Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2012, 4 (3):775-781
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Design development and evaluation of alfuzosin hydrochloride extended release tablets by using natural and synthetic polymers

Sreenivasa Reddy[1] and Dinakar[2]

[1]*Dept. of Pharmaceutics, Sun Institute of Pharmaceutical Education and Research, Nellore (AP), India.*
[2]*Dept. of Pharmaceutical Analysis, Sun Institute of Pharmaceutical Education and Research, Nellore (AP), India.*

ABSTRACT

Alfuzosin Hydrochloride extended release tablets were prepared by wet granulation method by using natural and synthetic polymers Guar gum, Eudragit RLPO and Hypromellose (Methocel K100M). The present study was to develop stable and robust formulation of Alfuzosin Hydrochloride ER tablets 10mg. The formulation containing binary mixer of Hypromellose at 31.0 % and Guar gum at 11.0 % were evaluated for various physicochemical parameters by official procedures showed consistent results. The in-vitro release study of tablets was carried out in 0.01N HCL for 20 hours. A time (hr.) interval 1, 2, 6, 12, and 20 has showed the best formulation releases when compared with the reference product. Both the diffusion and erosion mechanisms were responsible for drug release as shown by the power law. Dissolution data were fitted to zero order, first order, Higuchi's, Peppas & Korsmeyer, Hixson Crowell, Weibull and Baker Lonsdale release kinetics to evaluate kinetic data. The main effect and interaction terms were quantitatively evaluated using mathematical model. Hence the gradual release of Alfuzosin Hydrochloride over a prolonged time period of 20 hr. which indicates the usefulness of the formulation for once daily dosage form. Optimized formulation was found stable during accelerated stability study for 3 months at 40°C± 2°&75%±5 % RH.

Key Words: Alfuzosin Hydrochloride, Eudragit RLPO, Hypromellose (Methocel K100 M), Guar Gum, Release Kinetics Data.

INTRODUCTION

Alfuzosin Hydrochloride is anantagonist for alpha 1-adrenergic receptors in the lower urinary tract, which cause smooth muscle in the bladder neck and prostate to relax, resulting in improved urine flow and a reduction in symptoms of benign prostatic hyperplasia (BPH) [1].It can cause few cardiovascular adverse effects. The extended-release formulations showed lower frequency of cardiovascular adverse effects reported when compared with immediate-release formulation [2].

Alfuzosin Hydrochloride is freely soluble in water and readily absorbed after administration. The oral absorption is significantly aided by the presence of food. The usual dose of Alfuzosin Hydrochloride for patients with BPH is 2.5 mg twice or thrice daily of the IR formulation or 5 mg of ER Alfuzosin Hydrochloride twice daily or 10 mg of ER Alfuzosin Hydrochloride once daily.The absolute bioavailability of Alfuzosin Hydrochloride 10 mg tablets under fed conditions is 49%. Following multiple dosing of 10 mg Alfuzosin Hydrochloride under fed conditions, the time to maximum concentration is 8 hours. C_{max} and AUC0-24 are 13.6 (SD = 5.6) ng/mL and 194 (SD = 75) ng.h/mL, respectively [1]. Alfuzosin Hydrochloride exhibits linear kinetics following single and multiple dosing up to 30 mg. Steadystate plasma levels are reached with the second dose of Alfuzosin Hydrochlorideadministration.Steady-state Alfuzosin Hydrochloride plasma concentrations are 1.2to 1.6 fold higher than those observed after a single administration [12].

The aim of this work was to prepare and evaluate the Alfuzosin Hydrochlorideonce daily extended release tablets and to compare them with reference product. The most commonly used method for fabricating drugs in a controlled-release formulation is by incorporating them into a matrix containing a hydrophilic rate controlling polymer [3]. Matrix systems are widely used in oral controlled drug delivery because of their flexibility,cost effectiveness and broad regulatory acceptance [4]. Cellulose ethers like HydroxypropylmethylCellulose (HPMC), copolymers of acrylic-methacrylic acid (Eudragits) like Eudragit RL and RS and some natural gums like guar gum are widely used hydrophilic polymers as release retardants [4, 5].

MATERIALS AND METHODS

Alfuzosin HydrochloridePh.Eur was gift sample from Dr. Reddy's laboratory Limited., Gaur Gum NF and Microcrystalline Cellulose NF from Signet, Mumbai,Eudragit RLPO and Colloidal Silicon Dioxide NF from Evonik,Mumbai,Povidone from ISP, Mumbai, Hypromellose NF and Pregelatinized Starch (Starch 1500) NF from Colorcon, Goa, Magnesium Stearate NF from Ferro corp, Mumbai,All other materials used were of pharmaceutical grade.

