World Journal of Pharmaceutical Research
SJIF Impact Factor 5.045
Volume 3, Issue 6, 1859-1884. Research Article ISSN 2277 – 7105

FORMULATION AND EVALUATION OF FLOATING OSMOTIC DELIVERY SYSTEM OF CARVEDILOL

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Article Received on
22 June 2014,

Revised on 17 July 2014,
Accepted on 12 August 2014

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ABSTRACT

Floating osmotic delivery system is a combination of floating and osmotic systems that provides site specific and controlled drug release. Carvedilol is non- selective β blocker under bio pharmaceutical classification system (BCS) class II is widely used in the treatment of hypertension. Half-life of model drug is 6-8 h. The model drug showed promising pharmacokinetics and physico - chemical properties required for controlled releases dosages. Therefore this drug was selected for present investigation. Floating drug delivery system was developed initially by formulating the osmotic core tablet followed by multilayer coating for floating the system. Core tablet comprised of Carvedilol, Mannitol, and sodium bicarbonate which was coated with cellulose acetate (osmotic layer), followed by coating of floating layer with Hydroxyl propyl Methyl cellulose (E15 / E50) and sodium bicarbonate and further coated with entrapment layer composed of Eudragit RL30D.The drug and polymers were characterized by DSC and pre-compression like bulk density, tapped density and Hausner's ratio. The prepared tablets were evaluated for physical properties like floating lag time, duration of floatation. *Invitro* studies revealed that drug release depends on concentration of polymer, agitation speed and pH of the medium. From the results, it indicated that formulation were intact. Floating lag time and floating time were dependent on hydroxyl propyl methyl cellulose grade used in floating layer and coating percentage on entrapment layer. Drug release was controlled by changing the amount of mannitol in the core tablets.

KEY WORDS: Sustained release, Matrix tablets, Model drug, Sodium bicarbonate, Hydroxy propyl Methyl cellulose, Eudragit RL 30D,Mannitol, talc.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes of administration that has been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient compliance and cost effective manufacturing process. The dissolution rate of a drug from its dosage form is considered as an important parameter in the bioavailability. The rate determining step in the absorption of orally administered hydrophilic drugs is the rate of drug permeation through the biomembrane. In other words, absorption of such drugs is said to be permeation rate limited. These immediate release dosage forms have some limitations such as drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance. A typical peak-valley plasma concentration-time profile is obtained which makes difficult to attainment of steady state condition. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of modified drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[3] Osmotic tablets and osmotic pumps - Osmotic pump drug delivery systems (OPS) utilize osmotic pressure as the driving force for the delivery of drugs. The formulation of this system mainly consists of an osmotic core, which is coated with a semi-permeable membrane, and a delivery orifice on the membrane, which is created by a laser drill. After orally taking, as soon as the tablet comes into contact with water in stomach, water will be imbibed through the membrane because of the resultant osmotic pressure, and then the drug will be released through the orifice at a controlled rate.Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

MATERIALS AND METHODS

Carvedilol was obtained as a gift sample from Apollo Pharmaceuticals API manufacturers India Pvt. Ltd., (Mumbai, India) and Eudragit RS 30D and Klucel-LF was obtained from Coloron, India and HPMC K4M was obtained from CP Kelco, India, Cellulose acetate was purchased from FMC biopolymer, India. All other chemicals and reagents were of analytical

grade.

METHODS

Preparation of core tablets

Core tablets were prepared by wet granulation method. All ingredients were weighed accurately. API, polymer and binder were sifted through BSS # 30 Sieve separately. API, polymer were blended in a poly-bag. Binder was dissolved in isopropyl alcohol to get a clear solution. This solution is called as binder solution. Materials which were blended were granulated with binder solution. Granules that were formed after granulation were dried in rapid drier at 50 $^{\circ}$C for 40 min. These dried granules were passed through BSS sieve # 30. Diluent, glidant were sifted through BSS sieve # 40 and blended with granules that were prepared. Extra granular lubricant was sifted through BSS sieve # 60 and blended with above materials for 5 min. The resultant blend was then compressed in to tablets using 16 station compression machine with 9 mm diameter standard concave punches depending on the final tablet weight. The amount of drug was kept constant at 40 mg while the amounts of other excipients were varied. The formulation chart is shown in table no. 1 and 2.

Table No. 1: Formulation chart

Ingredients	mg per tablet							
	F1	F2	F3	F4	F5	F6	F7	F8
Intra granular part								
Drug	40	40	40	40	40	40	40	40
Mannitol SD 200	100	100	100	100	100	100	100	100
Klucel-LF	10	10	10	10	10	10	10	10
Extra granular part								
MCC(102)	0	0	0	0	0	0	0	50
Pregelatinized starch	50	0	0	0	0	0	0	0
Methocel K4M	50	25	0	0	0	0	0	0
Xanthan gum	0	0	25	0	0	0	0	0
Klucel HF	0	0	0	25	0	0	0	0
PVP K-90	0	0	0	0	25	0	0	0
Polyox N80	0	0	0	0	0	25	0	0
Sodium bicarbonate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	0
Citric acid	12.5	12.5	12.5	12.5	12.5	12.5	12.5	0
Magnesium stearate	5	5	5	5	5	5	5	5
Total weight	280	205	205	205	205	205	180	205
Coating Composition	**Coating percentages (% weight gain)**							
Osmotic layer CA: PEG 400 (1:0.2)	10	10	10	10	10	10	10	10
Floating layer HPMC E15: NaHCO3: PEG 6000 (6:4:0.6)	5,15	5,15	5,15	5,15	5,15	5,15	5,15	5

Entrapment layer Eudragit RL 30D : Talc: TEC (1: 0.35: 0.2)	0,2,4,6,8	0,2,4,6,8	0,2,4,6,8	0,2,4,6,8	0,2,4,6,8	0,2,4,6,8	0,2,4,6,8	4,6,8

Table No. 2: Formulation chart

Ingredients	**mg per tablet**											
	F9	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**
Intra granular part												
Drug	40	40	40	40	40	40	40	40	40	40	40	40
Mannitol SD 200	100	100	100	100	100	100	100	100	50	50	50	80
Klucel-LF	10	10	10	10	10	10	10	10	10	10	10	10
Extra granular part												
MCC (102)	50	50	25	50	50	50	37.5	37.5	37.5	37.5	37.5	37.5
Sodium bicarbonate	0	0	12.5	0	0	0	12.5	12.5	12.5	12.5	12.5	12.5
Citric acid	0	0	12.5	0	0	0	0	0	0	0	0	0
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Total Weight	205	205	205	205	205	205	205	205	155	155	155	185
Coating Composition	**Coating percentages (% weight gain)**											
Osmotic layer CA: PEG 400 (1: 0.2)	10	10	10	10	10	4	4	4	4	4	4	4
Floating layer HPMC E15: NaHCO3: PEG 6000 (6:4:0.6)	5,15											
Floating layer HPMC E50 : NaHCO3: PEG 6000 (6:4:0.6)		5	5		5	5	5	5	5	2.5	5	2.5
Entrapment layer Eudragit RL 30D : Talc: TEC (1:0.35:0.2)		4,6,8	4,6,8		8	8	8	4	4	8	8	4
Entrapment layer eudragit RL 30D : Talc: TEC (1:0.15:0.15)	4,6, 8											

Coating composition

Coating of osmotic layer

Coating of the Osmotic layer was done using the components as mentioned in table 3. Membrane forming layer used was cellulose acetate. It is made to dissolve in acetone. Pore former like Poly ethylene glycol (400/600) was dissolved in water. Then PEG solution was made to disperse in the CA solution and this coating solution was used to coat the core tablets in hi-coater of varying percentage build up. Coating has to be done at normal room temperature since acetone which was used as solvent is highly volatile.

