ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Esomeprazole Enteric Coated Intestinal Fast Dissolving Tablets Compared With Marketed Products

Murali Krishna K *[1], Narisi Reddy P [2], Siva Nageswara Rao T [1] and Koteswara Rao KV [3]

[1] Department of Pharmaceutics, Gautham College of Pharmacy, Bangalore, India
[2] Department of Pharmacognosy, Nalanda Institute of Pharmaceutical Sciences, Sattenapalli, Andhra Pradesh, India
[3] Department of Pharmaceutics, Vishnu College of Pharmacy, Bhimavaram, Andhra Pradesh, India

ABSTRACT

Intestinal fast dissolving Esomeprazole tablets were formulated to get resistance from gastric juice in the presence of stomach because of Esomeprazole is degraded immediately in stomach/gastric juice. The tablets were prepared by direct compression technique using the super disintegrating agents like Crospovidone, Croscarmellose Sodium, Pre-gelatinized Starch, sodium bicarbonate and excipients are Mannitol in different ratios. These super disintegrates and excipients are used for the intestinal fast releasing of dose and the enteric coating solution was prepared by Acryl-EZE, Eudragit-L100-55. Pre-post compression parameters were conducted for prepared intestinal fast dissolving tablets.

Keywords: Esomeprazole magnesium, Direct compression, Enteric coated, Intestinal fast dissolving.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

One of the challenges in pharmaceutical research is site targeted dosage form design for acid liable drugs. These formulation can release active substance in the proximal part of small intestine (duodenum) through the enteric coating to treat bowel diseases by improving the systemic absorption of the drugs, Which are unstable in gastric juice or low P^H conditions, thus must be protected from the gastric acid by the coating with high P^H soluble polymers or aqueous soluble polymers (enteric coated polymers) when given orally. These formulations can administer in the form of enteric coated dosage form. It does not release the active substance until it reaches to the proximal part of small intestine [1-3].

Esomeprazole is s-isomer of omeprazole. It is benzimidazole derivative H_2 receptor blocker. Generally proton pump inhibitors are administered as an inactive prodrug form because these are acid labile drugs. When present in the gastric fluids, the drugs will be degraded so, by enteric-coating to avoid the acid degradation. When the enteric coating formulations are passing through the stomach into the proximal intestine the drug will release immediately in duodenum part of intestine by this formulation. Esomeprazole site of targeting is intestine for treatment of peptic ulcer. Its half-life is 1.2 hours, so when conventional dosage form reaches to the gastric fluids it will degrade by the gastric enzymes that problem is avoiding by the enteric coated formulation [4-6].

MATERIALS AND METHODS

Materials

Esomeprazole magnesium was obtained as gift sample from Stridesarco Lab, Bangalore. Crospovidone, Croscarmellose Sodium, Pre-gelatinized Starch, Sodium bi carbonate, Acryl-EZE and Eudragit L100 were obtained from Dr. Reddy's Lab, Hyderabad. Mannitol, magnesium stearate and talc were purchase from S.D fine chemicals, Mumbai. Potassium di-hydrogen ortho phosphate, di-sodium hydrogen ortho phosphate, concentrated HCl were purchase from E.Merck (India) limited, Mumbai.

Method of preparation:

Drug and all ingredients were accurately weighed as per the table 1, milled and sieved through sieve # 100/120 and then blended. The powder blended was studied for pre-formulation characteristics like angle of repose, bulk density, tapped density, corr's index and Hausner's ratio. The powder blended containing esomeprazole magnesium was compressed into tablets by direct compression technology, using multi station rotatory tablet punching machine (Riddhi 10 stn mini tablet press RDB4-10, Rimek, Ahmedabad, India) using 6mm flat punches at pressure 3-6 kg/cm^2. In each formulation 50 core tablets were prepared. To protect esomeprazole from gastric juice and directly to release in intestinal duodenum the core tablets

were coated with intestinal dissolving enteric coating polymers like Acryl-EZE and Eudragit L100.

