



Formulation and Optimization of Floating Microspheres of Ivabradine Hydrochloride by 3^2 Factorial Design Approach

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Abstract

The Present study is an attempt to design and formulate floating microsphere of Ivabradine Hydrochloride to achieve its release in a controlled manner and to avoid its repetitive administration thereby, to improve the bioavailability. Ivabradine floating microspheres were prepared by multiple emulsion solvent evaporation technique (w/o/w) using Ethyl Cellulose as polymer, Dichloro Methane as solvent for polymer and tween 80 was used as emulsifying agent. The Formulation was optimized by 3^2 factorial design, by means of polymer concentration and stirring speed as an independent variables and drug loading, particle size and % drug release was selected as a response along with other micromeritic properties such as particle size, bulk density, tapped density and flow ability. Formulation prepared by using 400 mg of Ethyl cellulose gives the highest yield of $89.10 \pm 10\%$, $91.5 \pm 0.10\%$ of drug loading, $162.55 \mu\text{m}$ of average particle size, $78.20 \pm 0.27\%$ percent of drug release in 8 hours and 92.10 ± 0.26 of Buoyancy. The optimized formulation was found suitable to be dispensed as a single unit dosage form in the form capsules.

Keywords

Ethyl Cellulose, Floating Microspheres, Ivabradine HCL, Solvent Evaporation technique, Tween 80.

INTRODUCTION

Cardiovascular diseases have now become the leading cause of mortality in India, attributed to cardiovascular disease (CVD). Ischemic Heart diseases like Angina Pectoris and Stroke are the leading cause of deaths in India and are responsible for > 80% of CVD deaths. Ivabradine HCL is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic

depolarization in the sinus node and regulates heart rate. The absolute bioavailability is around 40%, due to first-pass effect in the gut and liver; elimination Half half-life of 2 hours⁽¹⁾. The patient diagnosed with Angina Pectoris needs special attention in the treatment; since the Angina attack may be impulsive at the night or in the early morning hours⁽²⁾. This can be treated by maintaining therapeutic level of drug in plasma over the period of time, with sustained release formulation of Ivabradine.

The objective of the study was to formulate and evaluate the Ivabradine loaded Ethyl Cellulose floating microspheres and satisfy above need of the treatment.

MATERIALS AND METHOD

Materials

The Ivabradine Hydrochloride was provided as gift sample by Biocon Limited, Pashamylaram, Medak District, Andhra Pradesh. Ethyl cellulose (ETHOCEL Standard 4 Premium grade) was provided as gift sample by Colorcon Asia Pvt Limited, Verna Industrial Estate, Verna, Goa. Tween 80 and Dichloromethane were purchased from SD Fine Chemicals. All chemical and reagents used were of analytical grade⁽³⁾.

METHODOLOGY.

Drug Polymer Interaction Study.

Infrared Spectroscopic study was conducted over the Ivabradine HCl and Ethyl cellulose⁽⁴⁾ to ensure absence of any physical and chemical incompatibility between the drug and polymer in order to assure their suitability for the selected formulation.

The KBr dispersion pellet of the given sample of Ivabradine HCl, Ethyl Cellulose and Mixture of Ethyl Cellulose and Ivabradine HCl were prepared and scanning was done by using Bruker, Germany Model: 3000 Hyperion Microscope with Vertex 80 FTIR System SAIF, IIT Bombay, India.

Experimental design

Optimization of formulation was done by 3² factorial design experiments. The Influence of independent variables such as Polymer concentration (X1) and Stirring speed (X2) on responses say Percent drug loading (Y1), Particle size (Y2) and Percent drug release (Y3) was examined in factorial designed experiment. Three levels of independent variables, i.e., lower; medium and high of X1 and X2 were used in the formulation. Optimization of the formulation was done by Numerical Optimization Method using Design Expert 10.0 trial Version software⁽⁴⁾.

Preparation of microspheres

Microspheres were prepared by Multiple Emulsion Technique to obtain the W/O/W type of emulsion. A given quantity of Ivabradine HCl and Ethyl Cellulose (Formulation Table 01) was dissolved in a measured volume (10ML) of Dichloromethane; predefined volume of water as an internal phase was added to above drug-polymer solution in order to produce W/O primary emulsion. Primary emulsion was then emulsified into an aqueous phase containing Tween 80 as an emulsifier to produce a stable multiple W/O/W emulsion. The above mixture was stirred at 1000 RPM using three bladed Propellers for 30 minutes at given temperature to obtained

microspheres. The microspheres were isolated by filtration through sintered glass filter and dried in oven at 40⁰ C⁽⁴⁾.

