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Original Article

Development and statistical optimization of carvedilol floating beads for chronotherapeutic drug delivery

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ABSTRACT

Background and Aims: The aim of the present research work was to develop and optimize statistically carvedilol floating beads for chronotherapeutic drug delivery.

Methods: Multiple unit floating pulsatile beads of carvedilol were prepared by simple ionotropic gelation method intended for chronotherapy of hypertension. Pectin and sodium alginates were used as matrix forming, polymer and sodium bicarbonate was used as floating agent. A 2^3 full factorial design was applied to investigate the combined effect of three independent formulation variables namely amount of sodium alginate, sodium bicarbonate and calcium chloride on the dependent variables as % entrapment efficiency, floating lag time and drug release percentage.

Results: The formulation was optimized and tested based on its drug release pattern which presented minimum drug release in 0.1 N HCl and after 6 h lag time period and showed maximum drug release in 6.8 pH phosphate buffer by burst release within 45 mins. Surface response plots were presented graphically to represent the effect of independent variables on floating lag time, entrapment efficiency and drug release in 0.1 N HCl. The generated mathematical model for each response was validated and checked by formulating three extra-design checkpoint batches. There were no significant changes in drug content, floating lag time, entrapment efficiency and drug release of the formulation following its stability studies at 40 ^{0}C and 75% relative humidity.

Conclusion: It was concluded that the floating beads were successfully formulated for chronotherapy of hypertension giving site- and time specific release of drug.

Keywords: Floating beads, drug release, chronotherapy, ionotropic gelation, hypertension

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INTRODUCTION

Hypertension is one of the common cardiovascular disorders of modern times. Hypertension is the state of the body in which systolic blood pressure is 140/90 mmHg or more. One third of men and two fifth of women over 40 years of age are hypertensive because of age progression (Tripathi, 2002). Blood pressure is not steady over a 24 hours period, and also it is fluctuating according to a circadian pattern (Sajan, Cinu, Chacko, Litty, & Jaseeda, 2009). The chronobiology deals with the observation of each metabolic event goes through rhythmic changes in time that will be measured from seconds to seasons. During the chronotherapeutic treatment system in vivo drug has been timely available according to cyclic pulsing of drug related biological phenomenon to create maximum benefit and minimizing the harm. Biological rhythms at the level of cellular and sub cellular can raise the significant dosing-time differences in the pharmacodynamics of medications that are unrelated to their pharmacokinetics mechanism. This phenomenon is termed chronesthesy. Rhythms in receptor number or conformation, second messengers, metabolic pathways, or free-to bound fraction of medications are useful to elucidate this phenomenon. Blood pressure reaches its lowest point around 3 a.m. by gradual declination throughout the day and especially during sleep (Smolensky, & Peppas, 2007). This is because of many factors like the time of awakening, rise in physical activity, serum cortisol level and catecholamine levels which all increase blood pressure, heart rate and myocardial contractility. A pathophysiologic explanation for the myocardial infarction, sudden cardiac death and angina pectoris in the early morning hours is explained by the above factors (Sajan et al., 2009). Currently, chronotherapeutic calcium channel blockers are available in the market for the management of certain cardiovascular diseases. When administered at bedtime, these provide a peak effect coinciding with the rise in blood pressure and heart rate in the critical time period of 6:00 a.m. to noon, and trough concentrations during sleep (Singhai, Chopra, Nagar, Gautam, & Trivedi, 2010; Shan, & Kawashima, 2012).

Carvedilol has a beta-adrenergic receptor blocking ability and decreases the rate of heart, myocardial contractility, and myocardial oxygen requirement. Carvedilol is used to decrease systemic vascular resistance with its alpha-adrenergic receptor blocking properties. Its absorption after oral administration is rapid and extensive with an absolute bioavailability of approximately 25 % to 35 % due to the significant degree of first pass metabolism. Conventional dosage forms of carvedilol in the case of hypertension have several disadvantages like less bioavailability, more dose requirement, non-compliance of patient and other toxic adverse effects (Tanwar, Chauhan, & Sharma, 2007). Therefore, the present study of multiple unit dosage forms in the form of floating beads offers more reliability and flexibility than single-unit dosage forms.

Floating drug delivery system (FDDS) is helpful for drugs which have an absorption window in the stomach or in the upper small intestine. It is also helpful for drugs that act locally in the proximal part of gastrointestinal (GI) tract in case of antibiotic administration for *Helicobacter pylori* eradication in the treatment of peptic ulcer and for drugs that are poorly soluble or unstable in the intestinal fluid. A disadvantage of distinct unit floating systems like tablets and capsules is the high unpredictability of the GI transit time due to their all-or-nothing emptying processes (Patel, Dalvadi, & Shah, 2011). On the other hand, the multiple-unit dosage forms may be an attractive alternative since they have been shown to reduce inter and intra subject variability in drug absorption as well as lowers the possibility of dose dumping (Pongjanyakul, & Puttipipatkhachorn, 2007).

