Asian Journal of Pharmaceutical and Clinical Research

DESIGN AND CHARACTERIZATION OF CONTROLLED RELEASE MATRIX TABLETS OF ZIDOVUDINE

R.K.KAR,[*1] S.MOHAPATRA,[1] B.B.BARIK[2]

The investigation was concerned with design and characterization of oral controlled release matrix tablets of Zidovudine (AZT) in order to improve efficacy and better patient compliance. Tablets were prepared by direct compression method using various proportion of hydrophilic polymer viz; Eudragit RS100 and RL100 along or in combination with hydrophobic polymer ethyl cellulose. In vitro release studies were performed using USP type I apparatus (rotary basket type). The release kinetics were analysed using Zero-order model equation, Higuchi's square root equation and Korsmeyer and Peppas' emphirical equation. Compatibility of drug with various formulations excipients was also studied. Dissolution study revealed that either Eudragit RS100 or RL100 10%,20% w/w of tablet preparations were able to sustain the drug release up to 9 hours, but 30%, 40% as well as ethyl cellulose combination with 20% and 25% w/w of Eudragit RS100 and RL100 were able to sustaining the drug release for 12 hour. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets followed non-Fickian diffusion mechanism. No compatibility was observed between the drug and excipients used in the formulation of matrix tablets. The optimized formulation (F13) showed insignificant difference in release mechanism as well as release kinetics ($P>0.05$) when stability study was done for six months at 40 ± 2^{0}C and 75±5% RH.

Keywords : controlled release; matrix tablets; release kinetics; zidovudine.

INTRODUCTION

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages[1]. Controlled release (CR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high-potency drugs.[2]

Acquired Immunodeficiency Syndrome (AIDS), which threatens to cause a great plague in the present generation, was first identified in California in 1981. The joint United Nations programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) reported on global AIDS epidemic showed 38.0 million adults and 2.3 million children were living with human immunodeficiency virus (HIV) at the end of 2005. The annual number of AIDS deaths can be expected to increase for many years to come, unless more effective and patient compliant anti-retroviral medications are available at affordable prices.[3] The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance and huge cost of the therapy.[4,5] Zidovudine (AZT), the first anti-HIV compound approved for clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents. However, the main limitation to therapeutic effectiveness of AZT is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability.[6] In the systemic circulation, it is first converted to AZT triphosphate, which is pharmacologically active and prevents the replication of the HIV virus. The biological half-life of AZT-triphosphate is 4 hours, thus necessitating frequent administration (3 to 4 times a day) to maintain constant therapeutic drug levels. Treatment of AIDS using conventional formulations of AZT is found to have many drawbacks such as adverse side effects due to accumulation of drug in multi-dose therapy,[7-8] poor patient compliance[9] and high cost. So, CR formulations of AZT can overcome some of these problems.

AZT is absorbed throughout the GIT. The drug is freely soluble at any pH, hence judicious selection of release retarding excipients is necessary for achieving constant in-vivo release. The most commonly used method of modulating the drug release is to include it in a matrix system.[10] Matrix based CR tablet formulations are the most popular and easy to formulate on a commercial scale in an industry. The matrix tablets can be prepared via wet granulation or by direct compression.[11] Many polymers have been used in the formulation of matrix based CR drug delivery systems. Reports are found on the use of hydrophilic polymers like hydroxyl propyl methylcellulose (HPMC), methylcellulose, sodium car boxy methylcellulose,[12] carbopols[13] and polyvinyl alcohol[14] for

*Corresponding author: [*1] Jeypore College of Pharmacy, Rondapalli, Jeypore,Koraput, Orissa, India.
[2] UDPS, Utkal University, Vani Vihar, Bhubaneswar, Orissa, India.
e-mail: rajatkpharma@yahoo.com

the preparation of CR formulations of different drugs. Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance.[15] The hydrophilic polymers selected for the present study were Eudragit RS100 and RL100. These polymers provide pH-independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymers in the matrix system.[16]

Hence, in the present work, an attempt has been made to formulate the extended-release matrix tablets of AZT and tested for controlled delivery of drug using hydrophilic matrix material (Eudragit RS100 and RL100) along or in combination with hydrophobic ethyl cellulose.

