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Article

Novel ion exchange resin-based combination drug-delivery system for treatment of gastro esophageal reflux diseases

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The present study involves preparation and characterization of a combination tablet of ranitidine in immediate release form and domperidone in sustained release form, using ion exchange resins. Ranitidine lowers acid secretion, while domperidone release over a prolonged period improves gastric motility thus justifying this combination in gastro esophageal reflux diseases (GERD) and ensuring patient compliance. Drug loading was carried out by batch method & resinates were characterized using FTIR, XRPD. Resinates were formulated as a combination tablet and evaluated for tablet properties & *in vitro* drug release. Resinates provided sustained release of domperidone and immediate release of ranitidine. IR and X-ray studies indicate complexation of drug and resin along with monomolecular distribution of drugs in amorphous form in the resin matrix. The tablets of resinate combination showed good tablet properties. *In-vitro* drug release gave desired release profiles and ex-vivo drug absorption studies carried out by placing everted rat intestine in dissolution medium indicated statistically significant similarity in absorption from test and marketed formulation. The novelty of this study is that the retardation in release of domperidone from resinates is achieved by presence of weak resin in the formulation.

Uniterms: Drugs/delivery system. Ranitidine/tablets/immediate release. Domperidone/tablets/sustained release. Tablets/delivery system. Ion exchange resins/use/ drugs delivery system.

O presente estudo envolve a preparação e a caracterização de associação do comprimido de ranitidina de liberação imediata e domperidona de liberação prolongada, utilizando resinas de troca iônica. A ranitidina diminui a secreção ácida, enquanto a liberação prolongada de domperidona melhora a motilidade gástica, justificando, dessa forma, a associação em doenças de refluxo gastroesofágico (DRGE) e garantindo a adesão do paciente. A carga de fármaco foi efetuada pelo método em batelada e os resinatos, caracterizados utilizando-se FTIR e XRPD. Os resinatos foram formulados como comprimido da associação e avaliados com relação às propriedades dos comprimidos e liberação do fármaco *in vitro*. Os resinatos proporcionaram a liberação prolongada da domperidona e a liberação imediata da ranitidina. IV e estudos de difração de raios X indicaram a complexação do fármaco e da resina junto com a distribuição monomolecular dos fármacos, em estado amorfo, na matriz da resina. Os comprimidos da associação do resinato apresentaram boas propriedades. Obtiveram-se os perfis de liberação *in vitro* e os estudos de absorção dos fármacos *ex vivo* realizados com intestino de rato em meio de dissolução indicaram semelhança significativa na absorção entre as formulações teste e comercializada. A inovação do trabalho é que o retardamento da liberação da domperidona dos resinatos é atingido pela presença de resina fraca na formulação.

Unitermos: Fármacos/sistema de liberação. Ranitidina/comprimido/liberação imediata. Domperidona/comprimido/liberação prolongada. Comprimidos/sistema de liberação. Resinas de troca inônica/uso/liberação de fármacos.