Optimization and data analysis.

The design of experiments (DOE) was used to provide an efficient means to optimize the solvent evaporation (w/o/w multiple emulsion) method with the minimum number of experimental runs and to find out which process variables have the highest impact on the prepared microspheres. ANOVA was used to estimate the significance of the model and each response parameter and also to establish the statistical validation of the polynomial equations. A statistical model incorporating Two Factor Interactive (2FI) polynomial terms was used to evaluate the response with the help of the following equation.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2$$

Where, Y is the dependent variable, b₀ (intercept) is the arithmetic mean response of nine runs, b₁ is the estimated coefficient for the factor X₁ and b₂ is the estimated coefficient for the factor X₂ whereas b₁₂ is the coefficient of interaction between X₁X₂⁽⁵⁾.

CHARACTERIZATION OF MICROSPHERES

The percentage yield

Percentage yield of different formulations were determined by weighing the floating microspheres after drying. The percentage yield of different formulation were calculated as follows⁽⁶⁾.

$$\% \text{Yield} = (\text{Total weight of microspheres} / \text{total weight of drug and polymer}) \times 100.$$

Percentage of Drug Content / Drug Loading (%)

Fixed amounts of microspheres loaded with Ivabradine were dissolved in Phosphate Buffer of pH1.2 by ultra-sonication (Remi). The solution was then filtered through a 5µm membrane filter. Finally, drug concentration was determined by the UV Spectrophotometer at 286 λ max. Drug content was calculated according to following equation⁽⁷⁾.

Micromeritic properties

Particle Size

Particle size analysis of microspheres were conducted by Optical microscopy (Micron 80) and diameter is expressed as projected diameter (d_p). Slide of sample was prepared by putting small amount of microspheres over the slide. A drop of paraffin oil was added in order to prepare the dispersion. A thin smear of dispersion was prepared over the glass slide. The slide was observed under the microscope at (10x) magnification and sizes of the particles were recorded in terms of eyepiece divisions and converted to diameter⁽⁸⁾.

Tapped Density and Compressibility Index

The tapping method (USP) was used to determine the tapped density and percentage compressibility. Compressibility was calculated as follows.

$$\% \text{ Compressibility Index} = [1 - V/V_0] \times 100$$

Where V and V₀ are the volumes of the sample after and before the standard Tapping, respectively.

Bulk Density

The bulk density of the microspheres was determined by measuring the volume of known mass of the sample. Accurately weighed amounts of microspheres were transferred to 10 ml measuring cylinder. The volume occupied by the sample was noted.

Mass of a sample

$$\text{Bulk density} = \frac{\text{Mass of a sample}}{\text{Volume of a sample}} \quad \text{g/cc}$$

Floating Behavior

Formulated microspheres 100 mg were spread over the surface of 200 ml glass beaker filled with 100 ml of 0.1 N HCL containing 0.02% v/v Tween 80. The mixture was allowed to stay for 12 hours overnight. Floating microspheres were separated by decantation. Sinking Particles were again separated by filtration. Particles of both types were dried in desiccator until constant weight was obtained. Both fractions of the microsphere were weighed and percentage buoyancy was determined by using following formula and the results are recorded in table 02⁽⁹⁾.

$$\% \text{ Buoyancy} = \left\{ \frac{w_f}{w_f + w_s} \right\} \times 100$$

Where,

w_f = weight of floating microspheres,

w_s = weight of sinking microspheres.

Hausner's ratio

Hausner's ratio of microspheres was determined by comparing the tapped density to the bulk density using the Equation

Hausner's ratio = Tapped density/bulk density.

Surface Morphology of Ivabradine Microspheres

The external and internal morphology of the microspheres was studied by scanning electron microscopy (SEM).

DSC Study of Ivabradine Microspheres

Differential Scanning Calorimetry of Ivabradine loaded Microspheres was conducted to ascertain any significant modification in drug characteristics such melting point. A Study was conducted in Shimadzu DSC6. The endothermic melting peak of Ivabradine microspheres was found at 192.09°C against the reported melting point of 192-196°C. The onset of

the melting peak started at 189.06°C and end set at 193.89°C. The DSC spectrum is depicted in figure 02.

