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FORMULATION AND EVALUATION OF POLYMER EFFECT ON *in-vitro* KINETICS OF SUSTAINED RELEASE MATRIX TABLETS OF CARVEDILOL USING MODEL DEPENDENT METHODS

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Abstract

The present study was designed to evaluate the polymeric effect of METHOCEL K15MCR on the sustained release drug product of Carvedilol. Carvedilol matrix tablets were formulated by direct compression method using METHOCEL K15MCR polymer in various percentages. Physical parameters were tested and the dissolution procedure was performed by using USP (II) paddle method for eight hours to examine the release kinetics. In the study, METHOCEL K15MCR polymer was found to cause the strong retardation of the drug release. The release mechanism was explored and explained with zero order, first order, Higuchi and Korsmeyer-Peppas equations. In the context, it can be suggested with a satisfactory result that this sustained release Carvedilol tablets can be marketed to treat patient ensuring proper healthcare.

Keywords: Carvedilol, Sustained release drug, Methocel, Matrix tablet, Higuchi equation, Korsmeyer-Peppas.

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Introduction

Carvedilol is a nonselective antihypertensive drug, used for treating high blood pressure and mild to moderate conjestive heart failure. The aim of our present study was to formulate sustained release matrix tablet of Carvedilol using METHOCEL and evaluate its release profile to justify the formulation.

Sustained drug delivery involves the application of physical and polymer chemistry to produce well characterized and reproducible dosage forms, which control drug entry into the body within the specifications of the required drug delivery profile. In this type of dosage forms, the rate of drug release mainly controlled by the delivery system itself, though it may be influenced by external conditions, like pH, enzymes, ions, motility and physiological conditions[1].Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect[2]. Typically, sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. The drug release from matrix tablet depends on other factors such as pore permeability, shape and size of matrix, drug solubility, polymer molecular weight, drug loading, compression force, and hydrodynamic conditions[3.4]. Previous studies developed by Williams *et al*.[5] led to the conclusion that the type and level of excipients influence the rate and extension of drug release.

Materials and Methods

Materials

The ingredients and the equipments used in the formulations are mentioned in Table 1 and Table 2 respectively.

Table 1: List of active ingredient and other excipients used in the preparation of matrix tablets

Name	Category	Source	Country
Carvedilol	Active ingredient	Silva Pharmaceuticals Ltd	Merck, Germany
Lactose	Filler, Diluent	Colorcon	USA
Mg stearate	Antiadherent	Colorcon	USA
Avicel	Disintegrant	Colorcon	USA
Povidone	Binder	Colorcon	USA
Talc	Lubricant	Colorcon	USA
Methocelk15 MCR	Matrix forming agent	Colorcon	USA

Table 2: List of equipments used in the method of Carvedilol SR tablets

Name	Model	Source	Country
Sieve	-	Endecotts, Test Sieve	UK
Compression Machine	Manesty D type	-	UK
Electronic Balance	AR2140	OHAIS	Switzerland
Digital pH meter	pH 209	HANNA	Romania
Shaker	Power Sonic 505	Hwashin Technology	South Korea
Hardness tester	EH-01P	Electro Lab	India
Fribilator	EF-2	Electro Lab	India
Dissolution Tester	TDT-08L Plus	Electro Lab	India
UV-Spectrophotometer	UV-1800	Shimadzu Corporation	Japan

Preparetion of matrix tablet-Carvedilol

The tablets of each batch were prepared by direct compression method. In all the formulation the weight of the active ingredient, Carvedilol 6.25 mg and the total weight were adjusted to 180 mg (Table 3). At first the active ingredient and other excipients and polymer were accurately measured. Blending was then done following proper mixing with uniformity using a mortar. The API matrix forming polymer METHOCEL K15 MCR was then added, after that milling of the mixed ingredient was performed. At last talc, Mg stearate, avicel were added to the formulation. In the formulation technique the compression force was 3.5 ton.12 mm flat die was used in this tablet formulation.

Table 3: Different formulation of Carvedilol Sustained Released tablets

Ingredients	CMK15F1 mg	CMK15F2 mg	CMK15F3 mg	CMK15F4 mg
Carvedilol	6.25	6.25	6.25	6.25
Methocel K15MCR	60	54	45	36
Lactose	40	55	51.75	57.75
Mg Stearate	3	2	3	3
Avicel	33.50	30	42	30
Povidone	35.25	30.75	30	45

Talc	2	2	2	2

Evaluation of Tablets

Length, width, size and shape

The length and width of tablets depends on the die and punches selected for making the tablets. The tablets of various sizes and shapes are prepared but generally they are circular with either flat or biconvex faces. Here we prepared round cylindrical shape tablets.

