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Research Article

GASTRO-RETENTIVE FLOATING MICROSPHERES OF CARVEDILOL: FORMULATION, CHARACTERISATION AND IN-VITRO EVALUATION

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ABSTRACT

The objective of the present study was to formulate and evaluate floating microspheres of carvedilol. Carvedilol has a terminal half-life of 7-10 hr, but most of the drug is eliminated with a half-life of about 2 hr. Besides being a beneficial drug compared to other drugs of the same class, it has narrow absorption window in upper part of the gastro intestinal tract, hence a floating drug delivery system is preferred, such that the formulation will be available for a longer duration than usual for absorption. Floating microspheres were prepared by emulsion solvent diffusion method using ethanol and dichloromethane as solvents. Ethyl cellulose andHydroxy propyl methyl cellulose K 4 M(HPMC K 4 M) were used to prolong the release of the drug from microspheres. The prepared microspheres were subjected to various evaluatory studies. All the microspheres were found to have a size in the range of 20-40 µ and were nearly spherical in shape. Optimised batch F11 exhibited good buoyancy (73 ± 1.00 %) and sustained release (45.41 ± 0.13 % Cumulative drug dissolved) (% CDD) compared to other formulations. It was subjected to dissolution studies using USP type 1 apparatus and Rosette rice apparatus. Drug release data was compared with the release data obtained from marketed tablet Cardivas (Controlled Release) CR. The release kinetics obtained using Rosette Rice apparatus were good compared to USP type I apparatus. The release of the drug from microspheres and Cardivas CR followed non-fickiananamolous diffusion.

Keywords: Buoyancy, Emulsion solvent diffusion method, Hypertension, Optimised batch, Rosette rice apparatus.

INTRODUCTION

Hypertension is defined as persistent elevation of systolic blood pressure(BP) of 140 mmHg or greater and/or diastolic BP of 90 mmHg or greater. It is one of the most widely observed disorders (one billion adults all over the world). Various classes of drugs were developed to treat hypertension by regulating all the known pathways which promote hypertension. β-Blockers are a class of drugs that help in regulating blood pressure by blockade of β-receptors. Carvedilol belongs to the class β-Blockers. It is beneficial over traditional β-Blockers that it also helps in reduction of peripheral vascular resistance by α-Blockade. Carvedilol and several of its Metabolites are effective in inhibiting lipid peroxidation. The ability of carvedilol to preserve the endogenous anti-oxidants, vitamin E and glutathione, is of special importance in view of recent reports associating low levels of the anti-oxidant vitamins with increased risk of cardiovascular morbidity and mortality[1]. Carvedilol has an absolute bioavailability of 25-35 %. It has a half-life of about 7 -10 hr with an elimination half-life of 2 hr. It is well absorbed in the upper part of gastrointestinal tract so a floating drug delivery system which can release drug in a sustained manner is useful to enhance bioavailabilty of the drug. Hence floating microspheres were designed. Floating microspheres are hollow microspheres with drug and polymer dispersed as a coat enclosing a hollow cavity. They are able to remain buoyant on gastric fluid by virtue of their low density. As the system remains buoyant on gastric contents, drug gets released slowly at desired rate from the system. Once the release of drug gets ceased the residual system gets emptied from the stomach.

MATERIALS AND METHODS

Carvedilol was a gift sample obtained from AurobindoPharma (B. No: HCDC 09110044), Hyderabad. Ethyl cellulose (18-24 cps), HPMC K 4 M from SAS chemicals co, Mumbai, Ethanol from Changshuyangyuan chemical, China, Dichloromethane and HCl from Hi media laboratories pvt ltd, Mumbai.

Methods

Preformulation studies

Solubility of carvedilol in distilled water and in buffers of pH 1.2, pH 6.8 and pH 7.4 was performed. A saturated solution of Carvedilol in these buffers was made by keepingexcess of drug in small conical flasks kept in shaker water bath for 24 hr. The saturated solution was filtered through what man filter paper and the clear liquid was diluted suitably and absorbance was taken by UV-spectrophotometer. Using the standard plot the amount of Carvediol dissolved in the buffer was found out.Further DSC and FTIR studies were done for the drug and drug with excipients to ensure there is no interaction between them.