MATERIALS AND METHODS

Materials

AZT was obtained as a gift sample from Mecleod's Pharma (Mumbai,India), Eudragit and Ethyl Cellulose were obtained from Dr Reddy's Lab (Hyderabad, India), Micro Crystlline Cellulose and Mg. Stearate from Loba Chem(Mumbai, India). All other chemicals and ingredients were used for study are of commercial grade.

Methods

Matrix embedded controlled release tablets of AZT were prepared by direct compression technique using various concentration of Eudragit RS100 and RL100 along or in combination with Ethyl cellulose (Table-1). All ingredients except magnesium stearate were blended in glass mortar uniformly. After the sufficient mixing of drug as well as other components, magnesium stearate was added and mixed for additional 2-3 minutes. Finally compressed on an 8 station tablet compression machine (rotary tableting machine, Rimek Minipress–I, India) using 12-mm punches.

EVALUATION OF MATRIX TABLETS

Physical Characterization of the Designed Tablet

The properties of the compressed matrix tablets, such as hardness, friability, weight variation, and content uniformity were determined using reported procedure.[17] Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester. Friability was determined by testing 10 tablets in a Roche friability tester for 4 min at 25 rpm. The weight variation was determined by taking weight of 20 tablets using an electronic balance (Sartorious Electronic Balance, BT-2245). The drug content of the manufactured tablets of each batch was determined in triplicate. For each batch 20 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved in water, and analyzed after making appropriate dilutions.

In Vitro Drug Release Studies

Release rate of all the designed formulations were studied up to 12 hours using USP-22 type I dissolution apparatus at 50 rpm. The dissolution medium (900ml) consisted of 0.1N hydrochloric acid for first 2 hours and the distilled water from 3 to 12 hours, maintained at 37°C ± 0.5°C. Sample of 5 ml was withdrawn at specific time intervals through out the dissolution study of 12 hours for analysis and replaced with fresh dissolution medium. After appropriate dilution the samples were analyzed for AZT using a double beam UV-Visible spectrophotometer (V-570, Jasco, Tokyo, Japan) at 265.6nm for 0.1N HCl and 269nm for distilled water. The release studies were conducted in triplicate.

Characterization of Release Kinetics

To find out the mechanism of drug release from hydrophilic matrices, the dissolution data of tablets of each batch treated with different kinetics release equation.[18] Zero order: $Q = K_0 t$ (1); Higuchi's square root at time: $Q = K_H t^{½}$ (2) and Korsmeyer and Peppas: $M_t/M_8 = K_M t^n$ (3). Where Q is the amount of drug released at time t, M_t/M_8 is the fraction of drug released at time t. K_0 is Zero order release rate constant. K_H is Higuchi's square root of time kinetics drug release constant. K_M is constant incorporating geometric and structural characteristics of tablets and 'n' are the diffusion exponent indicative of the release mechanism. In case of tablets (which are of cylindrical shape), a value of n<0.45 indicates Fickian or Case I release; 0.45<n<0.89 for non-Fickian or anomalous release; n=0.89 for Case II release; and n>0.89 indicates Super Case II release.

THE MDT VALUES WERE CALCULATED BY THE FOLLOWING EQUATION

Where j is the sample number, n is the number of dissolution sample times, $t^{\wedge}_j$ is the time at midpoint between t_j and t_{j-1} (easily calculated with the expression, $(t_j+t_{j-1})/2$) and $?M_j$ is the additional amount of drug released between t_j and t_{j-1}.

$$MDT = \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

TABLE -1 Composition of different formulations

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Zidovudine	300	300	300	300	300	300	300	300	300	300	300	300	300
Eudragit RS100	55	110	165	220	137.5	110	---	---	---	---	---	---	55
Eudragit RL100	---	---	---	---	---	---	55	110	165	220	137.5	110	55
Ethyl cellulose	---	---	---	---	27.5	55	---	---	---	---	27.5	55	55
MCC	189	134	79	24	79	79	189	134	79	24	79	79	79
Magnesium stearate	6	6	6	6	6	6	6	6	6	6	6	6	6
Total Weight	550	550	550	550	550	550	550	550	550	550	550	550	550

TABLE -2 Physical characterization of prepared matrix tablets.

