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DESIGN AND DEVELOPMENT OF CONTROLLED RELEASE TABLETS OF BOSENTAN

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ABSTRACT

The present investigation attempt has been made to formulate controlled release matrix tablets of Bosentan using HPMC K15M, HPMC E-15 and Xanthan gum are rate controlling polymer, PVP K-30 used as binder, microcrystalline cellulose as filler. The prepared tablets were prepared by conventional wet granulation method and evaluated for pre compression and post compression parameters with different ratios. All the evaluated parameters of the formulations showed compliance with pharmacopoeial standards. The effect of polymer loading in in-vitro drug release and the mechanism of release was studied by different mathematical models. This could be retarded or maintained by the proper choice of controlling agent in order to achieve the desired release profile. The optimized formulation (F5) were subjected to stability studies as per ICH guidelines at different temperature and humidity conditions. It can be concluded that among all the formulations and the combinations of HPMC K15M, HEC & Metolose SR considered as the optimized formulations in the present research work. The optimized formulations follow zero order release kinetics and super case II transport release mechanism.

KEYWORDS: Bosentan, HPMC K15M, HPMC E-15, Xanthan gum, Avicel PH102, PVP K-30 and Magnesium stearate.

INTRODUCTION

Bosentan is a competitive antagonist of endothelin-1 at the endothelin-A (ET-A) and endothelin-B (ET-B) receptors. Under normal conditions, endothelin-1 binding of ET-A or ET-B receptors causes constriction of the pulmonary blood vessels by blocking this

interaction, bosentan decreases pulmonary vascular resistance. Bosentan has a slightly higher affinity for ET-A than ET-B.[1] Bosentan is used to treat pulmonary arterial hypertension (PAH). Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity easy in manufacturing, high level of reproducibility and easy of scale up and process validation. It improves your ability to exercise and prevents your condition from getting worse. It was chosen as a model drug with an aim to develop a controlled release matrix tablet. Different formulations were prepared by using different polymers like HPMC K15M, HPMC E-15, Xanthan gum, Avicel PH102, PVP K-30 and Talc etc. with different ratios were used in the development of formulations.

MATERIALS AND METHODS

MATERIALS

Bosentan (A Gift sample from Dr reddys, Hyderabad).

HPMC K15M, A Gift sample from Orchid health care, Chennai.

HPMC E15, A Gift sample from Orchid health care, Chennai.

Xanthan gum, A Gift sample from Orchid health care, Chennai.

PVP K30 A Gift sample from Orchid health care, Chennai.

Micro crystalline cellulose, A Gift sample from Moly chemicals.

Hydroxy Ethyl cellulose (Moly chemicals).

Metolose SR (Moly chemicals).

Mg stearate (Cheminova private limited).

Talc (Cheminova private limited).

METHODS

PREPARATION OF BOSENTAN MATRIX TABLETS

Controlled release tablets of Bosentan were prepared by conventional wet granulation technique using different concentrations of polymers like HPMC K15M, HPMC E15 and xanthan gum.[2,20] The Required quantity of all materials was weighed and then active ingredient (Bosentan) and polymers were mixed. A liquid binder solution of PVP K30 is added to the mixture to facilitate adhesion. A damp mass resembling dough is formed and used to prepare the granulation. The wet mass was pressed through a 10 number sieve to prepare the granules. The resultant granules are spread evenly on large pieces of paper in shallow trays and dried granules were dried in hot air oven at 60^0c for 1 hr. The granules

were passed through sieve number 20. Sizing of the granules is necessary so that the die cavity for tablet compression may be completely and rapid filled by the free flowing granulation. After completion of dry screening the granules were mixed with magnesium stearate and talc which acts as lubricants which prevents the adhesion of the tablet formulation to the punches and dies during compression. After blending with the polymers the granules were subjected to the compression using 10 stations tablet punching machine (Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujarat.).

Evaluation of Tablets

Thickness: Thickness Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

Hardness: The Mansanto hardness tester was used to determine the tablet hardness.

Friability: The loss was tested by Friabilator USP EF-2.

Dissolution Rate Study

The release rate of Bosentan from tablets was determined using United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle). The dissolution test was performed using 900 ml of pH 1.2, for first 2 hours then in phosphate buffer pH 6.8 for rest of the hours at 37 ± 0.5 C and 50 rpm. A sample (5 ml) of the solution was withdrawn upto 12 hours. The samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with respected dissolution medium. Absorbance of these solutions was measured using a UV-Visible Spectrophotometer (UV-1800) at 276 nm.

