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DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLETS OF RAMIPRIL AND EVALUATION OF POLYMER EFFECT ON *IN-VITRO* RELEASE PATTERN

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ABSTRACT: The objective of the current study was to design an oral sustained release matrix tablet of Ramipril and to evaluate the effect of polymer on release pattern of the drug. Tablets were prepared by direct compression method using Methocel (Hydroxy Propyl Methyl Cellulose) K100MCR and Methocel (Hydroxy Propyl Methyl Cellulose) K4MCR, as matrix forming polymer. Dissolution studies were carried out in 500 ml phosphate buffer (pH 6.5) for 8 hours. The release mechanism was explored with zero order, first order, Higuchi equation and Korsmeyer's equation. The drug release followed Higuchi equation. It was found that the release of drug from matrix tablet decrease with the increasing of percentage of polymer. The two high viscosity polymers (Methocel K4MCR and Methocel K100MCR) were found suitable for the study.

INTRODUCTION: Among all the developed and sophisticated solid drug delivery systems, tablets are the most convenient solid dosage form. All active pharmaceutical ingredients (APIs) do not have suitable physicochemical properties for tablet production, storage and administration. In this case coating may be used [5]. It can be used to improve taste, appearance and to mask odor. Additionally, coating is used in tablet production for the purpose of protecting the API-degradation in the stomach, and sustained-release coating is used to obtain favorable API absorption rate, and optimum plasma-release profile [3].

Sustained release dosage forms are designed to achieve a prolonged therapeutic action by continuous releasing medication over an extended period of time after administration of single dose. In order to achieve steady level of medication, biodegradable polymer may play a vital role due to their biodegradability [2]. One of the most favorable polymers is hydroxyl propyl methylcellulose (Methocel[11]) which is prepared by the reaction of methylchloride and propylene oxide with alkali cellulose [8]. Matrix system appears to be a very attractive approach from the economic as well as from the process development and scale up point of view in modified release system. Methocel is used frequently as a rate controlling polymer in matrix tablets. Methocel offers the advantage of being non toxic and relatively inexpensive; it can be compressed directly into matrix and is available in different chemical substitution, hydration rates and viscosity grades.

When hydrophilic matrices interact with aqueous media (water, buffers, physiological fluids etc.) both the polymer hydration and the dissolving of soluble components take place. Dissolution of the drug at tablet surface cause a burst effect in the release profile of the system. This is more or less pronounced depending on the drug solubility and the polymer hydration rate [7, 10].

The release kinetics working after the initial which inurn depends on the relative position of the eroding front and the swelling front.

MATERIALS AND METHODS:

Materials: Materials which were used in the research work are given by a table (**Table 1**) below.

TABLE 1: LIST OF RAW MATERIALS USED THROUGHOUT THE EXPERIMENT WITH THEIR FUNCTIONAL CATEGORY, SOURCE AND COUNTRY OF ORIGIN:

Name	Category	Source	Country of Origin
Ramipril	Active Ingredient	Silva Pharmaceuticals Ltd., Bangladesh	India
Microcrystalline Cellulose (PH 101)	Binder, Diluent	Ming Tai Chemical co. Ltd.	Taiwan
METHOCEL K4M CR	Matrix forming agent	Colorcon	USA
METHOCEL K100MCR	Matrix forming agent	Colorcon	USA
Povidone (PVP K 30)	Binder	Hanau Chemicals Ltd.	Japan
Magnesium stearate	Lubricant	Paul Lohman	Germany
Aerosil	Flow promoter	Degussa, Cobat	India
Lactose	Diluent, binder	Degussa, Cobat	India

Methods:

Preparation of matrix tablets of Ramipril: Matrix tablets, each containing 5 mg Ramipril were prepared by direct compression technique. The active ingredient and other excipients were accurately weighted for twenty five tablets according to the formulations. Properly weighed Methocel, magnesium stearate, microcrystalline cellulose, PVP K-30 and the active ingredient were blended in a laboratory designed small drum blender. Particular attention has been given to ensure thorough mixing and phase homogenization. The appropriate amounts of the mixture were accurately weighted in an electronic balance for the preparation of each tablet and finally compressed using a pilot plant tablet machine having round faced punch and die set. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight containers at room temperature for further study in an electronic balance for the preparation of each tablet and finally compressed using a pilot plant tablet machine having round faced punch and die set. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight containers at room temperature for further study.

