

Formulation Development of Floating Microspheres of Cefditoren Pivoxel by 3² Factorial Design and *in Vitro* Characterization

Swathi Chilukala¹, Vijaya Kumar Bontha¹, Rajeswara Rao Pragada²

¹Department of Pharmaceutics, Jangaon Institute of Pharmaceutical Sciences, Yeshwanthapur, Jangaon, Warangal, Telangana, India, ²Department of Pharmaceutical Sciences, College of Pharmacy, Andhra University, Visakhapatnam, Andhra Pradesh, India

Abstract

Aim: The main objective of the present research work was to develop floating microspheres of cefditoren pivoxel (CP) to provide the delivery of the drug at a sustained rate. **Materials and Methods:** Floating microspheres of CP were prepared by solvent evaporation technique using hydroxypropyl methylcellulose (HPMC) K4M and ethyl cellulose as the rate controlling polymers. The optimization of formulation was carried out by 3² factorial design using two factors; a total amount of polymer (X₁) and concentration of ethyl cellulose (X₂) as independent variables. The formulated floating microspheres were characterized by evaluating its yield, particle size, encapsulation efficiency, *in vitro* drug release, buoyancy, surface morphology (scanning electron microscopy analysis). **Results and Discussion:** The optimized formulation (F6) showed 91.5 ± 1.35% of drug release after 12 h and 75 ± 0.92% of entrapment efficiency. All the formulations have good buoyancy which was floated over 12 h in the dissolution medium. **Conclusion:** It can be concluded from the study that floating microspheres of CP can be prepared successfully using HPMC K4M and ethyl cellulose as the rate controlling polymers.

Key words: Cefditoren, entrapment efficiency, factorial design, floating, microspheres, pivoxel

INTRODUCTION

Oral drug delivery system has been known for decades as the most widely used route of administration among all the routes that have been explored for systemic delivery of drugs through various pharmaceutical products of different dosage forms.^[1] Drugs that are easily absorbed from the gastrointestinal tract and having short half-life are quickly eliminated from the blood circulation. To avoid these problems oral controlled release formulations have been developed.^[2,3] These systems should be aimed at achieving more predictable and increased bioavailability of the drugs and it is necessary to optimize both the residence of the system within the gastrointestinal tract and the release rate of the drug from the system.^[4] However, there are several physiological difficulties such as inability to restrain and localize the drug delivery system within desired regions of the gastrointestinal tract and the highly variable nature of the gastric emptying process.^[5,6] To

overcome these difficulties gastroretentive dosage forms which prolong the residence time of drug in the stomach and improve bioavailability have been developed.^[7] The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, and expansion/swelling. Among these approaches floating drug delivery is of particular interest due to its logical approach in the development of gastro retentive drug delivery system.^[8] A single unit floating dosage forms such as floating tablets are developed by utilizing matrices prepared by swellable polymers like methocel and natural polysaccharides and effervescent agents such as citric acid, tartaric acid, and sodium bicarbonate.^[8,9] Targeted drug

Address for correspondence:

Swathi Chilukala, Department of Pharmaceutics, Jangaon Institute of Pharmaceutical Sciences, Yeshwanthapur, Jangaon, Warangal – 506 167, Telangana, India.
E-mail: swathichpharma@gmail.com

Received: 16-12-2015

Revised: 25-01-2016

Accepted: 05-02-2016

delivery systems play a major role in delivering sufficient dose to the diseased lesions with the help of carriers. Nano and microparticulate carriers thus have important applications in the administration of therapeutic molecules. In the present study, an antibiotic drug CP is administered by encapsulating it in the microspheres.^[10,33]

CP is an advanced-generation, broad spectrum cephalosporin antibiotic approved for the treatment of acute bacterial exacerbation of chronic bronchitis, group-A beta-hemolytic streptococcal pharyngotonsillitis and uncomplicated skin/skin structure infections in adult and adolescent patients.^[25,27] CP has slightly bitter test and has half-life of 1.6 h and has poor water solubility. It is absorbed in the upper part of gastrointestinal tract (GIT). Based on these properties CP has been selected to develop floating drug delivery system.^[11] The objective of the present study was to develop multiunit floating drug delivery system of CP in order to provide the delivery of the drug at a sustained rate to improve bioavailability. Therefore, it was proposed to develop floating microspheres of CP by emulsion solvent evaporation method by optimizing formulation variables using hydroxypropyl methylcellulose (HPMC) K4M and ethyl cellulose as rate controlling polymers. From the literature, it has been found that no attempt has been reported yet to develop floating microspheres of CP to deliver the drug at a sustained rate in stomach and upper part of GIT, which is the absorption window of the drug, by optimizing formulation variables.

MATERIALS AND METHODS

CP was obtained as gift sample from Cadila Pharmaceuticals Limited (Ahmedabad). HPMC K4M and ethyl cellulose were purchased from Colorcon Pvt., Ltd., Hyderabad. All other reagents were of analytical grade and were used as received.