Data Analysis: The data analysed as per Zero order kinetic model (Cumulative % drug released versus time)**,** First order kinetic model (Log cumulative percent drug remaining versus time), Higuchi model (Cumulative percent drug released versus square root of time) and Korsmeyer equation / Peppa's model (Log cumulative percent drug released versus log time).

Stability Studies

Stability studies of optimized formula (F5) were done as per ICH guide lines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. The optimized formulations were stored

at different storage conditions at elevated temperatures such as $25^0C\pm 2^0C$ / 60% ± 5% RH, $30^0C \pm 2^0C$ / 65% ±5% RH and $40^0C \pm 2^0$ / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of fifteen days and checked for physical appearance and percentage drug release.

RESULTS AND DISCUSSIONS

Each tablet containing 16 mg of bosentan could be preparared by conventional wet granulation method employing Xanthan gum, HPMC K 15M, HPMC-E15. The weight loss in the friability was less than 1% in all the cases. All the matrix tablets prepared contained drug in the range of 98 to 102% of the labeled claims. The punches used to compress the tablets were 9mm, spherical shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 4.02 to 4.25 Kg/cm^2. It was within the range of monograph specification. Thicknesses of the tablets were found to be in the range of 3.42 to 3.87 mm. Weight variation test helps to check whether the tablet contain proper quantity of the drug. From each of the formulations ten tablets were randomly selected and weighed. The results are given in detail. The average weights of the tablets were found to be within the prescribed official limits (IP). The drug content for all the batches were found to be in the range of 96.48 to 99.59%. Xanthan gum, HPMC K 15M, HPMC-E15 was chosen for the formulations.

HPMC-E15 is a non toxic, biocompatible, cost effective and also reduces the risk of systemic toxicity due to dose dumping. HPMC K 15M also non toxic, non allergic, non irritating, biocompatible, soluble at pH higher than 6.5. So it was used to control the release of the drug according to specification given in USP. Xanthan gum is as a controlled-release carrier. The release of the drug in stomach was prevented by using acid resistance polymers. Hence by using the property of polymer, the drug was made to release in the intestine (pH 6-7) by escaping acidic environment of stomach without degradation of drug.

In-Vitro Release Study

All the 13 formulation of prepared tablets of Bosentan were subjected to in vitro release studies, these studies were carried out using dissolution medium, (pH 1.2 and Phosphate buffer pH 6.8). by using USP-2 (paddle type) dissolution apparatus. The results were evaluated for 12 hours. Among all the formulation, F5 showed 96.04%, release respectively at the end of 12 hours.

Kinetics

Different models like Zero order, First order, Higuchi's, and Krosmeyers-peppas plots were drawn. The regression coefficient (R^2) value for Zero order, First order, Higuchi's and Krosmeyers-peppas plots for formulation F5 were found to be 0.970, 0.763, 0.824,0.927. The optimized formulations F-5 follow Zero order and super case 2 transport mechanism.[21]

Stability Study

Stability studies were carried out on selected formulations (F-5) as per ICH guidelines. There was not much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant changes in physical appearance, drug release for the selected formulation F-5 after 90 days at $25^0C\pm 2^0C$ / 60% ± 5% RH, $30^0C \pm 2^0C$ / 65% ±5% RH and $40^0C \pm 2^0$ / 75% ± 5% RH.[22]

Table 1: Tablet composition of different formulations of Bosentan matrix tablets containing controlled release polymers.

Ingredients (mg)	Formulation Code												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Bosentan	16	16	16	16	16	16	16	16	16	16	16	16	16
HPMC K15M	61	56	51	46	41	36							
HPMC E15							51	46	41	36			
Xanthan gum											15	20	35
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10	10
Micro crystalline cellulose	35	35	35	35	35	35	35	35	35	35	35	35	35
Hydroxy Ethyl cellulose	15	15	15	15	15	15	15	15	15	15	15	15	15
Metolose SR	-	5	10	15	20	25	51	46	41	36	51	41	31
Mg stearate	8	8	8	8	8	8	8	8	8	8	8	8	8
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5
Total weight (mg)	150	150	150	150	150	150	150	150	150	150	150	150	150

Table 2: Cumulative Percent of Drug Dissolution of Prepared Tablets (F1 to F6).