TABLE 2: DIFFERENT FORMULATION OF RAMIPRIL SUSTAINED RELEASED TABLETS

Ingredients	K-1		K-2		L-1		L-2		L3	
	Amount per tablet (mg)	% w/w	Amount per tablet (mg)	% w/w	Amount per tablet (mg)	% w/w	Amount per tablet (mg)	% w/w	Amount per tablet (mg)	% w/w
Ramipril	5	2.5%	5	2.5%	5	2.5%	5	2.5%	5	2.5%
Methocel K100 MCR	-	-	-	-	20	10%	30	15%	40	20%
Methocel K4 MCR	20	10%	30	15%	-	-	-	-	-	-
PVP K. 30	6	3%	6	3%	6	3%	6	3%	6	3%
Magnesium Stearate	1	0.5%	1	0.5%	1	0.5%	1	0.5%	1	0.5%
Microcrystalline Cellulose, MCC (101)	126	63%	116	58%	116	58%	116	58%	106	53%
Lactose	40	20%	40	20%	50	25%	40	20%	40	20%
Aerosil	2	1%	2	1%	2	1%	2	1%	2	1%

Total weight of each tablet: 200mg.

Evaluation of Tablets:

1. **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.
2. **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.

thickness of the tablets was determined by using a Digital Caliper (range 0-150 mm).

3. **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) [2].

   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

4. **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 [1].

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

5. **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 [2]. 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 Ramipril:

Preparation Sample Solution: 200 mg of crushed tablet powder (equivalent to 5 mg) was dissolved in phosphate buffer 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:

% of Potency=

$$\frac{A_{spl} \text{ X } W_{std} \text{ X } P_{std} \text{ X Average Weight}}{A_{spl} \text{ X } W_{spl} \text{ X Label claimed value}}$$

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:**

Dissolution Study Procedure: 500 ml of 0.1 N potassium dihydrogen phosphate buffer was placed into each of two 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 210 nm by an UV spectrophotometer (Shimadzu, Japan) using 0.1 N Phosphate Buffer (pH 6.5) as blank. This operation was continued for 8 hours. At every 30 minutes interval 5mls samples were withdrawn from the dissolution vessel and replaced with fresh dissolution medium (phosphate buffer - pH 6.5) to maintain constant volume. The absorbance of sample solution was measured at 210 nm by an UV spectrophotometer (Shimadzu, Japan) using phosphate buffer as blank. The dissolution study was continued for 8 hours to get a simulated picture of the drug release in the in-vivo 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), Korsmeyer-Peppas (log cumulative percentage of drug release versus log time) and Hixson-Crowell (cubic root of percentage drug release versus 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* [9].

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

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 [12].

RESULTS AND DISCUSSIONS:

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 3**). The thickness of the tablets ranged from 3.19 to 3.54 mm. The hardness and percentage friability of the tablets of all batches ranged from 6.94 to 8.32 kg/cm^2 and 0.09 to 0.47 %, respectively. The average percentage deviation of 20 tablets of each formula was less than ±1.55 to 2.95%. Drug content among different batches of tablets ranged from 96.74 to 102.28 %.

