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Effect of various polymers on swelling and *in vitro* release of ramipril in effervescent system

Sudheer Nadendla*,Snehalatha, T.S.Nagaraja and Bharathi
Department of Pharmaceutics, SJM College of Pharmacy, Chitradurga, (Karnataka) -India

Abstract

Tablet can be Utilized for precise delivery of drugs and reduce the drug concentrations at sites other than the target organ. The present study performed by preparation and evaluation of floating tablets of Ramipril as model drug. For prolongation of gastric residence time floating effervescent tablets were formulated by various materials like. hydroxypropyl methylcellulose (HPMC) K 4M, K 15M, K 100M and micro crystalline cellulose and gas generating agent like sodium bicarbonate and evaluated for floating properties, swelling characteristics and drug release studies. In vitro drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow both the Higuchi and the Korsemeyer Peppas equation. The drug release mechanism was found non-fickian type in most of the formulations. The developed floating tablets of Ramipril may be used in clinic for prolonged drug release for at least 12 h, thereby improving the bioavailability and patient compliance.

Key-Words: Ramipril, HPMC, Microcrystalline cellulose, Higuchi, Korsemeyer Peppas equation, Non-fickian

Introduction

Ramipril inhibit angiotensin converting enzyme (ACE) which is identical to KININASE II catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex, thus inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase in serum potassium. Ramipril have dose proportional over the 2.5 - 20 mg dose range. The absolute bioavailabilities of Ramipril were 28 %, when 5mg of oral Ramipril was compared with the same dose of Ramipril given intravenously.[1]Being weak acid PKa – 3.41, Ramipril is well absorbed from the upper portion of the duodenum.[2]

The aim of this work was to prepare and evaluate the Ramipril once daily sustained release tablets and to compare them with marketed products. Wet granulation method was adopted for the preparation of tablets using different retardant polymer excipients namely; hydroxypropyl methyl cellulose K4M/K15M/K100M, microcrystalline cellulose (pH 102), sodium bicarbonate, povidone (PVPK-30), isopropyl alcohol magnesium stearate and talcum.

*** Corresponding Author**
E.mail: sudheerbabu467@gmail.com

The Controlled gartric rentention of solid dosage forms may be achieved by Mucoadhesion, [3] Floatation, Sedimentation and simultaneous administration of pharmacological agents. Gastrorententive floating drug delivery system (GRFDDS) has bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric content, the drug is released slowly at a desired rate from the system. Floating drug delivery systems offer important advantages: as they are less prone to gastric emptying resulting in reduced intra and inter-subject variability in plasma drug levels, effective for delivery of drugs with narrow Absorption windows, reduced dosing and increased patient compliance, reduced Cmax and prolonged drug levels above the minimum effective concentration, and improved safety profile for drugs with side-effects associated with high Cmax[4].

Material and Methods

Ramipril was received as a gift sample from Bal Pharmaceuticals Pvt. Ltd.Bengaluru, hydroxypropyl methylcellulose (HPMC K4M, K15M, K100M), microcrystalline cellulose (Avicel PH 101) were obtained as a gift samples from S D Chemicals, Mumbai, India. Sodium bicarbonate, PVP K30, hydrochloric acid, magnesium stearate, talc and all

other chemicals used were of analytical grade.

Tablets were prepared by conventional wet granulation method. The various excipients used were listed in Table 1(Effervescent System). Ingredients except glidants and lubricant were thoroughly mixed and passed through sieve no. 60. Granulation was done with a solution of calculated quantity of PVP K30 (binding agent) in sufficient isopropyl alcohol (granulating agent). The wet mass was passed through sieve no. 12 and dried at 50 °C for 2 h. The dried granules were lubricated with magnesium stearate and talc and compressed into tablets using single station tablet punch machine with 8 mm cancave faced punches.[5,6,7]

Floating properties

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form to constantly remain on surface of medium is called the total floating time (TFT). The buoyancy of the tablets was studied in Dissolution apparatus at 37±0.5 °C in 900 ml of 0.1N HCL (pH 1.2) the measurements were carried out for each formulation of tablets. The time of duration of floatation was observed visually.[8]