Therefore, this study investigated floating beads to treat hypertension by offering chronotherapeutic effect of carvedilol.

MATERIAL AND METHODS

Materials

Carvedilol was obtained as a gift sample from Sun Pharma Ltd., Vadodara, Gujarat. Low methoxy pectin with high molecular weight (6.08×105 Daltons or higher) was procured from Pecti Chem Industry, Jodhpur. Pectin and calcium chloride were purchased from Sulab Laboratory, Vadodara. Sodium bicarbonate was purchased from Chemdyes, Corporation, Baroda. Acetic acid was purchased from Sisco Research Laboratory, Pvt. Ltd. All the other chemicals and solvents used were of analytical grade.

Methods

Drug excipient compatibility study

Drug excipient compatibility was studied using Bruker alpha T FTIR spectroscopy (Bruker Optik GmbH, Germany). The FTIR studies were performed using the pressed Pellet technique with a KBr press. Potassium bromide (100 mg) was taken and kept in a hot air oven for two hours to remove any moisture if present. The drug powder and excipient mixture sample (10 mg) was mixed by using dried KBr crystals, and the mixture was pressed to form pellets with KBr press. The prepared pellet was placed in the sample holder and kept in the instrument to record the peaks (Ammanage, Rodriques, Kempwade, & Hiremath, 2020).

Preparation of preliminary trial batches for selection of the cross-linking medium, polymer concentration and sodium bicarbonate concentration

Preliminary trial batches of floating beads were formulated by varying concentrations of polymers, gas generating agent and calcium chloride as shown in Table 1. Cross linking solution was made by dissolving different concentrations of calcium chloride in the deionized water. For the selection of optimum polymer concentration, floating beads of various polymer concentrations were formulated and analyzed for morphology and drug entrapment efficiency (Table 2).

Preparation of floating beads

The beads are commonly prepared using ionotropic gelation technique. In this technique, an aqueous dispersion of negatively charged polymer together with a gas generating agent ($CaCO_3$ or $NaHCO_3$) was added drop-wise into acidic gelation medium consisting of divalent cations such as Ca^{2+}. As the droplet immerses into the acidic gelation medium, CO_2 is

Table 1. Preliminary trial batches for selection of concentration of sodium alginate (T1 to T4), sodium bicarbonate (T5 to T7) and calcium chloride along with curing time (T8 to T16).

Batch No.	Amount of drug (mg)	Sodium alginate (mg)	Concentration of calcium chloride (%)	Ratio of sodium alginate: Pectin (mg)	pH of cross linking solution	Concentration of sodium bicarbonate	Curing time
T1	5	50	2		1.2		
T2	5	100	2		1.2		
T3	5	150	2		1.2		
T4	5	300	2		1.2		
T5	5		2	300:300	1.2	100	
T6	5		2	300:300	1.2	300	
T7	5		2	300:300	1.2	500	
T8	5		2	300:300	1.2		15
T9	5		3	300:300	1.2		15
T10	5		4	300:300	1.2		45
T11	5		2	300:300	1.2		45
T12	5		3	300:300	1.2		30
T13	5		4	300:300	1.2		30
T14	5		2	300:300	1.2		30
T15	5		3	300:300	1.2		45
T16	5		4	300:300	1.2		15

Table 2. Selection of pH of the cross linking medium (T1 to T4), polymer concentration (T5 to T8), sodium bicarbonate (T9 to T11), calcium chloride and (T12 to T20) along with obtained FLT, FT and entrapment efficiency.

Batch code	Polymer Concentration (mg)	pH of the media	Morphology	Floating Lag time (mins)	Floating time (Hours)	Entrapment efficiency (%)
T1	300	6.2				34.01
T2	300	6.4				26.78
T3	300	1.4				56.34
T4	300	1.4				68.98
T5	50		Uneven			34.97
T6	100		Disc shaped			49
T7	150		Spherical			75.07
T8	300		Spherical			89
T9				10	4	76.7
T10				1	8	86
T11				<1	9	67
T12						61
T13						76.75
T14						78.06
T15						63.21
T16						61.56
T17						70
T18						63.45
T19						86
T20						79.42

released due to the gas-generating agent which is then captured in the gel matrix making it lighter than stomach fluids, and concurrently Ca^{2+} present in gelation medium interacts with anionic groups on polymer molecule resulting immediate formation of strong aggregation of pairs of helices giving strong bead shaped gel structures (Verma, Sharma, Verma, & Pandit, 2013).

Varying quantities of pectin and sodium alginate were dissolved in deionized water along with carvedilol with varying amounts of sodium bicarbonate as shown in Table 1. All these were mixed uniformly. The sonicated dispersion free of air bubbles was dropped via a 23-gauge syringe needle (0.65 mm internal diameter) into different concentrations of calcium chloride solution having 10 % acetic acid. The contents were stirred at 100 rpm with magnetic stirrer (Remi Instrument Ltd., Mumbai, India) for 15 mins. The beads were then filtered, washed three times with distilled water and subsequently dried in oven at 50 ^{0}C for 4h (Reddy, & Reddy, 2017; Abduljabbar, Badr-Eldin, & Aldawsari, 2015; Torre et al., 1998; Patil, Indikar, & Umarji, 2015).