TABLE 3: PHYSICAL PROPERTIES OF RAMIPRIL MATRIX TABLETS CONTAINING METHOCEL K4MCR AND METHOCEL K100MCR. (K-1 & K-2 indicates Methocel K4MCR, L-1, L-2 & L-3 indicates Methocel K100MCR)

Code	Weight variation* (%) ±SEM	Hardness (Kf)** ±SEM	Thickness (mm)** ±SEM	Drug content** (%) ±SEM	Friability (%) **
K-1	200.13±1.55	6.94±0.13	3.36±0.21	98.95±0.19	0.47
K-2	200.15±.35	7.48±0.17	3.45±0.22	96.74±0.21	0.28
L-1	200.18±1.27	7.91±0.18	3.54±0.16	97.51±0.9	0.31
L-2	200.13±3.35	7.84±0.16	3.22±0.14	102.28±0.12	0.19
L-3	200.19±2.95	8.32±0.21	3.19±0.1	99.1±0.1	0.09

*n=10, ** n=3

***In-vitro* Drug Release Studies:** Drug release from the matrix tablets in K100M formulation was found inversely proportional with polymer content. This is due to the formation of gel barrier of hydrophilic HPMC polymer. Increase in concentration of HPMC may result increased gel strength of the polymer. When HPMC polymer is exposed to aqueous medium, it undergoes rapid hydration and chain relaxation to form viscous gelatinous layer (gel layer). Failure to generate a uniform and coherent gel may cause rapid drug release. To know the mechanism of drug release from the trial formulations, the data were treated according to Higuchi s and Korsmeyer *et al*.'s equations. The release kinetics data has been mention in the **table 5**. From the table it has been seen that all these formulations of this class follow Higuchi (r2=0.861-0.886) kinetic models. From Higuchi model it is evident that Ramipril is released by diffusion process.

TABLE 4: RELEASE PROFILE OF RAMIPIRIL FROM FIVE DIFFERENT FORMULATION CONTAINING METHOCEL K4MCR 10%(K-1), K4MCR 15%(K-2) AND K100MCR 10%(L-1), K100MCR 15%(L-2), K100MCR 20%(L-3):

Time (hr)	Percent drug release				
	K-1	K-2	L-1	L-2	L-3
0	0	0	0	0	0
0.5	39.9	35.8	33.1	28.2	24.3
1	44.9	41.9	39.4	33.8	30.2
2	50.2	46.3	47.1	41.86	40.09
3	53.95	49.2	47.98	45.09	42.14
4	60.12	58.15	54.21	49.84	46.34
5	65.12	61.22	58.14	55.16	52.29
6	69.75	67.09	62.11	59.08	56.1
7	75.17	71.26	65.19	62.05	60.04
8	82.12	77.15	73.2	69.78	65.2