Water uptake study

It is important parameter for determining the swelling of the polymers by their ability to absorb water. The water uptake (WU) study of the tablets was done using USP 24 dissolution apparatus II. The medium used was 0.1 HCl, 900 ml at 37±0.5 °C rotated at 50 rpm. After predetermined intervals the tablets were withdrawn blotted to remove excess water and weighed.[8] Swelling characteristics of the tablets were expressed in terms of water uptake.[9]

WU%= (weight of the swollen tablet- initial weight of tablet) X 100 / initial weight of the tablet.

***In vitro* drug release study**

The drug release studiy of Ramipril was determined spectrophotometrically using USP paddle dissolution apparatus in 900 ml of 0.1 N HCL at 37±0.5°C rotated at 50 rpm. The Samples were withdrawn at predetermined time intervals each time fresh media was replaced in same amount. Sample absorbance was measured spectrophotometrically at a Wavelength of 210 nm. [10]

Results and Discussion

Preformulation study and drug excipients compatibility study was done initially and results directed the further course of formulation. IR Spectra studies revealed that the drug and the polymers used were compatible shown in the figure 1 are in the range of Ramipril i.e. 3464.99 cm^{-1}, 3280.72 cm^{-1}, 936.52 cm^{-1}, 2865.78 cm^{-1}, 1743.35 cm^{-1}, 1652.71 cm^{-1}.

Effervescent system

On immersion in 0.1 N HCL, pH 1.2 solution at 37± 0.5 °C all floating effervescent tablets float immediately and remain buoyant up to 12h without disintegration. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium (0.1N HCL). It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (methocel), thus decreasing the density of the tablet below 1 and tablet becomes buoyant.

The tablets with low-viscosity grade methocel K4M exhibited short floating lag time (25s) as compared with formulations containing high viscosity grade methocel K15M (42s) and K100M(60s). This indicated that the molecular weight distribution or viscosity of the gel-forming polymer methocel influenced the in vitro buoyancy.

It was found that increasing the concentration of HPMC act as a swelling agent which is capable of swelling when coming into contact with simulated gastric fluid. Three different concentration of each were formulated as the concentration of HPMC increase as 40 mg, 60 mg, 80 mg the drug release after 12 hrs found to be decrease. HPMC K100M gave comparatively good dissolution profile as compared to HPMC K4M, HPMC K15M after 12 hrs despite presence of high viscosity grade which sustained the drug release. To determine effect of various concentration of HPMC on drug release, formulation having 40 mg, 60mg and 80 mg were prepared. From the dissolution profile it was observed that increasing the concentration of HPMC, the burst drug release and on 12 hrs release rate of drug was decreased. High HPMC contents result in a greater amount of gel being formed. This gel increases diffusion path length of the drug. Its viscous nature also affects the diffusion coefficient of the drug. As a result reduction in drug release is obtained.

Analysis of drug release data

The drug release data were explored for the type of release mechanism followed. The best fit with the highest determination R^2 coefficients was shown by both the Higuchi and first order models followed by zero order which indicate the drug release *via* diffusion mechanism.

In controlled or sustained release formulations diffusion, swelling and erosion are the three most important rate controlling mechanism followed. The drug release from the polymeric system is mostly by diffusion and best described by fickian diffusion. But

in case of formulations containing swelling polymers, other processes include relaxation of polymers chain, imbition of water causing polymers to swell and changing them from initial glassy to rubbery state. Due to swelling considerable volume expansion takes place leading to moving diffusion boundaries complicating the solution of Fick's second law of diffusion.