Thickness

The thickness of a tablet can vary without any change in its weight. This is generally due to the difference of density of granules, pressure applied for compression and the speed of compression. The thickness of the tablets was determined by using a Digital Caliper (range 0-150 mm).

Uniformity of weight

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)[6].

The weights of 10 tablets of each batch were taken at individually and calculate the average weight of 10 tablets. The weights were determined by using an electronic balance (Adventurer TM electronic balance, Model AR2140, Capacity (Max) - 210 gm, Readability 0.0001 gm). Then determine the percentage of weight variation of each tablet by using following formula.
Percentage of weight variation= {(Average weight – Individual weight)/ Average wt.} ×100

Friability

Friability test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The instrument used for this test is known as 'Friability Test Apparatus' or 'Friabilator'. 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 (W_1) 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 (W_2) and the loss in weight indicates the friability. The acceptable limits of weights loss should not be more than 1 percent[7].

$$\text{Friability} = \{(W_1 - W_2)/W_1\} \times 100$$

Hardness

The hardness of tablet depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression. The hardness also depends on the nature and quantity of excipients used during compression.

The hardness of the tablets was determined by using a hand operated hardness tester apparatus (Electrolab, EH-01P). A tablet hardness of about 6-8 kg-ft was considered for mechanical stability[6]. If the finished tablet is too hard, it may not disintegrate in the required period of time and if the tablet is too soft it may not withstand the handling during packing and transporting. Therefore it is very necessary to check the hardness of tablets when they are being compressed and pressure adjusted accordingly on the tablet machine.

Assay of Carvedilol

Preparation Sample Solution

180 mg of crushed tablet powder (equivalent to 6.25 mg) was dissolved in 0.1 N HCl solution and made the volume up to 100 ml. The solution was diluted 100 times and absorbance was taken. Then the percentage of potency was calculated by the following equation:

$$\%\ \text{of Potency} = \frac{Aspl \times \text{Wstd} \times \text{Pstd} \times \text{Average weight}}{\text{Astd} \times \text{Wspl} \times \text{Label claimed value}}$$

Where,

A_{spl} =Absorbance of Sample

W_{std} =Weight of Standard

P_{std} =Potency of standard

A_{std} = Absorbance of standard

W_{spl} =Weight of sample

In-Vitro Release Studies

900 ml of 0.1 N HCl was placed into dissolution vessels and the temperature was set to 37^0 C. Tablets were transferred to each vessel. Basket was immersed in media. At the end of 30 minutes 5ml samples were withdrawn from each vessel. The withdrawn quantity of samples was replaced by the same. The absorbance was measured at 241 nm by the UV spectrophotometer using 0.1 N HCl as blank. At every 30 minutes 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 8 hours to get a simulated picture of the drug release in the *in-vitro* condition and drug dissolved at specified time periods was plotted as percent release versus time (hours) curve.

Analysis of Release Data

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of drug release versus square root of time), and Korsmeyer-Peppas (log cumulative percentage of drug release versus log time) equation models.

Dissolution data were also fitted according to the well-known exponential equation, which is often used to describe the drug release behavior from polymeric systems introduced by Korsmeyer-Peppas *et al.* [8]

$$M_t / M_\infty = k\, t^n$$

Where, M_t is the amount of drug release at time t, M_∞ 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 diffusion exponent indicative of the mechanism of drug release. 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[9].

Results and Discussion

Drug content and physical evaluation of Ramipril matrix tablets

After preparing the matrix tablets, all the tablets of the proposed formulations were subjected to various evaluation tests such as hardness, thickness, uniformity of weight, drug content and friability (Table 4).

Table 4: Physical properties of Carvedilol matrix tablets containing Methocel K15MCR

Formulation	Weight variation (%) ±SEM	Hardness (Kf) ±SEM	Thickness (mm) ±SEM	Drug content (%)	Friability (%)
CMK15F 1	0.99±1.55	6.08±0.13	3.87±0.21	99.98	0.70
CMK15F 2	0.97±0.35	7.95±0.17	3.71±0.22	98.78	0.74
CMK15F 3	0.98 ±1.27	6.10±0.18	4.76±0.16	99.65	0.75
CMK15F 4	0.98±3.35	5.62±0.16	4.17±0.14	98.79	0.69

Here, n = 10; SEM = Standard Error Mean

Evaluation of *in-vitro* release

It has been observed that with the decreased amount of the polymer and with the increased amount of lactose, the release of Carvedilol has been increased. The highest release percentage is 86.589% of the CMK15F4 formulation containing 20% of METHOCEL K15MCR and highest amount of lactose in 8 hours. On the other hand, the lowest percentage of release is 46.796% containing 33.33% of METHOCEL K15MCR and lowest amount of lactose in 8 hours. The rate of drug release was found to be inversely related to the amount of METHOCEL K15M CR (Table 5).

