Formulation and Evaluation of Sustained Release Matrix Tablets of Ramipril by using Natural and Synthetic Polymers

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Abstract- Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. Ramipril is an antihypertensive agent used in the treatment and management of hypertension. Ramipril has low bioavailability (28%) and short biological half-life (2-4 hrs) favours for the development of sustained release tablets. The aim of the research work is to formulate and evaluate ramipril sustained release tablets in order to enhance bioavailability by maintaining prolonged therapeutic concentrations in plasma. Natural polymers like pectin and okra gum were extracted from orange peel and ladies finger respectively. Nine formulations of ramipril containing varying concentrations of polymers (pectin, okra gum and HPMC K15M) were designed. The sustained release tablets of ramipril were prepared by wet granulation method. FT-IR studies revealed that no interaction between drug and polymers. The powder blend was evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio; all these values are within the specified limit which indicates good flow properties. The prepared tablets were evaluated for physicochemical parameters such as thickness, weight variation, hardness, friability and drug content. *In vitro* release studies revealed that out of 9 formulations, formulation F9 was found to be optimized which showed sustained drug release of 99.42% for 12 hours.

Key words: Bioavailability, Okra gum, Pectin, Ramipril, Sustained release.

INTRODUCTION

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system [1]. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system includes any drug delivery systems that achieves slow release of drug over an extended period of time [2]. If the systems can provide some control, whether this is of temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system [3].

These are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms [4]. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials [5]. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is

embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers [6].

Ramipril is an antihypertensive agent used in the treatment and management of hypertension. Conventional oral formulations of ramipril are administered multiple times a day due to shorter half life. Treatment of hypertension using conventional formulations of ramipril is found have many drawbacks and adverse effects that results in accumulation of drug in multi dose therapy and also poor patient compliance. Sustained release tablets are designed to prolong the residence time after oral administration. It is useful for achieving controlled plasma levels as well as improving bioavailability. With this objective ramipril sustained release tablets were designed. Ramipril has low bioavailability (28%) and short biological half-life (2-4 hrs) favors for the development of sustained release tablets. The aim of the research work is to formulate and evaluate ramipril sustained release tablets in order to enhance bioavailability by maintaining prolonged therapeutic concentrations in plasma. Improved hypertension therapy may be achieved by maximum availability of drug with minimum dose through formulation of ramipril sustained release tablets [7].

MATERIALS AND METHODS

Materials

Ramipril (Sms pharmaceuticals Ltd., Hyd), HPMC K15M (Hi Media Pvt. Ltd., Mumbai), Lactose, Magnesium stearate, Talc (Oxford Laboratory, Mumbai), PVK 30, Potassium dihydrogen phosphate, Sodium hydroxide (Sd fine chemicals Ltd., Mumbai).

PREPARATION OF RAMIPRIL SUSTAINED RELEASE TABLETS

Required quantities of Ramipril, HPMC, extracted polymers were mixed thoroughly and sufficient volume of binding agent (10% w/v PVP K30) was added slowly. After enough cohesive was obtained, the mass was sieved through 44 mesh. The granules were dried at 40°C. Talc and magnesium stearate were finally added as glidant and lubricants. The tablets were compressed using rotary compression machine. The total weight of tablet was 150 mg and each tablet contains 5 mg of Ramipril and other pharmaceutical ingredients as listed in the table 1. [8]

Table 1: Composition of different formulations of Ramipril tablets

Ingredients (mg)	Formulation code F1 F2 F3F4 F5 F6 F7 F8 F9								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ramipril	5	5	5	5	5	5	5	5	5
Pectin extract	20	40	60	-	-	-	-	-	-
Okra gum extract	-	-	-	20	40	60	-	-	-
HPMC K15M	-	-	-	-	-	-	20	40	60
Lactose	100	80	60	100	80	60	100	80	60
PVK 30	15	15	15	15	15	15	15	15	15
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total weight	150	150	150	150	150	150	150	150	150

EVALUATION OF RAMIPRIL SUSTAINED RELEASE TABLETS

The powder blend was subjected for the following studies [9]

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio

Angle of repose:

The angle of repose of powders was determined by the funnel method. Accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was

calculated by using the given formula. The results were tabulated in Table 3.

$$\tan\theta = \frac{h}{r}$$

Where,

h = height of the powder cone

r= radius of the powder cone

Bulk density and tapped density:

A quantity of 10gms of powder from each formula was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed. Then bulk density (BD) and tapped density (TD) were calculated by using the given formula and the results were tabulated in Table 3.

$$BD = \frac{\text{Weight of the powder}}{\text{Initial volume}}$$

$$TD = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Carr's index:

The Compressibility of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it is packed. The formula for carr's Index is given below and the results were tabulated in Table 3.

$$\text{Carr's index } (\%) = \frac{TD - BD}{TD} \times 100$$

Hausner's ratio:

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by using the given formula. The results were tabulated in Table 3.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

Post compression studies [10]

Thickness:

Tablet thickness can be measured using digital vernier calipers. 3 tablets were taken and their thickness was measured and the average thickness for each tablet was calculated. The results were tabulated in Table 4.

