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FORMULATION, OPTIMIZATION AND IN-VITRO EVALUATION OF FLOATING TABLET OF MISOPROSTOL

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ABSTRACT

The purpose of the present study to develop an optimized gastric floating drug delivery system (GFDDS) to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastro intestinal tract (GIT) for local and systemic effect. The present study has been a satisfactory attempt to formulate floating drug delivery system of Misoprostol, an orally administrated gastric Ulcers/ duodenal ulcers drug with a view of improving its oral bioavailability and giving sustained release of the drug. A number of parameters affect the characteristics of the formulated floating tablet. These parameters must be optimized to achieve floating layer with the desired attributed and characteristics viz. percent drug release and lag time. In the present work the relevant parameters (independent variables) were optimized using 3^3 factorial designs (Statease ver. 9.0). These 27 formulations are evaluated for parameters. All the formulations shows results in the acceptable range. All preliminary formulations are subjected to in-vitro bouyancy and dissolution study. The data obtained from the in vitro release study was fit to various kinetic models to explain the release profile of the drug. Kinetic models were used zero and first-order equations, Higuchi, Hixon Crowell Krosmeyers peppas models.

Keywords: Misoprostol, 3^3 factorial, optimization designs, floating drug delivery, kinetic models.

INTRODUCTION

Oral administration is the most convenient and preferred means of any delivery to the systemic circulation. The development of oral sustained controlled release formulation is an attempt to release the drug slowly into the gastro intestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for long time. Gastro retentive dosage form can remain in the gastric region for a longer period and hence significantly prolong the gastric retention time (GRT) of drugs [1]. Misoprostol is one of the recent gastrointestinal drugs for gastric Ulcers / duodenal ulcers. Misoprostol possesses good absorption in GIT. Dosing frequency is four times a day which leads to patient incompliance. The dose of misoprostol is very less and has a half life of 40 min [2, 3].

MATERIALS AND METHOD

Misoprostol purchased from Sris Pharmaceutical Pvt. Ltd Hyderabad, HPMC K4M, Carbopol 934P, Aerosil, Avicel-PH 201, citric acid, sodium bicarbonate, magnesium stearate and talc, all chemicals are purchased from Mapromax Life Sciences Pvt. Ltd., Dehradun.

FTIR Studies

Infrared spectrum of a substance is characteristic of that compound and it provides information about the chemical groups present in that particular compound.

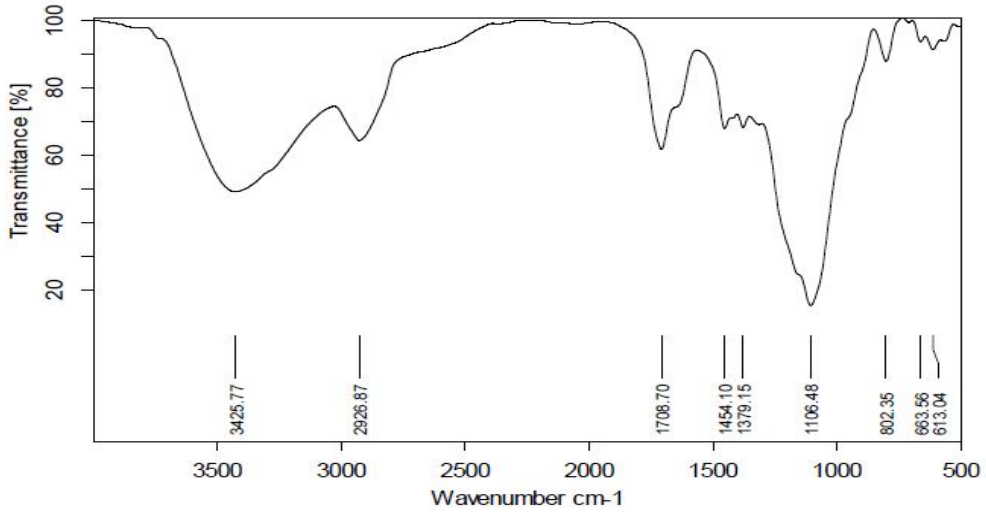

Fig. – 1: IR Spectra of MISOPROSTOL + HPMC + Carbopol + Avicel + Aerosil

Optimization Of Formulation Through Factorial Design

A number of parameters affect the characteristics of the formulated floating layer. These parameters must be optimized to achieve floating layer with the desired attributed and characteristics viz. percent drug release and lag time. In the present work the relevant parameters (independent variables) were optimized using 3^3 factorial designs (Statease ver. 9.0). Following independent variables were taken into consideration:

