

FORMULATION AND EVALUATION OF SUSTAINED RELEASE GASTRORETENTIVE FLOATING TABLETS OF ESOMEPRAZOLE FOR EFFECTIVE TREATMENT OF PEPTIC ULCER**Rajat Singh, Praveen Kumar, Pratyush Jain****RKDF College of Pharmacy, SRK University, Bhopal (M.P.)***Corresponding Author's E mail: singhrajat011@gmail.com

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ABSTRACT

The purpose of this research was to develop a novel gastroretentive drug delivery system based on direct compression method for sustained delivery of active agent to improve the bioavailability, reduce the number of doses and to increase patient compliance for the treatment of Zollinger Ellison syndrome and peptic ulcer disease. Quick GI transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to decreased efficacy of the administered dose. Gastroretentive floating tablets, which was designed to provide the desired sustained and complete release of drug for prolonged period of time. Gastroretentive floating tablets of esomeprazole were prepared by direct compression method using altered concentrations of HPMC K4, HPMC K15 as polymers. The prepared tablets of esomeprazole were evaluated for hardness, thickness, friability, weight variation, drug content uniformity, buoyancy lag time, total floating time, swelling index, in-vitro dissolution study, etc. All the compositions were resulted in adequate Pharmacopoeial limits. Compatibility studies was execution during FTIR and DSC shown that there was absence of probable chemical interaction between pure drug and excipients. The varying concentration of gas generating agent and polymers was found to affect on in-vitro drug release, floating lag time and swelling index. In vitro drug release of floating gastroretentive tablet of esomeprazole shown that the formulation F6 was found to be the best formulation as it releases 99.87% esomeprazole in a controlled manner for an extended period of time (up to 12 hrs). The results indicated that a decrease in release kinetics the drug was observed increasing the polymer concentration. The release data was fitted to various mathematical models such as Higuchi, Korsmeyer-Peppas, First order and Zero order to evaluate the kinetics and mechanism of the drug release. The Optimized formulation (F6) showed no significant change in physical appearance, drug content, floating lag time, in vitro dissolution studies after 75%±5% RH at 40±20C relative humidity for 6 months. Prepared floating tablets of esomeprazole may prove to be a potential candidate for safe and effective controlled drug delivery over an extended period of time for gastroretentive drug delivery system.

Keywords: Esomeprazole, Gastroretentive, Floating tablet, Total floating time.

INTRODUCTION

Peptic ulcer is an open sore in the lining of the stomach or intestine, much like mouth or skin ulcers. Peptic ulcers are usually caused by acid and pepsin, a digestive stomach enzyme. An ulcer forms when

there is an imbalance between aggressive and defensive factors. More than 50% of the world population is believed to be infected by *Helicobacter pylori* (*H. pylori*) a major pathogenic factor in peptic ulcer and gastric neoplasm. Peptic ulcer is caused by *H. pylori*, non-steroidal anti-inflammatory drugs and aspirin^{1,2}. Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that are locally active in the stomach, have narrow absorption window in gastrointestinal tract, are primarily absorbed from stomach and upper part of GIT, are unstable in the intestinal or colonic environment, disturb normal colonic bacteria and exhibit low solubility at high pH values. Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients^{3,4}. Esomeprazole is chemically bis (5- methoxy-2- [(S)-[(4-methoxy-3,5-dimethyl-2 pyridinyl) methyl] sulfinyl]-1-H-benzimidazole-1-yl), is a classical example of proton pump inhibitor used for the treatment of gastroesophageal reflux disease, duodenal ulcers caused by *H. pylori*, erosive esophagitis, nonerosive reflux disease (heartburn and regurgitation), gastrointestinal ulcers associated with Crohn's disease and for prevention of gastric ulcers in patients on chronic NSAID therapy. Esomeprazole is an S-isomer of omeprazole and the first proton pump inhibitor to be developed as an optical isomer. Esomeprazole is inactive at neutral pH, but at pH < 5 rearranges to two charged cationic forms (a sulphenic acid and a sulphenamide configurations) that react covalently with SH groups of the H⁺K⁺ATPase enzyme and inactivate it irreversibly, especially when two molecules of omeprazole react with one molecule of the enzyme⁵. Its bioavailability is 89% and plasma elimination half life is 1.5 hour. Single 20-40 mg oral doses generally give rise to peak plasma esomeprazole concentrations of 0.5-1.0 mg/L within 1-4 hours, but after several days of once daily administration, these levels may increase by about 50%. A 30 minute intravenous infusion of a similar dose usually produces peak plasma levels in the order of 1-3 mg/L. The drug is rapidly cleared from the body, largely by urinary excretion of pharmacologically inactive metabolites such as 5-hydroxymethylesomeprazole and 5-carboxyesomeprazole^{6,7}. Floating GTDDS is suitable for esomeprazole drug because of most common ulcers form in the lining of stomach, and or just below the stomach. Floating gastroretentive tablets of Esomeprazole were prepared with an objective to increases the bioavailability and site specific and local therapy for the ulcers.

