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“Design and Development of Carvedilol Phosphate Floating Microsphere.”

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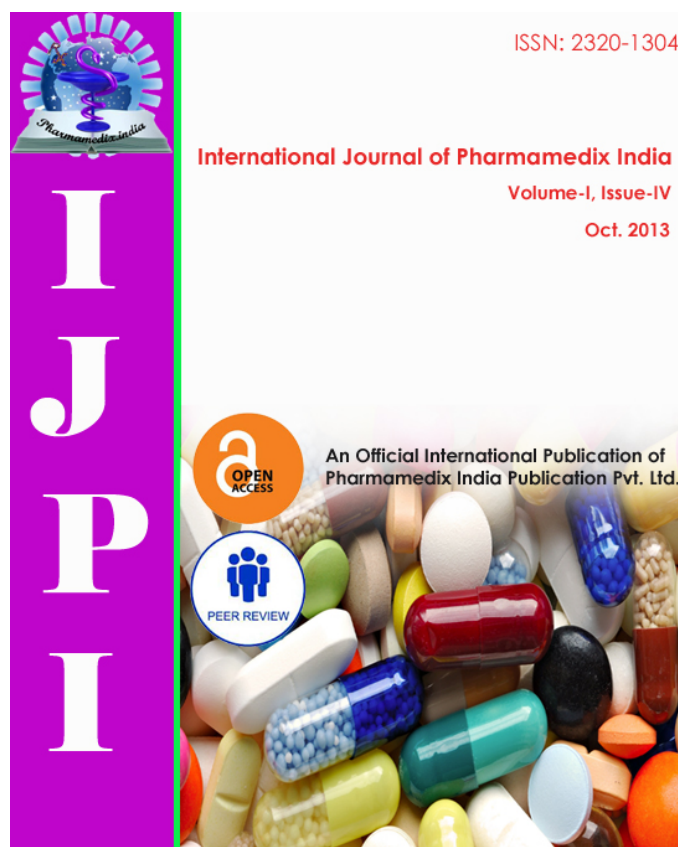
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Abstract:

Objective of present investigation was to develop carvedilol phosphate floating microsphere for retention in the upper part of the GIT to improve the dissolution where the solubility of carvedilol phosphate is more in acidic medium. Floating Microspheres were prepared by emulsion solvent diffusion method using ethylcellulose and eudragit RS 100 as polymer and 0.5% w/v polyvinyl alcohol as external medium. 3^2 full factorial design was used for optimizing the drug: polymer ratio(X1) and ethylcellulose: eudragit RS 100(X2) ratio were selected as independent variables, evaluated for various parameters which were analysed using ANOVA and surface response methodology. Batch F5 was selected as optimized, as provides desired zero order release profile as well as 77.25% buoyancy and 80.66% entrapment efficiency, 82.9% yield and mean particle size of 133.86 μm and spherical microsphere obtained confirmed by SEM study. Drug and excipients are compactible to each other was confirmed by FTIR study.

Keyword: Gastroretentive drug delivery systems, Factorial Design, Multiparticulate System, Surface Response.

Introduction

It is an established fact that the conventional immediate release drug delivery systems when taken frequently in a day can maintain drug concentration levels in therapeutically effective range but these results in significant fluctuations in plasma drug levels. Till date, remedies have been found for most of the diseases; but still research is going on in order to improve the existing therapy by use of “Novel Drug Delivery Systems” with improved bioavailability.^[1] Carvedilol has unique pharmacological profile. It blocks β_1 , β_2 , and α_1 receptors, used in the management

of hypertension and as an adjunct to standard therapy in symptomatic heart failure and also produces vasodilation^[2].

Drug molecules presenting no difficulties in their solubility and/or absorption problems are good candidates for oral controlled release formulations but Obstacle may arise for many drugs related to their solubility and/or absorption that may be overcome by formulating Gastroretentive systems which prolong the gastric retention time, improves solubility and hence improves bioavailability for drugs that are less soluble in a high pH environment^[3].

