RJC
http://www.rasayanjournal.com

RASĀYAN ***J. Chem.***
Vol.3, No.2 (2010), 368-374
ISSN: 0974-1496
CODEN: RJCABP

FORMULATION AND CHARACTERIZATIOIN OF BILAYER FLOATING TABLETS OF RANITIDINE

P.Dinesh Kumar*, Grace Rathnam[1], C.R. Prakash, G.Saravanan[2], V. Karthick and T. Panneer Selvam

*Department of Pharmaceutics, Rahul Institute of Pharmaceutical Science & Research, Chirala-523157, Andhra Pradesh, India.
[1]Department of Pharmaceutics, C.L.Baid Metha College of Pharmacy, Chennai-600096, Tamil Nadu, India.
[2]Medicinal Chemistry Research Laboratory, Bapatla College of Pharmacy, Bapatla-522101, Andhra Pradesh, India
*E-mail: dineshclbaid@yahoo.co.in

ABSTRACT

The purpose of this study is to prepare a bilayer gastro retentive tablet of ranitidine using direct compression technology and optimize the type and concentration of polymer to give maximum retentive effect with good drug release profile. Ranitidine H_2 receptor antagonist having short biological half life (2-3.5 h), absorption in the initial part of the small intestine and 50% absolute bioavailability of drug favor development of sustained release floating formulation. In this study, a bilayer tablet was prepared which contains an immediate release portion and a floating layer. HPMC-K-100, HPMC-K-4M, HPMC-E-15, CARBOPOL-934 were used as gel forming agents either alone or in combination. Sodium bicarbonate, and citric acid as gas generating agent, lactose as additive combine with the polymer to form the floating layer[1]. The bilayer tablets were characterized by lag time, floating time, weight variation, drug content and dissolution profile. Best Formulation BLF6 [HPMC-K100 (1:1)] shows lag time of 25 s, floating time of 24 h and drug release of 99.85%. The best formulation was taken up for animal studies as approved by Institutional Animal Ethical Committee. The X-ray studies for floating properties of tablet and the *in vivo* bioavailability studies for the formulation was carried out using rabbits which showed a significant increase in bioavailability of drug as compared with conventional dosage forms. The optimized formulation was subjected to stability studies at 40 ± 2^0 and $75 \pm 5\%$ RH for period of three months. Short term stability studies were carried for optimized formulation showed good result.

Key words: Bilayer tablet, Floating tablet, Gastro retentive tablet, Ranitidine tablet.

INTRODUCTION

Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Controlled/sustained release preparations using alternating routes have also been formulated but oral route still remains preferable. In recent years, per oral dosage forms for gastric retention have attracted more and more attention for their theoretical advantage in gaining control over the time and the site of drug release. This would be particularly valuable for drugs that exhibit an absorption window in the upper part of the small intestine. Gastric retention has received significant interest in the past few decades as most of the conventional oral delivery systems have shown some limitations related to fast gastric emptying time[2]. A gastro retentive dosage form (GRDF) can overcome this problem and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments.

The stomach is divided into 3 anatomic regions: fundus, body, and antrum (pylorus). The separation between stomach and duodenum is the pylorus. The part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern

of motility is however distinct for the two states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2–3 h. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases[3,4]-

• Phase I (basal phase) lasts for 40 to 60 min with rare contractions.
• Phase II (preburst phase) lasts for 40 to 60 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
• Phase III (burst phase) lasts for 4 to 6 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
• Phase IV lasts for 0–5 min is a transition period of decreasing activity until the next cycle begins.

Food effects and the complex motility of the stomach play a major role in gastric retention behaviour. Several approaches of non-effervescent and effervescent formulation technologies have been used and patented in order to increase gastric residence time of the GRDF.