Preparation of floating microspheres

The floating microspheres of CP were fabricated by emulsion solvent evaporation technique. First the polymer solution was prepared by dissolving hydroxyl propyl methyl cellulose (HPMC K4M) and ethyl cellulose in dichloromethane and ethanol mixture (40 ml) in the ratio of 1:1. Weighed amount of CP was added to the polymer solution (HPMC K4M:ethyl cellulose) at different ratios of 1:3, 1:4, and 1:5, respectively, at room temperature and kept for stirring on magnetic stirrer for 15 min for uniform distribution of the materials in the solvent system. The drug-polymer solution was then transferred to the processing medium, i.e., 1% polyvinyl alcohol (PVA) upon continuous stirring using 3 blade propeller. The agitation by propeller was continued for 6 h at 500 rpm, and the temperature was maintained at 40°C throughout the process. After the smell of dichloromethane disappears the solution was filtered, and the collected microspheres were

washed with an excess amount of distilled water to remove any remnants of PVA. The microspheres were dried at room temperature.^[12,30-32]

Experimental design

In the present research, work 3² factorial design was employed to develop the optimized formulation with the help of Design-Expert® 9 trial version software (Stat-Ease Inc., USA). A statistical model incorporating interactive and polynomial terms was used to evaluate the response (Equation 1):

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and b_i is the estimated coefficient for the factor X_i . The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low medium to a high value. The interaction terms X_1, X_2 shows how the response changes when two factors are changed simultaneously.^[13]

The independent and dependent variables selected were as follows:

Independent variables

- Total amount of polymer (X_1)
- Concentration of ethyl cellulose (X_2)

Dependent variables

- Percentage yield (Y_1)
- Particle size (Y_2)
- Entrapment efficiency (EE) (Y_3)
- Dissolution efficiency (DE) (Y_4)

The various levels of independent variables used in experimental trials are shown in Table 1 and the composition of floating microspheres is shown in Table 2.

In vitro evaluation of floating microspheres

Percentage yield

The prepared microspheres of all batches were accurately weighed. The weighed quantity of prepared microspheres was divided by the total amount of all the excipients and drug used in the fabrication of microspheres, which gave the total percentage yield of floating microspheres.^[14,15] The above experiment was done in triplicate, and the mean value of %

Table 1: Independent variables and their levels

Levels	Independent variables	
	Total amount of polymer (mg) (X_1)	Concentration of ethyl cellulose (%) (X_2)
-1	300	50
0	400	75
+1	500	83.3

Table 2: Composition of floating microspheres of cefditoren pivoxil

Formulation code	Amount of drug (mg)	Total amount of polymer (mg) (X ₁)	Concentration of ethyl cellulose (X ₂)		Concentration of HPMC K4M	
			%	mg	%	mg
F1	100	300	50	150	50	150
F2	100	300	75	225	25	75
F3	100	300	83.3	250	16.7	50
F4	100	400	50	200	50	200
F5	100	400	75	300	25	100
F6	100	400	83.3	333.33	16.7	66.66
F7	100	500	50	250	50	250
F8	100	500	75	375	25	125
F9	100	500	83.3	416.66	16.7	83.3

HPMC: Hydroxypropyl methylcellulose

yield was taken into consideration. It was calculated using the following formula:

$$\text{Percentage yield} = \frac{\text{Actual yield of product}}{\text{Total weight of excipients and drug}} \times 100$$

Particle size measurement

The particle size of prepared microspheres was measured using an optical microscope and the mean particle size was calculated by measuring 100 particles with the help of a calibrated eye piece micrometer.^[16] The average particle size was taken into consideration.

EE

The EE was determined based on the total drug content and the untrapped drug of the floating microspheres. The untrapped drug was determined by taking one dose equivalent of floating microspheres and washed with 0.1 N HCl to remove the surface associated drug. The absorbance of the filtrate was taken at 272 nm to estimate the surface drug content. The drug content of CP floating microspheres was determined by dispersing 50 mg of formulation (accurately weighed) in 10 ml of 0.1 N HCl, followed by agitation on magnetic stirrer for 12 h to extract the total drug. The drug concentration of both the solutions of untrapped drug and the total drug was determined spectrophotometrically at 272 nm by making desired dilution with 0.1 N HCl.^[15,17,18] The experiment was performed in triplicate. Percentage EE was calculated as follows:

$$\% \text{ Entrapment efficiency} = \frac{\text{Total drug content} - \text{untrapped drug}}{\text{Total drug content}} \times 100$$

In vitro buoyancy

The floating ability of the prepared microspheres was determined using USP dissolution apparatus type II (paddle).

Floating microspheres were spread over the surface of dissolution medium which contains 900 ml of 0.1 N HCl and was agitated by a paddle rotated at 50 rpm for 12 h. After agitation for 12 h, the microspheres remained on the surface were collected with the help of pipette and then the microspheres settled at the bottom were collected. After drying of each fraction of microspheres, percentage buoyancy was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.^[10,19,20]

$$\% \text{ Buoyancy} = Q_f / (Q_f + Q_s)$$

Where Q_f and Q_s are the weight of the floating and the settled microspheres, respectively.