Carvedilol is given in multiple doses due to its half-life ranging from 4–7 h. The daily dose may range from 6.25mg-50mg, also the fluctuations of drug concentration in the plasma is drawback of conventional dosage form. Another problem with respect to carvedilol is its poor solubility and it has stability-related issues. Carvedilol phosphate is a crystalline salt form with slightly more solubility and chemical stability than carvedilol; hence a controlled release formulation is desirable which reduce patients' dosing regimen, improve patient compliance, improve dissolution and hence bioavailability ^[4]. Carvedilol phosphate exhibits typical solubility behaviour in neutral or alkaline media that is, the solubility is maximum at pH 3 in the upper part of the gastrointestinal tract ^[5]. Due to its pH-dependent solubility, it is necessary to improve the concentration of the drug in the stomach so as to improve its absorption there which makes Carvedilol phosphate, a suitable candidate for GRDDS. Steady-state plasma concentration range of carvedilol is 22-160 ng/ml. ^[6]

Materials

Carvedilol phosphate was a gift sample from Cadila Healthcare Limited, Ahmedabad, India. Eudragit RS 100 was provided by Degussa India (Mumbai), Ethylcellulose (EC) from Colorcon Asia Pvt. Ltd., Goa and polyvinyl alcohol was purchased from S. D. Fine Chemicals Ltd., Mumbai, India. All

other chemicals, such As Methanol and dichloromethane were of analytical grade.

Method of Preparation

The Floating microspheres were prepared by emulsion solvent diffusion method. Polymers of different concentrations were dissolved in a mixture of 20 ml of methanol and dichloromethane at 1:1 ratio. The drug carvedilol phosphate was added in the polymer solution with constant stirring to get a uniform mixing. Water containing 0.5% w/v polyvinyl alcohol as surfactant was an aqueous phase. The polymeric solution was added drop wise with help of syringe in 150 ml external phase containing 0.5% w/v, polyvinyl alcohol and the mixture was continuously stirred at 800 rpm at room temperature for 3 hours. The formed microspheres were filtered using Whatmann filter paper and washed twice with distilled water. Finally the filtered microspheres were dried at room temperature for 24 hour. ^[7]

Experimental design

A 3² full factorial design was used in the present study for optimization of the formulation. In this design, two factors were evaluated, each at three levels, and experimental trials were performed at all nine possible combinations. The Drug : polymer ratio (X1) and ethylcellulose : eudragit[®] RS 100 ratio (X2) were chosen as independent variables in 3² full factorial design, % drug loading, Drug entrapment efficiency, Buoyancy (%) was taken as dependent

variables. The statistical analysis of the factorial batches was performed by multiple regression analysis using Microsoft Excel[®]2013. To demonstrate graphically the influence of each factor on response, the response surface plots was generated using Statistica software 10.0 (Stat soft. Inc, USA). The details of the design are shown in Table 1(a) and Table 1 (b).

Table 1(a): Selection of levels for independent variables

Coded value	Drug : Polymer ratio	Ethocel : Eudragit [®] RS 100
-1	1:3	3:1
0	1:4	1:1
1	1:5	1:3

Table 1(b): Design Layout of 3² factorial batches.

Batch Code	Coded Value		Actual value	
	Drug : polymer ratio	Ethyl-cellulose: Eudragit [®] RS 100	Drug : polymer ratio	Ethylcellulose: Eudragit [®] RS 100
F1	-1	-1	1:3	75:25
F2	0	-1	1:4	75:25
F3	1	-1	1:5	75:25
F4	-1	0	1:3	50:50
F5	0	0	1:4	50:50
F6	1	0	1:5	50:50
F7	-1	1	1:3	25:75
F8	0	1	1:4	25:75

F9	1	1	1:5	25:75
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Evaluation of microspheres

% yield

The percentage yields were calculated as per the formula mentioned below^[8].

% yield

$$= \frac{\text{Total weight of microsphere} \times 100}{\text{Total weight of drug and polymer}}$$

Determination of mean particle size

The particle size was measured using an optical microscope, and the mean particle size was calculated by measuring 300 particles with the help of a calibrated ocular micrometer. The slide containing microspheres was mounted on the stage of the microscope and diameter of at least 300 particles was measured using a calibrated optical micrometer^[9].