Materials and Methods

Materials

Esomeprazole was obtained as gift sample from Bioplus Life Science, Bangalore. Hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M) was procured from Meditab Specialities Pvt. Ltd., Satara. Sodium bicarbonate, magnesium stearate, talc were purchased from Mapromax, Life sciences Pvt. Ltd., Dehradun. Other solvents and chemicals used in the research were of LR grade.

Methods

Analytical method development

Determination of absorption maxima

A solution of containing the concentration 10 µg/ ml was prepared in 0.1N HCl; UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200-400nm.

Preparation calibration curve

10mg of drug was accurately weighed and dissolved in 10ml 0.1N HCl in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 5, 10, 15, 20, and 25 µg/ml with 0.1N HCl. The absorbance of standard solution was determined using UV/ VIS spectrophotometer (Labindia 3000+) at 282 nm. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which determined by least-square linear regression analysis.

Drug -excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical assortment were comparing with those of esomeprazole pure drug. Samples was assorted comprehensively through 100mg potassium bromide IR powder as well as compacted under vacuum at a pressure of concerning 12 psi for 3 minutes. The ensuing disc was mounted in an appropriate holder in Brukers Alpha IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Precompression evaluation

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, carr's index, and hausner ratio.

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just

touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation.

$$\theta = \tan^{-1}(h/r)$$

Where, h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

$$\text{LBD} = \text{Powder weight/volume of the packing}$$

$$\text{TBD} = \text{Powder weight /tapped volume of the packing}$$

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = [(TBD - LBD)/TBD] \times 100.$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula⁸⁻¹⁰.

$$\text{Hausner's ratio} = \text{Tapped density/Bulk density.}$$

Formulation development of Tablets

Direct compression method

Different tablets formulations were prepared by direct compression technique. All powders were passed through 40 meshes. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Lactose was used as diluent. Finally, the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests. The composition of esomeprazole floating tablets was shown in Table 1.

Table 1 Formulation composition for esomeprazole floating tablets

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Esomeprazole	40	40	40	40	40	40	40	40	40
HPMC K 4	120	140	180	-	-	-	60	70	90
HPMC K 15	-	-	-	120	140	180	60	70	90
Lactose	45	25	5	45	25	5	45	25	5
Sod. Bi	20	20	20	20	20	20	20	20	20
Carbonate									
Citric Acid	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total Weight	240	240	260	240	240	260	240	240	260

Evaluation of tablets

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape were evaluated. Appearance was judged visually.

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45 μ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λ_{max} of 282.0 nm using of 0.1 N HCl as blank.

Floating capacity

The *in vitro* buoyancy was determined by floating lag times. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The experiments were conducted in triplicate. Total floating times were measured during *in vitro* dissolution studies.

