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Research Article

Enteric coated capsules of eprosartan mesylate with pH-modifier for augmenting the dissolution

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ABSTRACT

Eprosartan mesylate, an antihypertensive, exhibits low oral bioavailability due to its ionization at alkaline pH. An attempt has been made to prepare enteric coated capsule containing drug and maleic acid, as dosage form. Maleic acid acts as pH-modifier, facilitates the absorption of drug by reducing the pH of intestinal environment (preferably duodenum) so as to reduce the ionization of eprosartan, once the capsule reaches the duodenum. The capsules were coated with eudragit L100-55 (enteric coating agent) by dip method and evaluated for % weight gain to ensure coating. The capsules coated with 300 mg eudragit L100 -55 in 5 ml acetone showed 9-10% weight gain and maximum drug release at the end of the 180 min. This was considered optimized formulation. The coated capsules were filled with drug and maleic acid and evaluated for drug release in the acid (pH 1.2) and alkaline (pH 6.2) media. The optimized capsules exhibited optimum dissolution profile with the maximum release of drug in the alkaline medium.

Keywords: pH-modification; Enteric coated capsules; Dissolution; Drug release.

INTRODUCTION

The pH-dependent solubility is an important criterion determining oral absorption of a few drugs. Sometime, poor oral absorption of pH-dependent soluble drugs lead to insufficient efficacy. Thus, the approach of modifying micro-environmental pH at the diffusion area can be adopted using pH-modifying excipients to improve dissolution of such drugs, possibly leading to better oral absorption (Taniguchi 2014).

Eprosartan mesylate is a non-biphenyl, non-tetrazole angiotensin II receptor (AT_1) antagonist. This antihypertensive agent has low bioavailability of 13% after oral administration. The low bioavailability of eprosartan is due to its pH-dependent solubility and permeability. At its absorption windowbetween the duodenum and jejunum it is less soluble. It has been reported that above pH 2, the drug starts ionizing to become a negatively charged ion and gets 2 or 3 negative charges as pH increases. It is taken on that due to the constitution of these ions the drug does not permeate the biomembrane as there would be repulsion between them. And likewise it can be assumed that ionization of drug increases due to its hydrophilic nature, which will reduce its permeation (Tenero 1998, Jae-Soon 2011). An approach with eprosartan-arginyl charge neutralization complex has been reported to enhance the bioavailability of the drug (Gudipati 2003). In the present study, attempts are being made to make a micro-pH environment of pH below 2, so as to reduce its ionization. The objective was to develop a duodenum targeted dosage form, where the drug and the pH-modifier (excipient) are used. It was hypothesized that the excipient will help to maintain a micro pH-environment to reduce the ionization of eprosartan mesylate. The enteric coated capsules filled with eprosartan mesylate and maleic acid, were developed.

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METHODOLOGY

1. Determination of Ionization constant (pK_a) of eprosartan mesylate

The ionization constant of the drug was found using the Henderson-Hasselbach equation.

2. Degradation studies of eprosartan mesylate 0.1N HCl, pH 1.2

The degradation of eprosartan mesylate was studied in 0.1N HCl of pH 1.2 at 25°C and 37°C. 100µg/ml drug solutions were prepared in 0.1N HCl. Different lots of drug solution were prepared in 0.1N HCl and observed for 32 days. The drug concentration was determined spectrophotometrically at 234.8nm. The tests were performed in duplicates.

3. Selection of pH-modifying agent

Citric acid and Maleic were evaluated as pH-modifiers (Kramer 2008). The pH reducing capacity of the acidic substances was found out by adding the weighed

amount of malice acid or citric acid to 10ml of buffers, pH 5.4 and pH 6.2. The change in the pH was observed.

4. Formulation ofenteric coated capsules

The enteric coated capsules filled with drug and Maleic acid were formulated in the present work. The enteric coated capsules should reach the intestine (duodenum is the target site) and release the drug and maleic acid creating micro-environmental pH suitable for eprosartan to be absorbed. Two methods were adopted to coat the capsules with an enteric coating solution.

a) Dip coating using forceps

In this method capsules were filled with 50 mg of drug and 300 mg of maleic acid and then locked. In a beaker, 500 mg of Eudragit L100 was dissolved in 10 ml of Isopropyl alcohol. At once the capsule was taken with a forceps and dipped in the solution, then removed and dried with the assist of a hair dryer.