FTIR Analysis of Ivabradine Microspheres

An Infrared Spectroscopic study was conducted over the Optimized formulation. The said study was aimed to confirm the absence of any physical and chemical incompatibility between the drug and polymer post formulation⁽³⁾.

In-vitro drug release study

The *In-Vitro* dissolution studies were performed using Dissolution apparatus I (Basket type). An accurately weighed sample of Ivabradine HCl loaded microspheres was placed into 900 ml of Phosphate buffer of pH 1.2 maintained at a temperature 37.0±0.5°C and stirred at a speed of 50 rpm. At different time intervals, 05 ml aliquot of the sample were withdrawn and the volume was replaced with an equal volume of plain dissolution medium kept at 37°C. The collected samples were filtered and analyzed at 286-λ max of drug using a UV-Visible spectrophotometer against buffer of pH 1.2 taken as blank⁽⁴⁾.

Data obtained from the study was analyzed for Model Fitting. In order to describe the kinetics of drug release from sustained release preparation, various mathematical and pharmacokinetic models have been proposed. Five kinetic models including zero order, first order, Higuchi matrix, Peppas Korsmeyer and Hixson-Crowell were applied to process the *in-vitro* release data of microspheres in order to find out the equation with a best fit model using PCP Disso software.

RESULT AND DISCUSSION.

FTIR Study

An Infrared Spectroscopic study was conducted over the physical mixture of both Ivabradine and Ethyl Cellulose. All the samples showed well resolved peaks at reported wave numbers; FTIR spectrum suggests that there was an absence of physical and chemical incompatibility between Ivabradine HCL and Ethyl cellulose, both found suitable for the selected formulation. The FTIR Spectrum is depicted in figure 01.

Evaluation of Microspheres

Percentage Drug Loading

Drug loading was found in the range of 77.16±0.53 to 91.5±0.10 in all EC1 to EC9 batches respectively. The maximum drug loading was found to be 91.5±0.10 followed by 91.1±0.15 corresponding to EC5 and EC3 respectively. The optimum drug loading may be attributed to higher concentration of Ethyl cellulose. Higher concentration of Ethyl cellulose causes sufficient entrapment of drug in polymer matrix.

Other formulations also showed drug entrapment, but their entrapment efficiency was found not satisfactory. However, the formulation EC5 showed relatively smaller particle size related to higher stirring rate.

Ivabradine HCL is water soluble, as a result, it is very difficult to achieve desired loading in microsphere by simple o/w emulsion solvent evaporation method. Therefore, modified w/o/w method was adopted, the presence of the oil phase, i.e., Dichloromethane prevents the diffusion of Ivabradine HCL in aqueous phase and thereby improve its loading.

In-vitro buoyancy study

The % buoyancy of all the preliminary formulations was found to be 84.37 ± 1.86 , 91.37 ± 1.31 , 92.03 ± 0.93 , 89.33 ± 0.81 , 92.10 ± 0.26 , 87.13 ± 0.75 , 87.83 ± 0.60 , 88.10 ± 0.61 , 87.90 ± 0.70 . The buoyancy is the important factor which directly affects the gastric retention of microspheres in the stomach, therefore it is necessary to achieve maximum buoyancy. The buoyancy of the microspheres is principally depending on the density of the microspheres, all the formulations have a bulk density less than the density of the 0.1 N HCL solution. Results are reported in table no 02.

Micromeritic study

Particle Size Analysis

The particle size may affect the flow ability and packing arrangement of the microspheres; therefore, it is necessary to obtain the optimum particle size. The particle size determination was conducted by the optical microscopic method. The mean geometric diameter (dp) of all the batches EC1 to EC9 was estimated in the range of $142.89 \mu\text{m}$ to $183.23 \mu\text{m}$. The maximum particle size, i.e. $183.23 \mu\text{m}$ (EC3) was attributed to higher concentration of Ethyl cellulose (400 mg) and lowest stirring speed (500 RPM). Lower stirring speed results in insufficient emulsification of organic and aqueous phase, as a result a large sized microsphere may be obtained.

