World Journal of Pharmaceutical research

Volume 2, Issue 6, 2696-2705. Research Article ISSN 2277 – 7105

SWELLING AND RELEASE STUDIES OF STAVUDINE HYDROPHILIC MATRICES CONTAINING DIFFERENT GRADES OF HYDROXYPROPYL METHYLCELLULOSE

Masheer Ahmed Khan *

School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshshila Campus, Khandwa Road, Indore, 452001, India.

Article Received on
24 August 2013,

Revised on 28 Sept. 2013,
Accepted on 30 October 2013

***Correspondence for Author:**

Dr. Masheer Ahmed Khan
School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshshila Campus, Khandwa Road, Indore, 452001, India
masheerak@yahoo.com

ABSTRACT

Sustained release stavudine hydrophilic matrices are used to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after oral administration. Stavudine is a thymidine analog approved for the treatment of HIV infection and once daily dose improves adherence and, therefore, enhances the effectiveness of antiretroviral therapy. The current study examines the relationship between swelling and drug release from the hydrophilic matrices of stavudine prepared using combination of different grades of hydroxypropyl methylcellulose (HPMC), viz, HPMCK4M, HPMCK15M and HPMCK100M. The Degree of Swelling and Percent water uptake were determined for the matrices containing different concentrations and combinations. The results indicate that swelling and release profiles were affected by concentration and viscosity grade of the polymer. When the amount of HPMC in the matrix is high, wetting improves and water uptake into matrices is enhanced. The higher amount of HPMC causes a greater degree of swelling this in turn reduces the drug release, as the diffusional path length of drug is now longer. Conversely, reduction in the amount of HPMC reduces the degree of swelling and the thickness of gel layer, this enables faster drug release. Higher viscosity grades swells to greater extent and has greater intrinsic water uptake property than that of the lower viscosity grades. Swelling studies reveals an inverse relationship between swelling and drug release in the sustained release stavudine matrices.

Key Words: Sustained release matrices, HPMC, Swelling.

INTRODUCTION

Stavudine, 2',3'-didehydro-3'-deoxythymidine (D4T) is a thymidine analog approved for the treatment of HIV infection like other member of this class of antiretrovirals, its purported active metabolite, D4T-5'-triphosphate, is an inhibitor of the HIV reverse transcriptase and acts as a chain terminator during DNA synthesis . Stavudine is currently approved by US-FDA for the treatment of patients who have become intolerant to or failed to response to zidovudine, didanosine or zalcitabine therapy. The mean serum elimination half life reported ranges between 1 to 1.67 hr in adults. It is given twice daily 40 mg. Main dose related adverse effect is peripheral neuropathy. Converting twice daily regimen of stavudine into once daily improve adherence and, therefore, enhances the effectiveness of antiretroviral therapy [1-4].

Sustained release drug delivery system is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. Hydrophilic matrices devices are one of the least complicated approaches in the formulation of sustained release dosage forms and are finding increasing application in the pharmaceutical field. The aim of the present study was to investigate relationship between swelling and drug release from the sustained release hydrophilic matrices of stavudine prepared using combination of different grades of hydroxypropyl methylcellulose (HPMC), viz, HPMCK4M, HPMCK15M and HPMCK100M [5-8]. Drug release data from HPMC matrices follows the classical Higuchi dissolution equation, relating drug release with square root of time. Swellable systems consisting of hydrophilic polymers, in the presence of water, absorb a significant amount of water to form a gel. As the dissolution medium penetrates the matrix, polymer material swelling starts and drug molecules begin to move out of the system by diffusion. The degree of swelling and percent water uptake is determined to find the relationship between the drug release and swelling. The release mechanism is obtained from the dissolution data and the value of release rate exponent is determined. The value of release rate exponent (n) is a function of geometric shape of the drug delivery device. The results indicate that the mechanism of release is influenced greatly by the polymer concentration of the formulations as can be seen from values of n and generally in accordance with these indications. The release is mainly determined by the Fickian diffusion which is also confirmed from the n values[9-14].

Experimental

Materials and Methods

Stavudine was obtained as a gift sample and tablets were prepared by direct compression using HPMCK4M, HPMCK15M and HPMCK100M polymer combinations. Other excipients used were Magnesium stearate, Talc, MCC and dibasic calcium phosphate.