BATCH CODE	AVG. WT. (mg)	HARDNESS (kg/cm^2)	DRUG CONTENT (%)*	FRIABILITY (%)
F1	546.25±6.257	5.84±0.337	97.292±2.282	0.587
F2	557.79±6.63	5.79±0.288	97.654±2.246	0.571
F3	557.79±6.63	5.88±0.265	97.932±2.064	0.582
F4	557.55±6.634	6.11±0.188	99.051±2.102	0.566
F5	556.768±5.491	6.29±0.219	98.83±2.21	0.549
F6	557.648±6.943	6.41±0.223	99.07±2.12	0.578
F7	557.947±6.210	7.11±0.324	99.314±2.024	0.553
F8	558.547±5.891	7.24±0.356	99.64±2.055	0.545
F9	558.091±6.113	7.43±0.405	100.04±2.271	0.573
F10	557.342±6.035	6.89±0.398	99.025±2.054	0.534
F11	558.341±6.148	7.01±0.28	99.145±2.144	0.562
F12	558.298±6.349	7.13±0.336	99.37±1.991	0.579
F13	556.822±6.413	6.48±0.225	98.774±2.191	0.575

* **Values are represented as mean ± S.D. (n = 3)**

TABLE -3 Release kintics parameters of designed controlled release matrix tablets of zidovudine.

BATCH CODE	r^2		Log K_H	n	MDT	$t_{25\%}$(hr)	$t_{50\%}$ (hr)	$t_{80\%}$ (hr)	DR_{2h}%	DR_{8h}%
	ZERO ORDER	HIGUCHI								
F1	0.901	0.995	1.57	0.49	2.01±0.03	0.4±0.01	1.95±0.05	4.3±0.1	50.7±1.1	---
F2	0.922	0.993	1.49	0.53	2.7±0.1	0.6±0.03	2.5±0.05	5.2±0.05	41.6±0.9	94.4±1.1
F3	0.949	0.996	1.39	0.56	3.7±0.05	1.1±0.05	3.6±0.06	7.9±0.25	34.3±1.1	80.8±1.0
F4	0.965	0.992	1.28	0.6	4.21±0.04	1.4±0.05	4.6±0.1	11.3±0.1	29.8±1.1	68.1±0.9
F5	0.94	0.996	1.37	0.55	4.05±0.02	1.2±0.1	3.6±0.1	8.65±0.2	33.4±0.5	75.5±1.1
F6	0.941	0.995	1.28	0.58	4.01±0.09	1.5±0.05	4.9±0.12	---	28.4±0.9	65.7±0.7
F7	0.914	0.997	1.59	0.50	1.8±0.05	0.4±0.01	1.7±0.06	3.9±0.1	53.8±0.5	---
F8	0.923	0.994	1.53	0.50	2.5±0.2	0.5±0.02	2.3±0.2	5±0.2	43.6±1.1	95.8±0.3
F9	0.952	0.994	1.41	0.56	3.6±0.2	1±0.1	3.0±0.15	7.5±0.1	34.5±1.1	81.1±1.1
F10	0.97	0.99	1.31	0.61	4.52±0.02	1.4±0.05	4.2±0.12	9.3±0.1	31.6±2	72.1±1.2
F11	0.92	0.996	1.441	0.51	3.6±0.08	0.8±0.2	3.1±0.2	7.5±0.17	37.9±1.1	82.3±1.4
F12	0.945	0.997	1.32	0.57	4.1±0.1	1.3±0.1	4.3±0.05	11±0.2	30.1±2.5	70.8±2.2
F13	0.948	0.997	1.29	0.58	4.6±0.1	1.5±0.06	4.7±0.15	11.5±0.11	29.9±1.1	67.8±1.6

