International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.2, No.2, pp 1163-1169, April-June 2010

Formulation and Characterization of Ranitidine Hydrochloride Fast Disintegrating Tablets

V.S. Mannur*, S.S. Karki, Ketan B. Ramani

*[1]Department of Pharmaceutics K. L. E. University's college of Pharmacy, Belgaum,Karnataka, India

[2]Department of Pharmaceutical Chemistry K. L. E. University's college of Pharmacy, Bangalore, Karnataka, India

*Corres.author: vinodhmannur@yahoo.com
Tel.no- 0831-2471399

ABSTRACT: Fast dispersible tablets disintegrate either rapidly in water, to form a stabilized suspension, or disperse instantaneously in the mouth to be swallowed without the aid of waters. A direct compression method was used to prepare these types of tablets using different super disintegrants viz. sodium carboxy methyl cellulose (SMC), pregelatinised starch and sodium starch glycolate (SSG). Mannitol was employed to improve the mouth feel and aspartame to improve the taste. The formulations were evaluated for both precompression and post compression parameters. The tablets showed satisfactory hardness and the drug content were also found to within the IP range for all the formulations. The tablets disintegrated within 19 to 22 seconds and wetting time of the tablets was found to be between 17 to 20 seconds. The formulation containing SMC showed a superior organoleptic properties along with and excellent in vitro drug release and dispersion time.

Key words: Fast disintegrating tablets, super disintegrants, Ranitidine Hydrochloride

INTRODUCTION

Recent advances in novel drug delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for administration. Difficulty in swallowing experienced by patients such as pediatrics, geriatrics, bedridden, disabled and psychiatrics, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of noncompliance and ineffective therapy. To improve the quality of life and treatment compliance of such patients, orally disintegrating or fast disintegrating tablets (FDT) dosage form is a better alternative for oral medication. FDTs are solid dosage form containing medicinal substances, which disintegrants rapidly, usually within matter of seconds when placed in upon tongue requiring no additional water to facilitate swallowing. FDTs can be prepared by different methods such as direct compression, wet granulation, spray drying, freeze drying, and sublimation method.[1-4]

Ranitidine hydrochloride, an H_2 receptor antagonist competitively inhibits the interaction of histamine with its receptors. The drug inhibits gastric acid secretion elicited by histamine and other H2 antagonists in a dose dependent, competitive manner; the degree of inhibition parallels the concentration of the drug in plasma over a wide range. It is used in the treatment of duodenal and gastric ulcer.[5-7]

The objective of this study was to enhance safety and efficacy of drug molecule, achieve better compliance, solve the problem of difficulty in swallowing, improve onset of action, and provide stable dosage form.

MATERIAL AND METHODS

Ranitidine HCl was provided as a gift sample by Strides Research pharmaceuticals, Bangalore, Mannitol was obtained from Ranbaxy Fine-Chem. Ltd,

Delhi, Magnesium stearate and Sucralose was purchased from Loba chemie Pvt. Ltd., Mumbai. Microcrystalline cellulose, Sodium carboxy methyl cellulose, Pregelatinized starch, Sodium starch glycolate and Colloidal silicon dioxide were obtained from Micro Labs Pvt. Ltd., India. All other chemicals were of analytical grade.

A. PREPARATION OF THE FAST DISINTEGRATING TABLET OF RANITIDINE HCL [8, 9]

Accurately weighed quantities of Ranitidine (RA), mannitol, aspartame and microcrystalline cellulose were mixed and passed through sieve no. 60. The blend was suspended in 100% of iso-propyl alcohol (IPA) for the period of 10 minutes, homogenously mixed by using normal mortar and pestle and granulation process was further carried out for the period of 15 minutes and passed through sieve no 50. The granules were dried at 40° C for 30 minutes in controlled humidity chamber. The obtained dry granules were regranulated by passing through a sieve no 40. The granules obtained were homogenized with microcrystalline cellulose and sodium carboxy methyl cellulose/pregelatinized starch/sodium starch glycolate and a mixture of magnesium stearate and colloidal silicon dioxide. The homogenized mixture was subjected for direct compression to produce 150 mg and 300 mg tablets by using Rimek 10 Station Press. The tablets obtained were containing 75 mg and 150 mg of ranitidine, respectively. The RA and composition of the ingredients are shown in Table 1.

