International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Issue 2, 2011

Research Article

FORMULATION AND EVALUTION OF SUSTAINED RELEASE ZIDOVUDINE MATRIX TABLETS

HIMANSU BHUSAN SAMAL[1], S.A.SREENIVAS[1], SUDDHASATTYA DEY[1] AND HIMANSHU SHARMA[2]

[1]Guru Nanak Institute of Pharmacy, Ibrahimpatnam, Hyderabad-501506, [2]Sandoz Pvt Ltd, Navi Mumbai [1]Email : hbsamal@yahoo.co.in

Received: 22 Sep 2010, Revised and Accepted: 24 Oct 2010

ABSTRACT

The investigation was concerned with design and characterization of oral Sustained release matrix tablets of Zidovudine (AZT) in order to improve efficacy and better patient compliance. Matrix tablets were prepared by Wet granulation method using various proportions of hydrophilic polymers like Sodium CMC, HPMC, Eudragit-L155, & Xanthan gum along or in combination with hydrophobic polymer ethyl cellulose. In vitro drug release studies were performed using USP type II apparatus (rotary paddle type). The release kinetics was analyzed using Zero order, First order, Higuchi and Hixson Crowell. Compatibility of drug with various formulations excipients was also studied. In this study Formulations X_3, X_4, X_5, X_7, X_9, X_{12} and X_{14} shows zero-order kinetic of release with 80% to 97% of drug released. As these formulations containing a combination of two polymer i.e. Xanthan gum, combine with EC, Sodium CMC, HPMC in the different ratios. But in presence of sodium CMC in the formulation X_4, X_9, X_{14}, E_3, E_7 and E_{11}, the drug released in 12 hour was in the range of 75% to 85% and shows zero-order kinetics. The formulation X_4 & E_3 containing Na CMC with Xanthan gum and EC respectively in the ratio 1:1 gave more sustaining action i.e. 79.16% and 65.21% respectively in 12 hour. From the above study it was concluded that presence of sodium CMC gives zero-order release kinetics and the linearity ranges from 0.990 to 0.996. It has also good drug entrapment efficiency ranges from 96 to 106% of drug. Formulation containing sodium CMC with Xanthan gum and EC gives sustained release of drug more than 12hrs.

Keywords: Sustained release; Matrix tablets; Release kinetics; Zidovudine; Hydrophilic & Hydrophobic polymers

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]. Sustained release (SR) 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].

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[3-4]. 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[5].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[6-7], poor patient compliance[8] and high cost. So, SR 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[9]. Matrix tablets can be prepared via wet granulation or by direct compression[10]. Many polymers have been used in the formulation of matrix based SR drug delivery systems. Reports are found on the use of hydrophilic polymers like hydroxyl propyl methylcellulose (HPMC), methylcellulose, sodium carboxy methylcellulose[11], carbopols[12] and polyvinyl alcohol[13] for the preparation of CR formulations of different drugs. Hydrophilic polymer matrix systems[14-19] 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[20]. Hydrophilic 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[21].

Hence, in the present work, an attempt has been made to formulate the Sustained-release matrix tablets of AZT using hydrophilic matrix material (HPMC, Sodium CMC, Xanthan gum & Eudragit-L155) along or in combination with hydrophobic polymer material (ethyl cellulose).

MATERIALS AND METHODS

Zidovudine was received as a gift sample from Cipla Ltd. Goa, Ethyl cellulose, Xanthan Gum, Hydroxy propyl methyl cellulose(HPMC-ELV-15), Magnesium stearate and Starch(potato) from Loba Chemie Pvt. Ltd,Carboxy Methyl Cellulose from Merck specialities Pvt. Ltd, Eudragit-L155 gift sample from Cipla Ltd. Goa,Potassium dihydrogen Phosphate & Sodium hydroxide from Merck specialities Pvt. Ltd, Compression Machine(CIP Machineries Pvt. Ltd., Ahmedabad, India), FTIR-Spectrophotometer model NEXUS 870 [THERMO NICOLET], Eight Stage Dissolution Apparatus model TDT-08L ELECTROLAB, Roche Friabilator Indian Equipment Corporation, Bombay, Monsanto Hardness Tester Rupa Industries, India. Hot air oven, Unilab, India.