% drug loading

To determine the % drug loading, 20 mg microspheres were accurately weighed, thoroughly triturated and dissolved in minimum amount of methanol and sonicated for 10 minute. The resulting solution was made up to 100 ml with 0.1 N HCl and then filtered using whatmann paper. Drug content was analyzed spectrophotometrically at 241 nm. The percentage drug loading were calculated using equation given below^[9].

% drug loading

$$= \frac{\text{Actual drug present} \times 100}{\text{weight of microsphere taken (g)}}$$

Entrapment Efficiency: The weighed amount of microspheres containing 20 mg equivalent of drug were crushed in a glass mortar and dissolved in minimum amount of methanol and sonicated for 10 minute. The resulting solution was made up to 100 ml with 0.1 N HCl and filtered using whatmann paper and analyzed spectrophotometrically at 241 nm Entrapment Efficiency calculated using equation given below [9].

Entrapment Efficiency

$$= \frac{\text{Actual drug content} \times 100}{\text{Theoretical drug content}}$$

% Buoyancy

Floating behavior of hollow microspheres was studied using a USP dissolution test apparatus II. The microspheres (50 mg) was spread on 900 mL of 0.1 M HCl containing 0.02% Tween 80 as surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 h, both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed and the percentage of floating microspheres was calculated using equation given below^[9].

$$\% \text{ Buoyancy} = \frac{W_f \times 100}{W_f + W_s}$$

Where, W_f and W_s are the weights of the floating and settled microspheres.

Micromeritic Properties^[10]

The optimized formulation was also characterized by their micromeritic properties, such as true density, tapped density, compressibility index and flow properties.

The tapped density and percent compressibility index of the microparticles was measured by a tapping method. Angle of repose (θ) of the microparticles, which measures the resistance to particle flow, was determined by a fixed funnel method and all parameters calculated using following equation.

Bulk density

$$= \frac{\text{Mass of microsphere}}{\text{Volume of microsphere before tapping}}$$

Tapped density

$$= \frac{\text{Mass of microsphere}}{\text{Volume of microsphere after tapping}}$$

$$\text{Husner's ratio} = \frac{\text{Tapped density}}{\text{bulk density}}$$

Carr's index

$$= \frac{(\text{Tapped density} - \text{Bulk density}) \times 100}{\text{Tapped density}}$$

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where, h = Height of the powder cone and r = Radius of powder cone.

In-vitro drug release study

The *In-vitro* drug release study of floating microspheres was carried out using the USP type II Dissolution test apparatus. microspheres equivalent to 25 mg of Carvedilol phosphate were taken and filled in capsule (size No. 0) and subjected to dissolution test in dissolution media containing 900 ml of 0.1N HCl (pH 1.2) maintained at $37 \pm 0.5^\circ\text{C}$ and rotated at 50 rpm. 5 ml sample was withdrawn at

predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. Samples were suitably diluted with 0.1 N HCl and analysed double beam using Spectrophotometer at 241 nm to determine the concentration of drug present in the dissolution medium.

Scanning Electron Microscopy and Morphology Characterisation

The surface morphology and internal texture of the microspheres were studied by scanning electron microscopy. Scanning Electron Microscope XL 30 ESEM (Philips, Netherlands) Acceleration voltage set at 3 kV at Magnification level 23x, 45x, 90x. The samples were then randomly scanned and microphotographs were taken on different magnification. Then morphological characteristics of microspheres were determined from photograph of SEM ^[11].

Drug polymer interaction study

Fourier transform infrared spectroscopy has been used to study the physical and chemical interactions between drug and the excipients used. Fourier transform infrared (FTIR) spectra of Carvedilol phosphate, and carvedilol phosphate loaded microsphere was recorded using KBr mixing method on FTIR-8400S, Shimadzu, and Kyoto, Japan ^[11].