B. EVALUATION OF THE TABLETS

1. PRECOMPRESSION PARAMETERS [10]

The static angle of repose was measured according to the fixed funnel and free standing cone method. The flowability of the mixed powder was calculated by determining the Hausner's ratio and Carr's index from poured and bulk densities of a known weight of sample using measuring cylinder and following formula Hausner's ratio=$D_p \div D_t$. Carr's Index % = $[(D_p–D_t)\div D_p]X$ 100, where D_p = poured density, D_t = tapped density.

2. POST COMPRESSION PARAMETERS

a) Measurement of the tablet tensile strength and friability [10, 11]

Uncoated tablets were examined under a lens for the shape of the tablet and color was observed by keeping the tablets in light. Thickness and diameter were measured using a calibrated dial caliper. Six tablets of each formulation were picked randomly and dimensions were determined. Hardness of tablets was examined using a hardness tester to measure the crushing strength of the tablets (Monsanto Hardness tester, Bombay). The mean hardness was calculated and expressed as Kg/cm^3. The friability of tablets was determined using Roche Friabilator (USP) at 25rpm for 4 minutes. It is expressed in percentage (%).

b) Drug content uniformity [11-14]

Tablet containing 75mg and 150mg of drug is dissolved in 100ml of simulated gastric fluid (SGF) pH 1.2. The drug is allowed to dissolve in the solvent, the solution was filtered, and 1ml of filtrate was suitably diluted with phosphate buffer pH 1.2 and analyzed spectrophotometrically at 225nm. The amount of ranitidine was estimated by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each batch of formulation.

c) Wetting time and Water absorption ratio [2, 4]

The tablet was placed in a Petri dish having a 6.5cm in diameter, containing 10ml of water and the time for complete wetting was recorded. The experiment was carried out in triplicate at room temperature. Water absorption ratio was calculated by keeping the tablet on a piece of tissue paper folded twice in a small Petri dish containing 6ml of distilled water. Time for complete wetting of tablet was recorded. The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation, $R = 10 \times [(W_a–W_b) \div W_b]$, Where, W_b = weight of the tablet before water absorption and W_a = weight of the tablet after water absorption.

d) In vitro disintegration time [10, 11]

Tablet disintegration was carried by placing one tablet in each tube of the basket and top portion of the each tube was closed with disc and run the apparatus containing pH 1.2 SGF (simulated gastric fluid) maintained at 37 ± 2^0C as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. The experiment was carried out in triplicate.

e) In vitro dissolution studies [10, 11]

The dissolution test was performed in triplicate by a dissolution test apparatus USP XXIII (Electrolab-Tablet Dissolution Tester) in 900ml of simulated gastric fluid pH 1.2 medium and at 37 ± 1^0C. The rotation speed was 50 rpm. 5 ml samples were withdrawn at 5min, and 5ml of the medium at the same temperature were added in. Samples were assayed at 225nm. Experiment was carried in triplicate.

f) Mouth feel and in vivo disintegration time [1]

To know the mouth feel, taste and disintegration of the tablets, selected formulations

were given to six healthy human volunteers, whose informed consent was first obtained and recorded, were selected for the study. The mouth feel, taste and disintegration was evaluated.

g) Stability Study [10,16,17]

The purpose of stability testing provides evidence on how the quality of the drug substance varies with time under the influence of variety of environmental factors such as temperature, humidity, and light, and enables recommended storage conditions, re-test periods and shelf lives to be established. In the present study, stability studies were carried out at 25^0C/60% RH and 40^0C/75% RH for a specific time period up to 30days for selected formulations

RESULTS AND DISCUSSION

1. PRECOMPRESSION PARAMETERS

Granules ready for compression containing drug and various excipients were subjected for pre-compression parameters (Micromeritic properties) to study the flow properties of granules, to achieve uniformity of tablet weight. The data obtained for angle of repose for all the formulations were tabulated in Table No. 2 and the values were found to be in the range of 26°21' to 31°15'. All the formulations showed the angle of repose less than 30°, which reveals good flow property. Loose bulk density (LBD) and tapped bulk density (TBD) for the blend is shown in Table No. 2. The loose bulk density and tapped bulk density for all the formulations blend varied from 0.482 gm/cm^3 to 0.645 gm/cm^3 and 0.573 gm/cm^3 to 0.754 gm/cm^3 respectively. The results of Carr's consolidation index or compressibility index (%) for all the formulations blend ranged from 12.53 to 17.25. The granules had shown excellent compressibility index values up to 15% result in good to excellent flow properties. The results for all the formulations were recorded in Table No. 2.