The current investigation aims at development of floating bilayer tablets of ranitidine by using a gas generating agent. Ranitidine[5] a potent H_2 receptor antagonist has been a market leader since 1977 for symptoms like erosive esophagitis and active gastric ulcers; until 1988 when proton pump inhibitors (PPI) came to replace it. However, the recent failure of PPIs to prevent night-time gastric acid surge (which is associated with high nocturnal histamine concentration) brings open a new door for delivery of ranitidine at specific times in relation to onset of symptoms. Colonic metabolism is partly responsible for poor bioavailability of ranitidine, thereby, favouring gastro-retentive delivery.

EXPERIMENTAL

Materials:

Ranitidine was obtained as a gift sample from m/s Micro labs pvt. ltd., Hosur Tamilnadu., HPMC-K-100, HPMC-K-4M, HPMC-E-15, CARBOPOL-934 were purchased from Rolex Laboratories Chennai., Sodium Bicarbonate was purchased from S.D. Fine Chemicals Mumbai. Citric acid from Merk India Ltd, Mumbai. Other chemicals used where analytical grade.

Preparation of bilayer floating tablets:

Tablets were prepared by direct compression technology using cadmach single punch machine. Bilayer floating tablets were prepared in two stages. First stage was formulation of floating layer tablets. The drug, polymer, sodium bicarbonate, citric acid and lactose are mixed geometrically and compressed to produce floating layer tablets. Second stage was formulation of bilayer floating tablets. The drug and lactose are mixed separately for immediate release layer. Floating layer was placed in punching die. Then contents of immediate release layer were placed over the floating layer tablet and compressed to produce bilayer floating tablets. The compositions details of Bilayer floating tablets are given in Table-1.

Physical Characterization of the Designed Tablet:

The properties of the compressed matrix tablets, such as hardness, friability, weight variation, and content uniformity were determined using reported procedure. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester. Friability was determined by testing 10 tablets in a Roche friability tester for 4 min at 25 rpm. The weight variation was determined by taking weight of 20 tablets using an electronic balance. The drug content of the manufactured tablets of each batch was determined in triplicate. For each batch 20 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved in water and analyzed after making appropriate dilutions.

***In vitro* Buoyancy Studies:**

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a beaker containing 100mL 0.1N HCl and the time required for the tablet to rise to the surface and float was determined as floating lag time[6, 7].

***In vitro* Dissolution Studies:**

The *in vitro* release rate of ranitidine from floating tablets (n = 3) was determined using *United States Pharmacopeia (USP)* 24. Dissolution testing apparatus 2 (paddle method)[8]. The dissolution test was performed using 900 mL of 0.1N HCl, at 37 ± 0.5^0 and 75 rpm. A sample (10 mL) of the solution was withdrawn from the dissolution apparatus at specified time intervals and the samples were replaced with 10ml of fresh dissolution medium. The samples were filtered through a 0.45-µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 315 nm using a Shimadzu UV-1601 UV/Vis double-beam spectrophotometer (Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

***In vivo* X-Rays Studies:**

An *in vivo X-rays study* was approved by the Institutional Animal Ethical Committee [reference no. IAEC xvi\02\CLBMCP\2006-2007]. The floating property of the selected BLF tablets was studied by X-ray technique. Male rabbits with weight of 1.5 kg and with age of 12 months were selected. The animal was housed individually under environmental condition (25^0, 12 h light and dark cycle). The rabbit was fasted 36 h and allowed free accesses to water only. The rabbit was administrated with best formulation (BLF6). The tablet was administered orally by placing them in hollow polyethylene tube. The tube was inserted into the mouth of rabbit and blown using rubber bulb. X-rays were taken at interval of 30 min,3 h and 5 h.

