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FORMULATION AND EVALUATION OF MATRIX TABLETS OF RAMIPRIL USING HYDROPHILIC POLYMER (HPMCK15M) AND KARAYAGUM

Dr. A. Samabasiva Rao[1] and M. Hareesh Reddy [2]*

[1] Professor and Principal, Sri Indu Institute of Pharmacy, Hyderabad.

[2]Associate Professor, Shadan College of Pharmacy, Hyderabad.

Abstract:

Ramipril is an angiotensin- converting enzyme (ACE) inhibitor, used to Hypertension (high blood pressure) and congestive heart failure (CHF). These inhibitors relax (arterioles) the muscles around small arteries. They expand the arterioles and allow to blood flow through more easily. This reduces blood pressure (B.P). Controlled release matrix tablets of Ramipril were prepared by using three polymers, one of the hydrophilic polymer hydroxy propyl methyl cellulose K15M (HPMCK15M) with four concentrations (drug: polymer ratios-1:1, 1:2, 1:3, 1:4), PVPK300, and Karayagum by wet granulation method. The granules were evaluated for bulk density, tapered density, bulkiness, angle of repose, Hausners ratio and compressibility index. In vitro release studies revealed that Ramipril formulation with high proportion of HPMCK15M (1:4) was able to control the drug release for 12 hours (85.4±1.26). The in-vitro drug release data, curve-fitting kinetic analysis and all the formulations followed the mechanism of erosion and diffusion. All the formulations were subjected to stability analysis for stored at 45° ±2°C, 75±5%RH up to 45 days.

Keywords: *Controlled release, HPMC K15M, PVPK30, Karayagum, wet granulation, Ramipril, Hydrophilic polymer, ACE inhibitor.*

Corresponding author:

M. Hareesh Reddy,
Associate Professor,
Shadan College of Pharmacy,
Hyderabad.

QR code

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INTRODUCTION:

CR formulations of Ramipril can overcome some of these problems. Most of the matrix tablets can be prepared by wet granulation method. Among many polymers (hydrophilic, lipophilic, natural gums, Hydrogels and Mucoadhesive polymers) in the formulation of matrix based controlled release drug delivery systems[1-5]. Their flexibility to obtain a desirable drug release profile, broad regulatory acceptance and cost effectiveness are advantages of hydrophilic polymer matrix systems. The benefits providing hydroxypropyl methylcellulose (HPMCK15M) for formulation of hydrophilic matrix system like nonionic nature[5-7].

Robust mechanism, consistent reproducible release profile, choice of viscosity grades, effectiveness of cost, and utilization of conventional methods and equipments. The following factors like drug dissolution, water penetration, polymer swelling, drug diffusion and matrix erosion are controlled by the hydration of HPMC, due to forms the gel barrier through which the drug diffuses[8-15].

MATERIALS AND METHODS:

Materials

Ramipril was kind gift sample from yarrow chemicals private limited, Mumbai India. HPMCK15M, Talc, and Magnesium stearate were procured from KP labs, Hyderabad, India. Lactose, Karayagum, Isopropyl alcohol, Polyvinyl pyrrolidone were procured from S.d fine chemicals Pvt Ltd; Mumbai, India. All other chemicals and reagents were used of analytical grade.

Preparation of Ramipril controlled release tablets

Four formulations of controlled release tablets of Ramipril using HPMCK15M with four formulations **(1:1, 1:2, and 1:3, 1:4)** were prepared by wet granulation method. The details of each formulation and with composition are shown to table-1

Ramipril (drug) and polymers HPMCK15M, Karayagum were mixed separately. Lactose and cross caramellose sodium were added to the polymer-drug mixture and blended thoroughly for 5-6 minutes. A coherent mass is formed to dissolve the polyvinyl pyrrolidone (PVP) in sufficient quantity of isopropyl alcohol (IPA) and finally added to drug mixture. Then the coherent mass was passed through sieve number-16 to form granules and the collected granules were dried at $40°C \pm 2°c$ for 2 hours. The dried granules were passed through the sieve number-22.The granules retained on sieve number-22 were evaluated for tapped density, bulk density, bulkiness, compressibility index, Hausners index and angle of repose(Table-2). Then the granules were mixed with talc, magnesium stearate and finally compressed in to tablets. The same procedure was followed to prepare Ramipril tablets without polymers.