PREPARATION OF MATRIX TABLETS

The tablets were prepared by wet granulation technique. The compositions of the tablet formulations are given in Table 1. Weighedamounts of Alfuzosin Hydrochloride, retardant (HPMC, Guar gum, Eudragit RLPOand other excipients (Microcrystalline Cellulose, Pregelatinized Starch and Povidone) were sifted through 40# sieve and mixed in rapid mixing granulator (RMG) for 15min.Then the blend was granulated using purified water asthe granulating agent. The wet granules were sifted through 14 # sieve. The mass was dried in a hot air oven at 60 ± 5°C inlet temperature till the moisture comes below 3% and sieved through 20 # sieve.Magnesium stearateand colloidal silicon dioxide (previously shifted through # 40 mesh) were then added to the dried, sievedgranules and mixed for about 5 min in a double cone blender.The efficiencyof mixing was verified by the determination of drug content. The produced mixture was compressed into tablets using 8 station tablet compression machine, (Cadmach, KMP-8) equipped with an 8.8 mm round shaped with standard concave punches.

Table No.: 1 Composition of extended release tablet formulation

Excipients	**mg/tablet**					
Formulation Batches	**F001**	**F002**	**F003**	**F004**	**F005**	**F006**
Alfuzosin Hydrochloride	10.00	10.00	10.00	10.00	10.00	10.00
Microcrystalline Cellulose (Avicel PH-101)	90.50	158.00	204.00	194.00	184.00	174.00
Pregelatinized Starch (1500)	15.00	---	---	---	---	---
Eudragit RLPO	---	120.00	---	---	---	---
Povidone (K-30)	---	9.0	---	---	---	---
Guar Gum	180.00	---	30.00	35.00	40.00	45.00
Hypromellose (Methocel K100 M)	---	---	100.00	105.00	110.00	115.00
Purified Water	qs	qs	qs	qs	qs	qs
Colloidal Silicon Dioxide	1.50	---	2.00	2.00	2.00	2.00
Magnesium Stearate	3.00	3.00	4.00	4.00	4.00	4.00
Tablet Weight	**300.00**	**300.00**	**350.00**	**350.00**	**350.00**	**350.00**

EVALUATION OF GRANULES:

Flow property of the granules evaluated by using below methods [14],

Bulk Density = Weight of the powder (m) / Unsettles apparent volume(V_0) = g/ml

Tapped Density = Weight of the powder (m) / Final tapped volume (V_f) = g/ml
Compressibility Index (%) = $(V_0\text{-}Vf)\times 100/V_f$

Hausner's Ratio = V_0/V_f

The physical properties of granules were shown in Table 2.

PHYSICAL EVALUATION OF TABLETS:

Weight variation

20 tablets from each formulation were weighed using an electronic balance (Mettler-Toledo,AB104, Germany) and mean and relative standard deviation of the weight were determined basedon an official method.

Hardness and Thickness

The diametrical crushing strength test was performed on 10 tablets from each formulation.
10 tablets were tested using a Dr.Schleuniger, 6D, hardness tester.
The thickness of the tablets was measured with a Verniercaliper (Mitutoyo, CD-8 CSX).

Friability

For each formulation, the friability of 20 tablets was determined using a Roche type friabilator (Electrolab EF-2W). 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min. After removing ofdust, tablets were re-weighed and friability percentage was calculated using the following equation:

% Friability = $(W_0\text{-}W)/ W_0 \times 100$.

(W_0= initial weight and W= Final weight)

DRUG CONTENT (ASSAY):

20 tablets were weighed and finely powdered. Transfer an accurately weighed portion of the powder, equivalent to 10 mg of Alfuzosin Hydrochlorideto a 200 ml volumetric flask with the aid of 120ml methanol and sonicate the flask with occasional shaking for about 15min, allow the solution to equilibrate to room temperature. Dilute to volume with buffer solution and mix well. Centrifuge a portion of sample for about 15min prior to dilution. Transfer 5.0ml of sample solution into individual 10.0ml volumetric flask. Dilute to volume with diluent and mix well. Alfuzosin hydrochloride was estimated by HPLC using Column: Symmetry C18, 4.6×150mm, 5micron or equivalent and Buffer: Acetonitrile: THF (810:180:10v/v) as mobile phase with Flow rate: 1.5 ml/min at 245 nm.

