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Formulation development and evaluation of sustained release matrix tablet of Lamivudine using tamarind seed polysaccharide

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ABSTRACT

Hydrophilic matrices are an interesting option when developing an oral sustained-release formulation. They can be used for controlled release of both water-soluble and water-insoluble drugs. The present work is related with exploitation of tamarind seed polysaccharide (TSP) as an excipient in drug delivery systems. The main aim of proposed work is to focus on the possibilities of using this polysaccharide in industries with particular reference to its physical, chemical properties for the formation of new drug delivery systems. This objective motivates for developing newer synthetic excipient and exploiting the presently own limitation in term of toxicity, compatibility and cost effectiveness. Present study aimed at development and characterization of sustained release matrix tablet of lamivudine by using combination of TSP with ethylcellulose for treatment of HIV. The matrix tablets of lamivudine were prepared by direct compression method and evaluated for it's drug release characteristics. The drug release was decreased with the increase in TSP concentration and with the addition of ethylcellulose. Drug release kinetics was explained by Higuchi's equation, as the plots showed the highest linearity, but a close relationship was also noted with zero-order kinetics. The in vivo investigation in rabbits showed sustained release pharmacokinetic profile of lamivudine from the matrix tablets formulated using TSP and ethylcellulose. The optimized formulation was also subjected for stability testing and was found to have good stability with no appreciable drug degradation. Hence, it was found to be a better combination for the formulation of sustained release matrix tablets of lamivudine.

Key Words: Lamivudine, hydrophilic matrix, tamarind seed polysaccharide, matrix tablets, treatment of HIV.

INTRODUCTION

Hydrophilic matrices are an interesting option when developing an oral sustained release formulation. The drug release from such matrices can be controlled through their physical properties[1]. Polysaccharides are the choice of materials among the hydrophilic polymers used,

because they are nontoxic and acceptable by the regulating authorities[2]. The various polysaccharides used in drug delivery application are cellulose ethers[3], xanthan gum[4], locust bean gum[5] and guar gum[6]. Another natural polysaccharide, Tamarind seed polysaccharide (TSP) obtained from the seed kernel of Tamarindus indica, possesses properties like high viscosity, broad pH tolerance,[7] noncarcinogenicity [8], mucoadhesive nature, and biocompatibility[9]. It is used as stabilizer, thickener, gelling agent, and binder in food and pharmaceutical industries. The tamarind seed polysaccharide constitutes about 65% of the tamarind seed components[10]. It is a branched polysaccharide with a main chain of β -d-(1,4)-linked glucopyranosyl units, and that a side chain consisting of single d-xylopyranosyl unit attached to every second, third, and fourth d-glucopyrnosyl unit through an α-d-(1,6) linkage. One d-galatopyranosyl unit is attached to one of the xylopyranosyl units through a β - d-(1,2) linkage[11]. Lamivudine is a potent antiviral agent used in the treatment of AIDS. Conventional oral formulation of lamivudine are administered multiple times a day (150mg twice daily) because of it's moderate half-life (t1/2 =5-7 hrs [12,13]. Treatment of AIDS using conventional formulations of lamivudine is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multidose thrapy[14], poor patient compliance, and high cost. Sustained release once-daily formulation of lamivudine can overcome some of these problems. The present study was aimed to evaluate the feasibility of using TSP as matrix material for prolonged drug release of lamivudine.

MATERIALS AND METHODS

Materials

Tamarind kernel powder was obtained as gift sample from Prepem Gums Pvt. Ltd., Mumbai. Lamivudine was obtained as gift sample from Ranbaxy Research Lab. Dewas(India). Ethylcellulose, Magnesium Sterate, Microcrystalline cellulose were purchased from CDH (P) Ltd, New Delhi, India. Absolute ethanol was purchased from Merck Ltd., India. All the chemicals used were of A.R grade.

Isolation of TSP

TSP was isolated following the method reported by Rao et al (1973).[10,15]. To 20g of tamarind kernel powder, 200ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800ml of boiling distilled water. The solution was boiled for 20 minutes under stirring condition in a water bath. The resulting thin clear solution was kept overnight so that most of the proteins and fibers settled out. The solution was then centrifuged at 5000 rpm for 20 minutes. The supernatant was separated and poured into twice the volume of absolute ethanol by continuous stirring. The product was filtered through muslin cloth and was pressed between felt. The precipitate was washed with absolute ethanol, iso-propanol and methanol and then dried at -50-60^{0}C under freeze dryer. The dried material was ground and sieved to obtain granules of different particle size range and stored in a desiccator until further use.

