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Research Article

Formulation and evaluation of sustained release tablets of carvedilol

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ABSTRACT
The object of this research work was to formulate, develop and evaluate the Sustained Release (SR) Tablets of anti hypertensive drug (Carvedilol). The tablets were prepared relatively small dose of 20 mg by direct compression method. For the Sustained release formulation the dissolution time of the tablet must be optimized in order to have a prolonged release of drug in the dissolution profile. The dissolution time is managed by using polymers like Hydroxy propyl methyl cellulose and polyethylene oxide in the formulation. These trails were optimized by incorporating varying composition of Lactose, Micro crystalline cellulose as diluents, Magnesium strate as gildent. The different excipients were tested for their compatibility with anti hypertensive drug (Carvedilol), which revealed that there was no chemical and physical interaction occurred. The preformulation parameters such as bulk density, tapped density, compressibility index and hausner's ratio were analysed for prepared granules before compression. The thickness, hardness, friability, weight variation and drug content uniformity was evaluated for tablets. The effect of this variable on the drug release profile of carvedilol was also studied. The in-vitro drug release were performed in the USP Apparatus-II (Paddle) using 0.1N HCl as a dissolution media at 50rpm speed and temperature of 37^0C ± 0.5^0C. The sampling was done at periodic time intervals of 1, 2, 4, 8, 12 and 16 hrs, and was replaced with equal volume of dissolution media after each with drawl. The cumulative amount of drug release at different time interval was estimated using UV method. These results indicate that the selected formulation was stable during the period of accelerated stability studies. All evaluated formulation results was found to be satisfied.
Keywords- Carvedilol, sustained release tablets, HPMC

INTRODUCTION

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity. This is widely used as anti-hypertensive drug. [1] The use of sustained release (SR) formulations offers many potential advantages, such as sustained blood levels, attenuation of adverse effects and improved patient compliance. It is important especially in the case of antihypertensive agents to maintain constant blood levels, as otherwise dose dumping may cause hypotension. 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.[1] Its conventional tablet dosage form is used to treat mild-to-moderate hypertension and angina pectoris. 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%. The half-life of the drug is 6 - 8 h. It's very poor aqueous solubility indicates that its absorption is dissolution rate-limited which results in irregular and delayed absorption.[2] Therefore 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 of the patient. Sustained release carvedilol is prepared as an extended-release-matrix tablet. The extended-release-matrix tablet contains polymers of HPMC and PEO. Drug release from such a tablet follows the first order kinetics. The sustained release dosage form of carvedilol can be evaluated *in-vitro* by 'USP Dissolution Test Apparatus' using rotating paddle test apparatus. Assay is also another procedure carried for its evaluation. The components like diluents, binder disintegrate and lubricant may be suspended and/or dissolved in a suitable vehicle according to their nature. Hydration of polymers

results in the formation of a gel layer that controls the release rate of drug from the core of matrix tablets.

The aim of this work was to prepare matrix tablets containing carvedilol, hydroxyl propyl methyl cellulose (HPMC) as matrix formers to control drug release. The mechanism of drug release was also determined using various kinetic models.

MATERIALS AND METHODS

Raw materials

Carvedilol IP, Hydroxy propyl methyl cellulose JP, Polyethylene oxide USP, Anhydrous lactose USP, microcrystalline cellulose BP, magnesium stearate BP, Colloidal silicon dioxide(Aerosil) USP.

Preparation of matrix tablets: [3,4]

The matrix tablets were prepared by simple direct compression method. In this method, all the excipients and drug were geometrically mixed and that blend was directly used for compression. Different polymers were used in different concentrations to get good sustained release of drug, which imitate the drug release of the best formula. Different excipients were used, i.e., direct compressible excipients, lubricants and glidants to get good physical properties of the tablets. The weight of all tablets were kept constant i.e., 100 mg to minimize the effect of surface area/volume on the drug release pattern.

