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Original Article

DESIGN, DEVELOPMENT AND CHARACTERIZATION OF MUCOADHESIVE GASTRO SPHERES OF CARVEDILOL

S. S. SAKHARE*, A. V. YADAV, P. D. JADHAV

Department of Pharmaceutics, Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara, Shivaji University, Kolhapur
Email: sfurti_28@rediffmail.com

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ABSTRACT

Objective: The purpose of this study was to design mucoadhesive gastro spheres of carvedilol targeting to upper GIT, and optimize it in terms of its entrapment efficiency and drug release. A 3^2 full factorial design was employed to study the effect of independent variables like sodium alginate and sodium carboxyl methyl cellulose on entrapment efficiency and *in vitro* drug release.

Methods: Mucoadhesive gastro spheres were prepared by Orifice-Ionic gelation method, in which drug is uniformly distributed in the polymer solution so drug can be loaded easily in the polymer.3^2 full factorial designs were used to study the effect of process variables on formulation characteristics by applying statistical analysis.

Results: FTIR, XRD and DSC analyses apparently did not indicate any interaction of the drug with the polymers. However, the drug content, drug entrapment efficiency and morphology of the gastro spheres were found to be influenced by the method of preparation, composition of gastro spheres as well as exposure to the cross linking agent. *In vitro* drug release study showed that drug release can be modified by varying drug to polymer ratio. The release rate was found to be decreased in accordance with the increase in the ratio of polymer used.

Conclusion: From the study, we successfully developed carvedilol gastro spheres by using mucoadhesive polymer like SCMC and rate retardant sodium alginate polymer.

Keywords: Carvedilol, Mucoadhesive, Gastro spheres, Factorial design

INTRODUCTION

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have an enormous impact upon the healthcare system. The oral route of drug administration is the most largely used and preferred means of drug delivery to the systemic circulation of the body. However, the drugs which are administered through oral route in the form of conventional dosage have limitations of their inability to limit and localize the system at gastrointestinal tract. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as a microsphere, nanoparticles, etc., which modulates the release and absorption characteristics of the drug [1].

Microspheres/micro particles constitute an important part of this particulate drug delivery system by virtue of their small size and efficient carrier characteristics. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Such systems often use macromolecules as carriers for the drugs [1].

Multiparticulate delivery systems like gastro spheres are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target the drug to specific sites. They can distribute in the GI tract homogeneously, thus maximizing drug absorption and reducing peak plasma fluctuations, minimizing the risk of local GI tract irritation and dose dumping, decreasing dosing frequency and increasing patient compliance, improving the safety and efficacy of the active ingredient [2].

Gastro spheres are the particulate drug delivery systems which achieve the target of gastric retention by mainly two mechanisms, i.e.; buoyancy and bio-adhesion. Due to their small size and efficient carrier characteristics, gastro spheres constitute an important part through the particulate novel drug delivery system. The limitation of gastro spheres is due to their short residence time on the site of absorption, and it can be overcome by providing an intimate contact of the drug-delivery system with the absorbing membrane. This can be accomplished by coupling bio-adhesion characteristics to gastro spheres and developing mucoadhesive gastro spheres [3]. Extending the residence time with a dosage form at a particular site and controlling the release of drug from the dosage form are useful, especially for achieving controlled plasma level of the drug as well as improving bioavailability.

Carvedilol is a non-selective α1, β1, β2-adrenergic antagonist used for the treatment of hypertension and stable angina pectoris. It also possesses antioxidant and anti-proliferating effects, which may enhance its ability to fight the deleterious effects of sympathetic nervous system activation in heart failure. Carvedilol is having poor water solubility (BCS class II) [4-6]. The formulation of a poorly soluble drug for oral delivery will be one of the biggest challenges. Carvedilol microspheres are reported to have good spherical geometry with prolongation of drug release at a constant and controlled rate. Carvedilol microcapsules have also been beneficial for increasing its bioavailability [7]. The present investigation relates to the development of mucoadhesive gastro spheres of Carvedilol, which will increase the gastric residence time and allow more of the drug to penetrate through the gastric mucus layer which may help to improve the bioavailability of carvedilol.