***In vivo* Bioavailability studies:**

An *in vivo* bioavailability studies[9] approved by Institute of Animal Ethical Committee [Protocol approval No.IAEC xvi\02\CLBMCP\2006-2007]. The bilayer floating formulation BLF6 was selected for *in vivo* studies. Male rabbits with weight of 1.5 kg and with age of 12 months were selected. Total 9 rabbits were divided into 3 groups. Each group had 3 rabbits. The animals were housed individually under environment conditions (25^0, 12 h light and dark cycle). The rabbits were fasted overnight and allowed free accesses to water only. Best formulation (BLF6) was administered orally by placing the tablet in a hollow polyethylene tube. The tube was inserted into the mouth of rabbit and blown using rubber bulbs. Marketed ranitine tablet of 150 mg (Rantac) were selected. Ten tablets were taken and powdered 165.64 mg of powder equivalent to78.95 mg of ranitidine were dispersed in 1% sodium carboxy methyl cellulose. The suspension was administered orally to the rabbits by gastric intubation method. Ranitidine intravenous injection of marketed product (Rantac) of dose 1.2 mg was administered by I.V route to the rabbits. Blood samples of 1 mL were withdrawn at specific time interval for bilayer tablet and marketed tablet. For intravenous injection the blood samples of 1 ml were withdrawn at specific time intervals. Blood samples were collected from the marginal vein of the rabbit

HPLC Method[10]:

COLOUMN – C_{18} ODS (octyl decyl silane) hypersil stainless steel coloumn as stationary phase. Mobile Phase – A degassed mixture of 75 volumes of Acetonitrile and 25 volumes of buffer solution was used as mobile phase with flow rate of 1 mL/min. Plasma samples of 0.5 ml were separated and 0.5 mL of 5N sodium hydroxide and 3N sodium chloride was added. The samples were mixed thoroughly for 1 min. Then 8 mL of diethyl ether was added and stirred for 1 min and the samples were centrifuged at 3000 rpm for 10 min. The organic layer was separated and evaporated to dryness at 60^0. The dry residue was rediscovered using 1 mL of mobile phase and injected into the HPLC system. The samples are detected at wavelength of 315 nm. Ranitidine concentration in plasma was calculated.

Stability Studies:

The optimized formulation was subjected to stability at 40 ± 2^0C and 75 ± 5 % RH for period of three months. After each month tablet sample was analyzed for physical characteristics and drug release profile.

RESULTS AND DISCUSSION

The physical characteristics of BLF tablets (BLF1 to BLF11) such as tablet size, hardness, friability and weight variation were determined and the results are shown in Table-2. The hardness of the formulations satisfied the acceptance criteria. The friability and weight variation was found to be within the limits specified in Pharmacopoeia. The drug content was found spectrophotometricaly for all the formulations

(BLF1 to BLF11). The values are shown in Table-2. The drug content was found to be within a narrow range as specified in Pharmacopoeia (90 - 110%) in all formulations. Buoyancy lag time and duration of floating were determined using 100 mL beaker containing 0.1N HCl medium are shown in Table-2. The Bilayer floating formulations BLF1 to BLF11 were subjected for the dissolution studies using USP dissolution apparatus 2 (paddle) in 900 mL of 0.1N HCl medium. Average value were obtained from the triplicate values and taken as the final value. The results are given in Figures 1and 2. The formulation BLF6 showed a constant rate of release in a sustained manner similar to zero order kinetics with good buoyancy property. Hence BLF6 was chosen as the best formulation. Best formulation (BLF6) was subjected to *in vivo* X-rays studies in the rabbit. Floating property was determined by X-rays studies and the results showed that the tablet floated for 5 h and shown in Figures 4 t0 6.The best formulation (BLF6) was subjected to *in vivo* bioavailability in the rabbits. In the bioavailability studies, the best formulation (BLF6) was compared with marketed formulation (Rantac) and intravenous solution (Rantac). Results of Bilayer Floating tablets (BLF-6) were determined by HPLC which showed increased bioavailability for the bilayer floating formulation. The results are shown in Figure 3. Best formulation (BLF-6) was subjected to stability study and results are given in Table-3. From the results it was observed that there was no significant change in physicochemical properties and release profile after the storage at 40^0 for three months. It may be inferred that there was no degradation and change in the release system.

