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FORMULATION, EVALUATION AND OPTIMIZATION OF FLOATING PULSATILE RELEASE TABLETS OF ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

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ABSTRACT

The aim of present study was to develop, evaluate and optimisefloating pulsatile release system of esomeprazole by combining floating and pulsatile principles in achieving the chronotherapeutic approach of nocturnal acid break through. The system consists of primarily preparation of rapid release core tablets using superdisintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate. The prepared core tablets were evaluated for various flow properties, post compression parameters, drug content, disintegration and dissolution studies.Different concentrations of methocel E15 and E50 was used for dry coating of selected core tablet and evaluated the formulations for hardness, friability and *Invitro* dissolution studies.A 32 full factorial design was employed to investigate the influence of buoyant layer on the lag time and % drug release. For the experimental runs created from the factorial design dissolution studies were performed to obtain theoptimised formulation with desired lag time.X-ray scintigraphy and pharmacokinetic studies were performed for the optimised formulation in rabbits. The data were statistically analyzed using ANOVA, and $P < 0.05$ was statistically significant.

INTRODUCTION:

Conventional pulsatile release dosage forms following oral administration are meant to release drug after lag period of 5-6 h usually in the large intestine. However, the viscous content of lower part of GI tract cause hindrance to the drug diffusion and also enzymatic degradation of some drugs makes it an unfavourable site for drug release. Further, highly variable nature of gastric emptying process may result in *invivo* variability and bioavailability problems.[1]Gastro retentive dosage forms reside in stomach only and are not affected by variability in pH, local environment or gastric emptying rate. These considerations led to the development of pulsatile release possessing gastro retention capabilities. Of the numerous approaches to prolong gastric

retention, floating drug delivery system is the most widely used technique to increased gastric residency through inherent buoyancy. [2]. Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of H^+k^+ATPase in gastric parietal cell. It blocks the final step in acid production , thus reducing gastric acidity. Esomeprazole is used for the treatment of gastro esophageal reflux disease (GERD) ,Peptic ulcer disease, H pylori eradication and prevention of gastrointestinal bleeds with NSIADs use. [3] 3^2FFD was employed using design expert version 11 to investigate the effect of two factors i.e. different amounts of HPMC K15 (polymer used in the buoyant layer) and sodium bicarbonate (independent variables) on the dependent variables like lag time and % drug release.Response surface methodology (RSM) is a collection of statistical and mathematical techniques, useful for developing, improving and optimizing process. [4]

The current study was aimed to develop a floating pulsatile drug delivery system of esomeprazole to provide night time relief from gastric acid break through. It was developed by combining pulsatile and floating principles to modulate pulsatile release profile from a time-lagged press coating of different concentrations of erodible polymers like methocel E15 and methocel E50.

MATERIALS AND METHODS

Materials:

Esomeprazole magnesium trihydrate was a gift sample from Aurobindo lab Hyderabad. superdisintegrants such as crospovidone, cross carmellose sodium, Sodium starch glycolate, talc,Mg stearateobtained from Bright scientifics Hyderabad, were used as the components for the preparation of rapid release core tablets by direct compression method. Methocel E15 and Methocel E50obtained from Bright scientifics, Hyderabad, were used as components or the dry coating. HPMCK15 and sodium bicarbonate are the components of buoyant layer.All other ingredients and reagents were used of analytical grade.

METHODS

Preparation of rapid release core tablets (RCT):The rapid release core tablets were prepared using superdisintegrants such as crospovidone, cross carmellose sodium, Sodium starch glycolate by direct compression method. All the ingredients were mixed in geometrical order and blended in a dry form using double cone blender for about 15min. The resultant powder blend were evaluated for flow properties such as true density, bulk density, angle of repose, Hausner's ratio and Carr's index and compressed using single punch compression machine to get RCT of 80mg. The composition of RCT was shown in Table 1.[5]

Evaluation of RCT: The RCTwere evaluated for its thickness, hardness, friability, Drug content, disintegration time and dissolution studies.

