www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2015; 4(4): 26-29

www.thepharmajournal.com
Received: 10-04-2015
Accepted: 13-05-2015

Rashmi G Kolli
BLDEA's College Of Pharmacy, BLDE University Campus, Bijapur 586103, Karnataka

V M Reddy
BLDEA's College Of Pharmacy, BLDE University Campus, Bijapur 586103, Karnataka

C.C. Patil
BLDEA's College Of Pharmacy, BLDE University Campus, Bijapur 586103, Karnataka

R.V. Kulkarni
BLDEA's College Of Pharmacy, BLDE University Campus, Bijapur 586103, Karnataka

N.V. Kalyani
BLDEA's College Of Pharmacy, BLDE University Campus, Bijapur 586103, Karnataka

Correspondence:
Rashmi G Kolli
BLDEA's College Of Pharmacy, BLDE University Campus, Bijapur 586103, Karnataka

Formulation and evaluation of matrix tablet of ramipril

Rashmi G Kolli, V M Reddy, C.C. Patil, R.V. Kulkarni, N.V. Kalyani

Abstract
Matrix tablets are providing the promising way to decrease the side effect of drug by preventing the fluctuation of therapeutic concentration of the drug in the body. The main objective of the study was to develop matrix tablet of Ramiprill. Tablets of Ramiprill were prepared by the wet granulation method using polymers like Hydroxy propyl methylcellulose, Ethyl cellulose, Guar gum in different ratios. Matrix tablet were evaluated by different methods for parameters such as thickness, hardness, weight uniformity, drug content uniformity, and in vitro drug release studies, stability studies. The tablets were evaluated for in vitro release in pH7.4 phosphate buffer for 12 hours in standard dissolution apparatus. Mucoadhesion strength is increased with increase in the concentration of HPMC and in combination of polymers. In order to determine the mode of release, the data was subjected to Zero order, First order, Higuchi and Peppas diffusion model.
Short term stability studies on the promising formulation indicated that, there are no significant changes in drug content. IR spectroscopic indicated that there are no drug- excipients interaction. All the granules of the formulation showed in compliance with Pharmcopeial Standards. The developed sustain released matrix tablet of Ramipril drug showed 12 hours of drug release and overcome the disadvantage of conventional tablets.

Keywords: Matrix tablet, Ramiprill, HPMC, Ethyl cellulose, Guar Gum. pH 7.4

1. Introduction
The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form 2-5. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix system is widely used for the purpose of sustained release [1].
Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in developing a sustained-release drug delivery system. Recent trend in development of sustained-release drug delivery systems was the use of gums of plant origin to fulfil the aim of retarding the drug release. Natural gums are biodegradable, non-toxic and have capability to swell on contact with aqueous media. The natural polymers used do hold advantages over the synthetic polymers generally because they are non toxic, less expensive and freely available. Most common examples of natural gums are Guar gum, Xanthan gum, Pectin and Gum Tragacanth. Guar gum is a polysaccharide derivative having glycosidic linkage which is intended to be used as a matrix former for controlled release of drugs like Diltiazem. Pectin, a natural hydrophilic polymer is rich in galacturonic acid is used as a gelling agent and thickening agent [2].
Ramipril is freely soluble in methanol and partially soluble in water. Ramipril is a long-acting angiotensin converting enzyme (ACE) inhibitor. Ramipril is almost completely metabolized to Ramiprilat, which has about 6 times the ACE inhibitory activity of Ramipril. Ramipril works by relaxing blood vessels, causing them to widen. Lowering high blood pressure helps prevent strokes and heart attacks. The usual dose of Ramipril is 2.5-20 mg a day in two divided doses.

following oral administration of Ramipril, peak plasma concentrations of Ramipril are reached within one hour. The extent of absorption is at least 50-60% and is not significantly influenced by the presence of food in the gastrointestinal tract, although the rate of absorption is reduced. The absolute bioavailability of Ramipril is 28%. Elimination half-life of Ramipril is about 2-4 hours. Side effects of Ramipril include kidney failure and increased levels of potassium in the blood. The most serious but, very rare side effects are liver failure and angioedema.