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INTRODUCTION

Research over the past few years has revealed that ion exchange resins are equally suitable for drug delivery technologies, including controlled release, site-specific fast dissolving, iontophoretically-assisted transdermal, nasal, topical, and taste masked systems. (Borodkin *et al.*,1971). Literature review (Anand *et al.*, 2001) A literature review (Anand *et al.*, 2001) revealed that ion exchange resins have versatile properties as a drug delivery vehicle. Moreover, resin characteristics such as acid or base strength, porosity, degree of cross linkage and particle size can be chosen from among the many available ion exchange resins to achieve the intended purpose (Vimaladevi *et al.*, 2001). Combination products have the advantages of combination therapy besides reducing the complexity of the dosage regimen. Thus, combination therapy, if used optimally, has the advantages of increased efficacy and improved clinical effectiveness, broadening the array of therapeutic options, offering customization of the treatment to suit specific patient needs, enhanced patient adherence and reduction in cost of administration. (Wetheimer *et al.*, 2002). Gastro esophageal reflux disease (GERD), reflux esophagitis, Peptic ulcer, gastric ulcer and other gastric acid-related disorders have pathogenesis related to reduced gastric motility and release of excessive gastric acid. GERD and gastric ulcer have been successfully treated with a range of gastric acid inhibitors, such as ranitidine, which are acid suppressing agents. Stimulation of gastric motility has been proposed to accelerate the healing of gastric ulcer and prokinetic agents such as domperidone are known to enhance gastrointestinal motility and prevent duodenogastric reflux. The aim of combining two or more drugs with complementary modes of action using ion exchange resins is to produce the desired release pattern and therapeutic benefits along with the advantage of reducing the complexity of the dosage regimen thus leading to patient compliance (Norris *et al.*, 2005). In the present study, sustained release of domperidone was achieved by complexing with Indion 244 while the immediate release form of ranitidine hydrochloride was prepared by complexing with Indion 294. *In vitro* drug release from resinates was studied. Resinates were formulated into combination tablets and tablets were evaluated for hardness, thickness, friability, weight variation & *in-vitro* drug release. An everted rat intestine model was employed for studying *ex-vivo* absorption and was compared with marketed preparation.

EXPERIMENTAL

Material

Ranitidine HCl was a gift from Wockhardt Pharma Ltd. Domperidone was from BURGEON Pharmaceuticals Pvt. Ltd.. Indion 244, Indion 294 were provided by Ion exchange India Ltd. Ranitidine HCL and domperidone were analyzed by Jasco V-530 UV/ VIS spectrophotometer. Resinates were evaluated by Jasco FT/IR-460.

Methods

The ranitidine & domperidone were simultaneously estimated by simultaneous equation method spectrophotometricaly at 326 nm & 287 nm using Jasco V-530 UV/ VIS Spectrophotometer.

Drug loading was carried out by batch method described elsewhere in the literature. (Vimaladevi *et al.,* 2001; Plaizier *et al.*, 1992).

The weak cation exchange resin Indion 234 was selected for binding ranitidine as ranitidine is a basic drug and is needed in immediate release form, whereas Indion 244, a strong cation exchange resin, was chosen to produce sustained release resinates of domperidone, again a basic drug. Both the drugs ranitidine hydrochloride & domperidone (100 mg each) were separately added to 100 mL of deionised water, and Indion 294 & Indion 244 (100 mg each), respectively was placed into the solutions and stirred for four hours on a mechanical stirrer. The solutions were filtered and the amount of drug remaining in the filtrate was determined spectrophotometrically.

The amount of drug adsorbed was determined by the difference between the amount of drug present in stock solution and amount remaining in filtrate at the end of stirring.

Evaluation of physical properties of resins and resonates (Lordi et al., 1991)

Different physical parameters of resinates including

TABLE I - Properties of Indion 244 and Indion 294

Resin	Functionality	Matrix	Form	Ion exchange capacity
Indion 244	$-SO_3H$	Cross linked polystyrene	H^+	4.5 meq/grygm
Indion 294	-COOH	Cross linked polyacrylic	K^+	NA

shape, flow properties, bulk density, tap density and packing ability were determined.

Characterization of resin and resinates

The FT-IR studies were carried out using a Jasco FT/IR-460. The X- ray diffraction studies were carried on a Phillips analytical X-ray BV(PW 1710) device using cu anode 40 kv voltage and 30 ma current.

In-vitro *drug release from resinates:*

Resinates of ranitidine hydrochloride with Indion 294, and domperidone with Indion 244, were subjected to *in-vitro* dissolution studies using an USP type II apparatus at 100 rpm. The dissolution medium was 900 ml 0.1 N HCl at 37 ± 0.5 ºC.

In-vitro *drug release from combination of resinates:*

Resinates of ranitidine hydrochloride and domperidone, equivalent to their doses, were combined together. The combination of resinates were then subjected to *in-vitro* dissolution studies using an USP type II apparatus at 100 rpm. The dissolution medium was 900 ml 0.1 N HCl at 37 ± 0.5 ºC.