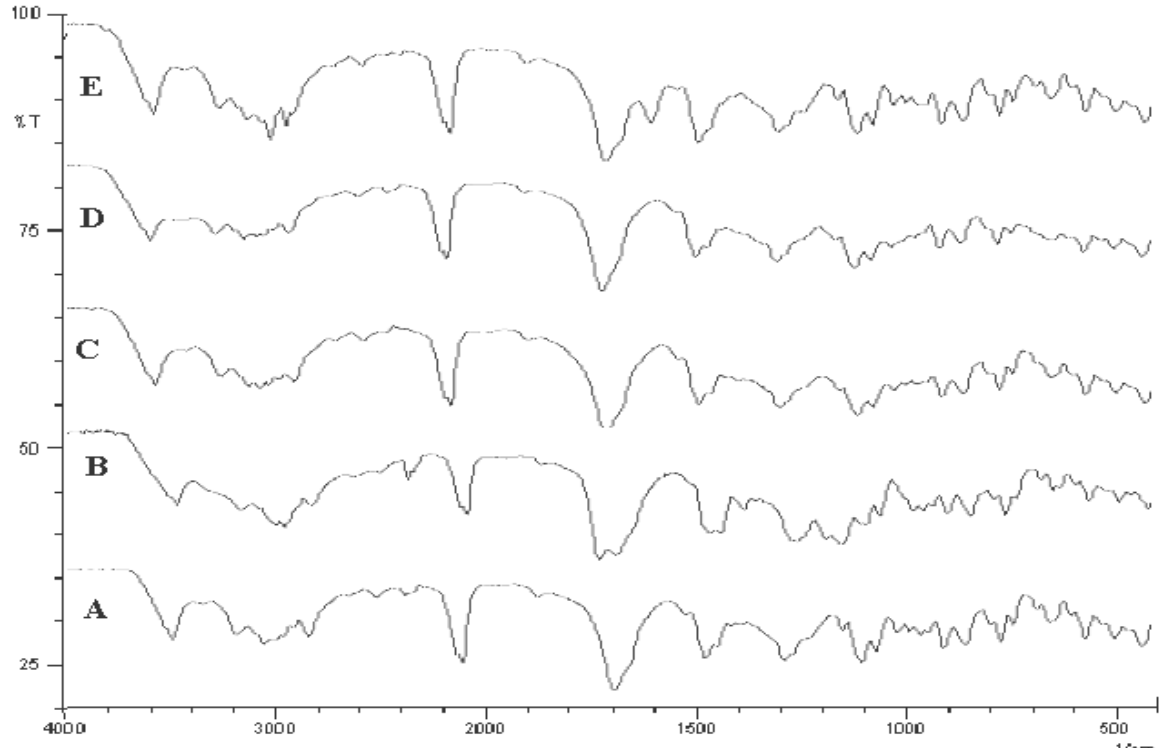

FIGURE 1. Fourier transform infrared spectra of A: Zidovudin (AZT), Solid admixture of B: Azt with edragit, C: azt with ethyl cellulose, D: Azt with micro crystalline cellulose (MCC), E: Azt with magnesium stearate.

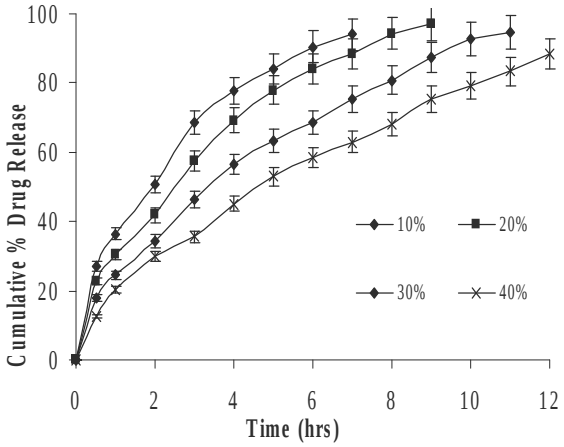

FIGURE 2. In Vitro release profiles showing the effect of different concentration of eudragit rs 100 on zidovudine release from matrix tablets, data are represented as mean± sd (n=3).