There is a need to formulate Ramipril as matrix tablet dosage form because, the developed matrix tablets help in reduction of frequency of administration by maintaining prolonged therapeutic concentrations in plasma, thereby patient compliance can be improved. Improved hypertension therapy may be achieved by maximum availability of drug with minimum dose through formulation of matrix tablets of Ramipril.

Hence, Proposed work invoves the development of matrix tablets of Ramipril by using the polymer HPMC, Guar gum, Ethyl cellulose (wet granulation method).

2. Materials and Methods

Matrix tablets were prepared by a wet granulation method according to the formulations given in below table. The powder ingredients were passed through US Standard Sieve No. 80 before preparation of the granules. Lactose was chosen as the filler because lactose tablets are reported to possess low friability and low weight variation, with no sticking, binding, or capping. Because lactose is a water soluble filler (about 2 g/ml at 37 °C), there must be a sufficient increase in viscosity due to the presence of the hydrated and swollen polymer at the tablet interface with the release medium to resist erosion.

Required quantities of Ramipril, HPMC, Ethyl cellulose, Guar Gum polymers were mixed thoroughly and sufficient volume of binding agent (5%w/v starch) was added slowly. After enough cohesive was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40 ˚C for 12 hrs. Once dry the granules retained on 44 mesh were mixed with 10% of fines (granules that passed through 44 mesh). 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 100mg and each tablet contains 5 mg of Ramipril and other pharmaceutical ingredients as listed in the table.

The Formule for Preperation of Matrix Tablet of Ramipril

INGREDIENTS (mg/tab)	FORMULATION CODE											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
RAMIPRILL	5	5	5	5	5	5	5	5	5	5	5	5
GUAR GUM	50	60	70	-	-	-	-	-	-	35	-	35
ETHYL CELLULOSE	-	-	-	50	60	70	-	-	-	35	35	-
HPMC	-	-	-	-	-	-	50	60	70	-	35	35
LACTOSE	42	32	22	42	32	22	42	32	22	22	22	22
MAGNESIUM STEARATE	2	2	2	2	2	2	2	2	2	2	2	2
TALC	1	1	1	1	1	1	1	1	1	1	1	1

3. Evaluation of Matrix Tablet

The prepared tablets were evaluated for weight variation, hardness, thickness, friability, drug content, and stability studies. Pifzer hardness 5 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 tablet were weighed and the weight was compared with an average weight. the tablet was placed in contact between the plunger and the handle was pressed, the force of fracture was recorded. In this work, for each formulation the hardness of 6 tablet was evaluated. The crown to crown thickness of ten tablet from each batch were determined using varnier calipers 5. The friability of the tablets was determined using Roche friabilator. This device subjects the tablet 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 tablet was placed in friabilator and were subjected to 100 revolutions. Tablets were dedudsted using soft muslin cloth and reweighed. The friability (F) is given by the formula.6

$$F= (1-W0/W) \times 100$$

Where, W0 is the weight of the tablets before the test and W is the weight of tablet after the test. For the determination of drug content at last three tablets from each formulation were weighed individually, pulverized, and diluted 250 ml with sufficient amount of phosphate buffer 7.2.After that an aliquot of the filtrate was diluted and analyzed spectrometric ally at 210 nm.

In vitro drug release studies for the prepared matrix tablets were conducted for the period of 12 hours using a apparatus at 37 degree centigrade and at 100 rpm speed. The in vitro release study was performed in phosphate buffer 7.2 pH up to 12 hours. At every interval 5ml of sample was withdrawn from the dissolution medium to maintain volume constant. After the filtration and appropriate dilution, the sample solution were analysed at 210nm for Ramipril by using uv visible spectrophotometer. The amount of drug present in the samples was calculated.

4. FTIR Studies

IR spectra for Ramipril and formulation F10, F11, F12 tablets were recorded in fourier transform infrared spectrophotometer with KBr pallets.

5. DSC Studies

DSC scan of about 5mg; using an automatic thermal analyser system performed accurately weighed Ramipril. Sealed and perforated aluminium pans were used in the experiments for the sample. Temperature calibration were performed using indium as standard. An empty pan sealed in the same way as the sample was used as reference. The entire samples were run at scaning rate of 10 degree celcius/min from 50 to 300 degree

celsius.