Table1: Composition of matrix tablet formulation of Ramipril

Ingredients	**Ratio of drug and polymer (Ramipril:HPMCK15M)**				Control (Without polymer)
	1:1	**1:2**	**1:3**	**1:4**	
Ramipril	10	10	10	10	10
HPMC K15M	10	20	30	40	
PVPK-300	3	3	3	3	3
Karayagum	10	10	10	10	10
Lactose monohydrate	52	42	32	22	62
Talc	6	6	6	6	6
Magnesium stearate	4	4	4	4	4
Cross caramellose sodium	5	5	5	5	5
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s
Total	100	100	100	100	100

IR spectral analysis

The drug (Ramipril) and polymers like (HPMC K15M, Karayagum) must be compatible with one another to produce a stable product. FTIR (Shimadzu, japan, model-8400s) using studied by interaction between drug and polymer as per the method described by Sharma. IR spectral analysis of pure Ramipril, Ramipril with HPMC K15M, and Ramipril with Karayagum were carried out. The peaks and patterns produced by the pure drug were compared with combination of polymers and pure drug.

Evaluation of tablets

Hardness

The tablets to be tested by Monsanto hardness test apparatus. The test was performed by the tablet are held between a fixed and moving jaw of apparatus and the reading of the indicator is adjusted to zero (0). The screw knob was moved forward until the tablet breaks and noted the reading, force required to break the tablet.

Friability test

The Roche friabilator is used to performance of friability test. The weighing ten (10) tablets and placed in the friabilator, which was then operated for 25 revolutions per minute (RPM). After 100 revolutions the tablets were dusted and reweighed. The formula used to determine the percentage of friability was

Percentage friability = Initialweight-Finalweight/Initial weight$\times$100

Weight variation

For weight variation test, twenty (20) tablets were randomly selected and weighed individually. The individual weights were compared with average weight for determination of weight variation.

Dissolution test studies

In-vitro dissolution release studies were performed using USP apparatus type-II at 50 rpm. The dissolution medium was 900 ml of phosphate buffer at PH7.4. The temperature was maintained at $37\pm0.5^{\circ}C$. The drug release rate was evaluated by taking 10 ml sample, which was replaced with fresh medium every one one-hour interval up to 12 hours and suitable diluted with phosphate buffer (PH 7.4) and absorbance was measured at 208 nm using UV spectrophotometer

Drug content

Ten tablets (10) were weighed and powdered. The powder equivalent to 100 mg of Ramipril was dissolved in 10 ml of 0.1 M Hcl, then make up to 100ml of phosphate buffer PH 7.4 in 100 ml standard flask. From this $10_{\mu g/ml}$, equivalent solution was prepared and analyzed at 208 nm using UV spectrophotometer.

Kinetic analysis

The mechanism of drug release rate kinetics of all the formulations to analyze the results of in-vitro release profiles were fitted in to zero order kinetic model, first order kinetic model, Higuchi model and korsmeyer Peppas model. The results of in-vitro release profiles were plotted in models of data treatment as follows

Zero order kinetic model – Log cumulative percent drug released versus time

First order kinetic model – Log cumulative percent drug remaining versus time

Higuchi model – Cumulative percent drug release versus squire root of time

Korsmeyer model - Log cumulative percent drug released versus log time

Stability studies

Stability studies were analyzed to assess the stability of all controlled release formulations of Ramipril tablets. The prepared CR tablets were kept at $45^{\circ}C \pm 2^{\circ}C$, $75\pm 5\%$RH for 45 days. At 15 days intervals the tablets were evaluated for all physical parameters. The perentage of Ramipril content and in-vitro drug release studies were also determined.

RESULTS AND DISCUSSION:

Evaluation of Ramipril granules and tablets

The prepared granules for compression of matrix tablets were evaluated for their flow properties. The bulk density ranged between0.38 to0.45gm/cm3. Tapped density was within the range of 0.41 to 0.50 gm/cm3. Bulkiness was found to be the range of 2.12 to 2.41 gm/cm3. Compressibility index was found to be the range of 11.21 to 12.65. Angle of repose was within the range of 26.9 to 29.6 and Hausners ratio ranged from. These above values indicate that the prepared granules were exhibited good flow properties.