Preparation of Matrices

Nine formulations employed for investigations containing different ratios of HPMC of different grades were prepared by direct compression and coded C1, C2, C3, D1, D2, D3, E1, E2 and E3. The ratios of different grades of HPMC employed are shown in Table 1. The amount of drug, magnesium stearate, MCC and talc were kept constant while dicalcium phosphate was taken in sufficient quantity to maintain a constant tablet weight. All the products and process variables (other than the concentrations of two polymers) like mixing time, compaction force, etc, were kept constant. Ten tablets from each batch were weighed individually and subjected to physical evaluation.

Table 1. Different ratios employed in formulations containing HPMC of different grades.

Formulation Code	HPMCK4M	HPMCK100M	STAVUDINE
C1	1	1	1
C2	2	2	1
C3	3	3	1
Formulation Code	HPMCK4M	HPMCK15M	STAVUDINE
D1	1	1	1
D2	2	2	1
D3	3	3	1
Formulation Code	HPMCK15M	HPMCK100M	STAVUDINE
E1	1	1	1
E2	2	2	1
E3	3	3	1

Matrix Swelling and Water Uptake Studies

Swelling was evaluated by weight of the matrices. The matrices were placed in 900 ml dissolution medium pH 6.3, at 37^0C. At different time intervals, the previously weighed

tablets were removed, gently wiped with a tissue to remove surface water, and reweighed. The percent water uptake i.e., degree of swelling due to absorbed test liquid, can be estimated at regular time intervals using the following equation –

% water Uptake = (Ws-Wi)/Wp *100

Where, Ws = Wt. of the swollen matrix at time t, Wi = Initial wt. of the matrix, Wp = wt. of the polymer in the matrix. The polymer swelling or water uptake are mean of three determinations. The degree of swelling can be calculated by the following formula –

Degree of swelling = Ws-Wd/Wd*100

Where, Wd = Final dry wt. of the matrix, Ws = Swollen wt. of the same matrix at immersion time (t). The swelling degree is the mean of at least three determinations.

Dissolution Studies

Dissolution studies were carried out for all the nine formulations in triplicate, employing dissolution apparatus, using distilled water pH 6.3 as the dissolution medium at 50 rpm and 37 ± 0.5^0C. An aliquot of sample was periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of plain dissolution medium. The drug was analyzed by UV spectrophotometer (UV 1601 Shimadzu, Japan) at 266nm.

Physical Characteristics

The tablet weights of all the batches vary between 120-127mg, and tablet hardness between 5.5-5.8kg. The tablet friability ranged between 0.5-0.8%. The physical parameters of the manually compressed tablets were found within control.

Table 2. Final dry weight and weight of polymer in matrix tablets of different Formulations

Formulation Code	Final Dry weight (Wd) (mg)	Weight of polymer in matrix (Wp) (mg)
C1	125	24
C2	124	48
C3	127	72
D1	127	24
D2	125	48
D3	126	72
E1	120	24
E2	124	48
E3	125	72

Table 3. Percent water uptake of formulations as a function of time									
	C1	C2	C3	D1	D2	D3	E1	E2	E3
0.5	104.17	47.92	52.77	70.83	41.67	44.44	154.17	85.42	69.44
1	195.83	110.42	87.50	100.00	81.25	58.33	200.00	125.00	97.22
2	433.33	235.42	176.39	387.50	222.92	179.17	354.17	241.67	206.94
3	558.33	302.08	222.22	454.17	293.75	206.94	516.67	335.42	256.94
4	687.50	360.42	265.28	604.17	341.67	254.17	729.17	379.17	312.50
5	804.17	458.33	325.00	675.00	414.58	288.89	791.67	458.33	333.33
6	895.83	500.00	358.33	850.00	458.33	313.89	925.00	504.17	361.11
8	1000.00	558.33	427.78	920.83	493.75	375.00	1050.00	568.75	444.44
10	1187.50	656.25	515.28	1037.50	608.33	415.28	1154.17	668.75	555.56
12	1295.83	770.83	600.00	1225.00	735.42	477.78	1354.17	835.42	597.22