Evaluation of floating beads

Flow property

The floating beads were evaluated for particle size, bulk density, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose (Aulton, 2002; Lachman, Lieberman, & Kanig, 1991; Patrick, 2006).

Particle size determination

The particle sizes of formulations were measured by using an optical microscope fitted with an ocular and stage micrometer. In all measurements at least 100 particles were examined, and each experiment was carried out in triplicate (Khonsari, Zakeri-Milani, & Jelvehgarid, 2014).

Surface analysis by scanning electron microscopy (SEM)

Morphology and surface characteristics of the floating beads were performed by using a scanning electron microscope (SEM) JSM 840 [Jeol, Tokyo, Japan] **(**Patil, Indikar, & Umarji, 2015; Lachman, Lieberman, & Kanig, 1991**)**. For assessment of the internal structure of the beads, they were cut into a half with a steel blade.

Determination of entrapment efficiency

Carvedilol content in the floating beads was determined at 332 nm by a UV-spectrophotometric method. (UV 1800 Shimadzu) (Abbas, & Alhamdany, 2020; Gupta, & Pathak, 2008). The drug entrapment efficiency was determined using following equation

Drug Entrapment Efficiency % = (Actual drug content/ Theoretical drug content) x 100.

Floating study

Floating properties of beads were evaluated in a dissolution vessel of USP type II dissolution Tester (Electrolab TDT-08L, Electrolab (India) Pvt. Ltd.) using 500 ml of simulated gastric fluid (pH 1.2). Paddle rotation speed of 0 and 100 rpm were tested maintaining the temperature at 37 ± 0.2 ° C. Fifty beads were placed in the media, and floating time was measured by visual observation (Aulton, 2002).

Dissolution study

The dissolution study of the beads equivalent to 10 mg of carvedilol was performed using a USP rotating basket apparatus (Electrolab TDT-08L). The drug release study was performed in 0.1N hydrochloric acid primarily for 2 or 9 hours depending on the floating characteristics of the beads followed by dissolution in phosphate buffer pH 6.8 for two hours. Each 900 ml of dissolution medium was maintained at 37±0.5 0 C and agitated at 100 rpm. Periodically, the samples were withdrawn and filtered through Whatman filter paper, and the concentration of carvedilol was measured using UV spectrophotometer at 332 nm. Withdrawn volume of dissolution medium was replaced by adding fresh dissolution medium to maintain sink condition (Lachman, Lieberman, & Kanig, 1991; Aulton, 2002). All the batches F1-F8 were subjected to dissolution study in simulated gastric fluid without enzymes initially for 2-9 h based on floating time (T80) of the beads followed by dissolution in phosphate buffer for two hours. Chronotropic drug delivery systems require drug release as soon as possible after the predetermined lag time for lowering hypertension in the early morning. Predetermined lag time for relieving hypertension in the early morning is 6 h.

Further drug release mechanism was studied using power law equation (Siepmann & Peppas, 2001; Zhang, Zhang, & Wu, 2003).

$$Mt/M\infty = K(t-T)^n \quad (1)$$

Where Mt and M∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively; K is a constant, T is lag time and n is the release exponent, indicative of the mechanism of drug release.

Design of experiment for optimization of formulations

A 3^2 factorial design was performed with Design-Expert (8.0.7.1 Trial Stat Ease Inc., Minneapolis, USA). It was used for exploring quadratic response surfaces and constructing polynomial models. In this three factors X1, X2 and X3 were evaluated at two levels, and experimental trials were carried out at all eight possible combinations. The factors were selected based on the trial batches. The concentration of sodium alginate (X1), concentration of sodium bicarbonate (X2) and concentration of calcium chloride (X3) were selected as independent variables. The entrapment efficiency (Y1) in pH 6.8 phosphate buffers, floating lag time (Y2) and drug release (Y3) in 0.1N HCl were selected as dependent variables (Dhoranwala, Shah, & Shah, 2015).

Statistical analysis and mathematical model fitting

The targeted response parameters were statistically analyzed by applying one-way ANOVA (analysis of variance), and the significance of the model was estimated using the Design Expert software. The individual parameters were evaluated using F test, and mathematical relationship was generated between the factors (independent variables) and the responses (dependent variables) using multiple linear regression analysis

for determining the level of factors which yield optimum dissolution responses (Menini, Furalanetto, Maestrelli, Pinzauti, & Mura, 2008).

Validation of mathematical model

To find the reliability of the developed mathematical model, all of three responses were checked for three additional random check point batches (C1, C2 and C3) covering the entire range of experimental domain. For each of these test runs, responses were estimated by use of generated mathematical model and by the experimental procedure.