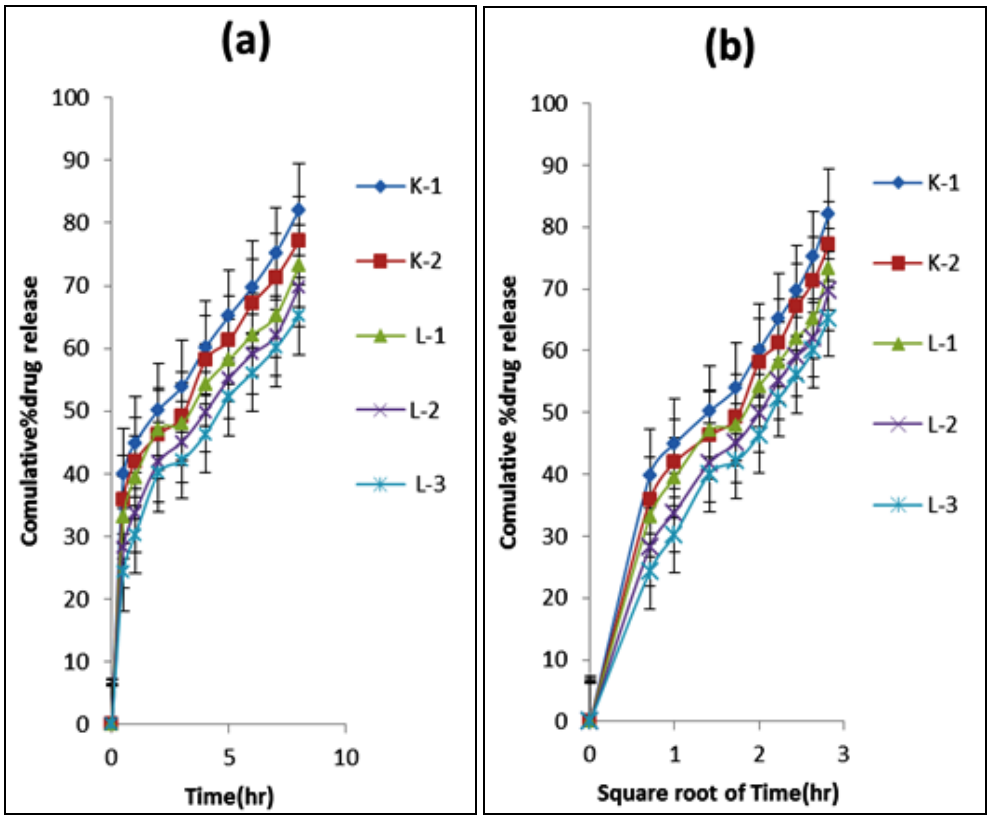

FIG. 1 :(A) ZERO ORDER PLOT OF RELEASE KINETICS OF RAMIPRIL FROM METHOCEL K4MCR 10%(K-1), K4MCR 15%(K-2) AND K100MCR 10%(L-1), K100MCR 15%(L-2), K100MCR 20%(L-3) BASED MATRIX TABLETS. (B) HIGUCHI PLOT OF RAMIPIRIL FROM METHOCEL K4MCR 10%(K-1), K4MCR 15%(K-2) AND K100MCR 10%(L-1), K100MCR 15%(L-2), K100MCR 20%(L-3) BASED MATRIX TABLETS.

Release rates of Ramipril according to Higuchi equation:

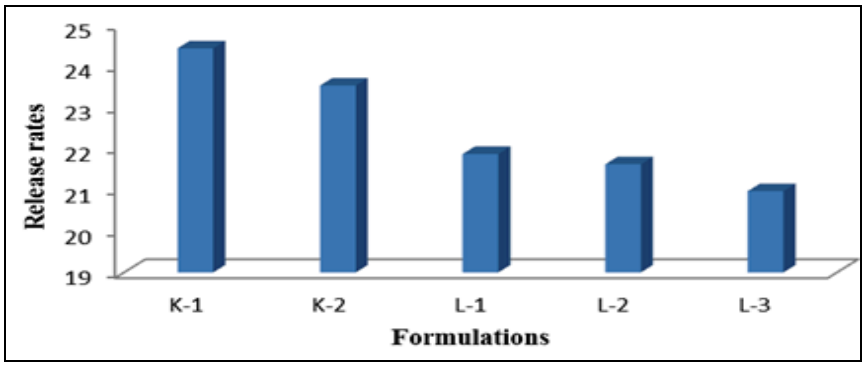

FIG. 2: EFFECT OF POLYMER ON DIFFERENT FORMULATIONS' RELEASE RATES

TABLE 5: RELEASE KINETICS OF RAMIPRIL MATRIX TABLETS OF K4MCR (K-1&K-2) FORMULATIONS

Code	Zero order	First order	Higuchi	Korsmeyer
	r^2	r^2	r^2	r^2
K-1(K4MCR 10%)	0.242	29.4	0.861	4.01
K-2 (K4 MCR 15%)	0.312	38.7	0.886	4.35

TABLE 6: RELEASE KINETICS OF RAMIPRIL MATRIX TABLETS OF K100M (L-1, L-2&L-3) FORMULATIONS

Code	Zero order	First order	Higuchi	Korsmeyer
	r^2	r^2	r^2	r^2
L-1 (K100MCR 10%)	0.249	-52.1	0.930	5.23
L-2 (K100MCR 15%)	0.43	-61.3	0.930	4.98
L-3 (K100MCR 20%)	0.504	-73.8	0.953	4.95

Drug release from the matrix tablets in K100M formulation was found inversely proportional with polymer content. This is due to the formation of gel barrier of hydrophilic HPMC polymer. Increase in concentration of HPMC may result increased gel strength of the polymer. When HPMC polymer is exposed to aqueous medium, it undergoes rapid hydration and chain relaxation to form viscous gelatinous layer (gel layer). Failure to generate a uniform and coherent gel may cause rapid drug release.