In vitro drug release study

The drug release study was carried out using USP dissolution apparatus type II (paddle) at 37 ± 0.5°C and at 50 rpm using 900 ml of 0.1 N HCl (pH 1.2) as a dissolution medium. 5 ml of sample solution was withdrawn at predetermined time intervals (1, 2, 4, 6, 8, 10, and 12 h) and simultaneously equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. The samples were diluted suitably and analyzed spectrophotometrically with UV-visible spectrophotometer at a wavelength of 272 nm. The dissolution studies were performed in triplicate, and the average percentage drug release was taken into consideration.^[21-23]

DE

DE was calculated based on the results of *in vitro* drug release. It is determined by the following equation:

$$\text{Dissolution efficiency} = \frac{\int_0^t Y \cdot dt}{Y_{100 \cdot t}} \times 100$$

The equation of DE can also be represented in the simple terms as follows:^[24,28,29]

$$\text{Dissolution efficiency} = \frac{\text{AUC}}{\text{Total area}} \times 100$$

Morphological studies

The surface morphology and surface characteristics of the best formulation were examined by scanning electron microscope (SEM). Microspheres were scanned and examined under electron microscope connected with fine coat, ion sputter. The sample was loaded on the copper sample holder and sputter coated with followed by gold.^[15] The surface morphology of microspheres explains about their floating ability and the mechanism of drug release.

RESULTS AND DISCUSSION

Formulation development of floating microspheres of CP

Floating microspheres of CP were successfully fabricated by solvent evaporation technique by applying 3² factorial design. All the nine possible experimental trials were successfully carried out according to the design layout and were further evaluated.

In vitro evaluation of floating microspheres of CP

Percentage yield

The floating microspheres were prepared, and percentage yield was calculated for all the formulations. The results of % yield are shown in Table 3. The percentage yield was in the range of 60-80% for all the formulations. The recovery of microspheres was high as there is an increase in the concentration of the polymers which are used in the formulation for controlling the release rate.

Particle size measurement

The particle size was measured using calibrated optical microscope, and the average particle size of floating microspheres was found to be in the range of 50-85 μm as shown in Table 3. As the concentration of polymer increases, the particle size also increases. This is because of the viscosity of the polymers used in the formulation. The higher the concentration of the polymer solution, the lower is the stirring efficiency. Due to this nature, the polymer rapidly precipitates and leads to hardening which in turn avoids further reduction in the particle size during solvent evaporation.

EE

The EE of floating microspheres of CP was calculated, and the results are depicted in Table 3. The EE was high at lower concentrations of the water-insoluble polymer ethyl cellulose. The EE was found to be in the range of 60-80% for all the formulations.

In vitro buoyancy

The percentage buoyancy was calculated for all the formulations and it was found that all the formulations were able to float on the dissolution medium (0.1 N HCl) over a period of 12-h. Even after 12 h of agitation of the dissolution medium, the microspheres continued to float without any apparent gelation. The high buoyancy of the microspheres is mainly due to the presence of pores and cavities which were formed during solvent evaporation. The percentage buoyancy was slightly decreased as the concentration of the polymers increased. This is because of the high viscosity of the polymer solution which in turn is the reason for the less formation of pores and cavities in microspheres during solvent evaporation. The results of *in vitro* buoyancy studies are shown in Table 3.

In vitro drug release study

Dissolution studies of all the nine formulations were carried out using USP dissolution apparatus type II (paddle).

Table 3: Observations of *in vitro* evaluation parameters of floating microspheres of cefditoren pivoxil

Formulation code	% Yield*	Particle size** (μm)	Entrapment efficiency*	% Buoyancy*
F1	58.2±1.7	53.2±1.8	68.3±1.3	88±2.1
F2	63.6±1.55	59.8±2.2	63.4±1.2	90±1.5
F3	65.5±1.82	69.1±2.5	59±0.9	91.2±1.9
F4	61±1.2	66.5±1.77	76±1.3	85.7±2.48
F5	67.2±1.62	71.8±0.94	73±1.1	90±2.23
F6	70±1.09	79.8±1.1	75±0.85	92±1.88
F7	66.76±1.23	63.8±1.92	80±1.6	85±1.42
F8	71.3±1.3	82.4±1.2	77.2±2.3	78.6±2.7
F9	72.1±1.46	83.7±1.6	72±1.5	76±2.31

*All values represent mean±SD; n=3, **All values represent mean±SD; n=100. SD: Standard deviation

The dissolution profiles were compared among different formulations. The results obtained in the *in vitro* drug release studies were plotted in five models of data treatment as follows.^[24]

- The amount of drug remained to be released versus time (h) – Zero order kinetics.
- Log amount of drug remained to be released versus time (h) – First order kinetics
- Higuchi's classical equation (Higuchi's matrix) in which cumulative amount of drug release was plotted against square root time.
- Hixson-Crowell equation, in which cube root of cumulative percentage drug retained was plotted against time (h).
- Korsmeyer–Peppas model, in which a graph was plotted by taking log time on X axis and log Mt/M (log fraction dissolved) on Y axis and it gives a straight line.