CONCLUSIONS

The present work was to produce bilayer floating tablet of ranitidine with good sustained release profile and increased bioavailability. The tablets were obtained by direct compression for all the formulations BLF1 to BLF11 and evaluated for the buoyancy lag time and floating time, hardness, weight variation and drug content. Based on the performance with respect to buoyancy lag time, floating time and the release characteristics, the formula (BLF6) was selected as the best formula (Prototype formulation) as it showed a buoyancy time 25 s and a floatation time of 24 h. This formulation (BLF6) showed a sustained release rate throughout its release period. *in vivo* bioavailability and X- ray's studies has showed the dosage form had better bioavailability compared with marketed products and good floating property. It may be concluded that bilayer floating ranitidine tablets by direct compression technology had shown good floating property and sustained drug release characters However; it needs further *in vivo* studies to show how bilayer floating dosage forms act in fed state. More clinical trials and statistical data are required for the bilayer floating dosage forms to enter the pharmaceutical market.

REFERENCES

1. S.A. Ekheshen, A.E. Yasin, S. Aiswayeh and F.A. Alkhaled, *Pharm. Ind.* ,**66(11)**,1364(2004).
2. N. Ozdemir, S. Ordu, and Y. Ozkan, *Drug Dev.Ind. Pharm.*,**26(8)**, 857(2001).
3. W.L.Xu, X.D. Tu and Z.D.Cu, *ACTA. Pharm.*, **26**, 541(1991).
4. B.M.Regmi, J.P.Liu, and X.D. Ju, *ACTA. Pharm.*,**31**, 54(1996).
5. A.B. Daves, A.F. Amin and M.M. Patel, *Pharma. Sci.Tech.* ,**5(2)**,article 34(2004)
6. Y. Diao, and X.D. Tu, ACTA. Pharm., **26**, 695(1991).
7. S. Baumgartner, J. Kristel, F. Vreer, P. Vodopivec, and B. Zorko, *Int. J. Pharm.*, **95**, 125(2001).
8. R. Ziyauk, A. Mushir, and K.K. Khan, *ACTA. Pharm.*,**56**, 49(2006).
9. S. Desai, and S. Balton, *Pharm. Res.*,**10**, 1321(1993).
10. M.A.Campanero, A. Lopezocariz, E. Garicia Quetglas, B. Sadaba, and A. Delamaza, *Chromatographia*., **47**, 391(2006).

Table-1: Composition of BLF Tablets of Ranitidine (BLF1 to BLF11)

S.No	Ingredients	BLF 1	BLF 2	BLF 3	BLF 4	BLF 5	BLF 6	BLF 7	BLF 8	BLF 9	BLF10	BLF11
Floating layer												
1.	Ranitidine	120	120	120	120	120	120	120	120	120	120	120
2.	HPMC K-100	75	100	112.5	75	75	150	100	112.5	-	100	112.5
3.	HPMC K – 4M	75	50	37.5	-	-	-	-	-	-	50	-
4.	HPMC E – 15	-	-	-	75	-	-	-	-	-	-	37.5
5.	Carbopol 934	-	-	-	-	75	-	50	37.5	150	-	-
6.	Sodium Bicarbonate	25	25	25	25	25	25	25	25	25	25	25
7.	Citric Acid	25	25	25	25	25	25	25	25	25	25	25
8.	Lactose	20	20	20	20	20	20	20	20	20	20	20
Immediate Layer												
1.	Ranitidine	30	30	30	30	30	30	30	30	30	30	30
2.	Lactose	10	10	10	10	10	10	10	10	10	10	10

Table-2: Physicochemical Characterization of BLF Tablets Ranitidine (BLF1 to BLF11)

