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PREPARATION AND EVALUATION OF BILAYER FLOATING FORMULATIONS OF CARVEDILOL

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ABSTRACT

Studies were conducted for the preparation of Bilayer floating formulations of Carvedilol. Solubility studies showed Carvedilol, highly soluble in methanol acidic pH but poorly soluble in water. FTIR studies showed no incompatibility between drug, polymer and various excipients used in the formulations. Formulated tablets gave satisfactory results for various evaluation parameters like tablet dimensions, hardness, weight variation, friability, content uniformity, swelling index, *in vitro* buoyancy properties and *in vitro* drug release. In tablet formulations F3, F5, F8 and F11 gave better controlled drug release and floating properties in comparison to the other formulations.F8 is release 98.33% in 12hrs and float for 12hrs and other parameters like hardness, thickness,assay,friability all within limits and well satisfactory. The drugs release from the optimised tablets was sufficiently sustained and fickian transport of drugs from tablets was confirmed as the release exponent value was less than 0.5. *In vivo* radiographic studies of single unit tablets (F8) indicated that the tablets remained in the stomach for 6h, which indicates the increase in the GRT is due to floating and swelling principle

Key Words: Carvedilol, Bilayer floating formulations

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INTRODUCTION

Floating system is retained in the gastric region due to their floating ability on the gastric fluid. The floating system is further divided into single unit system such as floating tablets and multi particulate systems such as floating microspheres, which offer more advantages as compared to single unit system.

The floating system is further divided into effervescent and The non-effervescent floating system based on their mechanism of floating. Bioadhesive systems adhere to the gastric mucosa due to which they are retained in the gastric region. High density systems are retained due to their increased density then the gastric fluid. Beside this, passage delaying food as well as drugs can be administered simultaneously to retain the dosage form in the gastric region. Gastro retentive dosage forms (GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal tract and improve the bioavailability of medications those are characterized by a narrow absorption window. The aim of this study was first to develop and physico-chemically characterize an optimal single unit bilayer

floating tablet for Carvedilol phosphate (CP) prepared by direct compression technology with using different grades of HPMC. Carvedilol (CV) is a non-cardio selective alpha1- beta adrenergic blocking agent with no intrinsic sympathomimetic activity and weak membrane-stabilising activity. The alpha 1-adrenergic blocking activity of CV causes vasodilatation and reduces peripheral vascular resistance. At higher doses calcium channel blocking activity also observed. CV is most effective in management of hypertension, in angina pectoris, heart failure, and left ventricular dysfunction with myocardial infarction. CV has a terminal half-life of 7-10 hr, but most of the drug is eliminated with a half-life of about 2 hr, and the recommended oral dose for adult is two times a day. CV has advantage over traditional β-blockers with respect to hemodynamic and metabolic effects. Such results indicate its safe and effective therapeutic application particularly in patients with complicated Cardiovascular Diseases (CVDs). It is widely known that gastric residence time (GRT) is one of the important factors affecting the drug bioavailability of pharmaceutical dosage forms. Variable and short gastric emptying time can result in incomplete drug release from the dosage form (DF) above the absorption zone (stomach or upper part of small intestine), leading to a diminished efficacy of the administered dose. Aim of this study is to prepare a bilayer floating tablet which makes treatment so comfortable. Initially fast dissolving layer release so fast and produce activity and later on floating layer release the drug for longer times. It will increase bio availability of drug. As per its pharmacological use and other factors like solubility and halflife, this drug absorption rater is high at GIT region (1-5). So we aim for this preparation.

MATERIALS AND METHODS

Construction of Calibration Curves

Standard graph of in 0.1N HCl

Stock solution was prepared by transferring an accurately weighed amount of 100mg of into 100 ml volumetric flask, containing 0.1N HCl to dissolve. Then, the volume was made up to the mark with 0.1N HCl. From this stock solution, necessary dilutions were made to give concentration ranging from 0-10 µg/ml. The absorbance of each test solution was measured at λ_{max} of i.e. 286 nm using UV/ Visible spectrophotometer against 0.1 N HCl as blank and plotted graphically to give the standard graphs.

