

FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF DIACEREIN BY IONIC GELATION METHOD

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ABSTRACT

Background: Floating microspheres containing Diacerein were prepared by ionotropic gelation technique by using HPMC (K 100 M), and sodium alginate as polymers, sodium bicarbonate as gas generating agent and calcium chloride as cross linking agent. **Objective:** To formulate a system to remain in the stomach for controlled and predictable period in order to enhance the drug bioavailability. **Method:** Totally 12 different formulations of Diacerein were prepared by using the above polymers. All formulations were evaluated for percentage yield, particle size, swelling index, entrapment efficiency, floating time and total floating time, Morphology of the microspheres and *in-vitro* drug release. **Results:** The percentage yield was found to be in the range of 45.0% to 80.62%. The average particle size was found to be in the range of 816 to 1292.7 μm . % Drug entrapment efficiency of Diacerein floating microspheres ranged from 27 % to 110 %. From the observations the total floating time was high for formulations F7, F8, F9. The swelling index of different formulations from F1 to F12 was found to be from 5 to 40%. The cumulative percent drug release of Optimized formulation F9 was found to be 95.42 % at 180 min. SEM study showed that pores were found on the surface of microspheres with a possible indication that the drug is released by diffusion mechanism. The ideal formulation, F9 followed first order kinetics and kosemeyers-peppas release model and value of "n," is calculated to be 0.7187 indicated that the drug release shows Non-Fickian diffusion. The formulation was stable at the end of 30 days with stability study. **Conclusion:** The optimized formulation showed good floating for > 3hrs. The formulation was stable at the end of 30 days with stability study.

KEYWORDS: Diacerein, Ionotropic gelation method, HPMC (K 100 M), Sodium Alginate, floating lag time, Total Floating time, Stability studies.

INTRODUCTION

Oral route of drug administration is the most suitable and commonly used method of drug delivery but this route more often produces gastric emptying rate that varies from person to person with a short stomach transit time and the existence of large absorption window in the upper small intestine for several drugs.^[1] Floating systems are low-density systems that have adequate buoyancy to float over the gastric content and remain buoyant in the stomach without affecting gastric emptying rate for an extended period of time, which results in an augmented gastric retention time and a better control of fluctuation in plasma drug concentration. After release of drug, the residual system is emptied from the stomach. These difficulties have encouraged researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period.^[2] Attempts are being made to develop a drug delivery system which can provide therapeutically effective

plasma drug concentration for a longer period, thereby reducing the dosing frequency and minimizing fluctuation in plasma drug concentration at steady state by delivering the drug in a controlled and reproducible manner.

Diacerein is an anthraquinone drug that works by blocking the actions of interleukin-1 beta, a protein involved in the inflammation and destruction of cartilage that play a role in the development of symptoms of degenerative joint diseases such as osteoarthritis.

MATERIALS AND METHODS

Materials

Diacerein was procured as a gift sample from Azico Pharmaceutical Pvt Ltd., Hyderabad. HPMC K100 M, Calcium Chloride, Sodium bicarbonate, Sodium alginate was procured from SD Fine chem. Ltd., Mumbai.

Preparation of Floating Microspheres of Diacerein

For preparation of floating microspheres of Diacerein, HPMC K100 and Sodium alginate were passed through the sieve no 40. All the ingredients were mixed in the proportions shown in table 1. The floating microspheres

were prepared by ionotropic gelation method.^[3] It was then collected by filtration and allowed to dry in a desiccator for about 24 hours. The formed microspheres were then subjected to evaluation studies.

Table 1: Formulation Chart of Floating Microspheres of Diacerein.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Diacerein	40	40	40	40	40	40	40	40	40	40	40	40
Sodium Alginate	10	20	30	20	40	60	30	60	90	40	80	120
HPMC K 100 M	30	20	10	60	40	20	90	60	30	120	80	40
NaHCO ₃	75	75	75	75	75	75	75	75	75	75	75	75
CaCl ₂	5	5	5	5	5	5	5	5	5	5	5	5

I. Pre formulation Parameters

Drug purity studies

The purity of the obtained drug sample was determined by comparing the melting point of the obtained sample with that of the official standards.^[4] The melting point of the drug was found to be 230°C.