Hardness:

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using monsanto hardness tester. An average of three observations is reported. The results were tabulated in Table 4.

Friability test:

Friability of the tablets was determined using Roche friability. 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. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Conventional tablets that lose less than 1% of their weight are acceptable. The results were tabulated in Table 4.

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight variation:

The weight variation test is done by weighing 20 tablets individually, calculating average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The results were tabulated in Table 4.

$$\%\text{ Weight variation} = \frac{\text{Average weight} - \text{Initial weight}}{\text{Average weight}} \times 100$$

Evaluation of Ramipril sustained release tablets

Drug content

Five tablets were taken and powdered; the powder equivalent to 5 mg of ramipril was dissolved in 100 ml of phosphate buffer of pH 7.2, filtered, diluted suitably to 10 mcg/ml concentration and analyzed at 210 nm using UV-Visible spectrophotometer. The results were tabulated in Table 5.

In vitro dissolution studies:

In vitro drug release rate of Ramipril from sustained release tablets was determined using United States Pharmacopoeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 500 ml of phosphate buffer of pH 7.2 for 12 hrs. A sample (5 ml) of the solution was withdrawn from

the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with phosphate buffer of pH 7.2. Absorbance of these solutions was measured at 210 nm using a UV/ Visible spectrophotometer.

RESULTS AND DISCUSSION

Table 2: Standard curve data of Ramipril using phosphate buffer of pH 7.2

Concentration (mcg/ml)	Absorbance
0	0
5	0.143 ± 0.001
10	0.292 ±0.002
15	0.444 ±0.002
20	0.592 ±0.002
25	0.741 ±0.001

n=3

In the present study, analytical method obeyed the Beer-lamberts law in the concentration range of 5-25 µg/ml and was suitable for the estimation of ramipril in phosphate buffer of pH 7.2. The value of r (correlation coefficient) for the linear regression equation was found to be more than 0.99 which indicates a positive correlation between the concentration of drug and the corresponding absorbance values.

FTIR studies:

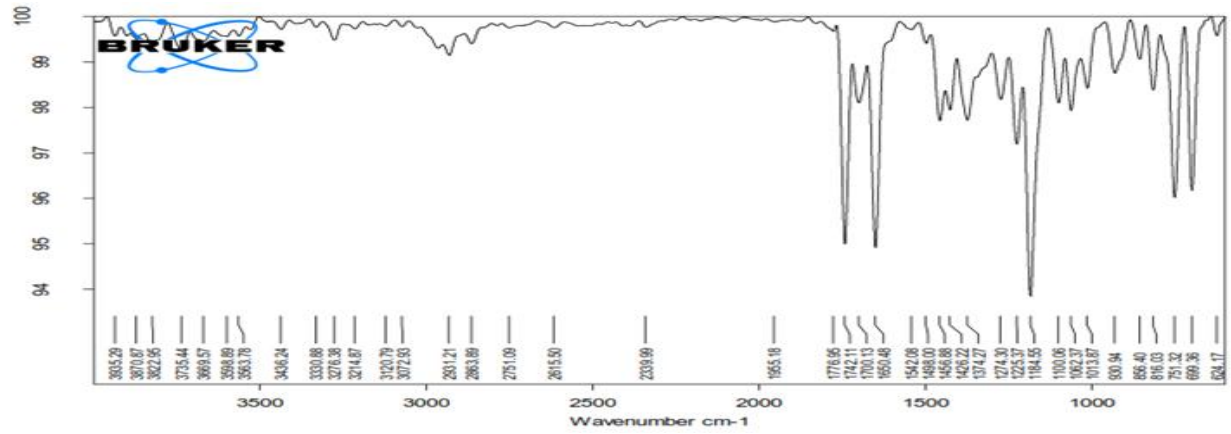

Figure 1: FT-IR spectrum of Ramipril

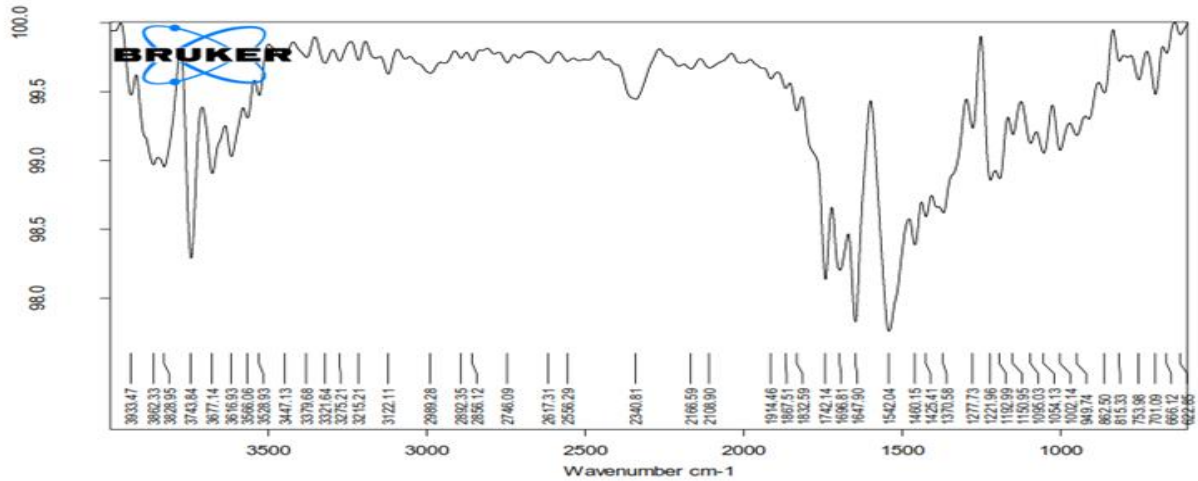

Figure 2: FT-IR spectrum of Ramipril with Pectin

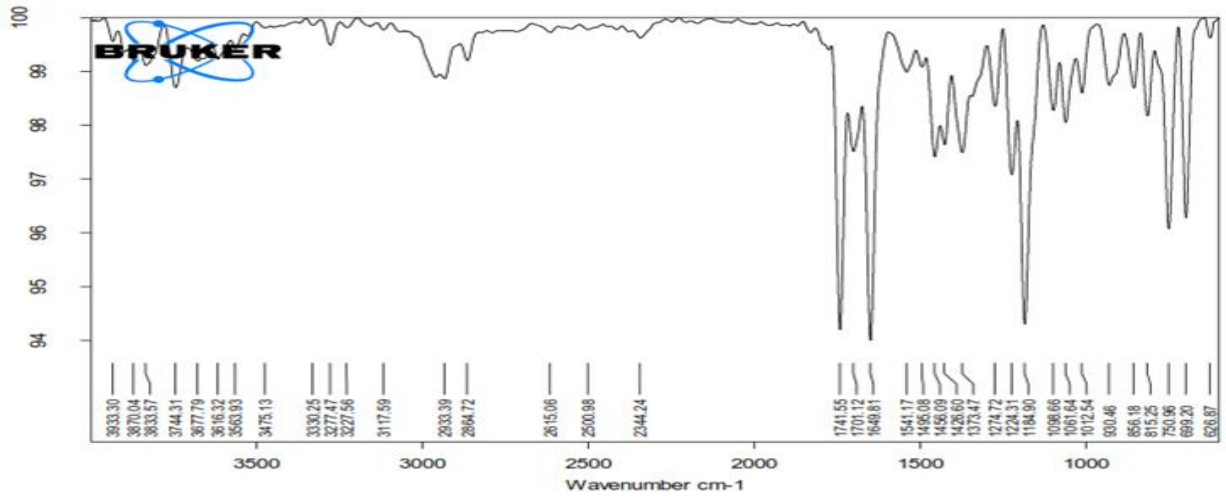

Figure 3: FT-IR spectrum of Ramipril with okra gum

FT-IR spectra of Ramipril and Ramipril with Polymers were shown Figure 1, 2 and 3. Pure Ramipril showed principal absorption peaks at 699.36 cm^{-1} (C-H Bending), 1184.55 cm^{-1} (C-N stretching), 1650.48 cm-1 (N-H bending) 1742.11 cm^{-1} (C=O stretching) and 3214.87 (O-H stretching). The identical peaks of C-H Bending, C-N stretching, N-H bending, C=O stretching and O-H stretching vibrations were also noticed in the spectra of drug with polymers. FT-IR spectra revealed that there was no interaction between the drug and the polymer used for tablet formulations.