***IN-VITRO* DRUG RELEASE STUDY:**

In-vitro drug release studies [11] were carried out using 900 ml of 0.01N Hydrochloric acid as dissolution medium using USP Apparatus-II (Electrolab) at 100 rpm and the temperature was maintained at 37±0.5°C. The dissolution was continued for 20 hours while samples of 10ml were withdrawn at regular interval and replaced with equal volume of fresh dissolution medium to maintain the volume constant. The samples were filtered, diluted and analyzed for drug content. The amount of drug released was determined by HPLC at 245 nm using Column: Symmetry C18, 150×4.6mm, 5µ or equivalent with Flow rate: 0.8ml/min. Drug release at specified time points was calculated.

KINETICS OF DRUG RELEASE

The kinetic data for the *in vitro* release was estimated using different kinetic orders (zero- and first-order) and systems such as Higuchi's diffusion model , the Hixson-Crowel cub root law [8], theBaker-Lonsdale equation [9], korsmeyer – peppas[10]and A special computer program was used to calculate the kinetic treatments, kinetic parameters and kinetic data for the *in vitro* release

STABILITY STUDY:

Stability study of selected formulation was tested according to international conference of harmonization guidelines. The tablets were stored in Alu-Alu blister for 3 months in stability chamber at 40°C± 2°&75%±5 % RH. Tablets were tested for drug content and in vitro dissolution.

Table: 2 Physical parameters of the granules

S.No	Physical Parameters	F001	F002	F003	F004	F005	F006
1	Bulk density(g/ml)	0.345	0.339	0.342	0.361	0.341	0.334
2	Tap density(g/ml)	0.490	0.479	0.480	0.500	0.469	0.464
3	Carr's index (%)	29.59	29.22	28.76	27.71	27.273	27.907
4	Hausner's ratio	1.420	1.412	1.403	1.383	1.375	1.387

RESULTS AND DISCUSSION

Table No.: 3 Physical evaluation of tablets

S.No	Parameters	F001	F002	F003	F004	F005	F006
1	Weight of individualtablets(in mg)	340-360	350-358	349-352	347-353	355-360	348-357
2	Weight of 10 tablets (in g)	3.492	3.5508	3.5108	3.5193	3.538	3.4916
3	Hardness(in kp)	12-13	11.5-13.2	9.1-10.6	9.0-10.6	10.7-12.2	10.8-12.1
4	Thickness(in mm)	5.80-5.90	5.75-5.85	5.70-5.75	5.65-5.75	5.45-5.57	5.70-5.75
5	Friability(%w/w)	0.22	0.32	0.14	0.15	0.13	0.14

Stability Study

The selected batch (F5) was kept at 40°C± 2°&75%±5 % RHand the samples were withdrawn at 30, 60 and 90 days for physical and *in vitro* evaluation of drug release.

Table No.: 4 Dissolution Profile reference product With Developed formulas

Trial. No	Cumulative % Drug Release				
	1hr	2hr	6hr	12hr	20hr
F001	26.2	39.1	68.5	93.20	99.10
F002	26.2	92.1	---	---	---
F003	24	36	62	84	95
F004	24	34	61	80	95
F005	21	31	55	76	91
F006	17	24	50	71	89
Reference	**20**	**28**	**52**	**80**	**97**

Figure No.: 1 Dissolution profile Compare with reference product

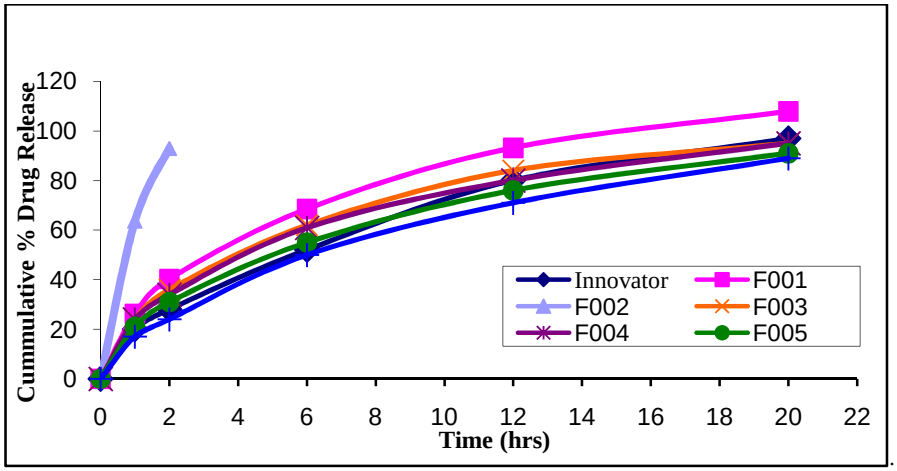


Table No.: 5 In vitro release kinetics of Alfuzosin Hydrochloride ER tablets

.

