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Research Article

Formulation and Evaluation of Sustained Release Matrix Tablet of Carvedilol Using Natural and Synthetic Polymers

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ABSTRACT

Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The main objective of this research work was to develop and evaluate the sustained release (SR) tablets of Carvedilol. Carvedilol is an antihypertensive agent. It is most effective in management of hypertension and to relive symptoms of angina pectoris. The tablets were prepared relatively small dose of 20 mg by direct compression method using different polymers. The results of both pre and post-compressional parameters were within I.P prescribed limits. The in-vitro drug release were performed in the USP Apparatus-II (Paddle) using 0.5% SLS as a dissolution media at 50 rpm speed and temperature of $37^0C \pm 0.5^0C$ upto 12 hrs. Majority of designed sustained-release tablets containing carvedilol with all the other polymers displayed drug release 61.15 to 99.43% drug in 12hrs. This F7 and F9 formulations containing HPMCK15M, MCC, β-Cyclodextrins and xanthan gum. So the HPMCK15M decreasing the solubility of Carvedilol and drug release is 99.80 at 13hrs. FTIR spectral analysis showed that characteristic peak of Carvedilol pure drug were retained in the spectra of all the formulations within the same range indicating the there was no interaction between drug and excipients used. Kinetic study reveals that all formulations follow first order kinetics. The stability studies of the optimized tablet F7 and F9 were carried out according to ICH guidelines. The stability study shows no significant changes in hardness, friability and drug content. Finally concluded that the formulations F7 and F9 showed best release of 99.81% at 13 hrs. Among all the formulations the F7 and F9 formulations is best formulation because it may be presence of both synthetic and natural polymers.

INTRODUCTION

Sustain release with the introduction of extended release matrix tablet have proved to be an effective tool to control the release of drug without involving the complex production procedures. Numerous sustain release oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of sustained release systems for poorly water soluble drugs.

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But making a consideration of the drawbacks seen with the conventional drug delivery system (repeated dosing and dose fluctuation) the sustain release helps to achieve the following goals: i) Uniform release of drug over prolong period of time. ii) Reduced dosing frequency. iii) Less fluctuating blood levels. In many instances, conventional method is more preferred to deliver the drug, but some drugs are unstable and toxic by frequently dosing. These kinds of drug have narrow therapeutic range and face solubility difficulties[1,2]. In recent years the basic aim has been designing of drug products to reduce the frequency of dosing by modifying rate of the drug release from the formulation[3]. Regular research has been carried in this field for the use of naturally occurring biocompatible

polymeric material in designing the dosage form for oral controlled release administration[4,5]. Hydrophilic swell able polymers are widely used to control the release of the drugs from polymer matrix formulations[6,7]. Gums of natural sources are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media; and these have been used for the preparation of single use dosage forms[8]. Drug release from hydrophilic matrix tablets are sustained by formation of hydrated viscous layer around the tablet which acts as a barrier to drug release by opposing penetration of water in to the tablet and also the movement of dissolved solute out of matrix tablet[9]. Hydrophilic polymers have attracted considerable attention in recent years as sustained controlled release devices for the delivery of water soluble and water insoluble agents. Their characteristics and their ability to hydrate and form a gel layer are well known and essential to sustain and control drug release from matrices[10]. The hydrated gel layer thickness determines the diffusion path of the drug molecules through the polymer mass in to dissolution medium[11]. A number of natural and number of polysaccharides, such as xanthan gum, guar gum and Karaya gum, have been showed to be useful for controlled release due to their hydrophilic properties [12].

Carvedilol is chemically (+)-1-(Carbazol-4-yloxy)-3-{[2-(o-methoxy phenoxy) ethyl] amino}-propan-2-ol and is an antihypertensive drug with multiple mechanisms of action. It acts as a non-selective β and α-1 adrenergic receptor blocker and it also has vasodilating property that is attributed mainly to its α-1 receptor antagonist activity[13,14]. Its conventional tablet dosage form is used to treat mild-to-moderate hypertension and angina pectoris[15]. Carvedilol base is practically insoluble in water (0.583 mg/L) and thus poorly absorbed from the gastrointestinal tract. It exhibits poor absolute bioavailability of 25-35% [16]. The half-life of the drug is 6 - 8 hrs [17]. The conventional tablets are required to be administered 3 - 4 times a day. A suitable sustained release dosage form of Carvedilol should provide prolonged action and better compliance by the patient. In the proposed research work we are planning to prepare matrix tablet with the following objectives. Carvedilol Matrix tablet will be prepared using some natural and synthetic polymers in varying concentrations.