Analysis for residual solvent in the formulation

Residual solvent analysis was carried out by headspace gas chromatography using the

instrument gas chromatograph (Clarus 500). The mobile phase was nitrogen gas with RTX-5 capillary column (30 mm × 0.53 mm) at a temperature of 170°C for column and 230°C for flame ionization detector. Sample inserted in the sample compartment and then the analysis run and chromatogram obtained was compared with that of reference chromatogram and the amount of residual solvent present in the formulation was calculated ^[12,13].

Release kinetics and statistical analysis

The drug released data of all batches were fitted with desired kinetic model such as Zero order kinetic, First order kinetic, Higuchi model and Korsemeyer peppas model to ascertain the drug release. The Zero order and First order drug release explain the drug release depend on drug concentration or not. The Korsemeyer peppas model described the method of drug release and Higuchi model described the diffusional drug release ^[14,15].

Result & discussion

Drug excipient compatibility study

After the interpretation of FT-IR spectra, from the figure 1, it can be concluded that major peaks of pure drug were preserved in the drug with individual excipients. In this interpretation the peaks due to -OH Stretching, -C-H stretching (aromatic), -C-O-C Stretching, -N-H aromatic, -N-H 2° amine which contribute to the main functional groups of the drug have been taken into

consideration. The peaks appearing at 3346, 3061, 1504, 1257, 1215, and 1176 cm^{-1} for carvedilol are also appearing in the carvedilol

-loaded microspheres, indicating the chemical stability of carvedilol in all cases, concluding that there was no evident chemical interaction [13].

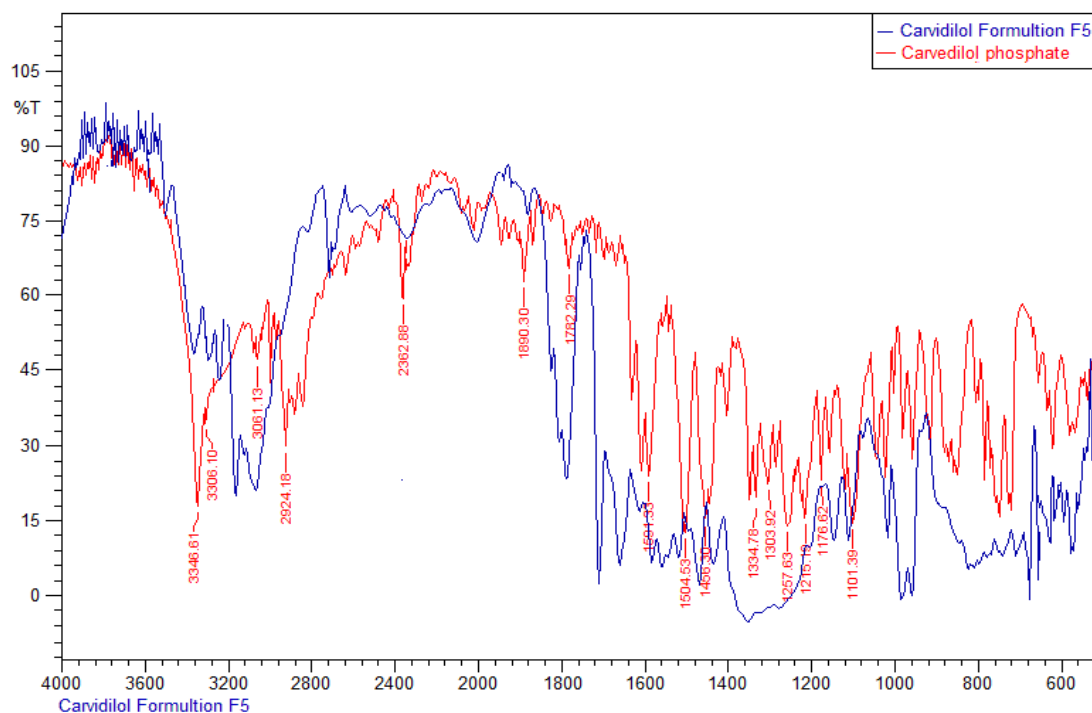


Figure 1: FTIR spectra of pure carvedilol phosphate and formulation F5

Micromeritic properties of floating microspheres

The values of Carr's index and the angle of repose indicate excellent flow properties. Obviously the density values of the floating microspheres ($<1.000 \text{ g/cm}^3$) were less than that of the gastric fluid ($\sim 1.004 \text{ g/cm}^3$), thereby, implying that these microcapsules will exhibit an excellent buoyancy effect in vivo. Also, Hausner's ratio found 1.13-1.20 that indicates greater cohesion between particles. Thus, it is an added advantage while processing the formulation using high-speed packaging equipments.