Solubility study of Carvedilol

Excess amount of was placed in 0.1 N HCl, The samples were shaken for 24 h at 37 °C in a horizontal shaker (HS 501 Digital, IKA-Labortechnik, Staufen, Germany). The supernatant was filtered and the filtrate was diluted with the respective medium and assayed by UV/ Visible Spectrophotometer at 286 nm.

Formulation of bilayer tablets by direct compression method (6-8)

The ingredients in the formula are weighed accurately and mixed to form a homogeneous blend of drug and excipients separately for both layers.(Patil et al formulated amoxicillin trihydrate as IR 50mg,SR 200mg) First compressed the immediate release layer and followed by floating release layer using CADMACH punching machine to produce round tablets weighing 450mg(flat punch 12mm,5-6).

Drug Content

Six tablets were taken, powdered and the powder equivalent to one dose each was transferred to a 100 ml volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and diluted suitably and drug content in the samples was estimated using UV-spectrophotometer at 286 nm.

In vitro Drug Release Studies

The *in vitro* drug release study was performed for the single- & multiple-unit tablets using USP Type II dissolution apparatus. At predetermined time intervals samples (5 ml) were collected and replenished with same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 286 nm.

RESULTS AND DISCUSSION

Calibration curves of Carvedilol

An UV- Spectrophotometrically method was used for estimation of Carvedilol. A solution of (10µg/ml) was scanned in the wavelength range of 200-400 nm and found to have maximum absorption (λ_{max}) at 286 nm. The standard plots were prepared in 0.1 N HCl (pH 1.2). The standard graphs showed good linearity with R^2 value 0.998 (Table-1 and Fig-1)

Table-1 Absorbance at different concentrations at λ_{max} (286 nm)

CONC.	ABSB.
0	0
2	0.082
4	0.151
6	0.211
8	0.291
10	0.351

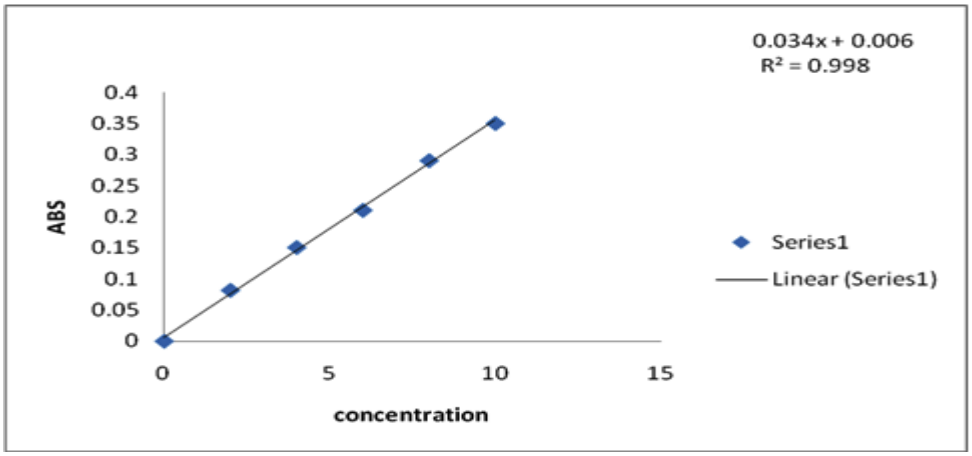

Fig-1Standard graph of carvedilolin 0.1N HCL

Evaluation of physical parameters of bilayer floating tablets of sustaine release tablets

All the prepared formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeias limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good (Table-2).