The cumulative percentage drug release was decreased with increase in the polymer concentration. Based on the results of *in vitro* drug release studies, it was found that F6 has shown sustained drug release for 12 h. The results of the *in vitro* drug release studies are shown in Table 4 and the dissolution profile in Figure 1. The *in vitro* release kinetics revealed that

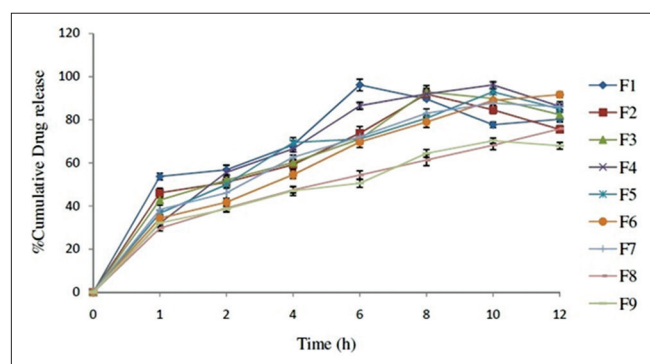


Figure 1: Dissolution profile of floating microspheres of cefditoren pivoxil

the optimized formulation (F6) release the drug in first order manner with non-Fickian diffusion mechanism based on the regression values of first order, Higuchi and Korsmeyer–Peppas model, respectively. Observed R^2 values, n values and the relative plots of the optimized formulation are shown in Table 5.

Experimental design

Floating microspheres of CP were successfully fabricated by solvent evaporation technique. 3 level 2 factor experimental design was applied to know the effect of formulation variables on prepared floating microspheres of CP. In the present investigation, the effect of total amount of polymer and the concentration of ethyl cellulose on % yield, particle size, EE and DE revealed wide variation as shown in Table 6. The data clearly indicates that the dependent variables are dependent on the independent variables. The fitted equation relating the response % yield, particle size, % EE and DE to the transformed factor are shown in the equations 2, 3, 4, and 5, respectively. The value of correlation coefficient indicates a good fit as shown in Table 7. The polynomial equation can be used to draw a conclusion after considering the magnitude of the coefficient and the mathematical sign it carries (+/-). To demonstrate the effect of the independent variables on the prepared floating microspheres, the response surface plots and contour plots were generated for the dependent variables using Design-Expert® 9 trial version software (Stat-Ease Inc., USA).

Effect of formulation variables on the dependent variables

Effect of formulation variables on % yield

The results of multiple linear regression analysis reveal that, on increasing the total amount of polymer (X_1), concentration of ethyl cellulose (X_2), an increase in the percentage yield was observed. In the equation b_1 and b_2 bears positive sign that

Table 4: *In vitro* drug release profile of floating microspheres of cefditoren pivoxil

Formulation code	Cumulative percentage of drug release*						
	Time (h)						
	1	2	4	6	8	10	12
F1	53.6±1.56	56.7±2.14	68.2±2.07	96.11±2.7	89.5±0.45	77.6±1.3	80.1±1.16
F2	46.9±2.21	50.8±2.56	59.1±2.10	73.7±3.11	91.8±2.71	84.5±1.67	75.4±1.49
F3	42.7±1.27	51.9±2.42	60.1±1.56	71.1±2.32	92.8±2.99	89.7±3.15	82.3±1.77
F4	32±1.86	55.4±1.31	66.4±1.48	86.4±1.65	91.9±1.97	96±1.58	86±1.24
F5	36.7±1.34	49.9±1.57	69.4±2.33	71.0±0.98	80.7±1.29	92.9±1.12	85±1.46
F6	34.2±1.5	41.7±1.16	54.9±1.82	69.6±2.55	78.8±2.47	88.9±0.87	91.5±1.35
F7	38.3±2.18	46.1±2.56	62.5±1.09	72±1.88	83±1.98	87.6±2.11	85.9±2.4
F8	29.7±1.23	39.0±1.71	47.4±1.52	54.3±2.01	61.2±2.54	68.2±2.18	75.7±1.47
F9	32.1±0.44	38.5±1.3	46.9±2.13	50.5±1.99	64.3±1.78	70.2±1.28	67.9±1.55

