Journal of Pharmaceutical Research

ISSN - 0973-7200 | online- ISSN-2454-8405

www.journalofpharmaceuticalresearch.org

Research Article

AUGMENTATION OF PERMEABILITY OF DRUGS HAVING P-GLYCOPROTEIN INHIBITION FOR EFFICIENCY IN NOCTURNAL ACID BREAKTHROUGH

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ABSTRACT

Purpose : Ranitidine is a BCS class III drug having low oral, lipophilicity and is susceptible to the P-glycoprotein (P-gp) efflux mechanism. Permeation enhancers enhance the bioavailability of ranitidine by increasing the partition coefficient ($K_{oct/buffer}$) there by increasing the lipophilicity and permeability. The main aim of the present work is to overcome the problems of ranitidine bioavailability by expending permeation enhancers and P-gp inhibitors.

Methodology : The existence of synergistic activity in permeation enhancement effect was studied using EDTA, citric acid, oleic acid, caprylic acid, sodium glycocholate and sodium deoxycholate. The P-gp inhibitor used here was felodipine, a first generation inhibitor showed P-gp inhibition activity at a concentration where it shows it pharmacological action. Three formulations were formulated and subjected to various physiochemical evaluations like weight variation, friability, hardness, drug content, in vitro drug release and kinetic studies.A continuous dissolution–absorption system was designed using everted intestine segment.

Results : Synergistic effect in enhancing the permeability of ranitidine was found to exist between chelating agents in combination with fatty acids and its derivatives. From the precompression parameters data of the lubricated blend, it was found that the flow ability was good and can be compressed into tablets by direct compression method. The formulated ranitidine immediate release tablets exhibited first order release kinetics, resulting in rapid and complete release for two h.

Conclusion : The effective drug permeability (P_{eff}) after three h or formulations TAB, TAB37, TAB37-PGP and TAB-MARK is 2.60, 3.17, 3.66 and 2.68, respectively. This shows that the permeability through chick intestine is more from TAB37-PGP by increased P-gp inhibition.

KEYWORDS: *Bioavailability, dissolution-absorption system, lipophilicity, permeation enhancement, P-gp inhibition, ranitidine.*

Received on : 27-12-2016 Revised on : 24-01-2017 Accepted on : 04-02-2017

INTRODUCTION

A great number of currently available drugs fall under the class III of the biopharmaceutical classification system, possess high therapeutic potential but cannot be delivered by oral route because of their poor permeation across the gastro intestinal (GI) epithelia[1]. The low intrinsic membrane permeability of drugs maybe because of their zwitterionic character at physiological pH, low lipophilicity, high molecular weight and substrate to drug efflux pumps like P-glycoprotein (P-gp) ionic charge[2].

Normal gastric acid secretion follows a circadian rhythm, when gastric pH level goes far below for at least 1 h in the midnight with a sudden surge of gastric acidity[3]. Heartburn, coughing or choking due

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DOI : 10.18579/jpcrkc/2017/16/1/112478

to fluid in the throat, breathlessness, wheezing and morning phlegm are common symptoms commonly reported throughout this time. This patho-physiological condition is termed as nocturnal acid breakthrough (NAB) and is even more prolonged and clinically critical for H. pylori-negative patients on proton pump inhibitor therapy. NAB is one of the foremost reasons of treatment failure of gastro esophageal reflux disease (GERD) compromising therapeutic goals in patients[4].

One of the most challenging histamine-H_2 receptor antagonists (H_2RA) is ranitidine HCl with maximum absorption from the stomach and upper part of the GIT and is rapidly metabolized in the intestine due to colonic bacteria[5]. Ranitidine is a BCS class III drug having low oral bioavailability ranging from 39-88%. The main problem associated in the development of oral tablet formulation of ranitidine is its lower lipophilicity and its susceptibility to the P-gp efflux mechanism[6,7]. Hence in the present investigation, permeation enhancers (PE) and P-gp inhibitors were used to overcome the problems of ranitidine bioavailability[8]. Ranitidine tablets containing permeation enhancer and P-gp inhibitor were prepared by direct compression method.