Angle of Repose

The angle of repose is the measure of the flow ability of powders, the angle of repose of all the formulation batches was found in the range of 18.4 ± 0.006 to 29.3 ± 0.057 which designate the excellent to good flow ability of microspheres. The Carr's index value of all the formulation batches EC1 to EC9 was found to be in the range of 12.22 ± 0.136 to 15.78 ± 0.757 ; indicating good flow ability. The good flow ability is attributed to smaller and uniform particle size of the microspheres. The results of the study are reported in table 03.

Bulk Density

The bulk density of all the formulations EC1 to EC9 were found in the range of 0.654 to 0.725 g/cc. The bulk density represents the packing arrangement of the particles in the bulk. All the formulations showed the bulk density less than the density of the dissolution medium, which suggest that the microsphere have loose packing arrangement in the bulk and at the same it will help to float over the gastric fluid. Results are reported in table 03.

Tapped Density

Tapped density of all the formulations was determined and their values are quoted in table 03. Tapped density of all the formulations found in the range of 0.777 ± 0.005 to 0.831 ± 0.002 g/cc, indicating no significant variation in the densities.

In-vitro drug Release Study

The drug releases of Ivabradine HCL from all the batches were tested in a dissolution fluid at pH1.2. Release study was conducted on USP Type-I Basket apparatus at 50RPM and $37^\circ\text{C} \pm 2^\circ\text{C}$. Cumulative drug release of all EC1, EC2, EC3, EC4, EC5, EC6, EC7, EC8 and EC9 batches at the 8th hour was found to be 91.11 ± 0.09 , $79.01 \pm$, 78.66 ± 0.00 , 85.55 ± 0.09 , 78.20 ± 0.27 , 84.46 ± 0.09 , 91.08 ± 0.12 , 82.72 ± 0.23 and 89.11 ± 0.13 respectively. The optimum release of the drug was found to be 78.20 ± 0.27 at the 8th hour in EC5 batch; corresponding to 400 mg of Ethyl cellulose.

In the drug release kinetic study all the batches were found to release the drug by Korsmeyer Peppas model which suggest the release of the drug from microsphere by erosion followed by diffusion mechanism.

Statistical Analysis

The fitted linear regression equation relating the response percentage drug loading, particle size and % drug release to the transformed factor are shown below.

$$\% \text{ Drug Loading} = 56.825 + 0.081800(X1)$$

$$+ 0.0048234.82333(X2) - 0.000008(X1X2)$$

$$\text{Particle Size} = 135.968 + 0.14555(X1) - 0.016660(X2) - 0.000016(X1X2)$$

$$\% \text{ Drug Release} = 105.58667 - 0.066600(X1) - 0.00343833(X2) + 0.00000755(X1X2)$$

The model showed both X1 and X2 had a positive effect on drug loading, negative effect on % drug release and found significant with $P < 0.05$, whereas X1 showed a positive influence and X2 had a negative effect on particle size. The particle size was found to be increased with increase in polymer concentration and decreased with increase in stirring rate. The drug release was found to be decreasing with an increase in polymer concentration and decreasing with an

increase in stirring speed. In this model, interaction terms X1X2 showed positive coefficients possibly because of dominance of X2 found no significant $p>0.05$. The Surface response graphs illustrating the effect of the independent variables over responses are reported in figure 03,04 and 05.

Optimization of Processing Variables

The following combination of variables was suggested by the software with the desirability function of 0.813 as reported in **Table 05**, polymer concentration = 400 mg and stirring speed =1500

(rpm). The desirability function value (0.813) is closer to 1. Ivabradine HCl microspheres were prepared using the optimal “variables” settings and evaluated for the responses. The optimized batch of microspheres (F9) showed % entrapment efficiency of 91.2 ± 0.81 particle size of $165.5\text{ }\mu\text{m}$ and %Drug release of 77.9 ± 0.3 with small error value. It was suggested that the generated models were well suited to optimize ivabradine HCl floating microsphere.