2. POST-COMPRESSION PARAMETERS

The tablets prepared by direct compression by liquid comprising granulating method were subjected for evaluation according to various official specifications and other parameters. Shape, thickness, hardness, friability, weight variation, wetting time, *in vitro* water absorption ratio, drug content, disintegration time, *in vitro* dissolution studies, *in vivo* taste, mouth feel, and disintegration were performed. Formulations prepared were randomly picked from each batch examined under lens for shape and in presence of light for color. Tablets showed flat, circular shape and white in color. Thickness of the tablets was measured by dial caliper by picking tablets randomly from all the batches. The results of thickness for tablets were shown in Table No.3. The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 2.10±0.002 to 2.12±0.006 and 2.59±0.005to 2.70±0.005mm, respectively. The standard deviation values indicated that all the formulations were within the range. The hardness of the tablets was found in the range of 4.29±0.25 to 4.55±0.25 and 4.45±0.21 to 4.79±0.18 Kg/cm3, respectively. The mean hardness test results are tabulated in Table No. 3. Friability of the all the formulation was in the range of 0.212±0.044 to 0.347±0.016 and 0.228±0.081 to 0.312±0.075%, respectively. The obtained results were found to be well within the approved range (<1%) in all designed formulations. The results are shown in Table No.3.The content uniformity was performed for all the formulations and results are tabulated in Table No.3. The drug content was found to be 97.983±0.17 to 99.466±0.24 %. The results were within the range and that indicated uniformity of mixing of the drug with excipients in the developed formulations. The weight variation for all the formulations is shown in Table No.3. All the tablets were passed weight variation test, average percentage weight variation was found within the pharmacopoeial limits of ±10%. The obtained results were found to be 147.45±1.2 to 151.03±0.9 and 296.80±1.0 to 300.03±0.1%, respectively.

In vitro disintegration time

The disintegration time recorded of all the formulation found in the range of 14.46±0.06 to 19.67±0.01 and 18.15±0.05 to 22.28±0.09 seconds, respectively. All the formulations are disintegrated less than 21 seconds. The results are shown in Table No. 3 and figure 3.

Wetting time and Water absorption ratio

Wetting time of all the formulations recorded was found to be 17.58±2.16 to 20.98±1.85 and 19.98±1.35 to 23.72±1.63, seconds, respectively. The result of wetting time is shown in Table No 3. Wetting time is closely related to the inner structure of the tablet. The obtained results mimic the action of saliva in contact with the tablet to illustrate the water uptake and subsequent wetting of the tablet. The wetting process was very rapid in all the formulations. This phenomenon may be due to ability of swelling and also capacity of water absorption and cause swelling. The hydration studies demonstrated that all tablets were characterized by very similar hydration profiles. They hydrated quickly and showed high hydration percentage 65.69±2.28 to 68.85±3.18 and 68.14±3.15 72.83±2.35 in 15 seconds. Tablet hydration capacity is a very important parameter in the design of a new drug fast disintegrable dosage forms because of a strict relationship between water absorption and the drug release mechanism. The obtained results are shown in Table No. 3 and figure 3

In vitro dissolution studies

All the formulations were subjected for *in-vitro* dissolution studies. *In-vitro* release profiles of the ranitidine formulation were shown in Fig.1&2. All the formulations showed rapid drug release 89.63±1.9 to 96.28±3.4 and 91.51±4.6 to 95.86±3.2 %, respectively. The fast dissolution might be due to the presence of super disintegrated agents used in the formulations which enhanced the immediate particulates of the granules and rapid absorption of water.

Mouth feel and in-vivo disintegration

The selected formulation subjected human volunteers to evaluate the taste, mouth feel and in vivo disintegration time. Results showed that, volunteers felt good taste, mouth feel and tablets disintegration time was found to be 17.35±0.02 to 21.67±0.05 and 20.86±0.08 to 24.76±0.05 seconds. In the formulations, the bitter taste of ranitidine and mouth feel was enhanced by adding sweeteners like sucralose and mannitol. The results are shown in Table No. 3 and figure 3.