In the present investigation, the intestinal permeability of ranitidine was studied in the presence of various classes of permeation enhancers such as chelating agents, bile salts and fatty acids and P-gp inhibitors such as felodipine. The partition coefficient of ranitidine was determined in the presence of various categories of permeation enhancers like EDTA, citric acid, sodium glycocholate, sodium deoxycholate, sodium caprate and oleic acid etc. The optimum molar concentration of PE was selected at which maximum increase in the partition coefficient of ranitidine was obtained[9]. The effective drug permeability (P_{eff}) and enhancement ratio of prepared formulations was compared with the marketed formulation.

MATERIALSAND METHODS

Materials:

Ranitidine was purchased from yarrow chemical products, Mumbai, India. EDTA, citric acid, oleic acid, caprylic acid, sodium glycocholate and sodium deoxycholate, micro crystalline cellulose, dicalcium phosphate, cab-o-sil, magnesium stearate were purchased from commercial suppliers. Marketed formulation of Ranitidine tablets were purchased from local drug store in Visakhapatnam city after checking their manufacturing, production and expiry date. All the chemicals and solvents used were of analytical grade.

Procedure for determination of partition coefficient ($K_{oct/buffer}$):

The partition coefficients of ranitidine with and without permeation enhancers in different molar ratio were determined between pH7.4 phosphate buffer and n-octanol. Approximately 100mg of ranitidine was added to a 24 h saturated solution containing 10 ml of n-octanol and 10 ml of phosphate buffer (pH 7.4). It was then kept for shaking on a rotary shaker for 24 h at room temperature and transferred into a separating funnel for collection of the two phases. The drug content was analysed spectrophotometrically at 313 nm in both the solvents. The partition coefficient i.e.,$K_{oct/buffer}$of ranitidine was determined by substituting the concentrations of ranitidine in octanol and phosphate buffer 7.4 in the following equation[10].

$$K_{oct/buffer} = a_o / a_b$$

Where a_o and a_b are the concentrations of the drug in n-octanol and buffer respectively.

Procedure for optimization of molar concentrations of permeation enhancers:

Partition coefficient of ranitidine in the presence of permeation enhancers (chelating agents like EDTA; fatty acids and its derivatives such as citric acid, oleic acid and caprylic acid; bile salts and its derivatives such as sodium glycocholate and sodium deoxycholate) at different molar concentrations was determined. The partition coefficients of mixed molar concentrations and their corresponding individual concentrations were compared[11]. The molar concentration of permeation enhancer that exhibited maximum increase in partition coefficient $K_{oct/buffer}$of ranitidine was selected for further study.

Method for preparation of ranitidine tablets:

All the ingredients were weighed accurately as given in Table 1 and passed through sieve #40 separately. Ranitidine was taken and with the remaining ingredients were mixed in geometrical ratio in a polythene bag. Finally magnesium stearate was added and mixed thoroughly to get free flowing powder. The powder blend was subjected to

evaluation of precompression parameters before direct compression into ranitidine tablets (TAB, TAB37 and TAB37-PGP).

Table 1: Formula for preparation of ranitidine direct compression tablets

Ingredients	Quantity per tablet (mg)		
	TAB	TAB37	TAB37-PGP
Ranitidine	15	15	15
Felodipine	-	-	0.5
Citric acid	-	3.0	3.0
Caprylic acid	-	3.0	3.0
Micro crystalline cellulose	4.3	1.2	1.0
Dicalcium phosphate	4.0	1.1	0.8
Cab-O-Sil	0.4	0.4	0.4
Magnesium stearate	1.3	1.3	1.3
Total Weight (mg)	25	25	25

Drug – excipient compatibility studies using FTIR:

Drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for pure drug, pure excipient, and physical mixture of drug and excipient. The spectrum of sample was obtained by using FTIR- BRUKER. The procedure used was KBr disc method. In this method the sample was mixed with KBr and triturated in a mortar and pestle to ensure uniform mixing. This mixture was pressed into discs using hydraulic press at 7 tons pressure for 3 min. The pellet was placed in the light path and the spectrum was recorded in the range of 4000-500 cm^{-1}.

Precompression studies:

Flow properties:

Flow properties of the powders are important parameter in the formulation of tablets. The flow properties of the powder of pure drug and blend of pure drug were evaluated by using parameters like angle of repose, Carr's index and Hausner ratio.

Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Lower the angle of repose, better the flow property. Rough and irregular surface of particles gives higher angle of repose. Non uniform flow results in weight variation, which affects the dose of the drug per tablet and also creates a problem of hardness during compression of tablets.