MATERIALS AND METHODS

Carvedilol was provided ex gratis by Alembic Pvt. Ltd, (Vadodara). Sodium alginate (Research Lab. Pvt. Ltd. Mumbai), sodium carboxy methyl cellulose (LobaChem. Pvt. Ltd. Mumbai), Calcium chloride (Research Lab. Pvt. Ltd. Mumbai). All other chemicals employed were of analytical grade.

Formulation of mucoadhesive gastro spheres

Carvedilol-Sodium alginate gastro spheres containing sodium carboxyl methyl cellulose was prepared using calcium chloride ($CaCl_2$) as cross-linking agent by ionic gelation method. Briefly, required amounts of sodium alginate and sodium carboxyl methyl cellulose were dissolved in distilled water (20 ml) using a magnetic stirrer for 30 min. Afterward, carvedilol was added to the mixture

solutions of sodium alginate and sodium carboxyl methyl cellulose for each formulation and mixed thoroughly using a magnetic stirrer (Remi Motors, India). The final sodium alginate-sodium carboxymethyl mixture cellulose solutions containing carvedilol were ultra-sonicated for five min for debubbling. The resulting dispersion was then added via a 21-gauge needle dropwise into 40 ml of 10% (w/v) $CaCl_2$ solutions. Added droplets were retained in the $CaCl_2$ solutions for 15 min to complete the curing reaction and to produce rigid spherical gastro spheres. The gastro spheres were collected by decantation and washed two times with distilled water and dried at 37 ◦C for overnight. The dried gastro spheres were stored in a desiccator until used.

Experimental design for optimization

In order to obtain "optimized product," nine different formulations was generated using 3^2 factorial designs. The amount of sodium alginate (X1) and the amount of sodium carboxyl methyl cellulose (X2) were taken as independent formulation variables while % drug content (Y1), % entrapment efficiency (Y2) and % drug release at 12 h (Y3) were considered as dependent or response variables. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. Design Expert (Version 7.0.0) software was used during the generation and evaluation of the statistical experimental design [9, 10]. The effects of independent variables were modeled using a quadratic mathematical equation generated by a 3^2 factorial design such as $Y= b0+b1X1+ b2X2+b12X1X2+b11X12+b22X22$.

Where Y is the response; b0 is the intercept, and b1, b2, b12, b11; b22 are regression coefficients. X1 and X2 are individual effects; X12 and X22 are quadratic effects; X1 X2 is the interaction effect. One-way ANOVA was applied to estimate the significance of models ($p<0.05$). Individual response parameters were evaluated using the F test. The response surface plots were analyzed to reveal the effect of independent factors (amount of SCMC and sodium alginate) on the measured responses (% DC, % DEE and % DR). The details in the design are shown in table No.1 and 2.

Table 1: Selection of levels of independent variables

Coded value	Sodium alginate (mg) X1	Sodium carboxyl methyl cellulose (mg) X2
-1	300	100
0	400	200
1	500	300

*X1: amount of sodium alginate, X2: amount of sodium carboxyl methyl cellulose, mg: milligram

Table 2: Design layout of composition of 3^2 factorial batches of gastro spheres

Batch code	Code value		Actual value		Drug (mg)
	SA	SCMC	SA (mg)	SCMC (mg)	
F1	-1	-1	300	100	400
F2	-1	0	300	200	400
F3	-1	+1	300	300	400
F4	0	-1	400	100	400
F5	0	0	400	200	400
F6	0	+1	400	300	400
F7	+1	-1	500	100	400
F8	+1	0	500	200	400
F9	+1	+1	500	300	400