Table 1: Formulation development of floating microspheres of Carvedilol

Batch code	Ethyl Cellulose	HPMC K 4 M	Drug	Ethanol	Dichloro-methane	Tween 80	Stirring speed
F1	200 mg	200 mg	50 mg	10 ml	10 ml	0.2%	1200
F2	300 mg	300 mg	50 mg	10 ml	10 ml	0.2%	1200
F3	100 mg	100 mg	50 mg	10 ml	10 ml	0.2%	1200
F4	200 mg	-	50 mg	10 ml	10 ml	0.2%	1200
F5	400 mg	-	50 mg	10 ml	10 ml	0.2%	1200
F6	100 mg	200 mg	50 mg	10 ml	10 ml	0.2%	1200
F7	300 mg	200 mg	50 mg	10 ml	10 ml	0.2%	1200
F8	400 mg	200 mg	50 mg	10 ml	10 ml	0.2%	1200
F9	200 mg	100 mg	50 mg	10 ml	10 ml	0.2%	1200
F10	200 mg	300 mg	50 mg	10 ml	10 ml	0.2%	1200
F11	200 mg	400 mg	50 mg	10 ml	10 ml	0.2%	1200

Preparation of floating microspheres of carvedilol [2]

Floating microspheres of Carvedilol were prepared by emulsion solvent diffusion method**.** Drug, Ethyl cellulose and HPMC K 4 M were dispersed in Ethanol and Dichloromethane mixture. This dispersion was transferred slowly into a beaker containing distilled water with tween 80andkept on a magnetic stirrer set to desired rpm (table 1 shown below). The stirring was done for 2 hours. Then

the formed microspheres were collected by vacuum filtration and they were dried in hot air oven. They were preserved in desiccator for future use.

Evaluation of floating microspheres of Carvedilol

Determination of drug content and entrapment efficiency [2]

10 mg of microspheres were added to 10 ml methanol in a beaker and was kept for stirring overnight so as to extract the drug. The extract was subjected to centrifugation to collect clear solution. One ml of this clear solution was diluted using 0.1N HCl and was evaluated spectrophotometrically to get the amount of drug in 10 mg of microspheres. From this the amount of drug in the entire batch of microspheres was calculated. Entrapment efficiency indicates the amount of drug that has been entrapped into the microspheres.

Determination of micromeretic properties

Microspheres were evaluated for angle of repose, bulk density and tapped density by usual methods and hence theCarrs index, Hausner'sratio werecalculated.

Determination of size of microspheres

Size of microspheres was determined using Olympus DP 20 microscope by adopting calibrated ocular micrometer.

Determination of percentage buoyancy [2]

Buoyancy studies were conducted in USP type II paddle apparatus. 100 mg of microspheres from each batch were taken and placed in 400 ml of 0.1 N HCl with 0.02% tween 20. Stirring was applied at 100 rpm for 8 hrs. Then the layers of microspheres that remained buoyant after 8 hr were decanted and were collected by filtration. Similarly the sinking layers of microspheres were also collected by filtration. The collected microspheres were dried in an oven and dry weight was determined using weighing balance. The percentage buoyancy was calculated as:

$$\text{Buoyancy \%} = \frac{[\text{weight of floating microspheres}]}{[\text{wt. of floating microspheres + wt. sinked microspheres}]}\ [100]$$

***In-vitro* release studies**

a) By USP type I basket apparatus [2]

Invitro release studies were carried out in USP type I basket apparatus. A suitable weight of microspheres equivalent to 20mg drug were placed in the baskets and further the baskets were wrapped in muslin cloth.The baskets were immersed in 900 ml of 0.1 N HCl maintained at 37 ± 2°C. Baskets were rotated at 100 rpm. 5 ml of samples were taken periodically for 8 hours and were analyzed spectrophotometricaly to calculate %CDD.

b) By modified beaker apparatus (Rosette – Rice apparatus) [3]

Optimized batch microspheres with 20 mg drug equivalent weight were packed in muslin cloth and were immersed in 70 ml of 0.1 N HCl in the beaker apparatus. Stirring was applied at 100 rpm. 5 ml of samples were taken periodically for 8 hours and were analyzed spectrophotometricaly to calculate %CDD.