In vitro release studies of RC: The invitrorelease studiesfor the RCT formulations were carried out using USP type- II dissolution apparatus at 37.5±0.5ºC in 0.1N HCl at a speed maintained at 50rpm. The samples were withdrawn at time intervals of 0, 5, 10, 15, 30, 45 and 60 minutes respectively and analysed at 300nm using UV-Visible spectrophotometer.

***Preparation of pulsatile release system (PRS)*[5]**: The optimisedRCT formulation was used for the preparation of PRS using polymers like methocel E15 and methocel E50 at different concentrations such as 50, 100, 150mg of each polymer.All the ingredients were sieved through Dry coating method involves filling of 50% of

polymer in 10mm die followed by RCT in the center of the die slightly compress to fix the polymer around the RCT and then remaining quantity was added and compressed using single punch tablet machine .

Evaluation of PRS: The prepared PRS were evaluated for its hardness, thickness, % friability and *invitro*dissolution studies. Based on the results obtained the best formulation was selected for floating pulsatile release system (FRS)

Application of 3^2 full factorial design: The composition of experimental runs are shown in Table 2.Totally nine formulations were created using different concentrations of independent variables as explained above. The experimental design for the drug is shown in the Table 3.

Preparation of floating pulsatile release tablet: The FRS was prepared by placing buoyant layer on the top of selected PRS and compressing the layer to obtain FRS.The mixture of buoyant layer and $NaHCO_3$ were passed through the sieve # 60 to obtain uniformly dispersed powder and addition of talc to that powder blend. The buoyant powder were filled into the 10mm diameter die and PRS was placed and compressed using single punch tablet machine to get the required hardness.[6]

Evaluation of FRS: Prepared FRS was evaluated for its hardness, floating onset time (time period between placing of FRS into the container and beginning of buoyancy), floating duration and *invitro*dissolution studies.

Drug-Excipient interactions: The physicochemical compatibilities of the drug and the used excipients were tested by FTIR studies and DSC studies.

X-ray Scintigraphic studies in rabbits:Scintigraphic studies were performed for the optimisedformulation at time intervals of 2,6 and 8h respectively useful in tracing the dosage form and its release in Gastro intestinal tract.

Estimation of pharmacokinetic parameters in rabbits: Four healthy adult male rabbits (Weighed: 3.2 - 3.5 Kg, mean 3.3 ± 0.12 Kg, aged: 8-10 months) were enrolled in the study. The studies were carried out with registration no. IAEC/769/2011/CPCSEA.Rabbits were fasted for 12 hours with free access to water by *add libitum* before the study started. A single dose, two crossover design study was used in rabbits. There was a washout period of one week between the two doses. In first stage,four rabbits received a dose of test formulations of esomeprazole whereas after one week, the in second stage rabbits received the same dose of Esofag 40mg (Reference product) to complete the cross-over design.

RESULTS AND DISCUSSION

Evaluation of RCT: The hardness values ranges from 4.2 ± 0.16 to 5.2± 0.18 possesses good mechanical strength. The thickness values were in between 3.5 ± 0.083 to 3.51±0 .11mm. The friability ranged from 0.15 ± 0.05 to 0.56 ± 0.01. The disintegration time of core tablets prepared were in the range of 3.33 ± 0.5 to 12.33 ± 1.52 minutes. The formulation EC3 showed lowest disintegration time compared with the remaining formulations i.e. 180 sec. The % drug content of all formulations ranged from 98.87 ± 0.29to 101.17±0.97% fallwithin the acceptable limits.

Invitro release studies of RCT: Based on the results obtained from the dissolution study of RCT in 0.1 N HCl all formulations except EC3showed 88% of drug release within 10 min. The EC3 formulation formulated with croscarmellose sodium of 9mg provided a burst release of 94% within 10 min which was the maximum drug

release compared to other formulations and therefore was selected for pulsatile coating.

Evaluation of PRS: The hardness values of all coated formulations ranged from 4.8 - 5.2 kg/cm^{2}which revealssatisfactory mechanical strength. The thickness values were found to be between 3.7- 3.78mm. The average weight was in the range of 240 - 242 mg. The friability ranged from 0.10 - 0.22%. All the obtained values are in acceptable limits. The drug release from all the formulations except EP5 and EP6 started from 30 minutes onwards. The formulation EP1 showed complete drug release in 4th hour. EP2, EP3 and EP4 at 5th hour. The formulation EP6 sustain the release of drug upto 5h and burst release of drug was observed. Hence the formulation was selected for floating pulsatile system.