Table 2: Evaluation of Ramipril granules

Parameters	Ratio of drug and polymer (Ramipril:HPMCK15M)				Control
	1:1	1:2	1:3	1:4	
Bulk density(gm/cm3)*	0.38±0.11	0.42±0.10	0.45±0.50	0.40±0.76	0.43±0.19
Tapped density(gm/cm3)*	0.50±0.91	0.49±0.21	0.41±0.11	0.46±0.32	0.44±0.56
Bulkiness(gm/cm3)*	2.12±0.16	2.36±0.71	2.29±0.11	2.36±0.95	2.41±0.26
Angle of repose *	29.6±0.94	27.1±0.82	26.9±0.25	27.7±0.12	27.59±0.72
Compressibility index (%)*	11.50±0.26	12.24±0.22	12.65±0.91	11.21 ±0.51	11.56±0.35
Hausners ratio*	0.76	0.85	1.09	0.86	0.97

Table 3: Evaluation of Ramipril tablets

Parameters	Ratio of drug and polymer (Ramipril:HPMCK15M)				Control
	1:1	1:2	1:3	1:4	
Hardness (kg/cm2)	4.94±0.12	4.96±0.07	4.95±0.15	4.92±0.14	4.93±0.12
Friability(%)	0.32±0.04	0.41±0.01	0.19±0.04	0.21±0.07	0.26±0.03
Weight variation(mg)	99.6±4.7	99.5±4.4	99.1±2.5	99.2±3.2	99.5±3.2
Content uniformity(%)	99.46±0.33	97.6±1.10	98.2±0.60	97.4±0.20	98.4±0.42
Thickness(mm)	3.12±0.02	3.21±0.12	3.19±0.04	3.26±0.14	3.12±0.02
Diameter(mm)	7.42±0.31	7.56±0.15	7.38±0.08	7.44±0.02	7.50±0.06

All the prepared tablets show good elegance and appearance. All formulated tablets the hardness range was found to be 4.92 to 4.96 kg/cm2, indicating good mechanical strength. In the friabilty test the particle loss was below 1% for all the formulations, which is an indication of satisfactory or good mechanical resistance of the tablets. The weight variation was within the range of ± 7.5% complying with Pharmacopoeial standards. The percentage of Ramipril in all formulations was ranging from 97.4 to 99.46% indicating content uniformity was within the limits (10%). The range of thickness and diameter of Ramipril tablets was found to be 3.12 to 3.26mm and 7.42 to 7.56mm respectively which showed uniform diameter and thickness.

IR spectral analysis

The IR spectral studies of pure Ramipril and combinations of Ramipril with HPMC K15M (1:1) were carried out to study the interaction between the drug and polymers (HPMC K15M, Karayagum) used. C-H stretching, C-H deformation, N-H stretching of primary amine and N-H out of plain bending of pure Ramipril and Ramipril with polymers were almost in the same wave number region ranging from 678 cm^{-} to 3654 cm^{-}. It showed there was no significant interaction between the polymers and drug and they are compatible with each other.

Dissolution studies

In- vitro dissolution release studies were performed to determine the percentage of drug released from Ramipril matrix tablet formulations with polymer, marketed tablet and Ramipril tablet formulation without polymer (control formulation). Results of the in-vitro dissolution release studies of Ramipril matrix tablet formulation with polymer are show in table-4.

The percentage drug release of all formulations after 12 hours using HPMC K15M as polymer was found to be 92.4% (P1), 90.2% (P2), 87.1 (P3) and 85.4(P4). It was found that the cumulative percentage drug release in the formulation P1 was more than P2, P3 and P4. The cumulative percentage of drug release in the formulation P4 showed controlled release than P1, P2 and P3. A major role played in drug release was the polymer concentration. At higher polymer concentration, the drug release was prolonged than the lower concentration of the polymer. The graphical presentation data of the Ramipril matrix tablet formulations with polymer is shown in (Figure – 1)
In-vitro dissolution of Ramipril from the tablet formulation without polymer (control) was found to be 95.3% where as the Ramipril release from marketed matrix tablet was 94.1% in 30 minutes.

Table 4: Percentage drug release of Ramipril Matrix Tablet Formulations

Time(hrs)	Cumulative percentage drug release *			
	P1(1:1)	**P2(1:2)**	**P3 (1:3)**	**P4(1:4)**
1	17.6±1.20	15.1±1.46	13.9±1.54	12.4±1.76C
2	23.1±1.39	22.0±1.21	21.2±1.94	20.4±1.80
3	31.7±1.19	29.6±1.98	28.1±1.02	26.9±1.21
4	39.2±1.78	37.3±1.64	36.0±1.33	35.2±1.91
5	44.6±1.81	43.7±142	41.9±1.56	40.0±1.76
6	50.9±1.20	48.9±1.84	45.6±1.44	43.1±1.65
7	58.1±1.16	56.4±1.06	55.3±1.54	53.6±1.34
8	64.6±1.21	63.6±1.09	61.2±1.89	59.6±1.02
9	70.9±1.18	69.3±1.55	68.0±1.81	66.6±1.73
10	78.6±1.26	76.1±1.73	75.3±1.76	74.5±1.38
11	86.9±1.63	85.6±1.04	83.1±1.51	82.4±1.96
12	92.4±1.16	90.2±1.36	87.1±1.01	85.4±1.99