Formulation of Tablets

Matrix tablets were prepared by direct compression method. The ingredients as given in table 1 were mixed in geometric dilution principle and were blended in a polybag. The blend was compressed using twelve station rotatory tablet punching machine (RIMEK) using 11.5 mm standard concave punches.

Evaluation Parameters:
The properties of the matrix tablet, such as hardness, friability, weight variation and drug content were determined using reported procedure.[16] Briefly, hardness was determined using Monsanto hardness tester. Friability was determined by using Roche friability testing apparatus. Weight variation and drug content was performed according to IP procedures.[16]. The drug content was determined by weighing 10 tablets individually and powdered equivalent to 100mg of drug was extracted with water. The solution was filtered and after suitable dilution its absorbance was measured at 270nm by UV visible spectrophotometer (Shimadzu 1700).

***In vitro* drug release**: -
In vitro drug release studies of the prepared matrix tablets were conducted for a period of 24 hours using USP II dissolution tester apparatus (Electrolab-TDT-08L) at 37 ± 0.5 C and 50 rpm speed using 900ml phosphate buffer pH 6.8 as dissolution media. The dissolution study was carried out under sink condition. At appropriate time interval samples were withdrawn from dissolution media and were replaced with fresh media to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed by UV spectrophotometer[17].

Model used for drug release kinetics:
The drug release kinetics was analyzed by plotting the log fraction released versus log time and data fitted to the following exponential model:

$$Mt / M\infty = k\ t^n$$

Where Mt / M∞t is the fractional drug release into the dissolution medium time t, k is the constant related to the properties of the drug delivery system and n is related to release mechanism, its value ranges from 0.5 (fickian release) to 1.0 (Case II transport) whereas n values between 0.5 and 1.0 are indicative of non fickian or anomalous release.

***In vivo* studies**
In vivo studies were performed on rabbits (weighing 2.8-3.2 kg). The tablets were administered orally. The tablets were put behind the tongue to avoid their destruction due to biting. Food was withdrawn from the rabbits 12 hrs before drug administration and 24 hrs after postdosing. All rabbits had free access to water throughout the study. All studies were approved by Institutional Animal Care and Use Committee and were conducted in accordance with the NIH guidelines for the care and use of laboratory animals.

The blood samples were collected from marginal ear vein, in a heparinized micro centrifuge tube and were centrifuged at 5000 rpm for 10 minutes. The supernatant were collected and precipitated using acetonitrile in ratio of 1:2 v/v and was further centrifuge at 5000 rpm for 10 minutes. The supernatant were collected, filtered and were stored under deep freezer for further analysis.

Quantitative estimation of drug in plasma

The quantitative estimation of drug in plasma was performed by HPLC assay using methanol and water mixture in ratio of 60:40 v/v as mobile phase. The pH of mobile phase was adjusted to 4.5

using acetic acid and flow rate was set at 0.8 ml/min. Twenty microlitres of injection was eluted in C18 column at room temperature. The chromatogram was monitored at 271nm using diode array UV detector.

Stability study

Stability studies were carried out for the optimized formulation. The tablets were placed in glass vials and stored in stability chambers set at 25ºC±2^{0}C, 30ºC±2^{0}C and 40ºC±2^{0}C temperature and 60%±5, 65%±5 and 75%±5 relative humidity respectively. The samples were assayed for drug content at regular intervals.

RESULTS AND DISCUSSION:

The compatibility between the drug and the isolated polysaccharide (TSP) was found to be good by the DSC studies. The matrix tablets of lamivudine were prepared by direct compression method. Table 2 shows the data obtained from the evaluation of tablets. The hardness of the tablets was found to be in the range of 8-10 kg/cm^2. The tablets showed 96-99 % of the labeled amount of drug, indicating uniformity in drug content. The individual weight variation was found to be within ±7.5% of the average tablet weight. The friability values were found to be in the range of 0.57-0.8 % for all the formulations. The drug release decreased as the concentration of TSP in the matrix increased. The in-vitro drug release profile of lamivudine from all the formulations is shown in Fig.2. The results indicated retardant release of drug from all the formulations with increase in the polymer concentration. The formulations showed a slow and complete drug release of over a period of 24 hrs.