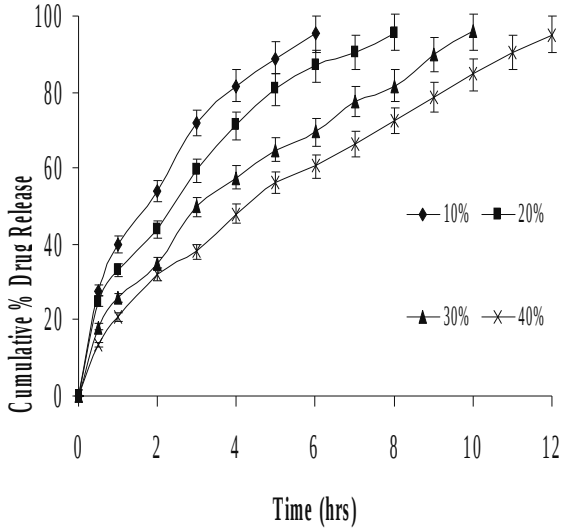

FIGURE 3. In vitro release profiles showing the effect of different concentration of Eudragit RL100 on Zidovudine release from matrix tablets. Data are represented as mean ± SD (n=3).

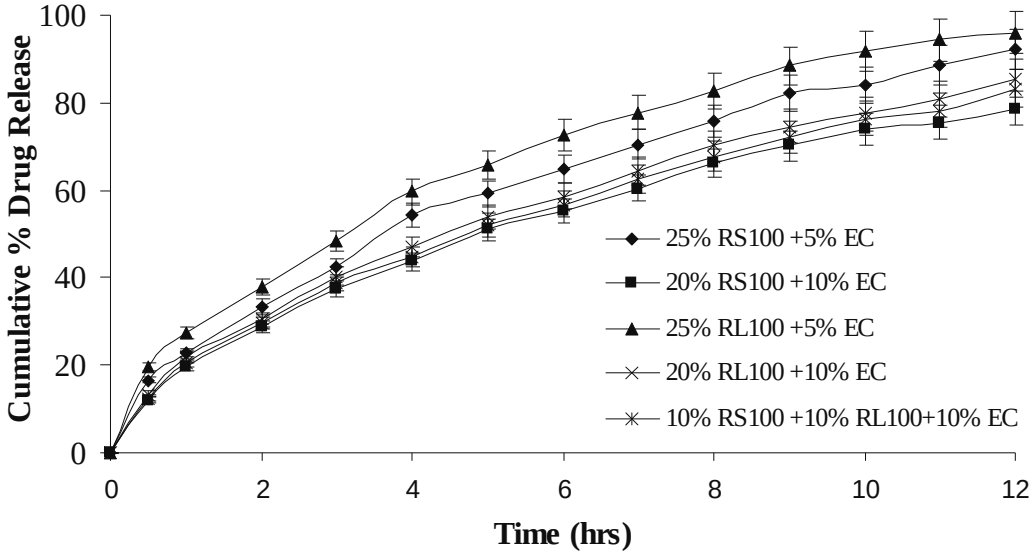

FIGURE 4. In vitro release profiles showing the effect of different concentration of Eudragit RS100 AND RL100 WITH Ethyl cellulose on Zidovudine release from matrix tablets. Data are represented as mean ± SD (n=3).