Table-2 Physical parameters of Bilayer floating tablets of Formulations

Formulation code	Weight variation (mg)(n=10)	Hardness (kg/cm^2)(n=3)	Thickness (mm)(n=3)	Friability (%)	Assay (%)
F1	301.38±3.84	6.0±0.3	6.84±0.05	0.35	97.23
F2	300.52±2.87	6.1±0.5	6.76±0.06	0.19	98.65
F3	300.23±2.73	6.6±0.4	6.86±0.03	0.28	99.12
F4	301.6±2.13	6±0.5	6.76±0.04	0.32	101.3
F5	300.19±3.48	7±0.2	6.63±0.06	0.29	98.23
F6	299.71±2.3	6.6±0.4	6.65 ±0.06	0.22	98.63
F7	300.2±1.19	6.8±0.5	6.68±0.05	0.30	102.3
F8	299.46±2.27	5.9±0.2	6.55±0.25	0.26	97.65
F9	300.67±3.84	6.8±0.5	6.506±0.04	0.29	98.45
F10	300.38±3.84	6.7±0.3	6.62±0.07	0.37	97.64
F11	300.52±2.87	6.8±0.5	6.78±0.02	0.45	98.12
F12	300.23±2.73	6.9±0.2	6.60±0.04	0.56	97.72

Floating lag time and Total floating time

All the formulations were tested for floating properties like floating lag time and total floating time. The results of the tests were tabulated. All the batches showed good *in vitro* buoyancy. Floating was affecting the release of drug from formulations and duration of action (Khanvilkar *et al*. studied the effects, Incorporating a low viscosity grade of HPMC in the formulation would lead to a significantly shorter lag time). The floating lag time of bi-layer tablets was found to be in the range of 101 sec to 211sec and total floating time of bi-layer tablets was found in the range of less than 12hours for all the formulations (F1toF12) (Fig-2).

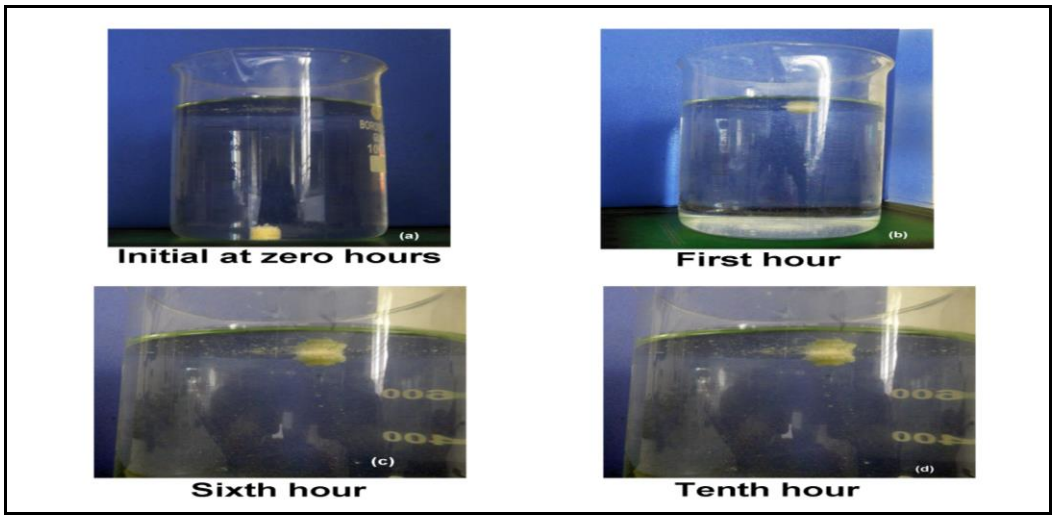

Fig-2 Floating of optimized formulation

Release profiles of formulations containing HPMC $K_{15}M$ and Ethyl cellulose

From the Fig-3 it was evident that the polymer HPMC K15M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F1, F2 and F3 was, 98.33(6hr), 97.93(8hr) & 98.38(10) h respectively. All formulations release drug immediately up to above 20%due to burst release (Patil et al,studied the effect of SSG on drug release), from fast release layer. Formulation F1 was unable to sustain the drug release desired period of time (total drug was released within 6 hr). Formulations F2 release the drug release within the desired time.F3 with high HPMC concentration and sustained drug release for more than 11hr and it is satisfactory formulation. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. Formulation F3 was considered as best formulation among all the three formulations (Reynolds *et al*. found that; drug release resulting from polymer erosion was linear vs time and was found to be a function of the number average molecular weight of the polymer (HPMC).