Characterization of gastro spheres

Drug entrapment efficiency

Gastro spheres equivalent to 5 mg of carvedilol was taken and was crushed using pestle and mortar. The crushed powders of drug containing gastro spheres were placed in 25 ml of 0.1N HCl and kept for 24 h with occasionally shaking at 37+/-0.5 ◦C. After the stipulated time, the mixture was stirred at 500 rpm for 20 min using a magnetic stirrer (Remi Motors, India). The polymer debris formed after the disintegration of gastro spheres was removed filtering through Whatman® filter paper (No. 40). The drug content in the filtrate was determined using a UV-VIS spectrophotometer (LabIndia) at 280 nm against appropriate blank. The drug entrapment efficiency was calculated using the following formula.

$$\text{DEE (\%)} = \left(\frac{\text{Actual}}{\text{Theoretical}}\ \text{Drug Content}\right) \times 100$$

Particle sizes analysis

The particle size of 100 dried gastro spheres from each batch was measured by the optical microscopic method for average particle size using an optical microscope. The ocular micrometer was previously calibrated by stage micrometer.

Fourier transforms infrared spectroscopy

Fourier transform infrared spectra were obtained using Shimadzu FTIR-8400S spectrometer, Japan. Samples of carvedilol, physical mixtures and optimized formulation of microsphere were taken for the study. The scanning range was 500 to 4000 cm-1and the resolution was 4 cm^{-1}.

Powder X-ray diffraction (PXRD)

PXRD patterns were recorded using BRUCKER D2 PHASER A26-X1 ABOB2A, fitted with a copper target, a voltage of 40 kV, and a current of 30mA. The scanning rate was 1 °/min over a 2 θ range of 1-50 °. PXRD patterns were traced for carvedilol, physical mixture, and formulation. The samples were slightly ground and packed into the aluminum sample container.

Differential scanning calorimetric (DSC)

DSC analysis of the samples was carried out on a Perkin-Elmer DSC7, USA. Samples (6.5-10 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10 °C/min over the temperature range of 5 and 300 °C. DSC analysis was carried out under nitrogen gas flow of 20 lb/in2.

Scanning electron microscopy and morphology characterization (SEM)

The surface morphology of the gastro spheres was studied by scanning electron microscopy Scanning Electron Microscope JSM 6330 JEOL (Japan). Acceleration voltage set at 3Kv at Magnification level 65x, 500x, 2000x, 5000 x. The samples were then randomly scanned and microphotographs were taken on different magnification. Then morphological characteristics of gastro spheres were determined from a photograph of SEM.

***In vitro* mucoadhesive test**

The mucoadhesive property of optimized carvedilol gastro spheres was evaluated by ex vivo wash-off method. Freshly excised pieces of goat intestinal mucosa (2 cm × 2 cm) (collected from the slaughterhouse) were mounted in the glass slide (7.5 cm × 2.5 cm) using thread. About 20 gastro spheres were spread onto the wet tissue specimen, and the prepared slide was hung onto a groove of the disintegration test apparatus. The tissue specimen was given a regular up and down movement in a vessel containing 900 ml of 0.1 N HCl at 37+/-0.5 ◦C. After regular time intervals, the machine was stopped and the number of gastro spheres still adhering to the tissue was counted [8].

***In vitro* drug release study**

The release of carvedilol from various gastrosphere was tested using a dissolution apparatus USP type II. The dissolution rates were measured at 37+/-1 ◦C under 50 rpm speed. Accurately weighed quantities of gastro spheres containing carvedilol equivalent to 50 mg were added to 900 ml of 0.1 N HCl. 5 ml of aliquots was collected at regular time intervals, and the same amount of a fresh dissolution mediums was replaced into the dissolution vessel to maintain the sink condition throughout the experiment. The collected aliquots were filtered and suitably diluted to determine the absorbance using a UV–vis spectrophotometer (Lab India) at 280 nm against an appropriate blank.