*All values represent mean±SD; (n=3). SD: Standard deviation

Table 5: Drug release kinetics of cefditoren pivoxil floating microspheres

Formulation code	Kinetic models				
	Zero order release (R^2)	First order release (R^2)	Higuchi (R^2)	Hixson-Crowell (R^2)	Korsmeyer–Peppas (n value)
F1	0.517	0.342	0.759	0.449	0.205
F2	0.660	0.626	0.863	0.676	0.265
F3	0.738	0.734	0.915	0.649	0.310
F4	0.741	0.774	0.921	0.802	0.413
F5	0.770	0.851	0.945	0.858	0.356
F6	0.888	0.986	0.992	0.978	0.469
F7	0.804	0.945	0.981	0.913	0.356
F8	0.853	0.959	0.965	0.934	0.360
F9	0.807	0.907	0.956	0.880	0.323

Table 6: Observed responses from 3^2 factorial design

Formulation code	Independent variables		Dependent variables			
	X_1	X_2	Y_1	Y_2	Y_3	Y_4
F1	-1	-1	58.2	53.2	68.3	65.2
F2	-1	0	63.6	59.8	63.4	61.1
F3	-1	1	65.5	69.1	59	58.3
F4	0	-1	61	66.5	76	63.8
F5	0	0	67.2	71.8	73	58.3
F6	0	1	70	79.8	75	55.5
F7	1	-1	66.76	63.8	80	56.9
F8	1	0	71.3	82.4	77.2	44.4
F9	1	1	72.1	83.7	72	44

X_1 =Total amount of polymer; X_2 =Concentration of ethyl cellulose;
 Y_1 =% yield; Y_2 =Particle size; Y_3 =% Entrapment efficiency;
 Y_4 =Dissolution efficiency

indicates when increasing the amount of polymer and polymer blend ratio, there is an increase in the % yield was observed and is pictorially represented by the response surface plots (A) and contour plots (B) in Figure 2. This suggests that as the concentration of polymer increases there is an increase in the viscosity which will play a major role in preventing the loss of hydrophilic polymers into the processing medium (PVA).

$$Y1 = 67.25 + 3.81X_1 - 3.61X_2 - 0.49X_1X_2 + 0.18X_1X_1 - 1.77X_2X_2 \quad (2)$$

Effect of formulation variables on particle size

The results of multiple linear regression analysis reveal that, on increasing the total amount of polymer (X_1), concentration of ethyl cellulose (X_2), an increase in the particle size was observed. In the equation, b_1 and b_2 bears positive sign that indicates when increasing the amount of polymer and polymer blend ratio there is an increase in the particle size was observed and is pictorially represented by the response surface plots (A) and contour plots (B) in Figure 3.

$$Y2 = 74.03 + 7.99X_1 + 8.20X_2 + 1.00X_1X_2 - 4.00X_1X_1 - 1.98X_2X_2 \quad (3)$$

Effect of formulation variables on EE

The results of multiple linear regression analysis reveal that, on increasing the total amount of polymer (X_1), an increase in the EE (Y_3) and increasing the concentration of ethyl cellulose (X_2), a decrease in the EE was found. In the equation, b_1 bears positive sign that indicates when increasing the amount of polymer there is an increase in the EE b_2 bears negative sign that indicates decrease in the EE which might be due to decrease in the concentration of HPMC K4M which is able to swollen gel that can entrap more amount of drug. The results are pictorially represented by the response surface plots (A) and contour plots (B) in Figure 4.

$$Y3 = 75.06 + 6.47X_1 - 3.38X_2 + 0.32X_1X_2 - 4.63X_1X_1 - 0.58X_2X_2 \quad (4)$$

Effect of formulation variables on DE

The results of multiple linear regression analysis reveal that, on increasing the total amount of polymer and the concentration of ethyl cellulose, a decrease in the DE was found. In the equation, b_1 and b_2 bears negative sign that indicates when increasing the amount of polymer (X_1) and increasing the concentration of ethyl cellulose (X_2) decrease in the DE was found and is pictorially represented by the response surface plots (A) and contour plots (B) in Figure 5.

$$Y4 = 57.1 - 6.55X_1 - 4.68X_2 - 1.50X_1X_2 - 4.22X_1X_1 + 2.68X_2X_2 \quad (5)$$

Morphological studies

The surface morphology of the floating microspheres was studied using SEM. The surface morphology of optimized formulation (F6) was studied; it was revealed that the microspheres were spherical in shape with a rough surface and porous in nature as shown in Figure 6.

Table 7: Regression coefficients for the responses

Parameters	Coefficients of regression parameters						R ² value	P value
	b ₀	b ₁	b ₂	b ₁₂	b ₁₁	b ₂₂		
% Yield	+67.25	+3.81	+3.61	-0.49	+0.18	-1.77	0.9863	0.0054
Particle size	+74.03	+7.99	+8.20	+1.00	-4.00	-1.98	0.9414	0.0456
% Entrapment efficiency	+75.06	+6.47	-3.38	+0.32	-4.63	-0.58	0.9689	0.0181
Dissolution efficiency	+57.1	-6.55	-4.68	-1.50	-4.22	+2.68	0.9732	0.0146