Drug-Excipient Interaction studies

The infrared spectra of Diacerein pure drug, excipients, physical mixture of drug and excipients (optimised formula) were recorded between 500-4000cm⁻¹. The FTIR spectra were obtained using KBr disk method using an Fourier transform Infrared spectroscopy (FTIR) spectrophotometer^[5].

II. Post formulation parameters

Percentage yield

The percentage yield of Diacerein in the formulated product is determined by using the formula:

$$\frac{\text{Weight of the formulation}}{\text{Theoretical weight of drug and polymer}} \times 100$$

Particle size

The test is performed to determine the uniformity of the prepared formulation. The particle size of the each formulation was determined using optical microscopy technique were diameter of 100 particles each was recorded to determine the average particle size of each formulation.^[6]

Floating lag Time

The time taken by the microspheres to emerge onto the surface of the liquid after adding to the dissolution medium simulated gastric fluid without pepsin, at pH 1.2, temperature 37°C with paddle rotation at 50 rpm it is measured using stopwatch.^[7]

Total floating time: The time taken by the microspheres to float constantly on the surface of the gastric fluid without pepsin, at pH 1.2, temperature 37°C, paddle rotation at 50 rpm, it is measured using stopwatch.^[8]

Determination of swelling index

The swelling index of a dosage unit was measured by studying its weight gain. The swelling index of a

microspheres was determined by placing the microspheres in 10ml 0.1N HCl in a petri dish.^[9] After every one hour up to 12 hours, each microspheres was removed and blotted with tissue paper to remove the excess water and weighed on the balance. The experiment was performed in triplicate for each time point. The swelling index is expressed as a percentage and was calculated from the equation

$$\text{Swelling index (S.I)} = \left\{ \frac{W_t - W_o}{W_o} \right\} \times 100$$

Where, W_t = Weight of microspheres at time t
W_o = weight of microspheres before immersion.

Drug Entrapment Efficiency

The drug entrapment efficiency of the prepared formulations was determined by taking 20mg of the prepared microspheres and triturating with 100ml of 0.1N HCl and allowed to stand.^[10] The concentration of the drug present is calculated by recording the absorbance and concentration of each formulation. The total drug entrapment efficiency was determined using the formula,

$$\frac{\text{Concentration of drug in sample} \times 100}{\text{Total concentration of drug}}$$

Drug Dissolution studies

Dissolution test was carried out using USP XXIV (model DISSO, M/s. Labindia) rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 0.1 N HCL was used as dissolution medium (900ml). It was maintained at 37 ± 5 c .samples of 5 ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium^[11]. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the Diacerein 268nm by using a double beam UV spectrometer (Labindia-3000). Each dissolution study was performed for three times and the mean values were taken. % drug release was calculated using simultaneous equation method.

Shape and Surface Morphology (SEM)

Morphology of the microspheres was investigated by Scanning Electron Microscopy.^[12]

Kinetics and Mechanism of Release Analysis

To study the release kinetics, the data obtained from *in vitro* drug release studies were plotted in various order of reactions and kinetic models such as Zero order, First order and Higuchi's model, Hixson-Crowell cube root law, Korsmeyer *peppas* model.^[13]