Compressibility index (I):

Compressibility or Carr's index is a measure of potential strength that a powder could build up in its arch in a hopper and also the ease with which such an arch could be broken. Compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area because all these can influence the observed compressibility index

Hausner ratio:

Hausner ratio is a number that is correlated to the flowability of a powder or granular material, its importance is in inter-particulate interactions of the free flowing powder. The initial bulk and tapped densities will be more similar than in poor flowing powders which yield greater differences between the two values. Hausner ratio is not an absolute property of a material. Its value can vary depending on the methodology used to determine it. This was calculated by using bulk and tapped densities of powder samples which give the information regarding the flow properties of the powder, which enables to decide the required quantity and the type of glidant to be added in the formulation.

Hausner ratio = Dt/Db

D_t is the tapped density of the powder.

D_b is the bulk density of the powder.

Post compression parameters evaluation:

Hardness:

Tablet hardness has been defined as the force required in breaking a tablet in a diametric compression test. To perform this test, a tablet was placed between two anvils, force is applied to the anvils and the crushing strength that just caused the tablet to break was recorded. Hardness is thus sometimes termed as tablet crushing strength. Five tablets were selected at random and the hardness of each tablet was measured on Monsanto hardness tester and expressed in Kg/cm^2.

Friability:

Friability is the loss of weight of tablet in the container packaging due to removal of fine particles from the surface. Rather than a measure of the force required to crush a tablet, friability test is carried out to assess the ability of the tablet to withstand abrasion in packaging, handling and transport. The friability test was carried out in Roche friabilator as the tablet weight is <650 mg. According to I.P tablets with a weight equivalent to 6.5 g (w_o) are to be taken in a rotating drum, they were allowed to fall from the height of 6 inches for 100 revolutions at a rate of 25 rpm. After completion of rotations, the tablets were dedusted and weighed again (w).

The percent weight loss or friability (f) was calculated by the formula given below

$F = [(w_o - w)/w_o] \times 100\%$

Prepared tablets complies the test if the percentage of friability is within the pharmacopoeial limits of less than 1%.

Uniformity of weight:

Twenty tablets were selected randomly and average weight was determined. Individual tablet was weighed and compared with the average weight. Percent deviation and weight variation were calculated for all the batches. The tablets complies with not more than two of the individual weights deviate from the average weight by more than percentage shown in table and none of them deviate by more than twice the percentage were qualified.

Uniformity of Content:

From each batch, 10 tablets were randomly selected, powdered in a glass mortar and the powder equivalent to 100 mg of felodipine was placed in 100 ml volumetric flask containing phosphate buffer pH 7.4. The flask was shaken to mix the contents thoroughly in mechanical shaker for 1 h and filter into a 100 ml volumetric flask through 0.45µm Millipore nylon filter and made up to mark with phosphate buffer 7.4. Further appropriate dilutions were made with phosphate buffer 7.4 and the absorbance was measured at 232 nm against blank.

Disintegration time:

The disintegration time for sublingual tablets was determined by using USP disintegration test apparatus. In this six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water bath was maintained at 37^0 C ± 0.5^0C and the time taken for all tablets to disintegrate completely was noted.

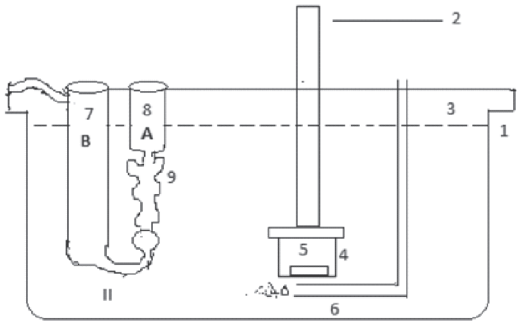
Absorption studies:

Isolation of everted intestine:

Male white Leghorn chicks weighing between 500 and 600 g were bought from the local market. The Krebs–Ringer solution was prepared by combining 6.3 g NaCl, 0.35 g KCl, 0.14 g $CaCl_2$ 0.16 g KH_2PO_4 0.15 g $MgSO_4 7 H_2O$ 2.1 g $NaHCO_3$ and 5 g glucose in one litre of distilled water. For isolation of everted intestine, the chicks were slaughtered, a median incision of the abdomen was performed, and the small intestine was freed. The lumen was carefully cleared from mucus by rinsing with a pH 7.4 buffer solution (Krebs–Ringer solution). An intestinal segment of the first 6 cm length was removed and transferred to oxygenated Krebs–Ringer solution. It was washed thoroughly with warm Krebs–Ringer solution. The proximal extremity of the intestine was turned back and ligated on a glass rod to form an everted bag.