S.No	Evaluation parameters	BLF1	BLF2	BLF3	BLF4	BLF5	BLF6	BLF7	BLF8	BLF9	BLF10	BLF11
1.	Thickness (mm)	7.61± 0.035	7.57± 0.084	7.63± 0.041	7.60± 0.070	7.62± 0.049	7.59± 0.074	7.63± 0.063	7.62± 0.038	7.58± 0.068	7.59± 0.053	7.60± 0.073
2.	Weight variation (%)	380± 0.50	370± 0.70	382± 0.80	376± 1.20	374± 0.50	382± 1.50	370± 1.04	372± 0.80	375± 0.50	371± 1.40	385± 1.80
3.	Hardness (kg/cm^2)	2.5± 0.165	3.0± 0.170	2.5± 0.196	2.5± 0.160	7.0± 0.165	2.5± 0.153	7.0± 0.098	2.5± 0.172	7.5± 0.333	2.5± 0.123	2.5± 0.140
4.	Drug content (mg/tablet)	106.66±0.702	104.48 ±0.953	93.60± 0.495	90.46± 0.424	96.40± 0.636	109.46 ±0.832	94.34± 0.346	103.96 ±0.141	110.12 ±0.534	91.38± 0.707	98.24± 0.278
5.	Friability (%)	0.90± 0.05	0.74± 0.06	0.91± 0.04	0.95± 0.07	0.06± 0.03	0.90± 0.02	0.44± 0.08	0.51± 0.05	0.05± 0.04	0.89± 0.07	0.93± 0.04
6.	Buoyancy lag time (s)	60.2± 2.5	95.4± 3.2	105.3± 4.0	45.2± 2.1	145.9± 2.8	25.1± 1.5	285.7± 3.2	211.3± 4.1	1060.8 ±3.4	60.6± 2.2	65.4± 3.2
7	Total buoyancy time (h)	>24	>24	>24	>24	>24	>24	>24	>24	4± 0.317	>24	>24
All values are mean ± S D of three determinations												

Table-3: Stability Studies of Optimized BLF Tablet (BLF6) of Ranitidine

Characteristic	15 days	1 month	2 months	3 months
Physical appearance	Off white, smooth, flat faced	Off white, smooth, flat faced	Off white, smooth, flat faced	Off white, smooth, flat faced
Hardness (kg/cm^2)	2.5±0.165	2.5±0.170	2.5±0.196	2.5±0.333
Drug content (mg/tablet)	109.46±0.832	109.10±0.946	108.52±1.084	107.22±1.832
Buoyancy lag time (s)	25.1±1.5	26.4±3.4	26.8±2.8	27.2±2.3
Total buoyancy time (h)	>24	>24	>24	>24
In vitro drug release	99.41±0.70	98.56±0.20	97.35±0.68	97.10±0.70