Polymers used - HPMC K15M, PEO
Diluents used - Lactose, MCC
Lubricants used- Magnesium Stearate, Aerosil.

Evaluation of tablets [5]

The prepared tablets were evaluated for weight variation, hardness, thickness, friability, drug content, and stability studies. Pfizer hardness tester was used for the determination of the hardness. In weight variation test twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture was recorded. In this work, for each formulation the hardness of 6 tablets was evaluated. The crown-to-crown thicknesses of ten tablets from each batch were determined using vernier calipers. The Friability of the tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula: $F = (1- W_0 / W) \times 100$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

In vitro release studies [6]

In vitro drug release studies for the prepared matrix tablets were conducted for a period of 12 hrs using an 8 station USP paddle type II (Electro lab, Mumbai.) apparatus at 37±0.5 and at 50 rpm speed, the in vitro release study was performed in 0.1 N HCl pH 1.2 for 16 hrs. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 242 nm for Carvedilol by a UV-Visible spectrophotometer. The amount of drug present in the samples was calculated.

Release kinetics [7]

Different kinetic models (zero-order, first-order, Higuchi's, and Korsmeyer's equation) were applied to interpret the release profile (the order and mechanism of Carvedilol release) from matrix system. To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equation. However, two factors diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential equation (Korsmeyer equation), Eq. (1), which is often used to describe the drug release behavior from polymeric systems.

$$\text{Log } (Mt / Mf) = \text{Log } k + n \text{ Log } t \quad \text{-- (1)}$$

Where, Mt is the amount of drug release at time t; Mf is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release. To clarify the release exponent for different batches of matrix tablets, the log value of percentage drug dissolved was plotted against log time for each batch according to the equation 1. A value of n = 0.45 indicates Fickian (case I) release; >0.45 but <0.89 for non-Fickian (anomalous) release; and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.

Stability Studies [8]

The stability study of the tablets F5 were carried out according to ICH guidelines at

40±2°C/75±5% RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber.

Table: 1 Formulation of tablets using polymers in different concentrations

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Carvedilol (mg)	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
PEO (mg)	**--**	**--**	**--**	**--**	**--**	**--**	**20**	**30**	**25**	**25**	**20**
HPMC K15M (mg)	**40**	**50**	**60**	**40**	**50**	**60**	**30**	**20**	**25**	**25**	**30**
Lactose (mg)	**--**	**--**	**--**	**38**	**28**	**18**	**28**	**28**	**28**	**--**	**--**
MCC (mg)	**38**	**28**	**18**	**--**	**--**	**--**	**--**	**--**	**--**	**28**	**28**
Mg.stearate (mg)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Aerosil (mg)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Total (mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

RESULTS AND DISCUSSION

Precompressional parameters of Carvedilol blends were evaluated for bulk density, tapped density, angle of repose, compressibility index and hausner's ratio shows (Table 2). The Bulk densities were found to be in the range of 0.337 to 0.348 gm/cc, Tapped densities were in the range of 0.396 to 0.405 gm/cc, Compressibility index and Hausner's ratio were in the range of 13.05 to 15.99% and 1.149 to 1.191 and Angle of repose were found to be between 27.74 to 31.87^0. Table 3 shows postcompressional parameters i. e. hardness (2.5 to 3 Kg/cm^2), friability (0.31 to 0.57%) and thickness (1.24 to 1.36 mm). Drug content was within the acceptable official limits. Dissolution study of all the formulations was carried out using 0.1 N HCl pH 1.2 for 16 hrs. Formulations F1 to F11 were prepared by using ratio of drug and polymer as shown in figure-1, 2, 3 & 4.