b) Dip coating using glass rods

Two glass rods of outer diameter that fit firmly to the body and cap of the capsule were selected. The weight of the capsule (W_1) was recorded before coating. To get enteric coated, respective glass rods were inserted into the body and the cap of the capsules and dipped up to the level of their length in a beaker containing the coating solution. These capsules were dried using a hair dryer and after some time they were transferred from the glass rods. The weight of the capsules (W_2) was recorded again after coating. The %weight gain was computed utilizing the formula:

$$\%\,Weight\ gain = \frac{Final\ wt\ of\ the\ capsule - Initial\ wt\ of\ the\ capsule}{Initial\ wt\ of\ the\ capsule} \times 100$$

Now these capsules were filled with the eprosartan mesylate and maleic acid. The capsules were sealed and subjected to dissolution.

5. Dissolution of the enteric coated capsules

Dissolution study was performed to check the drug release from the capsules. Both paddle and basket types were used to determine the drug release. For the first 2 hours, the drug release was determined in buffer, pH 1.2 (acidic medium) and for the next 1 hour in buffer, pH 6.2 (alkaline medium) mimicking the physiological state. The sample was withdrawn for every 30 min (i.e., 30, 60, 90 and 120 min) in acidic medium and the amount of drug was determined spectrophotometrically at 234.8nm. Whereas, in alkaline medium, the sample was withdrawn for every 15 min (i.e.,150, 165 and 180 min from the beginning) and the amount of drug was determined spectrophotometrically at 232nm (Chunnuan 2013).

RESULTS AND DISCUSSION

1. Determination of $pK_a$of eprosartan mesylate

The various analytical methods are available to determine the ionization of drugs, such as, spectrofluoremetry, UV, conductometry and titrimetry. Since analytical methods were not observed to be suitable for eprosartan mesylate, the % ionization of the drug was estimated using the Henderson-Hasselbach equation (Reijenga 2013). Previously, it is reported in the literature that eprosartan mesylate has three pK_a values but it is not mentioned that which pK_a exists at which particular pH. Hence, % drug ionization values were obtained at different pH for all three pKa values. According to Henderson-Hasselbach equation, % drug ionized for weak acids is estimated utilizing the formula:

$$\%\ DrugIonized = \frac{10^{(pH-pK_a)}}{1+10^{(pH-pK_a)}} \times 100$$

The three reported pK_avalues of eprosartan mesylate are pKa_1= 2.9, pKa_2=5.9 and pKa_3=6.8. The % drug ionized values at a particular pH is shown in the Table 1. % ionization was not calculated below pH 2 because eprosartan mesylate exists in unionized state.

2. Degradation studies of eprosartan mesylate in 0.1N HCl, pH 1.2

The stability of eprosartan mesylate was studied in 0.1N HCl of pH 1.2 at both ambient temperature (i.e., 25°C) and physiological temperature (i.e., 37°C). The degradation study was conducted to evaluate the result of acidic pH on the stability of eprosartan mesylate as the formulation comprises an acidic substance.The drug was found to be stable up to 32 days with 97 -99% concentration (Fig. 1).

3. Selection of pH-modifying agent

The measurement of micro-environmental pH and release of pH-modifier would provide theoretical insight for the selectionof an appropriate pH-modifier and optimization of the formulation.The volume of the duodenum isreported to be around 490 ml. It is not possible to maintaining an environment of pH less than 2 in the complete duodenum and also may lead to toxicities. Therefore, the pH-reducing capacities of the acidic substances was evaluated for 10 ml of buffer in *in vitro* studies. The pH-reducing capacity of two excipients, maleic acid and citric acid were observed using different buffers (depicted in Tables 2 and 3). The maleic acid was found to be suitable and thus selected as micro-environmental pH-modifying agent.The turbidity was observed in phthalate buffer due to physical incompatibility between phthalic acid and maleic acid.The effervescence was observed in sodium bicarbonate buffer due to release of CO_2.