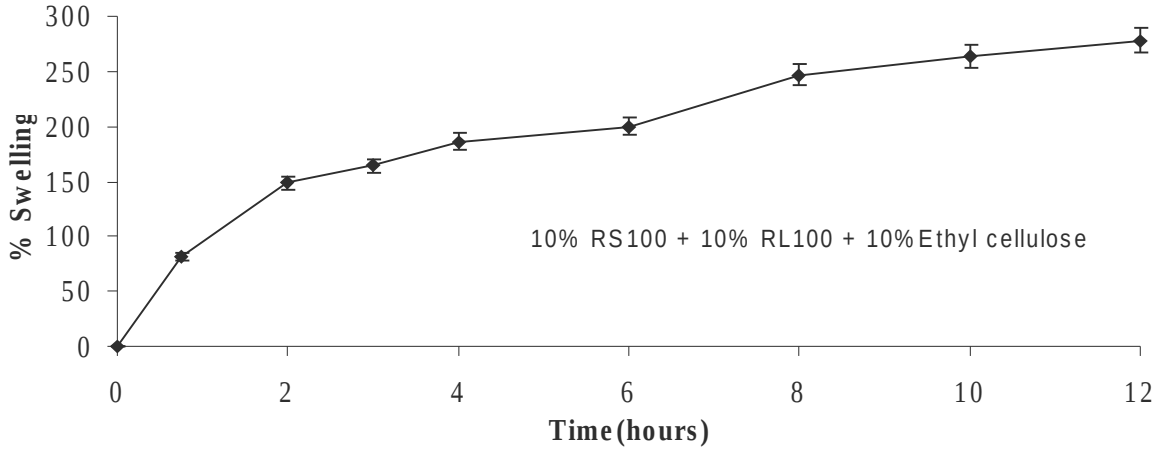

FIGURE-5 Swelling behavior of optimized batch of matrix tablets (Formulations F13).Data are represented as mean ± SD (n=3).

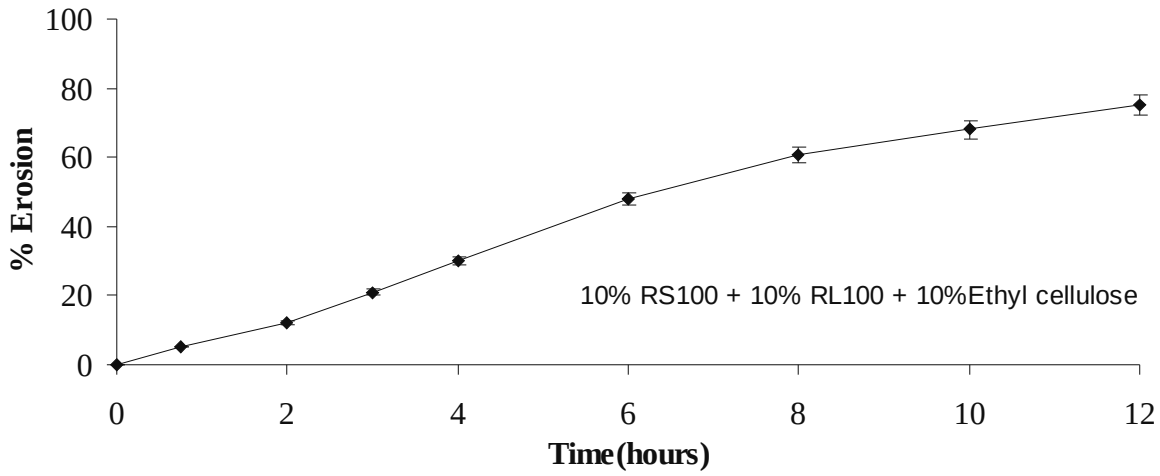

FIGURE- 6Eroding behavior of optimized batch of matrix tablets (Formulations F13).Data are represented as mean ± SD (n=3).

Swelling and Erosion Study

Swelling and erosion studies were carried out according to the method reported by Al- Taani and Tashtoush[19] to understand the influence of swelling and erosion behavior on drug release and also to determine the effect of polymer viscosity on the swelling and erosion. Matrix tablets were introduced into the dissolution apparatus under the standard set of conditions as specified for release rate studies. The tablets were removed using a small basket and swollen weight of each tablet was determined. To determine matrix erosion, swollen tablets were dried in a vacuum oven at 45°C to a constant weight. Swelling (%) and erosion (%) were calculated according to the following formula: % swelling = S/R ?100 (5), % erosion = (T-R)/T ? 100 (6); Where, *S* is the weight of the matrix after swelling; *R* is the weight of the eroded matrix; and *T* is the initial weight of the matrix.

Stability Studies[20]

The optimized formulation was subjected to stability at 40 ± 2^0 C and 75 ± 5 % RH for period of six months. After each month tablet sample was analyzed for physical characteristics and drug release profile.

Statistical Analysis

All statistical calculations were performed using Sigma Stat 3.5 demo version software. Data were analyzed using students't' test and one way analysis of variance (ANOVA). Differences were considered statistically significant at $P<0.05$.

