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FORMULATION, EVALUATION AND OPTIMIZATION OF FLOATING MATRIX TABLETS OF CARVEDILOL

Jamshiya.E[1]and Anju.P[2]

[1]National College of Pharmacy, Manassery-P.O, Mukkam, Kozhikode-673602

[2]College of Pharmaceutical Sciences, Govt medical college, Calicut

Abstract:

Bilayer floating tablets were prepared by direct compression using HPMC K100M and Ethyl cellulose as the release controlling polymers and sodium bicarbonate as a gas generating agent. The optimum concentrations of the above ingredients were determined under experimental conditions and on the basis of trial batches of the tablets. In the present study bilayer tablet was prepared manually using single station punching machine. Accurately weighed 150mg of sustained release layer powder mixture was fed manually into die cavity. Sustained release layer was compressed at mild compression force (2-3 kg/cm^2). After that accurately weighed 100mg of immediate release powder mixture was manually fed into the die over sustained release layer and compressed. Eleven formulations were prepared and evaluated for various evaluation parameters of bilayer tablet for physical properties, floating and in vitro drug release. All the formulations showed optimum flow properties, percentage of weight variation and friability. Accordingly, the increase of sodium bicarbonate from 0.5 to 9 % in the polymer resulted in a decrease in FLT from 9 to 1 min (F1-F3). Because of the amount of sodium bicarbonate also affected the drug release from the formulation, F2 have optimum concentration (4.5%) of sodium bicarbonate. The drug release pattern and drug uniformity were found to be satisfactory. Considering the in vitro drug release studies batch F9 was selected as optimized formulation

Keywords: *Bilayer floating matrix tablet, carvedilol, HPMCK100M, Sodium bicarbonate, sodium starch glycolate*

Corresponding author:

Jamshiya.E,
National College of Pharmacy,
Manassery-P.O
Mukkam,
Kozhikode-673602

QR code

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INTRODUCTION:

Hypertension is chronic medical conditions were the blood pressure in the arteries are elevated. Hypertension is defined as either a sustained systolic blood pressure of 140mm Hg or more or a sustained diastolic pressure of greater than 90mm Hg [1].

Carvedilol is a non-cardio selective alpha 1- beta adrenergic blocking agent. The drug effective in managing hypertension, angina pectoris, heart failure and left ventricular dysfunction with myocardial infarction [1].

Matrix tablets may be defined as the "oral solid dosage form in which the drug or active ingredient is homogenously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". The retardant delay the interaction of the core with the dissolution medium by reducing the surface available for drug release and thus limiting liquid penetration. These formulations are designed to deliver the drugs at a sustained and predetermined rate, thus maintaining their therapeutically effective concentrations in the systemic circulation for prolonged periods of time [2]. Bi-layer matrix tablet is new era for development of controlled release formulation. They are prepared with one layer of drug for immediate release while second layer designed to release the drug in sustained release manner. The control of overall release is primarily determined by the composition of each layer [3].

Gastro retentive drug delivery systems (GRDDS) prolong the retention time of dosage form in the stomach or upper gastro intestinal tract, as to improve solubility, bioavailability and therapeutic efficacy of the drugs. Carvedilol having higher solubility in gastric region is a suitable candidate for GRDDS. Depending on material characteristics these systems may swell, gel, erode, and finally dissolve in the gastrointestinal tract. Thus in the present study it was intended to formulate and evaluate bilayer floating matrix tablet of carvedilol for controlled release and to increase bio availability [4].

MATERIALS AND METHODS:

Materials Used

Carvedilol (Yarrow Chem. Pvt. Ltd, Mumbai), HPMC K100M (Yarrow Chem. Pvt. Ltd, Mumbai), HPMC K4M (Yarrow Chem. Pvt. Ltd, Mumbai), Ethyl cellulose, Carboxy methyl cellulose(Nice chemicals Pvt. Ltd. Cochin), Sodium bi carbonate (Nice chemicals Pvt. Ltd. Cochin), Talc(Nice chemicals Pvt. Ltd. Cochin), Magnecium stearate(Nice chemicals Pvt. Ltd. Cochin) and Sodium starch glycolate(Yarrow Chem.. Pvt. Ltd, Mumbai)

Methods

Raw material analysis [5- 6- 7]

Analysis of drug:

Physical appearance of drug:

Physical appearance of the drug was studied to check whether the drug complies with official standard.

Identification by FTIR spectroscopy:

Infrared (IR) Spectroscopy was conducted for the drug sample by using Schimadzu IR SPECTROPHOTOMETER and the spectrum was recorded in the wavelength region of 4000-400 cm^{-1}.

The procedure consists of dispersing 10 gram of drug sample in potassium bromide and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and spectrum was obtained.

Melting point

Melting point of carvedilol was determined by capillary method. Fine powder of carvedilol was filled in glass capillary tube (previously sealed at one end). The capillary tube was inserted in to the melting point apparatus and observed the temperature at which drug started to melt by using thermometer which was already immersed in to the liquid paraffin in the apparatus.

Assay

An accurately weighed quantity of about 0.350g of carvedilol was dissolved in 60 ml of anhydrous glacial acetic acid. Titrated with 0.1 M perchloric acid using 1-naphtholbenzein solution as indicator to a green end point. Performed a blank determination to make any necessary correction. Each ml of 0.1 M Perchloric acid is equivalent to 40.65g of $C_{24}H_{26}N_2O_4$.