Design of continuous dissolution–absorption system using everted intestine segment:

The in vitro continuous dissolution–absorption system design was illustrated in Figure 1. The system consisted of USP dissolution Apparatus 1 and a side-by-side perfusion apparatus holding isolated everted intestine segment (Figure 1-II). In this system, drug dissolution from the slow release tablet and permeation across everted intestine occurred simultaneously[12]. The dissolution medium used was 1000 ml of distilled water maintained at 37 ± 0.5 °C. The perfusion apparatus consisted of two glass tubes, A and B, connected together (Figure 1-II). Tube B had a bent cannula at its lower end, and tube A, a straight cannula at its lower end. The distance between the two cannulas was kept constant. The isolated everted intestinal segment was fixed between the ends of tubes A and B as shown in the Figure 1- II. The ends of the intestine were tied in position with a thread. The apparatus was immersed completely into the dissolution vessel.



1. Dissolution flask
2. Rotating shaft
3. Dissolution medium
4. Basket
5. Tablet
6. Oxygen tube
7. Tube A
8. Tube B
9. Everted intestine
I. Dissolution - absorption system
II. Absorption (perfusion) apparatus

Fig.1: Design of continuous dissolution–absorption using isolated everted intestine system

Procedure for absorption studies in the continuous dissolution–absorption system:

In the proposed design of a continuous dissolution–absorption system, sampling can be done simultaneously for measurement of the in vitro

dissolution and absorption profiles of the drug[13]. The dissolution–absorption studies were performed in two parts. The dissolution medium consisted of 1000 ml distilled water maintained at 37 ± 0.5 °C. A fresh intestinal segment was clamped to the perfusion apparatus. The total volume of the absorption compartment (tube A and tube B of perfusion apparatus) was 35 ml of Krebs–Ringer solution. The drug diffused from dissolution medium (mucosal side) to the serosal side (absorption compartment). The formulated and marketed tablets were transferred to the dissolution basket of the designed system. The tablet was rotated at 75 rpm speed. Dissolution samples (3 ml) were withdrawn at preselected time interval up to 3 h. The dissolution samples were taken with replacement at 10, 20, 30, 40, 50, 60, 90, 120, 150 and 180 m, and the released metformin was determined spectrophotometrically at 313 nm. The transported drug from the absorption compartment was sampled with replacement (Krebs–Ringer solution) at 13, 23, 33, 43, 53, 63, 93, 123, 153 and 183 min and analysed spectrophotometrically for transported metformin at 313 nm. To allow time for drug to circulate from the dissolution vessel to the everted intestine surface, absorption samples were collected 3 m later than their corresponding dissolution samples. The whole experiment was repeated in triplicate (n=3) using fresh dissolution medium as well as fresh intestinal segment each time. The effective drug permeability (P_{eff}) across the membrane and Enhancement ratio (Er) was calculated.

The effective drug permeability (P_{eff}) across the membrane was calculation from the formula:

$P_{eff} = (dm/dt)/AC$

Where, dm is the drug accumulation in the absorption compartment during time interval dt .
A=Exposed area of tissue
C= Concentration of drug in donar compartment
Enhancement ratio (Er) was determined from the formula,

$$\text{Enancement ratio} = \frac{\text{(Amount of drug permeated with permeation enhancer)}}{\text{(Amount of drug permeated without permeation enhancer)}}$$

RESULTS AND DISCUSSION

Optimization and selection of permeation enhancer:

The partition coefficient of ranitidine was determined and the $K_{oct/buffer}$ of ranitidine was found to be 0.223. The $K_{oct/buffer}$ of ranitidine along with EDTA, citric acid, oleic acid, caprylic acid, sodium glycocholate and sodium deoxycholate as permeation enhancers in different molar concentrations are shown in Table 2. The maximum increase in $K_{oct/buffer}$ of ranitidine with EDTA, citric acid, oleic acid, caprylic acid, sodium glycocholate and sodium deoxycholate was observed in batches HR8, HR13, HR19, HR23, HR27 and HR33 with $k_{oct/buffer}$ values 1.14, 1.24, 0.98, 1.39, 1.13 and 1.04, respectively.