The different modes of data treatment are shown in Table 3. These values indicates that all the matrix tablet formulation releases the drug in sustained manner up to 24 hrs, but formulation F2 released 98.82% of drug and release was found to be extended over a period of 24 hrs, hence, the formulation could be considered as a once-daily sustained release matrix tablet of lamivudine. The formulation showed acceptable pharmacotechinical properties and assay requirement. Drug release kinetics indicated that drug release pattern was best explained by Higuchi's equation, as the plots showed the highest linearity (r^2 = 0.9968), but a close relationship was also noted with zero-order kinetics (r^2 = 0.9518).

The *in vivo* study of lamivudine matrix tablet was performed on albino rabbits. The pharmacokinetic parameters are shown in table 7.5. The values of C_{max}, T_{max}, and AUC for formulation F2 were found to be 2.9µg/ml, 6hr and 50.67 µg hr/ml, respectively.

Stability studies of optimized formulation were performed at normal, intermediate and accelerated conditions. The data are shown in figure3 and table 4. It was found that formulation placed at 25ºC show very less amount of drug loss, which indicates that formulation is more stable at room temperature

Hence, it was found to be a better combination for the formulation of sustained release matrix tablets of lamivudine.

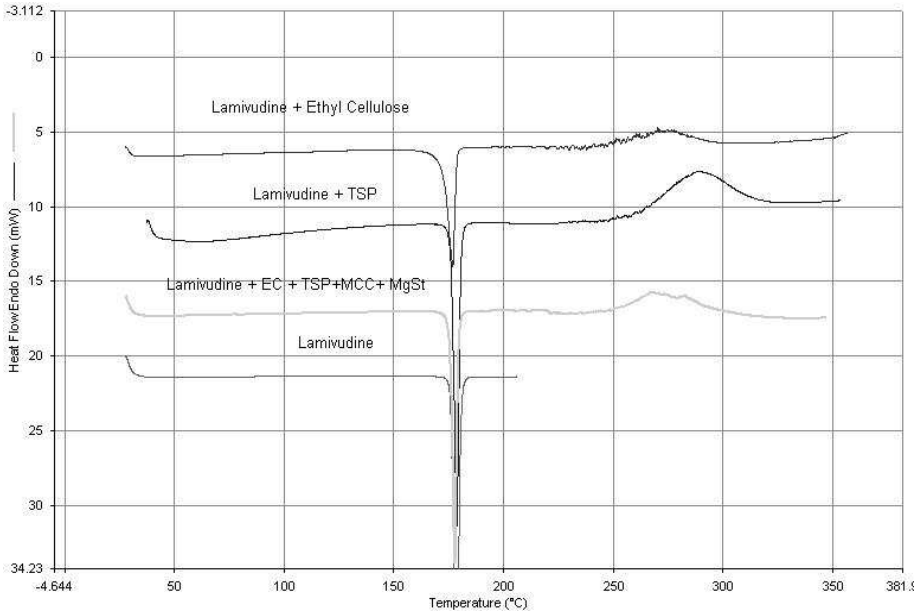

Figure 1 DSC data of lamivudine and its physical mixture with other tablet ingredients.

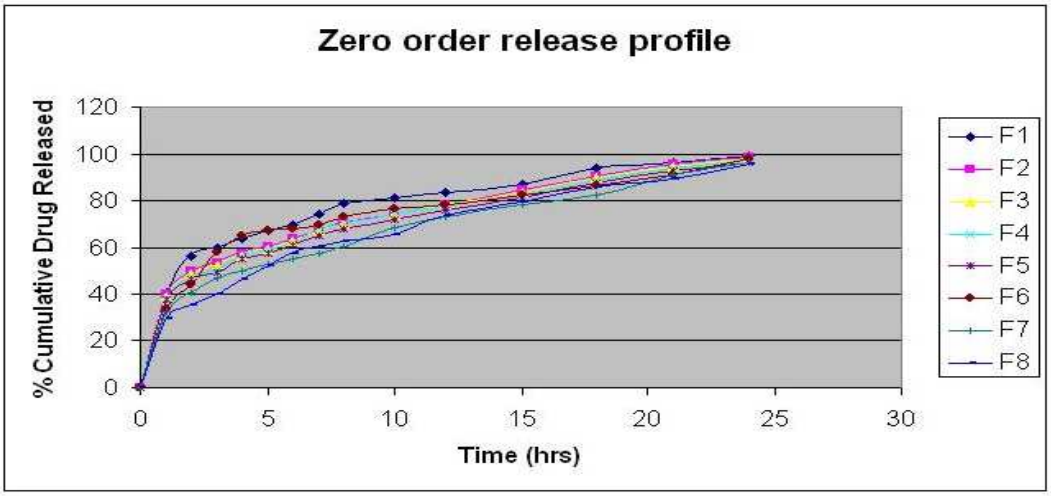

Figure 2 Comparative *in vitro* drug release from various matrix tablet formulations (F1-F12)