Analysis of polymer.

HPMC.

Identification test:

The spectrum obtained by infra-red absorption spectrophotometry, was compared with that obtained with reference spectrum of HPMC as in IP (2014).

Test A: Gently added 1gm of HPMC to the top of the 100ml of water in a beaker and allowed to disperse over the surface, tapping the top of the container to ensure an even dispersion of substance. After 5hrs, swirled the beaker to wet the remaining substance. An equal volume of 1N NaOH or 1N HCL was added to the mixture A. RAW MATERIAL ANALYSIS[25, 26, 27,28]

Sodium starch glycolate

Identification test

The spectrum obtained by infra-red absorption spectrophotometry, was compared with that obtained with reference spectrum of SSG as in IP (2014).

Pre Formulation Studies [6]

Solubility analysis

The solubility of carvedilol in various solvents was determined. An excess amount of carvedilol was added to each beaker containing 5ml of selected solvent. The mixture was sonicated for 6 hrs. The saturated solution was filtered using whatman filter paper and analyzed at 241 nm using UV spectrophotometer after suitable dilution.

Drug-excipient compatibility studies

One of the requirements for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. It was done by FTIR spectroscopy.

FTIR spectroscopy

The compatibility between the drug, polymer, were evaluated using FTIR peak matching method. The drug and polymer mixture was finely ground with KBr to prepare pellets under a hydraulic pressure of 600 psig and a spectrum was scanned in the wavelength range of 400-4000 cm^{-1}.

Calculation of Loading Dose and Maintenance Dose:

Conventional dose: 25mg (12.5 mg twice daily).
Half-life: 4-7 hr
Elimination rate constant: 0.126
T max: 1.2hr
Dosing interval T: 24hrs
Now if

Initial dose $D_i = C_{SS}$ Vd / F _____1

Where C_{ss} = steady state concentration, v_d = volume of distribution, F = fraction of bio available dose. ,

But, C_{ss} = F X0 / Ke Vd T _____2

So substituting the value of C_{SS} in to the equation no: 1

Di = F X0 Vd / Ke Vd T F

Ultimately Di = X0 / Ke T
= 25/0.126*24 =8.2672 mg

Desired rate of drug release
Ks = Di * Ke
= 8.2672*0.126 = 1.04167hr^{-1}

Maintenance Dose (DM):
DM = Ks * 24
= 1.049*24
= 25mg

Corrected Initial Dose (D*i):
D*I = Di – (Ks * tp)
=8.267-1.2588
=7.009mg

Preparation

For preparation of IR powder blend, all the ingredients were accurately weighed and blended uniformly by using mortar and pestle, sieved by using sieve no 100 in order to get uniform particle size.

For preparation of sustained release floating layer powder blend, all the ingredients were accurately weighed and blended uniformly by using mortar and pestle, sieved by using sieve no 100 in order to get uniform particle size.

Bilayer floating tablets were prepared by direct compression using HPMC K100M and Ethyl cellulose as the release controlling polymers and sodium bicarbonate as a gas generating agent. The optimum concentrations of the above ingredients were determined under experimental conditions and on the basis of trial batches of the tablets. In the present study bilayer tablet was prepared manually using single station punching machine. Accurately weighed 150mg of sustained release layer powder mixture was fed manually into die cavity. Sustained release layer was compressed at mild compression force (2-3 kg/cm^2). After that accurately weighed 100mg of immediate release powder mixture was manually fed into the die over sustained release layer and compressed. Both layer are distinguished by adding coloring agent, Amaranth powder in the immediate release layer.

Table 1: Formula for immediate release layer.

Ingredients	IR (mg)
Carvedilol	7
Sodium starch glycolate	4
Micro crystalline cellulose	87
Talc	1
Magnesium stearate	1
Amaranth powder	q.s
Total weight	100

Table 2: Formula or sustained release layer.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Carvedilol	25	25	25	25	25	25	25	25	25	25	25
HPMC k100M	22.5	22.5	22.5	52.5	-	22.5	22.5	37.5	37.5	52.5	52.5
HPMC K4 M	-	-	-	-	52.5	-	-	-	-	-	-
Ethyl cellulose	35	35	35	-	-	25	35	25	35	25	35
MCC	71.5	57	62.5	62	62	67	57	52	42	37	27
Sodium bi carbonate	3	7.5	12	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Talc	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Magnesium stearate	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Total	150	150	150	150	150	150	150	150	150	150	150

Study of Flow Properties of Prepared Granules

Precompression studies include,

Bulk density:

The bulk density of powder mix was determined by weighing accurately 5gm of powder mix, which was taken in a 50ml measuring cylinder. Bulk density calculated three times by using formula mentioned below. It is expressed in gm/ml.

$$\rho_b = M/V_b$$

Where, M and V_b are mass of powder and bulk volume of the powder respectively.

Tapped density

Weighed out 5gm of powder mix and was taken in a 50ml measuring cylinder. It was then tapped on a wooden surface until a constant volume was obtained. The tapped density of the powder was calculated three times by using the formula.

$$Pt = M/V_t.$$

Where M-Weight of the sample.

V_t- Tapped volume of sample.

Carr's compressibility index

The compressibility index of the granules was determined by Carr's compressibility index which was calculated by using the following formula.

$$C= (\rho_t - \rho_b / \rho_t) \times 100$$

Where ρ_t- Tapped density, ρ_b- Bulk density.