HPMC (mg) : (50%, 75% and 100%), Carbopol (mg) : (50%, 75% and 100%), Citric acid (mg) : (15%, 20% and 25%)

In 3^3 factorial design, 3 factor 3 level full factorial was applied resulting in 27 different formulations of the floating layer. The formulations were formulated and analyzed with respect to the dependent variables viz. floating lag time (sec) and percent drug release at the end of 12 hours as shown in table 1.

Table – 1: Variables And Their Levels In Polynomial Quadratic Model

Independent Variables	Levels		
	Low (-1)	Medium (0)	High (+1)
A- HPMC (mg)	50	75	100
B- Carbopol(mg)	50	75	100
C- Citric acid(mg)	15	20	25
Dependent variables			
Y1- % Drug release			
Y2- Lag time (sec)			

Table – 2: Factorial Design of Floating Tablet of Misoprostol

Formulation code	Independent variable level			Lag time in (sec)	Percent drug release (%)
	HPMC	Carbopol	Citric acid		
1	50	50	15	70	84.64
2	75	50	15	65	73.45
3	100	50	15	55	79.32
4	50	75	15	50	74.96
5	75	75	15	65	74.21
6	100	75	15	60	77.58
7	50	100	15	65	78.12
8	75	100	15	65	75.68
9	100	100	15	60	89.12
10	50	50	20	55	82.21
11	75	50	20	55	75.23
12	100	50	20	55	73.41
13	50	75	20	60	74.14
14	**75**	**75**	**20**	**55**	**72.52**

15	100	75	20	50	76.65
16	50	100	20	55	78.32
17	75	100	20	50	76.94
18	100	100	20	50	85.16
19	50	50	25	45	85.12
20	75	50	25	40	74.32
21	100	50	25	45	79.11
22	50	75	25	45	75.36
23	75	75	25	40	73.54
24	100	75	25	45	78.32
25	50	100	25	40	77.48
26	75	100	25	45	76.32
27	100	100	25	40	85.37

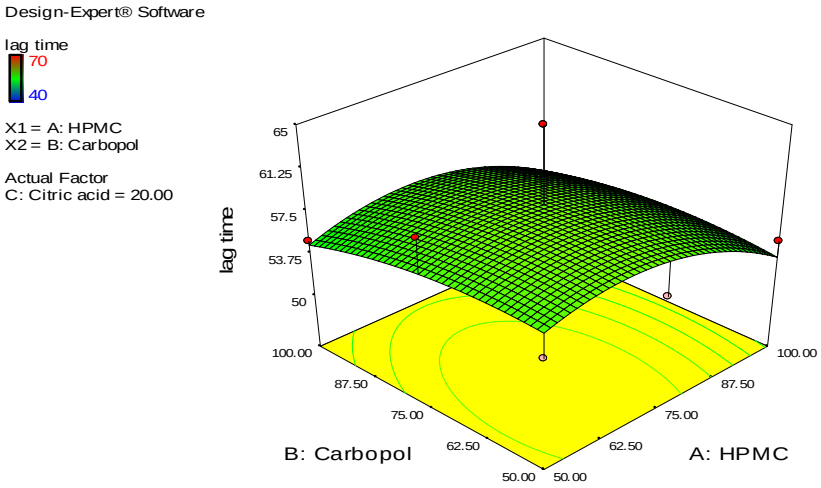

Fig. – 2: Graph showing effect of Carbopol and HPMC on lag time of floating layer of Misoprostol