Time (hr)	Cumulative percent drug release					
	F1	F2	F3	F4	F5	F6
0	0.0	0.0	0.0	0.0	0.0	0.0
1	7.85	6.69	6.41	5.02	4.87	4.23
2	14.02	13.80	12.58	11.64	10.66	9.52
3	17.45	16.78	16.12	15.54	14.26	12.11
4	21.02	20.56	19.74	18.75	18.70	15.25
5	30.45	29.30	28.79	26.97	25.64	23.64
6	39.85	37.74	36.63	34.47	32.11	30.08
7	51.26	49.46	47.85	45.20	43.49	41.36
8	68.79	66.37	62.02	57.89	56.68	53.38
9	76.63	74.48	70.59	68.87	64.32	62.25
10	87.96	85.52	83.37	80.81	75.57	72.20
11	92.50	90.10	90.10	90.39	87.84	81.89
12	93.1	91.0	92.1	91.1	96.04	91.18

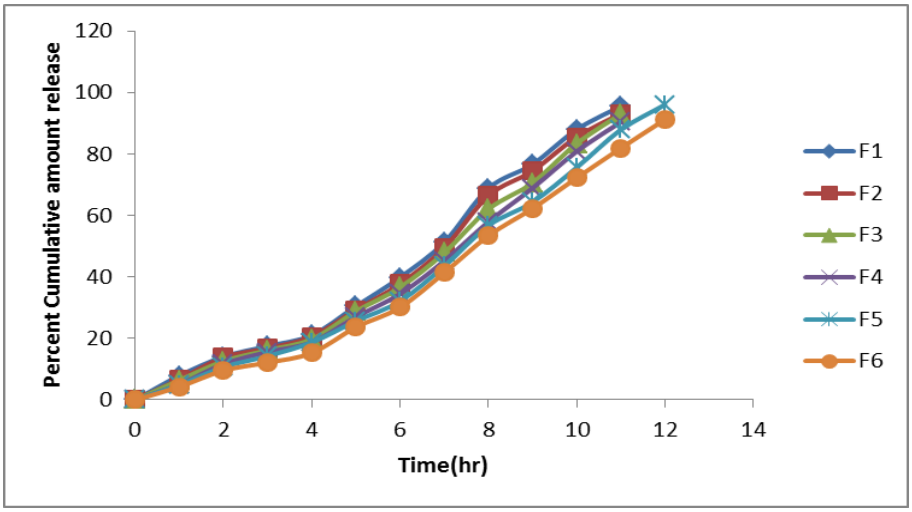

Fig 1: Cumulative Percent of Dissolution Date of Prepared tablets (F1 to F6).

Table 3: Cumulative Percent of Drug Dissolution of Prepared tablets (F7 to F13).

Time(hr)	Cumulative percent drug release						
	F7	F8	F9	F10	F11	F12	F13
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	14.43	11.36	9.63	8.97	7.90	7.11	6.87
2	23.27	21.26	19.20	16.55	13.09	10.45	9.16
3	31.20	27.56	25.63	23.38	21.23	19.97	17.64
4	42.63	38.69	36.69	30.09	28.16	25.87	22.45
5	51.02	47.41	42.4	40.49	32.23	30.03	27.03
6	65.66	60.70	55.8	52.77	47.92	42.28	36.74
7	78.75	73.37	66.30	63.38	54.27	48.77	40.54
8	89.96	86.30	82.15	76.67	66.50	59.60	46.23
9	96.73	95.52	92.16	85.80	76.22	68.87	58.12
10	--	--	--	95.15	80.51	73.26	65.61
11	--	--	--	--	86.26	79.8	72.02
12	--	--	--	--	94.51	85.50	81.03