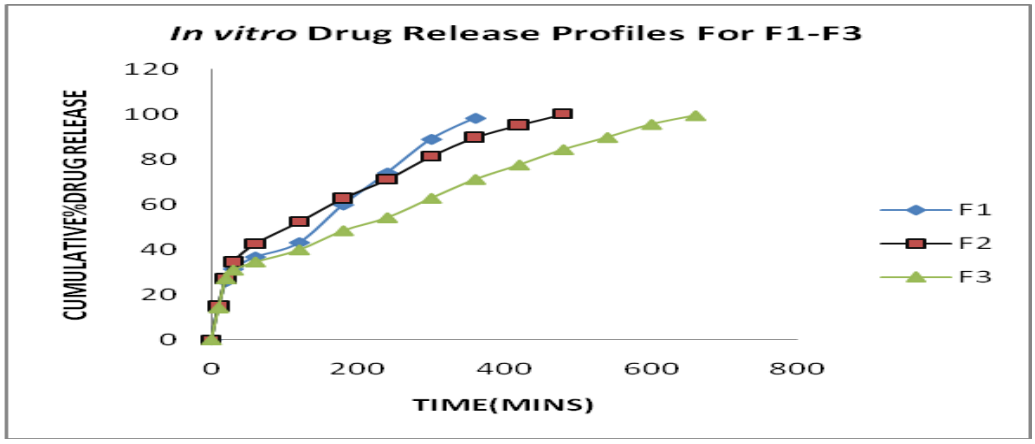

Fig-3 Zero order plots between %drug release vs time for (F1, F2, & F3)

From the Fig-4 it was evident that the polymer HPMC K15M alone has unable to sustain the drug release up to the desired time (12 hr). So, ethyl cellulose was incorporated into the formulation as release modifier. (Soskolne *et al*. have demonstrated the ability of HPMC along with EC to decrese the release rate) Ethylcellulose has been used as release retardant polymer in controlled release dosageforms EC reduces the drug release due to a reduction in the penetration of the solvent molecules into the system because of the hydrophobic nature of ethyl cellulose present on the surface of the tablet, *i.e.* the rate of release is controlled by the permeability of matrix structure .As the proportion of ethylcellulose increase, the release process of decreares Formulations F4, F5 and F6 were prepared with HPMC K15M in combination with ethyl cellulose. All formulations release drug immediately up to above 20%due to burst release, from fast release layer. Formulations F4, F5and F6 were prolonged the drug release up to 12 hr, respectively. The percent of drug release from formulations F4, F5 and F6 was, 76.02, 92.69& 82.69 in 12 h respectively. Formulation F5 was considered as best formulation among all the three formulationsas (Sandip *et al*. studied the effect of concentration of hydrophilic (HPMC) and hydrophobic polymers (hydrogenated castor oil [HCO] and EC) on the release rate of tramadol(kamal et al 2008). The results showed that hydrophobic matrix tablets resulted in sustained in vitro drug release (>20 h) as compared with hydrophilic matrix tablets (<14 h).

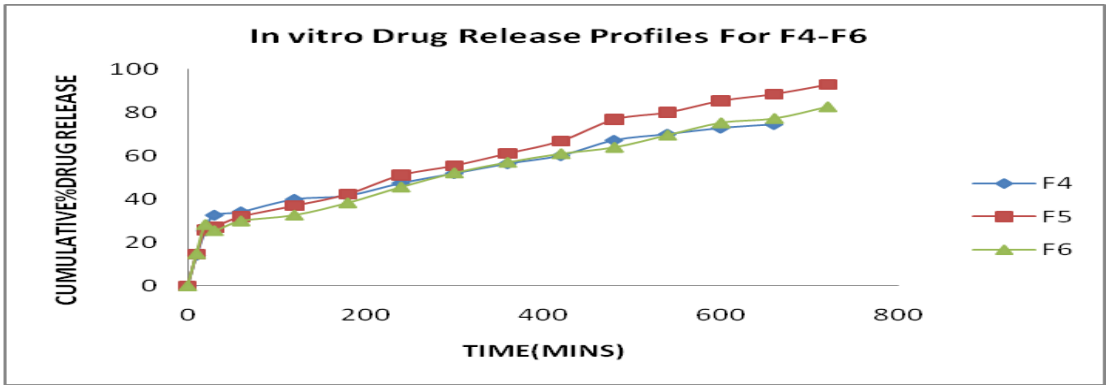

Fig-4 Zero order plots between %drug release vs time for (F4 F5& F6)