Stability studies

The studies were performed at 40±2 ^{0}C and 75±5 % relative humidity (RH) in the sealed glass chambers with saturated salt solution for up to 1 month. A visual inspection, drug content, floating study *and in vitro* drug release studies were carried out every 15 days for the entire period of stability study (EMA, 2003).

RESULTS AND DISCUSSION

Drug excipient compatibility study

FTIR spectra of pure drug (carvedilol) showed the characteristic peak at 1594.26 cm^{-1} (-C-C- stretching), 3343.76 cm^{-1} (-N-H- bending), 3058.50 cm^{-1} (-O-H stretching), 1214.18 cm^{-1} (-C-O-C stretching), 3058 cm^{-1} (C-H stretching). IR spectra of formulation showed the characteristics peak at 1586.83 cm^{-1} (-C-C- stretching), 3410.69 cm^{-1} (-N-H- bending), 2933.51 cm^{-1} (-O-H stretching),1218.40 cm^{-1} (-C-O-C stretching), 2933.91 cm^{-1} (C-H stretching). The FTIR spectra of formulation of the drug with excipients and peaks present in IR spectra of formulation were nearly similar to the frequency of principle peaks present in IR spectra of pure drug which confirmed the absence of any chemical interaction between them. The results are revealed in Figure 1.

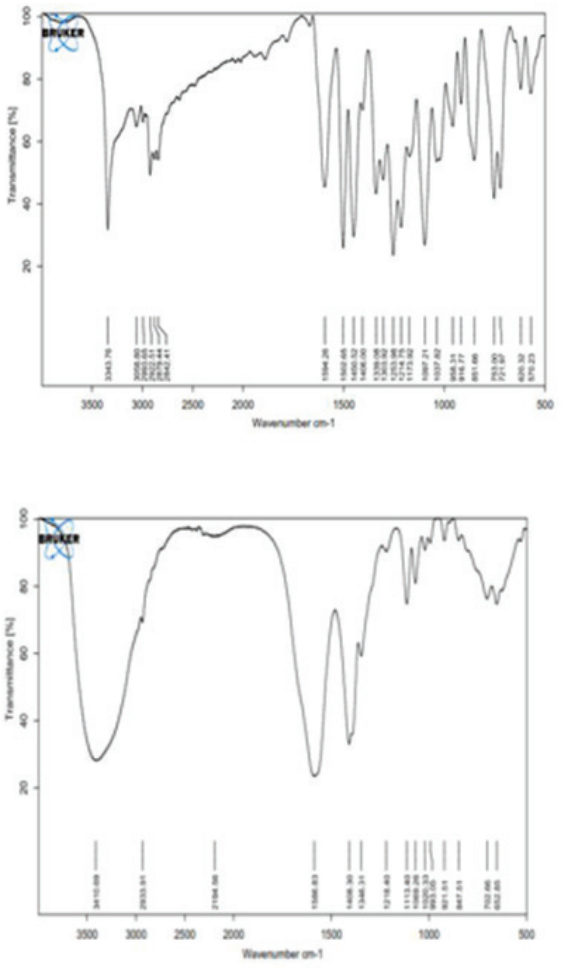

Figure 1. IR spectra of pure Carvedilol and floating beads formulation.

Preparation of preliminary trial batches for selection of the cross linking medium, polymer concentration and sodium bicarbonate concentration

It was observed from the preliminary trial batches that beads prepared by aqueous calcium chloride solution were having very low entrapment efficiency. It was found that at low polymer concentration, beads were of disc shaped and had a weak gelling capacity. Low gelation capacity resulted in low entrapment efficiency. It was found from the trial batches that as polymer concentration increased, the shapes of the beads were shifted towards spherical, and drug entrapment efficiency was also found to increase up to optimum level. This might be due to the increase in the polymer concentration; there is a greater availability of active calcium binding sites in the polymeric chains and greater degree of cross linking. On the other hand, the increase in the polymer concentration may also reduce the loss of the drug in the curing medium due to formation of dense matrix structure.

The beads prepared from 50 mg alginate solution had entrapment efficiency of 34.97%, while the beads prepared from 100 mg and 150 mg alginate solution were having entrapment efficiency 75.07% and 89%, respectively, which showed good entrapment. By increasing the polymer concentration, viscosity was also increased, and the shape of the beads was spherical, and the size was also uniform. The results are shown in Table 2.

From the results, it was found that as the concentration of sodium bicarbonate was increased floating efficiency, and floating time was also increased and floating lag time was decreased. By decreasing the concentration simultaneously, the beads were ruptured, and so entrapment efficiency was decreased, but at optimum concentration, entrapment efficiency was found to increase. In these trial batches, T9 batch was found to have 76.7% entrapment efficiency, but time of floating was decreased, and floating lag time was more than 10 mins which is undesirable. In the batch T10 entrapment, efficiency and floating time was 86% and 8 h, respectively. But, at higher concentration in T11 batch due to fast generation of carbon dioxide beads were ruptured, and hence it is concluded that higher concentration decreased the entrapment efficiency as revealed in Table 2.