Table 4. Degree of swelling of different formulations as a function of time									
TIME HRS	C1	C2	C3	D1	D2	D3	E1	E2	E3
0.5	20.00	18.40	32.00	13.39	16.00	25.40	30.83	33.06	40.00
1	37.60	42.40	52.00	18.90	31.20	33.33	40.00	48.39	56.00
2	83.20	90.40	103.20	73.23	85.60	102.38	70.83	93.55	119.20
3	107.20	116.00	129.60	85.83	112.80	118.25	103.33	129.84	148.00
4	132.00	138.40	154.40	114.17	131.20	145.24	145.83	146.77	180.00
5	154.40	176.00	188.80	127.56	159.20	165.08	158.33	177.42	192.00
6	172.00	192.00	208.00	160.63	176.00	179.37	185.00	195.16	208.00
8	192.00	214.40	248.00	174.02	189.60	214.29	210.00	220.16	256.00
10	228.00	252.00	298.40	196.06	233.60	237.30	230.83	258.87	320.00
12	248.80	296.00	347.20	231.50	282.40	280.95	270.83	323.39	344.00

RESULTS AND DISCUSSION

The weight of the polymer in the matrix (Wp) and final dry weight of the matrix (Wd) are shown in Table 2. The percent water uptake and degree of swelling as a function of time is reported in Table 3and Table 4 respectively. The results of swelling studies are shown graphically for different formulations. Fig1a shows the plot for water uptake as a function of time for formulation codes C1, C2, C3 containing HPMC K4M and K100M combinations

with different ratios and Fig1b shows plot for degree of swelling as a function of time for formulation codes C1, C2, C3. Similar plots are shown in Fig 2a and Fig 2b for formulation codes D1, D2, D3, containing HPMC K4M and K15M combinations with different ratios and Fig 3a and Fig 3b for formulation codes E1, E2, E3, containing HPMC K15M and K100M combinations with different ratios. The dissolution parameters of varied formulation with different ratios of polymer combinations obtained during studies are shown in Table 5.

Formulation C1 has n= 0.501, C2 has n=0.448 and C3 has n=0.438 indicating that the release mechanism is very close to Fickian transport i.e. belong to the Higuchi model. Similar results are observed with formulations D1, D2, D3 as well as with formulations E1, E2 and E3. In this investigation it has been clearly demonstrated that an inverse relationship exists between the drug release rate and matrix-swelling rate. When the amount of HPMC in the matrix is high, wetting improves and water uptake into matrices is enhanced. The higher amount of HPMC irrespective of different grades causes a greater degree of swelling. This in turn reduces the drug release, as the diffusional path length of drug is now longer. Conversely, reduction in the amount of HPMC reduces the degree of swelling and the thickness of gel layer and thus enables faster drug release. It is also demonstrated that HPMC of higher viscosity grades swells to greater extent and has greater intrinsic water uptake property than that of the lower viscosity grades.

Table 5. Dissolution parameters of different formulations

Formulation Code	Release at 12 hr	n	Degree of Swelling (%)	Percent of water uptake
C1	98.34	0.501	248.8	1295.83
C2	85.96	0.448	296.0	770.83
C3	76.7	0.438	347.2	600.00
D1	104.6	0.540	231.5	1225.00
D2	103.6	0.538	282.4	735.42
D3	87.46	0.456	280.95	477.78
E1	95.80	0.490	270.83	1354.17
E2	76.84	0.436	323.39	835.42
E3	66.20	0.430	344.00	597.22

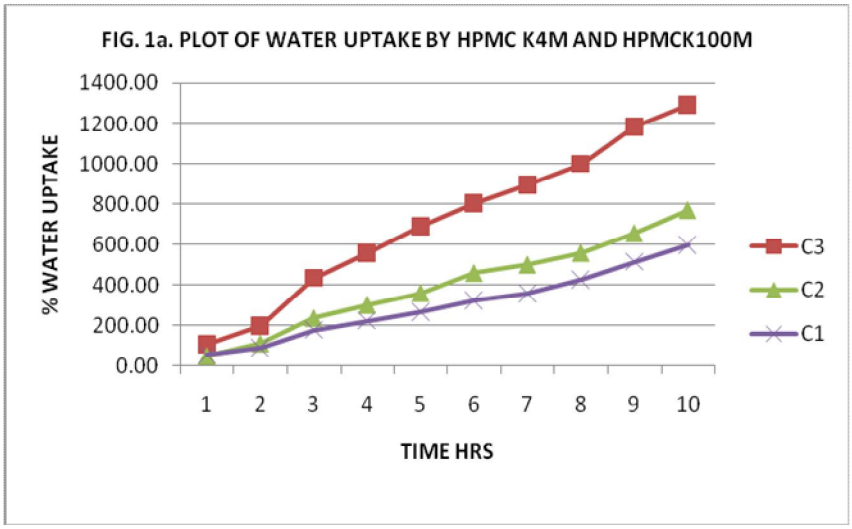
FIG. 1a. PLOT OF WATER UPTAKE BY HPMC K4M AND HPMCK100M
% WATER UPTAKE
1400.00
1200.00
1000.00
800.00
600.00
400.00
200.00
0.00
1 2 3 4 5 6 7 8 9 10
TIME HRS
C3
C2
C1