6. Result and Discussion

Ramipril matrix tablet were prepared by using Guar gum(F1,F2,F3),Ethyl cellulose(F4,F5,F6), HPMC (F7,F8,F9) and combination of these 3 polymers (F10,F11,F12). Precompressional parameter of shows (Table 2) and post compressional parameters shows in (Table 3).The granules were evaluated for the Bulk density and tapped density. The results of these two parameters are in the range of 0.277 to 0.333 gm/cc and 0.326 to 0.370 gm/cc respectively. A good packing ability of the granules was indicated by carr's compressibility index and hausner ratio. The granules were evaluated for 22.89^0 to 27.11^0. The results of the granules evaluation suggests that all the granules exhibits good flow properties, as the angle of repose value were less than 30^0.

The hardness of the prepared matrix tablet was in the range of 5.2 kg/cm2 to 6.2 kg/cm2 hardness increases with increasing hydroxypropyl methylcellulose proportion in the formulation.

The tablets were evaluated for friability and results were in the range of 0.31% to 0.92%. Less than 1% indicates good mechanical strength to withstand the rigors of handling and transportation.

The tablets were evaluated for the drug content which was in range of 94.3% to 97.6%. The prepared tablets were subjected to weight variation, the results were found to be in the range of 100 to 103 mg which was within the IP limit for the weight variation.

The in vitro residence time was determined using USP disintegration apparatus. Among the twelve formulation for this study F3, F6, F9, F11 showed maximum residence time for 12 hours. Dissolution study of all the formulation carried out using phosphate buffer 7.2PH.Formulation F1 to F3 were prepared by using polymer as guar gum Figure1 shows release profile of formulation F1 to F3. Among those formulation F3 shows high sustained capacity because concentration of polymer more. Figure 2 shows dissolution profile of formulation F5 to F6 by using polymer ethyl cellulose. Figure 3 shows dissolution profile of formulation of F7 to F9 by using polymer HPMC. Figure 4 shows dissolution profile of formulation of F10 to F12 by using combination of polymer. Dissolution profiles shows among 12 formulation F11 formulation shows high sustained release.

7. FTIR Sudy

The FTIR spectra of ramipril as shown in the characteristic peak at about 3279CM^{-1} for N-H stretching, 3066-3025 CM^{-1} C-H Aromatic stretching, 2965-2864CM^{-1} for C-H aliphatic stretching, 1742-16514 CM^{-1} for C=O stretching. The same characteristic peak its slight variations were also noticed in the spectra of formulation F3, F6, F9, F11. It indicates that the stability of the drug in the formulations.

DSC Study; Figure 5,6,7 shows the DSC thermographs of pure drug and formulation F10,F11,F12. Thermograph obtained by DSC studies, revealed that the melting point of pure drug is 109 degree celsius and that of drug in the formulation is 107 degree celsius as there is no much difference in the melting point of the drug in the thermograph of drug and that of in the formulation. It may be concluded that the drug in the same pure state even in the formulation without interacting with the polymers.

Table 2: Pre Compression Evaluation of Granules of Ramipril Matrix Tablet.

Formulation	Bulk density	Tap density	Carr's index (%)	Hausner Ratio	Angle of repose
F1	0.345	0.365	13.68	1.158	26.86
F2	0.386	0.406	17.34	1.209	27.70
F3	0.383	0.398	16.32	1.181	26.52
F4	0.379	0.409	8.88	1.084	26.88
F5	0.349	0.371	10.90	1.178	24.30
F6	0.322	0.342	14.81	1.176	25.80
F7	0.342	0.365	7.92	1.085	26.19
F8	0.329	0.348	13.68	1.090	25.40
F9	0.389	0.401	10.20	1.077	27.11
F10	0.353	0.395	9.27	1.101	22.89
F11	0.372	0.410	11.11	1.055	24.97
F12	0.352	0.376	12.50	1.102	25.15

Table 3: Post Compression Evaluation of Ramipril Matrix Tablet.