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It was calculated by the following formula.

$$\text{Hausner's ratio} = \rho_t / \rho_b$$

Where ρ_t- Tapped density

ρ_b- Bulk density

Until the apex of conical pile just touched the tip of the funnel. The radius of the pile was determined.

$$\theta = \tan^{-1} (h/r)$$

Where h- Height of the pile.

r- Radius of pile.

Evaluation [5-7]

Tablet thickness and diameter

Thickness and diameter of tablets were determined by using screw Gauge. Five tablets from each batch were used and the average value was calculated. It was measured in mm.

Weight variation:

20 tablets were weighed individually on an electronic balance and an average weight of one tablet was calculated. The weight variation of each tablet from the average weight was then calculated.

Hardness

The hardness of tablet was measured by Monsanto hardness tester. The hardness was measured in terms of Kg/cm^2.

Friability

The tablets were weighed and placed in the plastic chamber of Roche friabilator, which was adjusted to revolve at a speed of 25rpm for 4 minutes. Tablets were taken out, dusted and reweighed.

$$f = (1- W0 / W) \times 100$$

Where, W0 is weight of the tablets before the test

W is the weight of the tablet after test.

Content uniformity

5 tablets were selected, powdered in a mortar and the average weight equivalent to one tablet was taken. It was dissolved in 50ml of methanol and diluted to 100ml with 0.1N HCl. 1ml was pipette out and made up to 100ml and was assayed by UV spectrophotometer at 241nm.

Floating lag time and the total floating time

Floating behaviour studies were carried out on both the floating layer and bilayer floating tablet by using USP Dissolution Testing Apparatus II (Paddle type) at paddle speed 50 rpm in 900ml of 0.1 N HCl at 37 ± 0.5°C for 24 hrs to mimic in vivo conditions. For determining the optimized floating lag time and total floating time of the delivery system, various formulations prepared as per table 1 were studied. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating lag time. The duration of system floatation and the relative matrix integrity was observed visually [8].

***Invitro* dissolution studies**

In vitro dissolution studies of the formulated tablets were carried out using USP dissolution Apparatus II (paddle type). The study was carried out in 900 ml of 0.1N HCl. The temperature was maintained at 37^0C ± 0.5. The rotation speed was 50 rpm. 5ml of aliquot were withdrawn at predetermined time intervals and filtered through whatman filter paper. The medium was replaced with 5ml of buffer each time. Sample was analyzed by using UV spectrophotometer at 241 nm [5].

Optimization:

Optimizations of floating lag time total duration of floating:

Shortest floating lag time and higher total duration of floating is needed for an optimized formulation.

Optimization of *in vitro* drug release:

On increasing the concentration of HPMC and ethyl cellulose the percentage cumulative drug release is calculated and optimized based on release.

Stability Studies:

Stability is defined as the extent to which a product retains, within specified limits and throughout its period of storage and use (i.e. its shelf life), the same properties and characteristics that it possessed at the time of its manufacture. Stability testing is performed to ensure that drug products retain their fitness for use until the end of their expiration dates. Adequate stability data of the drug and its dosage form is essential to ensure the strength, safety, identity, quality, purity and in vitro release rate, at the time of use that they claimed to have. A controlled release product should release a predetermined amount of the drug at specified time intervals, which should not change on storage. Any considerable deviation from the appropriate release would render the controlled release product useless.

Groups of three formulation of optimized formulation were kept at room temperature for two months in a closed container. Examined for drug content by spectrophotometrically and any physical change visually.

RESULTS AND DISCUSSIONS:

Raw material analysis

Analysis of drug

Appearance:

The appearance of carvedilol was white odorless crystalline powder. Hence confirm the description as per IP (2014)

Identification test:

Carvedilol was identified by FTIR spectroscopy. The FTIR spectrum of carvedilol (fig: 7-1) was compared with the standard spectrum and the sample spectrum showed all the characteristic peaks in the relevant region. So it confirms the identity of carvedilol.

Melting point:

The melting point of carvedilol was determined and was found to be 117 .33˚C which is in compliance with description as per IP (2014).

Assay:

The percentage purity of carvedilol was found to be 98.9%w/v which is within the limits according to IP 2014.

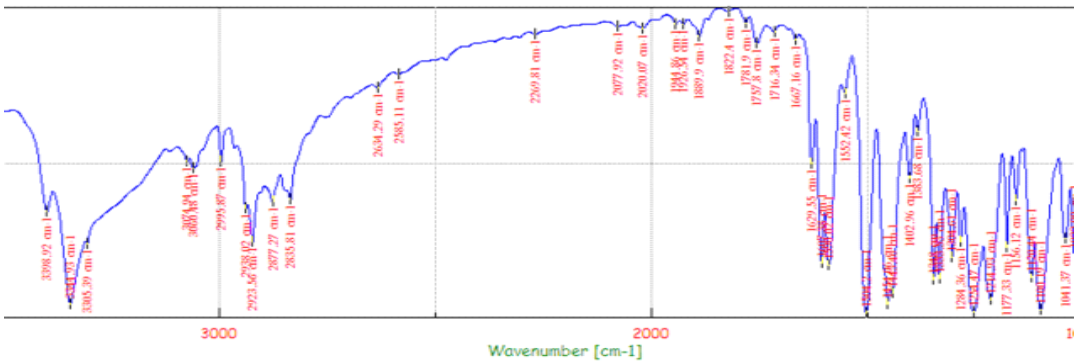

Fig. 1: FTIR spectrum of carvedilol

Table 3: Data for group assign to different peak of IR spectrum

Peak observed(cm^{-1})	Interpretation
3346.27	AromaticOH, NH Stretching
2925	CH stretching vibration
1598	NH bending vibration
1253	OH bending and CO stretching