Evaluation of PRS: Totally nine formulations were created and prepared by applying 3^2 full factorial design. The release profiles were shown in Figures 1& 2.The "Pred R-Squared" of 0.8992 is in reasonable agreement with the "Adj R-Squared" of 0.9061, i.e the difference is less than 0.2. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The suggested ratio of adeq Precision 19.01 indicates an adequate signal. This model can be used to navigate the design.

X-ray scintigraphic studies in rabbits: *Invivo*X-ray imaging was conducted in rabbits in order to trace the movement and behaviour of the capsule in GI tract. Images were taken at 2, 4 and 6h after administration of radiolabeled tablet .The results of X- ray imaging study are shown in Figures 18, 19 and 20.Scintigraphy scans obtained for the optimised formulation at the time intervals of 2h, 4h and 7h. The figures showed that there was no drug release observed at 2h and 4h. After completion of lag time (6h) burst release of dosage was observed.The results showed that the values of pharmacokinetic parameters like T_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for the optimised novel formulation were found to be higher compared with the marketed product which met the chronotherapuetic approach for the treatment nocturnal acid break through.This floating pulsatile release system was formulated using RCT of 80mg, PRS of 240mg and compressed with mixture of buoyant layer and gas generating agent of 100mg, 12mg was successful in relieving from nocturnal acid secretions with the desired lag time of 6h. Hence this novel formulation desired to achieve chronotherapeutic approach of anti-ulcer activity.

SUMMARY AND CONCLUSION

The present study demonstrates that esomeprazole floating pulsatile release system could be successfully achieved the chronotherapeutic approach of nocturnal acid secretion which is high during night time needs the release of drug at higher concentrations.Regarding the optimization, central composite design can be successfully used for achieving desired responses, floating lag time and drug release profile, after preprogramed off period. From the response surface methodology, it is easy to understand the change of responses with independent variables and for locating the desired area of interest. *In vivo*X-raystudy has shown the prepared optimised formulation maintained the desired lag time of 6h followed by burst release of drug.The optimized formulation when compared to the marketed formulation shown better pharmacokinetics parameters for the effective treatment of ulcers.

Table 1: Composition of rapid release core tablet (RCT)

S.no	Ingredients	EC1	EC2	EC3	EC4	EC5	EC6	EC7	EC8	EC9
1	Esomeprazole	40	40	40	40	40	40	40	40	40
2	Cross carmellose sodium	5	7	9	-	-	-	-	-	-
3	Cross povidone	-	-	-	5	7	9	-	-	-
4	Sodium starch glycolate	-	-	-	-	-	-	5	7	9
5	Aerosil	2	2	2	2	2	2	2	2	2
6	Magnesium stearate	2	2	2	2	2	2	2	2	2
7	MCC (Avicel)	31	29	27	31	29	27	31	29	27
8	Total wt(mg)	80	80	80	80	80	80	80	80	80

Table 2 Composition of factorial experimental runs

S.No.	Ingredients	EPF1	EPF2	EPF3	EPF4	EPF5	EPF6	EPF7	EPF8	EPF9
1	Pulsatile tablet	240	240	240	240	240	240	240	240	240
2	HPMC K15	50	50	50	75	75	75	100	100	100
3	$NaHCO_3$	8	10	12	8	10	12	8	10	12
4	Talc	5	5	5	5	5	5	5	5	5
5	MCC	57	55	53	32	30	28	7	5	3
6	Total wt(mg)	360	360	360	360	360	360	360	360	360

Table 3 Experimental design

Factors (independent variables)	Levels used			Response (dependent variable)
	-1	0	+1	
X1= Amount of $HPMCK_{15}$ (buoyant layer) mg	50	75	100	Y1 = % drug release in 7h
X_2= Wt. of Sodium Bicarbonate (gas generating agent) mg	8	10	12	