Formulation	F001	F003	F004	F005	F006	Reference
ZeroOrder	0.8593	0.9009	0.9212	0.9348	0.9505	0.9546
First Order	0.9961	0.9916	0.9881	0.9899	0.9932	0.9781
Higuchi	0.9543	0.9781	0.9874	0.9926	0.9963	0.9949
Peppas	0.9804	0.9893	0.9939	0.9960	0.9957	0.9975
Hixson Crowell	0.9826	0.9876	0.9952	0.9942	0.9969	0.9989
Banker Lonsdale	0.9818	0.9978	0.9970	0.9976	0.9904	0.9811
Weibull	0.9880	0.9939	0.9886	0.9930	0.9962	0.9726

Selected formulation Kinetic models plots (F005)

Figure No.: 2
Zero order of Alfuzosin Hydrochloride

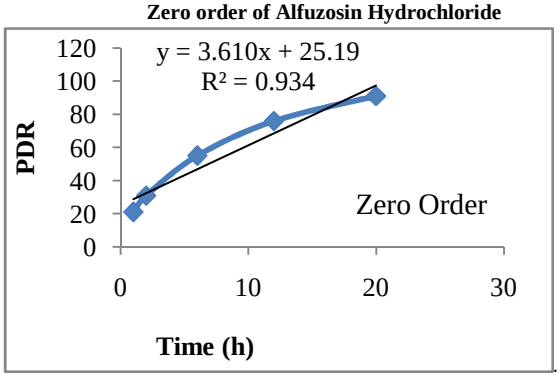


Figure No.: 3
First order of Alfuzosin Hydrochloride

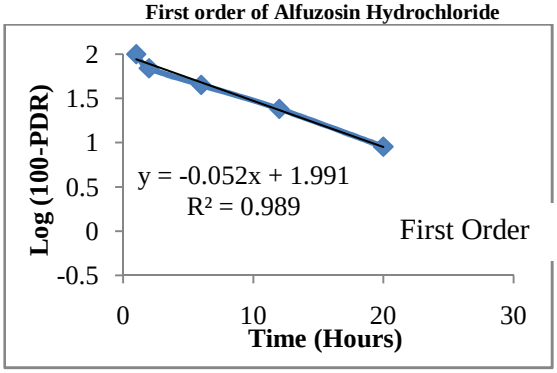


Figure No.: 4
Higuchi Model of Alfuzosin Hydrochloride

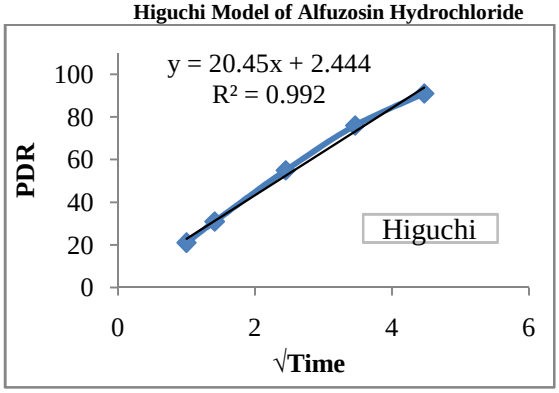


Figure No.: 5
Peppas Model of Alfuzosin Hydrochloride.