Analysis of polymer – HPMC

- Hydroxy propyl methyl cellulose resulted in a stable mixture on conducting identification test A which confirmed the identity of sample.
- The ash value was found to be 0.45 % w / w which is within the limits as per IP 2014.
- Identification test B resulted in liquid that was an opalescent mucilaginous colloidal mixture, which confirmed the identity of sample.
- Test C give a thin self-sustaining film.
- The loss of drying was below 10%v/v which is within the limits.
- HPMC was identified by FTIR spectroscopy. The FTIR spectrum of HPMC (fig: 7.2) compared with the standard spectrum and the sample spectrum showed all the characteristic peaks in the relevant region. So it confirms the identity of HPMC

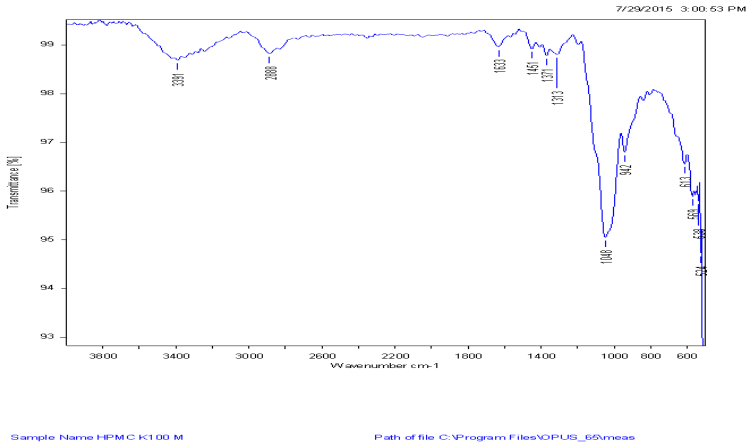

Fig. 2: FTIR spectra of HPMC K100M

Analysis of polymer-Sodium starch glycolate.

SSG was identified by FTIR spectroscopy. The FTIR spectrum of SSG (fig: 7-3) compared with the standard spectrum and the sample spectrum showed all the characteristic peaks in the relevant region. So it confirms the identity of SSG

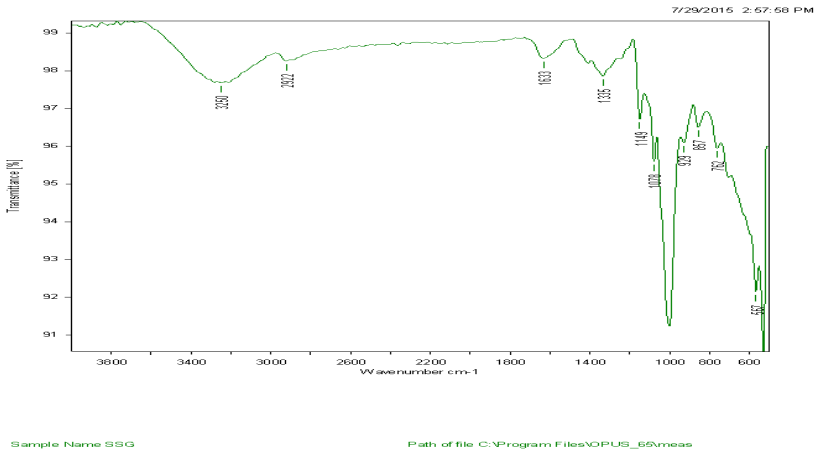

Fig.3: FTIR spectra of SSG.

PREFORMULATION STUDEIS

Solubility

Solubility of the drug in water, 0.1N HCl and phosphate buffer (P^{H-} 6.4) was examined. The drug is slightly soluble in water and soluble in alcohol and in acetone solution which was in conformity with Pharmacopoeial specifications.

Table 4: solubility of carvedilol

Solvent	Solubility (mg/ml)
Distilled water	Slightly soluble(0.088)
Alcohol, Acetone	Freely Soluble
0.1 N HCl	Slightly soluble (0.24)
Phosphate buffer (6.4).	Slightly soluble(0.15)

Compatibility studies

The compatibility studies were carried out to evaluate the compatibility of pure drug carvedilol with the polymers before the preparation of bilayer floating matrix tablet. The individual IR spectra of pure drug fig: 7-1 as well as the combination spectra of the drug and polymer figure:7-4 ,there are no disappearance or marked shift in the band of carvedilol when mixed with polymers, which indicates that no interaction between carvedilol and polymer mixture.

