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Review Article

Effect of Stirring Speed on In Vitro Evaluation of Eudragit Floating Microspheres of Ramipril

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Abstract

In the present study, an attempt was made to develop GRDDS for Ramiprill using Ethyl cellulose and HPMC as a release retarded material by emulsion solvent diffusion technique. Different batches of microspheres were prepared by varying the concentration of Eudragit RS100 and Eudragit RL100. The microspheres were characterized for drug content, percentage yield, particle size analysis and surface morphology. It was observed the increase in concentration of Eudragit RS100 and Eudragit RL100 increases the entrapment efficiency and mean particle size of the microspheres. The effect of polymer concentration on the *in vitro* release of Ramiprill from the microspheres was also studied. It can be seen that by increasing the polymer concentration, decreases the rate of drug release from the microspheres dramatically. The best microsphere formulation was selected based on the *in vitro* release profile and subjected for further kinetic studies.

Key words: Ramiprill, Floating microspheres, emulsion solvent diffusion technique, Eudragit RS100 and Eudragit RL100

Introduction

The Gastroretentive drug delivery system (GRDDS) is of special interest in improving the bioavailability of drugs that are poorly soluble or unstable at higher pH of the intestinal or colonic environment[1]. In order to obtain local and sustained drug delivery in the stomach and proximal parts of the small intestine, it is desired to have prolonged gastric retention of the drug. This helps to have improved bioavailability and therapeutic efficacy which may also results in the reduction in dosing frequency of the dosage form.[2-4] The diminished efficacy of the administered dose may be observed due to intersubject variability and short time of gastric emptying which may results because of incomplete drug release from the drug delivery system above the absorption zone (stomach, upper part of small intestine).[5] Moreover, it has been reported that drug delivery system is one of the commercial system which attributed to obtain the higher bioavailability than that of the non-floating system. [6]

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The GRDDS system is widely useful for the drugs which effectively act in the stomach and have absorption window in stomach. [1, 7] To formulate GRDDS the drug moiety should have good solubility at acidic pH and absorption window in upper GIT and short half-life. To overcome the disadvantages of conventional dosage forms, such as the intersubject variability of GI transit time, due to their all or none effect of the multiple unit dosage form systems are developed. Multiple unit dosage form have proven the lower possibility of dose dumping and reduced inter and intra subject variability of the drug absorption. [8-10]

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.[11-12]

MATERIALS AND METHODS

2.1.

Materials

Ramipril was obtained as a gift sample from Bal Pharmaceutical Ltd. (Bengaluru, India) Eudragit RS100 and Eudragit RL100 was supplied by SD fine chemicals. All solvents used were of analytical grades and were used as obtained.

2.2. Preparation of Ramipril microspheres

Microspheres containing Ramipril as a core material were prepared by emulsion solvent diffusion technique. Drug, Eudragit RS100 and Eudragit RL100 were mixed in dichloro-methane and ethanol at 1:1 ratio at room temperature. The resulting drug-polymer solutions were poured gradually into 200ml of water containing 0.50%w/v polyvinyl alcohol, maintained between 30-40^{0}C and the preparation was stirred at 500,700,1000 rpm for one hour using a mechanical stirrer equipped with three bladed propellers. The microspheres obtained were washed repeatedly with water until it was free from polyvinyl alcohol. The collected microspheres were dried overnight at 60^{O}C.[13-16]

2.3. Drug-polymer interaction studies

Interaction between drug-polymer was studied by infrared spectroscopy using FTIR spectrometer with diffuse reflectance principle. Sample preparation involved mixing the sample with potassium bromide (KBr), triturating in glass mortar and finally placing in the sample holder. The spectrum was scanned over a frequency range 40000-400 cm^{-1}

2.4. Particle size analysis

The size was measured using an optical microscope and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer .[17]

2.5. Drug entrapment efficiency

About 10 mg of accurately weighed drug loaded microspheres were added into 10ml of methanol and the drug concentrations were determined spectrophotometrically at 210 nm in UV-visible double beam spectrophotometer. [7]

% Drug entrapment efficiency = Actual drug content/ Theoretical drug load expected x 100

2.6. Percentage yield

The prepared microspheres were collected and weighed. The yield was calculated by dividing the measured weight by the total weight of all non-volatile components. The percentage yield of microspheres was calculated as follows [20].

$$\% \ Yield = \frac{Weight\ of\ microspheres}{Theoretical\ weight\ of\ drug\ and\ polymer} \times 100$$

2.7. Floating ability

Floating behavior of hollow microspheres was studied in a USP dissolution test apparatus by spreading the microspheres (100 mg) on a 0.1 M HCl containing 0.02% Tween 80 as a surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12h, both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microsphere. [18]

2.8. In vitro drug release studies

The release rate of Ramipril from microspheres was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 mL of 0.1N HCl, at 37 ± 0.5°C and 50 rpm[17]. Microspheres equivalent to 200 mg of Ramipril were used for the test. A 1 mL sample solution was withdrawn from the dissolution apparatus for 1 h, and there after every 1 h upto 12 h. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatmann filter paper and solutions after appropriate dilution were analyzed at 210nm by UV Spectrophotometer. Cumulative percentage drug release was calculated using PCP Disso v2.08 Software (Poona College of Pharmacy, Pune).