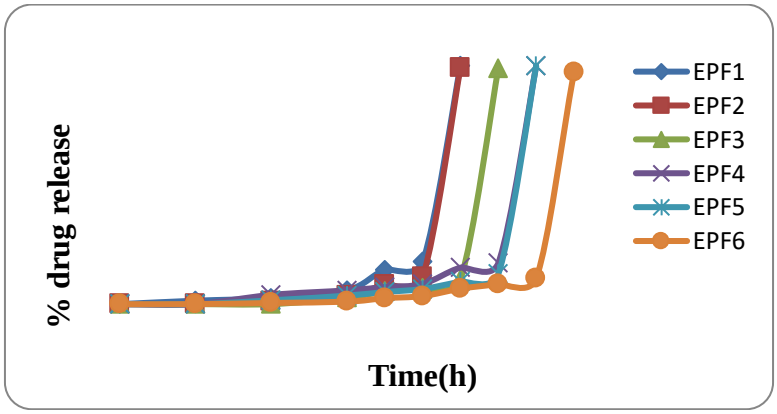


Fig. 1.Dissolution profile of factorial floating formulations

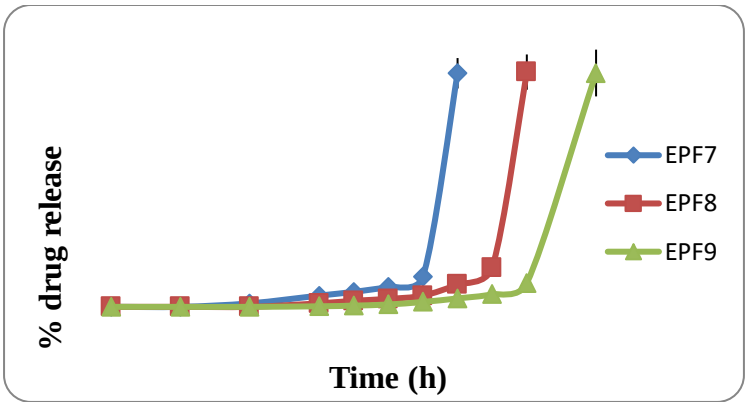


Fig. 2.Dissolution profile of factorial floating formulations

Table 4 Experimental design

Std	Run	Factor 1 A : Wt. of Buoyant layer(HPMC K15)	Factor 2 B: Wt. of gas generating agent ($NaHCO_3$)	Response 1 Floating lag time(min)
1	13	-1	-1	140
2	7	0	-1	260
3	10	0	0	280
4	6	0	1	320
5	12	-1	0	180
6	11	0	0	280
7	2	-1	1	230
8	3	1	1	355
9	4	0	0	280
10	5	1	-1	290
11	1	0	0	280
12	8	1	0	330
13	9	0	0	280

Fit statistics for response: floating lag time

Std. Dev.	**19.90**	**R^2**	**0.9430**
Mean	269.92	Adjusted R^2	0.9061
C.V. %	7.37	Predicted R^2	0.8992
		Adeq Precision	19.01