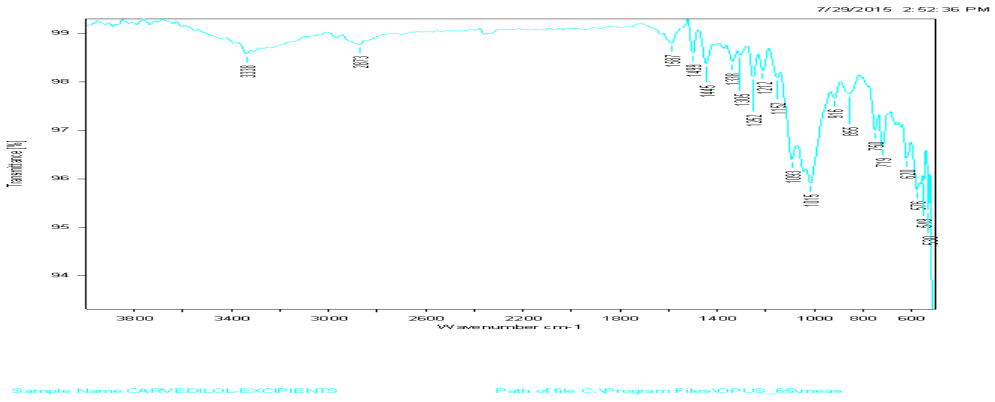

Fig.4: FTIR spectra of drug polymer mixture

Preparation

Bilayer floating matrix tablets of carvedilol was prepared successfully by using HPMC K 100 and HPMC K4 M by direct compression technique. Ethyl cellulose was used as a retardant to prolong the release. Since the tablets prepared with K4M was having total duration of floating less than 18hrs, HPMC K100M was selected for further formulations.

Direct compression technique have many advantages over wet granulation, which is suitable for moisture and heat sensitive API's and also cost effective since the direct compression requires only few unit operations.

Flow property of granules.

The poured density, tapped density and the percentage compressibility was studied for immediate release layer powder blend as well as sustained released layer powder blend. The flow properties mainly affect the compressibility of granules.

The bulk density was determined as per IP procedure. For immediate release layer, the average bulk density was found to be 0.48 and for sustained release layer ranges from 0.45-0.48 g/cm^3.

The tapped density was determined as per IP procedure, for immediate release layer average tapped density was found to be 0.57 g/cm^3 and for sustained release layer ranges from 0.52-0.55 g/cm^3. The tapped density and bulk density was used for calculation of compressibility index and Hausner's ratio.

The Carr's index is the compressibility index. According to IP, carr's index should be less than 20%. In this study both immediate release layer powder mix and sustained release layer powder mix which is within the limit as per IP. From these observations it is clear that all the formulations showed good to fair flow property and compressibility.

According to IP the Hausner's ratio should be less than 1.25. The immediate release powder mix show an average value of 1.18, which is within limits. For sustained release layer the ratio ranging from 1.10-1.19 which is also within limits.

The angle of repose of all the formulations were done by fixed funnel method. Both immediate release layer (28.5) as well as sustained release layer (27-30) showed good flow properties.

Table 4: Flow properties of Immediate release layer

Product code	Bulk density±S.D (g/cm^3) N=3	Tapped density±S.D (g/cm^3) N=3	Carr's index±S.D (%) N=3	Hausner's ratio±S.D N=3	Angle of repose±S.D (θ) N=3
IR 1	0.48±0.176	0.57±0.701	15.78±0.691	1.18±0.481	28.5±0.691

Table 5: Flow properties of Sustained release layer

Product code	Bulk density±S.D (g/cm^3)N=3	Tapped density±S.D (g/cm^3) N=3	Carr's index±S.D (%) N=3	Hausener's ratio±S.D N=3	Angle of repose (θ) ±S.D N=3
F1	0.45±0.289	0.534±0.5678	15.73±0.6780	1.18±0.6709	28±0,391
F2	0.451±0592	0.522±0.6987	13.39±0.8795	1.16±0.5132	27±0.847
F3	0.460±0.591	0.532±0.2345	13.53±0.1567	1.15±0.3489	29±0.591
F4	0.461±0.691	0.524±0.7896	12.02±0.6745	1.13±0.5470	30±0.711
F5	0.470±0.851	0.548±0.1123	14.28±0.3451	1.10±0.2746	27±0.619
F6	0.465±0.890	0.530±0.4567	12.20±0.6908	1.13±0.6791	28±0.634
F7	0.454±0.173	0.534±0.4356	14.98±0.7943	1.16±0.3452	29±0.739
F8	0.462±0.226	0.541±0.6789	14.61±0.5690	1.17±0.9871	27±0.819
F9	0.459±0.951	0.532±0.1234	13.78±0.3498	1.15±0.4532	27±0.105
F10	0.46±0.710	0.547±0.5678	15.90±0.4678	1.18±0.5391	28±0.703
F11	0.471±0.582	0.527±0.4389	10.62±0.9231	1.16±0.4891	29±0.956

EVALUATION

Thickness, Hardness, Friability of bilayer tablet.

Thickness of bilayer floating matrix of carvedilol was determined by using screw gauge. The thickness was ranging from 3-5 mm.

Hardness was determined by using Monsanto hardness tester. The hardness of the prepared formulations was ranging from 4-5 kg/cm^2 which were satisfactory. The hardness of a tablet can affect the floatability as well as the drug release from the tablet. All the formulations have nearly same hardness. So the hardness don't affected to the floatability and drug release of the dosage form.

Friability was determined by using Roche friabilator. The friability values of all the formulation are given in table 7.5. According to IP procedure Percentage weight loss should be less than 1%, for prepared formulations the loss of weight ranges from 0.5-0.7%, which is within acceptable limit.

Drug content.

The percentage drug content in different formulations prepared ranges from 93-95% as given in table 7.6. It was observed from the drug content data that there was no significant difference in the uniformity of the drug content among the prepared formulations. However, when compared with the theoretical drug content, the estimated drug content was slightly less which is an indication of drug loss during formulation of the tablets.