Table 3: Coating composition and coating parameters of semipermeable Membrane

Coating Composition	
Polymer	Cellulose acetate
Plasticizer	PEG 400
Solvent	Acetone: water (90:10)
Solid content	6 % w/w
Coating Parameters	
Parameter	Operating condition
Pan rotations	14-18 rpm
Inlet temperature	28-30 °C
Bed temperature	20-24 °C
Spray rate	5-7 ml/min

Coating of floating layer

Coating of the floating layer was done using the components as mentioned in table 4. Accurately weighed amount of HPMC is dispersed in 50 % of hot water. Required amount of plasticizer and effervescent agent was dissolved in remaining 50 % of cool water this solution was added to the HPMC dispersion slowly at rapid mixing speed to form clear solution.

Table 4: Coating composition and coating parameters of floating layer

Coating composition	
Polymer	HPMC (E15/E50)
Plasticizer	PEG 6000
Effervescent agent	Sodium bicarbonate
Solvent	Water
Solid content	4 %w/w
Coating parameters	
Parameter	**Operating condition**
Pan rotations	16-20 rpm
Inlet temperature	85-90 °C
Bed temperature	38-42 °C
Spray rate	3-5 ml/min

Coating of the entrapment layer was done using the components as mentioned in table 5. Accurately weighed quantity of TEC was mixed with sufficient amount of water and to this solution accurately weighed amount of talc was added under high mixing speed to form uniform dispersion, to the dispersion required amount of eudragit RL 30 D was added at high mixing speed.

Table 5: Coating composition and coating parameters of entrapment layer

Polymer	Eudragit RL 30 D
Plasticizer	TEC
Coating aid	Talc
Solvent	Water
Solid content	15 % w/w
Coating	**Parameters**
Parameter	Operating condition
Pan rotations	16-20 rpm
Inlet temperature	85-90 °C
Bed temperature	38-42 °C
Spray rate	3-5 ml/min

Evaluation of Precompression parameters

1. Organoleptic evaluation

The colour, odour and taste of the drug were evaluated and tabulated using descriptive terminology.

2. Drug-Excipients compatibility study

a. Thermal analysis

A differential scanning calorimeter was used for thermal analysis of drug and mixture of drug and excipients. The drug and excipients were passed through the 60 # sieve and mixed. Accurately transferred 5 mg of drug alone and mixture of drug and excipients in to the pierced DSC aluminum pan and scanned at the temperature range of 25-250 ℃ at heating rate of 20 ℃/min. The thermo grams obtained were compared for any interaction between the drug and excipients with that of thermo gram of only drug. After every week of study, physical appearance of these compositions were made and compared with the initial observations.

3. Particle size distribution

10.35 g of sample was taken and added to an assembly of sieves consisting Average Size of Test Measurements (ASTM) sieve numbers # 30, 40, 60, 80,100,120 base. Then assembly was closed and kept on sieve shaker and started analysis. Weights retained were checked for every 5 min and process was continued until variation in weights retained was not more than 5 % or 0.1 g. 20 min was set as end point based on the observation. Calculations were made to obtain cumulative percentage weight retained and tabulated.

4. Bulk density

Bulk density was determined by pouring 15 g of drug (previously passed through 18 # sieve to remove any lumps) into a graduated cylinder inclined at 45° to horizontal surface. The cylinder was then brought to standing position and measured the volume occupied by material to the nearest possible and calculated BD using following formula.

Bulk density = Weight / Bulk volume.

5. Tapped density

Tapped density is determined by using electrolab tap density tester according to USP method I. A 50 ml measuring cylinder was taken and the weight of the cylinder was noted. 15 g of drug was weighed and added to the cylinder and weight and volume of the cylinder was noted. The measuring cylinder was subjected to 500 taps in TD apparatus, then Volume was noted, then again subjected to 750 taps and volume (V_a) was noted, then the tapping was continued for 1250 taps and volume (V_b) was noted, the difference between V_a and V_b was less than 1 % so V_a was selected as final tapped volume. Tapped density was calculated using following formula. **Tapped density = Weight / Tapped volume**

6. Carr's Index

Carr's index was calculated using the following equation

CI = (Tapped density-Bulk density) / Tapped density x100

7. Hausner's Ratio

The Hausner's ratio is another index of the flow-ability of the pharmaceutical powders. It was calculated using following equation

Hausner's Ratio = Tapped density/Bulk density

8. Saturation solubility

Excess drug was added carefully using a spatula to 10 ml of the aqueous buffer in a conical flask, while stirring until a heterogeneous system (solid sample and liquid) was obtained. The solution containing excess solid was then capped, and stirred at 150 rpm at the room temperature for 24 h. Then the solution containing excess solid was filtered using 0.22 µm PVDF filter, appropriate dilutions were then made and analyzed using UV spectrophotometer at 241 nm.

9. Solubility studies in different buffer solutions

Drug was added in excess quantity in 10 ml of each buffer (pH.1.2, pH 4.5 and pH 6.8) in 50 ml volumetric flasks. Then the volumetric flasks were kept in a mechanical shaker for 24 h at 37 ± 0.5 $^{\circ}$C for equilibration. After 24 h content of each flask was filtered with 0.45 µm filter and the filtrate was suitably diluted with respective medium and analyzed for the drug content using UV Spectrophotometer at 241 nm.

% solubility = (test absorbance / standard absorbance) × (standard concentration / test concentration) × 100

Evaluation of the prepared tablets

Weight variation test

Twenty (20) tablets from each batch were individually weighed. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight. Weight Variation limits as per USP

Thickness test

The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets by using a vernier Caliper's.

Hardness test

Tablet hardness was measured using a schleuniger hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2.

Friability

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 min (100 rotations) in the electrolab friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets. % Friability= Initial wt- Final wt / Initial wt x100

***In vitro* Buoyancy**

In vitro buoyancy and duration of floatation study was performed in 250 ml of 0.1 N HCl. Floating lag time was found to be less than one minute with the formulation containing no entrapment layer. The time taken for the tablet to rise to the surface and float was taken as floating time. The overall floating time was calculated during the dissolution studies.

***In vitro* drug release studies**

In vitro drug release of model drug from formulations were evaluated in triplicate at 37 ± 0.5 ºC using USPXXIV dissolution apparatus type II at rotational speed of 50 rpm in 900 ml of pH 1.2 HCl buffer for 14 h. At regular time intervals 10 ml of the dissolution medium were withdrawn, replaced with an equivalent volume of the fresh dissolution fluid and analyzed for drug content using UV spectrophotometer at 241nm.

Effect of *in vitro* simulated gastric motility on drug release

In order to study the effect of agitation intensity of the release media, release studies of the formulations were carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP-II (paddle) at 50, 75, and 100 rev. /min. Samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45-mm nylon membrane filters.