Table 2: Results of micromeritic evaluation of optimized batch F5

Batch code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)	Angle of repose(θ)
F5	0.449	0.53	1.18	15.28	24.85

Table 3: Results of F1-F9 batch for various parameters

Batch code	% Yield	%Buoyancy	Particle size (µm)	Drug loading (%)	Entrapment efficiency (%)
F1	80.62	80.17	152.9	19.13	76.54
F2	88	82.69	161.46	15.6	78.09
F3	86.66	83.02	168.3	13.21	79.38
F4	79.37	73.91	162.84	19.30	77.22
F5	82.97	77.25	133.86	16.13	80.66
F6	81.66	79.46	154.56	14.41	86.59
F7	76.87	71.32	132.48	20.24	80.99
F8	78.66	74.99	139.3	16.73	83.66
F9	78.88	78.21	131.11	14.67	88.13

Particle Size, Yield, Buoyancy, Drug Loading and Entrapment Efficiency

The mean particle size of the microspheres found in the range of 168.3-131.11 µm. Although stirring speed directly affects the particle size, it was noted that particle size increased with the increasing ethylcellulose concentration and a minor decrease in the particle size observed in the batches prepared using higher amount of eudragit RS 100. The yield of the resulting microspheres increased with increasing concentration of ethylcellulose (batch F1-F3) and slight decrease in the %yield observed with increase in the concentration of eudragit RS 100. The drug loading of microspheres varied from 13.21% to 20.24% and the drug entrapment efficiency of microspheres varied from 76.53% to 88.13%, Results demonstrated that as the drug: polymer ratio increases, there is decrease in drug loading of the microspheres

was noted. It was noted that entrapment efficiency is not significantly affected by Drug: Polymer ratio but affected by the ethylcellulose: eudragit RS 100 ratio and concluded that eudragit RS 100 is more efficient polymer for encapsulating the drug in the microsphere. The microspheres containing more ethylcellulose compared to eudragit RS 100 showed good floating ability and conclusion made that ethylcellulose being insoluble and unswellable remained floated, whereas eudragit RS100 swelled and eroded with time. The results also showed a tendency that larger the particle size more the buoyancy.

In-vitro drug release study

From the results of the dissolution study as shown in figure 2, Important conclusion drawn that Drug present on the surface was responsible for the 'burst effect' or 'burst

release' in initial time or at first hour after administration of dosage form. As Drug: Polymer ratio increases, further retardation in drug release observed. Another observation made is that when concentration of eudragit RS 100 among two polymer increases then more release of drug observed (F7-F9) compared to those batches containing less amount of eudragit RS 100 (F1-F3). Moreover, from the results it is also clear that no burst effect was seen and drug release was significantly sustained. It was observed that as the concentration of ethylcellulose increased, percentage cumulative release of carvedilol phosphate from microsphere decreased and as the concentration of eudragit RS 100 increases in formulation, increase in the %cumulative release observed. Among nine batches, batch F5 was selected as optimized batch after calculating the similarity factor for dissolution test and compared to theoretical profile required for sustained release dosage forms.