The highest METHOCEL K15MCR containing formulation CMK15F1 also showed the highest MDT and t_{50} value which indicates the rate retarding effect of METHOCEL K15M CR (Table 6). From Figure 1- 4, we can see the zero order, first order, Higuchi and Korsmeyer-Peppas release kinetics of the formulated drugs respectively.

Table 5: Percentage of release of the formulated tablet Carvedilol

Time(hrs)	CMK15F1	CMK15F2	CMK15F3	CMK15F4
0	0	0	0	0
1	13.73599	19.46474	14.25678	25.45389
2	23.44702	28.0358	28.78807	43.82315
3	30.40108	39.54033	38.24268	59.68391
4	38.12116	44.68174	44.15371	66.51971
5	43.50199	49.6575	49.39421	75.29729
6	44.18264	52.80976	53.45931	82.37649
7	45.22785	54.91031	55.43472	83.71754
8	46.79602	58.82785	59.48117	86.58915

Table 6: MDT and t_{50} value of the drug Carvedilol

Formulation	MDT (hr)	t_{50} (hr)
CMK15F 1	11.07	9.32
CMK15F 2	7.92	6.57
CMK15F 3	6.85	5.4
CMK15F 4	2.72	2.39

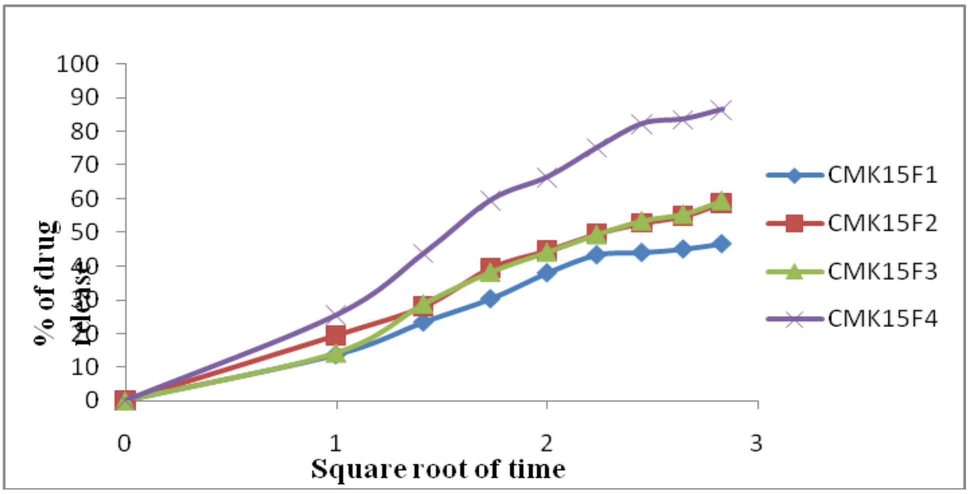

Figure 1: Zero order release kinetics of Carvedilol from METHOCEL K15MCR matrices

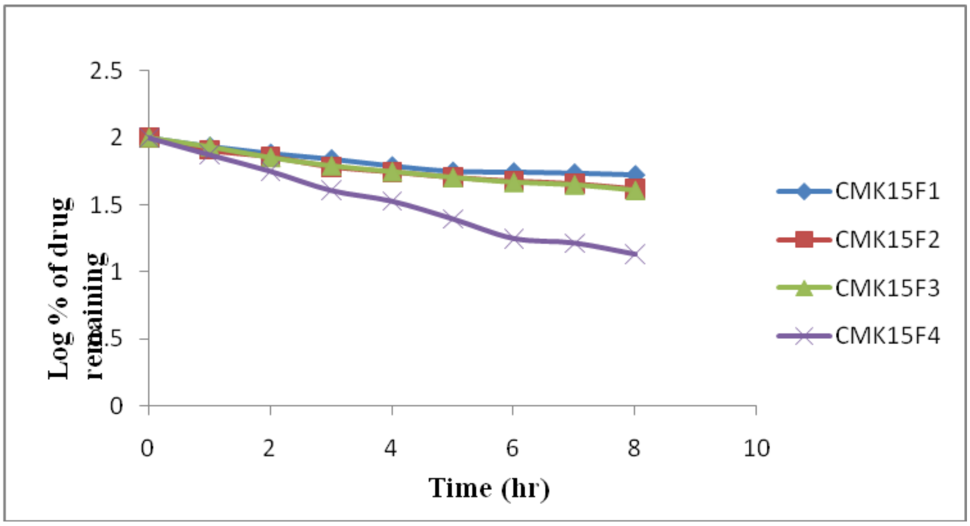

Figure 2: First order release kinetics of Carvedilol from METHOCEL K15MCR matrices