C) In-vitro release study of marketed tablet Cardivas CR

In-vitro release study from marketed controlled release tablet Cardivas CR was carried out in 0.1 N HCl buffer using USP type 2 paddle apparatus. Stirring was applied at 100 rpm. 5 ml of samples were taken periodically for 8 hours and were determined using UV spectrophotometer.

RESULTS AND DISCUSSION

Solubility studies shows that Carvedilol is better soluble in buffer pH 1.2 (32.619 ± 0.765 µg/ml) than in buffer pH 6.8 (31.124 ± 0.890 µg/ml), buffer pH 7.4 (29.421 ± 0.598 µg/ml) and distilled water (2.89 ± 0.876 µg/ml) owing to its weak basic nature.

Differential scanning calorimetry (DSC) (figure 1) and Fourier transform-Infrared spectroscopy (FT-IR) (figure 2) revealed that the drug and polymers were compatible.

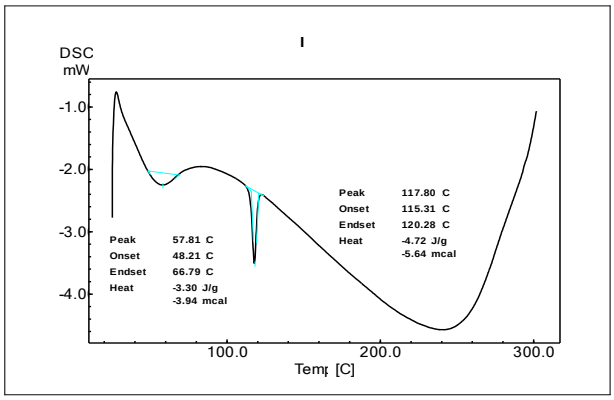

Fig. 1: DSC thermogram of physical mixture of Carvedilol, HPMC K 4 M and Ethyl Cellulose

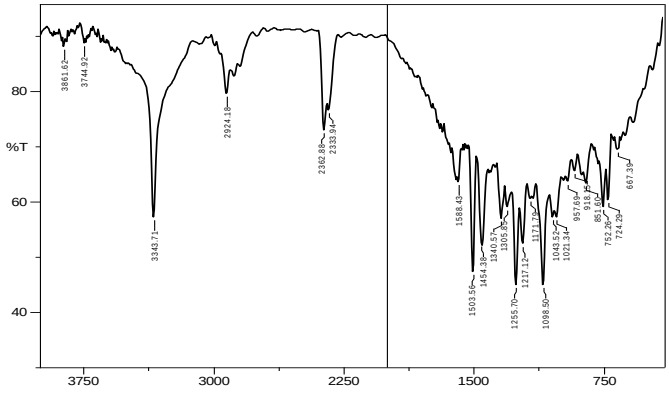

Fig. 2: FT-IR spectrum of physical mixture of Ethylcellulose,HPMC K 4 M and Carvedilol

Evaluation of floating microspheres of Carvedilol

Microscopic evaluation

Micromeritic properties are summarized in table 2 shown below.

Table 2: Results of micromereticproperties of floating microspheres of Carvedilol

Batch code	Carss index (Type of flow)	Hausner's ratio (Type of flow)	Angle of repose (Type of flow)
F1	18.18 (fair)	1.22 (good)	25.84 (good)
F2	9.02 (excellent)	1.10 (good)	25.128 (good)
F3	10.345 (excellent)	1.115 (good)	26.347 (good)
F4	9.090 (excellent)	1.100 (good)	29.82 (good)
F5	9.543 (excellent)	1.038 (good)	28.792 (good)
F6	16.66 (good)	1.20 (good)	18.06 (good)
F7	8.051 (excellent)	1.087 (good)	27.22 (good)
F8	11.13 (excellent)	1.125 (good)	28.64 (good)
F9	8.564 (excellent)	1.035 (good)	26.62 (good)
F10	15.675 (good)	1.02 (good)	28.243 (good)
F11	14.740 (good)	1.023 (good)	26.048 (good)

Particle size was measured using Olympus DP 20 microscope. It was observed that all the particles fall in the range of 20 to 40 μ). Highest particle size was reported by formulation F11 (36.789 ± 11.624 μ) and lowest particle size was reported by formulation F4 (20.038 ± 12.159 μ) (table 3). Particle size was found to be increased with increase in polymer proportion which may be due to increased viscosity of feed solution which influences the interaction between disperse phase and dispersion medium that affects the size distribution of particles. All microspheres were found to be nearly spherical in shape (figure 3).