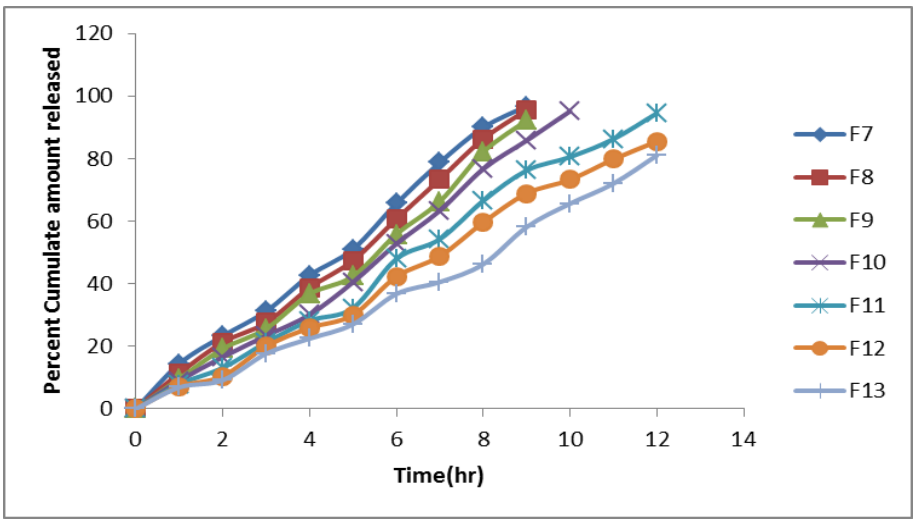

Fig 2: Cumulative Percent of Drug Dissolution of Prepared tablets (F7 to F13).

Fig 3: First order Drug Dissolution profile of Optimized Formulation (F5).

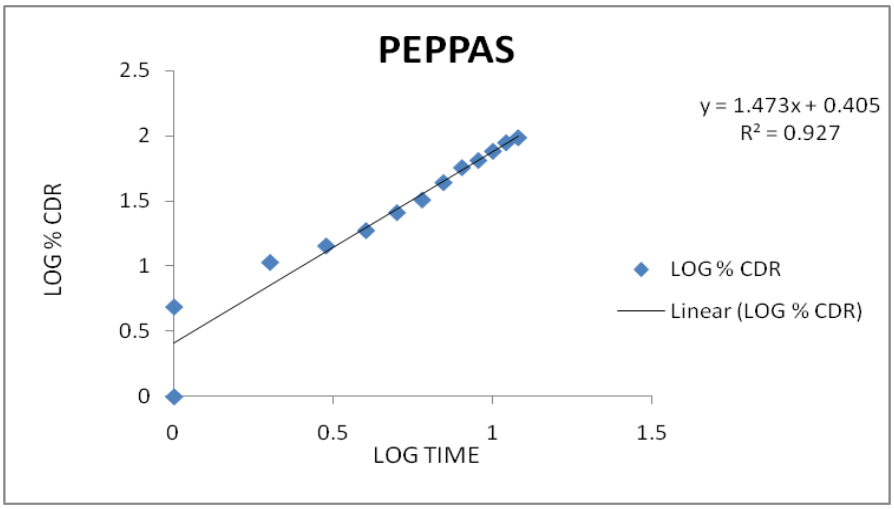

Fig 4: Pappas Model- Dissolution profile of Optimized Formulation (F5).

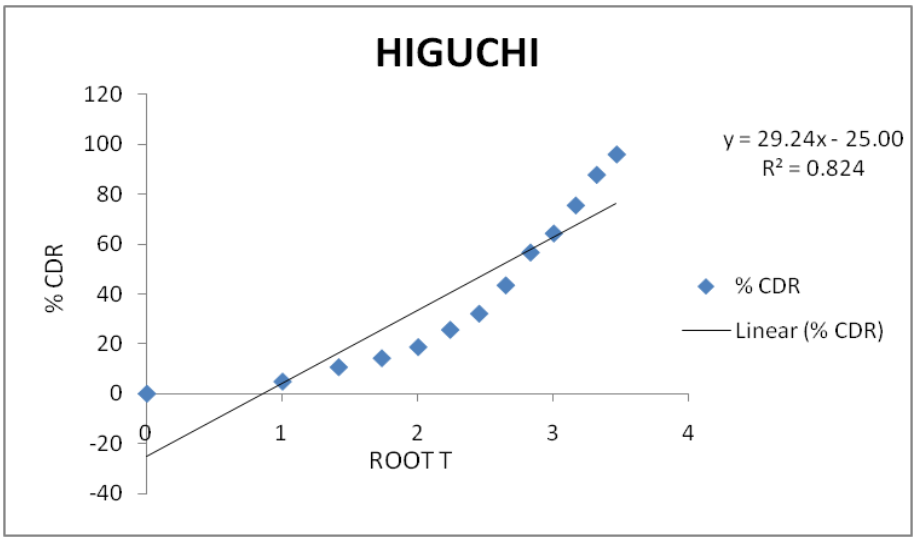

Fig 5: Higuchi Model Drug Dissolution profile of Optimized Formulation (F5).