Stability study

The formulation RA3, RA4, RA6, RA8, and RA10 were selected for stability studies on the basis of high cumulative % drug release and also result of in vitro disintegration time and in vivo dispersion studies. These were stored at 25^0C/60% RH and 40^0C/75% RH. For every 10 days time interval the tablets were analyzed for drug content uniformity, hardness, disintegration time, and friability up to 30 days. These formulations showed not much variation in any parameter. The results indicated that formulations RA3, RA4, RA6, RA8, and RA10 are stable and retained their original properties.

CONCLUSION

From the present study it can be concluded that direct compression is a better technique to prepare fast dissolving tablets. The prepared tablets showed a better disintegration time both in vitro and in vivo and also almost 80% of the drug was released from all formulation within the 15 minutes. Thus a stable, effective, and fast dissolving dosage form has been developed with good balance between mechanical strength and disintegration time.

Table 1: Composition of Ranitidine fast dissolving tablets

Ingredients	Quantity (mg)											
	RA1	**RA2**	**RA3**	**RA4**	**RA5**	**RA6**	**RA7**	**RA8**	**RA9**	**RA10**	**RA11**	**RA12**
Ranitidine HCl	84	84	84	84	84	84	168	168	168	168	168	168
[1]MCC	50.55	44.55	50.55	44.55	50.55	46.55	101.10	89.10	101.10	89.10	101.10	89.10
Sucralose	0.3	0.3	0.3	0.3	0.3	0.3	0.6	0.6	0.6	0.6	0.6	0.6
Mannitol	7.5	7.5	7.5	7.5	7.5	7.5	15.0	15.0	15.0	15.0	15.0	15.0
[2]SMC	6.0	12.0	--	--	--	--	12.0	24.0	--	--	---	--
[3]PGS	--	--	6.0	12.0	--	--	--	--	12.0	24.0	--	--
[4]SSG	--	--	--	--	6.0	12.0	--	--	--	--	12.0	24.0
[5]MGST	1.5	1.5	1.5	1.5	1.5	1.5	3.0	3.0	3.0	3.0	3.0	3.0
[6]CSD	0.15	0.15	0.15	0.15	0.15	0.15	0.3	0.3	0.3	0.3	0.3	0.3
Total	150	150	150	150	150	150	300	300	300	300	300	300

Ranitidine hydrchloride 84 mg is equivalent to 75 mg of ranitdine

Ranitidine hydrchloride 168 mg is equivalent to 150 mg of ranitdine

[1]MCC- Microcrystalline cellulose, [2]SMC- Sodium carboxy methyl cellulose, [3]PGS-pregelatinized starch, [4]SSG- Sodium starch glycolate, [5]MGST- Magnesium Stearate, [6]CSD – Colloidal silicon dioxide

Table 2: Evaluation of Mixed Blend of Drug and Excipients

Formulations	Angle of Repose (θ)	Loose Bulk Density (gm/cm^3)	Tapped Bulk Density (gm/cm^3)	% Compressibility
RA1	26° 28	0.499	0.573	12.90
RA2	27° 51’	0.567	0.738	12.59
RA3	26° 21’	0.629	0.695	15.73
RA4	29°27’	0.587	0.670	14.66
RA5	30° 61’	0.521	0.591	13.75
RA6	33° 15’	0.620	0.665	12.53
RA7	29° 32’	0.645	0. 687	16.32
RA8	28° 47’	0.591	0.754	17.25
RA9	27° 55’	0.566	0.692	15.47
RA10	29° 38’	0.571	0.659	15.55
RA11	27° 35’	0.499	0.573	14.86
RA12	27° 61’	0.588	0.651	15.12

Fig. 1&2: In-vitro drug release profile of Ranitidine fast disintegrating Tablets