RESULTS AND DISCUSSION

The drug excipient compatibility studies reveal that there were no physical changes observed in drug and polymer mixtures. The IR spectrums of the drug, drug Eudragit RS100 and Eudragit RL100 mixture were compared to find any change in frequency of functional group in microspheres with respective functional group of the drug. The spectral observations indicated that the principal IR absorption peaks observed in the spectra of drug were close to those in the spectra of the microspheres containing drug. IR spectrums of the microspheres indicate that there is no strong interaction between the drug and the polymers (Fig.1, 2, 3).

Drug entrapment efficiency was found to be in the range of 81.63 ± 0.005% to 90.42 ± 0.03% and the mean particle size of the microspheres significantly increased with increasing Eudragit RS100 and Eudragit RL100 concentration and was in the range of 85±0.87 µm to 108.66±0.42µm (shown in Table 2) indicates that on increasing the concentration of drug polymer ratio, the particle size was increased. The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities. This results in the formation of larger particles. As the ratio of drug-to-polymer increases, encapsulation efficiency increased; this is due to higher ratio of drug-to-polymer, which would produce large size droplets with decrease surface area, here diffusion of drug from such microspheres will be slow, resulting in higher encapsulation efficiency.

From the data indicates that on increasing stirring speed, particle size was decreased and formations of microspheres were irregular in shape. The fact that high shearing rate required for emulsification caused the breakdown of the viscous drug polymer solution into fine globules resulting in small microspheres. The stirring speed has negative effect on % drug entrapment i.e. as the stirring speed was increased the % drug entrapment was decreased.

Floating ability of different formulations was found to be differed according to the polymer ratio. Microspheres of Batches F1-F9 remained floating for more than 12 hrs. The floating properties of microspheres may be attributed to their low density.

The drug release from formulation F1to F9 show percentage drug release 58.538 to 87.35 at end of 12 hour. Among all formulation F9 was found to be the best formulation as it release Ramipril in a sustained

manner with constant fashion over extended period of time (after 12 hr). The drug release data were explored for the type of release mechanism best fit.

The best fit with the highest determination R^2 coefficients was shown by both Higuchi and Peppas. The R2 value indicated that Higuchi model is the best fitted model to the release profile of F1, F2, F3, F8and the remaining formulations follows Peppas. The values of 'n' were in the range of 0.6318 to 0.9183 ('n' is more than 0.5) indicating Non Fickian release governed by the drug diffusion. However, as indicated by the values of R^2 both of the models (Peppas and Higuchi) were found to be efficient in describing the release of Ramipril from the floating microspheres.

CONCLUSION

In-vitro data obtained for floating microspheres of Ramipril shows that high shearing rate required for emulsification caused the breakdown of the viscous drug polymer solution into fine globules resulting in small microspheres. The stirring speed has negative effect on % drug entrapment i.e. as the stirring speed was increased the % drug entrapment was decreased. From the results it can be concluded that the drug release from the floating microspheres matrix was controlled by the polymer proportion and stirring speed. Prepared formulation showed best appropriate balance between buoyancy and drug release rate and kinetics indicating Non Fickian release governed by the drug diffusion.

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Table 1: Formulation of floating microspheres of Ramipril: F1-F9

Sr.no.	Formulation code	Drug (mg)	Polymers		Stirring Rate (rpm)
			Eudragit S100 (mg)	Eudragit L100	
1.	F1	500	250	250	500
2.	F2	500	250	250	700
3.	F3	500	250	250	1000
4	F4	500	500	500	500
5	F5	500	500	500	700
6	F6	500	500	500	1000
7	F7	500	750	750	500
8	F8	500	750	750	700
9	F9	500	750	750	1000

Table 2: Particle size drug entrapment efficiency and Practical yield of floating microspheres of Ramipril: F1-F9