MATERIALS AND METHODS

Carvedilol drug is procured as a gift sample from Shasun Pharmaceuticals Pvt Ltd, Puduchery, India. HPMC K4M procured as a gift sample from AstraZeneca Pvt Ltd Bangalore. HPMC K15M, MCC, and lactose purchased from Hi media laboratories Pvt. Ltd, Mumbai. India, magnesium stearate and talc were purchased from S.D. Fine Chemicals, Mumbai. β-Cyclodextrin was procured as a gift sample from Yarrow chem. products. All other materials used were of pharmaceutical grade.

Drug - Excipients Compatibility Studies

A successful formulation of stable and effective solid dosage form depend on careful selection of excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and not been used in formulation containing the active substance, the compatibility studies are of paramount importance.

FTIR Studies

IR spectra for pure drug carvedilol and combination of different polymers with drug were recorded in Fourier transform infrared (FTIR) spectrophotometer with KBr pellets.

Preparation of Carvedilol Sustained Release Matrix Tablet [18, 19]

Carvedilol matrix tablet were prepared by direct compression method. In this MCC is used as a diluents, magnesium stearate and talc used as a lubricant and glident. Then the ingredients weighed and mixed in geometrical order after sufficient mixing of drug as well as other components the powder blend compressed into tablets of F1 to F10 formulations were 300 mg using 15mm round flat punches on 11-stationary rotary tablet machine. Compression force mission was adjusted to obtain the hardness of 4-5kg/cm^2. Composition of matrix tablet is given in Table 1.

The powdered blends were evaluated for pre-compressional parameters to find out the flow properties of powder blend. The pre-compressional parameters such as Bulk density, Tapped density, Angle of repose, Compressibility index and Hausner ratio.

Table 1: Composition of carvedilol matrix tablet

INGRADEDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Carvedilol	20	20	20	20	20	20	20	20	20	20
β-Cyclodextrin	20	20	20	20	20	20	20	20	20	20
HPMC K4M	50	60	70	-	-	-	-	70	-	70
HPMC K15M	-	-	-	50	60	70	60	-	70	-
Xanthan gum	-	-	-	-	-	-	90	100	90	100
MCC	50	50	50	50	50	50	50	50	50	50
Lactose	156	146	136	156	146	136	66	76	66	76
Mag Stearate	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2
TOTAL WEIGHT	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

Table 2: Pre-compressional parameters of carvedilol sustained release matrix tablets

Formula code	Angle of repose (degree)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr'index (%)	Hausner's ratio
F1	23.18 ±.070	0.485 ±0.01	0.602 ±0.02	20.03 ±0.14	1.16 ±0.08
F2	24.78 ±0.99	0.441 ±0.06	0.544 ±0.02	19.43 ±0.14	1.15 ±0.06
F3	25.62 ±0.34	0.425 ±0.07	0.542 ±0.01	16.45 ±0.32	1.13 ±0.12
F4	25.14 ±0.60	0.421 ± 0.06	0.542 ± 0.02	21.56 ± 0.12	1.22 ±0.02
F5	24.42 ±0.78	0.502 ±0.09	0.604 ±0.02	23.67 ±1.36	1.16 ±0.03
F6	24.61 ±0.59	0.446 ±0.02	0.558 ±0.02	19.65 ±1.23	1.20 ±0.01
F7	24.84 ±0.76	0.431 ±0.06	0.563 ±0.01	19.65 ±0.14	1.26 ±0.09
F8	24.92 ±0.38	0.485 ±0.13	0.602 ±0.01	20.03 ±0.14	1.16 ±0.08
F9	25.25 ±0.65	0.462 ±0.07	0.583 ±0.01	21.34 ±1.03	1.18 ±0.03
F10	25.39±0.48	0.469 ±0.09	0.586 ±0.02	21.34 ±1.36	1.24 ±0.03

Average value ± SD, n=3

Table 3: Post-compressional parameters of carvedilol sustained release matrix tablet