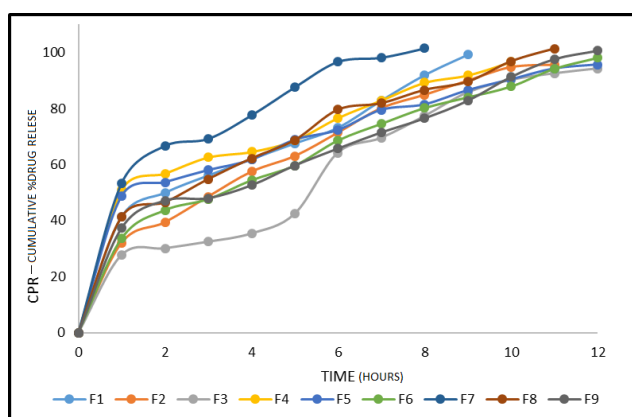


Figure 2: In-vitro drug release profile of F1-F9 batches

Residual solvent Analysis

Amount of methanol and dichloromethane

from Quantification report of the headspace GC analysis for microsphere batch F5 was found to be 0.00064% and 0.00008% respectively. As the dose of carvedilol phosphate is 25 mg once or twice in a day, maximum 310 mg of microsphere need to be administered per day that contains 0.0001984 mg methanol and 0.0000248 mg of dichloromethane that indicates sample complies with the limit of class 2 solvents as per ICH guideline. Hence, the solvent diffusion method was efficient in complete removal of solvent from microsphere well below permissible levels.^[12]

Scanning Electron Microscopy and Morphology Characterization:

Spherical microspheres formed during the solvent diffusion process could be evidently seen from photographs of SEM (figure 3). Inward dents were seen on the surface, probably due to collapse of the walls of the microspheres during the in situ drying process. Thus, removal of the solvent from the embryonic microspheres influences the morphology of the product. The microspheres were rough and grossly spherical and slightly aggregated and shows few pores on surface, due to the rapid escape of the volatile solvents during formulation. Very less particulate matter of the drug and polymer were seen on the surface of the microspheres, indicating uniform distribution of the drug in the polymeric network.

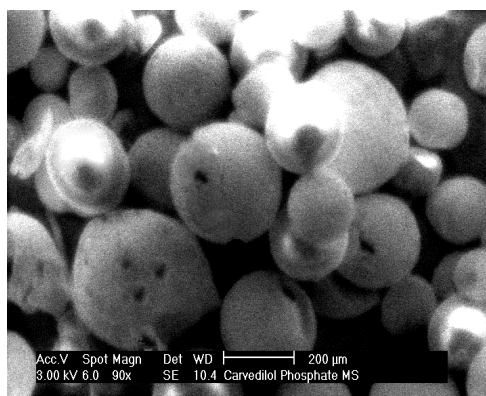


Figure 3: Scanning electron photomicrograph of drug-loaded microsphere (magnification, ×90 times)

Statistical Analysis for drug loading

$$Y = 16.17019249 - 2.730131504 (X_1) + 0.614636935 (X_2) + 0.0857639 (X_{12}) + 0.6718246 (X_1)^2 - 0.0142938 (X_2)^2 \dots\dots\dots(1)$$

Equation 1 is full model equation for drug loading in microsphere. The significance levels of the coefficients b_{12} and b_{22} were found to be $P=0.599$ and 0.949 respectively so they were omitted from the full model to generate a reduced model. The coefficients b_1 , b_2 and b_{11} were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_1 , b_2 and b_{11} contribute significance information to the prediction of drug loading. The critical value of F for $\alpha = 0.05$ is equal to 9.55 ($df=2, 3$). Since the calculated value ($F=0.173$) is less than critical value ($F=9.55$), it may be concluded that the interaction term b_{12} and b_{22} do not contribute significantly to the prediction of drug loading and can be omitted from the full model to generate the reduced model. As shown in figure 4, from the surface plot of %drug

loading, it can be concluded that as X_1 (drug: polymer ratio) increases, %drug loading decreases and as X_2 (EC: Eudragit RS 100 ratio) increases i.e. as amount of EC compared to Eudragit RS increases then %drug loading also increases in microsphere.