Table 1: Composition of Esomeprazole core tablets

S.No	Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	Esomeprazole. Mg	40	40	40	40	40	40	40
2	Crospovidone	50	-	-	25	25	-	20
3	Croscarmellose Na	-	50	-	25	-	25	20
4	Pre-Gelatin Starch	-	-	50	-	25	25	20
5	Sodium bi carbonate	40	40	40	40	40	40	40
6	Mg. Stearate	8	8	8	8	8	8	8
7	Talc	2	2	2	2	2	2	2
8	Manitol	40	40	40	40	40	40	30
Total weight (Mg)		180	180	180	180	180	180	180

Table 2: Composition of enteric coating solution

Ingredients	F1a	F1b	F1c	F3a	F3b	F3c	F7a	F7b	F7c
Acryl-EZE (%w/v)	3	-	1.5	3	-	1.5	3	-	1.5
Eudragit L100-55(%w/v)	-	3	1.5	-	3	1.5	-	3	1.5

Preparation of coating solution

The coating solution was prepared by different concentrations of Acryl-EZE and Eudragit L100-55 in Acetone (shown in table 2). The core tablets were coated with prepared enteric coating polymeric solution by dipping method. The desired tablet coating continued the dipping until to achieve the desired level of coating. The coated tablets were studied for its weight variation, thickness, acid uptake test and in-vitro dissolution studies.

EVALUATIONS

Pre-compression and post compression parameters for the formulated tablets

Bulk density and tapped density was found out using measuring cylinder method. Angle of repose was found out using the fennel method. The dimensional specifications (thickness and diameter) were measured using vernier calipers (Mitutoyo, Japan). Hardness test was performed by using Monsanto hardness tester (Lab tech, India). The friability test was performed using Roche friabilator (Ketan instruments, India). Weight variation study was carried for 20 tablets from each formulation using electronic weighing balance (Citizen, Japan).The assay was performed for the average weight of five tablets and triturating the tablets and taking triturate was equivalent to 100 mg of drug transferred in 100 mL phosphate buffer pH 6.8 solution to the concentration of 1000 µg / mL. 10 mL from this stock solution was taken and diluted to 100 mL with phosphate buffer pH 6.8 solution. Then 20 µg / mL solutions were prepared by taking 2 mL from the above stock solution and diluting to 10 mL. The Absorbance was measured at 301 nm for Esomeprazole magnesium using by UV

ISSN: 0975-8585

Spectrophotometric method (U.V-1800, Shimadzu, Japan). The results were shown in Table 3 and 4 [7-12].

Table 3: Pre-compression parameters for all formulations

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.466 ± 0.002	0.521 ± 0.003	10.54 ± 0.141	1.117 ± 0.002	21.03 ± 0.542
F2	0.457 ± 0.008	0.554 ± 0.002	17.47 ± 0.359	1.211 ± 0.005	27.07 ±0.460
F3	0.455 ± 0.005	0.523 ± 0.005	12.95 ± 0.148	1.148 ± 0.019	25.57 ± 0.260
F4	0.476 ± 0.002	0.536 ± 0.006	11.16 ± 0.340	1.125 ± 0.004	27.93 ± 0.862
F5	0.444 ± 0.006	0.503 ± 0.005	11.46 ± 0.271	1.129 ± 0.003	26.99 ± 0.922
F6	0.441 ± 0.004	0.506 ± 0.006	12.82 ± 0.122	1.146 ± 0.002	26.47 ± 0.731
F7	0.443 ± 0.009	0.502 ± 0.007	11.84 ± 0.142	1.134 ± 0.003	19.46 ± 0.732

Table 4: Post compression parameters for all formulations (core tablets)

Formulation code	Thickness (mm)	Diameter (mm)	Hardness (kg / cm^2)	Friability (%)	Disintegration time (sec)	Drug content (%)
F1	4.134 ± 0.165	5.95 ± 0.008	4.16 ± 0.763	0.677	28.49 ± 3.34	97.34 ± 0.932
F2	4.243 ± 0.124	5.82 ± 0.029	5.14 ± 0.788	0.777	180.4 ± 10.5	91.96 ± 0.827
F3	4.124 ± 0.156	5.98 ± 0.016	4.27 ± 0.404	0.369	33.11 ± 7.74	97.12 ± 0.628
F4	4.363 ± 0.112	5.55 ± 0.011	5.60 ± 0.763	0.587	153.8 ± 18.8	92.29 ± 0.716
F5	4.542 ± 0.111	5.54 ± 0.042	5.23 ± 0.500	0.795	168.2 ± 6.54	98.16 ± 0.829
F6	4.236 ± 0.119	5.86 ± 0.027	5.42 ± 0.529	0.524	142.2 ± 8.29	92.98 ± 0.611
F7	4.152 ± 0.129	5.92 ± 0.019	4.48 ± 0.506	0.505	29.62 ± 4.42	94.11 ± 0.798

Disintegration test

The disintegration test was performed according to I.P. 2007. Six core tablets were placed in alkaline phase consisting the mixed phosphate buffer pH 6.8 that was maintained at 37 ± 0.5 ^oC, the results were shown in table 4 [13-14].