To know the mechanism of drug release from the trial formulations, the data were treated according to Higuchi s and Korsmeyer *et al*.'s equations. The release kinetics data has been mention in the **table 6**. From the table it has been seen that all these formulations of this class follow Higuchi (r2=0.930-0.953) kinetic models. From Higuchi model it is evident that Ramipril is released by diffusion process.

TABLE 7: T_{50}% OF METHOCEL K4M (K-&K-2) K100MCR(L-1,L-2&L-3) BASED MATRIX TABLETS:

Formulation	T_{50}%
K-1(K4MCR 10%)	2.72
K-2 (K4 MCR 15%)	3.06
L-1 (K100MCR 10%)	3.93
L-2 (K100MCR 15%)	3.93
L-3 (K100MCR 20%)	4.42

Based on highest regression coefficient value (r^2) the best-fit model for all formulations was Higuchi model. Time required for 50% of drug release was corrected using linear equation of Higuchi plot.

Difference between effect of K4MCR and K100MCR on release pattern of Ramipril from sustain release matrix tablet: From Table 4, it is evident that K4MCR (K-1) showed 82.12%, K4MCR (K-2) showed 77.15% drug release after 8 hours. So it can retard drug release quite efficiently. From table 3, it is also evident that K100MCR (L-1) showed 73.12%, K4MCR (L-2) showed 69.78% and K100MCR (L-3) showed 65.2% drug release after 8 hours. So it can also retard drug release quite efficiently. So it can be said that both K4MCR and K100MCR can be used as release retardant in the preparation of sustained release matrix tablet of Ramipril.

Again from **table 7**, it is evident that, the values of t_{50}% enhanced markedly from 2.72 hrs, to as high as 3.06 hrs, this finding indicated considerable release retarding potential of K4MCR and from table 7, it is evident that, the values of t_{50}% enhanced markedly from 3.93 hrs, to as high as 4.42 hrs, this finding indicated considerable release retarding potential of K100MCR.

The drug release followed Higuchi kinetic model for both grades of methocel, K4MCR and K100MCR but there was difference in the percent drug release after 8 hours though the polymer percentage were same as seen in formulation 2 and formulation 4 in table 4.In formulation 2 percentage of K4MCR was 15% and release was 77.15% but in formulation 4 percentage of K4MCR was also15% but release was 69.78%. From Table 7, it can be seen that t50% value was 3.06 hours for formulation 2 and 3.93 hours for formulation 4 though the both formulation contained same percentage of polymer. From above discussion it can be said that K100MCR is more effective and efficient release retarding polymer than K4MCR in the development of sustained release matrix tablet of Ramipril.

From this study, its helps to predict that Methocel of both types when incorporated it slower the dissolution rate as described in Banik S *et al* [6]**.**

CONCLUSION: The demand of sustained release dosage form is increasing throughout the world. For this reason Ramipril is chosen due to its short biological half life. Different polymers are used as release modifier to control the drug release from the system. In this study it was investigated to prepare a good sustained release formulation of Ramipril using Methocel K100MCR and Methocel K4MCR as release retardants and to see effect of these polymer on release of Ramipril from compressed matrix tablets.

The drug release followed Higuchi equation. It was found that the release of drug from matrix tablet decrease with the increasing of percentage of polymer. The two high viscosity polymers (Methocel K4M CR and Methocel K100MCR) were found suitable for the study. It was also found that K100MCR is more effective and efficient release retarding polymer than K4MCR in the development of sustained release matrix tablet of Ramipril. Therefore more investigation may be recommended 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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