Selection of calcium chloride and curing time

From the results, it was found that as the concentration of calcium chloride increased cross linking increased, and hence entrapment efficiency was also increased. As curing time increased, the entrapment efficiency was increased, but it was insufficient. In Batch T14, at higher concentration of calcium

chloride and at more curing time the drug entrapment, efficiency was increased. In Batch T12, it was found less (Table 2).

From the results of the preliminary trial batches, two different levels of sodium alginate, sodium bicarbonate and calcium chloride were selected to optimize the formulation using 2^3 factorial design. The formulations batches using factorial design are shown in Table 3.

Evaluations of floating beads

Flow property

As shown in Table 4, as the concentration of sodium bicarbonate was increased, the size of the particles was found to increase. Batches F1, F3, F5, F8 have the particle size greater than the other batches. The results of bulk density and Carr's index for all the batches F1-F8 were found to comply the suggested range. The angle of repose for all the formulation was found 27.20^0 ±0.87 to 30.27^0 ±0.77, which indicated good flow property.

The results showed that all the formulations batches had the good flow properties.

Entrapment efficiency

It was observed that with the increase in the polymer concentration entrapment, efficiency was found to increase (Table 4). It was affected by the polymer concentration and calcium chloride concentration. Increased in the calcium chloride concentration, the cross-linking ability was also increased because of the more availability of the spare chloride ions. Thus, Batch F1 has highest entrapment efficiency of 89.41 %, which was more than other batches.

Floating study

The results of the floating study showed that with the increase in concentration of sodium bicarbonate, carbon dioxide gas generation was increased, and the beads were found to float for longer period of time. Floating lag time was decreased as the sodium bicarbonate increased. Thus, F1, F3, and F8 have less floating lag time than the other batches (Table 4).

Surface analysis by SEM

The SEM study of the floating beads showed that the beads were having uniform spherical shape and presence of entrapped gas bubbles. The surface examination of uniform spheres under higher magnification showed smooth surface. The results are revealed in Figure 2.

Dissolution study

All the batches of the beads released 1.1±0.45 % to 24.0±0.37 % of the drug in 0.1 N HCl. Thus, the floating beads showed

Table 3. Formulation of floating beads using 2^3 factorial designs.

Batch No.	Sodium Alginate concentration (mg)	Sodium bicarbonate concentration (mg)	Calcium chloride (%)
F1	300(+)	225(+)	4(+)
F2	300(+)	115(-)	4(+)
F3	300(+)	225(+)	3(-)
F4	0(-)	115(-)	3(-)
F5	0(-)	225(+)	3(-)
F6	0(-)	115(-)	4(+)
F7	300(+)	115(-)	3(-)
F8	0(-)	225(+)	4(+)

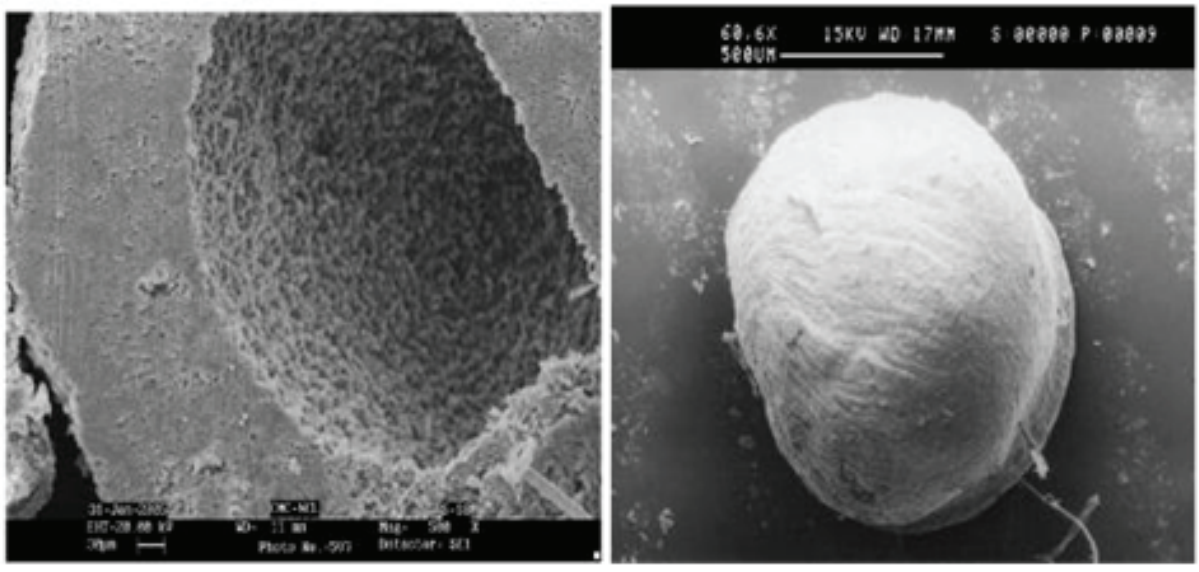

Figure 2. SEM images for surface analysis of floating beads (Optimized batch C3).

excellent lag time in drug release at acidic pH. All the batches of the floating beads released 84.00±0.75 % to 98.0±0.20 % cumulative release in pH 6.8 phosphate buffer. The results are revealed in Figure 3.