Acid uptake testing

In this method, six enteric coated tablets were weighed individually and place in the disintegration tubes. The disintegration basket was contained 900 mL of 0.1N HCl and performed test upto 2 hrs in acidic medium. The tablets were removed from the disintegration basket then dried with tissue paper and reweighed. The percentage of weight gain was reported as percentage acid uptake. While during this test the tablet was fully disintegrated hence, it counted as 100% acid uptake. In this method has been measured an acid uptake resistance of enteric coating and acid uptake values <5% suggests that the tablets would readily pass the acid phase of the delayed release dissolution testing [15-16]. The results were showed in table 5. The % acid uptake by the tablet was calculated by formula

$$F_A = (T_F - T_I / T_I) \times 100$$

ISSN: 0975-8585

Where,
F_A = percentage of aciduptake,
T_F = final weight of the enteric tablet,
T_I = initial weight of the enteric tablet.

In-vitro release profile for enteric coated Esomeprazole magnesium tablets

The release of Esomeprazole magnesium from enteric coated tablets were determined by using USP type-II dissolution apparatus (USP XXIII dissolution test apparatus - II paddle model, TDL 084, Elctrolab, India) using 900mL of 0.1N HCl for 2 hrs and later the assembly was lifted and the dissolution fluid was replaced with pH 6.8 phosphate buffer solution. The medium was stirred at 50rpm at a temperature of 37 ± 0.5^{o}C. Aliquot of dissolution medium (1 mL) was withdrawn periodically upto complete dissolved hours and replaced with equal volume of fresh medium to maintain the sink conditions.. The absorbance of filtered solution was measured at 301 nm for Esomeprazole magnesium using by UV Spectrophotometric method (U.V-1800, Shimadzu, Japan) and concentration of the drug was determined from standard calibration curve (shown in Table 6) [17].

Table 5: Enteric coated tablets of Esomeprazole magnesium acid uptake study

Formulation code	Initial weight	Final weight	Deviation	Percentage of acid uptake
F1a	198	205	7	3.53
F1b	196	202	6	3.06
F1c	195	203	8	4.10
F3a	205	213	8	3.39
F3b	199	205	6	3.01
F3c	202	210	8	3.96
F7a	194	201	7	3.60
F7 b	201	208	7	3.48
F7c	203	212	9	4.43

Table 6: *In-vitro* drug release of Esomeprazole magnesium enteric coated formulations

Formulation code	Time (min)	%CDR
F1a	150	96.54 ± 0.989
F1b	165	97.86 ± 0.745
F1c	135	95.76 ± 0.894
F3a	150	97.85 ± 0.689
F3b	165	94.89 ± 0.945
F3c	135	96.15 ± 0.654
F7a	150	96.89 ± 0.723
F7b	165	96.54 ± 0.926
F7c	135	97.58 ± 0.758
Marketed product (CESO)	210	89.94 ± 0.851

ISSN: 0975-8585

Table 7: Stability studies at 25 ± 2 °C / 60 ± 5% R.H for formulation F1a, F1b, F1c, F3a, F3b, F3c, F7a, F7b and F7c.

Formulation code	Accelerated stability studies for drug content (%)			
	0 month	1st month	2nd month	3rd month
F1a	97.34 ± 0.932	97.45 ±1.235	97.10 ±1.189	96.98 ±1.402
F1b	97.34 ± 0.932	97.23 ±1.152	97.12 ± 1.745	96.54 ±1.111
F1c	97.34 ± 0.932	97.15 ±1.192	96.89 ±1.169	96.27 ±1.175
F3a	97.12 ± 0.628	96.98 ±1.125	96.56 ±1.851	96.17 ±1.156
F3b	97.12 ± 0.628	96.47 ±1.132	96.23 ±0.963	95.78 ±1.165
F3c	97.12 ± 0.628	96.87 ±1.752	96.46 ±1.678	95.89 ±1.874
F7a	94.11 ± 0.798	93.85 ±1.175	93.69 ±1.745	93.35 ±1.165
F7b	94.11 ± 0.798	93.65 ±1.356	93.37 ±1.547	93.19 ±1.856
F7c	94.11 ± 0.798	93.91 ±1.861	93.64 ±1.171	93.28 ± 1.489

Table 8: Accelerated Stability studies at 40 ± 2 °C / 75 ± 5% R.H for formulation F1a, F1b, F1c, F3a, F3b, F3c, F7a, F7b and F7c.