From the Fig-5 it was evident that the polymer HPMC K100M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F7, F8 and F9 was, 98.87(6hr), 98.33(8hr) & 76.69(12) h respectively. All formulations release drug immediately up to above 25%due to burst release, in 20mins from fast release layer. Formulation F7 was unable to sustain the drug release desired period of time (total drug was released within 9hr). Formulations F9 release the drug within the desired time.F8 with high HPMC concentration and sustained drug release for more than 12hr and it is satisfactory formulation. The difference in the drug release

profiles of various formulations was due to the presence of different concentrations of polymer. Formulation F8 was considered as best formulation among all the three formulations as it showed good buoyancy properties (floating lag time: 101 sec & floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

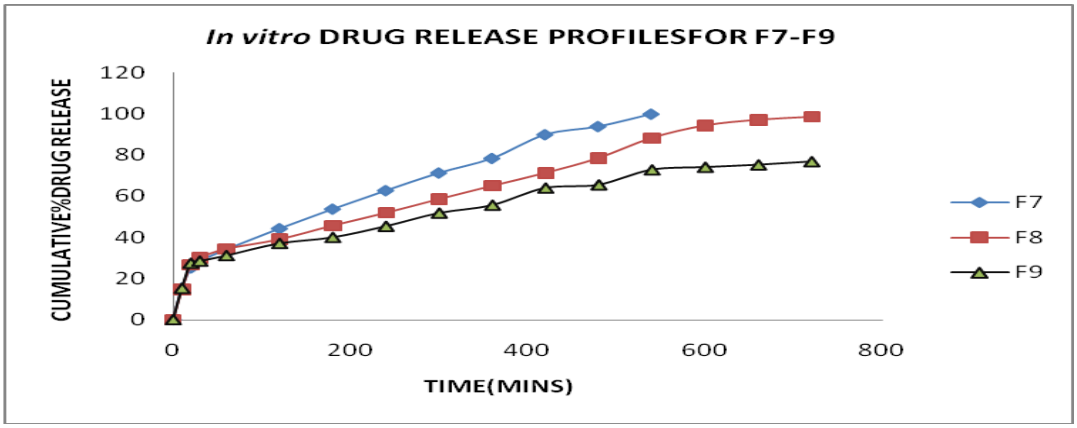

Fig-5 Zero order plots between %drug release vs time for (F7, F8& F9)

From the Fig-6 it was evident that the polymer HPMC K100M alone has unable to sustain the drug release up to the desired time (12 hr). So, ethyl cellulose was incorporated into the formulation as release modifier. Ethylcellulose has been used as release retardant polymer in controlled release dosageforms EC reduces the drug release due to a reduction in the penetration of the solvent molecules into the system because of the hydrophobic nature of ethyl cellulose present on the surface of the tablet, *i.e.* the rate of release is controlled by the permeabilityof matrix structure .As the proportion of ethylcellulose increase, the releaseprocess of decreares Formulations F10, F11 & F12 were prepared with HPMC K100M in combination with ethyl cellulose. All formulations release drug immediately up to above 23%due to burst release,in 20mins from fast release layer. Formulations F10, F11and F12 were prolonged the drug release up to 12 hr, respectively. The percent of drug release from formulations F10, F11 and F12 was, 73.84, 94.1& 76.6 in 12 h respectively. Formulation F11 was considered as best formulation among all the three formulations as it showed good buoyancy properties (F5floating lag time: 105 sec & floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