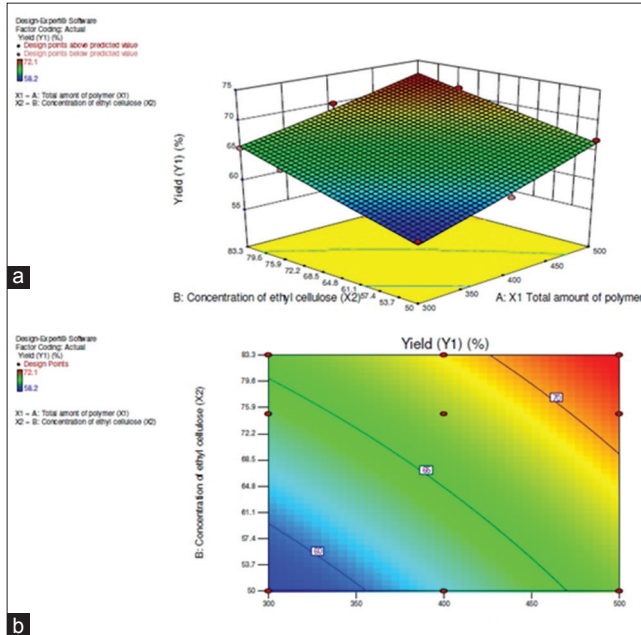


Figure 2: Response surface plots (A) and contour plots (B) showing effect of the total amount of polymer (X1) and concentration of ethyl cellulose (X2) on % yield (Y1)

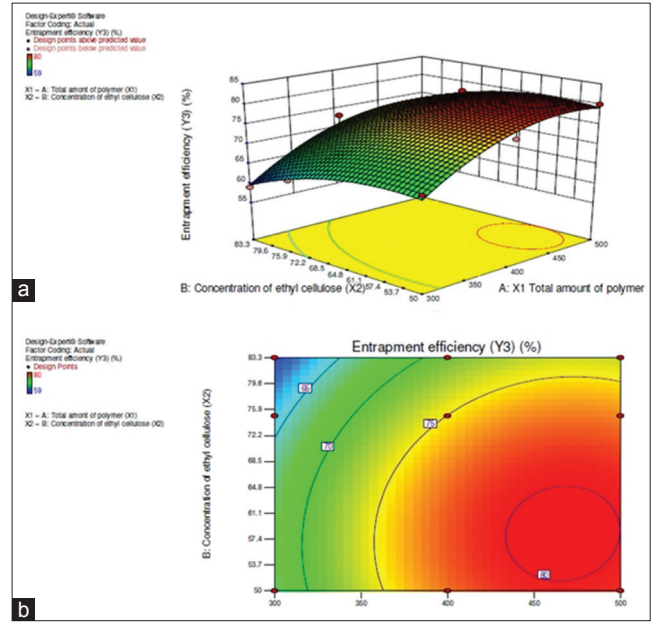


Figure 4: Response surface plots (A) and contour plots (B) showing effect of the total amount of polymer (X1) and concentration of ethyl cellulose (X2) on % entrapment efficiency (Y3)

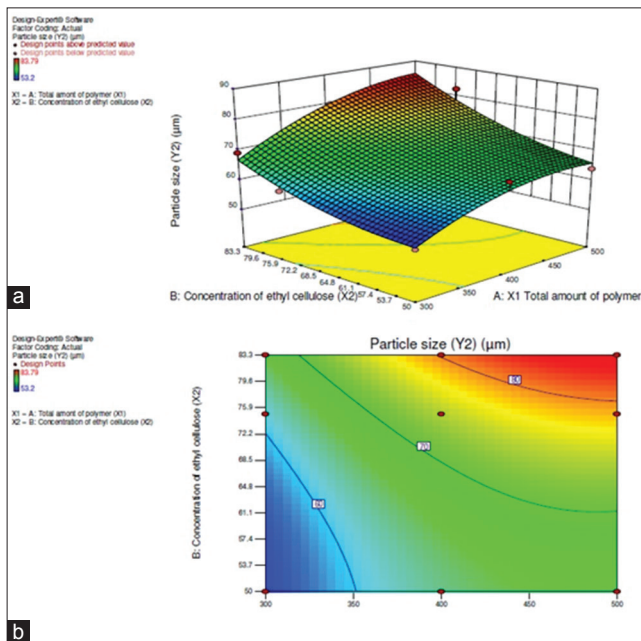


Figure 3: Response surface plots (A) and contour plots (B) showing effect of the total amount of polymer (X1) and concentration of ethyl cellulose (X2) on particle size (Y2)