RESULTS AND DISCUSSION

Factorial design with surface plots & optimization of process variables

The influences of factors on investigating responses were elucidated by response surface methodology. Response surface methodology is a widely used approach for the development and optimization of drug delivery formulations, which has been utilized by the formulators to investigate the combined effect of investigating factors on the desired responses. The three-dimensional response surface graphs are very useful in learning about the main effects and interaction effects of the independent variables. The three-dimensional response surface plots (fig. 1, 2) were presented to estimate the effects of the independent variables (factors) on each response investigated.

X_1 = Sodium alginate

X_2 = sodium carboxymethyl cellulose

An interactive statistical second-order complete model equation was generated to evaluate the selected response which is as follows:

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_{12}+b_{22}X_{22}$$

Where Y is the predicted response, b_0 is the arithmetic mean response of 9 runs and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low value to its high value. The interaction (X_1X_2) shows how drug content of formulation as well as encapsulation efficiency changes when two factors are simultaneously changed, and the exponential terms (and) represent curvature. The coefficients corresponding linear effects (b_1 and b_2), interaction (b_{12}) and the quadratic effects (b_{11} and b_{12}) were determined from the results from the experiment (STAT-EASE, design expert, 7.0.0) [8, 10].

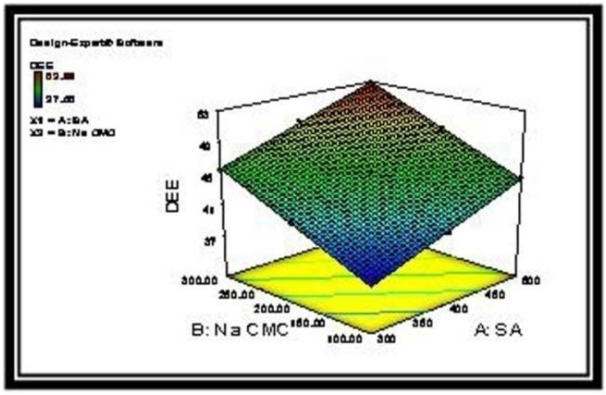

Fig. 1: Response surface plot for drug entrapment efficiency of carvedilol gastro spheres

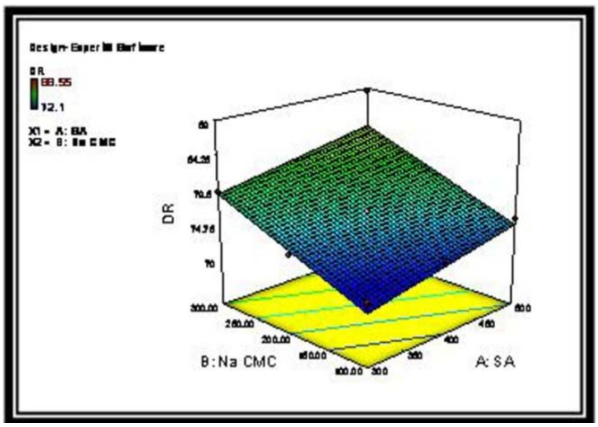

Fig. 2: Response surface plot for %drug release of carvedilol gastro spheres

Drug entrapment efficiency

The encapsulation efficiency determines the percentage of encapsulated drug with respect to the total drug introduced into the polymer solution. Effect of polymer content on encapsulation efficiency was studied.

The encapsulation efficiency in 0.1 N HCl was in the range of 37.65% to 52.88% respectively (table 3). It is evident that with the increase in the polymer concentration encapsulation efficiency also increased. This may be due to the increase in viscosity of the polymer solutions with the increase in the concentration of polymer. This might have prevented drug discharge from the prepared microsphere to the cross-linking solution [9, 14]. Encapsulation efficiencies from the 9 batch experiments were used to generate predictor equations for carvedilol gastro spheres with independent variables as sodium alginate concentration (X_1) and sodium carboxymethyl cellulose (X_2).