Formulations	Weight (mg)	Hardness (Kg/cm2)	Friability (%)	Drug content (%)
F1	100	6.2	0.41	93.27
F2	102	5.8	0.78	97.36
F3	101	6.0	0.82	95.18
F4	101	6.1	0.4	94.64
F5	103	6.2	0.78	95.45
F6	100	6.0	0.39	96.00
F7	102	6.5	0.78	96.00
F8	101	6.0	0.73	96.27
F9	100	6.1	0.92	94.21
F10	104	5.2	0.31	92.63
F11	102	6.2	0.91	90.88
F12	100	5.8	0.48	90.16

Table 4: Kinetic Value of Pioglitazone Matrix Tablet

Formulation Code	Regression coefficient values				Slope value (n)	
	Zero Order	First Order	Higuchi	Peppas	Higuchi	Peppas
F1	0.9916	0.994	0.979	0.809	0.036	0.713
F2	0.991	0.986	0.979	0.809	0.037	0.716
F3	0.989	0.984	0.981	0.802	0.040	0.723
F4	0.990	0.986	0.983	0.804	0.040	0.712
F5	0.989	0.887	0.983	0.805	0.039	0.719
F6	0.987	0.983	0.981	0.801	0.042	0.731
F7	0.989	0.979	0.981	0.804	0.039	0.718
F8	0.989	0.979	0.981	0.802	0.040	0.723
F9	0.989	0.979	0.982	0.800	0.042	0.718
F10	0.990	0.993	0.980	0.807	0.037	0.715
F11	0.988	0.966	0.984	0.796	0.039	0.715
F12	0.988	0.966	0.984	0.804	0.038	0.712

8. Result and Discussion

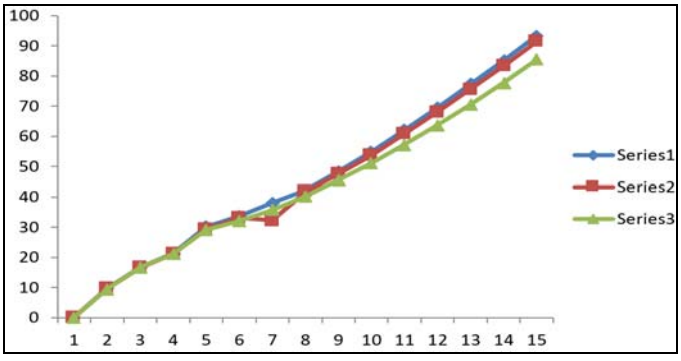

Fig 1: Cumulative percent drug released Vs Time plots(zero order) of formulations of F1,F2,F3.

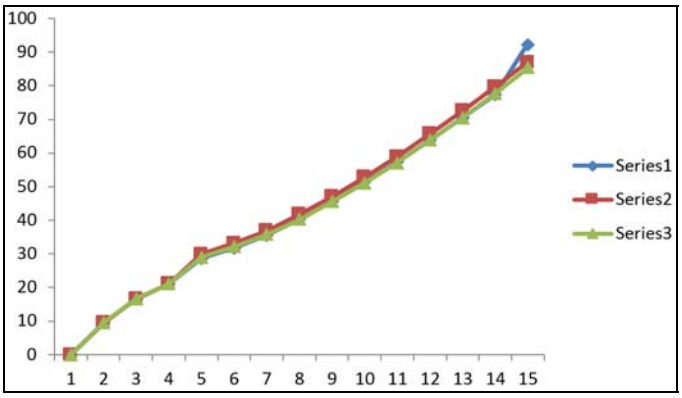

Fig 2: Cumulative percent drug released Vs Time plots(zero order) of formulations of F4,F5,F6.