Stability Studies

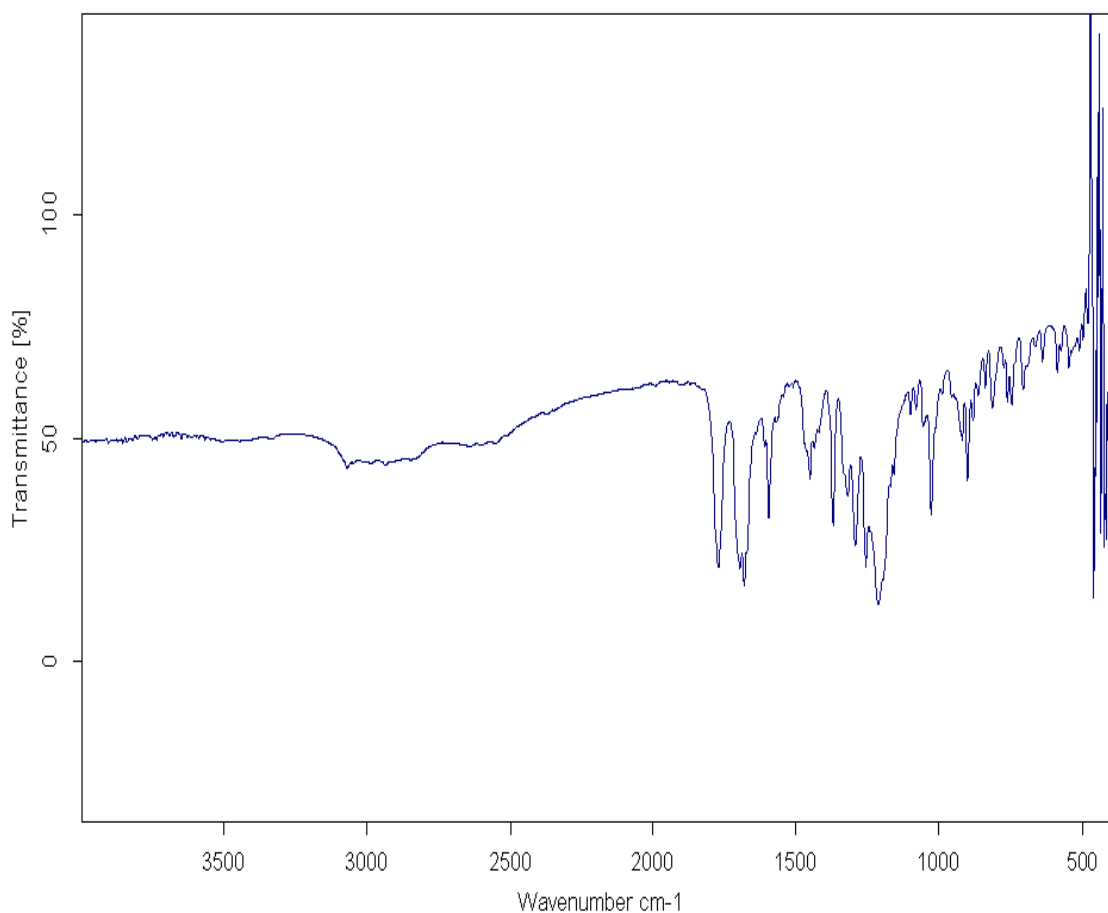
The stability studies of optimized formulations F9 was carried out at accelerated condition of $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$, 75% RH conditions for a period of 1 months.^[14] The microspheres were withdrawn at every week and evaluated for the percent entrapment efficiency. Samples were analyzed after 1 month for their entrapment efficiency.

RESULTS AND DISCUSSION

Microspheres of Diacerein were formulated using Sodium alginate and HPMC K100M by ionotropic

gelation method. The determination of purity was determined using a simple melting point apparatus and compared with that of the official standards. The melting point of the sample drug Diacerein was found to be 230°C .