Evaluation of Ramipril sustained release tablets

Precompression parameters

Table 3: Physical parameters of powder blend

S. No	Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0})
1	F1	0.892	0.961	7.1	1.076	27.9
2	F2	0.914	0.986	7.3	1.078	28.8
3	F3	0.892	0.961	7.1	1.076	27.4
4	F4	0.872	0.937	6.9	1.075	28.3
5	F5	0.852	0.914	6.7	1.073	26.5
6	F6	0.872	0.937	6.9	1.075	26.5
7	F7	0.937	0.986	4.9	1.052	24.7
8	F8	0.914	0.986	7.3	1.078	25.6
9	F9	0.892	0.961	7.1	1.076	22.7

The bulk density of all formulations, powder blend containing excipients was found to be in the range of 0.852 to 0.937 gm/ml, whereas the tapped density was observed between 0.914 to 0.986 gm/ml. From the values of bulk density and tapped density the values for compressibility index and hausner's ratio were calculated. The values for compressibility index were found between 4.9 to 7.3%. The values for hausner's ratio were found in between 1.052 to 1.078. All these values are within the specified limit which indicates good flow properties. Angle of repose was found to be less than 30 which indicate good flow of powder. Overall these values indicate good flow properties of powder blend, uniform die fill and better compression ability.

Postcompression parameters

Table 4: Physical parameters of Ramipril sustained release tablets

S. No	Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	% Friability	% Weight variation
1	F1	1.70±0.20	3.03±0.01	0.73	1.798
2	F2	1.97±0.12	3.00±0.05	0.53	2.137

3	F3	2.33±0.21	3.06±0.01	0.60	2.235
4	F4	1.80±0.20	2.92±0.03	0.60	2.199
5	F5	2.07±0.06	3.02±0.03	0.80	2.081
6	F6	2.37±0.25	3.06±0.01	0.87	1.799
7	F7	1.87±0.06	2.97±0.01	0.67	3.057
8	F8	2.23±0.12	3.06±0.03	0.94	3.114
9	F9	2.83±0.06	3.05±0.01	0.66	3.169

n=3

Hardness test for all formulations was carried out and observations obtained were in the range of 1.70 to 2.83 kg/cm^2. Hardness for all formulations was observed to be proper, which signify that crushing strength of all formulations was maintained after direct compression. The thickness of all formulations was found to be uniform as it was obtained in the range of 2.92 to 3.06 mm. Friability test was conducted for all formulations, % friability was less than 1%, which showed the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation. The % weight variation of all formulations was found to be in the range of less than 7.5%. None of the tablet was found to deviate from the average weight of tablets (variation with deviation less than ± 7.5, which complies with USP specification) signifies that there is uniformity in flow of powder blend which leads to uniform die fill.

Table 5: Evaluation tests of Ramipril sustained release tablets

Formulation code	% Drug content	Formulation code	% Drug content
F1	91.89±0.40	F6	96.58±0.59
F2	94.18±0.59	F7	92.58±0.40
F3	95.78±0.40	F8	95.89±0.91
F4	92.35±0.99	F9	99.54±0.79
F5	94.63±0.79		

n=3

Drug content of all formulations was observed between 91.89 to 99.54%. Drug content for all formulations showed uniformity which indicated that there was uniform flow and uniform distribution of drug.