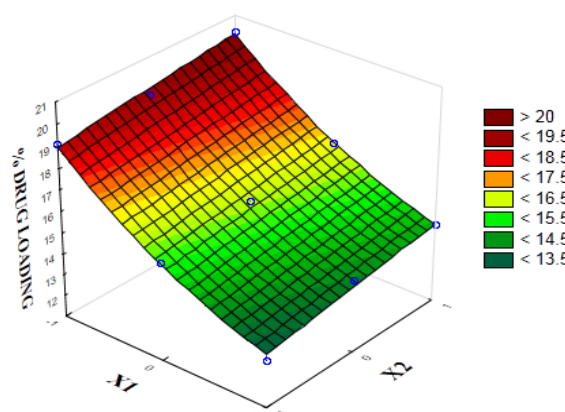


Figure 4: Surface Plot of %Drug Loading

Statistical Analysis for Entrapment efficiency

$$Y = 81.04211771 + 3.22416756 (X_1) + 3.13181964 (X_2) + 1.0742303 (X_{12}) + 0.6712802 (X_1)^2 - 0.35829139 (X_2)^2 \dots\dots\dots(2)$$

Equation 2 is full model equation for entrapment efficiency in microsphere. The significance levels of the coefficients b_{12} , b_{11} and b_{22} were found to be $P= 0.256$, 0.580 and 0.763 respectively (Table 5.20), so they were omitted from the full model to generate a reduced model. The coefficients b_1 and b_2 were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_1 and b_2 contribute significance information to the prediction of Entrapment efficiency. The

critical value of F for $\alpha = 0.05$ is equal to 9.27 (df=3, 3). Since the calculated value ($F = 0.8167$) is less than critical value ($F = 9.27$), it may be concluded that the interaction term b_1 , b_{12} , b_{13} and b_{23} do not contribute significantly to the prediction of entrapment efficiency and can be omitted from the full model to generate the reduced model.

As shown in figure 5, the surface plot of entrapment efficiency it can be concluded that as X_1 (drug: polymer ratio) increases, entrapment efficiency increases and as X_2 (ethylcellulose: eudragit RS 100 ratio) increases i.e. as amount of ethylcellulose compared to Eudragit RS increases then entrapment efficiency also increases.

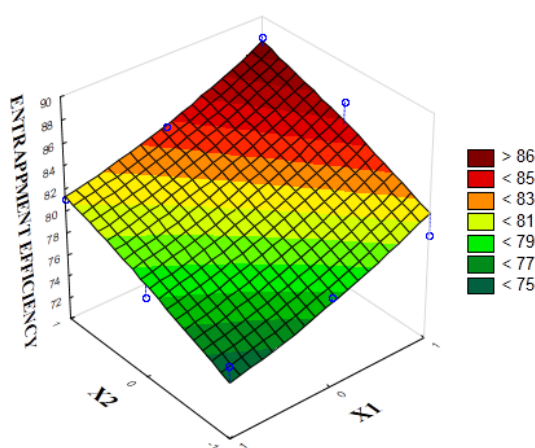


Figure 5: Surface Plot of Entrapment Efficiency

Statistical Analysis for %Buoyancy

$$Y = 77.29357685 + 2.54906682 (X_1) - 3.560756648 (X_2) + 1.012193747 (X_{12}) - 0.630187049 (X_1)^2 + 1.528138132 (X_2)^2 \dots\dots\dots(3)$$

Equation 3 is full model equation for Buoyancy in microsphere. The significance

levels of the coefficient b_{11} was found to be $P = 0.0958$ (Table 5.19), so it was omitted from the full model to generate a reduced model. The coefficients b_1 , b_2 , b_{12} and b_{22} were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_1 , b_2 , b_{12} and b_{22} contribute significance information to the prediction of %Buoyancy. The critical value of F for $\alpha = 0.05$ is equal to 10.12 (df=1, 3). Since the calculated value ($F = 5.76$) is less than critical value ($F = 10.12$), it may be concluded that the interaction term b_{11} do not contribute significantly to the prediction of %Buoyancy and can be omitted from the full model to generate the reduced model. As shown in figure 6, From the %Buoyancy surface plot it can be concluded that as X_1 (drug: polymer ratio) increases buoyancy also increases but as X_2 (EC: Eudragit RS 100 ratio) increases i.e. amount of EC compared to Eudragit RS 100 decreases then buoyancy also decreases.