Weight variation test

Weight variation test was carried out for 20 tablets from each formulation. The result of the test complied with the official standard as per IP Not more than two tablets deviated from the specific percentage (7.5%) mentioned and none of the tablets deviated by more than two times the mentioned percentage, all the formulations have weight uniformity.

Table 6: Thickness, Hardness, Friability, percentage drug content, Average weight

Product code	Thickness±S.D in N= 3 (mm)	Hardness±S.D N= 3 (Kg/cm$^{2)}$	Friability±S.D N= 3 (%)	Percentage Drug content±S.D N=3	Average weight ± SD. N=20
F1	4.2±0.435	4.2±0.174	0.61±0.113	94.10±0.345	248±0.457
F2	3.7±0.456	4.6±0.435	0.68±0.341	94.90±0.592	243±0.589
F3	3.8±0.478	5.0±0.347	0.67±0.456	94.20±0.491	251±0.289
F4	4.1±0.187	4.8±0.274	0.58±0.457	93.89±0.286	247±0.189
F5	4.4±0.275	5.0±0.223	0.62±0.348	94.10±0.118	249±0.792
F6	4.2±0.457	4.6±0.275	0.59±0.789	93.80±0.934	250±0.743
F7	4.5±0.378	4.4±0.154	0.55±0.789	93.89±0.502	251±0.669
F8	4.1±0.458	4.8±0.895	0.52±0.345	94.07±0.691	246±0.913
F9	3.9±0.435	5.0±0.123	0.57±0.941	94.04±0.391	249±0.591
F10	3.7±0.158	4.4±0.157	0.62±0.547	94.00±0.820	248±0.993
F11	3.6±0.560	4.6±0.567	0.713±0.47	93.50±0.116	251±0.915

Floating lag time and total duration of floating.

The short floating lag time will help to retain the dosage form in the upper GIT by preventing them from trans-locating to the lower part, thereby providing maximum drug absorption and therapeutic effect in the stomach. Therefore, the study of the *in vitro* floating behavior of a floating dosage form is important. The incorporation of sodium bicarbonate in to the formulation would help to decrease the density of the tablets and thus achieve flotation because CO_2 produced by reaction between sodium bicarbonate and gastric acid becomes trapped in the gel layer of the polymer. The increase of sodium bicarbonate from 2 to 8% percent of the polymer resulted in a decrease in FLT from 9 to 1 min (F1-F3).

All the formulations except F5 show 24hr total floating time. In the formulation F5, HPMC K4M is used as polymer which has lesser viscosity than that of HPMC K 100M and hence its floating ability is also less than that of HPMC K 100 M.

Table 7: Floating lag time and total duration of floating

Product code	Floating lag time.(minutes)	Duration of floating.(hr)
F1	8-9	>24
F2	4-5	>24
F3	1-2	>24
F4	4-5	>24
F5	4-5	<18
F6	4-5	>24
F7	4-5	>24
F8	4-5	>24
F9	4-5	>24
F10	4-5	> 24
F11	4-5	>24

***In vitro* drug release profile.**

In vitro dissolution study was performed for all the eleven formulations. The cumulative amount of drug released at the intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24hr and the percentage cumulative drug release were determined. Then CDR was plotted against time in hours for all formulation and optimized based on drug release. Out of eleven formulations, F9 was found to be showing optimum release because it has optimum release at all the time intervals.

Table 8: *in vitro* dissolution data

Time	Cumulative drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	22.00±0.892	22.28±0.249	30.22±0.547	23.71±0.489	23.14±0.105
1	25.20±0.834	25.41±0.379	33.17±0.432	28.52±0.198	28.01±0.774
2	29.72±0.765	30.16±0.271	35.50±0.965	36.33±0.287	36.05±0.927
3	34.86±0.923	35.35±0.914	39.22±0.189	43.95±0.726	43.20±0.886
4	37.58±0.997	38.07±0.724	43.56±0.576	48.43±0.497	47.821±0.190
5	43.37±0.794	43.61±0.497	46.20±0.347	54.22±0.341	53.22±0.883
6	48.27±0.906	48.43±0.648	48.77±0.248	59.40±0.518	59.18±0.189
7	50.33±0.897	50.57±0.187	50.63±0.429	67.91±0.616	67.1±0.691
8	52.18±0.243	53.49±0.278	52.64±0.754	72.60±0.845	71.9±0.883
9	54.91±0.915	56.18±0.681	56.52±0.289	75.96±0.934	75.3±0.812
10	59.27±0.795	59.30±0.571	59.6±0.929	78.28±0.289	77.59±0.779
11	61.16±0.794	61.82±0.379	61.11±0.248	81.04±0.762	81.13±0.109
12	64.94±0.867	65.54±0.493	66.18±0.322	83.08±0.387	82.78±0.268
24	94.11±0.589	94.23±0.226	94.89±0.712	94.01±0.678	94.2±0.781