Mathematical model fitting

The *in vitro* release data were fitted into various mathematical models using PCP. Disso – V2.08 software to know which mathematical model will best fit the obtained release profile. The parameters like 'n' the diffusion exponent and 'R' the regression co – efficient were determined to know the release mechanisms. The model with highest correlation coefficient values or determination coefficient (R^2) was considered as the best fit model.

Stability studies

The objective of stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature and relative humidity (RH) conditions. Optimized formulations were selected for stability studies. Optimized formulations were packed in a screw capped bottle and studies were carried out for 30 days by keeping at

1. 25 ± 2 ºC and 60 ± 5 % RH
2. 40 ± 2 ºC and 75 ± 5 % RH

Samples were withdrawn on 15th and 30th day and were analyzed for drug content spectrometrically at 241 nm as per ICH Q1A (R2) guidelines.

RESULTS AND DISCUSSION

Evaluation Studies

Organoleptic properties

Carvedilol was characterized for various organoleptic properties and the results are discussed below.The XRD studies revealed that the drug was found to be crystalline in nature. Also, the drug is found to white in color and bitter in taste.

Drug-excipient compatibility study

Observation of physical mixtures

The samples were observed physically for any changes. Physical mixture of drug and other excipients after storage period of 4 weeks at 40 °C / 75 % RH showed no physical changes like color change, caking, odor etc. as shown in table 14 indicating the compatibility of excipients with drug.

Table 6: Physical appearance of drug and excipients

Physical appearance					
Composition code	**Initial**	**I Week 40 °C / 75 % RH**	**II Weeks, 40 °C / 75 % RH**	**III Weeks, 40 °C / 75 % RH**	**IV Weeks, 40 °C / 75 % RH**
Carvedilol	White powder	White powder	White powder	White powder	White powder
Drug + Mannitol SD200	White powder	White powder	White powder	White powder	White powder
Drug+ HPMC k 100M	Cream powder	Cream powder	Cream powder	Cream powder	Cream powder
Drug+ HPMC k4 M	Cream powder	Cream powder	Cream powder	Cream powder	Cream powder
Drug+ Klucel LF	White powder	White powder	White powder	White powder	White powder
Drug+ Eudragit RL30D	White powder	White powder	White powder	White powder	White powder
Drug+ Cellulose Acetate	White powder	White powder	White powder	White powder	White powder
Drug+Sodium icarbonate	White powder	White powder	White powder	White powder	White powder
Drug+ Mg Stearate	White powder	White powder	White powder	White powder	White powder

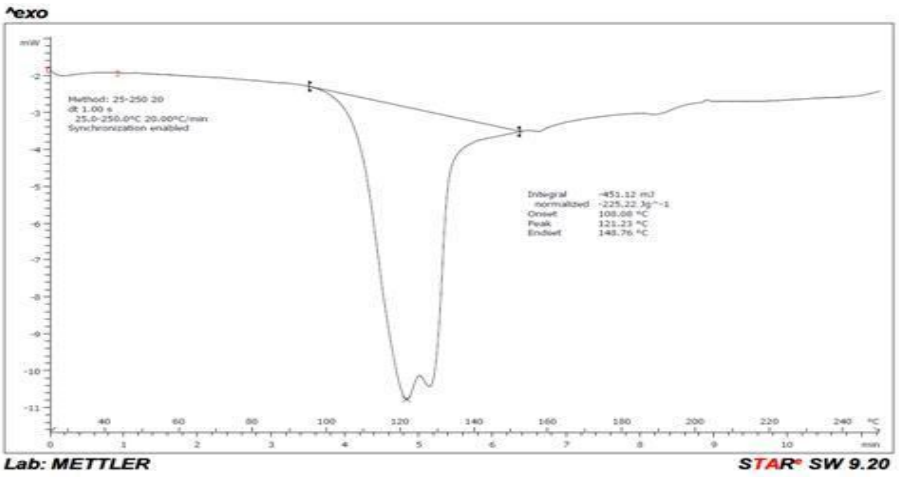

Fig 1: DSC thermogram of Carvedilol

Differential scanning calorimetric studies

Carvedilol

DSC thermogram of the model drug showed sharp peaks with the melting point 121.23 ˚C while the onset of peak was observed at 108.08 ˚C and end point of the peak was observed at 145.78 ˚C. Hence the said excipients may be used for the preparation of the sustained release tablets of Carvedilol. **Carvedilol + Mannitol**

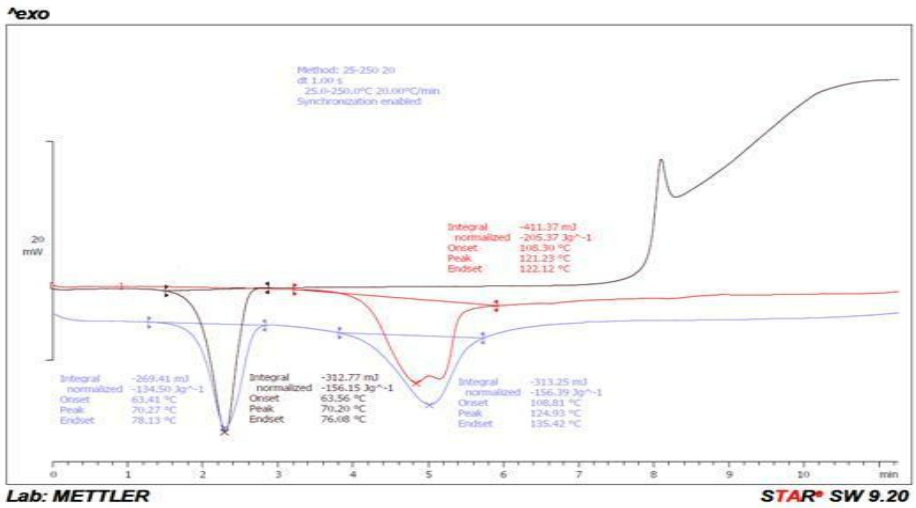

Fig 2: DSC thermogram of Carvedilol, Mannitol, Carvedilol + Mannitol physical mixture

When drug was studied in combination with Mannitol no change in melting point of drug was observed, no additional peaks were observed indicating compatibility of two materials. Mannitol showed sharp peak at 70.27 ˚C while the onset of peak was observed at 63.41 ˚C and end point was observed at 78.13 ˚C. Sharp melting peaks were observed for drug indicating the crystalline nature of drug. **Carvedilol + Klucel LF**

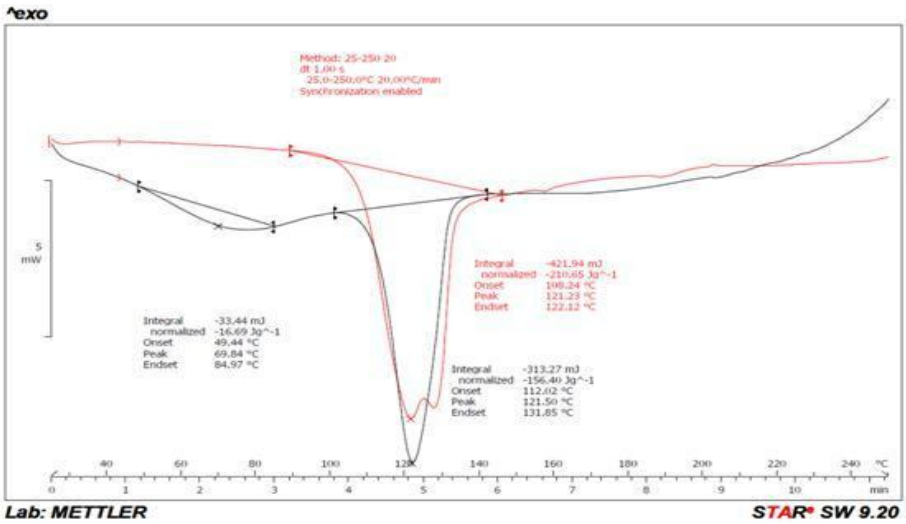

Fig 3: DSC thermogram of Carvedilol, Klucel LF, Carvedilol + Klucel LF physical mixture