Table 2: Partition coefficient of ranitidine

Ingredients	Batch	Proportion	Concentration in buffer mg/mL	Concentration in octanol mg/mL	$k_{oct/buffer}$
Ranitidine	Hr1	1:0	81.70	18.30	0.22
	HR2	1:1	60.73	39.27	0.65
	HR3	1:2	58.19	41.81	0.72
	HR4	1:3	57.24	42.76	0.75
	HR5	1:4	54.70	45.30	0.83
Ranitidine: EDTA	HR6	1:5	52.77	47.23	0.90
	HR7	1:6	52.38	47.62	0.91
	HR8	1:7	46.71	53.29	1.14
	HR9	1:8	48.43	51.57	1.07
	HR10	1:9	50.55	49.45	0.98
	HR11	1:10	51.80	48.20	0.93
	HR12	1:0.1	50.51	49.49	0.98
Ranitidine: Citric acid	HR13	1:0.2	44.49	55.51	1.25
	HR14	1:0.3	48.31	51.69	1.07
	HR15	1:0.4	55.58	44.42	0.79
	HR16	1:0.5	58.61	41.39	0.71
	HR17	1:0.5	54.25	45.75	0.84
Ranitidine: Oleic acid	HR18	1:1	55.12	44.88	0.81
	HR19	1:2	50.45	49.55	0.98
	HR20	1:3	53.77	46.23	0.86
	HR21	1:4	56.57	43.43	0.77
	HR22	1:0.1	45.98	54.02	1.17
Ranitidine: Caprylic acid	HR23	1:0.2	41.83	58.17	1.39
	HR24	1:0.3	44.28	55.72	1.26
	HR25	1:0.4	46.65	53.35	1.14
	HR26	1:0.5	49.74	50.26	1.01
	HR27	1:0.1	46.85	53.15	1.13
Ranitidine: Sodium glycholate	HR28	1:0.2	48.89	51.11	1.05
	HR29	1:0.3	50.97	49.03	0.96
	HR30	1:0.4	55.16	44.84	0.81
	HR31	1:0.5	58.61	41.39	0.71
	HR32	1:0.1	50.97	49.03	0.96
Ranitidine: Sodium deoxycholate	HR33	1:0.2	48.93	51.07	1.04
	HR34	1:0.3	51.63	48.37	0.94
	HR35	1:0.4	53.35	46.65	0.87
	HR36	1:0.5	53.75	46.25	0.86
Ranitidine: Citric acid: Caprylic acid: Sodium glycholate	HR37	1:0.2:0.2:0.0	38.48	61.52	1.60
	HR38	1:0.0:0.2:0.1	44.07	55.93	1.27
	HR39	1:0.2:0.0:0.1	45.36	54.64	1.21

Among the chelating agents, batch HR13 showed maximum increase in $K_{oct/buffer}$ value. Similarly from fatty acids and its derivatives and bile salts and its derivatives, the batches HR23 and HR27 showed maximum increase in $K_{oct/buffer}$ value. These three batches were screened for synergistic action and batch HR37 showed $K_{oct/buffer}$ value, 1.59 indicating presence of synergistic effect between chelating agents and fatty acids and their derivatives. Batch HR37 showed maximum $K_{oct/buffer}$ value, 1.59 and it was used for further studies.

Drug- excipient compatibility studies using FTIR:

The FTIR spectra of ranitidine, felodipine and TAB37-PGP (ranitidine containing all the formulation excipients and P-gp inhibitor-felodipine) are shown in Figure 2.