So to explore the release pattern, results of the *in vitro* release data were fitted to Korsmeyer Peppas equation ($M_t/M_\infty=kt^n$, where $M_t/M_\infty$is the fraction of drug released after time t in respect to amount of drug released at infinite time, k is the rate constant and n is the diffusion exponent) which characterize the transport mechanism. This equation is a generalization of the observation that superposes two apparently independent mechanism of drug transport, fickian diffusion and a case II transport describes drug release from a swelling polymer. The value of n gives an indication of the release mechanism; When n=1, the release rate is independent of time (Zero order) (case II transport), n=0.5 for fickian diffusion and when between 0.5 and 1.0, diffusion and non-fickian transport are implicated. Lastly when n is more than 1.0 supercase II transport is apparent. 'n' is the slope value of logM_t/M_∞*vs.* log time curve. The value of n with regression coefficient for all the formulations is shown in Table 2.

The values of n were in the range of 0.6287 to 0.9122, indicating non fickian release governed by the drug diffusion. However, it indicated by the values of R^2 both of the models (Higuchi and Peppas) were found to be efficient in describing the release of Ramipril from the floating tablets.

Conclusion

We concluded that HPMC different viscous grades in combination with microcrystalline cellulose can be promising polymers for effervescent gastroretentive drug delivery system. Swelling studies indicate significant water uptake and contributed to drug release and could be significant in gastric retention. The formulations followed Higuchi kinetics while the drug release was found to be diffusion controlled. The developed floating tablets of Ramipril may be used for prolonged drug release, thereby improving the bioavailability and patient compliance.

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Table 1: Ramipril in effervescent system

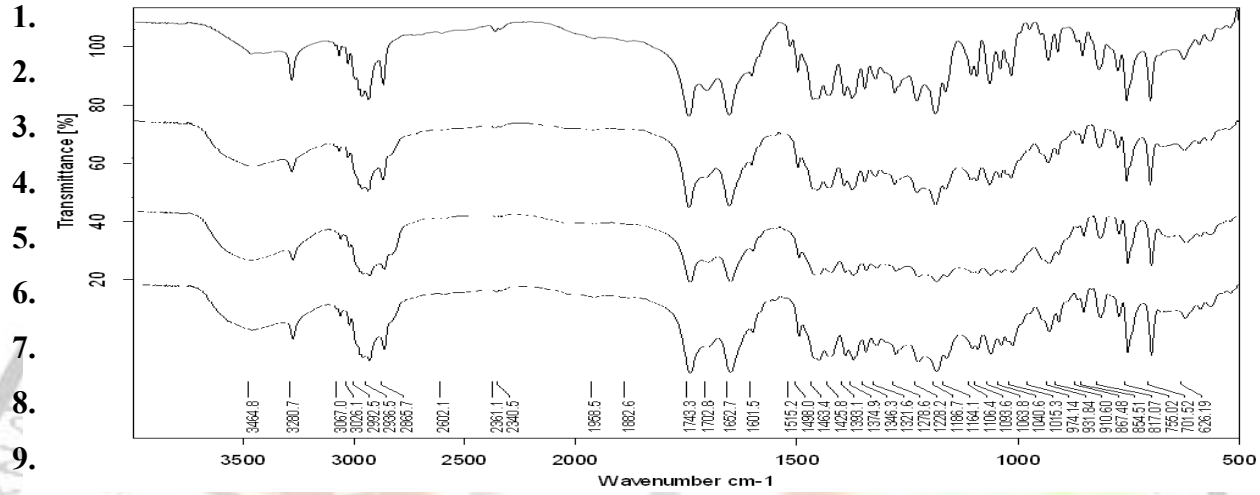
Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	5	5	5	5	5	5	5	5	5
HPMC K4M	40	60	80	-	-	-	-	-	-
HPMC K15M	-	-	-	40	60	80	-	-	-
HPMC K100M	-	-	-	-	-	-	40	60	80
Microcrystalline Cellulose	110	90	70	110	90	70	110	90	70
Sodium Bicarbonate	30	30	30	30	30	30	30	30	30
PVP K30	10	10	10	10	10	10	10	10	10
Mg Steareate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total	200	200	200	200	200	200	200	200	200