The exponents were calculated by using equation $Mt/M\infty = K(t-T)^n$. R^2= 0.7383 and n= 0.27, indicating that swelling-controlled drug release mechanism is involved in the drug release. Thus, chronotherapeutic release of the drug in the morning for the treatment of hypertension was achieved by preparation of floating beads.

Table 4. Evaluation of floating beads.

Batch No.	Particle size* (mm)	Bulk Density* (g/cm³)	Carr's Index (%)	Entrapment efficiency* (%)	Floating Lag time (mins)	Angle of Repose* (degrees)
F1	1.97± 0.09	0.320±0.02	10.36	89.41±0.02	1	27.20 ±0.87
F2	1.43± 0.05	0.485±0.02	2.53	82.52±0.02	6	28.65 ±1.65
F3	1.82± 0.09	0.658±0.01	3.99	86.98±0.03	1	30.20 ±0.85
F4	1.41± 0.05	0.699±0.10	1.92	76.79±0.03	7	30.33 ±0.75
F5	1.92± 0.08	0.481±0.03	9.10	85±0.02	1.5	28.24 ±0.54
F6	1.38± 0.05	0.357±0.07	8.98	81.5±40.02	6.5	28.98 ±0.93
F7	1.45± 0.05	0.645±0.06	4.89	80.27±0.03	8	29.59± 1.65
F8	1.86± 0.08	0.627±0.11	5.76	86.98±0.03	1	30.27 ±0.77

*Mean±SD;n=3

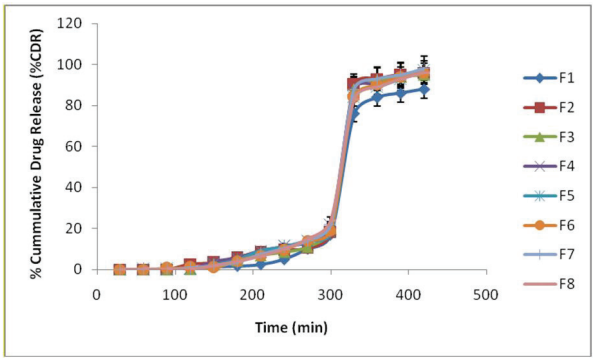

Figure 3. Dissolution study of batches F1-F8.

Optimization of formulation using 2^3 factorial designs

Batches F1 and F4 were found to release the drug almost completely within 40 mins in 6.8 pH phosphate buffer, while Batches F5 and F8 were found to release the drug 97.00±0.63 and 96.060±0.87, respectively within 40 mins. So, cumulative drug release in pH 6.8 phosphate buffer within 40 mins was selected as one of the response parameters. The formulation should also have sufficient floating time in the stomach to release the drug specifically to the small intestine, and the formulation was supposed to have minimum drug release in gastric acid condition to provide a lag time.

Statistical analysis and mathematical model fitting

The F-value 60.62 of entrapment efficiency implied the model was significant. The ratio of 20.853 indicated an adequate signal.