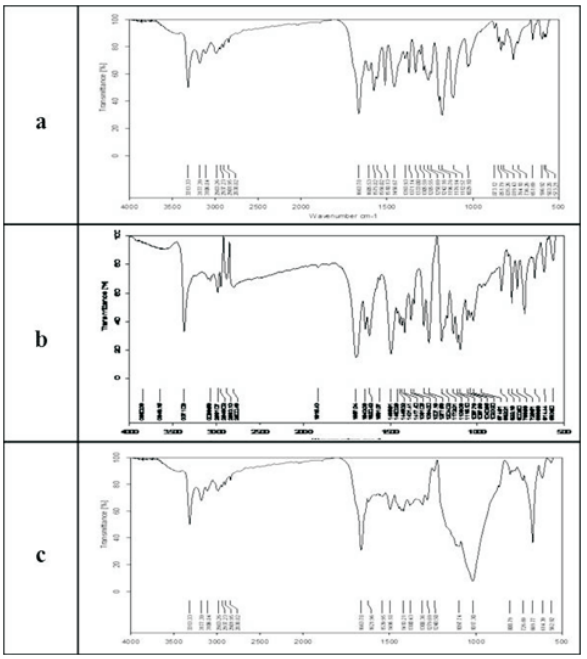


Fig. 2 : FT-IR Spectras of (a) ranitidine, (b) felodipine and (c) TAB37-SPGP

The characteristic troughs of ranitidine are -N-H stretching at 3350-3300 cm^{-1} and wagging at 910-665 cm^{-1}. There is a C-N(aromatic amine) stretch at 1335-1250 cm^{-1}. There is a NO_2 trough at 1600 cm^{-1}. The characteristic trough of felodipine include aromatic C=C stretch at 3050-3150 cm^{-1} and -N-H stretching at 3350-3300 cm^{-1}. The FTIR spectra of TAB37-PGP contain -N-H stretching at 3350-3300 cm^{-1} which is one of the characteristic troughs of both ranitidine and felodipine. As the secondary amine stretching is not disturbed, we can confirm the compatibility of ranitidine and felodipine with other excipients used in the formulation.

Pre-compression parameters:

The flowability of lubricated blends of TAB, TAB37, TAB-PGP was determined by angle of repose, Carr's compressibility Index and Hausner ratio and values are shown in Table 3. The values are in the range of 31-35°, 11-14, and 1.12-1.18 for angle of repose, Carr's compressibility Index and Hausner ratio respectively. Results indicated that flow of the lubricated blend was found to be good and can be compressed in to tablets by direct compression method.

Table 3 : Evaluation of formulated batches of ranitidine tablets

Formulation code	Pre-compression parameters (mean ± S.D, n=3)			Post compression parameters (mean ± S.D.)				
	Angle of repose (θ)	Compressibility Index (I)	Hausner Ratio	Hardness (Kg/cm2) (n=3)	Friability (%) (n=6)	Uniformity of weight (mg) (n=10)	Uniformity of Content (%w/w) (n=10)	Disintegration time (sec) (n=3)
TAB	33.4±0.4	14.5±0.5	1.1±0.0	4.8±0.1	0.5±0.0	249.5±0.0	99.5±0.0	112±0.1
TAB37	34.4±0.4	13.2±0.6	1.2±0.0	4.4±0.1	0.6±0.0	249.5±0.0	99.5±0.1	112±0.0
TAB37 PGP	34.1±0.3	13.4±0.5	1.2±0.0	4.6±0.0	0.6±0.1	248.9±0.1	98.4±0.0	119±0.0

Post-compression parameters:

The post compression parameters like hardness, friability, weight variation, drug content and disintegration time. Hardness of tablet formulations was measured using Monsanto hardness tester and they were found to be in the range of 4-6 Kg/cm^2 and are well within the acceptable limits. Friability of the tablet formulations was determined using Roche friabilator and they are found to be well below the acceptable limit i.e., a maximum loss of weight (from a single test or from the mean of the three tests) was not greater than 1 percent. The uniformity of weight test was carried out for tablets and results are shown in Table 3. All the prepared tablets passed weight variation test, as %weight variation was within the Pharmacopoeial limit 7.5%.

Uniformity of drug content was carried out for ten tablets. The preparation complied with the test as individual drug content was 85 to 115 per cent of the average content. Disintegration time was determined for tablet formulations and it was found to be well within the desirable range.

Dissolution- Absorption studies:

The drug release from all the formulations was rapid and it was observed from the cumulative percent drug release versus time curve shown in Figure3. The dissolution data says that the release rate was fast and 90% of drug is released within 30 min from all the four formulations. In order to establish the order of drug release from all the four formulations, the experimental data was fitted tozero-order and first order models and the values are given in Table 4.The correlation coefficients of formulations TAB, TAB37, TAB37-PGP and TAB-MARK are shown

in table and all the four formulations shows greater "r" values in first order model than zero order models, so, we can say that the drug release follows first order kinetics[14,15].