Determination of encapsulation efficiency

Effect of polymer content on encapsulation efficiency was studied. It is evident that with increase in polymer quantity encapsulation efficiency also increased. This may be due to increase in viscosity with increased polymer concentration, such that drug molecules cannot leave without getting entrapped in oil globules [4] . Highest % encapsulation efficiency was observed with formulation F8 (93.147 ± 1.017%) while the lowest % encapsulation efficiency was reported by formulation F4 (28.956 ± 0.173%) (table 3). Incorporation of HPMC K 4 M has resulted in enhanced % encapsulation efficiency this may be due to its gel forming tendency by which the viscosity of the medium increases and hence the % encapsulation efficiency increases. Increase in amount of ethyl cellulose alone didn't show significant increase in % encapsulation efficiency which was shown by formulations F4 (28.956 ± 0.173%) and F5 (29.051 ± 0.473%).

Buoyancy studies

Buoyancy studies done for all the formulations from F1 – F11 for 8 h indicate that the microspheres have good floatability. All microspheres exhibited instant buoyancy with no lag time. Highest buoyancy was shown by formulation F11 (73 ± 1.00%) while the lowest with formulation F4 (51.630 ± 0.370%)(table 3). An increase in buoyancy was found with increase in polymer: drug ratio. Further increase in content of HPMC K 4 M has shown an increase in buoyancy. This may be due to air entrapment because of gelling and swelling properties of HPMC K 4 M [5].

Table 3: Results of various evaluatory studies on floating microspheres of Carvedilol

Batch code	% Encapsulation efficiency (in 10 mg microspheres) (n=2)	Drug content(in 10 mg)	Particle size (in μ ± sd^n) (n=50)	% Buoyancy ± sd^n (n=2)	% CDD ± sd^n (n=3)
F1	70.69 ± 0.52	1.88	30.20 ± 11.36	61.76 ± 0.44	70.42 ± 0.23
F2	75.00 ± 0.02	1.78	35.75 ± 13.75	71.26 ± 0.94	48.28 ± 1.32
F3	62.80 ± 0.38	2.58	26.96 ± 9.95	53.93 ± 0.82	79.19 ± 2.13
F4	28.95 ± 0.17	0.99	20.03 ± 12.15	51.63 ± 0.37	96.00 ± 1.48
F5	29.05 ± 047	0.65	33.21 ± 9.87	61.70 ± 0.48	75.62 ± 0.86
F6	59.83 ± 0.07	3.24	26.78 ± 12.27	58.96 ± 0.90	70.55 ± 0.53
F7	65.24 ± 0.93	1.21	31.95 ± 14.39	63.87 ± 0.12	67.62 ± 1.62
F8	93.14 ± 1.01	1.56	34.26 ± 13.54	70.03 ± 1.03	52.79 ± 0.70
F9	54.29 ± 0.04	1.32	28.40 ± 11.41	58.30 ± 0.66	72.04 ± 0.33
F10	89.06 ± 1.06	1.95	31.58 ± 14.07	66.23 ± 0.77	57.11 ± 1.59
F11	85.28 ± 0.38	1.47	36.78 ± 11.62	73.00 ± 1.00	45.41 ± 0.13