Table 2: Kinetic of invitro release from floating tablet of Ramipril

Code	Zeroorder (R^2)	First order (R^2)	Higuchi's Plot(R^2)	Koresmeyer plot	
				n	(R^2)
F1	0.9271	0.9061	0.9936	0.99956	0.6287
F2	0.9743	0.9167	0.9787	0.9894	0.7126
F3	0.9916	0.9561	0.9862	0.9985	0.9122
F4	0.9934	0.9770	0.9935	0.9916	0.8315
F5	0.9918	0.9638	0.9763	0.9962	0.7723
F6	0.9951	0.9713	0.9819	0.9989	0.6318
F7	0.9451	0.9913	0.9950	0.9939	0.6462
F8	0.9929	0.9790	0.9942	0.9912	0.8304
F9	0.9756	0.9916	0.9967	0.9961	0.7248

Fig. 1: IR Spectra of A. Ramipril, B. drug and HPMC K4M, C. drug and HPMC K15M, D. drug and HPMC

K100M



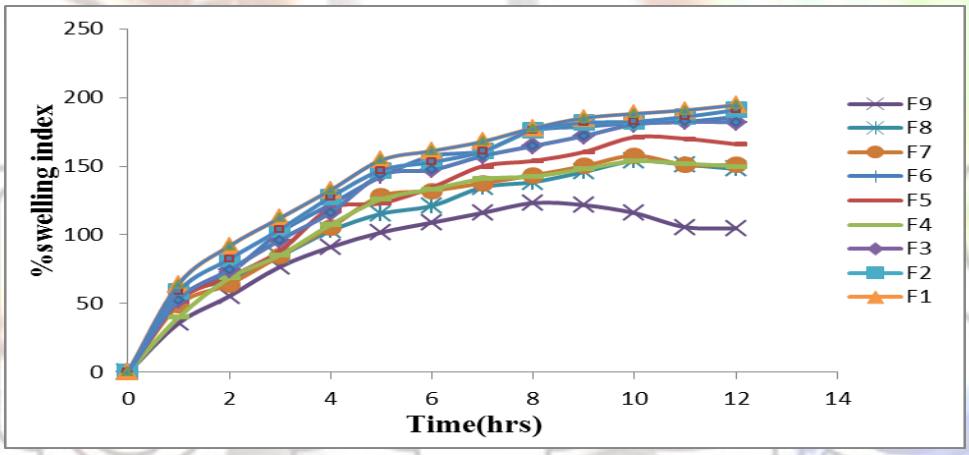


Fig. 2: Swelling index at the end of 12hrs

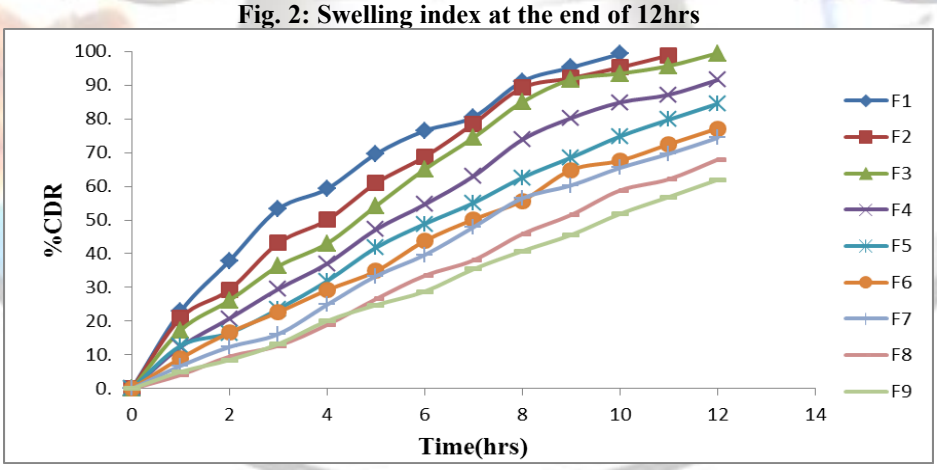


Fig. 3: Invitro release from floating tablet of Ramipril