Table 1: Factorial design (3²) Formulation table of Ivabradine loaded floating microsphere

Batch Code	Drug mg	Independent variables		Dependant variables		
		Polymer Ratio (X1)	RPM (X2)	Loading% (Y1)	Particle size (μm) (Y2)	%Drug Release (Y3)
EC1	100	-1	0	76.5 ± 0.45	142.89	91.11 ± 0.09
EC2	100	+1	0	90.5 ± 0.40	178.64	79.01 ± 0.18
EC3	100	+1	-1	91.1 ± 0.15	183.23	78.66 ± 0.00
EC4	100	0	-1	82.1 ± 0.40	172.19	85.55 ± 0.09
EC5	100	+1	+1	91.5 ± 0.10	162.55	78.20 ± 0.27
EC6	100	0	+1	86.97 ± 0.36	161.81	84.46 ± 0.09
EC7	100	-1	-1	75.16 ± 0.2	157.76	91.08 ± 0.12
EC8	100	0	0	83.1 ± 0.38	165.96	82.72 ± 0.23
EC9	100	-1	+1	77.16 ± 0.53	137.40	89.11 ± 0.13
Code Value	Actual Values		Variable Levels			
	X1	X2				
-1	200	500	Low			
0	300	1000	Medium			
+1	400	1500	High			

* n = 3, all values $\pm$ standard deviation, statistically significant at 0.05 level. X1 is polymer concentration (mg), and X2 is stirring speed (RPM). All batches contained 100 mg Ivabradine HCL.

Table 2: Drug loading, particle size and %buoyancy of Ivabradine Loaded Floating Microsphere

Batch Code	% Drug Loading	Particle Size μm	% Buoyancy
EC1	76.5 ± 0.45	142.89	84.37 ± 1.86
EC2	90.5 ± 0.40	178.64	91.37 ± 1.31
EC3	91.1 ± 0.15	183.23	92.03 ± 0.93
EC4	82.1 ± 0.40	172.19	89.33 ± 0.81
EC5	$91.5\pm0.10^*$	162.55^*	$92.10\pm0.26^*$
EC6	86.97 ± 0.36	161.81	87.13 ± 0.75
EC7	75.16 ± 0.2	157.76	87.83 ± 0.60
EC8	83.1 ± 0.38	165.96	88.10 ± 0.61
EC9	77.16 ± 0.53	137.40	87.90 ± 0.70

* n = 3, all values $\pm$ standard deviation, statistically significant at 0.05 level

Table 3: Estimated Micromeritic Properties of Ivabradine loaded microsphere.

Batch Code	Tapped Density g/cc	Bulk Density g/cc	True Density g/cc	Angle of Repose (θ)	Carr's Index	Hausner's ratio
EC1	0.831±0.002	0.725±0.005	1.33±0.006	26.0±0.058	12.72±0.686	2.56±0.021
EC2	0.803±0.002	0.682±0.002	1.38±0.012	24.9±0.058	15.14±0.480	1.17±0.005
EC3	0.805±0.003	0.692±0.003	1.39±0.006	26.4±0.021	14.05±0.508	1.17±0.011
EC4	0.821±0.004	0.720±0.003	1.37±0.010	26.1±0.069	12.33±0.136	1.17±0.007
EC5	0.803±0.004	0.683±0.002	1.25±0.006	21.0±0.035	15.02±0.417	1.13±0.005
EC6	0.781±0.004	0.661±0.004	1.29±0.006	18.4±0.061	15.32±0.040	1.14±0.012
EC7	0.805±0.004	0.689±0.002	1.28±0.006	18.4±0.006	14.49±0.522	1.15±0.010
EC8	0.777±0.005	0.654±0.002	1.26±0.006	29.3±0.057	15.78±0.757	1.20±0.008
EC9	0.804±0.004	0.687±0.002	1.26±0.006	19.4±0.006	15.49±0.522	1.45±0.010

* n = 3, all values ± standard deviation, statistically significant at 0.05 level

Table 4: Drug release kinetics of all EC1 to EC9 Batches

Batch	% Drug release	Korsmeyer Pepaps Model r ²	K (µg/min)
EC1	91.11±0.09	0.997	30.31
EC2	79.01±0.18	0.997	23.89
EC2	78.66±0.00	0.997	23.7
EC4	85.55±0.09	0.998	26.1
EC5	78.20±0.27	0.998	23.4
EC6	84.46±0.09	0.99	25.58
EC7	91.08±0.12	0.99	30.54
EC8	82.72±0.23	0.998	24.5
EC9	89.11±0.13	0.997	28.90

* n = 3, all values ± standard deviation, statistically significant at 0.05 level