Table 4: Stability Studies of Optimized Formulation (F5).

Temp. and relative humidity	Days				Parameters
	0	30	60	90	
$25^0C\pm 2^0C$ / 60% ± 5% RH	No change				Physical appearance
$30^0C\pm 2^0C$ / 65% ± 5% RH					
$40^0C\pm 2^0C$ / 75% ± 5% RH					

Table 5: Dissolution Study for Optimized Formulation After storage.

Time (Hr)	Cumulative percentage drug release								
	after 1 month			after 2 month			after 3 month		
	25±2°C 60±5% RH	30±2°C 65±5% RH	40±2°C 75±5% RH	25±2°C 60±5% RH	30±2°C 65±5% RH	40±2°C 75±5% RH	25±2°C 60±5% RH	30±2°C 65±5% RH	40±2°C 75±5% RH
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	4.80	4.82	4.85	4.80	4.83	4.85	4.82	4.80	4.83
2	10.54	10.55	10.58	10.60	10.64	10.67	10.61	10.60	10.64
3	14.18	14.22	14.25	14.22	14.24	14.26	14.19	14.23	14.28
4	18.66	18.68	18.65	18.65	18.59	18.68	18.68	18.71	18.69
5	25.59	25.60	25.63	25.62	25.58	25.60	25.57	25.60	25.63
6	32.08	32.10	32.14	32.07	32.08	32.12	32.06	32.05	32.10
7	43.40	43.43	43.48	43.35	43.39	43.47	43.40	43.45	43.49
8	56.61	56.64	56.65	56.60	56.62	56.65	56.61	56.65	56.67
9	64.30	64.27	64.29	64.30	64.28	64.32	64.28	64.30	64.31
10	75.49	75.51	75.53	75.48	75.51	75.52	75.49	75.52	75.57
11	87.80	87.84	87.82	87.80	87.84	87.82	87.76	87.80	87.82
12	96.03	96.01	96.04	96.05	95.98	96.02	95.98	96.01	96.06

CONCLUSION

1. Different parameters like hardness, friability, weight variation, drug content uniformity, in-vitro drug release were evaluated.
2. The bosentan were prepared by including analytic control of the production process and preparation using HPMC K15M, HPMC E15 and xanthan gum, polymers as retardant.
3. The drug-polymer ratio was found to influence the release of drug from the formulations. It was found that increase in the concentration of HPMC K15M in polymeric ratio decreases the drug release.
4. The formulations F5 showed good drug release with good matrix integrity release of 96.04% at the end of 12hr so the formulation F5 selected as the optimized formula.
5. The formulation F5 showed good drug release with good matrix integrity.
6. Based on these results formulation F5was found to be the most promising formulations. The regression coefficient (R^2) values of zero order of the optimized formulation F5 was greater than the R^2 values of first order. Thus, the drug release

follows zero order release kinetics and super case 2 transport.

7. Stability studies were conducted for the optimized formulations as per ICH guidelines for a period of 3 months which revealed the stability of the formulations. The results suggest that the developed controlled-release matrix tablets of Bosentan could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance.
8. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of Bosentan in the management of hypertensive. Bosentan with all evident advantages proved to be suitable candidates for development of a controlled release dosage form.

REFERENCE

1. Funke C, Farr M, Werner B, Dittmann S, Uberla K, Piper C, Niehaus K, Horstkotte D (Apr 2010). "Antiviral effect of Bosentan and Valsartan during coxsackievirus B3 infection of human endothelial cells.". Journal of General Virology. 91(8): 1959–1570.
2. Sallsa T. Veiga F, Pina ME. oral controlled – release dosage forms Cellulose ether polymers in hydrophilic – matrices. Drug Dev Ind Pharm, 1997; 23: 929– 938.
3. Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled – release dosage forms. Int. S. Pharm. Tech,. Prod. Manuf, 1984; 5: 1-9.
4. Gohel MC, Patel TP, BarigyaSH. Studies in preparation and evaluation of pH independent sustained – release matrix tablets of Verapamil Hcl using directly compressible Eudragits. Pharam Dev Technol, 2003; 8: 323 – 333. Pubmed Dol : 10. 1081 / PDT – 120024686.
5. Liv J, Zhang F, Mc GinityJw. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot – met extrusion. Eur J pharm Biopharm, 2001l; 42: 181–190. Pubmed Dol: 10. 1016/ S0939 – 6411 (01) 00162-x.
6. Robinson Joseph R, Lee Vincent HL. Design and fabrication of oral controlled release drug delivery system. In: Controlled drug delivery - Fundamentals and applications. Marcel Dekker, Inc., New York, 1987; 2nd edition: 24-36.
7. Anroop B. Nair, Hiral vyas and Ashok Kumar. Controlled release matrix uncoated tablets of enalapril maleate using HPMC alone, Journal of Basic and Clinical Pharmacy Vol-001 Issue-002 March 2010 – May 2010
8. Shantveer V. Salger, Lingaraj S. Danki, Abdul Sayeed, Shivanand Hiremath. Formulation and invitro evaluation of sustained release matrixtablets of anti-hypertensive drug