RESULT AND DISCUSSION

The supplied drug passed the various tests of identification and analysis. The pure drug (AZT) and the solid admixture of drug and various excipients used in the preparation of CR tablet formulations were characterized by FTIR spectroscopy to know the compatibility, Fig. 1.

All the tablets of different formulations showed acceptable results with respect to weight variation, drug content uniformity, friability, etc. Hardness within the range of 4.5 to 7.5 kg/cm^2, Table 2. All formulations showed less than 1% (w/w) friability that indicates the ability of tablets to withstand shocks which may be encountered during transport. The manufactured tablets showed low weight variations and a high degree of drug content uniformity was found among different batches of the tablets, and drug content was more than 97%.

The release rate patterns of all formulations are given in the table 3. A plot of cumulative percentage versus time for embedded matrix controlled release tablets revealed that the release pattern was slow as compared to conventional formulations. The initial drug released of all formulations containing Eudragit RS100 (formulations F1 to F4, Fig. 2) or RL100 (formulations F7 to F10, Fig. 3) varied in between 20% to 40%. However in later stage the release was found to be slower and more controlled in the tablets with higher proportions of polymer.

Formulations containing 10% and 20% either of the Eudragit released more than 30% of drug in first hour. This may be due to initial burst effect caused by surface erosion or disaggregations of matrix tablets prior to gel layer formation around the tablet core[21]. And also more than 90% of drug released in 9hours, hence the release pattern of the above formulations were not within the desirable limit. However in formulations containing 30% and 40% either of the polymers the release pattern decreased significantly($P<0.05$) showed release of drug less than 25% in first hour and not less than 80% in

11hours.

In formulations containing combinations of hydrophilic and hydrophobic polymers, F5, F6, F11, F12 and F13 showed a significant difference ($P<0.05$) of drug release as compared with 10% and 20% of either of the Eudragit preparation. Nearly 20% of drug released from the above formulations in first hour which reflects no burst effect and more than 80% of drug released in 12hours.

Comparing the parameter like time taken to release 25%($t_{25\%}$), 50%($t_{50\%}$) and 80% ($t_{80\%}$) and also drug released in 2hours DR_{2h}% and 8hours DR_{8h}% (Table-3) of all the formulations revealed that, formulations except F1, F2, F7 and F8 showed significantly higher values which indicated more sustained nature of formulations. Tablets containing combinations of Eudragit and ethyl cellulose (Formulation F13) was having the highest values of above parameters which reflected more sustained nature among all the formulations.

Mean dissolution time (MDT) value is to characterize drug release rate from a dosage form and indicated drug release retarding efficiency of polymer (Table-3). Formulation containing combination of Eudragit and ethyl cellulose showed highest MDT value 4.6±0.1 in comparison to all other formulations.

Further to characterize the release mechanism of AZT from matrix tablets, the dissolution datas were subjected to the Korsemeyer and Peppas diffusion model. The 'n' values for all formulations ranged from 0.48 to 0.62, indicating that the release mechanism was non-Fickian or anomalous release ($0.45 < n < 0.89$). It can be inferred that the release was dependent on both drug diffusion and polymer relaxation. The poor correlation coefficient (R^2 values) in kinetic parameter based on zero-order model equation was mainly due to the drug release mechanism. The values of 'n' were very close approximation to 0.45, hence the correlation coefficient (R^2 values) good fit with Higuchi's square root equation. But it cannot be concluded that release was totally based on diffusion, which generally in the case in Higuchi's square root equation. Based on swelling and erosion studies, it was concluded that matrix tablets undergo swelling (Figure 5) as well as (Figure 6) during the dissolution study, which indicates that polymer relaxation had a role in drug release mechanism. However, it can be concluded that effect of diffusion on the drug release was more than the effect of polymer relaxation as the values of 'n' approaches to 0.5.

Stability Study

No statistically significant differences were observed the release profiles of optimized formulations ($P>0.05$) and also release kinetics were unaltered lastly no significant physical characteristics were changed when stability study was done for six months at 40±2° C and 75±5% RH.

CONCLUSION

It can be concluded that stable formulation could be developed by incorporating both hydrophilic and hydrophobic polymer in a definite proportion. So that sustained released profile is maintained for an extended periods of time.