Table 5: Multiple Regression Output for Dependent Variables

Parameters	Coefficient of Regression Parameters					P value
	B ₀	Polymer Conc (X ₁)	Stirring Speed(X ₂)	(X ₁ X ₂)	R ²	
%Drug Loading	+56.82	0.081800	+0.00482	-0.00008.0	0.9805	<0.05
Particle size	+135.96	0.14555	-0.016660	-0.000016	0.9184	<0.05
%Drug release	+105.58667	-0.066600	-0.0034383	0.00000755	0.9789	<0.05

Table 6: ANOVA Results for Predicting % Drug Loading (Y₁)

Source	b-Coefficient	Sum of squares	d.f	Mean square	F-value	P Value
Model	+105.58667	211.85	3	70.62	77.44	0.0001
X ₁	-0.066600	209.21	1	209.21	229.42	< 0.0001
X ₂	-0.0034383	2.07	1	2.07	2.26	0.1927
X ₁ X ₂	+0.0000755	0.57	1	0.57	0.63	0.4650
Residual		4.56	5	0.91		
		216.41	8			

Table7: ANOVA Results for Predicting Particle size (Y2)

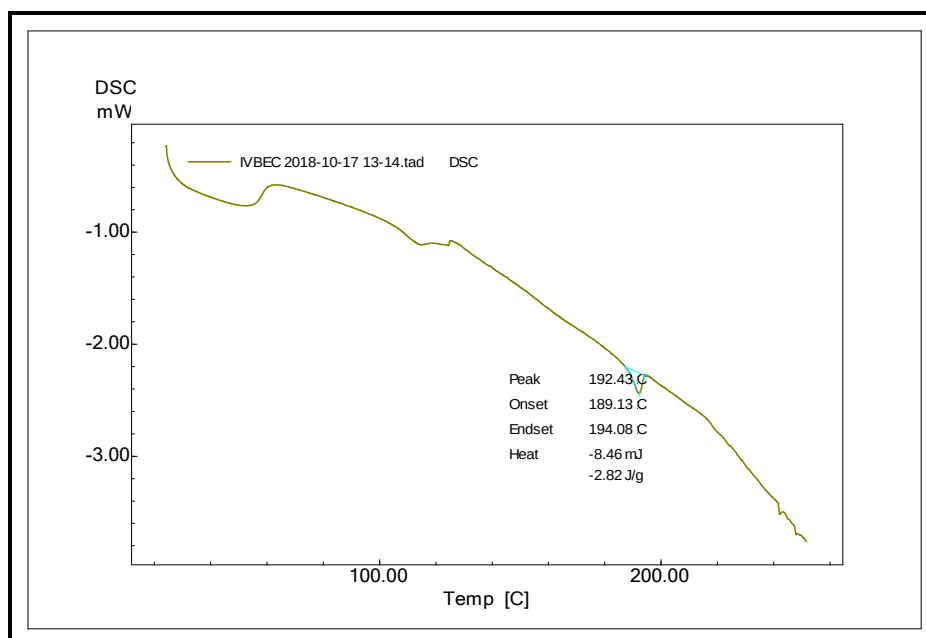
Source	b-Coefficient	Sum of squares	d.f	Mean square	F-value	P Value
Model	+135.96722	1683.99	3	561.33	18.76	0.0038
X1	+0.14555	1243.30	1	1243.30	41.55	0.0013
X2	-0.016660	440.67	1	440.67	14.73	0.0122
X1X2	-0.000016	0.026	1	0.026	0.0008.55	0.9778
Residual		149.62	5	29.92		
		1833.61	8			

Table 8: ANOVA Results for Predicting % Drug Release (Y3)

Source	b-Coefficient	Sum of squares	d.f	Mean square	F-value	P Value
Model	+56.824	336.24	3	112.08	83.75	0.0001
X1	+0.0818	326.79	1	326.79	244.18	< 0.0001
X2	+0.00482	8.81	1	8.81	6.58	0.0503
X1X2	-0.000008.	0.64	1	0.64	0.48	0.5200
Residual		6.69	5	1.34		
		679.17	8			

Table 9 Criterion for Numerical Optimization

Code	Solutions		Response variables				
	Process Variables		Experimental values		Predicted values	Error	Desirability Function
	X1	X2					
EC10	400	1500	% Loading	91.2±0.81	91.9794	-0.77	0.813
	mg	RPM	Particle size µm	165.5	168.237	-2.73	
			% release	78.2±0.27	78.3192	-0.12	