F1 to F12- formulation contain quantity of Lamivudine, Tamarind kernel powder (TSP), Ethylcellulose, Microcrystalline cellulose (MCC) and Magnesium Sterate as given in Table 1,

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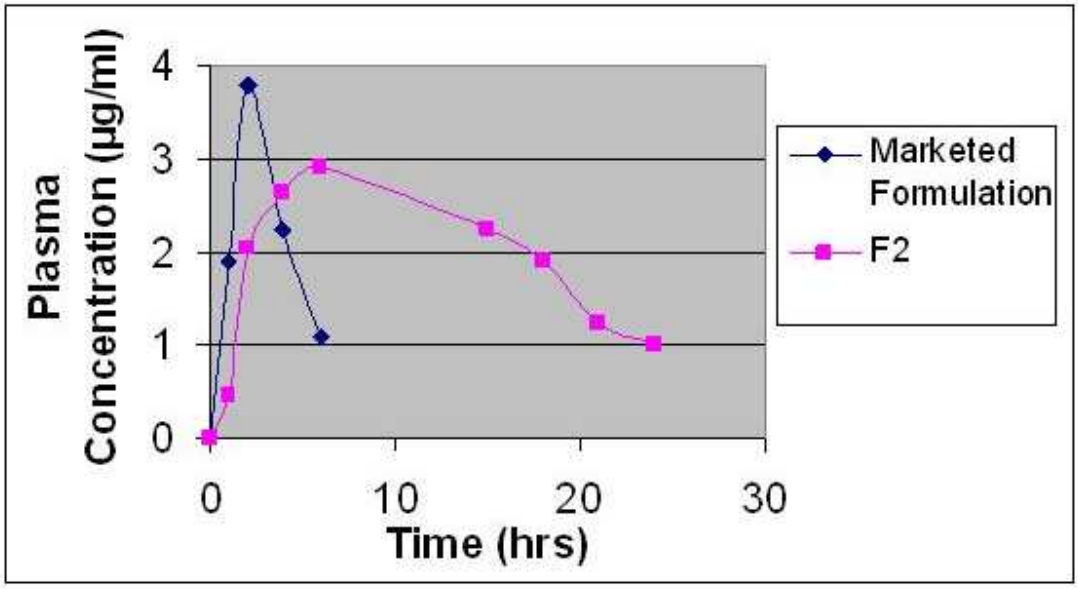

Figure 3 Comparison of plasma drug concentration-time profile of lamivudine
F2- formulation contain quantity of Lamivudine-200mg, Tamarind kernel powder (TSP)-100mg, Ethylcellulose-100mg, Microcrystalline cellulose (MCC)- 194mg and Magnesium Sterate-6mg