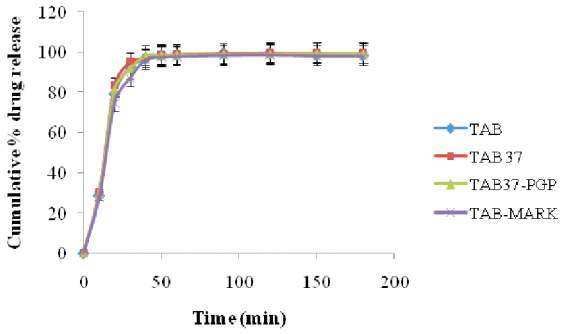


Fig. 3 : Cumulative percent drug release from different ranitidine formulations

Table 4: Correlation coefficient values of ranitidine formulations

S.No.	Formulation	Correlation coefficient value (r)	
		Zero order	First order
1.	TAB	0.901	0.986
2.	TAB37	0.924	0.983
3.	TAB37-PGP	0.911	0.994
4.	TAB - MARK	0.936	0.982

Effective drug permeability (P_{eff}) across the membrane and Enhancement ratio (Er) were calculated for formulations TAB, TAB37, TAB37-PGP and TAB-MARK. Effective drug permeability (P_{eff}) vs Time plot for formulations TAB, TAB37, TAB37-PGP and TAB-MARK and was shown in Figure 4. The effective drug permeability (P_{eff}) after three hours for formulations TAB, TAB37, TAB37-PGP and TAB-MARK was 2.60, 3.17, 3.66 and 2.68 respectively and this shows that the permeability through chick intestine was more from TAB37-PGP.

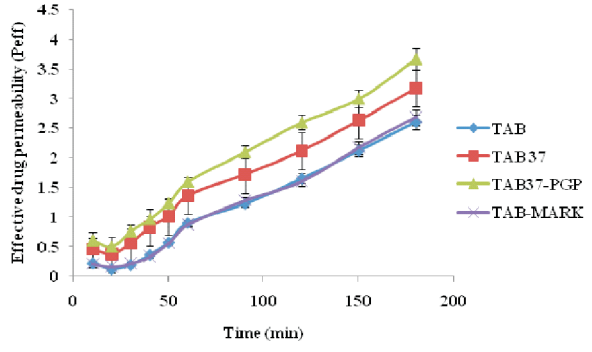


Fig. 4 : Effective drug permeability (Peff) from different ranitidine formulations

Enhancement ratio (Er) for formulations TAB, TAB37, TAB37-PGP and TAB-MARK was presented in Figure 5 inferring the enhancement of permeability. Enhancement ratio (Er) of formulations TAB37, TAB37-PGP and TAB-MARK was 1.16, 1.26 and 1.02. From the Enhancement ratio (Er) we conclude that TAB37-PGP and TAB37 enhanced permeability of ranitidine by 1.26 times and 1.16 times than that of formulation with permeation enhancers only (TAB).

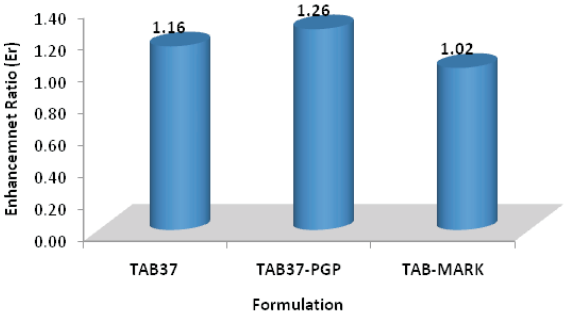


Fig. 5: Comparision of Enhancement Ratio (Er) of ranitidine from different formulations

CONCLUSION

From the present investigation among all the permeation enhancers studied, caprylic acid sodium showed the maximum increase in $K_{oct/buffer}$ values (1.39) at molar concentration ratio of 1:0.2. The $K_{oct/buffer}$ value of formulation HR37 (1.69) was greater than the $K_{oct/buffer}$ values obtained with the individual permeation enhancers indicate the presence of synergistic effect between chelating agents and fatty acids and their derivatives. The pre and post compression evaluation parameters were within the acceptable range. The P-gp inhibitor used here was felodipine, a first generation inhibitor showed P-gp inhibition activity at a concentration where it exhibits its pharmacological action. This increases the patient compliance and reduces the cost of treatment of drugs having P-gp inhibition. The P-gp inhibition increased permeability by about 0.5 times. The added advantage of using this technology was decreased dose and lowering the therapeutic window of drugs thus decreasing the chance of adverse effects.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest

ACKNOWLEDGMENT

Authors are thankful to A.U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, A.P., India, for providing necessary laboratory facilities to carry out this research studies.

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