ACKNOWLEDGEMENT

The authors are grateful to Mecleods Pharma, Mumbai, India and Dr Reddy's Lab, Hyderabad, India, for generous gift samples of AZT and Eudragit.

REFERNCES

1. Chien Y W, "Novel Drug Delivery Systems," ed. by Chien Y. W., Marcel Dekker, Inc., New York, U.S.A., 1992, pp. 139—196.
2. Vyas SP, Khar R K, "Controlled Drug Delivery: Concepts and Advances," ed. by Vyas S. P., Khar R K, Vallabh Prakashan, Delhi,2002; pp. 155—195.
3. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). "AIDS epidemic update 2005," Geneva: UNAIDS. Available at: http://www.unaids.org/epi/2005/doc/ EPIupdate2005_pdf_en/epi-update2005_en.pdf. Accessed 10 December,2006.
4. Richman D., Fischl M M, Grieco M H, Gottlieb M S, Volberding P A, Laskin O L, Leedom J M, Groopman J E, Mildvan D., Hirsch M S, Jackson G, Durack D T., Phil D., Nusinoff-Lehrman S., N. Engl. J. Med., 1987;317: 192—197 .
5. Lewis L D, Amin S., Civin C I, Lietman P S, Hum. Exp. Toxicol., 2004;23, 173—185.
6. Kieburtz KD, Seidllin M, Lambert JS, Dollis R, Reichman R, Valentine T. Extended follow-up of neuropathy in patients with AIDS and AIDS related complex treated with dideoxyinosine. J Acquir Immuno Defic Syndrom. 1992;5:60Y64.
7. Chitnis S, Mondal D, Agrawal K C, *Life Sci.*, 2002:**12;** 967—978.
8. Chariot P, Drogou I., de Lacroix-Szmania I., Eliezer-Vanerot M. C., Chazaud B., Lombes A., Schaeffer A., Zafrani E. S., *J. Hepatol.*, 1999:**30**; 156—160.
9. Re M. C., Bon I., Monari P., Gorini R., Schiavone P., Gibellini D., La Placa M., *New Microbiol.*, 2003;**26:** 405—413.
10. Salsa T, Veiga F, Pina ME. Oral controlled-release dosage forms. I. Cellulose ether polymers in hydrophilic matrices. Drug Dev Ind Pharm. 1997;23:929Y938.
11. Vargas C L, Ghaly E S, Drug Dev. Ind. Pharm., 1999;25: 1045—1050 .

12. Ranga R K V, Padmalatha D K, Buri B, Drug Dev. Ind. Pharm., 1988;14: 2299—2320.

13. Parojcic J, Duric Z, Jovanovic M, Ibric S, Drug Delivery, 2004;11: 59— 65.

14. Korsenmeyer R W, Peppas N A, "Macromolecular and Modeling Aspects of Swelling-Controlled Systems," ed. by Mansdorf S. Z., Roseman T. J., Marcel Dekker Inc., New York, 1983, p. 77.

15. Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int J Pharm Tech Prod Mfr. 1984;5:1Y9.

16. Liu J, Zhang F, McGinity JW. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. Eur J Pharm Biopharm. 2001;52:181Y190.

17. Government of India Ministry of Health and Family Welfare. The Pharmacopoeia of India. Delhi, India: Controller of Publication; 1996.

18. Gohel M.C., Panchal M.K., Pharm. Tech., 2001; 9: 62.

19. Al-Taani BM, Tashtoush BM. Effect of microenvironment pH of swellable and erodable buffered matrices on the release characteristics of diclofenac sodium. AAPS PharmSciTech. 2003; 4:E43.

20. Cartensen J.T., Drug Stability: Principle and Practices, Marcel Dakker, New Work, 2nd Ed., 1995; pp. 538-550.

21. Ebube N.K., Hikal A., Wyandt C.M., Beer D.C., Miller L.G. and Jones A.B.: Susatained release of acetomenophen from heterogeneous matrix tablets, influence of polymer ratio, polymer loading and coactive on drug release, phar Dev Technol. 1997;2: 161-170.