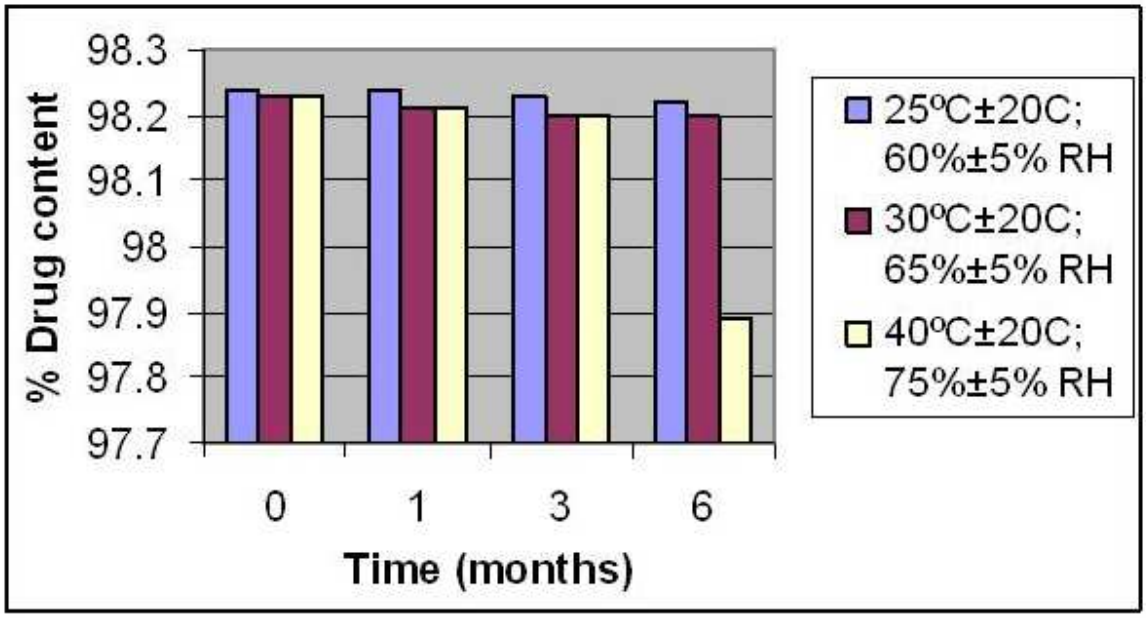

Fig. 4 Percentage drug content of lamivudine matrix tablet formulation at various temperature and humidity conditions

F1-F12- F1 to F12- formulation contain quantity of Lamivudine, Tamarind kernel powder (TSP), Ethylcellulose, Microcrystalline cellulose (MCC) and Magnesium Sterate as given in Table 1,

Table 1 Formulation design for sustained release matrix tablets of lamivudine

Formulation Code	Lamivudine (mg)	TSP (mg)	Ethylcellulose (mg)	MCC (mg)	Magnesium Sterate (mg)
F1	200	50	100	244	6
F2	200	100	100	194	6
F3	200	150	100	144	6
F4	200	200	100	94	6
F5	200	250	100	44	6
F6	200	50	150	194	6
F7	200	100	150	144	6
F8	200	150	150	94	6
F9	200	200	150	44	6
F10	200	50	200	144	6
F11	200	100	200	94	6
F12	200	150	200	44	6

TSP- *Tamarind seed powder*
MCC- *Microcrystalline cellulose*

Table 2 Evaluation parameter for matrix tablet of lamivudine

S. No.	Formulation Code	Weight Variation (%)	Hardness (kg/cm^2)	% Friability	% Drug content
1	F1	588 ±2.0	8.0	0.8	97.19
2	F2	582 ±3.0	8.67	0.74	98.23
3	F3	603 ±0.5	9.0	0.69	96.98
4	F4	584 ±2.67	9.17	0.62	97.72
5	F5	575 ±4.17	9.5	0.58	99.86
6	F6	610±1.02	9.33	0.65	98.45
7	F7	582±3.0	9.67	0.79	97.12
8	F8	571±4.83	9.17	0.54	96.52
9	F9	592±1.33	8.5	0.68	97.02
10	F10	608 ±1.33	10.0	0.59	98.04
11	F11	579 ±3.5	9.5	0.63	97.33
12	F12	587±2.17	8.83	0.57	98.67

Table 3 Kinetics model and regression coefficient of different matrix tablet formulations (F1-F-12)

S. No.	Formulation code	Zero order (r^2)	First order (r^2)	Higuchi pattern (r^2)	n value
1	F1	0.8756	0.911	0.9625	0.2568
2	F2	0.9518	0.9127	0.9968	0.2824
3	F3	0.9454	0.9368	0.996	0.2941
4	F4	0.9405	0.9302	0.9939	0.2993
5	F5	0.951	09226	0.9966	0.3016
6	F6	0.8135	0.9195	0.9254	0.3346
7	F7	0.9065	0.885	0.9794	0.3535
8	F8	0.9239	0.986	0.9879	0.3621
9	F9	0.9161	0.9548	0.986	0.3779
10	F10	0.9554	0.9364	0.9952	0.3918
11	F11	0.9136	0.9605	0.9832	0.3879
12	F12	0.9445	0.9748	0.9892	0.3836

F1-F12- F1 to F12- formulation contain quantity of Lamivudine, Tamarind kernel powder (TSP), Ethylcellulose, Microcrystalline cellulose (MCC) and Magnesium Sterate as given in Table 1,

