	39.68	38.56	44.12	43.63	45.20	45.69
5	65.22	55.36	46.86	45.63	48.36	52.30	51.12	54.36	55.30
6	74.90	61.20	54.16	51.78	58.12	60.14	62.56	63.12	63.02
7	79.20	74.26	63.46	63.25	68.20	71.36	70.30	71.56	74.36
8	84.02	80.20	70.20	70.56	77.69	80.52	78.56	80.15	82.59
9	86.20	84.36	84.20	75.68	85.63	84.20	86.20	87.20	88.20
10	89.20	88.20	88.36	81.36	88.02	88.36	91.63	94.14	95.36
11	91.88	92.12	94.15	88.2	94.20	95.46	96.54	96.05	99.20

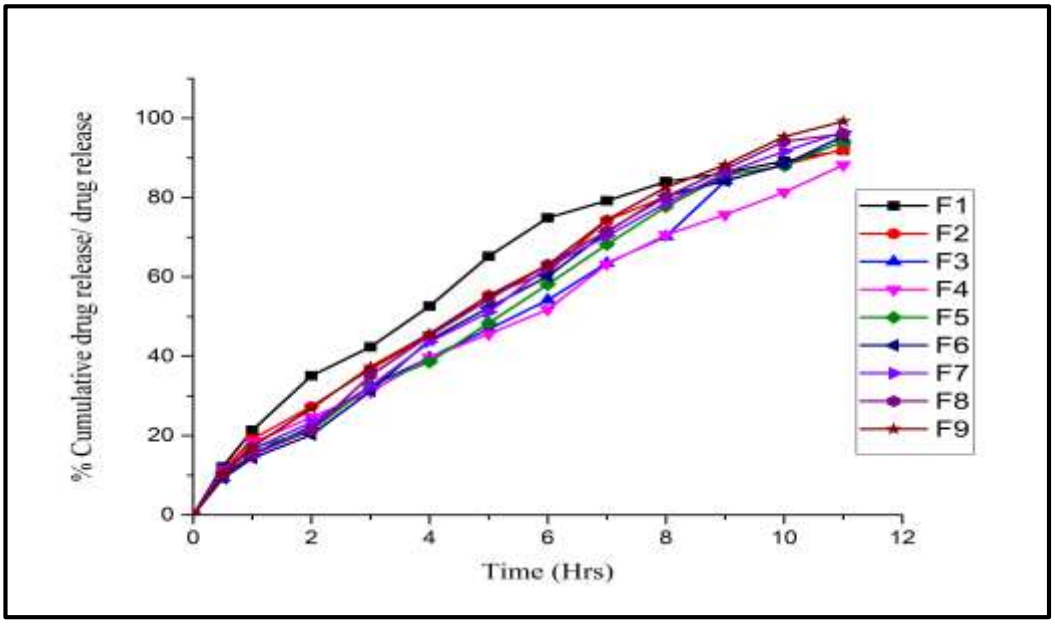

Figure 2. In-vitro dissolution drug release of F1-F9 formulations

A

B

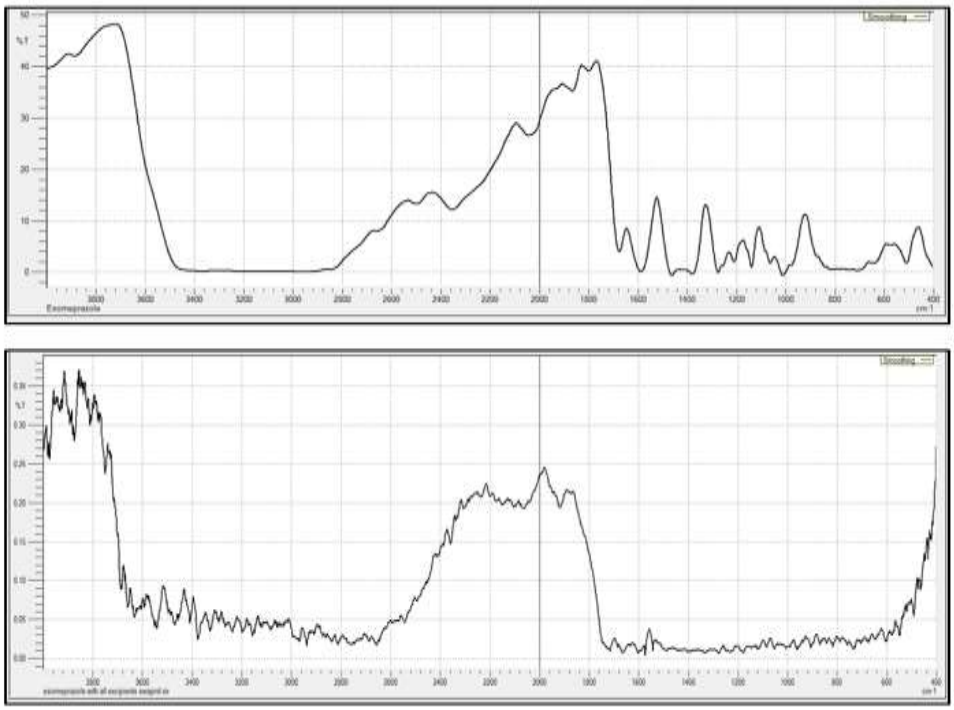

Figure 3. FTIR of (A)Esomeprazole (B) Optimized batch

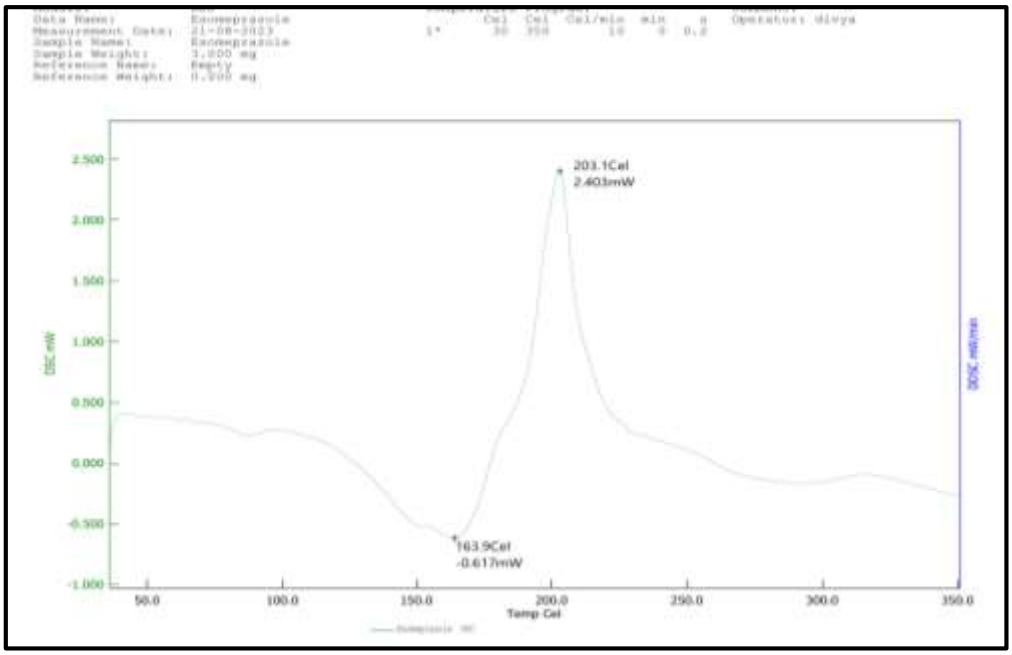

Figure 4. DSC of Esomeprazole.