Formulation code	Accelerated stability studies for drug release from the enteric tablets			
	0 month	1st month	2nd month	3rd month
F1a	96.54 ± 0.989	95.65 ± 1.235	95.21 ±1.802	94.89 ±1.899
F1b	97.86 ± 0.745	97.45 ± 1.560	96.12 ± 1.309	94.16 ± 1.055
F1c	95.76 ± 0.894	95.21 ± 1.485	94.89 ± 1.027	94.87 ± 1.224
F3a	97.85 ± 0.689	96.23 ± 1.864	95.45 ± 1.046	94.56 ± 1.681
F3b	94.89 ± 0.945	94.52 ± 1.356	94.11 ± 1.719	93.78 ± 1.645
F3c	96.15 ± 0.654	96.25 ± 1.356	95.98 ± 1.651	95.46 ± 1.740
F7a	96.89 ± 0.723	96.45 ± 1.894	96.16 ± 1.770	95.87 ± 1.092
F7b	96.54 ± 0.926	96.32 ± 1.756	95.99 ± 1.215	95.44 ± 1.296
F7c	97.58 ± 0.758	96.54 ± 1.764	96.26 ± 1.523	95.94 ± 1.156

Accelerated Stability studies

The stability studies were conducted to investigate the effect of temperature and relative humidity on the drug content and in-vitro drug release of various formulated tablets. The tablet formulations were exposed to a room temperature of 25 ± 2°C and relative humidity 60 ± 5% RH and accelerated temperature 40 ± 2 °C / 75 ± 5% RH. The samples were removed from the stability chamber at end of 1st, 2nd and 3rd month and analyzed for drug content and in-vitro drug release from the tablets. The observations were shown in table 8 and 9 with figures 3 and 4 respectively [18-19].

RESULTS AND DISCUSSION

Pre and post compression parameters of the formulation tablets

The compatibility studies to assess any possible interaction between the drug and excipients were carried out and analyzed using IR for a period of 4 weeks. The observed IR

spectra did not show any alteration in IR peaks, suggesting no possible inter-action between excipients and esomeprazole (Data not shown). Bulk density and tapped density was found out using measuring cylinder method. Angle of repose was measured by funnel method. The dimensional specifications (thickness and diameter) were measured using vernier calipers (Mitutoyo, Japan). Weight variation study was carried for 20 tablets from each formulation using electronic weighing balance (Citizen, Japan). Hardness test was performed using Monsanto hardness tester (Lab tech, India). The prepared core tablets were subjected to disintegration test at pH 6.8. Based on the disintegration test, F1, F3 and F7 formulation were selected for further enteric coating as this had shown minimum disintegration time. The friability test was performed using Roche friabilator (Ketan instruments, India). The assay was performed for the average weight of five tablets and triturating the tablets and taking triturate was equivalent to 100 mg of drug transferred in 100 mL phosphate buffer pH 6.8 solution to the conc. of 1000 µg / mL. From this stock solution10 mL was taken and diluted to 100 mL with phosphate buffer pH 6.8 solution. Then 20 µg / mL solutions were prepared by taking 2 mL from the above stock solution and diluting to 10 mL. The Absorbance was measured by UV Spectrophotometric method at 301 nm (shown in Table 3 and 4).

Acid uptake testing

Esomeprazole magnesium core tablets after enteric coating with acryl EZE and Eudragit L100-55 were studied for acid uptake, to evaluate the efficiency of acryl EZE and Eudragit L100-55 as enteric coating polymer to protect the acid liable esomeprazole in SGF. The results of all core tablet formulations showed acid uptake values in the range of 3.06 to 4.43 % which are less than 5 % indicating significant protection of drug by acryl EZE and Eudragit L100-55 enteric coating. The results were shown in table 5.

In-vitro dissolution Studies

Dissolution rate was studied by using USP type-II apparatus (USP XXIII dissolution test apparatus - II paddle model, TDL 084, Electrolab, India) using 900mL of 0.1N HCl for 2 hrs and 900 mL of phosphate buffer pH 6.8 for 22 hrs as dissolution medium. Temperature of the dissolution medium was maintained at 37 ^{o} ± 0.5 ^{o}C. Aliquots of dissolution medium (1 mL) was withdrawn at every 15 min upto 1 hrs 30 min interval in acidic medium and every 5 min interval in phosphate buffer and replaced with equal volume of fresh medium. The absorbance of filtered solution was measured by UV Spectrophotometric method at 301 nm and concentration of the drug was determined from standard calibration curve (shown in Table 5 and figure 1-4).