Table 4 Pharmacokinetic parameters of lamivudine

S. No.	Pharmacokinetic response	Marketed preparation	Formulation F2
1	C_{max}	3.8	2.9
2	$AUC_{0\rightarrow24}$	13.20	49.225
3	T_{max}	2	6

AUC- Area Under the curve

Table 4 Stability data of F2 formulation

S. No.	Condition	Drug content (%) at Time (months)			
		0	**1**	**3**	**6**
1	**25°C±2^{0}C;60%±5% RH**	98.24	98.24	98.23	98.22
2	**30°C±2^{0}C; 65%±5% RH**	98.23	98.21	98.20	98.20
3	**40°C±2^{0}C; 75%±5% RH**	98.23	98.21	98.20	97.89

CONCLUSION

The result of the present study demonstrated the isolated TSP can be used as a drug release retardant in combination with ethylcellulose, which was evident, from the results. The drug release was extended over a period of 24 hours and the mechanism of drug release was observed to be following higuchi model and a close relation with zero order release. The *in vivo* studies in rabbits showed sustained release of lamivudine up to 24 hrs.

Stability study was performed in accordance to ICH guidelines and no change in physical appearance and no appreciable drug loss were observed. This indicates that the formulation passes the stability test. Thus, the polymer could serve as a new effective drug release retardant with better patient compliance.

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REFERENCES

[1]. Vazquez M, Perez-Marcos B, Gomez-Amoza JL, Martines, Pacheco R, Souto C, Concheiro A. *Drug Dev Ind Pharm* **1992**, 18, 1355-75.
[2]. M.C. Bonferoni, S. Rossi, M. Tamayo, J.L. Pedraz, G.A. Dominguez, C. Caramella, *J Control Release*, **1993**, 26, 119-27.
[3]. J.L. Ford, M.H. Ribinstein, F. McCaul, J.E. Hogan, P.J. Edgar. *Int J Pharm* **1987**, 40, 223-34.

[4]. M.M. Talukdar, J. Plaizier-Vercammen.. *Drug Dev Ind Pharm* **1993**, 19(9): 1037-46.
[5]. J. Sujja-areevath, D.L. Munday, P.J. Cox, K.A. Khan. *Int J Pharm* **1996**,139, 53-62.
[6]. Khullar P, Khar RK, Agarwal SP. *Drug Dev Ind Pharm*, **1998**, 24(11): 1095-99.
[7]. P.S. Rao, T.P. Ghosh, S. Krishna, *J Sci Ind Research*, **1946**, 4, 705.
[8]. M. Sano, E. Miyata, S. Tamano, A. Hagiwara, N. Ito, T. Shirai. (**1996**). *Food and Chem Toxicol*, 34, 463-467.
[9]. S. Burgalassi, L. Panichi, M.F. Saettone, J. Jacobsen, M.R. Rassing, *Int J Pharm*, **1996**, 133:1-7.
[10]. P.S. Rao, H.C. Srivastava, Tamarind, in Whistler RL (ed), Industrial Gums. 2nd ed., Academic Press, New York.: **1973** 369-411.
[11]. M.J. Gidley, P.J, Lillford, D.W. Rowlands, *Carbohydrate Res.*, **1991**, 214: 299-314.
[12]. S.F. Anthony and H.L. Clifford. Human immunodeficiency virus (HIV) disease, AIDS and related disorders. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. Harrison's Principles of Internal Medicine. New york, NY: McGraw-Hill, **2001**, 1852-1913.
[13]. J.D. Betty, Human immunodeficiency virus (HIV) antiretroviral therapy. In: Herfindal ET, Gourley DR, eds. Textbook of Therapeutics: Drug and Disease Management. Philadelphia, PA: Lippincott Williams & Wilkins, **2000**,1555-82.
[14]. G. Moyle, **2000**, 22, 911-936.
[15]. P.S. Rao, T.P. Ghosh, S. Krishna, *J Sci Ind Research*, 19464, 705.
[16]. Government of India Ministry of Health and Family Welfare. (**2007**). The Pharmacopoeia of India. Delhi, India: Controller of Publication, 176-183.
[17]. P.R. Ravi, S. Ganga, R.N. Saha, *AAPS Pharm Sci Tech*. **2007**, 8(4), 101.