Formulation of combination tablets

Resinates of ranitidine HCl (441.17 mg) and domperidone (32.25 mg) equivalent to the therapeutic dose of free drug, were blended with mannitol (71.38 mg) and granulated with gelatin solution (10%). The granules were dried and blended with sodium starch glycolate (6 mg), talc(12 mg), magnesium stearate (6 mg), methyl paraben (1.08), and propyl paraben (0.12 mg) as excipients. Total weight of each tablet was kept at 600 mg. The tablets were compressed on a Karnavati Rimek press, using D tooling and a 12.5 mm flat punch with pressure adjusted to achieve hardness of 5 kg/cm^2 .

Evaluation of prepared tablets (Banker, Anderson, 1991)

The physical properties of tablets such as general appearance, hardness, thickness, friability and weight variation, were determined as described elsewhere in the literature.

In-vitro drug release profile of combination tablet and marketed tablets

Prepared tablets and marketed tablets were subjected to *in-vitro* dissolution studies using an USP type II apparatus at 100 rpm. Dissolution medium was 900 ml 0.1 N HCl at 37 ± 0.5 ºC.

Ex-vivo *study for absorption through everted rat intestine (Dixon et al., 1977; Chowhan, 1977)*

Ex-vivo study for absorption of drugs by the everted rat intestine technique was carried out using a modified perfusion apparatus.

The apparatus consist of 'U' shaped glass tubing having 1 cm inner diameter with cannulated cut on one arm of the 'U' tube. The volume capacity of apparatus was 25 mL. The distance between two cannulated arms was 8 cm where the intestine was tied. After placement of intestine on the perfusion apparatus, the apparatus were dipped into the dissolution media in the dissolution pan and the dissolution study was performed under the above-mentioned conditions.

From the prepared tablet, absorption of drugs through rat intestine was compared with marketed formulations of domperidone and ranitidine HCl.

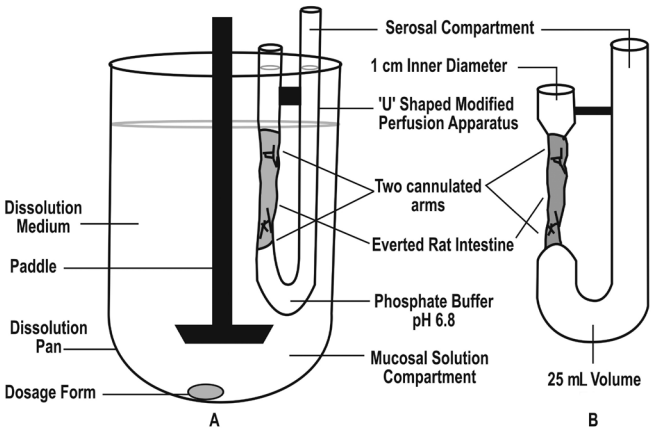

FIGURE 1 - [A] Modified perfusion apparatus in dissolution vessel. [B] Modified perfusion apparatus.

RESULT AND DISCUSSION

The batch process was used for drug loading. From preliminary experiments, 4 hours was found to be the optimum period for attainment of loading equilibrium of domperidone & ranitidine. The drug loading was carried out at 1:1 drug resin ratio for both drug resin combinations. Indion 244 domperidone showed 48.44% & Indion 294 - ranitidine showed 40.44% of drug content.

Table II summarizes the physical properties of resins and resinates. The shape of resinate affects the flow and packing properties & was found to be irregular for Indion 244 resin and resinate. Angle of repose was found to lie between 20-30 °C thus exhibiting good flow properties. Bulk density less than 1.2 gm/cm^3 exhibited good packing ability. Thus the results showed that resin and resinate

TABLE II - Physical properties of resins and resinates

Parameter	Indion 244 Resin	Domperidone Resinate	Indion 294 Resin	Ranitidine Resinate
Shape	Irregular	Irregular	Irregular	Irregular
Angle of repose	26.56	24.22	25.34	27.21
Bulk density	0.681	0.550	0.625	0.584
Tap density	0.789	0.610	0.731	0.652
Carr's index	15.85	13.27	16.96	11.64
Housner ratio	1.15	0.98	1.16	0.98

exhibit good flow properties. Carr's compressibility index i.e. % compressibility, and Hausner ratio indicate the packing ability of powders.