Table 3: Drug entrapment efficiency and particle size analysis*of gastro spheres

Formulation	%DEE	Particle Size(µm)
F1	37.65±0.158	730±0.33
F2	40.45±0.102	738±0.88
F3	44.61±0.186	740±0.66
F4	41.69±0.156	762±0.66
F5	45.30±0.093	778±1.52
F6	48.76±0.093	826±1.20
F7	45.59±0.098	854±0.33
F8	49.63±0.165	878±2.66
F9	52.88±0.241	902±0.88

*Indicates±SD (n = 3), SD: Standard deviation, µm: micro meter, DEE: Drug Entrapment efficiency.

The fitted model for drug entrapment efficiency is a quadratic model & expressed as:

Final equation in terms of coded factors

Drug Entrapment Efficiency =+45.17+3.55 * SA+4.23 * NaCMC

[R2 =0.9974; Adjusted R2 =0.9966; Predicted R2 =0.9940; F= 1167.58;P<0.05]

From the Response Surface plot for drug entrapment efficiency (fig. 1) it is observed that the change in concentration of sodium alginate and sodium carboxymethyl cellulose affects drug entrapment efficiency. It was observed that with an increase in the concentration of sodium alginate drug entrapment efficiency increases, however, increase in the concentration of sodium carboxymethyl cellulose drug entrapment efficiency decreases. From the statistical second-order complete model equation, it can be concluded that among the polymers used sodium carboxymethyl cellulose had a more profound effect on drug entrapment efficiency as compared to sodium alginate. All the formulations were spherical in particle shape with a smooth surface. The mean particle size of gastro spheres ranged from 730 to 902µm (table 3), which indicate narrower particle size distribution. It was also noted that increasing the drug to the polymer ratio increased the particle size this might be due to increased viscosity of feed solution, which influences the interaction between dispersing phase and dispersion medium who affects the size distribution of particle [16].

FT-IR spectroscopy

FTIR spectra of Carvedilol and its combination with excipients are shown in fig. 3. An IR spectrum of pure Carvedilol showed characteristic peaks at 3352.05 cm-1(O-H and N-H stretching vibration peaks), 2938.40 cm-1(C-H stretching vibrations), 1596.88 cm-1(N-H bending vibrations) and 1241.16 cm-1(O-H bending and C-O stretching vibrations). These peaks can be considered as characteristic peaks of Carvedilol and were not affected and prominently observed in IR spectra of Carvedilol along with excipients as shown in (fig. 3) it indicates no interaction between Carvedilol and excipients.

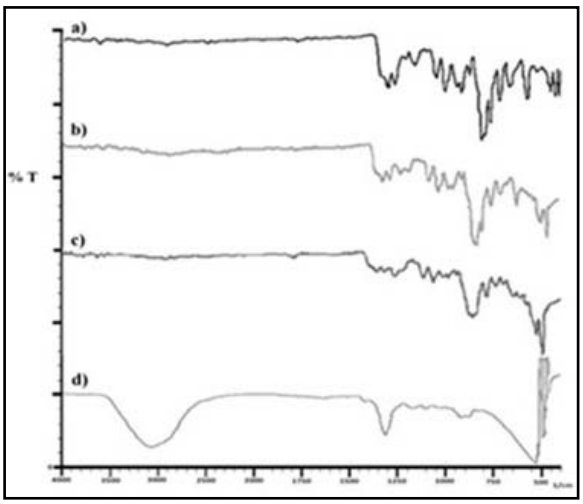

Fig. 3: IR Spectras of a) Carvedilol b) Carvedilol+SCMC c) Carvedilol+SCMC+NA. Alginate d) Formulation F5

The IR spectrum of the formulation showed that there was no significant evidence for interaction between drug and the polymer. Peaks of the drug were observed in formulations.