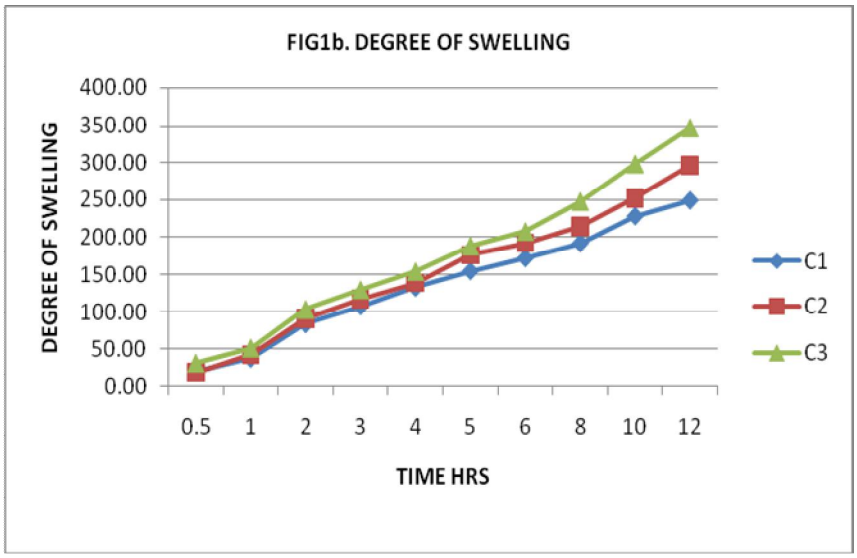
FIG1b. DEGREE OF SWELLING
DEGREE OF SWELLING
400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0.00
0.5 1 2 3 4 5 6 8 10 12
TIME HRS
C1
C2
C3

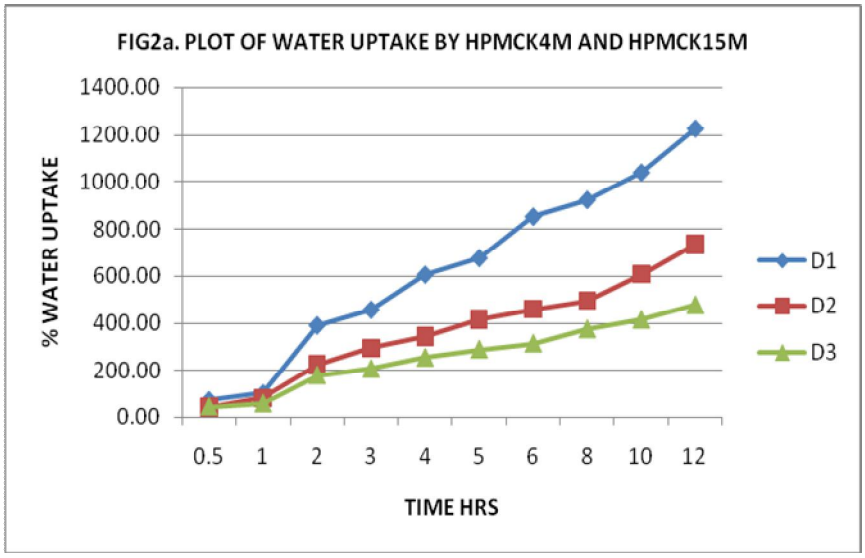
FIG2a. PLOT OF WATER UPTAKE BY HPMCK4M AND HPMCK15M
% WATER UPTAKE
1400.00
1200.00
1000.00
800.00
600.00
400.00
200.00
0.00
0.5 1 2 3 4 5 6 8 10 12
TIME HRS
D1
D2
D3