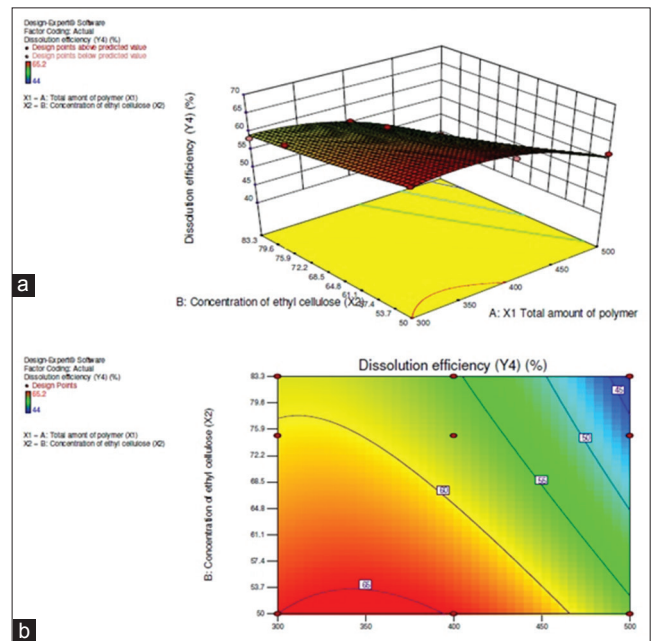


Figure 5: Response surface plots (A) and contour plots (B) showing effect of the total amount of polymer (X1) and concentration of ethyl cellulose (X2) on dissolution efficiency (Y4)

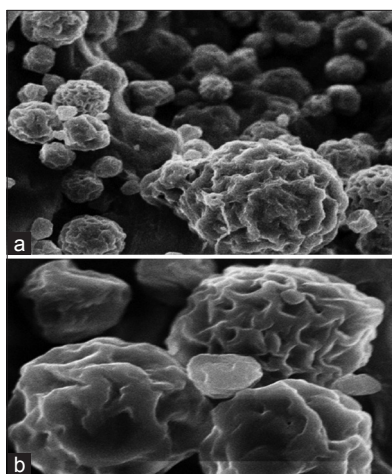


Figure 6: Scanning electron microscope images of formulation (F6) at different magnifications

CONCLUSION

Floating microspheres of CP were successfully prepared by solvent evaporation method using different ratios of HPMC K4M and ethyl cellulose as rate controlling polymers, by applying 3² factorial design. The prepared formulations were further evaluated and based on the results of *in vitro* evaluation studies F6 was chosen as the best formulation. To determine the effect of independent variables, response surface plots and contour plots were plotted, and the results of multiple linear regression analysis revealed that as the concentration of total amount of polymer and concentration of ethyl cellulose is increased, % yield, particle size and EE were increased and DE was decreased. The release kinetics revealed that the drug release from the floating microspheres of CP followed first order non-Fickian diffusion. Hence, the objective of the current research work has been achieved.

ACKNOWLEDGMENTS

The satisfaction that accomplished the successful completion of any task would be incomplete without the mention of the people who made it possible and whose constant guidance and encouragement crown all the effects with success. We would like to acknowledge Cadila Pharmaceuticals Limited, Ahmedabad for providing the gift sample of CP. We are grateful to Colorcon Pvt Ltd., for providing the gift sample of HPMC K4M, Ethyl Cellulose used in the study. We would also like to acknowledge the support of management of Janagaon Institute of Pharmaceutical Sciences for providing the required facilities for successful completion of the project.

REFERENCES

- Chien YW. Concepts and System Design for Rate-Controlled Drug Delivery in Novel Drug Delivery Systems. 2nd ed. New York: Marcel Dekker Inc.; 1992. p. 1-42.
- Soppimath KS, Kulkarni AR, Aminabhavi TM. Development of hollow microspheres as floating controlled-release systems for cardiovascular drugs: Preparation and release characteristics. *Drug Dev Ind Pharm* 2001;27:507-15.
- Aulton ME. *Pharmaceutics: The Science of Dosage form Design*. International Student Edition. London: Churchill Livingstone; 2002. p. 206-11.
- Ramachandran S, Shaheedha SM, Thirumurugan G, Dhanaraju MD. Floating controlled drug delivery system of famotidine loaded hollow microspheres (microballoons) in the stomach. *Curr Drug Deliv* 2010;7:93-7.
- Moës AJ. Gastroretentive dosage forms. *Crit Rev Ther Drug Carrier Syst* 1993;10:143-95.
- Deshpande AA, Rhodes CT, Shah NH, Malick AW. Drug delivery systems for prolonged gastric residence: An overview. *Drug Dev Ind Pharm* 1996;22:531-9.
- Chiao CS, Robinson JR. Sustained release drug delivery systems. In: Longor MA, Robinson JR, editors. *Remington: The Science and Practice of Industrial Pharmacy*. 19th ed., Vol. II. Eastern Pennsylvania: Mack Publication Company. 1995. p. 1660-75.
- Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review. *AAPS PharmSciTech* 2005;6:E372-90.
- Narang N. An updated review on: Floaiting drug delivery system. *Int J Appl Sci* 2011;3:1-7.
- Taneja R, Kataria MK, Bilandi A, Gupta A, Gedar S. Floating microsphere: A potential gastro-retentive drug delivery system. *Pharmacy Globale. Int J Compr Pharm* 2013;4:1-9.
- Mastiholimath VS, Dandagi PM, Gadad AP, Mathews R, Kulkarni AR. *In vitro* and *in vivo* evaluation of ranitidine hydrochloride ethyl cellulose floating microparticles. *J Microencapsul* 2008;25:307-14.
- Rakesh PP, Jagrut HD, Ajay MS. Formulation development and optimization of cefditoren pivoxil dispersible tablet. *Int J Pharm Pharm Sci* 2010; 2:20-5.
- Joshi VK, Jaimini M. Microballoons for drug delivery: A review. *Asian J Pharm Res Dev* 2013;1:7-17.
- Patel T, Vasava K, Patel P, Rajesh KS, Lalit JL. A factorial design approach for optimization of floating microspheres of cephalixin. *Pharmagene* 2013;1:33-8.
- Gattani YS, Bhagwat DA, Maske AP. Formulation and evaluation of intragastric floating drug delivery system of diltiazem hydrochloride. *Asian J Pharm* 2008;2:28-31.
- Gadad A, Chirag N, Patel K, Dandagi P, Vinayak M. Formulation and evaluation of floating microspheres of captopril for prolonged gastric residence time. *Indian J Novel Drug Deliv* 2011;3:17-23.
- Josephine LJ, Mehul RT, Wilson B, Shanaz B, Bincy R. Formulation and *in vitro* evaluation of floating