All values are mean ± S D o f three determinations

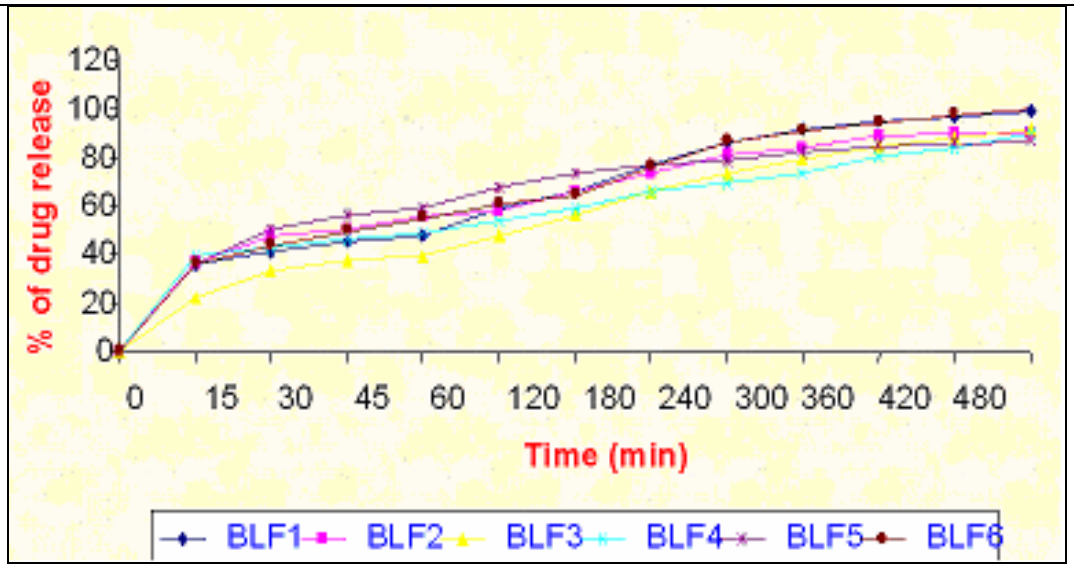


Fig.-1: *In vitro* dissolution of BLF1 to BLF6 tablets

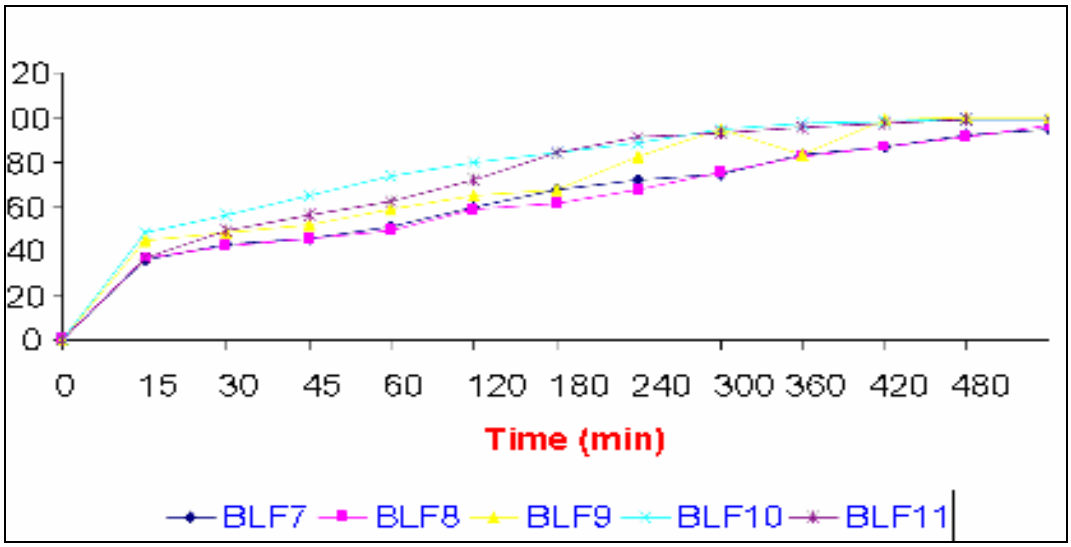


Fig.-2: *In vitro* dissolution of BLF7 to BLF11 tablets