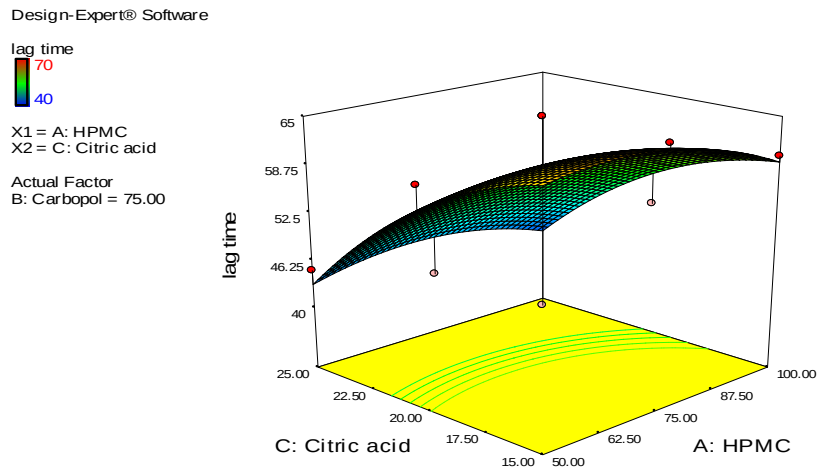

Fig. – 3: Graph showing effect of citric acid and HPMC on lag time of floating layer of Misoprostol

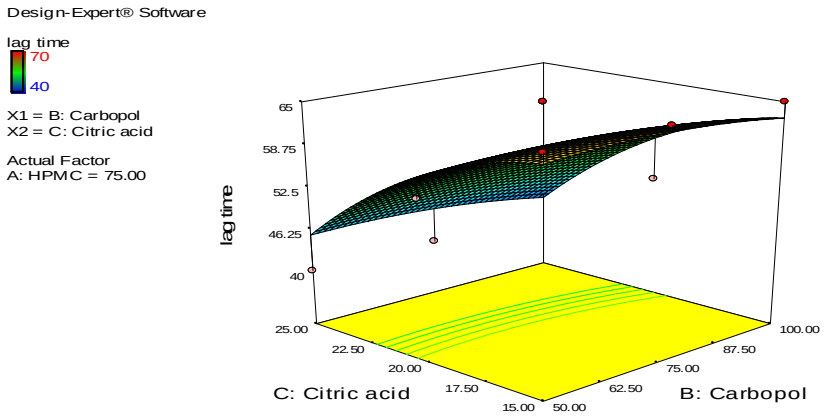

Fig. – 4: Graph showing effect of citric acid and carbopol on lag time of floating layer of Misoprostol

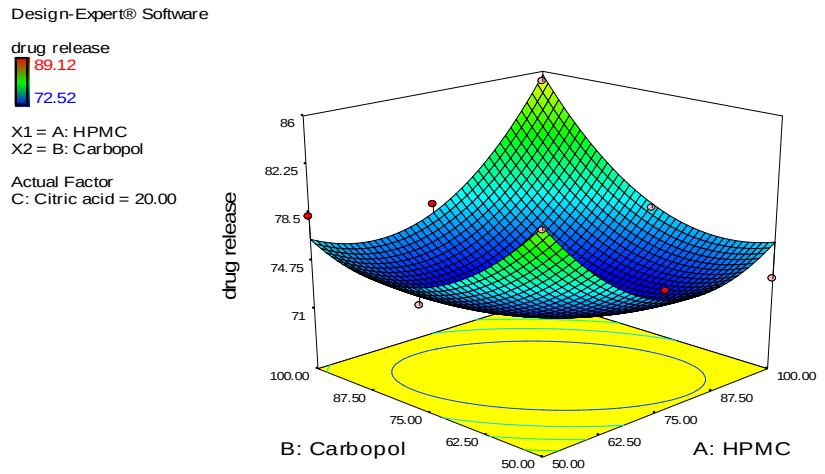

Fig. – 5: Graph showing effect of carbopol and HPMC on drug release of floating layer of Misoprostol