XRD

Carvedilol has crystalline characteristics, which are represented by peaks in X-ray diffraction, and the most evident peaks appear at 2θ = 12.67, 13.18, 19.60 and 22.14(fig. 4). These peaks were not observed in the Carvedilol loaded gastro spheres. This indicates that drug particles are dispersed at the molecular level in the polymer matrices since no indication about the crystalline nature of the drugs was observed in the drug loaded gastro spheres [14].

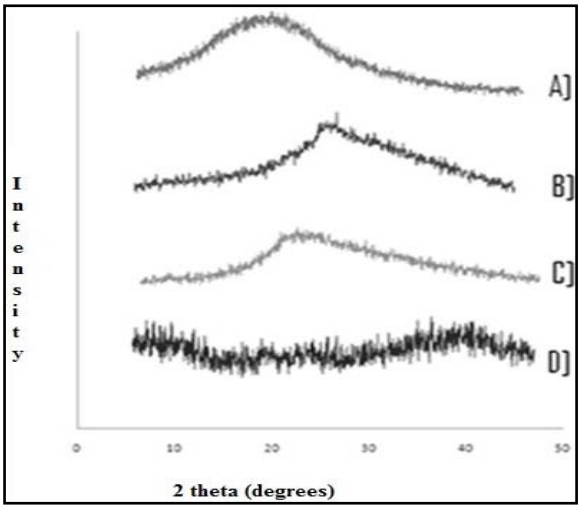

Fig. 4: X-Ray diffraction Spectras of A) Carvedilol B) Carvedilol+SCMC C) Carvedilol+SCMC+NA. Alginate D) formulation F5

DSC

DSC is a fast and reliable method for understanding polymorphic transition when screening drugs and excipients for compatibility, obtaining information about possible interactions. The results of DSC studies are shown in fig. 5. DSC thermogram showed an endothermic peak of Carvedilol at 87 ° C, which corresponds to its melting point. The presence of detectable peaks of Carvedilol in a physical mixture is an indication of uniform mixing of excipients. The absence of peaks of Carvedilol loaded gastro spheres in formulation F5 clearly indicates that Carvedilol was dispersed completely in the formulation, thus modifying the gastro spheres to an amorphous, disordered crystalline phase.

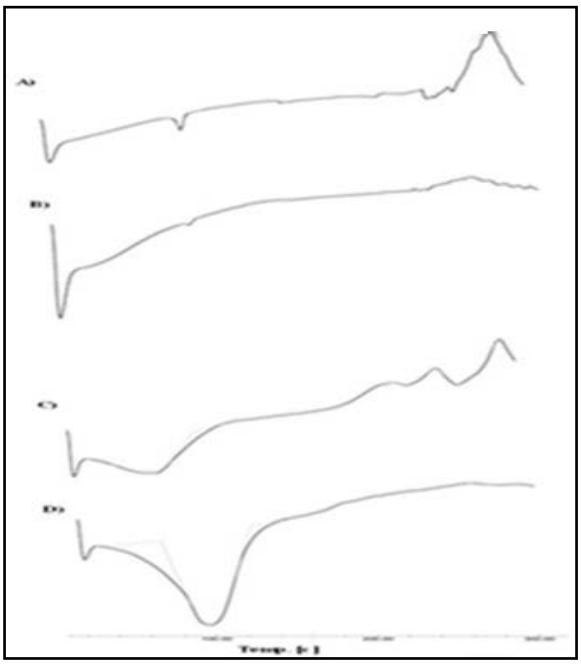

Fig. 5: DSC thermograms of A) pure carvedilol B) Carvedilol+SCMC C) Carvedilol+SCMC+NA. Alginate D) Formulation F5

The additional peak was observed due to loss of moisture (hydrate form) and degradation peak [14]. The absence of detectable crystalline domains of Carvedilol in drug loaded gastro spheres clearly indicates that Carvedilol encapsulated in gastro spheres is in the amorphous-crystalline phase or in the solid state solubilized form in the polymer matrix.