When compressibility index ranges from 5 to 16 and the Hausner ratio approaches 1 the material has good flow property and packing ability.

X-ray diffraction

The X–ray diffraction pattern (Figure 2) for drugs [A & D] contained a number of sharp peaks, while the resins [B & E] showed a diffused peak or halo pattern, where as only a diffused peak was observed in X–ray powder diffraction patterns for the resinates regardless of drug loading.

According to this data, the molecular state of drugs [A&D] was crystalline, but that of resins [B&E] was amorphous. The molecular state of drugs prepared as drug resin complexes was changed from crystalline state to amorphous state. This shows that entrapped drug molecules are monomolecularly dispersed in resin beads (Pisal *et al.* 2004).

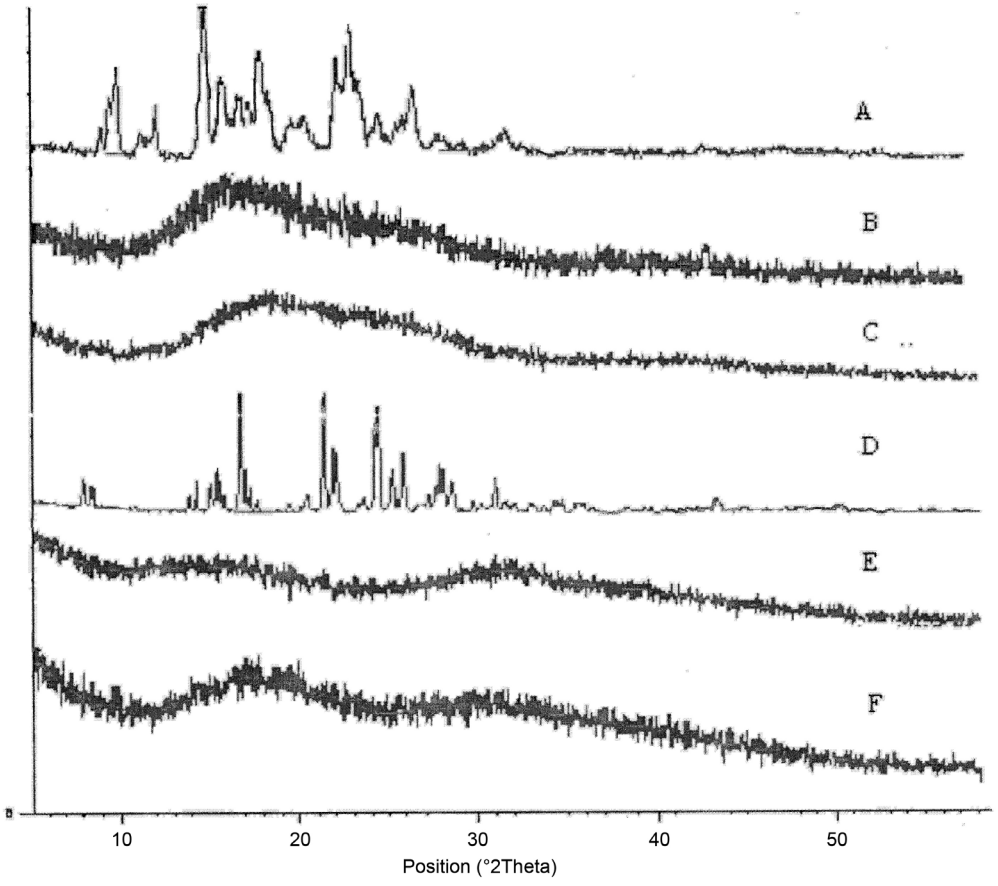

FIGURE 2 - X- ray powder diffraction pattern for A. Domperidone, B. Indion 244, C. Domperidone resinate, D. Ranitidine HCl, E. Indion 294, F. Ranitidine resinate.