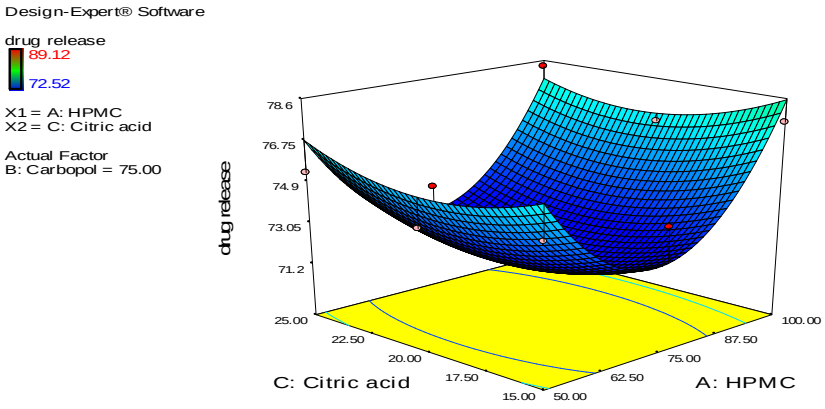

Fig. – 6: Graph showing effect of citric acid and HPMC on drug release of floating layer of Misoprostol

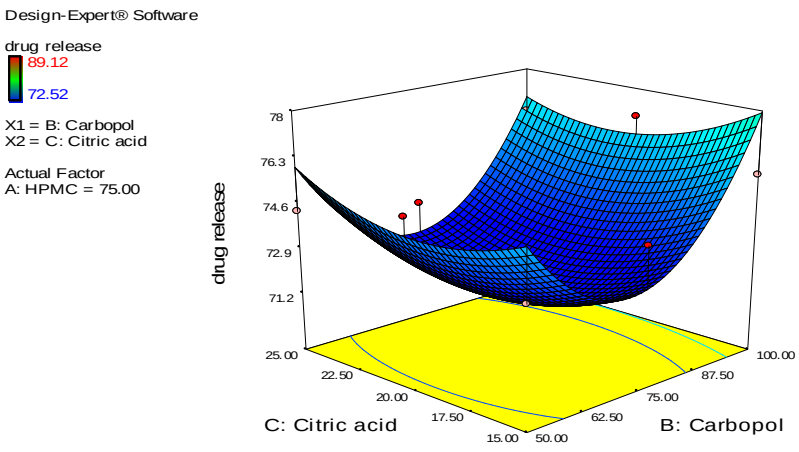

Fig. – 7: Graph showing effect of citric acid and carbopol on drug release of floating layer of Misoprostol

Table – 3: Optimum Formula for the Floating Tablet of Misoprostol (Formulation Code 14)

INGREDIENTS	Optimized floating Tablet (FC-14)
	Weight in mg
Misoprostol (1% Dispersion in HPMC)	40
HPMC K4M	75
Carbopol 934P	75
Sodium bicarbonate	20
Citric acid	20
Aerosil	1
Magnesium stearate	3
Avicel-PH 201	20

RESULTS

Evaluation of tablets [4, 5]

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. This may include size and shape, tablet thickness, tablet hardness, friability, weight variation, measurement of floating capacity, drug content uniformity.

Table – 4: Evaluation Parameter of Floating Tablets

Batch Code	Hardness (kg/cm^2) N=5	Thickness (mm) N=10	Friability (%)	Weight variation N=10	Drug content % of Misoprostol
FC-14	5.2 ± 0.24	5.0 ± 0.14	0.156	4.2± 0.97	99± 0.12

(Values are mean±S.D, where n=3).

Table – 5: *In vitro* buoyancy studies

Batch	lag time (sec) (n=3)	Floating time (hr)								
		1	2	3	4	5	6	8	10	12
FC-14	55±1	+	+	+	+	+	+	+	+	+

(Values reported are mean±S.D where n=3.)

+ → Floating of tablet, - → Non floating (either/solubility) of the tablet

Swelling Studies [6]

The individual tablets were weighed and kept in 50 ml of water. Tablets were taken out carefully after 60 minutes, blotted with filter paper to remove the water present on the surface and weighed accurately. Percent swelling was calculated by using formula.