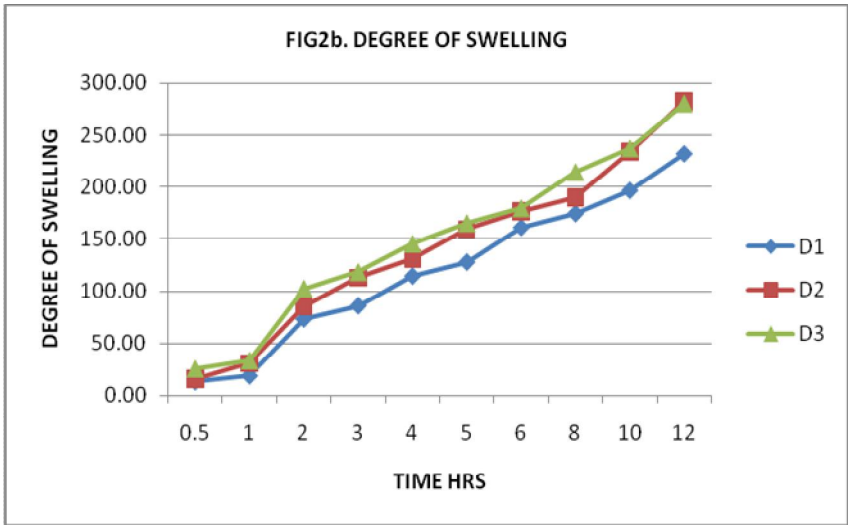
FIG2b. DEGREE OF SWELLING
DEGREE OF SWELLING
300.00
250.00
200.00
150.00
100.00
50.00
0.00
0.5 1 2 3 4 5 6 8 10 12
TIME HRS
D1
D2
D3

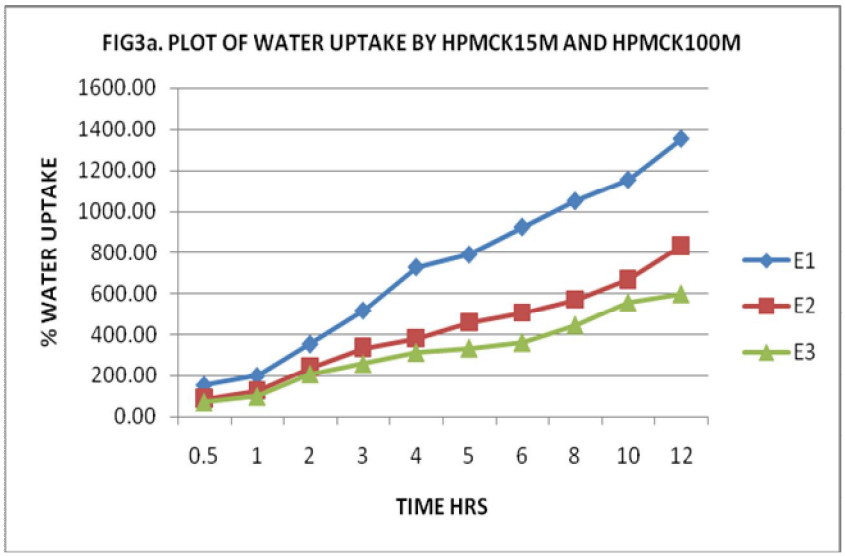
FIG3a. PLOT OF WATER UPTAKE BY HPMCK15M AND HPMCK100M
% WATER UPTAKE
1600.00
1400.00
1200.00
1000.00
800.00
600.00
400.00
200.00
0.00
0.5 1 2 3 4 5 6 8 10 12
TIME HRS
E1
E2
E3