FT-IR STUDIES

The IR spectra for the drugs (Figure 3) [A&D] shows peak at 3349 cm^{-1} corresponding to N-H stretching in a secondary amine. The absence of a peak at 3349 cm^{-1} in resinates [C&F] confirms the complexation of the secondary amine group in the drugs [A&D] with resins [B&E].

The *in-vitro* dissolution profile (Table III) shows that about 43.41% of domperidone was released in 60 min from resinate, and about 97.83% of domperidone was released

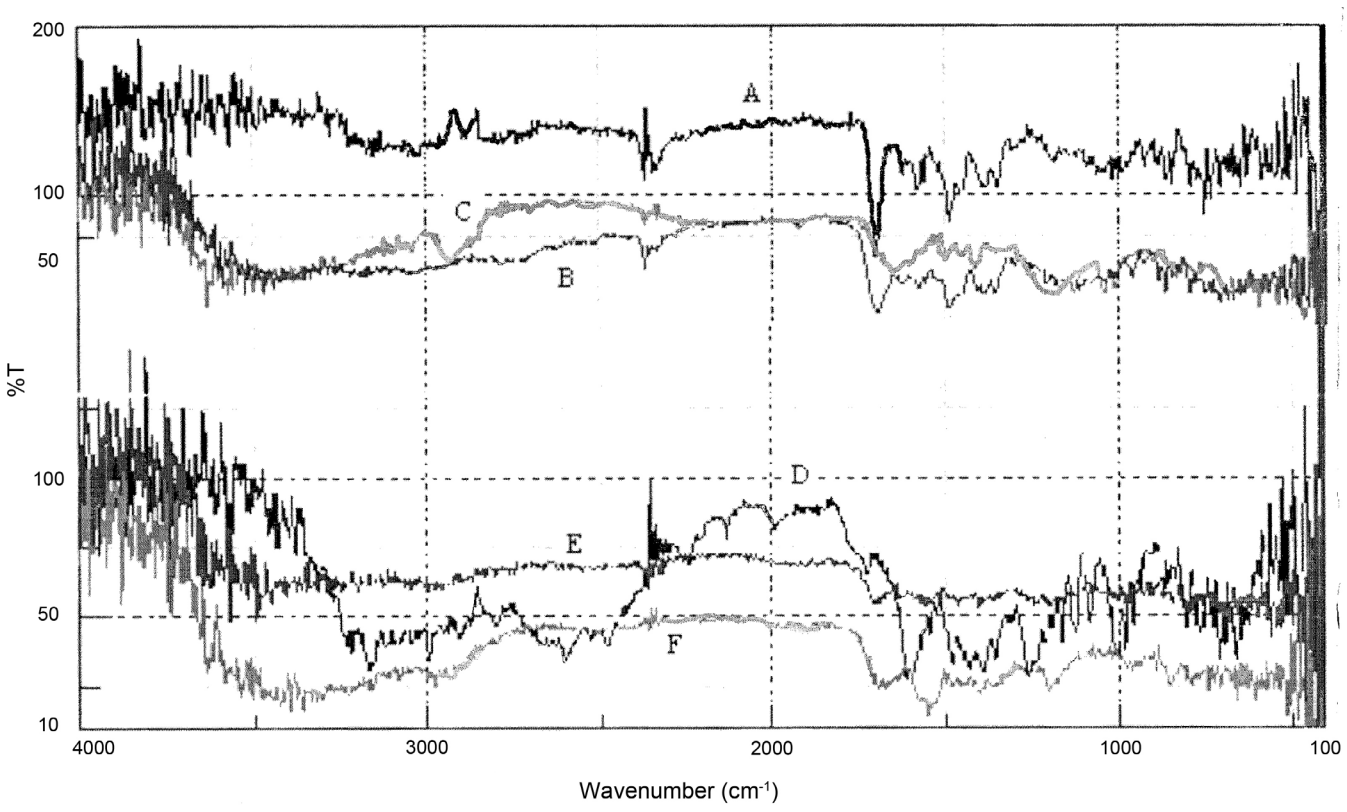

FIGURE 3 - Infrared spectra for A. Domperidone, B. Indion 244, C. Domperidone resinate, D. Ranitidine HCl, E. Indion 294, F. Ranitidine resinate.