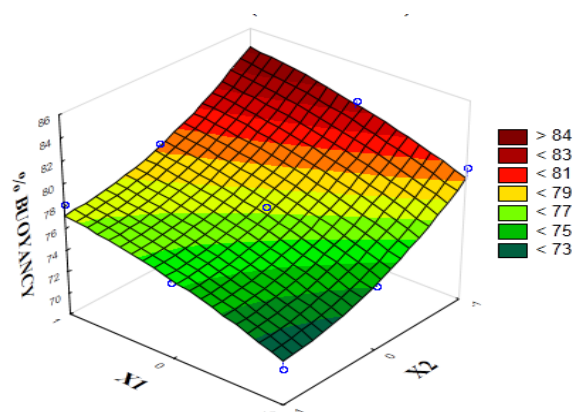


Figure 6: Surface Plot of %Buoyancy

Table 4: Result ANOVA for factorial design batches

% Drug Loading						
	DF	SS	MS	F	R ²	Significance F
Regression				111.3342	0.99464	
FM	5	47.92087	9.584175	277.0662	0.99402	0.00132612
RM	3	47.89104	15.96368			5.6202E-06
Error						
FM	3	0.288084	0.086085			
RM	5	0.258254	0.057617			
Entrapment efficiency						
	DF	SS	MS	F	R ²	Significance F
Regression						
FM	5	126.9952	25.39903	10.77844	0.92937	0.039180557
RM	2	121.2213	60.61065	28.31555	0.75227	0.000879192
Error						
FM	3	7.069397	2.356466			
RM	6	12.84326	2.140543			
%Buoyancy						
	DF	SS	MS	F	R ²	Significance F
Regression						
FM	5	124.6232	24.92461	0.000644	0.99669	0.000643733
RM	4	123.8289	30.95723	102.5288	0.99034	0.000278095
Error						
FM	3	0.413477	0.137825			
RM	4	1.207748	0.301937			
DF=Degree of freedom, SS=Sum of square, MS=Mean square, R ² =Square of correlation coefficient,						

Table 5: Result of regression analysis of factorial design batches

% Drug Loading						
Response	b0	b1	b2	b12	b11	b22
FM	16.17019	-2.7301	0.61463	0.0857*	0.671812	-0.0142*
RM	16.16066	-2.7301	0.61463	-	0.67181	-
Entrapment efficiency						
Response	b0	b1	b2	b12	b11	b22
FM	81.04217	3.22416	3.13181	1.07423	0.67128*	-0.3589*
RM	81.25084	3.22416	3.13182	-	-	-
% Buoyancy						
Response	b0	b1	b2	b12	b11	b22
FM	77.29358	2.54906	-3.5607	1.01219	-0.6301*	1.528138
RM	76.87345	2.54906	-3.5607	1.01219	-	1.528138
*indicates p value >0.05 and it is insignificant, FM= full model, RM= reduced model, b0= constant, b1, b2, b12, b11, b22 are the coefficient of the variables and their interaction.						

Drug Release Mechanism from microsphere

The value of diffusion exponent n for F1 to F9 factorial formulations was between 0.286-0.493 i.e. $n < 0.5$ indicating fickian diffusion of drug from the formulations. All the formulations were found to follow zero-order release kinetics. Kinetic Model Higuchi indicating that R^2 value of F1 to F9 was between 0.996 to 0.995, Shown that drug release type was diffusion type from matrix of

the polymer and extends drug release for longer period of time. Kinetic Model Zero order indicating that R^2 value of F1 to F9 was between 0.936 to 0.996 that is near about 1.000, clearly mentioned that drug release from microsphere was Zero order drug release that not depend on concentration of drug ^[16].

Conclusion

Formulation F5 prepared with 1:4 drug: polymer ratio and EC: Eudragit RS 100(50:50) found to be the optimized as

microspheres exhibited good encapsulation efficiencies, excellent floating and micromeritic properties for formulating as single-unit dosage forms like microsphere filled hard gelatin capsule. The microspheres having lower densities thus microspheres of carvedilol phosphate can be used for prolonged gastric residence of the drug and improves dissolution in stomach. Finally concluded that carvedilol floating microsphere are better promising alternative to conventional oral drug delivery system for the treatment of patients suffering from hypertension and congestive heart failure.

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