Table: 2 Pre compression parameters of tablet blends

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility index(%)	Hausner's ratio	Angle of repose (θ)
F1	0.341	0.4	14.67	1.172	29.42
F2	0.34	0.403	15.65	1.185	29.57
F3	0.339	0.399	14.94	1.175	29.58
F4	0.346	0.398	13.14	1.151	29.74
F5	0.347	0.399	13.06	1.150	27.75
F6	0.338	0.403	15.98	1.190	30.07
F7	0.342	0.4	14.46	1.169	31.18
F8	0.343	0.401	14.48	1.163	30.06
F9	0.342	0.402	15.04	1.177	31.86
F10	0.341	0.401	15.02	1.176	30.25
F11	0.342	0.404	15.29	1.180	29.58

Table: 3 Post-compression parameters of designed formulations

S.No.	Formulation	Hardness (kg/cm2)	Thickness (mm)	Diameter (mm)	Friability (%)	Weight variation
1	F1	2.8	1.3	5.995	0.32	Pass
2	F2	2.9	1.35	6.04	0.45	Pass
3	F3	2.8	1.3	6.0	0.51	Pass
4	F4	2.7	1.25	5.998	0.5	Pass
5	F5	2.8	1.3	6.02	0.37	Pass
6	F6	2.7	1.3	5.997	0.49	Pass
7	F7	2.9	1.35	5.995	0.49	Pass
8	F8	2.7	1.3	6.0	0.41	Pass
9	F9	2.6	1.25	6.05	0.51	Pass
10	F10	2.8	1.3	5.999	0.51	Pass
11	F11	2.8	1.25	6.03	0.56	Pass

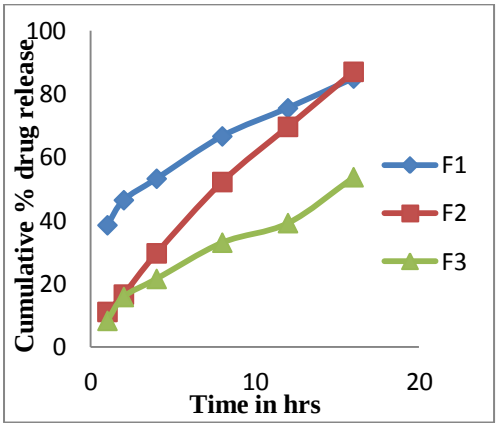

Fig. 1: Comparative release profile of formulation F1 to F3.

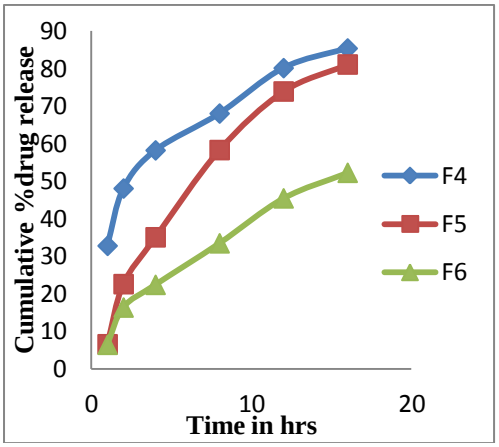

Fig. 2: Comparative release profile of formulation F4 to F6.

The use of hydrophilic polymer alone shows rapid diffusion of drug through the hydrophilic gel network. Concluded that F5 (formula-5) is showed that the proper sustained release profile according to USP limits.