propranolol hydrochloride, Scholars Research Library, Der Pharmacia Lettre, 2010; 2(5): 12-22.

9. Amit.S. Yadav, Ashok Kumar P, Vinod R, Someshwara Rao B, Suresh V Kulkarni. Design and Evaluation of Guar Gum Based Controlled Release Matrix Tablets of Zidovudine, Journal of Pharmaceutical Science and Technology, 2010; 2(3): 156-162.
10. GanesanV, Jayachandran DL Design and Evaluation of Matrix Tablets of Ambroxol Hydrochloride using Guargum Research J. Pharm. and Tech., 2008; 1(4): 507-12.
11. AbdelbaryGA, TadrosMI. Design and in vitro/in vivo evaluation of novel nicorandil extended release matrix tablets based on hydrophilic interpolymer complexes and a hydrophobic waxy polymer. Eur J Pharm Biopharm. 2008; 69(3): 1019-28.
12. Kulkarni R V, Shah A, Boppana R. Development and evaluation of xyloglucan matrix tablets containing naproxen. Asian J of pharmaceutics, 2008; 2(2): 102-5.
13. Amelia avachat, Vikram kotwal. Design and evaluation of matrix based controlled release tablets of Diclofenac Sodium and chondrotin Sulphate. AAPS Pharm Sci Tech. 2007; 8(4): E1-E6.
14. Emami J, Tavakoli N, Movahedian A. Formulation of sustained-release lithium carbonate matrix tablets: influence of hydrophilic materials on the release rate and in vitro-in vivo evaluation. J Pharm Pharmaceut Sci., 2004; 7(3): 338-44.
15. Reddy KR, Mutalik S, Reddy S. Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and In Vitro Evaluation. AAPS Pharm Sci Tech., 2003; 4(4): article 61.
16. NerkurJ, JunHW, ParkJC, ParkMO. Controlled-release matrix tablets of ibuprofen using cellulose ethers and carrageenans: effect of formulation factors on dissolution rates. Eur J Pharm Biopharm, 2005; 61(1-2): 56-68.
17. J. Ashtamkar, S. Nangude et al., Formulation and evaluation of controlled release tablets of miglitol using combination of hydrophilic polymers., International Journal of Pharmaceutical sciences and Research., 2013; 4(5): 1833-1837.
18. Y. Ganesh Kumar, J. Sreekanth, et al; Preparation and Evaluation of Sustained Release Matrix Tablets of Bosentan by Using Wet Granulation Technique., International Journal of Pharmaceutical Sciences Review and Research., Rev. Res., March – April 2015; 31(2): Article No. 26, Pages: 155-161.
19. P. Ganga Jyothi, K. Gnanaprakash et al; Development and characterization of matrix mini-tablets of bosentan for controlled drug release., 2014; 5(4): 245-250.

20. Y. Ganesh kumar, J. Sreekanth., et al., formulation development and in vitro evaluation of sustained release matrix tablets of bosentan by using synthetic polymers International Journal of Pharmacy and Pharmaceutical Sciences., 2014; 6: 11.
21. Korsemeyer RW, PeppasNA. Macromolecular and modeling aspects of swelling – controlled Systems. In: Mansdrofsz, Roseman TJ, ad, Controlled Release Delivery systems. New – York, NY: Marcel Dekker, 1983: 77.
22. ICH Q1A (R2) stability testing guidelines: stability testing of new drug substances and products. [Online]. 2003 [cited 2008 Nov 10]; Available from: URL:http://www.tga.health.gov.au/docs/pdf/euguide/inch/273699r2en.pdf