FC	Hardness	Friability	Thickness	Weight variation (mg)	Drug content (%)
F1	4.8 ± 042	0.27±0.05	2.23± 0.02	300.5 ± 1.38	98.46±1.2
F2	4.8 ± 0.23	0.67±0.10	2.32± 0.01	299.5 ± 1.23	97.26±1.3
F3	5.2 ± 0.15	0.31±0.09	2.21± 0.05	298.5 ± 1.34	99.48±0.6
F4	5.0 ± 0.25	0.71±0.14	2.76± 0.01	301.5 ± 1.46	97.46±1.6
F5	4.6± 0.11	0.69±0.23	2.66± 0.00	301.5 ± 1.41	96.98±0.9
F6	5.4 ± 1.23	0.65±0.34	2.76± 0.01	300.0 ± 2.12	98.24±1.6
F7	5.2 ± 0.34	0.68±0.43	3.11± 0.05	299.0± 1.87	97.76±1.3
F8	4.6 ± 0.89	0.79±0.29	3.23 ±0.02	300.0± 1.38	98.88±1.8
F9	4.8 ± 0.43	0.59±0.45	3.43± 0.03	299.5 ± 1.98	99.25±0.9
F10	5.2 ± 0.56	0.75±0.24	3.56± 0.04	300.5 ± 1.90	99.98±0.9

FC-formulation code, Average ± SD, n=3

Evaluation of Carvedilol Sustained Release Matrix

Hardness Test

Pfizer hardness tester was used to determine the hardness of tablet. Hardness is Measured is also with the help of hardness tester like Pfizer tester Strong cob tester. Hardness is measured in kg/ cm^2.

Friability Test [20]

The instrument used for this test is known as 'Friability Test Apparatus. It consists of a plastic chamber which is divided into two parts and revolves at a speed of 25 rpm. A number of tablets were weighed (W1) and placed in the tumbling chamber which was rotated for four minutes or for 100 revolutions. During each

revolution the tablets fall from a distance of six inches to undergo shock. After 100 revolutions the tablets were again weighed (W2) and the loss in weight indicates the friability. The acceptable limits of weights loss should not be more than 1 percent.

$$\text{Friability} = \{(W1 - W2)/W1\} \times 100$$

Weight Variation [21]

It is desirable that every individual tablet in a batch should be in uniform weight and weight variation within permissible limits. If any weight variation is there, that should fall within the prescribed limits (generally ±10% for tablets weighing 130 mg or less, ±7.5% for tablets weighing 130 to 324 mg and ± 5% for tablets weighing more than 324 mg). The weights of 10 tablets of each batch were taken at individually and calculate the average weight of 10 tablets.

Drug Content [22]

The amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch is to evaluate tablets potential for efficacy. To perform the test, ten tablets from each batch were weighed and powdered. Powder equivalent to the average weight of the tablet was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of distilled water. The solution was made up to the mark and mixed well. A portion of the sample was filtered and analyzed by a UV spectrophotometer at 243 nm.

***In-vitro* Dissolution Studies**

900 ml of 0.5 N SLS was placed into dissolution vessels and the temperature was set to 37^0C. Tablets were transferred to each vessel. Basket was immersed in media. At the end of 30 min 5ml samples were withdrawn from each vessel. The withdrawn quantity of samples was replaced by the same. At every 1 hrs interval 5ml samples were withdrawn from the dissolution vessel and replaced with fresh dissolution medium to maintain constant volume. The dissolution study was continued for 12 hrs. The absorbance was measured at 243 nm by the UV spectrophotometer using 0.5 N SLS as blank

***In-Vitro* Dissolution Studies Details**

Medium	:	0.5N SLS
Apparatus	:	USP II (Basket)
Speed	:	50 rpm
Time	:	1 hrs to 12 hrs
Temperature	:	37^oC
λ max	:	243 nm

Release Kinetics

Data obtained from *in-vitro* release studied was evaluated to check the goodness of fit to various kinetics equations for quantifying the phenomena controlling the release from microspheres. The kinetic models used were zero order, first order, and Higuchi and Korsmeyer-peppas model. The goodness of fit was evaluated using the correlation coefficient values (R2).

Interpretation of Diffusion Release Mechanisms from Tablets

N		Mechanism
0.5	:	Fickian diffusion
0.5<n<1	:	Non- fickian diffusion
1	:	Class II transport
>1.0	:	Class II transport

Stability Studies

Stability of drug has been defined as the ability of particular formulations, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

The purpose of stability testing is provide evidence on how the quality of a drug substances or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity an light and enables recommended storage conditions, re-test periods and shelf life to be established. The optimized tablets were carried out according to ICH guidelines at 40±2^{0}C/ 75±5%RH for three months.