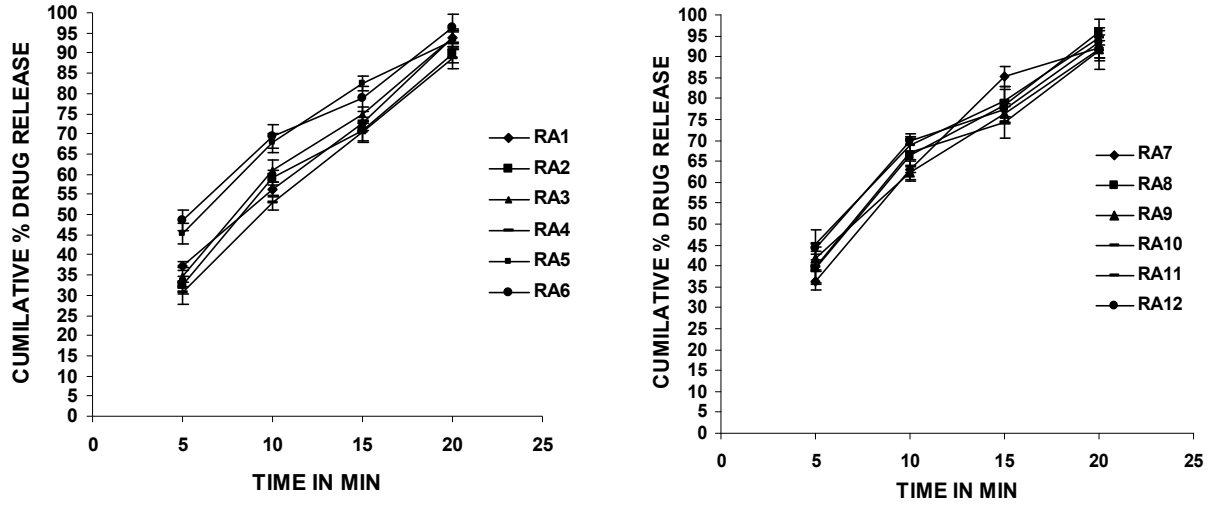
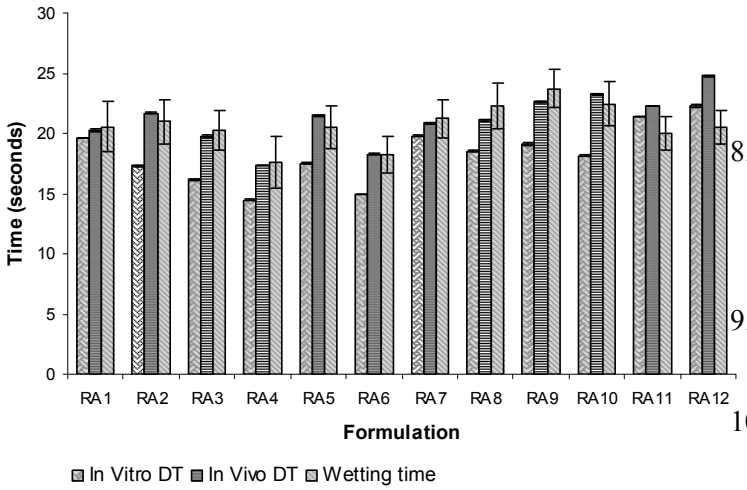


Table 3: Characterization of Ranitidine HCl Fast disintegrating Tablets

FMC	Thickness (mm)	Hardness (Kg/cm^3)	Friability (%)	Drug content (%)	Weight variation	In vitro DT (Sec)	Wetting Time in (Sec)	Water Absorption Ratio	In vivo DT (Sec)	Mouth Feel
RA1	2.10±0.002	4.29±0.25	0.226±0.024	98.174±0.21	149.16±1.0	19.67±0.01	20.56±2.13	68.34±2.32	20.25±0.08	+
RA2	2.11±0.003	4.53±0.23	0.323±0.023	99.466±0.24	151.03±0.9	17.33±0.07	20.98±1.85	65.69±2.28	21.67±0.05	+
RA3	2.10±0.008	4.47±0.29	0.212±0.044	99.405±0.18	148.60±0.8	16.14±0.04	20.24±1.69	66.25±4.15	19.74±0.08	+
RA4	2.12±0.006	4.46±0.15	0.347±0.016	98.308±0.17	149.80±0.9	14.46±0.06	17.58±2.16	66.15±2.12	17.35±0.02	+
RA5	2.11±0.002	4.55±0.25	0.279±0.041	98.967±0.14	150.01±0.1	17.53±0.04	20.56±1.78	68.85±3.18	21.51±0.06	+
RA6	2.10±0.005	4.34±0.18	0.256±0.033	97.983±0.17	147.45±1.2	14.89±0.01	18.28±1.53	67.66±3.22	18.25±0.06	+
RA7	2.70±0.008	4.75±0.14	0.269±0.047	99.008±0.16	298.60±1.3	19.78±0.08	21.21±1.61	68.14±3.15	20.86±0.08	+
RA8	2.68±0.002	4.72±0.28	0.312±0.075	98.709±0.13	300.03±0.1	18.53±0.09	22.27±1.86	69.78±4.53	21.12±0.07	+
RA9	2.59±0.005	4.54±0.13	0.284±0.013	99.004±0.11	298.06±0.5	19.11±0.07	23.72±1.63	70.91±2.65	22.63±0.06	+
RA10	2.66±0.001	4.77±0.25	0.255±0.066	99.008±0.11	297.98±0.7	18.15±0.05	22.45±1.87	71.49±2.88	23.23±0.01	+
RA11	2.68±0.002	4.79±0.18	0.228±0.081	99.109±0.10	297.87±0.9	21.39±0.04	19.98±1.35	72.83±2.35	22.28±0.03	+
RA12	2.70±0.005	4.45±0.21	0.252±0.040	99.110±0.10	296.80±1.0	22.28±0.09	20.51±1.39	69.61±2.58	24.76±0.05	+