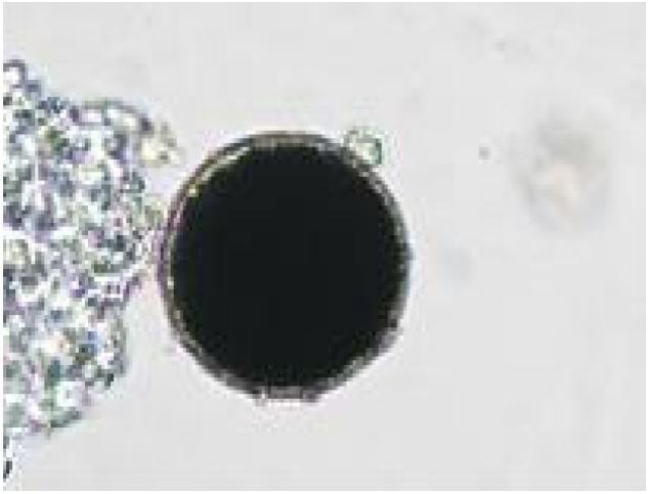

Fig. 3: Photomicrograph of microsphere of optimized batch F11

***Invitro* release studies**

Dissolution study was done for 8 h for all the formulations F1 – F11 in triplicate (table 3). *Invitro* release studies indicate highest release by formulation F4 (96.00 ± 1.48 %) (figure 4) while the lowest release was shown by formulation F11 (45.41 ± 0.13 %) (figure 5). Increase of polymer content reduced the rate of release of drug from the microspheres. HPMC K 4 M containing formulations exhibited low release rates, an increase in HPMC K 4 M content also reduced the rate of drug release and this may be due to its swelling properties which might have increased the diffusional path length [6].

***Invitro* release study of optimized batch F11**

Formulation F11 was chosen as optimized batch as it exhibited good buoyancy (73 ± 1.00 %) and sustained release (45.41 ± 0.13 %CDD) compared to other formulations. It was subjected to dissolution in Rosette rice apparatus and the dissolution data was compared with that obtained using USP type I apparatus. (figure 6).