Figure No. 1: FTIR Spectrum of physical mixture of Ivabradine HCl and Ethyl cellulose

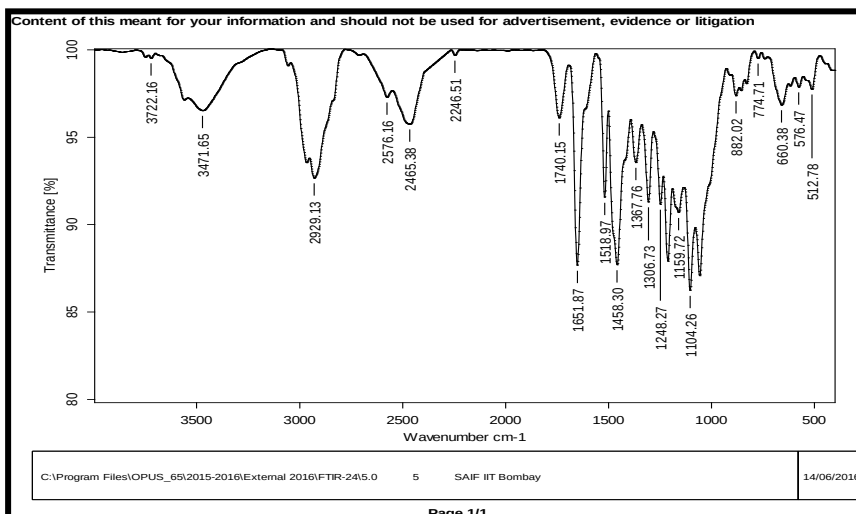


Figure No.2: DSC Thermogram of physical mixture of Ivabradine Hydrochloride and Ethyl Cellulose.

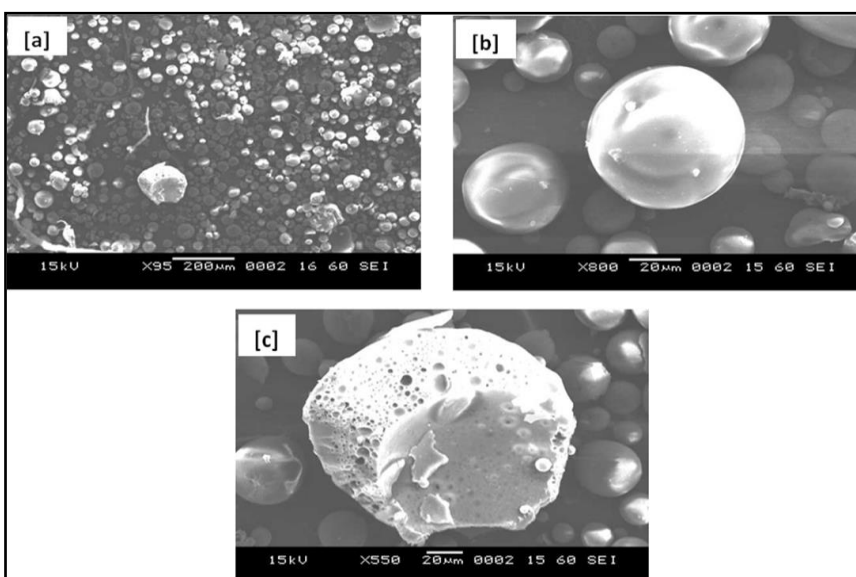


Figure No. 3: Scanning Electron Microscopic(SEM) Images of Microsphere.