SEM

The morphological analysis of the mucoadhesive gastro spheres was studied by Scanning Electron Microscopy (SEM). SEM photo micrographs of optimized formulation (F5) gastro spheres were rough spherical and shows few pore at the surface (fig. 6). Particulate matters of the drug and polymer were seen at the surface of the gastro spheres, indicating uniform distribution of the drug in the polymeric network [10]. The SEM photographs indicated that the gastro spheres were spherical and completely covered with polymer.

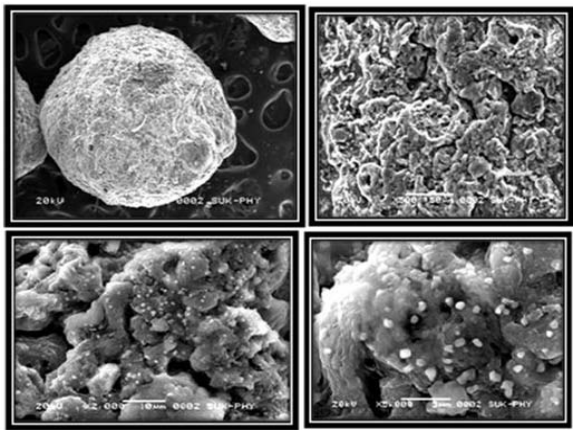

Fig. 6: Scanning electron photograph of drug loaded Gastrosphere (Magnification, X65, X500, X2000, and X5000)

The spherical shape and rough texture with shrinkage were due to the removal of water from gastro spheres during drying. Thus the rate of removal of water from gastro spheres exerts an influence on the morphology of final product [19]. The fig. 6 shows the appearance of white spot on the surface of gastro spheres, when increasing the concentration of carvedilol. Probably those spots represent Carvedilol crystal precipitation on the particle surface [20].

***In vitro* mucoadhesive test**

The in vitro mucoadhesive test using goat intestinal mucosa for assessing mucoadhesivity of gastro spheres containing carvedilol was performed in 0. 1N HCl for 8 h. The percentage of gastro spheres adhering to the goat intestinal mucosal tissue varied from 10% to 20 % over 8 h (fig. 7). Less mucoadhesion of gastro spheres containing carvedilol may be due to the reason that at lower concentration the polymer structure is looser and the polymer chain have more space to extend within the mucus, as the number of polymer chains penetrating in mucus is increased a strong bond, either chemical, mechanical or both is formed between the mucus and the polymer [8]. Amongst all nine batches F5 batch gives more mucoadhesive property.

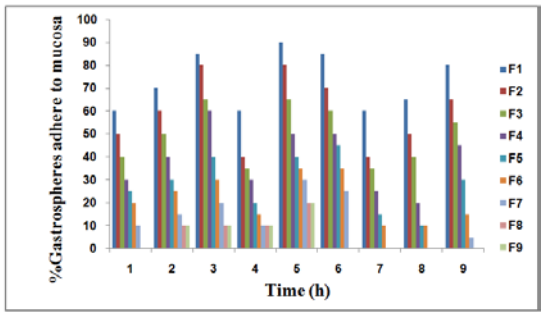

Fig. 7: *In vitro* mucoadhesive strength of carvedilol gastro spheres N=3, error bars omitted for clarity of the fig

***In vitro* drug release study**

Gastro spheres were subjected to *in vitro* release using basket type dissolution apparatus in 900 ml of 0.1N HCl medium. The results of the *in vitro* drug release studies are shown in fig. 8. The release rate was found to be decreased in accordance with the increase in the ratio of polymer used. Carvedilol release from the gastro spheres was studied in gastric buffer 0.1N HCl for 12 h. In the case of gastro spheres containing higher polymer contents, the more hydrophilic property of the polymers could probably bind better with water to form a viscous gel structure, which might block the pores on the surface of gastro sphere and could delay the drug release [8]. Among all the fabricated formulation, F5 was chosen as an ideal formulation showing an extended drug release over a period of 12h (88.55%) with the acceptable mucoadhesive property. The drug release from the 9 batches was used to generate predictor equations for Carvedilol gastro spheres with independent variables as sodium alginate concentration (X_1) and sodium carboxyl methyl cellulose (X_2).