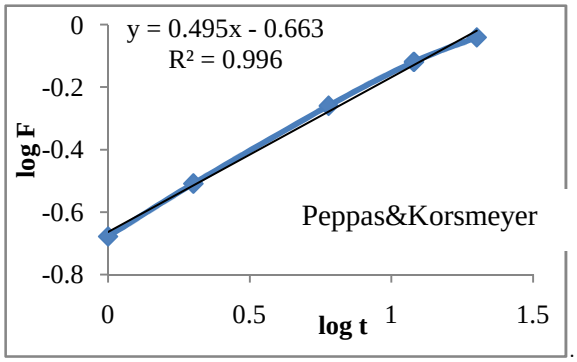


Figure No.: 6
Hixson of Alfuzosin Hydrochloride

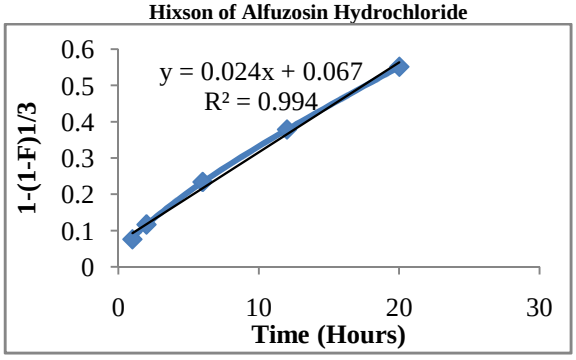


Figure No.: 7
Banker of Alfuzosin Hydrochloride

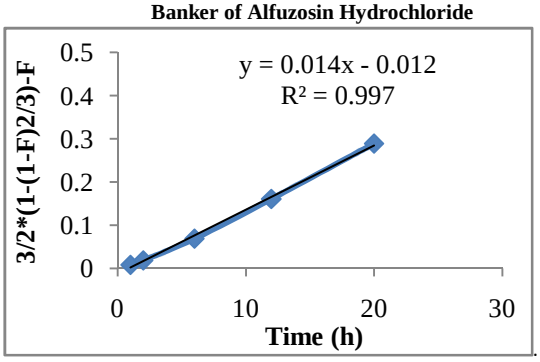


Figure No.: 8 Weibull of Alfuzosin Hydrochloride

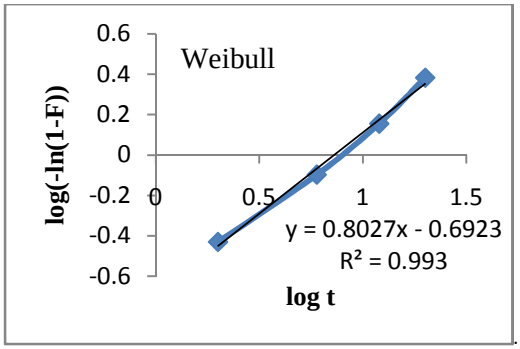
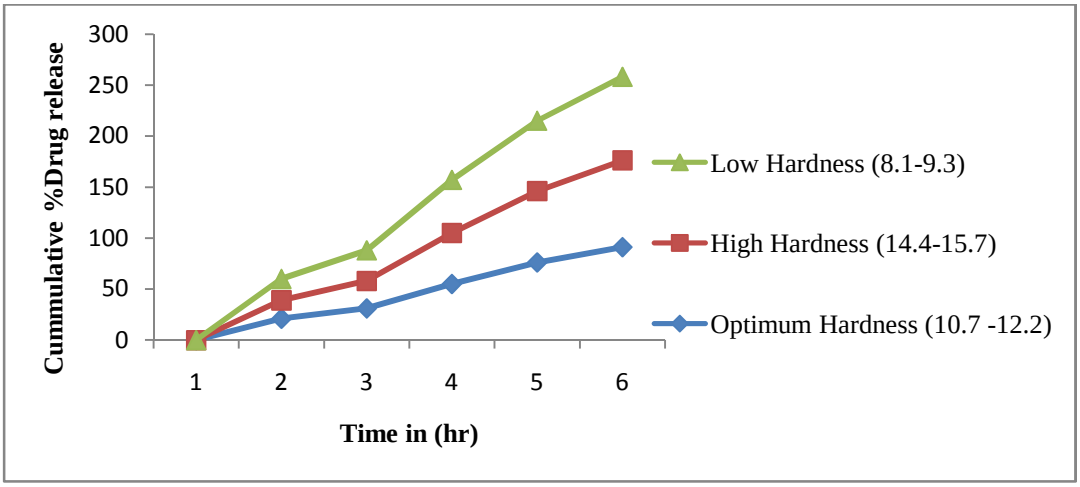


Table No: 6 Dissolution profile at different hardness of Alfuzosin Hydrochloride ER tablets

Time in (hr.)	Optimum Hardness (10.7 -12.2)	High Hardness (14.4-15.7)	Low Hardness (8.1-9.3)
1	21	18	21
2	31	27	30
6	55	50	52
12	76	70	69
20	91	85	82

Figure No.: 9 Dissolution profile at different Hardness of Alfuzosin Hydrochloride ER tablets



All the batches were evaluated for the flow properties of the granules, physical and in vitro release of tablets.Flow property was determined by Hausner's ratio and Carr's Index as shown in Table2.all the batches were shown the satisfactory flow characters.Physical properties of tablets Table-3are hardnessin the range shown in Table 3. Thickness in the range shown in Table 3,percentage weight loss in the friability test was less than 0.2% in all batches and weight variation was within the limit.