When drug was studied in combination with Klucel LF no change in melting point of drug was observed, no additional peaks were observed indicating compatibility of two materials. Klucel LF showed sharp peak at 112.50 ˚C while the onset of peak was observed at 112.02 ˚C and end point was observed at 131.85 ˚C. Sharp melting peaks were observed for drug indicating the crystalline nature of drug. **Carvedilol + HPMC**

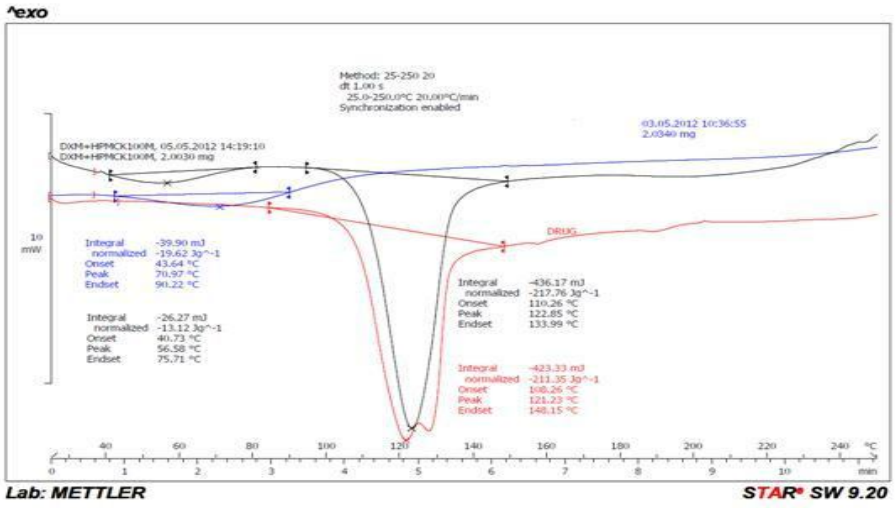

Fig 4: DSC thermogram of Carvedilol, HPMC, Carvedilol + HPMC physical mixture

When drug was studied in combination with HPMC no change in melting point of drug was observed, no additional peaks were observed indicating compatibility of two materials. HPMC showed sharp peak at 122.85 ˚C while the onset of peak was observed at 110.26 ˚C and end point was observed at 133.99 ˚C. Sharp melting peaks were observed for drug indicating the crystalline nature of drug.

Carvedilol + Sodium bicarbonate

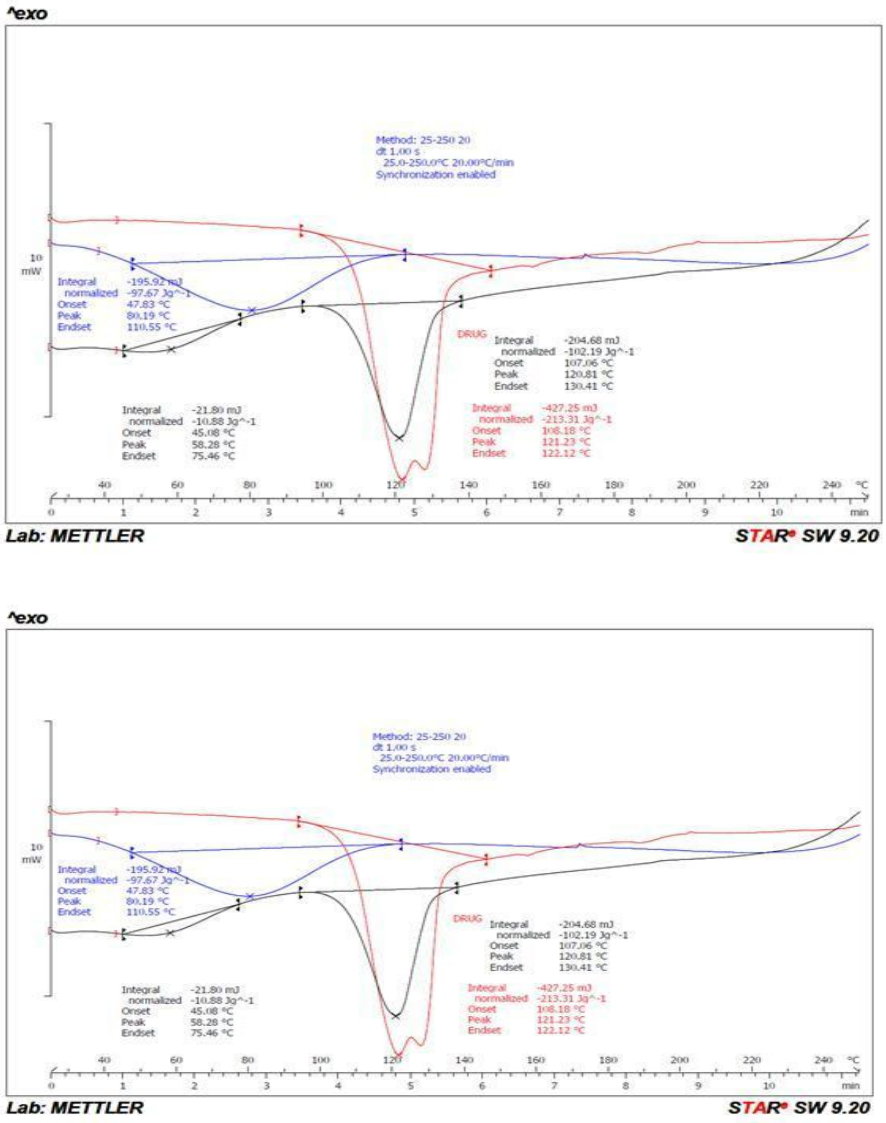

Fig 5: DSC thermogram of Carvedilol, Sodium bicarbonate, Carvedilol + Sodium bicarbonate physical mixture

When drug was studied in combination with Sodium bicarbonate no change in melting point of drug was observed, no additional peaks were observed indicating compatibility of two materials. Sodium bicarbonate showed sharp peak at 58.28 ˚C while the onset of peak was observed at 45.08 ˚C and end point was observed at 75.46˚C. Sharp melting peaks were observed for drug indicating the crystalline nature of drug.