Stability studies

Stability studies were performed as per ICH guidelines. Selected formulations of Esomeprazole enteric coated tablets were sealed in self-sealing cover and stored at room temperature (25^{o} ± 2^{o}C / 60 ± 5% R.H) and accelerated temperature 40 ± 2 ^{o}C / 75 ± 5% RH for a

ISSN: 0975-8585

period of 3 months. Samples from each formulation kept for examination were withdrawn at definite intervals. The withdrawn samples were assayed for percentage drug content and percentage drug release from the enteric coated tablets at 301 nm (shown in table 8 and 9).

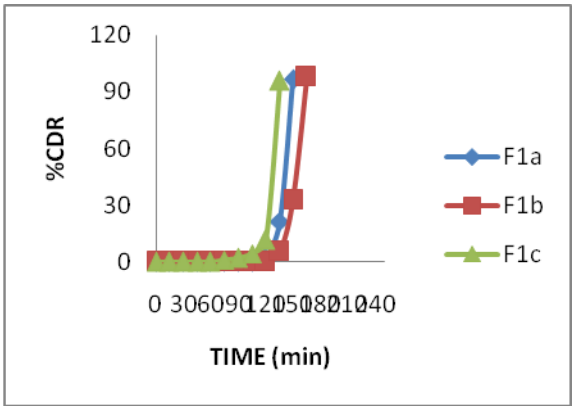

Figure 1: In-vitro release profile of Esomeprazole magnesium from F1a, F1b and F1c.

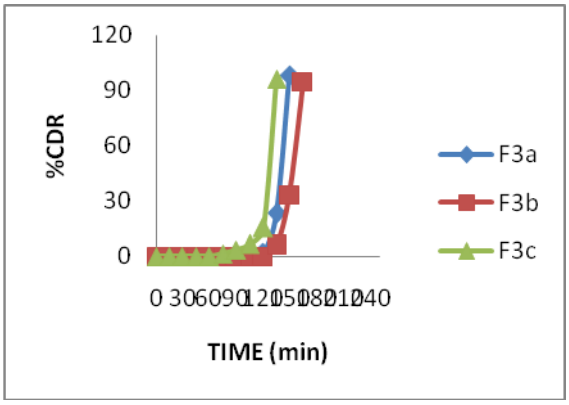

Figure 2: In-vitro release profile of Esomeprazole magnesium from F3a, F3b and F3c.

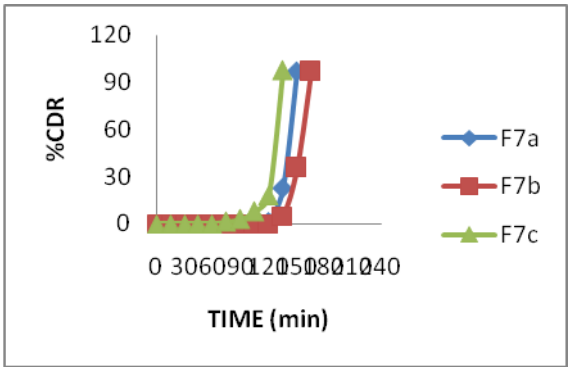

Figure 3: In-vitro release profile of Esomeprazole magnesium from F7a, F7b and F7c.

ISSN: 0975-8585

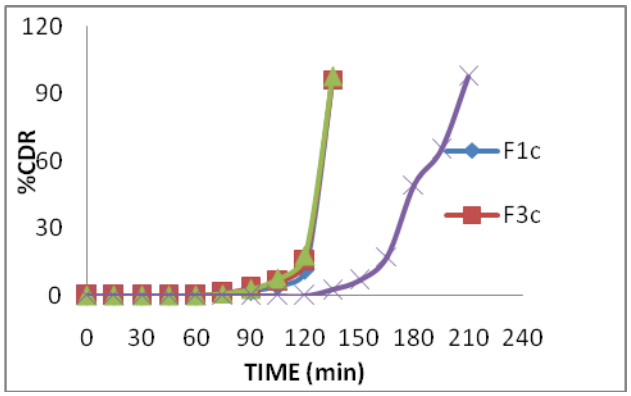

Figure 4: In-vitro drug releasing profile compared with marketed product

CONCLUSION

Esomeprazole core tablets were prepared by using different fast disintegrating agent. The prepared core tablets are coated with different enteric coating materials such as acryl-EZE and Eudragit L-100-55 polymers prevents the release of drug for first 2hrs. And then drug was released in pH6.8 buffer. These provide greater rotection to the core under acidic condition while at the same time show the fastest drug release under intestinal pH. The above formulations were found to be stable for three months