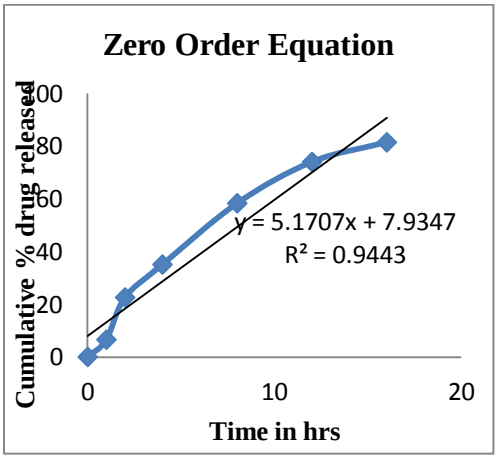

Fig.5:Zero Order Equation of Formula F5

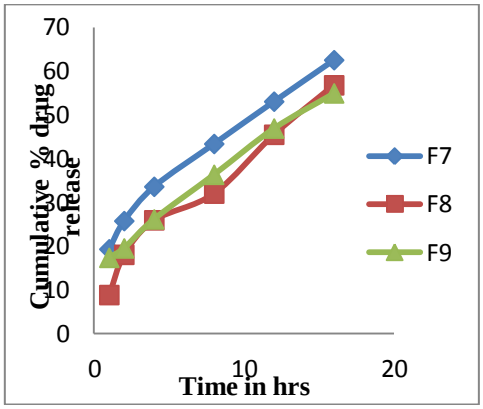

Fig. 3: Comparative release profile of formulation F7 to F9.

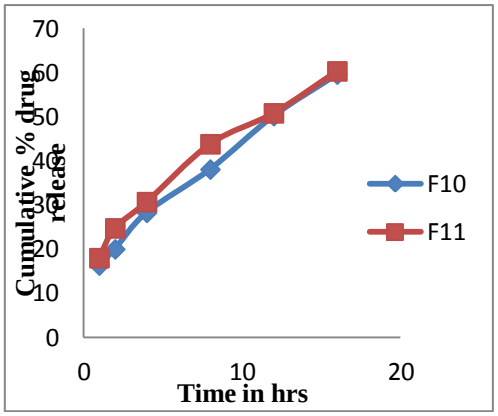

Fig. 4: Comparative release profile of formulation F10 & F11

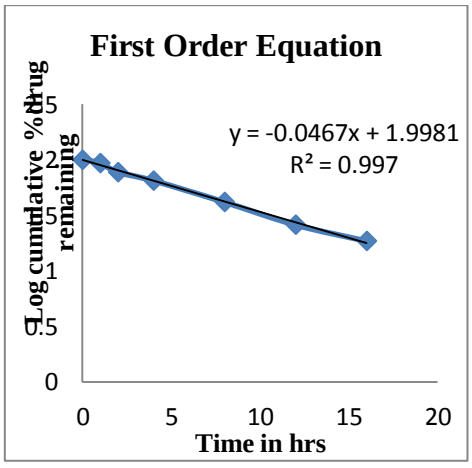

Fig.6:First Order Equation of Formula F5

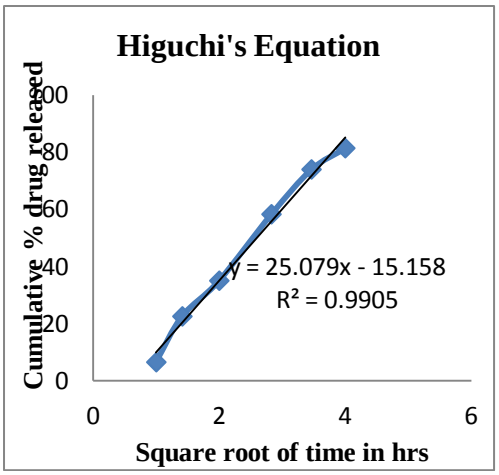

Fig.7: Higuchi's Equation of Formula F5

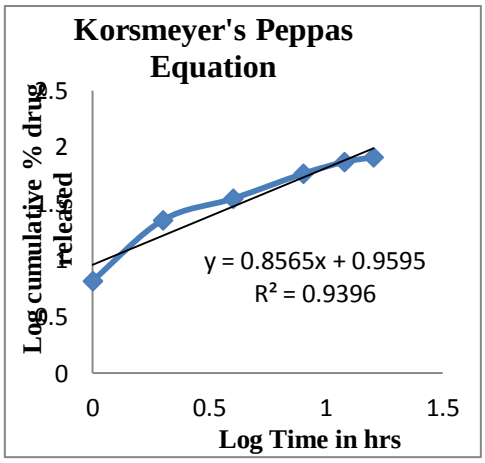

Fig.8: Korsmeyer's Peppas Equation of Formula F5

The release data follows first order reaction and shows high linearity with Koresmeyer model (r^2 = 0.939). The values of release exponent "n" were characteristics of anomalous kinetics (non-Fickian) and indicate a combined effect of diffusion and erosion mechanisms for controlled drug release.