Carvedilol + Cellulose acetate

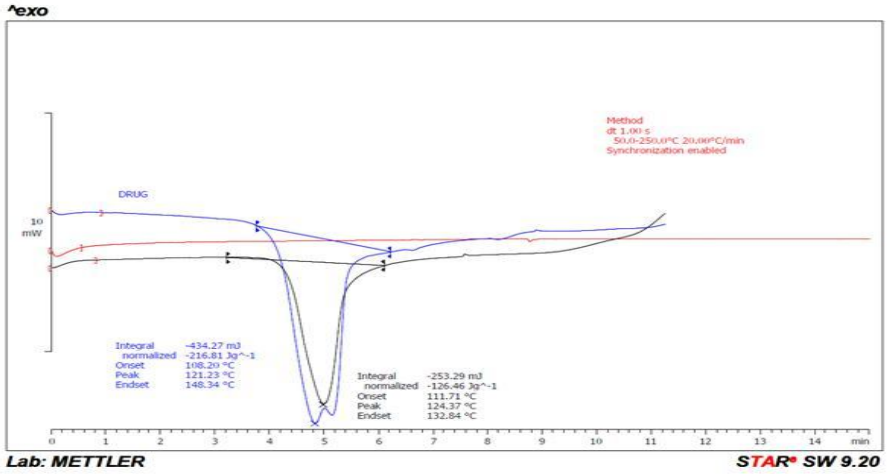

Fig 6: DSC thermogram of Carvedilol, Cellulose acetate, Carvedilol + Cellulose acetate physical mixture

When drug was studied in combination with cellulose acetate, no change in melting point of Carvedilol was observed, no additional peaks were observed indicating compatibility of two materials. Cellulose acetate showed sharp peak at 124.37 ˚C while the onset of peak was observed at 111.71 ˚C and end point was observed at 132.84 ˚C. Sharp melting peaks were observed for drug indicating the crystalline nature of drug.

Carvedilol + PEG6000

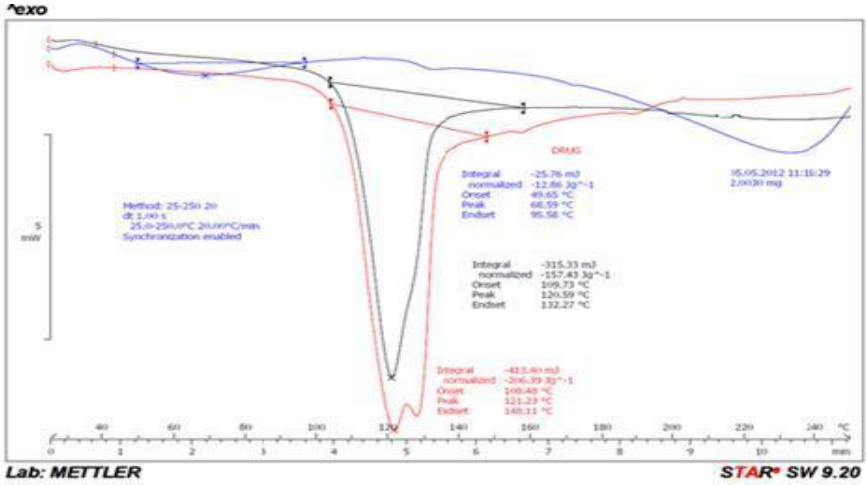

Fig 7: DSC thermogram of Carvedilol, PEG 6000, Carvedilol + PEG 6000 physical mixture

When drug was studied in combination with PEG 6000 no change in melting point of drug was observed, no additional peaks were observed indicating compatibility of two materials. PEG 6000 showed sharp peak at 68.59 ˚C while the onset of peak was observed at 43.65 ˚C and end point was observed at 95.58 ˚C. Sharp melting peaks were observed for drug indicating the crystalline nature of drug.

Carvedilol + Magnesium Stearate

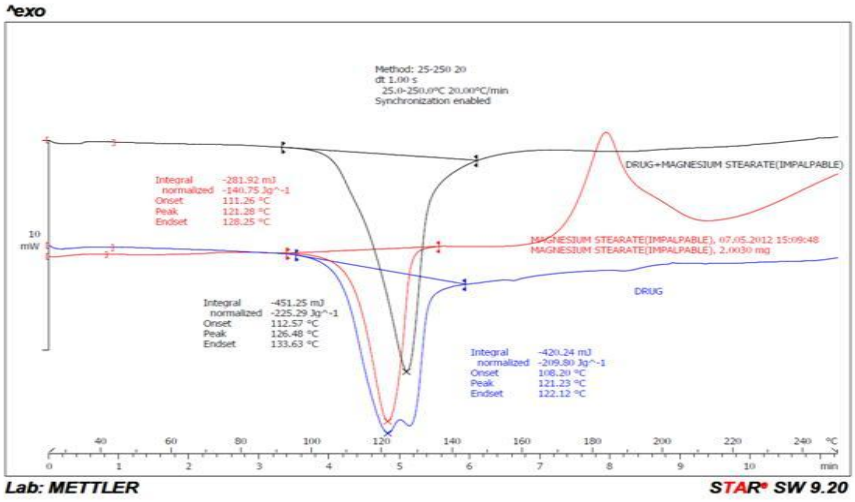

Fig 8: DSC thermogram of Carvedilol, Magnesium stearate, Carvedilol + Magnesium stearate physical mixture

When drug was studied in combination with Magnesium stearate no change in melting point of drug was observed, no additional peaks were observed indicating compatibility of two materials. Magnesium stearate showed sharp peak at 126.48 ˚C while the onset of peak was observed at 112.57 ˚C and end point was observed at 133.63˚C. Sharp melting peaks were observed for drug indicating the crystalline nature of drug.

Particle size distribution of final optimized granulated blend

Particle size distribution was performed by sieve analysis method for the final optimized blend and the results are shown in table 7.

Table 7: Particle size distribution of final optimized blend

Sieve mesh number	Sieve Size opening(µm)	Mass of sample retained on each sieve(g)	Percentage of sample retained on each sieve (%)	Cumulative percentage of sample retained on each sieve (%)
30	841	0.06	0.61037	0.6
40	425	1.15	11.6988	12.3
60	250	1.32	13.4288	25.7
80	180	0.55	5.5951	31.3
100	150	0.54	5.4933	36.8
120	130	0.40	4.0617	40.8
Pan	-	5.81	59.1047	99.9

From percentage cumulative size distribution it was found that around 25 % of particles was above 250 µm and 75 % were below 250 µm

Evaluation of granules

The powder characteristics like bulk density, tapped density, compressibility index and Hausner's ratio for the lubricated blend prepared were evaluated and the results are provided in the table 8.