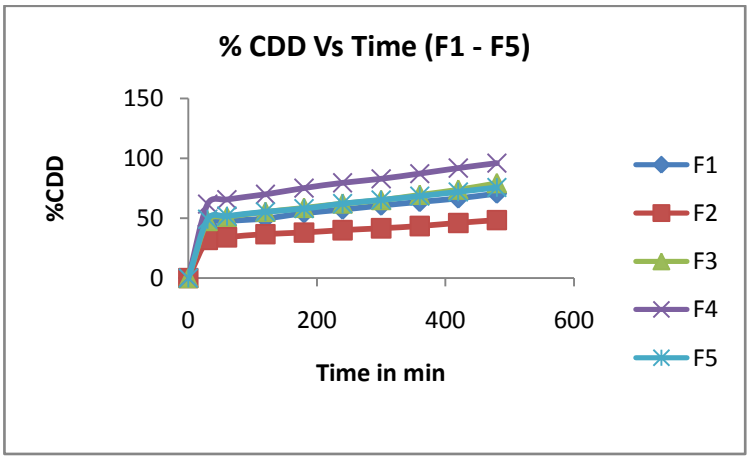

Fig. 4: In-vitro release release study of formulations F1-F5

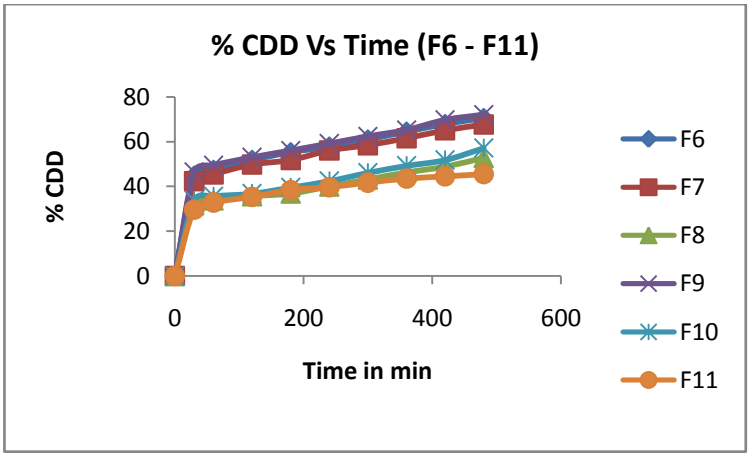

Fig. 5: In-vitro release release study of formulations F6-F11

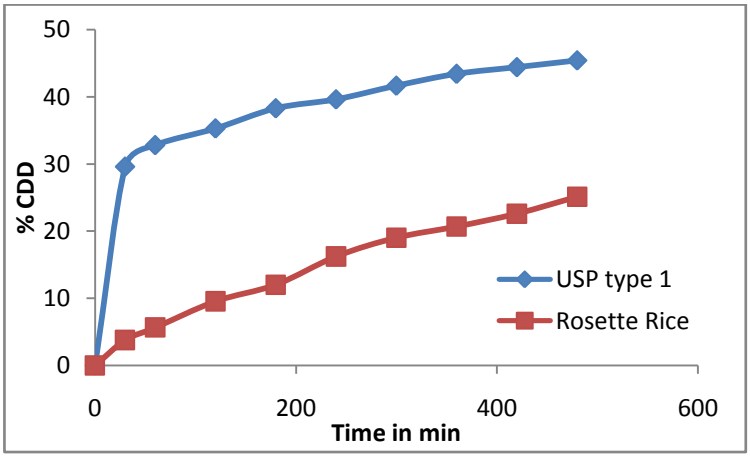

Fig. 6: Comparision of dissolution data of optimized batch F11 microspheres obtained using USP type 1 apparatus and Rosette Rice apparatus

The dissolution profile of the formulation F11 done in Rosette Rice did not match with that done in USP Type I apparatus indicating the former apparatus may not be suitable for substitution to Type I dissolution apparatus[3]

From the kinetic studies using both USP type I and Rosette Rice apparatus it is evident that the drug release followed first order and korsmeyerPeppas kinetics in USP type I apparatus. Drug release in Rosette rice apparatus followed zero order, Higchi, KorsmeyerPeppas kinetics. These results were derived based on regression values. Hence the kinetics obtained using Rosette Rice apparatus are good compared to USP type I apparatus this may be due to continuous flow of dissolution medium throughout the study period and contact of fresh medium with the dosage form directly in case of Rosette Rice apparatus. Drug release from Cardivas CR tablet follows zero order, higuchi and hixon-crowell kinetics. The n value from korsmeyerbPeppas plot in all the above three was found to be > 0.5 hence the release follows non-fickian anomalous diffusion in all the above three cases (table 4).

Stability studies

Stability studies at accelerated conditions of 40°C/75% Relative humidity(RH) for a period of one month were carried out for optimized formulation F11 of Carvedilol floating microspheres. There were no significant changes in the drug content and buoyancy. The drug release profile represented that there were no significant changes in physical as well as chemical characteristics of the formulation (table 5). Hence, it can be derived from the results that the developed Carvedilol floating microspheres were stable and retained their pharmaceutical properties over a period of one month.

Table 4: Comparative kinetic study between USP type I apparatus and Rosette Rice apparatus using optimized batch F11 and marketed tablet Cardivas CR

S. No.	Type of release kinetic study	USP type I apparatus (R^2 Value)	Modified beaker Apparatus (R^2 Value)	Cardivas CR (R^2 Value)
1	Zero order	0.5636	0.9798	0.9393
2	First order	0.9896	0.7278	0.8086
3	KorsmeyerPeppas	0.8607	0.9792	0.9939
	n=	0.5786	0.543	0.5672
4	Higuchi	0.7892	0.9792	0.9977
5	Hixon-Crowel	0.6311	0.968	0.968

Table 5: Comparison of results of various studies of microspheres of optimized batch F11before and after exposure to accelerated storage conditions

Parameter	Before stability study	Results after one month of storage under accelerated conditions
Drug content (in 10 mg microspheres)	1.47 mg	1.40 mg
% Buoyancy±sd^n (n=2)	73 ± 1.00 %	71±0.85 %
Invitro release study %CDD±sd^n(n=3)	45.41 ± 0.13%	45.67 ± 0.926 %

n*= number of trials

CONCLUSIONS

Floating microspheres were prepared with various proportions of polymers Ethyl cellulose and HPMC K 4 M. Particle size of the microspheres was found to be in the range of 20-40µ. All the formulations exhibited good flow properties. Formulation F11 exhibited prolonged release (45.31% CDD in 8 hr) and better buoyancy (73 ± 1.00%) compared to other batches. *Invitro*release studies were performed with optimized batch by USP type I apparatus, Rosette rice apparatus.. Drug release in Rosette riceapparatus followed zero order, Higchi, KorsmeyerPeppas kinetics while in USP type I the release followed first order and korsmeyerPeppas kinetics. The release of drug followed non-fickian anamolous diffusion similar to that of release of drug from marketed tablet Cardivas-CR. Better release was observed using Rosette rice apparatus. However the release was not matching with that obtained by USP type I apparatushence its application for evaluation of microspheres needs further investigation

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