RESULTS AND DISCUSSIONS

Fourier Transform Infrared Spectroscopy (FTIR)

FT-IR spectroscopy was used to investigate the probability of chemical interactions between ingredients of optimized formulae using infrared spectrophotometer Shimadzu IR- 435, Kyoto, Japan. The scanning was performed within a wave number of 4,000–500 cm^{-1}.

FTIR spectrum of pure drug Carvedilol and formulations F5, F7 and F9 were shown in (**Fig 1**). A broad peak was observed at 3344 to 3421 for the OH and NH bonding. A C=C stretching of an aromatic ring was observed at a region 1590. C-H stretching due to alkanes was observed at 2922 region. H-C=O stretching was observed at 1099. CH_3 rocking bending and CH bending groups are observed at 719 and 849 region.

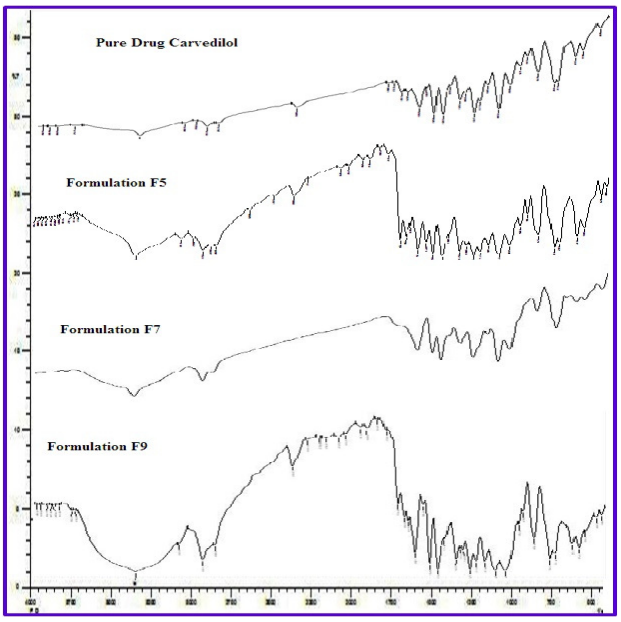

Figure 1: IR spectra of pure drug carvedilol and formulation F5, F7 and F9.

FTIR spectra for formulation F5 exhibited characteristic absorption bands at 3421cm^{-1}, 3345cm^{-1}, 3344cm^{-1} representing OH and NH stretching. 1654cm^{-1} and 1590cm^{-1} representing C=C aromatic stretching and C-H stretching due to alkanes indicating that there is no interaction between pure drug and drug and excipients physical mixtures, there was no chemical and physical change in the functional groups present in Carvedilol as the formulation showed absorption bands at near that of Carvedilol.

Similarly the IR spectrum of formulation F7 and F9 showed characteristic absorption bands and Carvedilol absorption bands are almost same with negligible shift signify that there was no chemical and physical change in the functional groups present in Carvedilol.

The values of pre-compression parameters of powdered blend were evaluated the results were within prescribed IP limits and indicated good free flowing property. The results of pre-compression parameters were given in **Table 2.**
The tablet hardness, friability, weight variation and drug content uniformity of all the formulations were found to be satisfactory results. The hardness of the tablet measured using Pfizer hardness tester. In the present study the hardness of Carvedilol tablet was found to be in the range of 4.6 to 5.4 kg/m^2 these values indicating that all tablet possessed sufficient mechanical strength to withstand physical and mechanical stress conditions while handling and during compression process. The result of hardness was within IP acceptable range for all the formulation. Friability is another to measure the tablet strength. The friability of carvedilol tablet was found to be in the range of 0.27% to 0.75%. In the present study, percent friability of all the tablets was below 1% limit as shown in the pharmacopeia indicating that the friability is within the standard limit. The weight variation test was performed according to the procedure given in the pharmacopeia. in weight variation test, pharmacopeia limit for the of deviation of tablets weighing more than 130mg and less than 324mg is ± 7.5 and 324mg and more ± 5%. For sustain release tablet weight variation in the range of 298 to 301.5. It is found within the limits. The drug content uniformity was performed for all the formulated tablets and result are tabulated in table.5. The average values of all formulations were calculated. The percentage of drug content of Carvedilol in all sustained release matrix tablets formulations was found in the range of 95.46 to 99.98. All the above parameters results were shown in **Table 3.**