Table 8: Evaluation of granules

Formulation	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	% Compressibility Index	Hausner's ratio
F 1	0.31 ± 0.02	0.38 ± 0.02	18.42 ± 0.03	1.22
F 2	0.32 ± 0.03	0.38 ± 0.05	15.78 ± 0.05	1.18
F 3	0.33 ± 0.02	0.41 ± 0.03	19.51 ± 0.03	1.24
F 4	0.32 ± 0.01	0.40 ± 0.06	20.00 ± 0.02	1.25
F 5	0.33 ± 0.04	0.41 ± 0.04	19.50 ± 0.06	1.24
F 6	0.34 ± 0.02	0.42 ± 0.01	19.04 ± 0.05	1.23
F 7	0.33 ± 0.04	0.42 ± 0.07	21.42 ± 0.04	1.27
F 8	0.34 ± 0.05	0.46 ± 0.02	26.08 ± 0.03	1.35
F 9	0.32 ± 0.04	0.41 ± 0.01	21.95 ± 0.02	1.28
F10	0.33 ± 0.03	0.40 ± 0.07	17.50 ± 0.02	1.21
F11	0.31 ± 0.02	0.38 ± 0.03	18.42 ± 0.02	1.22
F12	0.36 ± 0.06	0.42 ± 0.02	14.28 ± 0.01	1.16
F13	0.34 ± 0.01	0.39 ± 0.05	12.80 ± 0.04	1.14
F14	0.38 ± 0.02	0.46 ± 0.07	17.39 ± 0.07	1.21
F15	0.35 ± 0.04	0.42 ± 0.05	16.60 ± 0.05	1.20
F16	0.34 ± 0.03	0.42 ± 0.08	19.04 ± 0.01	1.23
F17	0.34 ± 0.02	0.40 ± 0.06	15.00 ± 0.04	1.17
F18	0.38 ± 0.01	0.43 ± 0.02	11.62 ± 0.02	1.13
F19	0.34 ± 0.02	0.39 ± 0.04	12.80 ± 0.02	1.14
F20	0.35 ± 0.05	0.42 ± 0.01	16.60 ± 0.07	1.20

Bulk densities of all the formulations were found to be between 0.31 g/cm^3 to 0.38 g/cm^3 and tapped densities of all the formulations were found to be between 0.38 g/cm^3 to 0.46 g/cm^3. Compressibility index of the formulations were in the range of 15 to 26.08 % □□Formulations F 1, F 3, F 4, F 5, F 6, F 10, F 11, F 14, F 15 and F 16 fair compressibility index. Formulations F 2, F 12, F 13, F 17, F 19, and F 20 showed good compressibility index. Formulations F 7, F 9 showed passable compressibility index. Formulation F 8 showed poor compressibility index. Formulation F 18 showed excellent compressibility index.

Hardness: The hardness for all formulations was found to be between 5.4± 0.24 kg/cm^2.

Table No.9: Evaluation of core tablets

Formulation	Weight variation	Weight variation (mm)	Hardness (kg/cm^2)	Friability (%)
F 1	280.2 ± 0.5	3.85 ± 0.3	5.1± 0.21	0.01
F 2	205.5 ± 0.4	3.83 ± 0.5	5.3± 0.21	0.02
F 3	180.3 ± 0.6	3.86 ± 0.6	5.2± 0.32	0.02

F 4	205.2 ± 0.3	3.82 ± 0.4	5.1± 0.24	0.02
F 5	205.4 ± 0.8	3.84 ± 0.4	5.5± 0.26	0.01
F 6	205.5 ± 0.4	3.78 ± 0.5	5.3± 0.28	0.20
F 7	180.2 ± 0.8	3.70 ± 0.8	5.6± 0.25	0.02
F 8	205.3 ± 1.2	3.78 ± 0.5	5.4± 0.23	0.02
F 9	205.5 ± 1.5	3.83 ± 0.5	5.6± 0.21	0.01
F 10	205.6 ± 0.6	3.82 ± 0.9	5.5± 0.24	0.01
F 11	205.5 ± 0.8	3.82 ± 0.9	5.9± 0.23	0.01
F 12	200.2 ± 0.4	3.84 ± 0.3	5.1± 0.27	0.02
F 13	199.6 ± 0.8	3.85 ± 0.2	5.8± 0.29	0.06
F 14	200.5 ± 1.2	3.86 ± 0.8	5.2± 0.24	0.10
F 15	201.1 ± 0.6	3.80 ± 0.6	5.8± 0.23	0.08
F 16	200.5 ± 0.4	3.82 ± 0.6	5.7± 0.22	0.20
F 17	200.4 ± 0.6	3.82 ± 0.6	5.4± 0.22	0.04
F 18	200.2 ± 0.8	3.84 ± 0.5	6.0± 0.31	0.02
F 19	200.6 ± 1.2	3.83 ± 0.6	5.7± 0.23	0.05
F 20	200.1 ± 0.6	3.81 ± 0.5	5.4± 0.29	0.08

The variation in weight was between 0.4 mg to 1.5 mg which was within the range of ± 7.5 % complying with pharmacopoeia specifications. The thickness of tablets was found to be between 3.70-3.86 mm. The hardness for all formulations was found to be between 5.4± 0.24 kg/cm^2. The friability was below 0.1 % for all the formulations indicating consistency in the manufacturing process.

Evaluation of floating lag time and duration of floatation time

Visual observations was made in 250ml 0.1N HCl and the result is shown in the table no.10

Table No. 10: Floating lag time and floatation time of Formulation 1

Coating percentage (Osmotic layer+ floating layer +entrapment layer)	Floating lag Time	Floatation time
10+5+0	20 sec	20 min
10+15+0	50 sec	60 min
10+5+2	7-8 min	4.5 h
10+5+4	9-10 min	5.5 h
10+5+6	12-13 min	7.5 h
10+5+8	15 min	>8 h
10+15+2	Bursting of the entrapment layer due to swelling of floating layer	
10+15+4		
10+15+6		
10+15+8	7 – 14 min	4 – 8 h

Floating lag time was found to be less than one minute with the formulation containing no entrapment layer. However, tablets were not able to float for more than one hour due to solubilization and erosion of floating layer and because of no entrapment layer to hold the

Carbon dioxide generated from the floating layer. With increase in floating layer coating percentage from 5 % to 15 % w/w, floating lag time increased from 20 sec to 50 sec and floating time was increased from 20 min to 60 min and exhibited correlation between percentage coating of floating layer and floating time. Floating lag time and floating time were increased with increase of entrapment layer coating percentage. Burst of entrapment and osmotic layers were observed at later part of the dissolution time points which was due to swelling of polymer present in the core tablets. With higher coating percentage of floating layer and different coating percentage of entrapment layer, burst of entrapment and osmotic layer was observed due to swelling of floating layer and swelling of core tablets respectively.

Table no. 11: Floating lag time and floatation time of formulation F2 to F20

Formulation	Floating lag time (min)	Floating time (h)
F2 to F 7	Bursting of osmotic system was observed	
F8	8 – 11	3 – 8
F9	7 – 11	1 – 3.5
F10	8 – 15	5 – 8
F11	Bursting of osmotic system was observed	
F12	Tablets were unable to float	
F13	7-8	16 h, with some tablets sinking after 8 h
F14	7-8	16 h, with some tablets sinking after 8 h
F15	4-5	24
F16	4-5	24
F17	4-5	24
F18	4-5	24
F19	4-5	24
F20	4-5	24