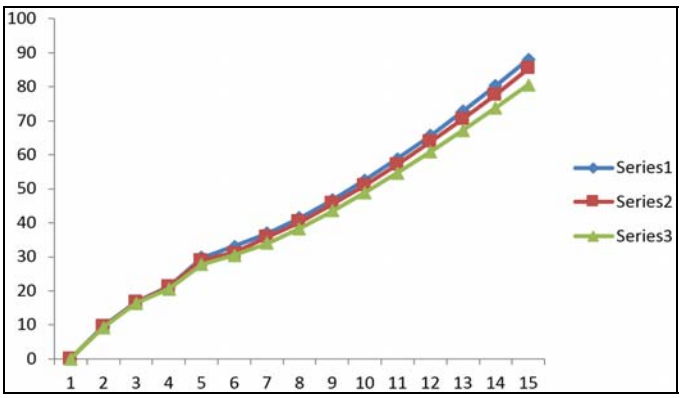

Fig 3: Cumulative percent drug released Vs Time plots (zero order) of formulations of F7, F8, F9

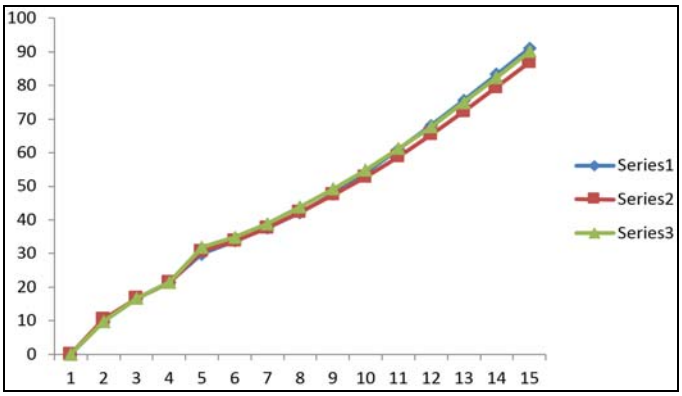

Fig 4: Cumulative percent drug released Vs Time plots (zero order) of formulations of F10, F11, F12.

9. Conclusion

From the present study the following conclusion can be drawn:-

- Matrix tablet of Ramipril can be prepared by wet granulation method using polymers like Hydroxy proply methylcellulose, Ethyl cellulose, guar gum in different ratios.
- The prepared tablets were evaluated for hardness, friability. Drug content, Fourier transforms infrared spectroscopy, Differential scanning calorimeter, in-vitro drug release.
- All prepared tablets formulations were found to be good without capping and chipping.
- In all the formulations 5% starch solution in water was used as binder which showed acceptable hardness of tablets.
- IR spectroscopy studies and DSC studies indicated that there are no drug-excipients interactions.
- Among 12 Formulations F11 is optimized because of their good strength and ability to sustained release of the drug from the matrix over 12hrs period.

10. Reference

1. Kamboj S, Gupta GD, Oberoy J. Matrix tablets: An important tool for oral controlled release dosage forms, http://www.pharmainfo.net/reviews
2. Kamboj S, Gupta GD, Jagmohan O. Matrix tablets: An important tool for oral controlled release dosage forms. http://www.pharmainfo.net/reviews
3. Roland A. Bodmeier, "Encyclopedia of Pharmaceutical Technology Edn 2, Volume-III by, 812-813.
4. Donald L, Wise, Hand book of Pharmaceutical Controlled Release Technology, First Indian Reprint, Marcel Dekker Inc. Madison, New York, 192-204.
5. Indian Pharmacopoeia ministry of health and Family Welfare. Delhi; Controller of publication, 1996.
6. N. Aruna, M. Kishore Babu. "Formulation And Evaluation of Sustained Release Matrix Tablets Containing Metformin Hcl and *Syzygium cumini.*" International Journal of Pharmaceutical & Biological Archives 2011; 2(3):900-905.
7. Prasanth Sai RV. "Formulation, Evaluation and Characterization of Sustained-Release Matrix Tablets of Timolol Maleate Using Hydrophilic, Hydrophobic and Plastic Polymers." IJPT 2011; 3(2):2807-2847.
8. Umarunnisha AM, Palanichamy S, Rajesh M, jeganth S. "Formulation and evalution of matrix tablet of Famotidine using hydrophilic polymer 2010; 2(3):212-220.
9. Venkatesh P, Soumya C, Rishikumar reddy D. "Formulation and Evaluation of sustained release tablet of Voriconazole", 2014, 1666-1673.
10. Sivannarayana P, A Prameela Rani, saikishor V. "Formulation and evaluation of ramipril sr matrix tablet by using tamarindus kernel mucilage as release retardant." ISSN: 0975-8585.