Dissolution rate studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the

temperature of $37 \pm 0.5^\circ\text{C}$ and rpm of 75. One Esomeprazole Control layer tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 12 hours. Sample measuring 5 ml were withdrawn after 30 min., 1.0 hr, 1.30 hr, 2.0 hr, 4.0 hr, 6.0 hr, 8.0, 10.0 hr, 12 hour using 10 ml pipette. The fresh dissolution medium was replaced every time with the same quantity of the sample.

Kinetics of drug release

The dissolution data obtained were fitted into various kinetic models, namely, zero order, first order, Higuchi and Korsmeyer–Peppas. This was to determine the mechanism of a drug release. Higuchi model relates the relationship between the quantity of drug released and the square root of time.

$$Q = KH t^{1/2}$$

The quantity of drug released was plotted against square root of time. The Higuchi release constant KH and r^2 value were extracted from the graph. The Higuchi constant reflects the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time¹¹. For zero order, from the equation $C = K_0t$, drug concentration was plotted against time. The zero order rate constant K_0 and the regression line (r^2) values were also extracted from the graph. For First order release kinetics, Log cumulative percent drug remaining was plotted against time. The first order rate constant K_1 and the regression line value (r^2) were extracted from the graph.

Korsmeyer *et al.* derived a simple relationship that described drug release from a polymeric system, Equation 2. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$$M_t/M_\infty = Kt^n$$

Where, M_t/M_∞ is a fraction of drug released at time t , k is the rate constant, and n is the release exponent. The n value is used to characterize different release mechanisms as given in Table 2¹².

Table 2 Different release mechanisms

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
$0.45 < n < 0.89$	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
$n > 0.89$	Super case-II transport

Stability studies

The optimized formulation of esomeprazole were packed in strips of 0.04 mm thick aluminum foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40°C and 75% RH for 6 months. The samples were withdrawn periodically and evaluated for their floating lag time, content uniformity and for in vitro drug release¹³.

RESULTS AND DISCUSSION

The melting point and partition coefficient of drug found to be in n-octanol: water was 171-173°C and 1.6 respectively. Graphs of Esomeprazole were taken in 0.1N HCl at 282 nm.

Table 3 Result of optical parameter of esomeprazole

Parameters	Observation
λ max	282.0 nm
Beer's law limit ($\mu\text{g/ml}$)	5-25
Regression equation	$Y = 0.084x + 0.008$
Correlation Coefficient (r^2)	0.995

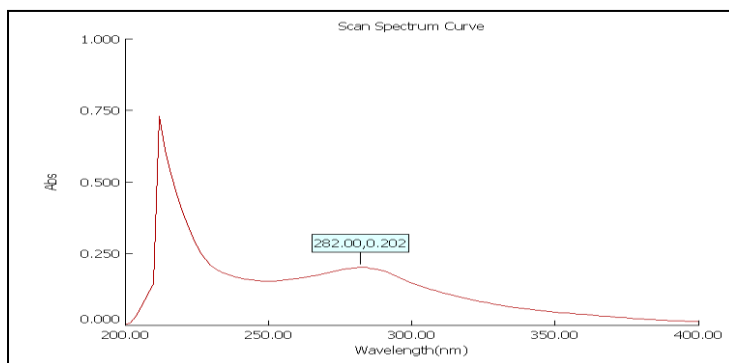


Figure 1 λ max of Esomeprazole

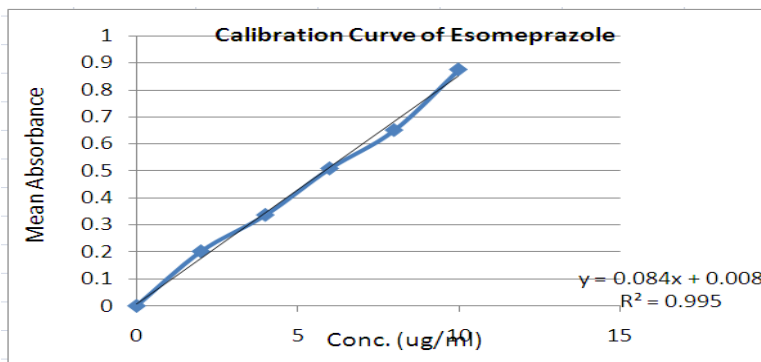


Figure 2 Calibration curve of standard esomeprazole

The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were shown in figure 3. The presence of characteristic peaks of drug in the FTIR spectra of physical mixture (Drug: Polymer) indicates the absence of chemical interaction between the drug and the polymers employed in the study.