All the batches were prepared by wet granulation method. Formulation F001, having Guar gum as retardant and pregelatinized starch as binder. Formulation F002, having Eudragit RLPO as retardant and povidone as binder. Formulation F003, F004, F005 and F006 was having guar gum and HPMC as retardants without any binding agents. Purified water used as granulating agent for all batches.Microcrystalline cellulose was used as diluents for all batches, colloidal silicon dioxide and magnesium stearate are used as glidant and lubricant respectively for all batches.

The in vitro drug release and their kinetic release was conducted for all batches along with the referencesample. The data of in vitro drug release and kinetic drug release was shown in table No. 5 and Table No. 6 respectively.

F005 was proven as better formulation after evaluation of the data with respect to in vitro drug release and their kinetic release.F005 was also shown better release kinetics thanreferencesample. When comes to reference product (UROXATRAL) [12, 13], it is formulated as tri layered tablet. There are many challenges in manufacturing the multi layered tablet formulation like manufacturing cost, tidy formulation procedure and more chances of change in in-process parameters which may affect the product specifications (like weight variation of the layers, difference in compression force between the layers etc…).Formulation F005 can overcome these challenges since it is one way process to control the all those parameters.

The in vitro release was also seen at different hardness ranges to observe the effect of hardness in drug release for optimized formula-F005.The drug release was found to be faster at lower compression force than at higher hardness because of the relatively larger matrix porosity of the tablet, which allowed greater penetration of dissolution fluid into the matrix, thus enhancing polymer disentanglement and drug dissolution.

Stability studies for Formulation F005 revealed that there was no significant change in appearance, assay, and drug release profile at 40°C± 2°&75% RH till 3 months.

CONCLUSION

In the present study, the formulation and production technology of Alfuzosin Hydrochloridehydrophilic matrixtablets have been developed.Alfuzosin Hydrochloride extended release tablets were successfully prepared (Formulation, F5) with HPMC K100M and Guar gum polymers by wet granulation method, which produced extended release with good physical characteristics, predictable and reproducible drug release profiles similar to the reference product(UROXATRAL). Results of the present study confirmed that the Guar gum and hardness plays a major role in drug release. The experiments revealed that HPMC was more efficient when used along with Guar gum in retarding drug release. As the hardness of the tablets increased the drug release was prolonged.

Acknowledgement
Authors are thankful to Sun Institute of Pharmaceutical Education and Research, Nellore (AP), India, for giving support to complete the proposed work successfully.

REFERENCES

[1]Madhu E Nicholas*, Karunakar R, Pavan Kumar K and Raghunadha Gupta C, *Journal of Pharmacy Research,* **2011**,*4(5),1436-1437.*
[2]M.Lee, American Journal of Health – System Pharmacy, Vol 60, 14, 1426-1439.
[3]SABravo, MC Lamas and CJ Salamon, *J. Pharm.Pharmaceut. Sci.* **2002**, 5, 213-219.
[4]Reddy KR, Mutalik S and Reddy S.,*AAPS PharmSciTech.,* **2003**, 4, articleno. 61.
[5]Arthur HK. *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association, London,**2000**, 3rd ed. , 271, 297, 463-464.
[6]Gennaro A. (ed.) *Remington: The Science and Practice of Pharmacy.* Mack Publishing Company, Easton,**2006**,21th ed.,917.
[7]Higuchi WI, Bernardo PD, Mehta SC.,Journal of Pharmaceutical sciences,**1967**; 56:200-207.
[8]Hixson AW, Crowell JH. Pharmaceutics of solids and solid dosage, JohnWiley & Sons, New York, **1977**; p. 163.
[9]. Baker RW, Lonsdale HK., Controlled Release of Biologically Active Agents,Plenum press, New York, USA, **1974**; pp.15-71.
[10]Hamid A. Merchant, Harris M. Shoaib, JaweriaTazeen and Rabia I. Yousuf., AAPS PharmSciTech **2006**;
[11]http://www.accessdata.fda.gov/scripts/cder/dissolution/
[12]http://www.rxlist.com/uroxatral-drug.htm
[13]Maggi; Lauretta, Synthelabo (Le Plessis-Robinson,FR), US 6149940 (**1997**).
[14]The United States of Pharmacopeia (33)/The NationalFormulary (28),The Unites States Pharmacopeial Convention, Rockville,**2010**, 35(3) ,715