- microspheres of anti-retro viral drug as a gastro retentive dosage form. *Int J Res Pharm Chem* 2011;1:519-27.
18. Dhanaraju MD, Bhaskar K, Vamsadhara C. A multiple emulsion method to entrap hydrophilic compound in to ethyl cellulose microspheres. *Indian Drugs* 2003;40:99-100.
 19. Murty SB, Wei Q, Thanoo BC, Deluca PP. *In vivo* release kinetics of ocreotide acetate from experimental polymeric microsphere formulations using oil/water and oil/oil processes. *AAPS PharmSciTech* 2004;5:90-9.
 20. Srivastava AK, Ridhurkar DN, Wadhwa S. Floating microspheres of cimetidine: Formulation, characterization and *in vitro* evaluation. *Acta Pharm* 2005;55:277-85.
 21. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resins containing tranilast and their drug release characteristics (*in vivo*). *J Control Release* 1991;16:279-90.
 22. Gohel MC, Amin AF. Studies in preparation of diclofenac sodium microspheres by solvent evaporation technique using response surface analysis. *Indian J Pharm Sci* 1999;61:48-53.
 23. Mehta PR, Gohel MC, Dave RK, Bariya NH. A more relevant dissolution method for evaluation of floating drug delivery system. *Dissolution Technol* 2004;11:22-5.
 24. Dhoka MV, Pande AV, Vaidya PD, Arora A. *In vitro* and *in vivo* evaluation of ethyl cellulose based floating microspheres of cefpodoxime proxetil. *Int J Pharm Biomed Res* 2010;1:122-8.
 25. Nagabandi VK, Bandari S, Jukanti R. *Experimental Approaches to Biopharmaceutics and Pharmacokinetics*. Hyderabad: PharmaMed Press; 2013. p. 94-9.
 26. Bhupesh D, Sanjay K, Deepashri S. A comparative evaluation of cefditoren pivoxel and rabeprazole in the treatment of gastritis and peptic ulcer: A double-blind, randomized study in Indian patients. *Br J Med Med Res* 2013;3:1187-98.
 27. Kamila MM, Mondal N, Gosh LK, Gupta BK. Multiunit floating drug delivery system of rosiglitazone maleate: Development, characterization, statistical optimization of drug release and *in vivo* evaluation. *AAPS PharmSciTech* 2009;10:887-99.
 28. Kazuro I, Tomohiko S, Seiichi H, Norifumi M, Susumu T. Pharmacokinetic and pharmacodynamic properties of cefditoren pivoxel after postprandial oral administration in healthy subjects: Comparison with famotidine. *Biol Pharm Bull* 2007;30:1003-6.
 29. Mohit S, Mehta T, Avani A. Preparation and characterization of inclusion complex of a calcium channel blocker. *Int J Res Pharm Biomed Sci* 2011;2:1731-8.
 30. Pandey M, Singh B, Kanoujia J, Saraf SA. Formulation and evaluation of floating microspheres of famotidine. *Int J Pharm Tech Res* 2010;2:1415-20.
 31. Patil SH, Talele GS. Formulation development and *in vitro* and *in vivo* evaluation of gastroretentive floating drug delivery system of cefditoren pivoxel. *Asian J Pharm* 2013;7:68-74.
 32. Patnaik A, Mantry S. Formulation and evaluation of gastroretentive floating microsphere of cinnarizine. *Asian J Pharm Clin Res* 2012;5:100-9.
 33. Davis SS. Formulation strategies for absorption windows. *Drug Discov Today* 2005;10:249-57.

Source of Support: Nil. **Conflict of Interest:** None declared.