TABLE III - *In-vitro* drug release profiles of ranitidine HCl and domperidone from resinates

% Drug Release For Ranitidine		% Drug Release For Domperidone	
Time (min)	% Drug Release	Time (min)	% Drug Release
5	39.42±0.28	60	43.41±0.36
10	52.28±0.43	120	53.30±0.24
20	61.27±0.25	180	65.95±0.18
30	68.60±0.36	240	67.31± 0.22
40	71.99±0.41	300	71.10±0.16
60	80.14±0.38	360	73.41±0.29
75	87.70±0.29	420	78.05±0.22
90	97.72±0.73	480	84.17±0.41
--	--	540	88.49±0.31
--	--	600	93.52±0.33
--	--	660	97.83±0.46

(Mean ± SD, n=3)

at the end of 660 min from resinate. The resinate showed initial high release but could retard the drug release beyond 480 min, therefore resinate of a 1:1 ratio showed potential to sustain the release of domperidone. The initial burst release may be attributed to lower particle size of resinate. (Borodkin *et al.*, 1991). The ranitidine release from ranitidine resinate was found to be 97.72% in 90 min.

A difference was observed between domperidone release from individual domperidone resinate & combination with ranitidine resinate (Figure 4), where the release was retarded from combination. Similar observations are reported in the literature (Hughes, 2002)

This can be explained as follows, after complete release of ranitidine from resinate, the weak resin was available as unloaded resin as it is experimentally demonstrated that the drug release is retarded in the presence of unloaded resin.

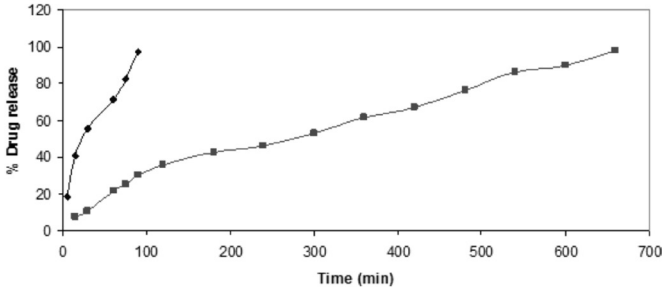

FIGURE 4- In-vitro ranitidine & domperidone release from combination of resinates. ◆ % release of ranitidine; ■ % release of domperidone.

TABLE IV - Evaluation of prepared tablets

Hardness kg/cm^2	Thickness (mm)	Weight uniformity+ (mg)	% Friability
5±0.25	4.49	600±0.5	0.7±0.43

(Mean ± SD, n=3)

Assay of prepared tablets

TABLE V - Assay analysis of prepared tablets

Sr.No.	Label claim (µg/mL)		Amount found (µg/mL)		% of label claim	
	RAN	**DOM**	**RAN**	**DOM**	**RAN**	**DOM**
1	5	0.2	5.02	0.199	100.4	99.5
2	5	0.2	4.93	0.198	98.8	98.6
3	5	0.2	4.91	0.199	99.4	99.5
4	5	0.2	5.01	0.202	100.2	101
5	5	0.2	4.99	0.201	98.8	100.5

In-vitro drug release profile of combination tablet and marketed tablet

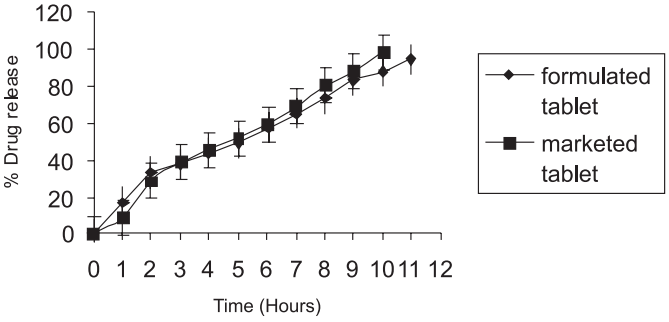

FIGURE 5 - *In-vitro* dissolution for domperidone from formulated and marketed tablet. ◆ Formulated tablet; ■ Marketed tablet

The results show that the formulated tablet released 94.05 % domperidone in 11 hours while the marketed tablet showed 98.24 % domperidone release in 10 hours (Figure 5). Thus, the formulated tablet showed better sustained release of domperidone than the marketed tablet. The f_2 value of the domperidone release from the combination tablet was found to be 83, comparable to the marketed tablet, showing that the formulated tablet had a similar release profile as that of the marketed tablet.