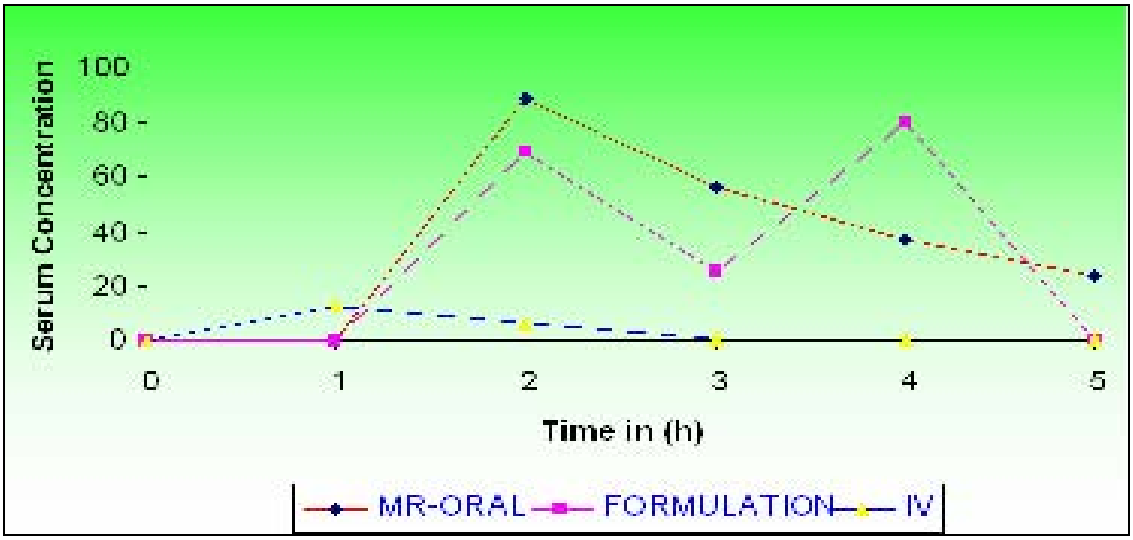
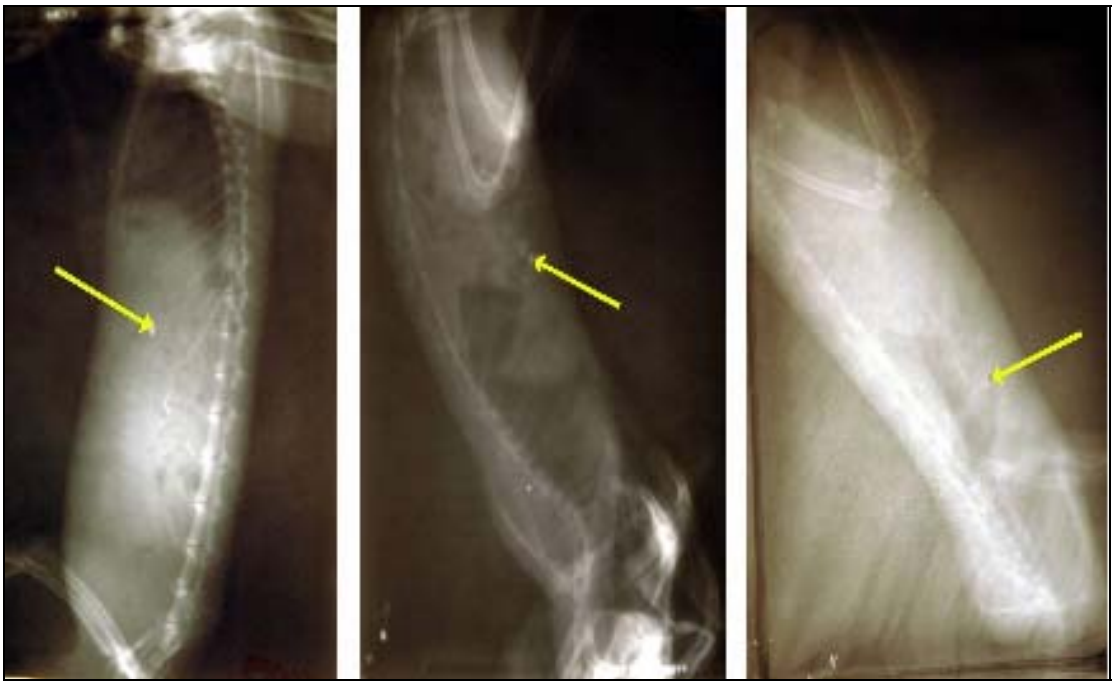


Fig.-3: *In vivo* Bioavailability studies



X-Ray Studies

Fig.-4: After 30 mins. Fig.-5: After 3hrs. Fig.-6: After 5hrs.

(Received: 31May 2010 Accepted: 9 June 2010 RJC-568)