Formulation code	Particle size µm	% Drug Entrapment Efficiency	Practical yield
F1	104 ± 0.35	81.63 ± 0.005	72.56 ± 0.67
F2	91 ± 0.5	83.57 ± 0.07	80.83 ± 0.63
F3	90 ± 1.5	76.35 ± 0.05	83.28 ± 0.57
F4	108.66 ± 0.42	90.42 ± 0.03	81.26 ± 0.69
F5	101 ± 0.67	88.84 ± 0.02	86.67 ± 0.45
F6	85 ± 0.87	82.47 ± 0.04	88.59 ± 0.38
F7	108.34 ± 0.59	89.22 ± 0.06	87.28 ± 0.76
8	103.33 ± 0.81	86.28 ± 0.02	91.53 ± 2.02
F9	94.67 ± 0.22	85.11 ± 0.03	94.39 ± 1.50

Fig 1: FTIR Spectra of Ramipril

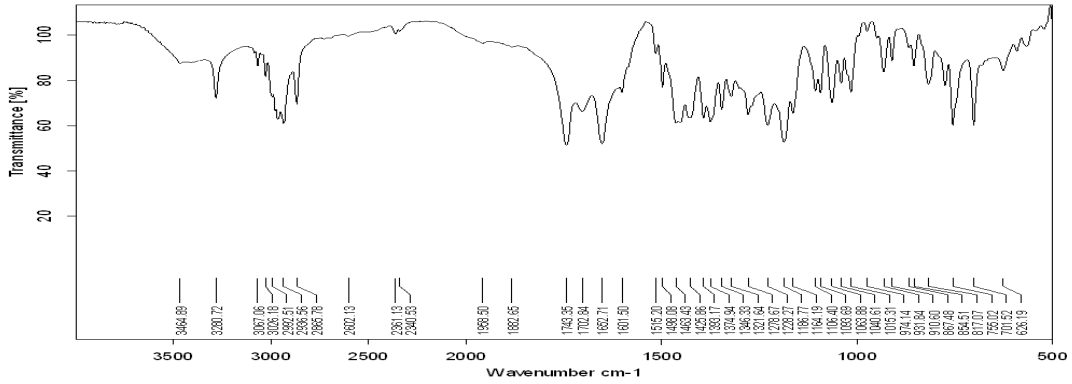

Fig 2: FTIR Spectra of Ramipril and Eudragit S100

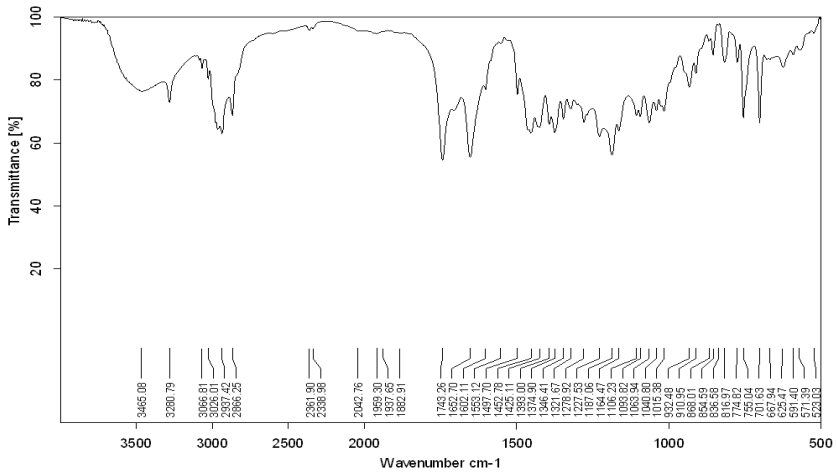

Fig 3:FTIR Spectra of Ramipril and Eudragit L100

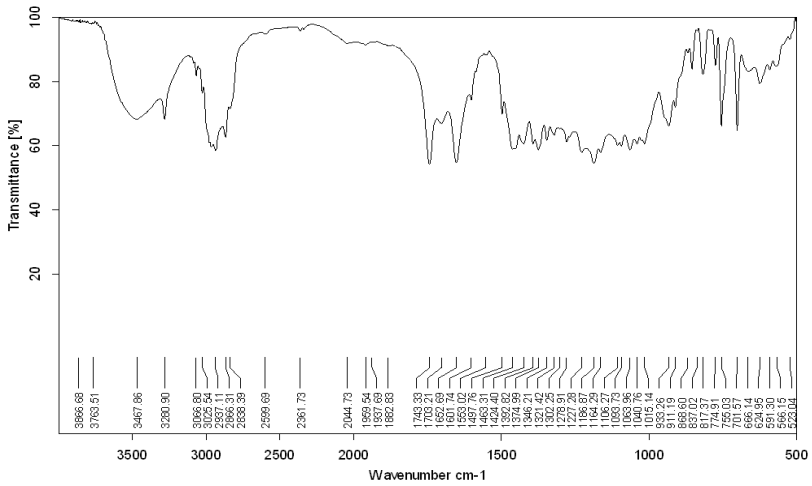

Fig.4. In vitro drug release profiles from Ramipril (F1-F9)