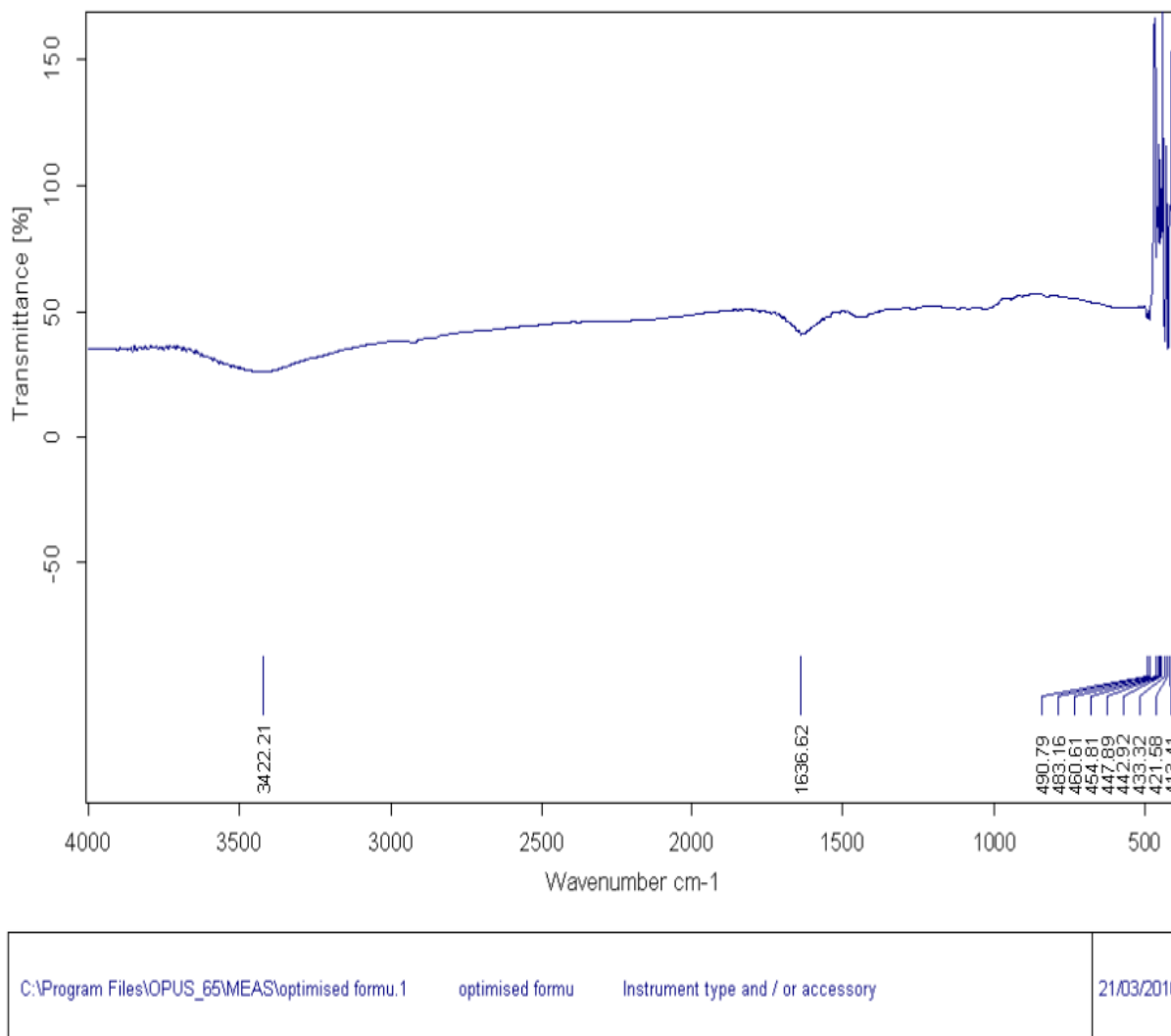
The spectral observations indicated that the principle IR absorption peaks observed in the spectra of the drug were close to those in the spectra of the microspheres indicates that there is no interaction between the drug and the polymer (Figure 1 & 2). The identical peaks corresponding to the functional groups and features confirm that neither the polymer nor the method of preparation has affected the drug stability.



C:\Program Files\OPUS_65\MEAS\diacerein.2	diacerein	Instrument type and / or accessory	21/03/2016
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Figure 1: FTIR spectrum of Diacerein Floating Microspheres.



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Figure 2: FTIR spectrum of Optimized Formulation F9.

Percentage yield of all formulations from F1 to F12 were calculated and it was observed that as the polymer ratio in the formulation increases, the product yield also increases. The percentage yield was found to be in the range of 45.0% to 80.62% (Table 2).

Particle size analysis of different formulations was done by optical microscopy. The average particle size was found to be in the range of 816 to 1292.7 μm (Table 2). The mean particle size was significantly varied according to type of polymer used for the preparation of microspheres; this may be due to the fact that difference in the viscosity of the polymer solution. Since high viscosity of the polymer solution requires high shearing energy for breaking of droplets of the emulsion.

% Drug entrapment efficiency of Diacerein floating microspheres ranged from 27 % to 110 %. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the polymers (Table 2).

The swelling index of different formulations from F1 to F12 was found to be from 5 to 40% (Table 2). Maximum swelling was observed with the F12 formulation containing sodium alginate and HPMC as polymers.