The stability studies for optimized formulation F5 was carried out based accelerated stability conditions & study of various parameters carried out at 0, 30, 60, 90 days of intervals and the results found satisfactorily and that revealed that the optimized formulation was stable under accelerated condition.

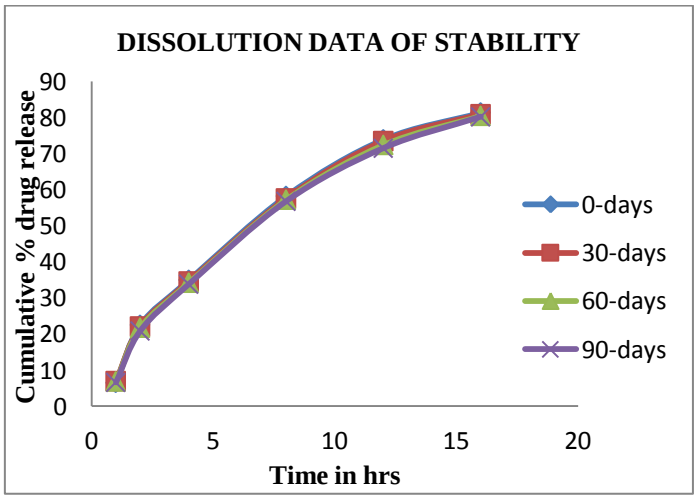

Fig.9: Dissolution Data of Stability of Formula F5

CONCLUSION

From the study, it is possible to conclude that the proposed tablet formulations were suitable for direct compression method. According to the release studies, the decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer of HPMC (K15M) was shown to be beneficial than the combination of HPMC and PEO as well as polymeric level in sustained drug release. The results of *in vitro* release studies indicated the possibility of achieving sustained release matrix tablets for Carvedilol by the use of HPMC K15M.

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REFERENCES

1. Subhashis Chakraborty, Dali Shukla, Brahmeshwar Mishra & Sanjay Singh.Clinical updates on carvedilol: a first choice beta-blocker in the treatment of cardiovascular diseases. *Expert Opin Drug Metab Toxicol*. **2010;** 6(2):237-50.

2. Horiuchi I, Nozawa T, Fujii N, et al. . "Pharmacokinetics of R- and S-carvedilol in routinely treated Japanese patients with heart failure". Biol. Pharm. Bull. **2008**; 31 (5): 976–80.
3. Robinson Jr, Lee V.H.L, Controlled drug delivery. Fundamentals and Applications. 2nd edn. Marcel Dekker, New york: **1978**; 24-36.
4. Lalla JK. Introduction to controlled release and oral controlled drug delivery systems. *The Eastern Pharmacist*, **1991**; 45:25-28.
5. Ronak N. Patel, R. S. Thakur, Sanket N Patel, M. C.Mamatha ,M. Madhushri , Formulation and Evaluation of Controlled Release Matrix Tablet of A Model Antibiotic Drug, *American Journal of PharmTech Research,***2010,** 2(2):681-691
6. Liu CH, Kao YH, Chen SC, Sokoloski TD, Sheu MT. In-vitro and in-vivo studies of the diclofenac sodium controlled-release matrix tablets, *J Pharm Pharmacol*. **1995** ;47(5):360-4.
7. Brahmankar D.M, Jaiswal S.B. Biopharmaceutics and Pharmacokinetics a treatise. 1st ed. Vallabh prakashan; New Delhi: **1995**; 64-70.
8. Leon Lachman. Physical and chemical stability testing of tablet dosage forms, Journal of Pharmaceutical Sciences; 1965; 54(10):1519–1526.

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