Table 1: % Drug ionized calculated at each pH using the Henderson-Hasselbach equation

pH	% Drug Ionized		
	If pKa_1 exists	If pKa_2 exists	If pKa_3 exists
2	11.7	0.0124	0.0014
3	55.73	0.011	0.0149
4	92.63	1.2	0.15
5	99.21	11.11	1.55
6	99.92	55.73	33.28
7	99.99	92.64	83.36

Table 2: pH-reducing capacity of maleic acid in buffers, pH 5.4 and pH 6.2

S. No	Amount of maleic acid added (mg)	Initial pH	Final pH	Observation
Phthalate buffer (pH 5.4)				
1	250	5.42	3.83	Turbidity
2	500	5.42	2.91	
Phosphate buffer (pH 5.4)				
3	250	5.40	1.94	Clear Solution
4	500	5.40	1.81	
Sodium bicarbonate buffer (pH 5.4)				
5	250	5.67	1.46	Effervescence was observed
6	500	5.67	1.37	
Phosphate buffer (pH 6.2)				
7	250	6.20	2.10	Clear solution
8	500	6.20	1.99	
9	300	6.20	1.97	
10	400	6.10	1.78	

Table 3: pH-reducing capacity of citric acid in buffers, pH 5.4 and pH 6.2

S. No.	Amount of citric acid added (mg)	Initial pH	Final pH	Observation
Phosphate buffer, pH 5.4				
1	250	5.40	3.11	Clear Solution
2	500	5.40	2.72	
3	1000	5.40	2.32	
Sodium bicarbonate buffer, pH 5.4				
4	250	5.43	2.05	Clear Solution
5	500	5.43	1.83	
6	1000	5.43	1.65	
Phosphate buffer, pH 6.2				
7	250	6.23	2.44	Clear Solution
8	300	6.18	2.40	
9	400	6.21	2.28	
6	500	6.17	2.22	
7	600	6.20	2.21	
8	1000	6.12	2.02	

4. Formulation of enteric coated capsules

The capsule filled with pure drug and maleic acid was chosen as dosage form with the hypothesis to get a maximum release of drug within half an hour after entering the duodenum (i.e.,150^{th} min). Earlier reports suggested that eudragit® L 30 D-55 and eudragit® FS 30 D HPMC coated hard gelatine capsule resulted in intestinal targeting with good retention time (Cole 2002). Eudragit L100-55 (Kilor 2010) was chosen as enteric coating agent in this study. Initially pan coating method was tried but the capsules stuck to the bottom of the pan. So, dip coating method was embraced. The % increase in weight after coating and dissolution profile (in alkaline medium) of the coated capsules filled with 50 mg of eprosartan mesylate were used as parameters for evaluation and optimization of coating.

In forceps method, forceps was sticking to the eudragit layer and when tried to remove it, the eudragit layer used to come out at the place it was held with forceps. The glass rod method was successful up to a certain extent, but the % gain in weight and dissolution profile, were not reproducible. The coating solution and num-

Table 4: Coating solution, no. of dips, % weight gain, dissolution parameters, drug release in alkaline stage

Batch code	Coating Solution	No of Dips	Wt Gain (%) (Mean ± SD)	Dissolution Apparatus	% Drug release (Mean ± SD)		
					120 min	150 min	180 min
1	500 mg eudragit in 15ml acetone	3	72.75 ± 13.79	Basket Type	0.50 ± 0.57	1.95 ± 0.10	4.40 ± 2.41
2	100 mg eudragit in 5ml acetone	2	7.88 ± 2.94		2.26 ± 1.74	23.55 ± 20.04	50.75 ± 38.41
3	100 mg eudragit in 5ml acetone	2	3.28 ± 0.19	Paddle Type Using basket as a sinker	5.35 ± 4.23	4.21 ± 5.95	15.53 ± 4.91
4	100 mg eudragit in 5 ml Acetone	3	4.63 ±0.62	Paddle Type Sinker- Spiral wire	17.20 ± 6.95	47.26 ± 18.72	88.34 ± 29.15
5		2	7.33 ± 1.58		20.18 ± 6.60	55.96 ± 11.31	96.46± 13.91
6	150 mg eudragit in 5 ml Acetone	2	7.34 ± 1.08	Paddle Type Sinker- Spiral wire	10.69 ± 1.08	70.42 ± 13.53	110.07 ± 0.39
7	250 mg eudragit in 5 ml IPA	1	10.29 ± 2.09	Paddle Type Sinker- Spiral wire	17.34 ± 9.57	44.65 ± 15.63	85.79 ± 22.04
8		2	18.01±2.10		16.97±8.16	49.81±13.48	89.50± 16.42
9	300 mg eudragit in 5 ml IPA	2	12.03 ±0.61	Paddle Type Sinker- Spiral wire	17.55 ± 3.51	51.75 ± 22.82	88.94 ± 17.84
10		1	10.22 ± 1.31		19.41 ± 10.84	53.88 ± 25.66	85.69 ± 22.85