ACKNOWLEDGEMENTS

The authors express their heartfelt thanks to Miss. Kalaivani, Madras pharmaceuticals, Chennai, India for providing pure sample and thankful to Dr. D. Venugopal, Dr.Reddy's laboratories, Hyderabad, India for providing the polymers. I am thankful to Dr. Vrushabendra Swamy. B. M and Mrs. Archana Swamy P for their valuable advice regarding the research work.

REFERENCES

[1] S Bozdag, S Calis and M Sumnu. S.T.P. Pharma Sciences 1999; 9 (4): 321-327.
[2] Putta Rajesh Kumar, Hiremath Doddayya and S Rajendra Reddy. Journal of Applied Pharmaceutical Science 2011; 1(6): 106-111.
[3] Sumit Chakraborty, Sibaji Sarkar and Sujit Kumar Debnath. International Journal of ChemTech Research 2009; 1(3); 663-666.
[4] Xiao-Yan Liang, Qing Gao, Neng-Ping Gong, Li-Ping Tang, Pi-Long Wang, Xiao-Hong Tao. World Journal of Gastroenterology 2008; 14(12): 1941-1945.
[5] Anroop B Nair, Rachna Gupta, Rachna Kumria, Shery Jacob and Mahesh Attimarad. Formulation and Evaluation of Enteric Coated Tablets of Proton Pump Inhibitor. Journal of Basic and Clinical Pharmacy.
[6] Sweetman SC. Martindale The complete drug reference, 36th edition. Royal pharmaceutical society; Britain 2009: 1729.

[7] Aulton ME. Pharmaceutics: The Science of Dosage Form Design. 2nd edition. Churchill Livingstone. Elsevier science Ltd; united states of America 2002; 33-134.
[8] Welling PG and Dobrinska MR. Dosing considerations and bioavailability assessment of controlled drug delivery systems. In: Controlled drug delivery: Fundamentals and applications. Robinson JR, Lee V H L. 2nd edition. Marcell Dekker; New York 1987; 29: 253-289.
[9] Ansel's NG, Pharmaceutical Dosage forms and drug delivery system. 8th edition. B.I publication 2006: 92-141.
[10] Cooper J, Gun C, Powder Flow and Compaction. Inc Carter S. J, Eds. Tutorial Pharmacy. New Delhi, hidix CBS Publishers and Distributors 1986; 211-233.
[11] Martin A, Micromeretics, In: Martin A, ed. PhysicalPharmacy. Baltimores, MD: Lippincott Williams and Wilkins 2001; 423-454.
[12] Liberman, Lachman L. The Theory and Practice of Industrial Pharmacy.3nd Edition, Verghese Publication House 1987; 293.
[13] Durriya Hashmat, M. Harris Shoaib, Zafar Alam Mehmood, Rabia Bushra, Rabia Ismail Yousuf and Fahim Lakhani. AAPS PharmSciTech 2008; 9 (1): 116-121.
[14] Rabia Bushra, Muhammad Harris Shoaib, Nousheen Aslam, Zafar Alam Mehmood, Durriya Hashmat. Brazilian Journal of Pharmaceutical Sciences 2010; 46 (1): 99-107.
[15] Investigation of a Modified USP Disintegration Test Method for Enteric Coated Tablets. Application data from colorcon.
[16] Putta Rajesh Kumar, Somashekar Shyale, M Mallikarjuna Gouda and SM Shanta Kumar. Pelagia Research Library 2011; 2 (3):31-42.
[17] KL Senthil Kumar, S Ashokkumar, RP Ezhilmuthu. Journal of Biomedical Science and Research 2010; 2(3): 126-131.
[18] Prajapati BG and Patel KR. International Journal of Medical and Clinical Research 2010; 1(1).
[19] Reza MS, Quadir MA, Haider SS. Journal of Pharm Pharmaceutical Science 2003; 6(2): 282-91.