Dissolution Study

Dissolution rate was studied by USP type-2 apparatus using 900ml of 0.5% SLS solution as dissolution medium. Temperature of the dissolution medium was maintained at 37 ± 0.5^0 C, aliquot of dissolution medium was withdrawn at different intervals and filtered. The absorbance was measured at 243 nm by the UV spectrophotometer using 0.5% SLS as blank. All the formulations were prepared by using polymers such as HPMCK4M, HPMCK15M, β-Cyclodextrin, Xanthan gum and MCC. The polymers are enhancing the solubility Carvedilol. The drug release result of carvedilol sustained release matrix tablets formulations were shown in **(Fig 2-4).**

The dissolution profile of Carvedilol containing F1 to F10 formulation showed maximum drug release 90% within 10hrs. The Carvedilol tablets (300mg) containing HPMCK4M, β-Cyclodextrin, MCC and β-Cyclodextrin (F1-F3) showed a maximum drug release 99.37 and 99.38 within 10hrs as the concentration of HPMC K4M increases drug release decreases. The Carvedilol tablets (300mg) containing HPMCK15M, β-Cyclodextrin, and MCC (F4-F6) showed a maximum drug release 99.38 and 99.93 within 10hrs. The Carvedilol (300mg) containing Xanthan gum and HPMCK4M (F7-F10) showed maximum release of 90≤% within 10hrs. Among

all the formulations F7 and F9 showed best release of 99.81% at 13 hrs. Xanthan gum is biocompatible with several gel-forming and non-gel-forming macromolecules and can form a stable gel in conjugation with suitable biopolymer systems. It has also been shown by several authors that xanthan gum can play a successful role in matrix formulations for oral controlled-release drug delivery[23,24]. The F7 and F9 formulations containing HPMCK15M, MCC, β-Cyclodextrins and Xanthan gum. The formulations F7 and F9 showed best release of 99.81% at 13 hrs this is may be presence of both synthetic and natural polymers like HPMCK15M and Xanthan gum.

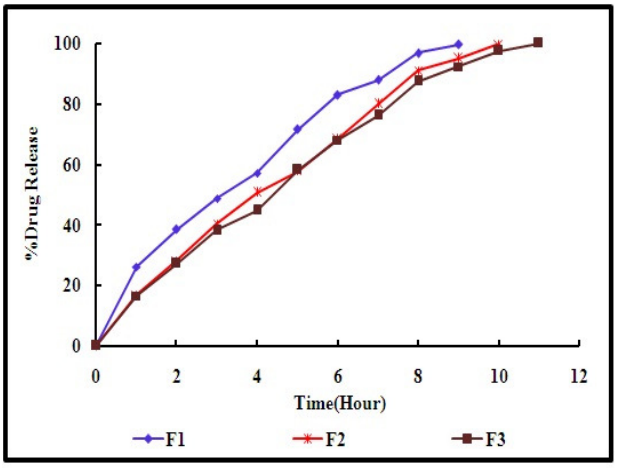

Figure 2: *In- vitro* release profile of formulation F1 to F3

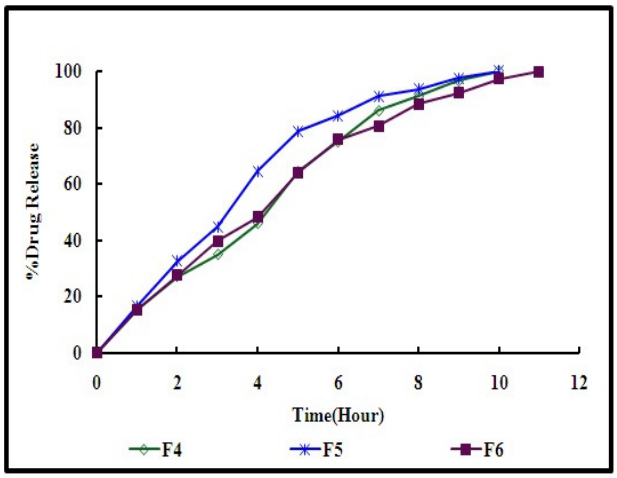

Figure 3: *In- vitro* release profile of formulation F4 to F6.