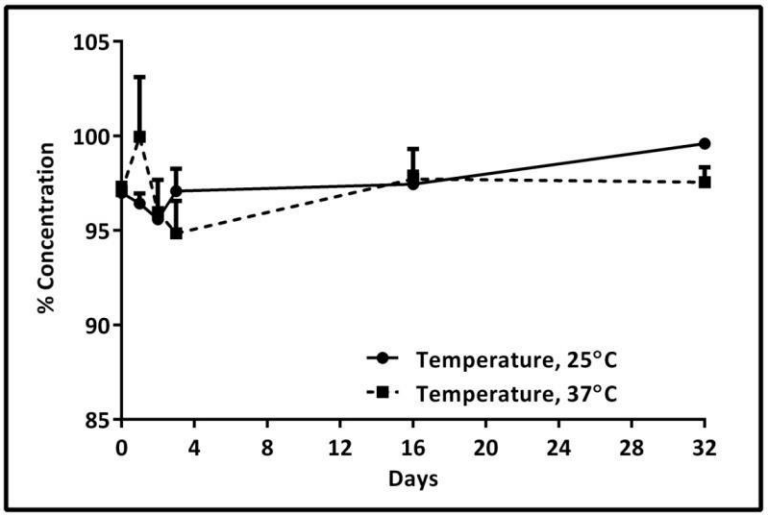

Figure 1: Degradation pattern of eprosartan mesylatein 0.1N HCl, pH 1.2 at 25°C and 37°C

ber of dips were optimized to achieve certain % gains in weight for the coating of capsules (Table 4). It is found that the % weight gain was more than 9-10% with 300 mg eudragit and also exhibited optimum dissolution profile using spiral wire as a sinker.

5. Dissolution studies of optimized batch of enteric coated capsules

It was found that capsules with 9-10% of weight gain exhibited minimum drug release in acid stage of *in vitro* dissolution. The drug release from the optimized formulation was determined using UV spectrophotometry. The graph plotted between time and average % cumulative drug release (CDR) values is shown in Fig. 2. The drug release was observed to be less than 24% in the acidic medium in the dissolution study. The release of drug increased in the alkaline medium and was observed to be 68% at 150th min and 90% at 180th min. Thus, it can be inferred that the enteric coated capsules released drug in the alkaline medium and drug was unionized because of micro-environmental pH created by maleic acid.

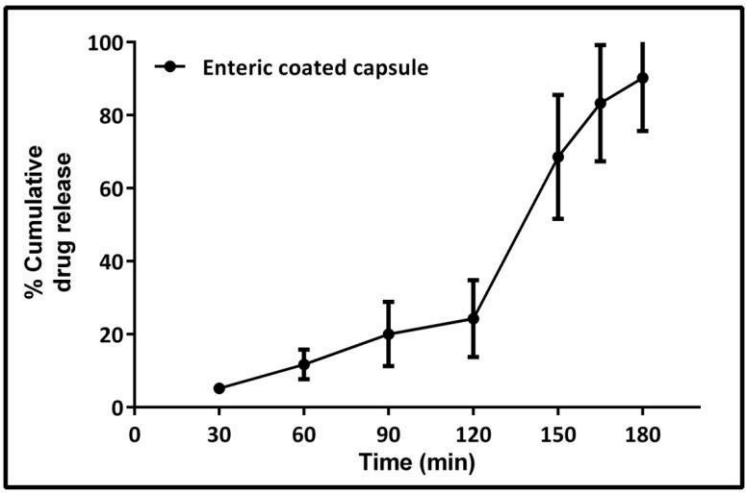

Figure 2: Graph showing the drug release from the optimized formulation

CONCLUSION

In the present work an attempt has been made such that the hard gelatin capsule containing the drug and maleic acid was enteric coated to ensure that the drug is released in the intestine (preferably duodenum) wherein the maleic acid is expected to reduce the pH of the environment so that maximum drug will be in the unionized form. Use of high quantity of maleic acid as pH-modifiers for duodenum targeting limits the application of this study. Nevertheless, an attempt has been made and it seems possible, which would be taken further to develop and evaluate the formulation. Thus, a proper optimization of formulation and pharmacokinetics study are required to establish the release of eprosartan mesylate in the duodenum of the prepared using the same concept of enteric coated capsules.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest. The authors alone are responsible for content and writing of the paper.

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