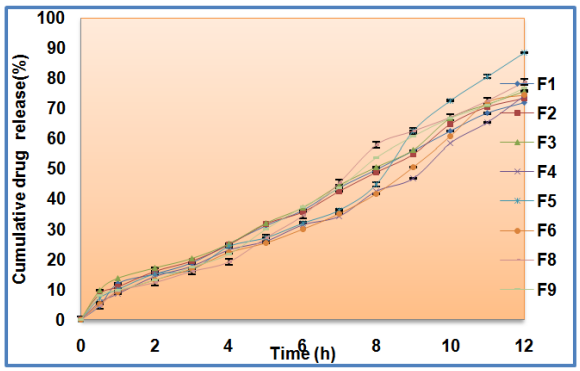

Fig. 8: *In vitro* drug release from various Carvedilol gastro spheres prepared through ionotropic gelation [mean+/-SD, n = 3]

Final equation in terms of coded factors

Drug Release =+77.14+2.17 * SA+4.26 * NaCMC

[R2 =0.7096;Adjusted R2 =0.6128;Predicted R2 =0.2562;F= 7.33;P<0.05]

From the Response Surface plot for drug entrapment efficiency (fig. 2) it was observed that the change in concentration of sodium alginate and sodium carboxyl methyl cellulose affected the drug release. It was observed that increase in the concentration of sodium alginate increases the drug release up to the certain extent the further increase in the concentration of sodium alginate retards the drug release values. However, a decrease in drug release values with the increasing SCMC amount (X_2) is indicated by the three-dimensional response surface graph relating drug release (fig. 2). Surface response plot indicates that sodium alginate concentration at the optimum level 400 mg yielded gastro spheres with the highest drug release with SCMC concentration at 200 mg. Hence the Optimized Batch was found to be F5 with the optimum level of sodium Alginate and SCMC. From the statistical second-order complete model equation, it can be concluded that among the polymers used sodium carboxyl methyl cellulose has a more profound effect on drug release as compared to sodium alginate.

Release kinetics

The *in vitro* drug release data from the various mucoadhesive gastro spheres containing carvedilol were evaluated kinetically using various mathematical models like zero order, first order, Higuchi, and Korsmeyer–Peppas model [8, 18]. When respective correlation coefficients of these gastro spheres were compared the Carvedilol release from these gastro spheres was found to follow the zero-order model (R2 = 0.956–0.996). In addition, Korsmeyer–Peppas model (R2 = 0.931–0.980) was found to be closer to the best fit zero order model. The best fit of the zero order model indicated that the drug release from these gastro spheres followed the sustained-

release pattern. The values of the release exponent (n) determined from *in vitro* drug release data of various Carvedilol gastro sphere F1, F2,F3, F4, F5, F6, F7and F9 follows the analomus non fickian drug release pattern (0.667-0.851) i.e. the rates of solvent penetration and drug release are in the same range. And F8 indicating the drug release from these gastro spheres followed the case II transport mechanism (0.906). The mechanisms controlled by swelling and relaxation of polymer in the matrix.

CONCLUSION

From the present study, it was concluded that mucoadhesive gastro sphere of Carvedilol can be prepared using the ionotropic gelation method. The preparation process was simple, reliable, and inexpensive. 3^2 full factorial designs are suitable to study the effect of process variables on formulation characteristics by applying statistical analysis. From the study, we successfully developed microparticulate drug delivery system of Carvedilol by using mucoadhesive polymers like Na CMC and rate retardant sodium alginate polymer. Further, *in vivo* investigation is required to establish efficiency and IVIVC of this formulation.

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CONFLICTS OF INTERESTS

Declare none

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