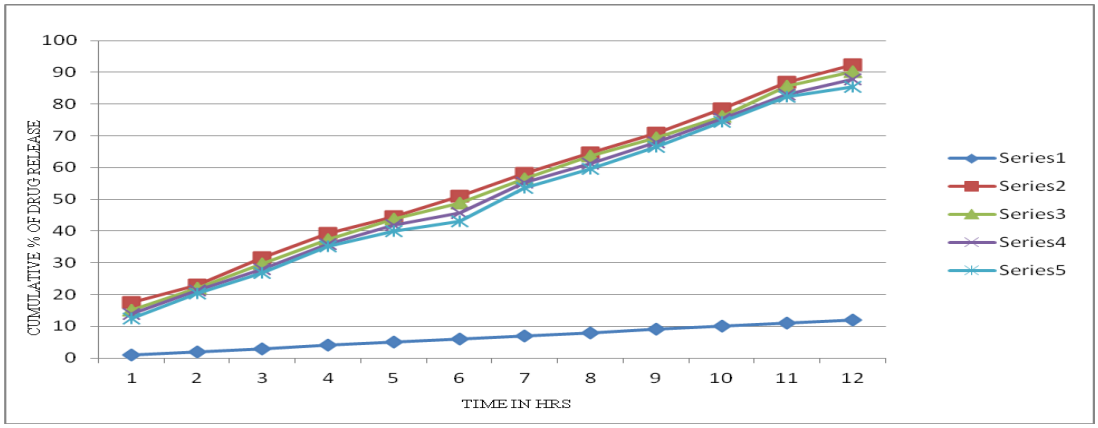

Fig 1: percentage drug release of Ramipril matrix tablet formulations

Table 5: Curve fitting analysis for Ramipril formulations

Formulation code	Regression co-efficient (R2)			Korsmeyer plot	
	Zero order plot	First order plot	Higuchi's plot	R2	Slope
P1	0.9814	0.9565	0.9650	0.6976	0.696
P2	0.9926	0.9595	0.9454	0.7065	0.724
P3	0.9952	0.9636	0.9566	0.7262	0.788
P4	0.9975	0.9672	0.9516	0.7496	0.828

Kinetic Analysis

The kinetic data for release rate of all formulations were shown in table-5. When the data were plotted according to zero order kinetics, the matrix formulations showed to a high linearity, with regression co-efficient (R2) values between 0.9814 to 0.9975. Huguchi's model explained by diffusion is related to transport of drug from the dosage form in to the in-vitro study, fluid depending on the concentration. In all the formulations the drug release profiles could be expressed by Higuchi's equations, as the plot showed high linearity with high regression co-efficient values between 0.9454 to 0.9650. By using korsmeyer Peppas model, if n value less than 0.45 it is fickian diffusion, if n value is 0.45 to 0.89 values between 0.696 to 0.828. It showed that all the formulations follow Non-Fickian transport mechanism and also follow the mechanism of both erosion and diffusion.

Stability analysis

All the formulations of Ramipril matrix tablets were stored at 45° ± 2°C, 75±5% RH up to 45 days. The evaluation tests of tablets were carried out at every 15 days intervals. Physically stable at all formulations. There were no deviations found in the evaluation tests and all formulations are within the limits. There were no significant change in in-vitro drug release profiles and drug content. It observed that all the formulations are chemically stable.

CONCLUSION:

The results of experimental studies of Ramipril matrix tablets proved that the granules of Ramipril showed good flow properties, evaluation tests of tablets are within the acceptable limits, Infra Red (IR) spectral analysis proved that there was no polymer-drug interaction, all the formulations of kinetic studies were followed zero order drug release and stability analysis revealed that all formulations were found to be stable after storing at 45° ± 2°C, 75±5% RH up to 45 days. The main drawbacks of the conventional dosage forms of Ramipril can be minimized by Ramipril controlled release (CR) tablets. Thus the results of the above study clearly indicated that Ramipril may be formulated as CR tablets using HPMC K15M as polymer by wet granulation method, which will be provide continuous release of drug at a predetermined rate and time.

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Abbreviations

HPMC = Hydroxy Propyl Methyl Cellulose, CR = Controlled Release, RH = Relative Humidity, UV = Ultra Violet.

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