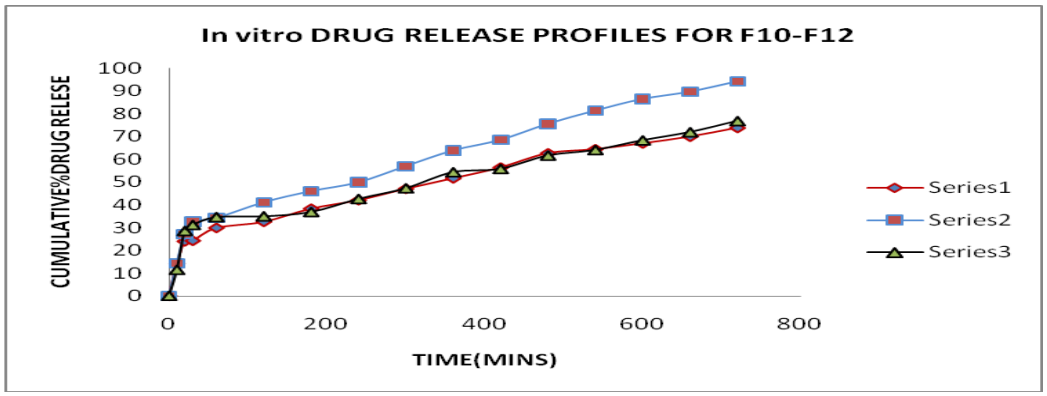

Fig-6 Zero order plots between %drug release vs time for (F10, F11& F12)

CONCLUSION

Systematic studies were conducted for the preparation of Bilayer floating formulations of Carvedilol. Solubility studies showed Carvedilol, highly soluble in methanol acidic pH but poorly soluble in water. FTIR studies showed no incompatibility between drug, polymer and various excipients used in the formulations. Bilayer floating formulations of Carvedilol were successfully prepared with hydrophilic polymers like HPMC K15M, HPMC K100M, EC and sodium starch glycolate by simple direct compression method. Formulated tablets gave

satisfactory results for various evaluation parameters like tablet dimensions, hardness, weight variation, friability, content uniformity, swelling index, *in vitro* buoyancy properties and *in vitro* drug release. From the swelling studies it is concluded that as the concentration of HPMC increases swelling tablet increases there by it decreases the release the of drug. In combination with EC swelling is quite low due to EC hydrophobic nature. In tablet formulations F3, F5, F8 and F11 gave better controlled drug release and floating properties in comparison to the other formulations.F8 is release 98.33% in 12hrs and float for 12hrs and other parameters like hardness, thickness,assay,friability all within limits and well satisfactory. The kinetic study results suggest that, the best linearity was found in Higuchi's equation plot (R^2=0.994) indicating the release of drug from matrix fallow higuchi model kinetics. The drugs release pattern from the optimized formulations (F8) was diffusion controlled, obeying Higuchi equation. By incorporating the total 12hrs of release data mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. The value of the release exponent in carvedilol bilayer floating release obtained as 0.473 & (R^2 =0.988) which as per table 19 is beyond the limits of Korsmeyer model so-called power law. The drugs release from the optimised tablets was sufficiently sustained and fickian transport of drugs from tablets was confirmed as the release exponent value was less than 0.5. *In vivo* radiographic studies of single unit tablets (F8) indicated that the tablets remained in the stomach for 6h, which indicates the increase in the GRT is due to floating and swelling principle. Oral solid dosage form based on bilayer floating drug delivery is promising to achieve bimodal drug release.bilayer tablets showed an initial burst effect to provide the loading dose of the drug followed by sustained release for 12hr, indicating a promising in patient compliance. This system can be useful for pharmaceutical following chronopharmacology and having limited physiological stability and absorption window in upper part of GIT tract. However further clinical studies are needed to explore potential of system for antibiotics to achieve maximum bioavailability and reduce side effects. This dual release of bilayer tablets shows better alternative to conventional dosage form. More clinical trials and statistical data are required for the bilayer floating tablet enter into pharmaceutical market. it can be concluded that, the formulation retained for longer periods of time in the stomach and provides controlled release of the drug. Hence, improve the therapeutic effect of the drug may lead to increasing its bioavailability.

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