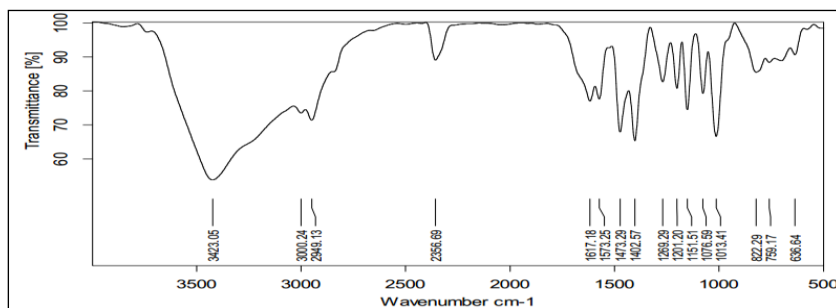


Figure 3 FT-IR Spectrum of Pure Drug (Esomeprazole)

The percentage of loss on drying was 0.15 %w/w. The pH determination of Esomeprazole was done by Digital pH meter and found to be 4.3. Tablet powder blend was subjected to various pre-formulation parameters Table 4. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.354 ± 0.007 to 0.389 ± 0.004 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.799 ± 0.008 to 0.854 ± 0.005 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 32.221 ± 0.015 to 41.444 ± 0.014 which shows that the powder has good flow properties. All the formulations have shown the hausner's ratio ranging between 0.430 ± 0.45 to 0.478 ± 0.56 indicating the powder has good flow properties.

Table 4 Result of pre compression properties of esomeprazole floating tablets

F. Code	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index	Hausner's ratio
F1	32.25	0.382 ± 0.003	0.810 ± 0.004	33.840 ± 0.012	0.472 ± 0.54
F2	30.26	0.385 ± 0.004	0.822 ± 0.007	35.717 ± 0.014	0.468 ± 0.58
F3	30.15	0.386 ± 0.002	0.799 ± 0.008	32.221 ± 0.015	0.483 ± 0.52
F4	29.26	0.380 ± 0.006	0.845 ± 0.004	40.715 ± 0.010	0.450 ± 0.56
F5	29.48	0.389 ± 0.004	0.854 ± 0.005	41.444 ± 0.014	0.456 ± 0.54
F6	28.58	0.354 ± 0.007	0.824 ± 0.006	41.411 ± 0.015	0.430 ± 0.45
F7	30.47	0.375 ± 0.005	0.814 ± 0.003	37.451 ± 0.017	0.461 ± 0.52
F8	30.56	0.387 ± 0.004	0.810 ± 0.007	35.548 ± 0.011	0.478 ± 0.56
F9	31.25	0.354 ± 0.006	0.825 ± 0.008	42.758 ± 0.012	0.429 ± 0.47

Esomeprazole Tablet quality control tests such as weight variation, hardness and friability, thickness, Drug content and drug release studies in different media were performed on the compression tablet. All the parameters such as weight variation, hardness, friability, thickness and drug content were found to be within limits Table 5 & 6.