% Entrapment efficiency (Y1) = 62.615+6.620X1+0.0598X2+3.0825X3

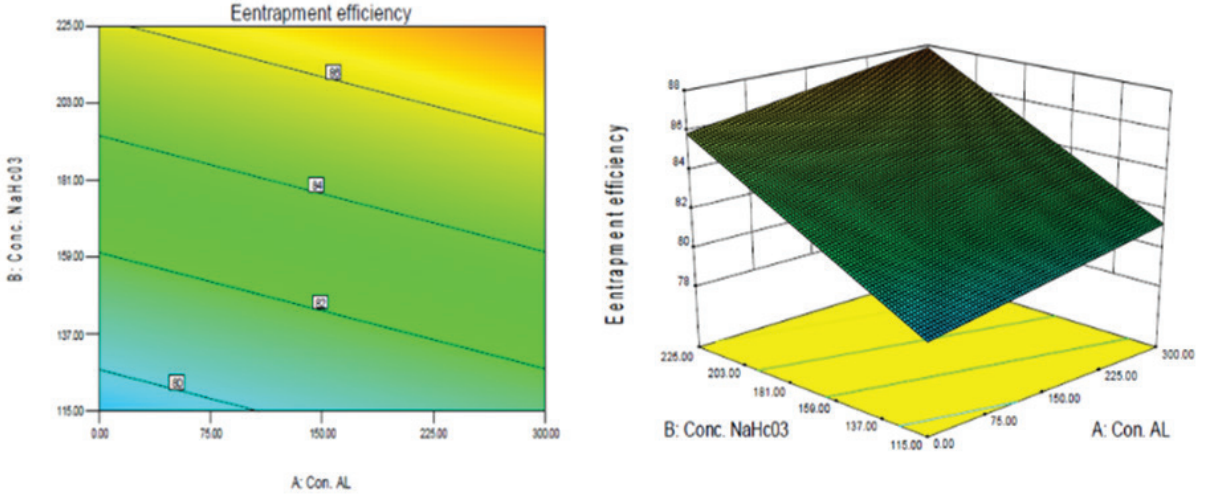

Figure 4. Countour plot and response surface plot for (%) entrapment.

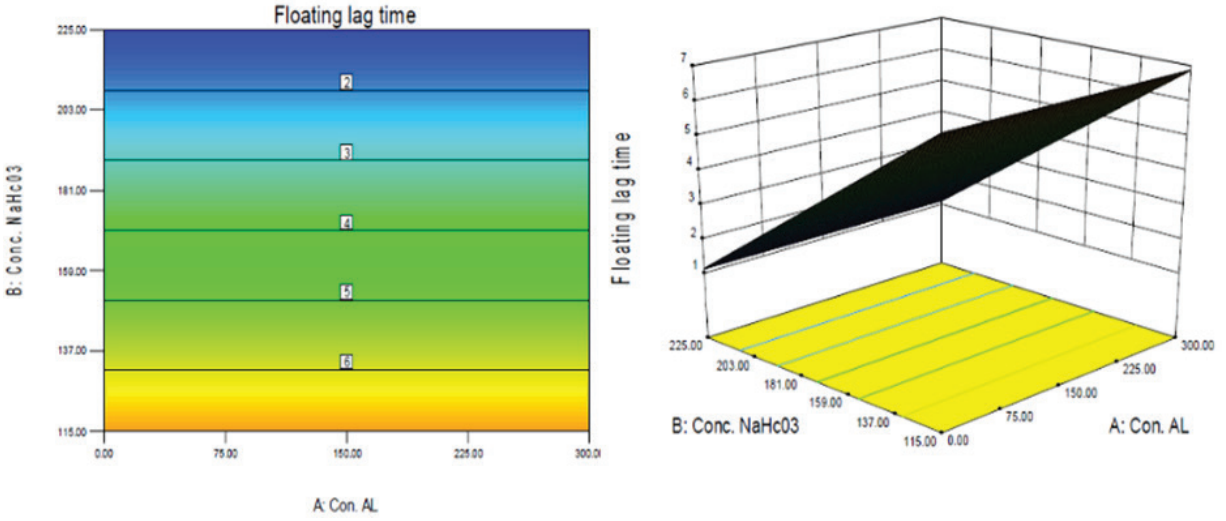

Figure 5. Countour plot and response surface plot for Floating Lag time (Y2).

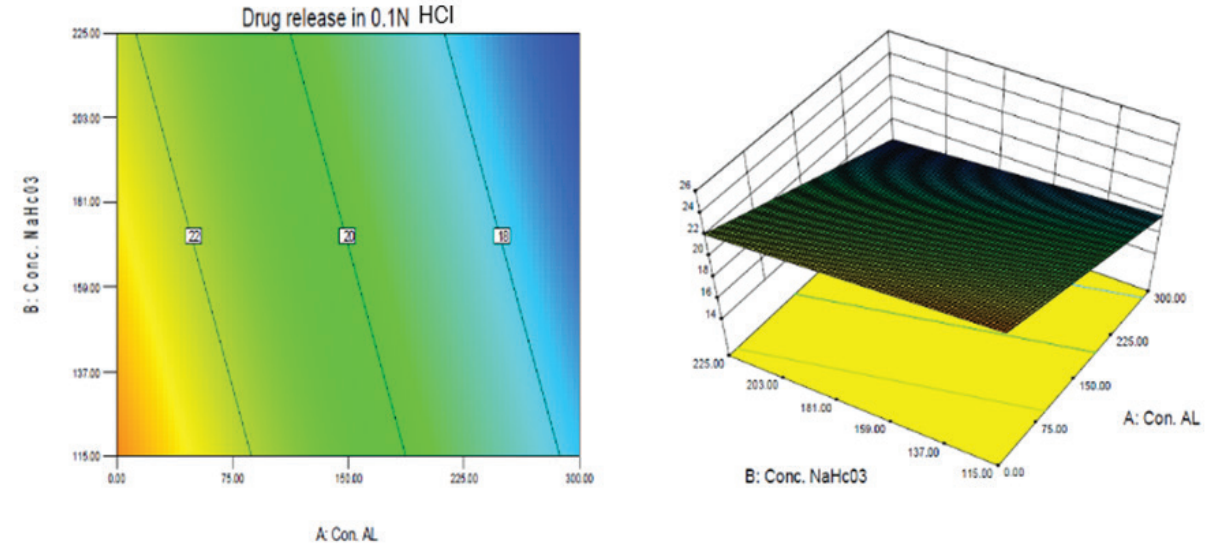

Figure 6. Countour plot and response surface plot for Drug Release in 0.1N HCl (Y3).