Table 9: *in vitro* dissolution data

	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	
0.5	22.456±0.682	22.28±0.279	22.79±0.435	21.57±0.436	21.92±0.667	21.57±0.436
1	26.119±0.123	25.40±0.718	26.01±0.678	23.51±0.228	24.28±0.487	23.51±0.228
2	31.978±0.196	30.16±0.387	31.02±0.965	27.22±0.719	29.49±0.897	27.22±0.719
3	36.361±0.309	35.30±0.643	35.81±0.165	32.63±0.710	34.81±0.762	32.63±0.710
4	40.231±0.195	38.07±0.236	38.30±0.947	35.3±0.669	38.96±0.238	35.3±0.669
5	44.578±0.198	43.69±0.689	43.23±0.673	37.7±0.117	42.95±0.379	37.7±0.117
6	48.561±0.589	48.41±0.268	45.81±0.238	39.92±0.669	46.91±0.678	39.92±0.669
7	52.349±0.117	50.57±0.375	49.89±0.951	42.69±0.883	49.91±0.384	42.69±0.883
8	56.734±0.934	56.87±0.219	53.51±0.492	43.55±0.779	52.81±0.479	43.55±0.779
9	60.594±0.698	56.87±0.219	56.93±0.387	45.6±0.116	55.47±0.697	45.6±0.116
10	63.56±0.112	59.30±0.537	59.87±0.276	47.19±0.661	58.62±0.218	47.19±0.661
11	66.77±0.896	61.82±0.691	62.81±0.860	49.26±0.668	61.44±0.197	49.26±0.668
12	66.77±0.896	94.69±0.679	66.80±0.297	52.22±0.551	64.55±0.315	52.22±0.551
24	94.12±0.118	94.69±0.679	94.13±0.435	94.30±0.883	93.22±0.639	94.30±0.883

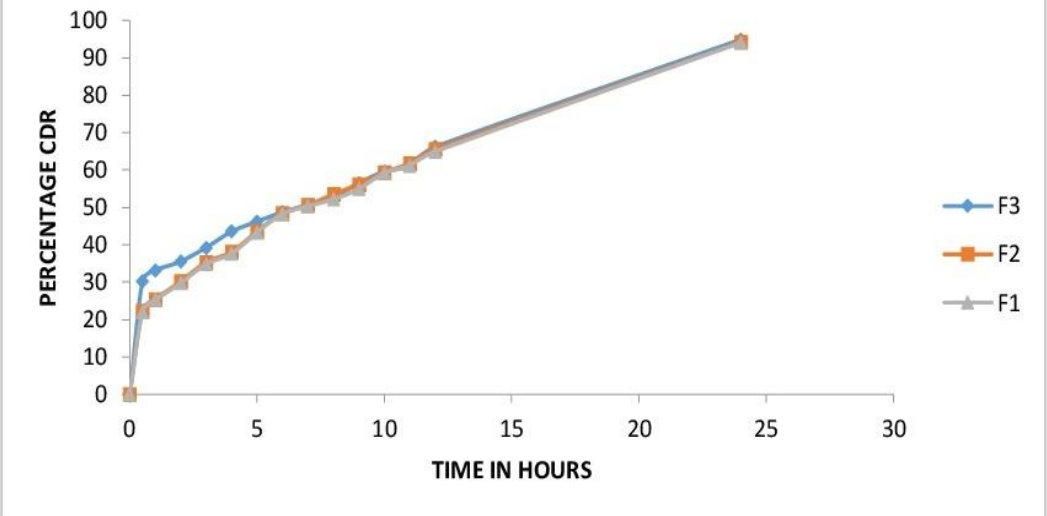

Fig: 5. *Invitro* dissolution study of F1, F2, F3.

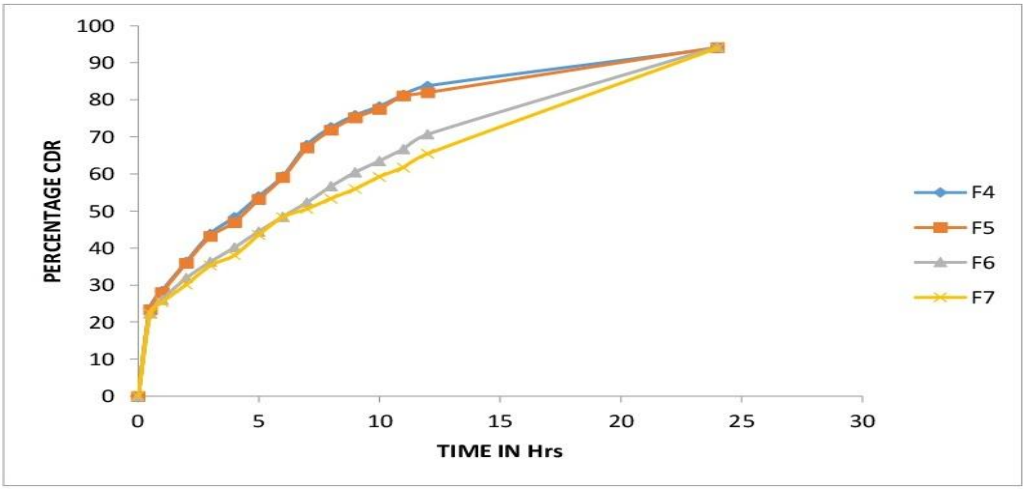

Fig.6: *Invitro* dissolution study of F4, F5, F6, F7.