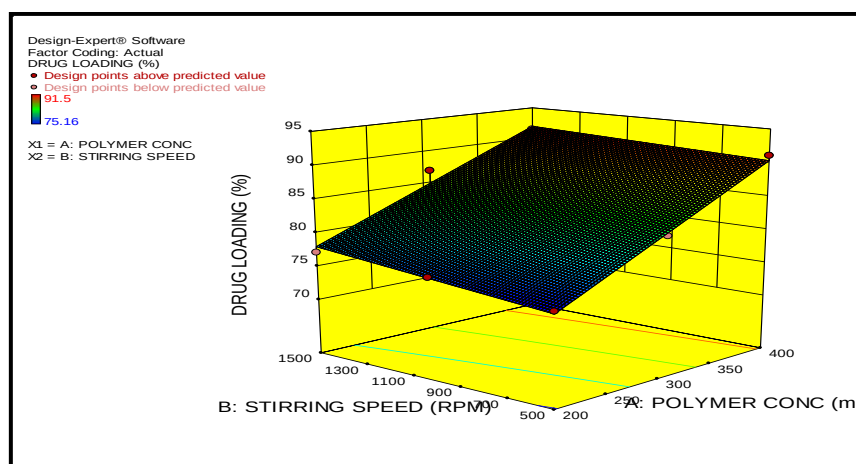


Figure No. 4: Surface response graph showing the effect of the Drug polymer ratio and Stirring speed over % Drug loading.

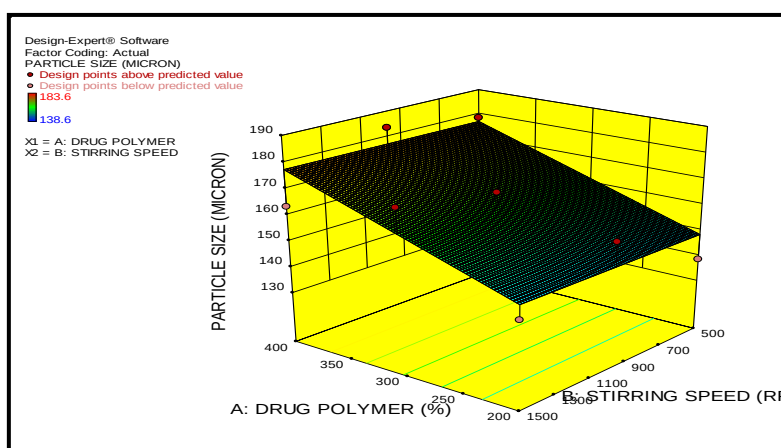


Figure No. 5: Surface response graph showing the effect of the Drug polymer ratio and Stirring speed over % Drug loading.

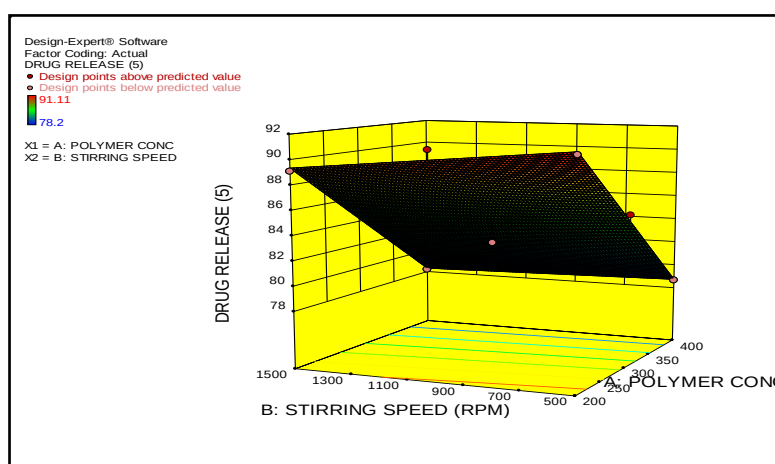


Figure No. 6: Surface response graph showing the effect of the Drug polymer ratio and Stirring speed over % Drug Release.

CONCLUSION

In this study sustained release floating microspheres of Ivabradine HCL was successfully designed by factorial design (3^2) and manufactured by multiple emulsion solvent evaporation method. The ANOVA results discovered that independent variables had a significant effect on predefined responses.

The optimization of formulation was done by numerical optimization with the desirability function of 0.813. Optimized formulation F10 showed the % drug loading of 91.2 ± 0.81 , particle size $165.5 \mu\text{m}$ and % release of 78.2 ± 0.27 .

These microspheres showed good flow properties, thus dose uniformity can be achieved during capsule filling. The SEM analysis assured that the microspheres were spherical with smooth surface. FTIR and DSC studies confirmed the absence of any interaction between drug and polymer.

The result of the optimized formulation showed no significant differences in observed values and predicted values. From the observation and the results, it is concluded that floating microsphere of Ivabradine Hydrochloride can be used as an alternative for conventional marketed formulation for its sustained release effect.

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CONFLICT OF INTEREST Nil

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