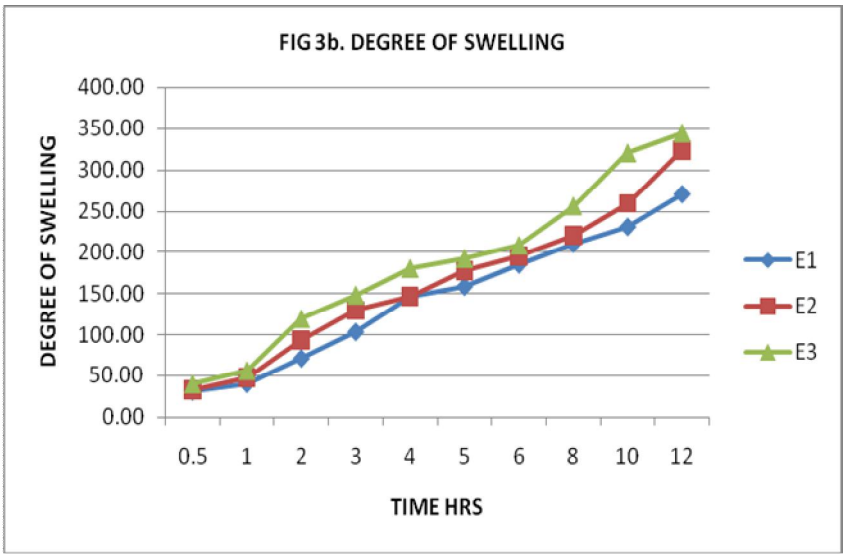
FIG 3b. DEGREE OF SWELLING
DEGREE OF SWELLING
400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0.00
0.5 1 2 3 4 5 6 8 10 12
TIME HRS
E1
E2
E3

CONCLUSION

Swelling studies reveals an inverse relationship between swelling and drug release in the sustained release stavudine matrices. The rational combination of different grades of hydroxypropyl methyl cellulose (HPMC) can be used satisfactorily to regulate the release of drug for extended period of time in such matrices.

REFERENCES

1. Lea AP, Fauld D, Stavudine: A review of its pharmacodynamics and pharmacokinetics properties and chemical potential in HIV infection. Drugs1996, 51,854-864.
2. Huang P, Farquhar d, Plunkett W, Selective action of 2',3' didehydro-2',3'-dideoxythymidinetriphosphate on human immune deficiency virus reverse transcriptase and human DNA polymerases, J. Biol. Chem. 1982, 267, 1817-1822.
3. Kumar D, Dave.V, Lewis.S, Parmar.B, Gajbhiye K R, and Paliwal S., Design and evaluation of sustained release matrix once daily formulation of stavudine, International Journal of Drug Delivery, 2 ,2010, 125-134.
4. Saravanakumar M, Venkateswaramurthy N, Dhachinamoorthi D, Perumal P. Extended release matrix tablets of Stavudine: Formulation and *in vitro* evaluation. Asian J Pharm 2010;4:219-23
5. Khan MA, and Maheshwari RK, Studies of relationship between swelling and drug release in the sustained release hydrophilic matrices containing different grades of hdroxypropylmethyl cellulose, Research Journal of Pharmaceutical, Biological and Chemical Sciences (RJPBCS), Vol. 2, Issue- 4 (2011),970-975.
6. Khan M.A. Studies of swelling effect and drug release in hydrophilic matrices containing different grades of polymers, Research J. of Pharm. Biological and Chemical Sci. (4)1,2013, 1241-1247.
7. Khan M.A. , Chaturvedi S C.,Swelling and Drug Release Studies from Hydrophilic Matrices Containing Combination of Different Grades of Hydroxyl Propyl Methylcellulose, Asian Journal of Chemistry, Vol. 22,Issue 6(2010), 3566-3568.
8. Khan M.A. Effect of Swelling and drug release relationship of sustained release matrices containing different grades of hydroxypropyl methyl cellulose, Research J. Pharma Dosage Forms and Tech, 5 (4), 2013 232-236.
9. Wan, L. S. C., and Wong, L.F., Drug Dev. Ind. Pharm., 19(10), (1993).
10. Efentakis M, Vlachou M, Choulis N.H, Drug Dev. Ind. Pharm, 23: (1997), 107-112.

11. M.J.Vazquez, M Casalderry, R.Duro, J.L.Gomez.-Amoza, R.M.Pacheco, C. Souto, A.Concherio, Atenolol release from hydrophilic matrix tablets with hydroxypropylmethylcellulose (HPMC) mixtures as gelling agent: effects of the viscosity of the HPMC mixture, Volume 4, Issue 1, January 1996, Pages 39–48.
12. Liberman H, Lachman L and Schwartz J, Pharmaceutical Dosage Forms: Tablets, vol.1, 2nd edition revised and expanded , Dekker, New York, 2005.
13. Goodman and Gilman's: The Pharmacological basis of therapeutics. 10th edition . Mc-Graw Hill 2001: 709-710.
14. Swarbric J, and Boylan J.C.; Encyclopedia of Pharmaceutical Technology, Marcell Dekker, New York, 1995.