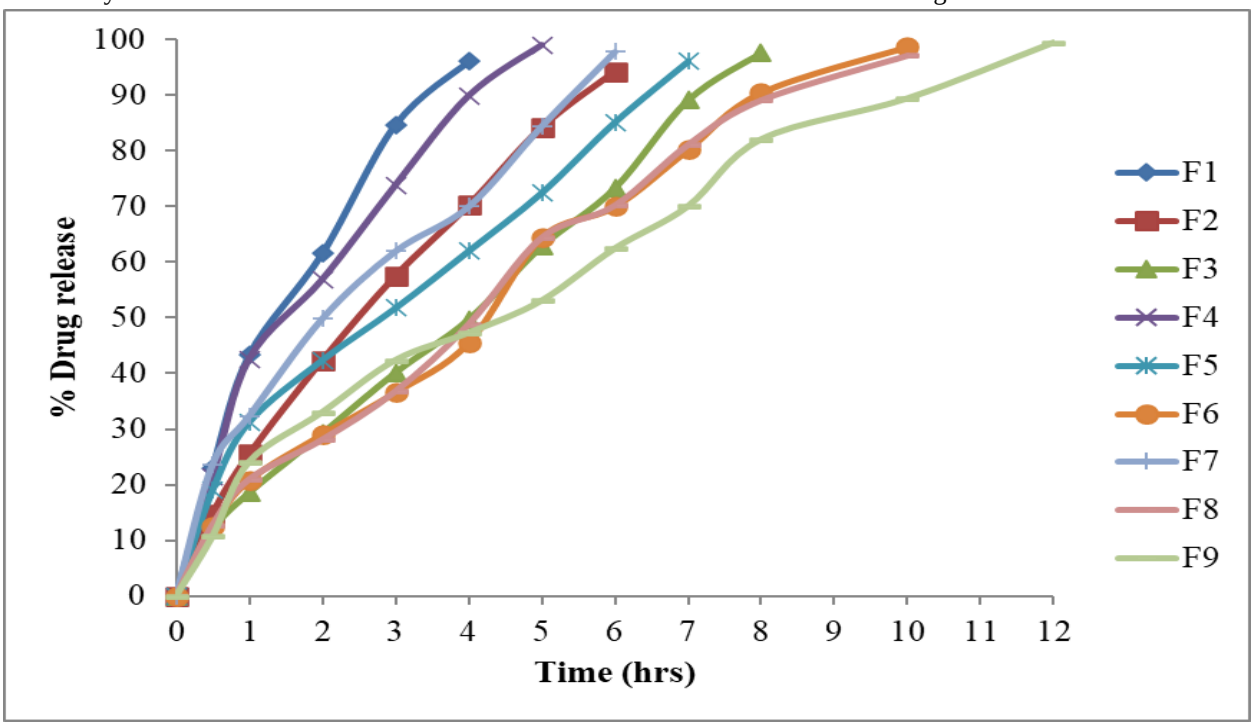

Figure 4: Comparative dissolution profile of Ramipril sustained release tablets

Ramipril sustained release tablets were prepared by wet granulation method. Dissolution data and profiles of all the formulations viz. F1-F9 are shown in Figure 4.

In case of Ramipril sustained release tablets prepared with Pectin *viz.* formulations F1-F3 have shown sustained action upto 8 hrs. The dissolution data and profiles observed for Ramipril sustained release tablets containing pectin at regular time intervals. F1 formulation containing Ramipril and Pectin (20 mg) shows the release of 96.08% in 4 hrs. F2 formulation containing Ramipril and Pectin (40 mg) shows the release of 94.30% in 6 hrs. F3 formulation containing Ramipril and Pectin (60 mg) shows the release of 97.64% in 8 hrs. In case of Ramipril sustained release tablets prepared with okra gum *viz.* formulations F4-F6 have shown sustained action upto 10 hrs. The dissolution data and profiles observed for Ramipril sustained release tablets containing okra gum at regular time intervals. F4 formulation containing Ramipril and okra gum (20 mg) shows the release of 98.98% in 5 hrs. F5 formulation containing Ramipril and okra gum (40 mg) shows the release of 96.08% in 7 hrs. F6 formulation containing Ramipril and okra gum (60 mg) shows the release of 98.75% in 10 hrs. In case of Ramipril sustained release tablets prepared with HPMC K15M *viz.* formulations F7-F9 have shown sustained action upto 12 hrs. The dissolution data and profiles observed for Ramipril sustained release tablets containing HPMC K15M at regular time intervals. F7 formulation containing Ramipril and HPMC K15M (20 mg) shows the release of 97.86% in 6 hrs.F8 formulation containing Ramipril and HPMC K15M (40 mg) shows the release of 97.19% in 10 hrs.F9 formulation containing Ramipril and HPMC K15M (60 mg) shows the release of 99.42% in 12 hrs. From the results it was revealed that Ramipril sustained release tablets prepared with HPMC K15 M showed better sustained drug release. The extracted polymers Pectin and Okra gum were also showed sustained drug release upto 8 hrs and 10 hrs respectively.

CONCLUSION

Conventional oral formulations of ramipril are administered multiple times a day. Treatment of hypertension using conventional formulations of ramipril is found to have drawbacks like accumulation of drug in multidose therapy and poor patient compliance. Sustained release tablets of ramipril can overcome these drawbacks. Ramipril sustained release tablets can improves bioavailability and reduces drug waste. In present work an attempt has been made to formulate sustained release tablets of ramipril using natural polymers like pectin extracted from orange peel and okra gum extracted from ladies finger and synthetic polymers like HPMC K15M. Sustained release tablets of ramipril were prepared by wet granulation method. The results of experimental studies revealed that the powder blend of ramipril showed good flow properties, post compression parameters were within acceptable limits. Amongst the formulations prepared (F1-F9), F9 was found to be optimized formulation which showed prolong drug release for 12hrs.

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