FMC-Formulation code**, DT**- Disintegration**, '+'** good palatable mouth feel, **'-'** poor palatable mouth feel
All values are indicated as Mean ± S.D (n=3).

Figure 3: Comparative profiles In Vtro DT, InVivo DT and Wetting time of all the formulations



REFERENCES

1. Amin, P. Gupta, S. Prabhu, N. Wadhwani, A. Fast disintegrating dosage form of ofloxacin and metronidazole benzoate. Indian Drugs 2005; 42(9): 614-7.
2. Mishra, D. N. Bindal, M. Singh, S.K.Vijay Kumar, S. G. Spray dried excipients base: A novel technique for the formulation of orally disintegrating tablets. Chem. Pharm. Bull. 2006, 54(1), pg no.: 99-102.
3. Schnidt, P. Simone, S. Fast dispersible ibuprofen tablets. Eur J Pharm Sci 2002; 15: 295-305.
4. Sharma, S.G. Gupta, D. Formulation and characterization of fast dissolving tablet of Promethazine theoclate. Asian j. pharm., 2008. pg no.: 70-72
5. Hoogerwerf, W.A. Pasricha, P.J. Agents used for control of gastric acidity and treatment of peptic ulcers and gastrooesophageal reflux disease. In; Hardman JG, limbird LE. Editors Godman and gilman's the pharmacological basis of therapeutics. 10th ed. New York, mcgraw-hill, 2001; 1003.
6. Kathleen parfitt K. Maritndale-The complete Drug reference; XXXII ed. 1209-11.
7. Thummel, K.E. Shen, D.D. Design and optimization of dosage regimen: Pharmacokinetic data. In: Hardman, J.G. Limbird, L.E. Editors Goodman and Gilman's the pharmacological basis of therapeutics. 10th ed. New York, mcgraw-hill, 2001; 2001.
8. Abdelbary, G. Prinderre, P. Eouani, C. Joachim, J. Reynier, J.P. Piccerelle, P.H. Preparation of orally disintegrating tablets using a hydrophilic waxy binder. International Journal of Pharmaceutics. 2004; 78: 423-433
9. Fekete, P. Ignacz, K. Szell, S.Z. Gora, L. Palfi, Z. Jambor, I. Unites states patent application. US2050163836A1.
10. Lachman, L. Libermann, H.A. Kanig, J.L. The theory and practice of industrial pharmacy, Varghese Publishing House, 3rd edn; 1991.
11. The United States Pharmacopoeia 24, NF 19, United state pharmacopoeial convention, Rockville, M.D. Asian Edi., 2000: 1462-5, 1913-4.
12. Indian Pharmacopoeia. Minsitry of Health and welfare, Delhi, Controller of publication; 1996, (II), 659-61.
13. Honjec, M. et al. Ranitidine HCl, in Florey K. Analytical Profile of drug substances: New York: American Pharmaceutical association, academic pres 1986; (15): 533-61.
14. Chattaraj, S.C. Das, S.K. Gupta, B.K. Spectophometric determination of ranitdine HCl. Indian drugs. 1989; 26 (7): 365-7.
15. Basit, A. Lacey, L. Colonic metabolism of ranitidine; implication for its delivery and absorption. Int.J. Pharm. 2001; 227: 157-65
16. Malke S, Shidhaye S and Kadam VJ. Formulation and evaluation of Oxcarbezepine fast dissolve tablet. Ind J Pharm Sci.2007; 69:211-14.
17. Natalie MC, Clure. Stability studies in overview of ICH guidelines for drug products. Matrix pharmaceutical Inc. 1992. Available online at http://www.mcclurenet.com.

*****