Burst of osmotic system was observed within one hour at dissolution conditions in formulations F 2 to F 7 irrespective of polymer type, and even though the polymer amount was reduced to 25 mg from 50 mg. Even the formulation without polymer (F 7) showed bursting. So, bursting of osmotic system may be due to rapid release of carbon dioxide gas by reaction between sodium bicarbonate and citric acid in acidic conditions. Formulation F8 showed floating lag times within desired range but floating times were less than 10 h. Decrease in floating time was observed with decrease in talc percentage from 35 % to 15 % in formulation F 9. Floating time was found to vary between 5 – 8 h for formulation F10. Floating time was increased because of higher viscosity grade HPMC. Floating times and uniformity in floating time can be improved by incorporation of effervescent agent in core

tablet so that core tablet has floating ability. This floating composition of floating layer and entrapment layer was used for further studies. Burst of osmotic system was observed within one hour at dissolution conditions, for formulation F 11. Bursting of osmotic system may be due to rapid release of carbon dioxide gas by reaction between sodium bicarbonate and citric acid in acidic conditions. Formulation F 12 could not able to show any floating at dissolution conditions which might be due to the absence of the gas generating agent i.e., Sodium bicarbonate. In both the formulations F 13 and F 14 some tablets were sinking in between 8-16h. So incorporation of small amounts of Sodium bicarbonate in the core tablet may improve the floating time. Formulation containing Sodium bicarbonate (F15) as floating aid showed longer floating time as compared to formulation without Sodium bicarbonate (F14). Presence of Sodium bicarbonate in the core tablet helps to improve floating time. Decrease in the amount of Mannitol in formulation F 17 did not alter either floating lag time or floatation. But the formulation F17 with less amount of Mannitol (50 mg/tablet) showed faster drug release compared to that of formulation F 16. No significant difference in floating time and floating lag time was observed between F 18 (2.5 %) and F 19 (5 %) floating layer build up. Formulation F 20 showed the floating lag time of < 5 min and total floating time was up to 24h h.

***In vitro* dissolution studies**

As per the specifications the floating lag and floating time were achieved, also dissolution studies were carried out for the formulations F11 to F 20.

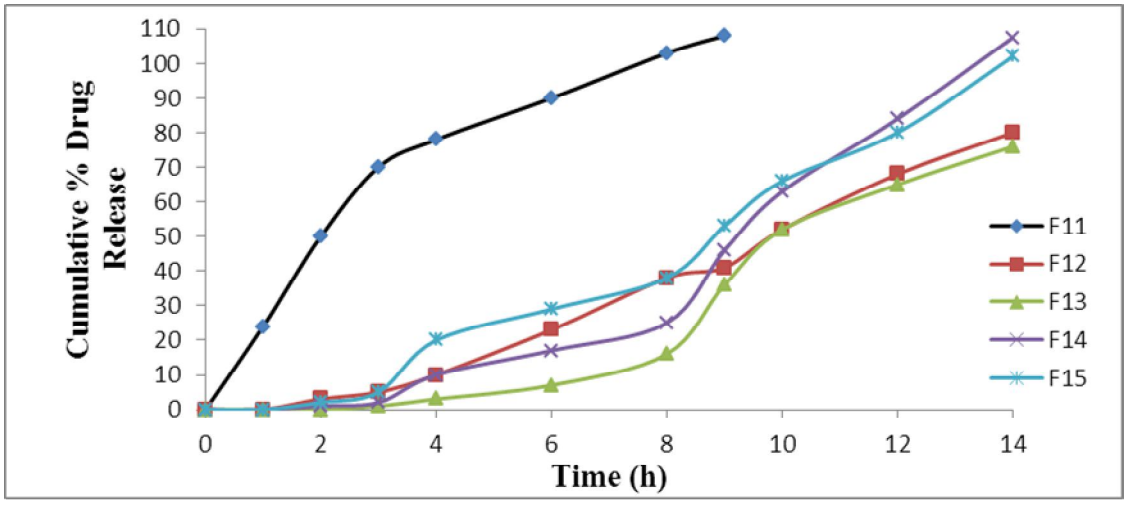

Fig 9: *Invitro* drug release of Formulation [F11-F15]

The drug release of F 11 was found to be more than 50 % at 2 h dissolution time point due to high pore former level in osmotic layer so, 20 % pore former is not a suitable level to control

the drug release. Burst of osmotic system is observed due to high pore former content, aiding release of gas from the system. Burst of osmotic system was not observed from formulation F 12. But only 80 % of drug was released from the osmotic system in 14 h, which had to be improved by reducing the coating percentage. System with 4 % CA coating (F 14) shows faster drug release compared to system with 10 % CA coating (F 13). Both the systems show very less drug release at initial time points which had to be improved. Drug release was found to be slightly faster from the formulation with sodium bicarbonate (F 15). Drug release at earlier time points was found to be less than 10 % and the same had to be improved in subsequent formulations.

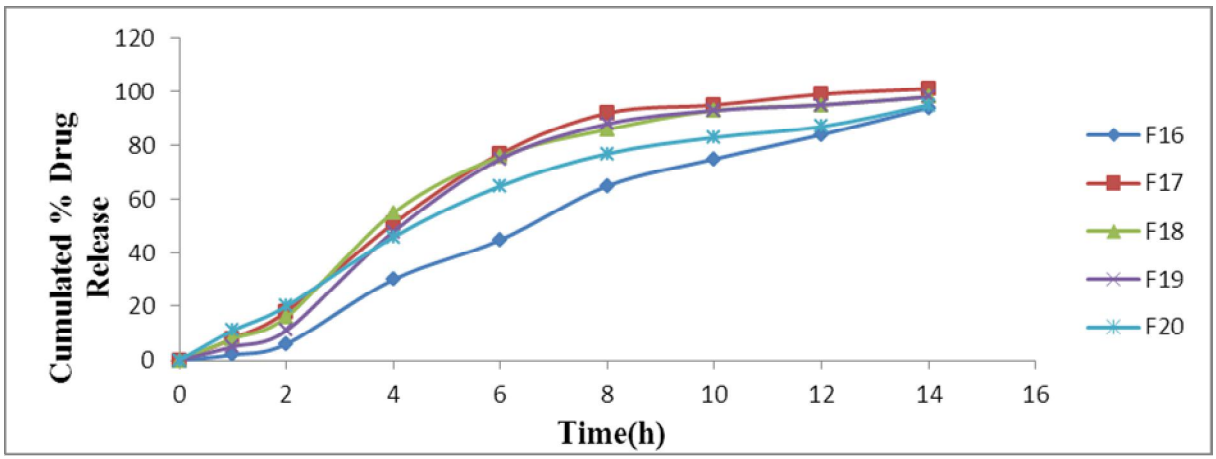

Fig 10: *Invitro* drug release of Formulation [F16-F20]

Formulation F 17 with 50 mg of mannitol showed faster release with 90 % drug release in 8 h whereas formulation F 16 with 100 mg mannitol showed slower and in complete release even after 14 h. Drug release was slightly slower with 5 % coating of floating layer (F 19) than 2.5 % coating (F 18) at initial time points but there was no significance difference at later time points. Drug release from the optimized formulation F 20 was found to be well controlled. Initially, the release was fast but with time release rate decreased showing desired release profile.

Effect of pH on drug release:

To estimate the drug release in different media, dissolution tests were carried out in pH 1.2 acidic buffer, pH 4.5 acetate buffer with 0.5 % SLS and pH 6.8 phosphate buffer with 0.5 % SLS for the optimized formulation F20 and the % drug release is shown in Fig no. 11.