In this equation, coefficients of X1, X2 and X3 showed positive signs, so increase in concentration of sodium alginate, sodium bicarbonate and calcium chloride increased the entrapment efficiency. The results are revealed in Figure 4.

The Model F-value of 71.73 for floating lag time implied the model was significant. The ratio of 16.44 indicated an adequate signal.

Floating lag time (Y2) = +15.51-3.140X1-0.0523X2-0.750X3

In this equation, coefficient of X1 showed a negative sign, so increase in concentration of sodium alginate increased floating lag time. The coefficient of X2 showed a negative sign, so increase in sodium bicarbonate concentration decreased the floating lag time, and coefficient X3 showed a positive sign, so increase in calcium chloride concentration increased entrapment efficiency. The results are revealed in Figure 5.

The Model F-value 14.67 of entrapment efficiency implied the model was significant. The ratio of 8.552 indicated an adequate signal.

Drug Release % in 0.1N HCl (Y3) =27.06878-0.02X1-0.0136X2-0.50X3

In this equation, coefficient of X1 showed a negative sign, so increase in concentration of sodium alginate decreased drug release in 0.1N HCl. The coefficient of X2 showed a negative sign, so increase in sodium bicarbonate concentration decreased the drug release in 0.1N HCl, and the coefficient X3 showed a negative sign so increase in calcium chloride concentration decreased drug release in 0.1N HCl. The results are revealed in Figure 6.

Validation of mathematical model

The close similarity between the observed and predicted response value assessed the robustness of predictions. These

values designate the validity of generated model. The results are revealed in Table 5.

Table 5. Validation of mathematical model.

Batch Code	Composition			Responses*	Predicted Value	Experimental value	%Error
	X1	X2	X3				
F1	300	225	4	Y1	89.40	89.41	0.013
				Y2	0.75	1	0.25
				Y3	16	16	0.00
C1	300	200	3	Y1	83.61	84.35	0.74
				Y2	2.36	1.50	0.86
				Y3	16.83	17.00	0.17
C2	200	225	3	Y1	84.40	81.03	-3.37
				Y2	1.11	1.00	0.11
				Y3	18.44	18	0.44
C3	300	200	4	Y1	86.90	85.07	1.83
				Y2	1.79	1.50	0.29
				Y3	16.52	17.00	0.48

***** Y1= (%) Entrapment efficiency, Y2= Floating lag time, Y3= (%) Drug release in 0.1N HCl.

Stability studies

No significant change in drug entrapment efficiency, floating time (T80) and drug release during storage indicated that the developed floating beads formulation of carvedilol were stable.

CONCLUSION

The present work was undertaken to formulate the floating beads of carvedilol for the chronotherapy of hypertension. In preliminary trial batches, various concentrations of sodium alginate, pectin and calcium chloride were used for preparation of carvedilol containing floating beads. It has been found that the increase in the concentration of sodium alginate increased - the entrapment efficiency. Increased in the concentration of sodium bicarbonate decreased the floating lag time. From the results of the preliminary trial batches, 2^3 factorial designs were employed for optimization of the formulation by selecting dependent variables as entrapment efficiency, floating lag time, drug release in 0.1N HCl and independent variables as concentration of sodium alginate, concentration of sodium bicarbonate and concentration of calcium chloride. The formulated floating beads were evaluated for micrometrics, scanning electron microscopy, entrapment efficiency, floating study and dissolution study. F1 batch found to have 1.97±0.09 mm particle size, 1min. floating lag time, 89.41±0.02 % entrapment efficiency, 15.5±0.1 % drug release in 0.1N HCl and 90.5±0.002 % drug release in pH 6.8 phosphate buffer. The optimized formulation F1 was selected on the basis of its good entrapment efficiency, less floating lag time and less drug release in 0.1 N HCl. The results of all F1-F8 batches justified by regression equation derived for responses like entrapment efficiency, floating lag time, and drug release in 0.1 N HCl by 2^3 factorial design. The response surface model and contour plots gave an idea about the effect of different concentrations on entrapment efficiency, floating lag time and drug release in 0.1 N HCl. The stability studies of an optimized batch showed no significant change in terms of the drug entrapment efficiency, floating lag time and drug release in 0.1 N HCl following storage at 40±2 ^{0}C and 75±5 % RH.

Thus, it can be concluded that the present work can be considered as one of the promising formulation techniques for preparing multi-particulate floating pulsatile drug delivery of carvedilol in the form of floating beads and can be effectively used in chronotherapeutic management of hypertension by opening a new therapeutic dimension to an existing drug molecule.

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