Table 5 Results of post compression properties of esomeprazole floating tablets

F. code	Thickness (mm)	Hardness (kg/cm ²)	Wt. variation (mg)	Friability (%)	Drug content (%)
F1	3.89 ±0.03	6.13 ± 0.21	Passes	0.5216± 0.04	98.53±0.48
F2	3.90 ±0.05	6.70 ± 0.30	Passes	0.6325 ±0.04	99.23±0.57
F3	3.89 ±0.03	6.51 ± 0.50	Passes	0.5215 ±0.08	99.77±0.67
F4	3.91 ±0.06	6.73 ± 0.29	Passes	0.6532 ±0.10	99.27±0.23
F5	3.89 ±0.03	6.81 ± 0.51	Passes	0.6485 ±0.04	98.42±0.61
F6	3.90 ±0.05	6.78 ± 0.51	Passes	0.5489 ±0.08	99.57±0.34
F7	3.87 ±0.04	6.80 ± 0.47	Passes	0.5325 ±0.10	99.87±0.56
F8	3.86± 0.04	6.83 ± 0.49	Passes	0.5369 ±0.15	97.37±0.60
F9	3.89± 0.04	6.81 ± 0.50	Passes	0.5425 ±0.15	98.50±0.61

Table 6 Results of Floating capacity

Formulation	Floating lag time	Total floating time
F1	Less than 1 min	< 12 hrs.
F2	Less than 1 min	< 12 hrs.
F3	Less than 1 min	< 12 hrs.
F4	Less than 1 min	< 12 hrs.
F5	Less than 1 min	< 12 hrs.
F6	Less than 1 min	< 12 hrs.
F7	Less than 1 min	< 12 hrs.
F8	Less than 1 min	< 12 hrs.
F9	Less than 1 min	< 12 hrs.

In the present study 9 formulations with variable concentration of polymer (HPMC K 15 HPMC K4) were prepared by direct compression method and evaluated for physicochemical properties, buoyancy lag time, total floating time, and invitro drug release. The results indicated that optimized formulation F6 on immersion in 0.1N HCl at 37±0.5⁰C tablets immediately and remain buoyant upto 12 hrs without disintegration. These two factors are essential for the tablet to acquire bulk density < 1, so that it remains buoyant on the gastric fluid. The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of higuchi was maximum i.e 0.896 hence indicating drug release from formulations was found to follow higuchi kinetics Table 7 & 8.

Table 7 *In vitro* drug release study of Floating tablet

Time (hr)	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	08.23	07.14	07.24	08.23	07.23	07.45	08.32	07.26	07.28
1	12.32	10.23	11.45	10.45	10.45	11.23	12.23	11.87	12.56
1.5	26.23	22.42	24.23	23.76	31.23	38.23	32.13	26.28	18.58
2	42.45	40.32	45.23	44.23	48.23	46.32	47.14	38.21	40.28
3	76.34	66.11	67.21	65.71	50.56	67.02	71.13	68.24	56.98
4	82.23	77.33	75.11	82.34	55.00	88.13	91.23	89.12	73.98
6	82.55	97.13	87.13	83.00	56.00	99.13	92.00	99.25	84.16
8	83.00	97.10	94.23	83.21	57.25	99.99	93.00	99.56	89.26
12	84.21	97.23	99.26	83.50	57.85	99.87	94.56	99.76	94.56

Table 8 Kinetic data of esomeprazole floating tablet in comparison with all formulation

F. Code		Zero Order	First Order	Higuchi	Korsmayer Papas	Best fitted Model
F1	r ²	0.441	0.631	0.810	0.849	Korsmayer Papas
F2	r ²	0.668	0.858	0.868	0.898	Korsmayer Papas
F3	r ²	0.675	0.981	0.896	0.896	First Order
F4	r ²	0.496	0.678	0.828	0.852	Korsmayer Papas
F5	r ²	0.154	0.333	0.762	0.755	Higuchi
F6	r ²	0.581	0.797	0.873	0.860	Higuchi
F7	r ²	0.512	0.793	0.847	0.859	Korsmayer Papas
F8	r ²	0.632	0.909	0.857	0.899	First Order
F9	r ²	0.708	0.969	0.894	0.916	First Order

CONCLUSION

In the present work, it can be concluded that the esomeprazole floating tablets can be an innovative and promising approach for the delivery of esomeprazole for the treatment of gastric ulcers. The optimized formulation **F6** containing HPMC K15 and a gas generating agent. The optimized formulation **F6** showed drug release of 99.87 % within 12h. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of higuchi was maximum i.e 0.977 hence indicating drug release from formulations was found to follow higuchi kinetics.

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