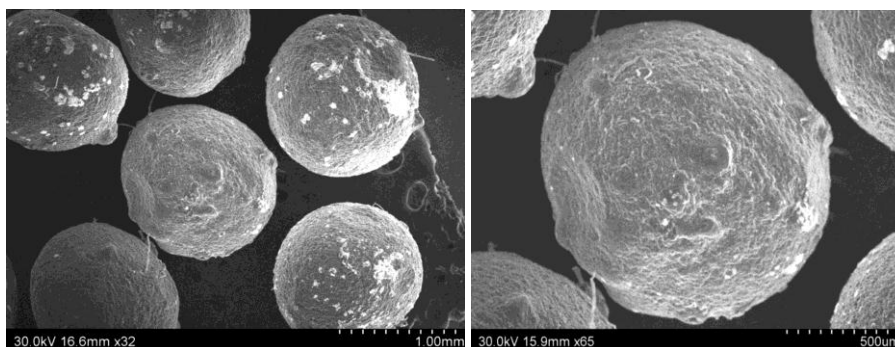
Floating lag time of formulations F4,F10,F11,F12 showed no floating whereas the other formulations show floating lag time of less than 5 seconds (Table 2).. From the observations the total floating time was high for formulations F7, F8, F9.

Table 2: Results of Percentage yield, Average particle size, % EE, % Swelling Index, Floating lag time, Total floating time.

Formulation Code	Percentage Yield	Average Particle Size	% EE	% Swelling Index	Floating Lag Time	Total Floating Time
F1	13.70%	797.6 μ m	75%	5	5 sec	45 minutes
F2	13.90%	956.0 μ m	95%	15	7sec	40 minutes
F3	17.80%	819.2 μ m	27.5%	5	5sec	1 hour 25 minutes
F4	24.08%	862.0 μ m	56.25%	5	No floating	-
F5	16.37%	849.0 μ m	29.75%	0	5sec	48 Minutes
F6	19.80%	906.0 μ m	42.5%	0	5sec	2 hours51 minutes
F7	24.20%	764.6 μ m	50%	35	5sec	>3 hours
F8	17.90%	767.3 μ m	40%	30	5sec	>3 hours
F9	26.70%	816.2 μ m	56%	10	5sec	>3 hours
F10	21.80%	1292.7 μ m	110%	20	No floating	-
F11	13.80%	1112.0 μ m	45%	10	No floating	-
F12	28.60%	1216.7 μ m	37.5%	40	No floating	-

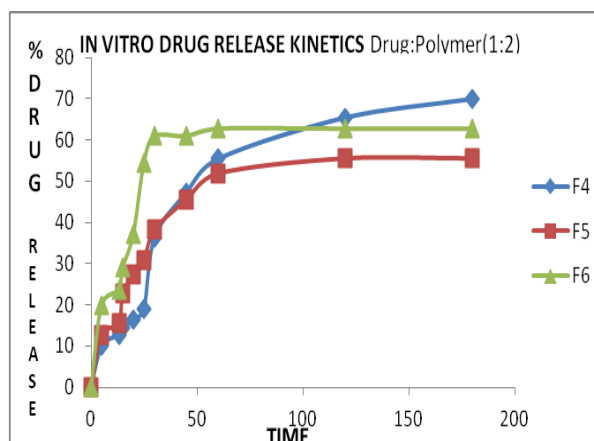
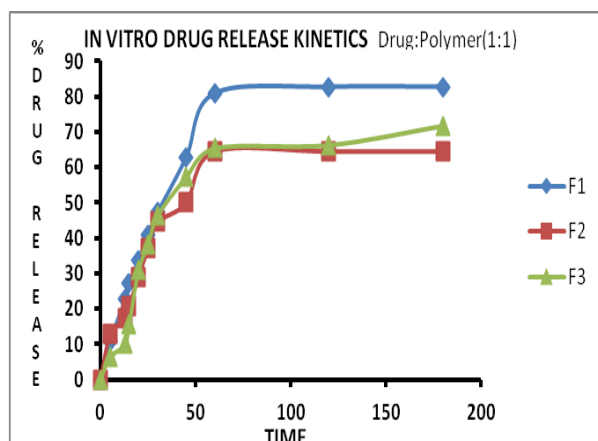
Morphology of the microspheres was investigated by Scanning Electron Microscopy. The results from SEM studies revealed that the microspheres of formulation F9 were spherical in shape with a rough outer surface morphology which might be due to surface associated

drug (Figure 3). SEM study showed that pores were found on the surface of microspheres with a possible indication that the drug is released by diffusion mechanism.