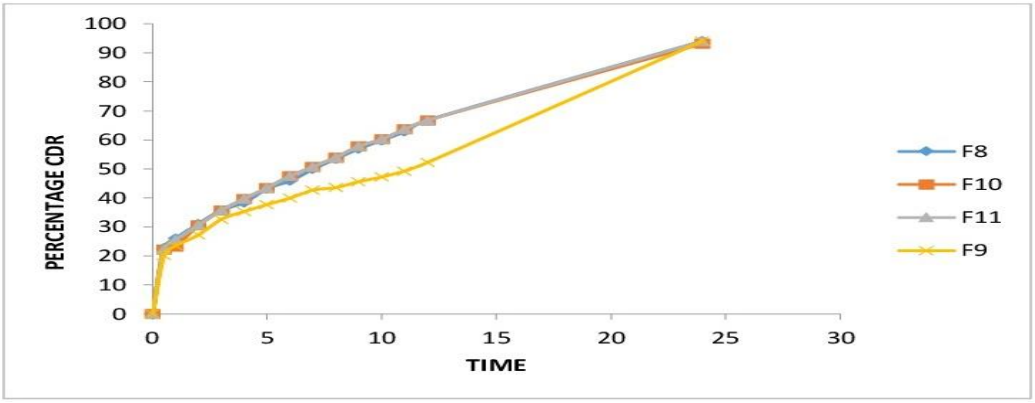

Fig.7: *Invitro* dissolution study of F8, F9, F10, F11.

Optimization

Optimization of floating lag time and total duration of floating.

Incorporation of sodium bicarbonate and its increased amount would help to decrease the density of the tablets and then achieve flotation because CO_2 produced by the reaction between sodium bicarbonate and gastric acid becomes trapped in the gel layer of the polymer. Accordingly, the increase of sodium bicarbonate from 0.5 to 9 % in the polymer resulted in a decrease in FLT from 9 to 1 min (F1-F3). An increased amount of sodium bicarbonate will also increase the drug release by increasing porosity of tablet at initial stages. Therefore 4.5 % of sodium bicarbonate was taken as the optimum concentration (F2: FLT 4-5 minutes) and was used for further formulations.

The total duration of floating is affected by the viscosity of the polymer. HPMC K100M was showing 24hr floating whereas HPMC K4M shows less than 18hr floatation. This is due to HPMC K 100 M have higher viscosity than HPMC K4 M. When viscosity increases the gelling capacity also increases. Therefore HPMC K100M was selected for further formulation.

Optimization of drug release.

HPMC, a hydrophilic matrix that can form a gel barrier around its matrix and allows the drug to be released in a diffusion or matrix erosion manner, was employed as a sustained-release material, but a hydrophilic polymer alone cannot retard the release of the drug for a sufficient duration of time. There for a hydrophobic polymer, ethyl cellulose was also incorporated in the formulation as a release retardant. Percentage of HPMC K 100 M in formulation was up to 37 percent (w/w). HPMC K 100 M alone (formulation F5) has sustained the release of carvedilol up to 12 h in a medium of 0.1 N HCl. Formulation F5 showed a maximum release at 12^{th} hour (83%) . Therefore ethyl cellulose was added as retardant material to further formulations in order to prolong the release up to 24hr. Considering F6, F7, F8 the release of the drug is higher at 12^{th} hour. So it can't be taken as optimum. Therefore formulation F9 that controlled the drug release over a period of 24hr was taken as optimum. Further increasing the polymer concentration of HPMC (F10, F11) increases the drug release

Increasing the amount of gas generating agent in formulations can produce higher levels of effervescence, resulting in an increase in the rate of pore generation, rapid hydration of the matrices and consequently a faster drug release.

As evident by our mechanism study, the drug release was diffusion-dependent, in which the drug diffused from the pores within the gel layer into the medium. The produced CO_2 would, however, get trapped in the gel barrier and then block the diffusion path if located in the pores, retarding the drug release.

The result of the study indicates that F9 can be considered as an optimized formulation because it has showed satisfactory release at all-time intervals.

Stability Studies

The optimized product was subjected to stability studies at room temperature for 2month in a closed container. The physical stability of bilayer floating matrix tablet was observed periodically the sample remained as such, no sign of deterioration like change in color, smell etc. There was no change in the drug content throughout the study period. The result of the stability study of F8 bath given in table no7.13

Table 10: Stability studies

Days	% drug content N= 3
0	94.04±0.391
30	93.95±0.228
60	93.91±0.693

CONCLUSION:

The present study was to design and develop a bilayer floating matrix tablets of carvedilol that would control the release over a 24hr period and improve bioavailability. By observing the short half-life and poor absorption of the drug due to short residence time in upper GIT, an attempt was made to sustain residence of the drug in the stomach by formulating carvedilol as a floating matrix tablet.

The real challenge in the development of floating sustained release system is not only just to control the drug release but also to prolong the retention of the dosage form in stomach. In this study bilayer floating matrix tablets was formulated in which one layer was an immediate release as loading dose and second layer was a floating matrix layer to maintain the dose and also to retain in the stomach for sufficient time so as to produce a 24hr extended release thereby avoiding multiple administrations.

From compatibility studies, it was concluded that HPMC K100 M, SSG and all other excipients were compatible with carvedilol and thus suitable for formulation in to bilayer floating matrix tablets.

Eleven formulations were prepared and evaluated for various evaluation parameters of bilayer tablet for physical properties, floating and *in vitro* drug release.

All the formulations were having optimum flow

properties, percentage of weight variation and friability. Accordingly, the increase of sodium bicarbonate from 0.5 to 9 % in the polymer resulted in a decrease in FLT from 9 to 1 min (F1-F3). Because of the amount of sodium bicarbonate also affected the drug release from the formulation, F2 have optimum concentration (4.5%) of sodium bicarbonate. The drug release pattern and drug uniformity were found to be satisfactory. Considering the *in vitro* drug release studies batch F9 was selected as optimized formulation

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