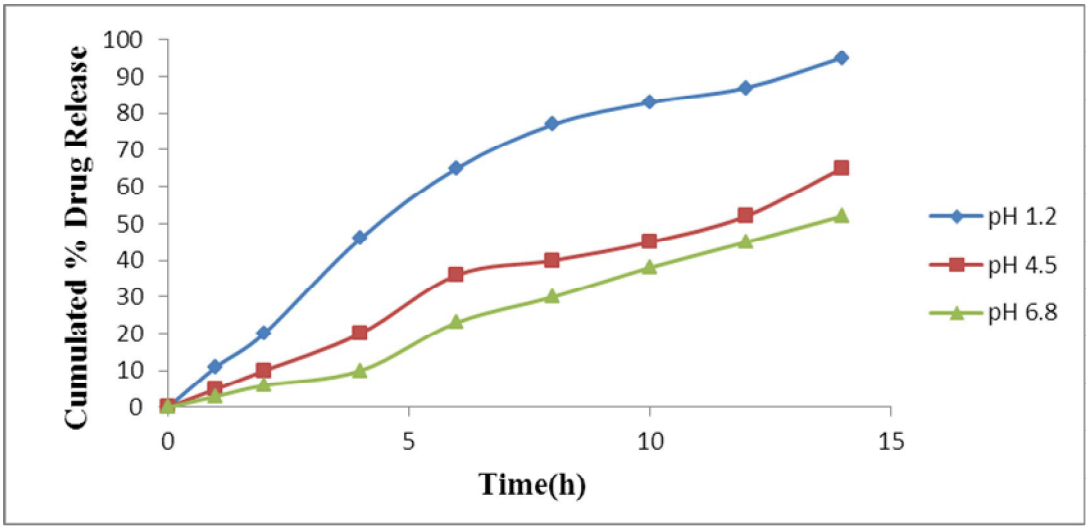

Fig 11: *Invitro* drug release in pH 1.2, pH 4.5, pH 6.8

The drug release from the formulation was found to be pH dependent where faster drug release was observed in pH 1.2 Hydrochloric acid buffer compared to the pH 4.5 Acetate and pH 6.8 Phosphate buffer. The difference in the drug release rate could be attributed to both polymer and drug properties. Since model drug is a weakly basic drug and because of higher solubility of the drug in the acidic medium, the drug release from the formulation in acidic dissolution medium was found to be slightly faster and higher compared to the other two dissolution medium.

Effect of agitation

The effect of agitation intensity of the release media was carried out in dissolution apparatus at different speeds. The results show that at increase in the agitation increase in the drug release from optimized formulations.

Table No.12: Effect of agitation intensity on release media for optimized formulation (F 20)

Time (h)	Cumulative % drug release		
	Formulation F20		
	50 rpm	75 rpm	100 rpm
1	11±	20±	26±
2	20±	40±	48±
4	46±	61±	67±
6	65±	75±	81±
8	77±	88±	92±
10	83±	93±	101±
12	87±	102±	-
14	95±	-	-

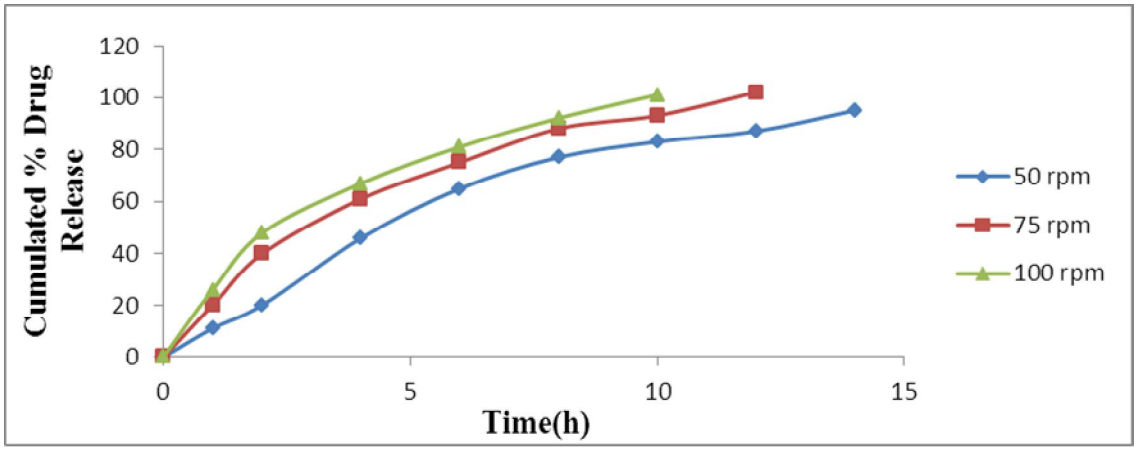

Fig 12: *In vitro* drug release at 50, 75, 100 rpm

In order to study the effect of agitation intensity of the release media, release studies of the formulations were carried out in dissolution apparatus at various rotational speeds. The drug release from the optimized formulation F 20 was varying with the agitation intensity. At 100 rpm complete drug release was observed within 10 h whereas at 75 rpm and 50 rpm release was extended up to 12 h and 14 h respectively. These results indicate that *in vivo* hydrodynamics conditions may affect the drug release as shown above in figure no. 12.

Mathematical model fitting

To analyze the mechanism of drug release from the matrix tablets, the dissolution data were fitted to various kinetic models, the release kinetic parameters and the fitting ability are listed below in Table no. 13.

Table No. 13: Release kinetics of prepared formulation (F11-F20)

Formulations	R^2 values				*n* values	Mechanism of drug release
	Zero order	First order	Higuchi' model	Korsmeyer - Peppas	Korsmeyer-Peppas	
F 11	0.9530	0.9822	0.9659	0.9796	0.3647	Korsmeyer- Peppas
F 12	0.8106	0.9568	0.8898	0.8803	0.3841	Higuchi
F 13	0.8332	0.9550	0.9550	0.8999	0.2964	Higuchi
F 14	0.7001	0.9210	0.8000	0.8199	0.3078	Korsmeyer- Peppas
F 15	0.8142	0.9603	0.9054	0.9210	0.3222	Korsmeyer- Peppas
F 16	0.7380	0.9695	0.8507	0.8891	0.3011	Korsmeyer- Peppas
F 17	0.6232	0.9198	0.7424	0.7955	0.2708	Korsmeyer- Peppas
F 18	0.9277	0.9322	0.9315	0.9221	0.2929	Higuchi
F 19	0.9151	0.9504	0.9479	0.9437	0.3059	Higuchi
F 20	0.9111	0.9728	0.9727	0.9898	0.3871	Korsmeyer- Peppas

In most of the formulations, the drug release follows first order release. The value of n less than 0.45 indicated the drug release followed Fickian diffusion process in most cases.

Stability studies

The optimized formulation was subjected to stability studies according to ICH guidelines by storing at 25 ºC / 60 % RH and 40 ºC / 75 % RH for 30 days. These samples were analyzed and checked for changes in physical appearance and drug content at regular intervals. The stability studies were out at 25 ºC / 60 % RH and 40 ºC / 75 % RH for 1 month. From the table 25, it was clear that the formulation did not undergo any chemical changes or interaction during the study period. There was no change in the color of the tablet after 1 month.

CONCLUSION

The objective of the present study was to prepare floating osmotic drug delivery containing a model drug. Core tablets were prepared by wet granulation and coated with three successive layers: osmotic layer, floating layer and gas entrapment layer. From the results, it can be concluded that the floating osmotic tablets formulation is easy to administer, simple, economical with increased patient compliance. Hence, carvedilol could be formulated into floating osmotic tablets as controlled release dosage form.

ACKNOWLEDGEMENT

I am thankful to Dr. H.G. Shivakumar, Principal, JSS College of Pharmacy and JSS University, Mysore for providing facilities to carryout research work.

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