**Figure 3: SEM photograph of Optimized Formulation F9.**

In-vitro dissolution study of Diacerein from prepared microspheres exhibited a biphasic mechanism. The release of Diacerein from microspheres was characterized by an initial phase of burst effect (higher release), which was due to the presence of drug particles on the surface of the microspheres followed by a second phase of moderate release. The initial burst effect may be

attributed as a desired effect to ensure initial therapeutic plasma concentration of the drug. It has been observed that the sustained release action was higher in formulations containing higher concentration of the rate controlling polymers. The cumulative percent drug release of Optimized formulation F9 was found to be 95.42 % at 180 min.



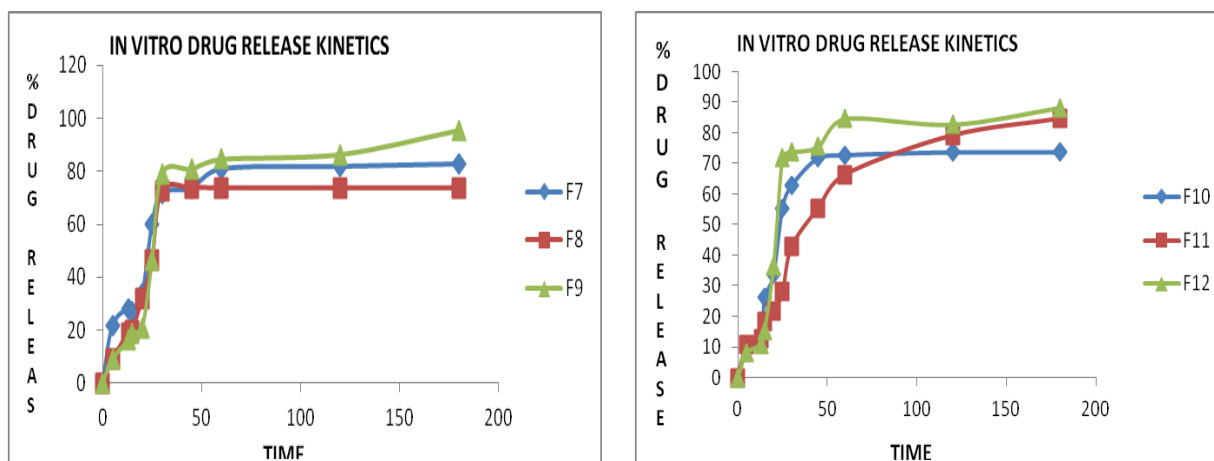


Figure 4-7: *In vitro* release profile of Diacerein floating microspheres of F1-F12.

The release data of Diacerein were processed into graphs to understand the linear relationship, i.e., Kinetic principles. The data were processed for regression analysis using MS-Excel statistical functions. Considering the correlation coefficient (R^2) values obtained showed that all the formulations (F1 to F12) had highest R^2 values for First order plots indicating that the dissolution data fits into First order equation (Table

3). To study the release mechanisms of Diacerein from the formulations the data of *in vitro* drug release was verified using Higuchi's, Korsmeyer-Peppas, and Hixson-Crowell cube root law models. The drug release from the most of the all formulations (F1 to F12) was found to follow kosemeyers-peppas release model. The formulation was stable at the end of 30 days with stability study.

Table 3: Mechanism of Drug Release.

Formulation Code	Regression coefficient of Higuchi Model	Regression coefficient of Hixson Crowell model	Korsmeyer Peppas model		Order of release
			Regression coefficient	n value	
F9	0.772	0.733	0.819	0.718	Non-Fickian diffusion

CONCLUSION

Formulation F9 showed good results with respect to the various evaluation parameters, so it was selected as the optimized formulation. From the Pre-formulation studies for drug excipient compatibility it was observed that there was no physical incompatibility between the drug and other excipients. All formulations were evaluated for percentage yield, particle size, swelling index, entrapment efficiency, floating time and total floating time. The results indicated that the final blend of both drugs and excipients showed sustained release characters. All formulations were tested for drug content and drug release, all estimated parameters were found to be within the limits, thus indicating that all the prepared formulations were good. All formulations were tested for buoyancy properties like floating lag time & total floating time. All formulations showed satisfactory results except for F4, F10, F11, F12 showed no floating. The formulation was stable at the end of 30 days with stability study

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