Swelling Index = wet weight – dry weight / dry weight x 100

Table – 6: Percent swelling index

Batch	Time in hrs					
	1	2	3	4	5	6
FC-14	58.65	99.56	130.87	147.32	158.89	168.34

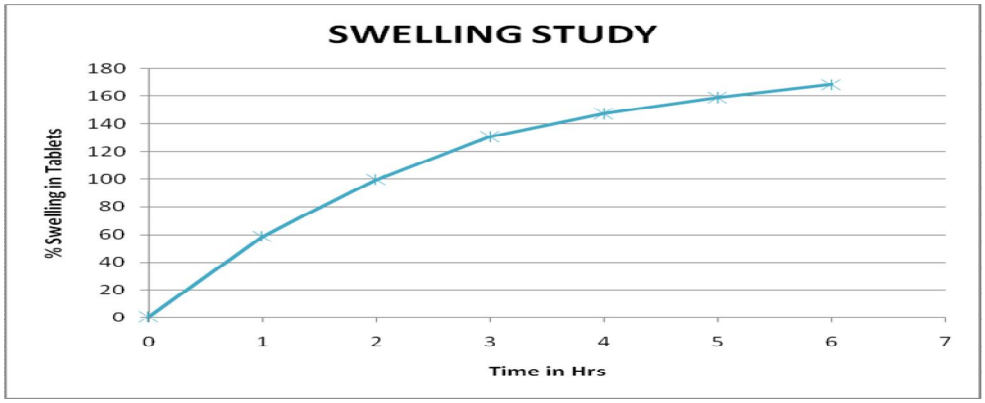

Fig. – 7: Swelling study of FC-14

***In vitro* drug release studies**

Table – 7: *In vitro* Release of Misoprostol Floating tablet

Time in hrs	FC-14
0.5	14.36 ± 0.21
1	21.35 ± 0.13
2	28.51 ± 0.14
3	36.68±0.82
4	43.68 ± 0.71
6	51.89±0.055
9	63.17±0.92
12	72.52±0.42

(Values reported are mean±SD where n=3)

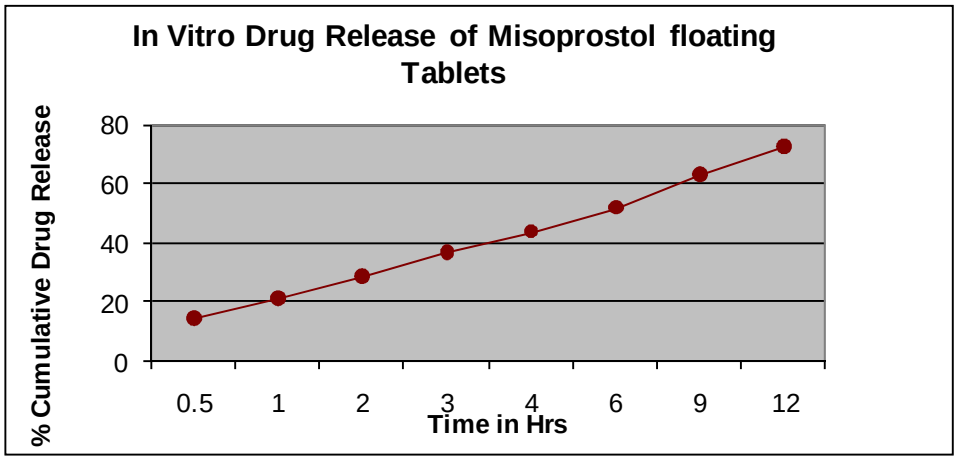

Fig. – 8: *In vitro* Drug Release of Misoprostol Floating tablet

Modeling and comparison of dissolution profiles

The pharmaceutical industry and the registration authorities do focus, nowadays, on drug dissolution studies. The quantitative analysis of the values obtained in dissolution / release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used. Some analytical definitions of the Q (t) function are commonly used, such as zero order, first order, Hixson–Crowell, Higuchi, Korsmeyer–Peppas models.

Table – 8: *In vitro* release profile of Misoprostol Floating Tablet (FC-14)

Time (hrs)	Root T	Log T	Cum% drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum. % drug retained	(% retained)$^{1/3}$
0.5	0.7071	-0.3010	14.36 ± 0.21	85.64	1.16	1.93	4.407
1	1	0	21.35 ± 0.13	78.65	1.33	1.89	4.284
2	1.4142	0.3010	28.51 ± 0.14	71.49	1.45	1.85	4.150
3	1.7320	0.4771	36.68±0.82	63.32	1.56	1.80	3.985
4	2	0.6020	43.68 ± 0.71	56.32	1.64	1.75	3.833
6	2.4494	0.7781	51.89±0.055	48.11	1.71	1.68	3.637
9	3	0.9542	63.17±0.92	36.83	1.80	1.58	3.327
12	3.4641	1.0791	72.52±0.42	27.48	1.86	1.43	3.017

DISCUSSION

IR Studies

The IR spectrum of Misoprostol showed peaks at 2930 cm-1, 1735 cm-1, 1381 cm-1, and 1050 cm-1 which represented various bending and stretching vibrations of the different groups present in the drug molecule shown in fig. - 1.