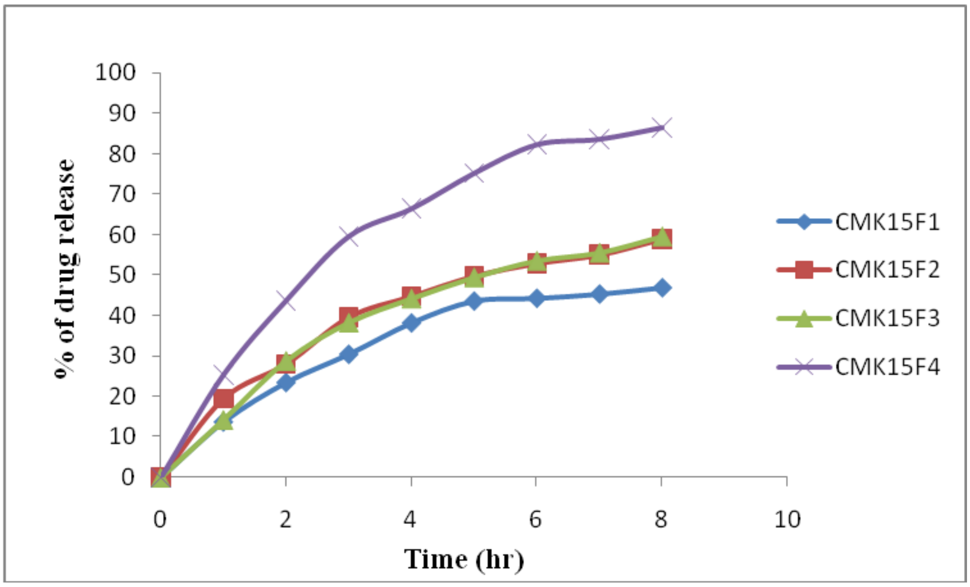

Figure 3: Higuchi release kinetics of Carvedilol from METHOCEL K15MCR matrices

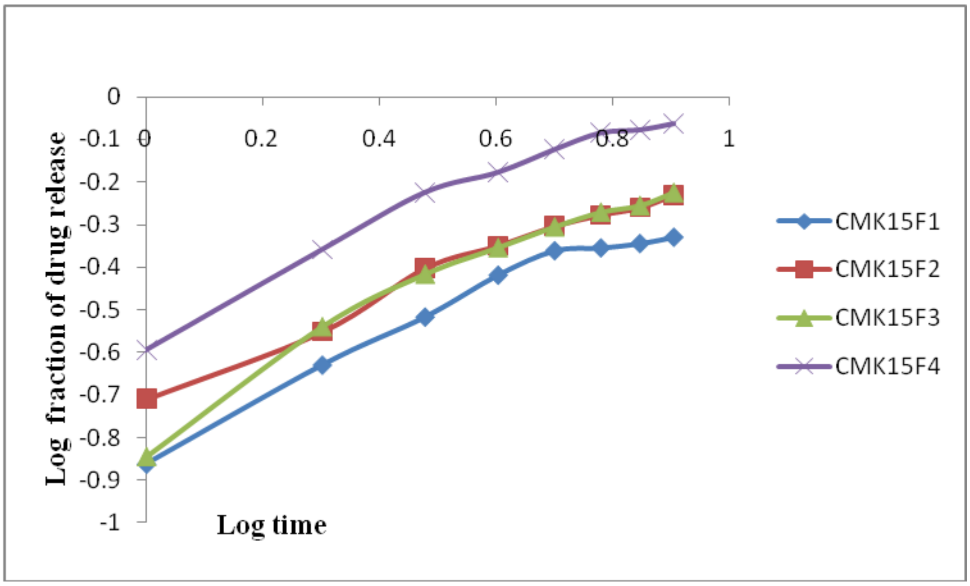

Figure 4: Korsmeyer- Peppas release kinetics of Carvedilol from METHOCEL K15MCR matrices

Conclusion

The study reveals that it is possible to design sustained release matrix tablets with METHOCEL K15MCR polymer. The polymeric effects on the formulated tablets are evident. The MDT and t_{50} value of the formulated tablets were also satisfactory. However, further investigation is required to establish *in-vivo-in-vitro* correlation to reveal the accurate pattern of drug release *in-vivo* environment from this polymeric system.

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