Kinetics and Mechanism of Drug Release

The values of release parameters, n and k, are inversely related. A higher value of k may suggest burst drug release from the matrix. According to the criteria for release kinetics from swellable systems, a value of release exponent, n= 0.45, 0.45<n<0.89 and 0.89<n<1.0 indicates Fickian (case I) diffusion, non-Fickian (anomalous) diffusion and zero order (case II) transport, respectively The initial dissolution profiles (≤60%) of the formulation were fitted into equation (1). The values of release parameters n and k, were determined after plotting the % drug released as a function of time according to equation (1) by subjecting the data points to least square linear regression method. A result shown in **Table 4** reveals that all formulations follow first order kinetics as correlation coefficient (r^2) values are higher than that of zero order release kinetics. The calculated n values from power law equation for drug release profiles were between 0.598-0.755 with a correlation coefficient (r^2) values >0.94, suggest that drug release mechanism from Carvedilol tablets followed non-Fickian (anomalous) transport mechanism.

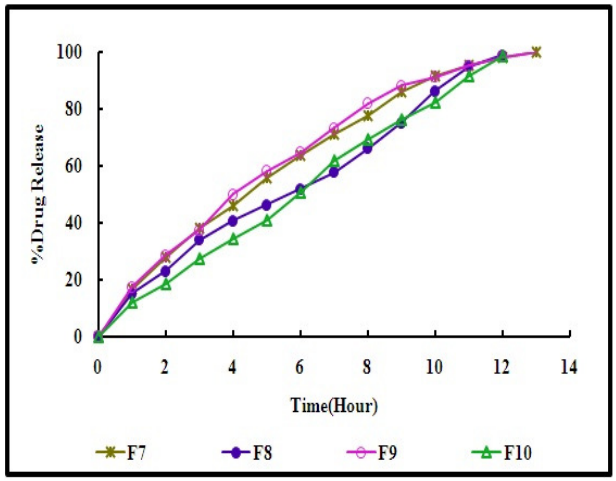

Figure 4: *In- vitro* release profile of formulation F7 to F10.

Stability Studies

The stability studies of the optimized tablet F7 and F9 were carried out as per ICH guidelines. **Table 5** shows drug content, hardness and friability did not vary with accelerated conditions. The stability study shows no significant changes in hardness, friability and drug content of selected optimum formulation from various release profile formulation after 3 months study as per ICH guidelines.

Table 4: Curve fitting analysis for different sustained release matrix tablets formulation

FC	Zero order R^2	First order R^2	Higuchi plot R^2	Kors.-Peppas (r^2)	Kors.-Peppas (n)
F1	0.991	0.997	0.981	0.996	0.755
F2	0.985	0.998	0.973	0.998	0.717
F3	0.985	0.987	0.975	0.992	0.698
F4	0.958	0.991	0.950	0.985	0.653
F5	0.971	0.994	0.963	0.991	0.655
F6	0.964	0.984	0.976	0.998	0.655
F7	0.971	0.991	0.971	0.985	0.632
F8	0.974	0.994	0.963	0.991	0.632
F9	0.978	0.989	0.929	0.991	0.741
F10	0.955	0.959	0.982	0.993	0.598

Table 5: Data after Stability Study

Formulation code	Stability period	Drug content (±SD), n=3	Hardness (kg/cm²) (±SD), n=3	Friability (%), (±SD), n=3
F7	30	97.76±1.3	5.2 ±	0.68±0.43
	60	98.12±0.41	5.3±0.18	0.71±0.11
	90	98.98±0.11	5.6±0.14	0.69±0.02
F 9	30	99.25±0.90	4.8 ±	0.59±0.45
	60	99.56±0.12	4.9 ±	0.63±0.12
	90	99.72±0.24	5.0 ±	0.65±0.24

CONCLUSIONS

The aim of this work was to develop a novel multifunctional and multiple unit dosage forms of Carvedilol to treat the symptoms of angina pectoris and myocardial infraction. A satisfactory attempt was made to develop sustained release of matrix tablet of Carvedilol using various polymers such as HPMCK4M, HPMCK15M, and other ingredients βcyclodextrin, MCC, Xanthan gum, lactose, magnesium stearate, talc are used. Finally it is concluded that the formulation F7 and F9 formulations showed best release of 99.81% at 13 hrs. Among all the formulations the F7 and F9 formulations is best formulation because it may be presence of both synthetic and natural polymers like HPMCK15M and xanthan gum.

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