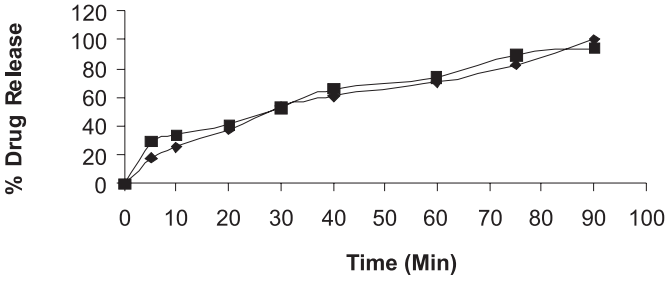

FIGURE 6 - *In-vitro* dissolution for ranitidine HCl from formulated and marketed tablet. ◆ Formulated tablet; ■ Marketed tablet.

In the case of ranitidine hydrochloride formulated tablets, the release was 99.45 % drug in 90 min while the marketed tablet showed 94.43 % ranitidine hydrochloride release in 90 min. Thus, there was no significant difference in release of ranitidine hydrochloride from formulated & marketed tablets. The f_2 value of the ranitidine release from the combination tablet was found to be 58.5, compared to the marketed tablet, showing that formulated tablet had a similar release profile as that of the marketed tablet.

TABLE VI - *Ex-vivo* study for absorption through everted rat intestine

Time (h)	% Drug Absorbed			
	From formulated tablet		From marketed tablet	
	Ranitidine hydrochloride	**Domperidone**	**Ranitidine hydrochloride**	**Domperidone**
0.5	67.23±1.23	24.56±0.68	72.64±0.25	15.20±0.49
1	73.44±0.67	25.68±0.29	77.50±0.65	18.27±0.69
2	81.63±0.72	26.36±0.89	79.71±0.81	27.34±0.83
3	--	32.04±0.78	--	33.46±0.79
4	--	36.83±0.64	--	36.66±0.91
5	--	37.41±0.69	--	38.53±0.48
6	--	37.88±0.73	--	41.16±0.77
7	--	43.45±0.75	--	44.38±0.59
8	--	49.37±0.71	--	49.58±0.82

(Mean ± SD, n=3)

Ex-vivo study for absorption through everted rat intestine

Data presented in Table VI represents the amount of domperidone & ranitidine transported across everted rat intestine, expressed as percent of amount of drugs released *in-vitro* over the time interval. Data suggest that there is no difference in *ex-vivo* drug absorption from marketed and prepared combination tablet.

The data was subjected to paired t test using Instat3.0 software. The mean of the differences between column A and column B was found not to differ significantly from zero. The one-tailed P value was 0.3041, considered non-significant at a 95% confidence interval.

By applying statistical treatment to the above data it was concluded that absorption of ranitidine hydrochloride and domperidone from formulated & marketed tablets did not differ significantly from each other.

CONCLUSION

Gastric acid inhibitors such as ranitidine HCl, and prokinetic agents such as domperidone, are known to enhance gastrointestinal motility and prevent duodenogastric reflux, and are widely used to treat gastro esophageal reflux diseases (GERDs). Hence, a combination of immediate release ranitidine and sustained release domperidone in a unit dosage form will be a useful therapeutic option, enhancing patient compatibility and therapeutic benefit.

Formulated tablet provided pH independent sustained release of domperidone, and fast release of ranitidine. *Ex-vivo* studies suggest that there is no difference in *ex-vivo* drug absorption from marketed and prepared combination tablet.

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