Optimization studies for floating layer

The floating tablet was optimized with respect to different variables. Since misoprostol is potent drug and needs to be released in a sustained manner in the body and therefore it is important that the floating layer be optimized carefully so as to control the release and other attributes as shown in table - 2.

Floating lag Time (Sec)

The effect of the independent variables on the floating lag time was visualized. A quadratic model was used to study the effect as shown in table - 2.

Percent Drug Release (12 hrs)

The model was studied with respect to the drug release to observe the effect of the independent variables. As in the case of the lag time the effect of HPMC, Carbopol and Citric acid at three levels were observed on the drug release. The model was found to be significant wit a model vlue of 19.39 and the pure error was 0.0 as shown in table - 2.

Evaluation Of Floating Tablets

Physical Properties of Tablets

Tablet dimensions

The dimensions determined for formulated tablets were tabulated in Table - 4

Hardness test

The hardness of tablets were tabulated in Table - 4

Friability Test

The values of friability test were tabulated in 4 and hence ensuring that the tablets formulated were mechanically stable.

Weight Variation Test

The percentage weight variations for all formulations were tabulated in Table - 4. The weights of all the tablets were found to be uniform with low standard deviation values.

Drug Content Uniformity

The percentage of drug content was shown in Table - 4. It complies with official specifications.

***In vitro* buoyancy studies**

From the lag time studies it was concluded that increase concentration of gas generating agents reduces the lag time of the formulation. All the data of buoyancy study tabulated in the Table - 5.

Swelling Study of Tablets

Swelling study was performed for 6 hour and their swelling index was given in Table - 6. While plot of swelling index against time (hr) depicted as Fig. - 7.

***In-Vitro* Release Study of Floating Tablet**

The results of in vitro release studies were plotted in different model of data treatment and was tabulated in table - 8.

CONCLUSION

Sustained release (SR)-gastroretentive dosage forms (GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. The present study was to develop misoprostol floating tablet in order to achieve an extended retention in the stomach, which m lay result in enhanced absorption and thereby improved bioavailability. Misoprostol is used for the treatment and prevention of stomach ulcers. The prepared floating formulations may prove to be potential candidate for multiple unit delivery, may result in new therapeutic possibilities with substantial benefit to the patient.

Misoprostol were generously provided by M/s Sris pharmaceuticals, Hyd, respectively as gift samples. The drug samples were tested for their identification and purity using spectroscopic techniques (UV spectroscopy and IR spectroscopy).

The melting point of Misoprostol was in the range of 261-263°C. The IR spectrum of Misoprostol showed peaks at 2930 cm-1, 1735 cm-1, 1381 cm-1, and 1050 cm-1 which represented various bending and stretching vibrations of the different groups present in the drug molecule. Solubility analysis for the drugs was performed in different solvents. It was found that the Misoprostol were sparingly soluble and soluble in water and Acetic acid respectively. The n-octanol:aqueous phase, partition coefficient of the drugs was calculated and was found to be less than 1. Hence it can be concluded that the drugs are highly hydrophilic in nature.

The drug compatibility studies were performed to have an insight of any possible interactions of the drugs with the polymers involved in the preparation of the drugs. There was practically no change in the absorbance of the mixture and of the pure drug in both the cases. The design of the delivery system was based on the sustained release formulation with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems. Different polymers, such as, HPMC K100M, Carbopol, Aerosil and avicel were used with different concentrations were tried in order to get the desired sustained release profile over a period of 24 hrs. The formulations were evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, and drug content. The optimized formulation was subjected to in vitro drug release profile and stability studies at different temperature and humidity conditions as per ICH guidelines.

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