Diagnostics plots and Model graphs

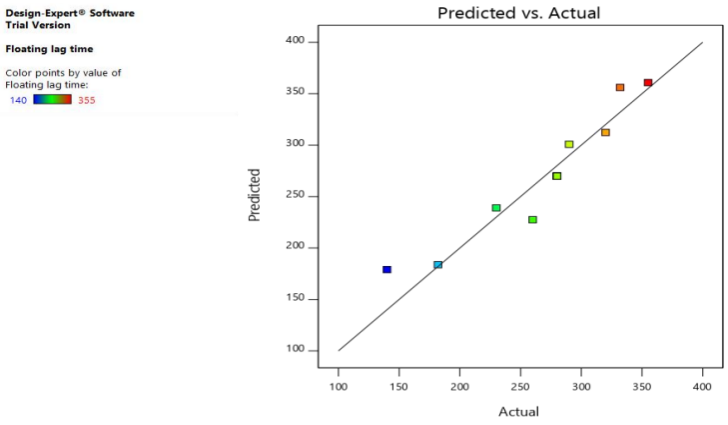


Fig. 13: Predictedvs Actual plot

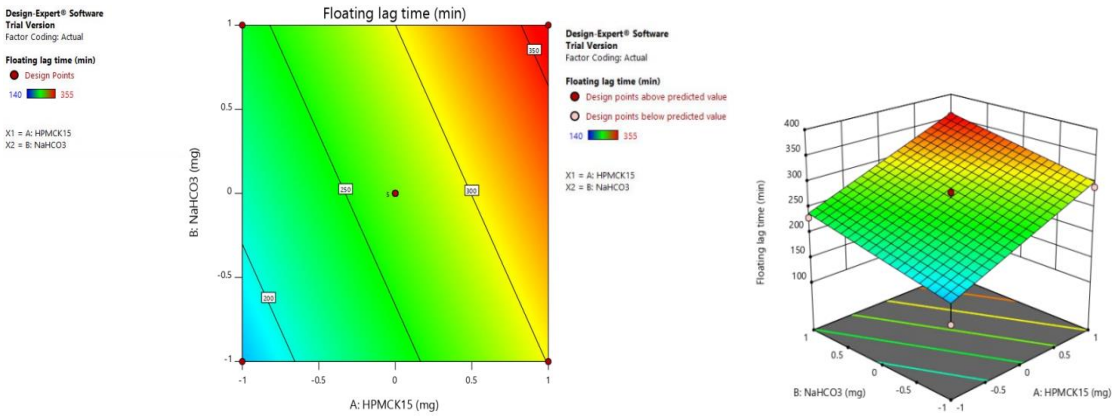
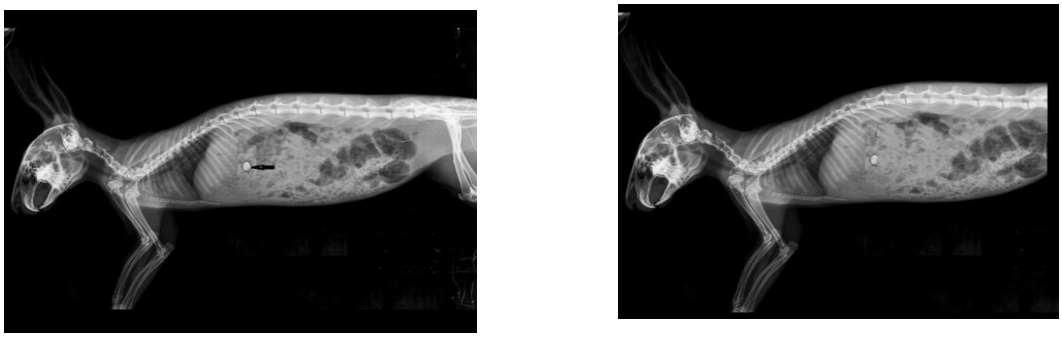


Fig. 14, 15: Contourand 3D surface plot



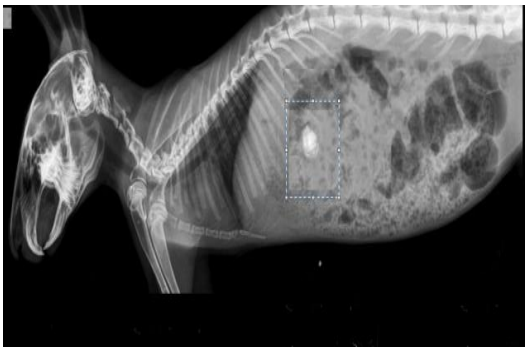


Fig. 18, 19& 20: X-ray images at 2, 4 and 7h

Pharmacokinetic values ofoptimised and marketed formulation

C max (ng/ml)	**1138.6**	**972.5**
Tmax	12hrs	8hrs
AUC (0-t)(ng.mg/ml)	10049.25	5664.5
Ke	0.092	0.234
T 1/2	7.532609	2.96158
AUC (t-inf)(ng.mg/ml	1408.696	0
AUC (0-inf)(ng.mg/ml	11457.95	5664.5

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