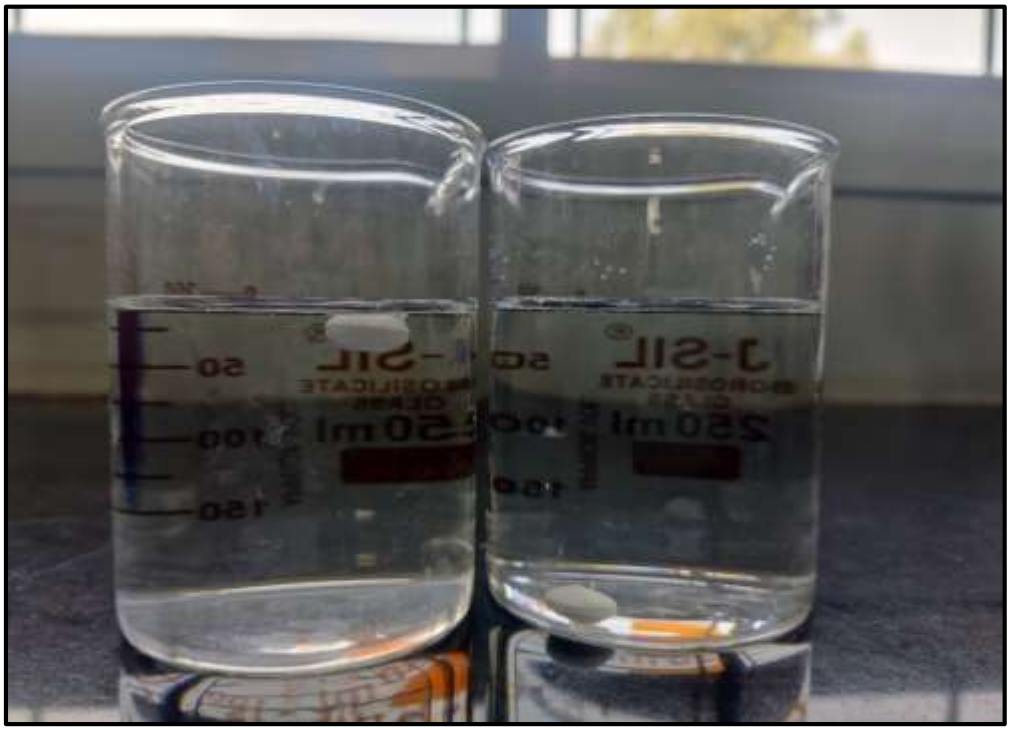

Figure 5. Buoyancy time / Floating Time of formulated esomeprazole tablet.

Stability Study

Short-term stability testing of the optimized F9 batch was carried out at 40°C in a humidity container with 75% relative humidity (RH) to determine the variation in the in vitro dissolution profile and during storage. Optimized batch F9 was selected for accelerated stability study.

Table 7. Stability study of optimized batch F9.

Physical Parameters	**Storage conditions**			
	40 °c ±2° c/75% RH±5% RH			
	Initial	**1st month**	**2nd month**	**3rd month**
Physical appearance	White,Round shape tablet	No Change	No Change	No Change
Avg. weight (mg)	195 ±0.3	195 ±0.7	194.9 ±0.3	194.9 ±0.5

Hardness (kg/cm^2)	4.6 ±0.01	4.6 ±07	4.6 ±0.3	4.6±0.6
Thickness (mm)	4.1 ± 0.01	4.1 ± 0.03	4.1± 0.1	4.1± 0.2
Drug content (%)	99.3± 0.2	99.3± 0.4	99.1± 0.1	98.8± 0.5

CONCLUSION

In accordance with present study, it was concluded that, floating tablet of Esomeprazole Magnesium Trihydrate increase the gastric residence time. The addition of gel forming polymer and gas generating agent sodium bicarbonate and citric acid was essential to achieve in vitro buoyancy. Method for preparation of floating tablets is simple and cost effective. Esomeprazole floating tablet of esomeprazole can be formulated with an approach to increase gastric residence time and thereby increasing drug bioavailability. Formulation was developed using HPMC, carbopol as polymer and sodium bicarbonate as gas generating agent and formulation was prepared by direct compression technique. The lag time of the formulation showed that they can be used for floating systems. Formulation F9, containing hydroxypropyl methylcellulose (HPMC) and Carbopol 980, demonstrated the best drug release profile, releasing approximately 99.20% of the drug over 11 h. The study was successful in formulating esomeprazole magnesium trihydrate floating tablets, but further research is needed to validate their efficacy in clinical applications.

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Conflict of Interest

None

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