Preparation of sustained release matrix tablet of Zidovudine

Different tablet formulations (Batch size of 50 tablets) were prepared by wet granulation technique X_1 to X_{15} (Table no-1) and E_1 to E_{12} (Table no-2).Before preparing the tablets all the ingredients to be pass through sieve no-60.Drug and polymer to be mixed by mortar and pestle for uniform drug distribution. The above mixture then to be granulated using granulating agent15%w/w of aqueous solution of starch and the dump mass of drug and polymer was passed through sieve no- 10 and dried at 60ºC in hot air oven till the granules contain less than 5% of moisture. After drying the granules are forcedly passed through a sieve no 22 screen. The prepared granules are lubricated with specified amount of magnesium stearate until it was well mixed. Finally the lubricated granules are compressed by 8-station rotary tableting machine using flat-faces 10mm die.

Evaluation of drug loaded granules

The angle of repose[22] of granules was determined by funnel method. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed

along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Bulk densities[23] of all types of granules were determined by pouring gently some amount of sample through a glass funnel into a 10ml graduated cylinder. The volumes occupied by the sample were recorded. Bulk density was calculated

$$\text{Bulk density (g/ml)} = \frac{\text{weight of sample in gms}}{\text{volume occupied by the smaple}}$$

Tapped densities[23] of all types of granules were determined by pouring gently some amount of sample through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained (300 taps). Volume occupied by the sample after tapping were recorded and tapped density was calculated.

$$\text{Tapped density (g/ml)} = \frac{\text{weight of sample in gms}}{\text{volume occupied by the smaple}}$$

% compressibility was determined by the Carr's compressibility index[23].

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

Evaluation of matrix tablets

The prepared matrix tablets were evaluated for Weight variation, hardness, friability & content uniformity were determined using reported procedure[24].Weight variation was evaluated on 20 tablets using an electronic balance and test was performed according to official method. Friability was determined by taking 10 tablets in a Roche Friabilator for 4min at 25 rpm.Tablet hardness was determined for 6 tablets using a Monsanto hardness tester.

Drug content

Five tablets were weighed accurately and powdered. Powder equivalent to 100 mg of Zidovudine was accurately weighed and transferred to a 100 ml volumetric flask. Initial about some amount of pH 7.4 phosphate buffer was added to the volumetric flask and the flask was shaken for 10 min and then the mixture was sonicated. Finally the volume was made up to 100 ml with phosphate buffer and then filtered by using of 0.45µm membrane filter paper. The filtrate was suitably diluted with pH 7.4 phosphate buffers and analyzed against blank (pH 7.4 phosphate buffers) solution for the drug content by spectrophotometerically at 267.0 nm.

The drug-polymer interaction was studied by FTIR spectroscopy. (NEXUS 870 THERMONICOLET).

Determination of in-vitro drug release studies

Drug release was evaluated by conventional *in-vitro* dissolution testing. The dissolution tests for matrix tablets were performed by using Dissolution Tester (USP)–Eight stages paddle model. The medium was 900 ml of pH-7.4 phosphate buffer at 37°C ± 0.5° C. The paddles were rotated a 100 rpm., 0.5 ml of sample were withdrawn at every one hour interval and replaced with the same amount of pH 7.4 buffer to maintain the perfect sink conditions. 0.5 ml of sample was made up to 10 ml with pH 7.4 buffer and the drug absorbance was measured at wavelength of 267.0 nm using a double beam UV spectrophotometer.

RESULTS AND DISCUSSION

The present investigation was to fabricated and evaluate the sustain release formulation Zidovudine matrix tablet. The sustained release granules of Zidovudine were prepared by using combined polymers i.e. Xanthan gum with Ethyl cellulose, HPMC (E.Lv-15), Na CMC, Eudragit -L155 and Ethyl cellulose with HPMC (E.Lv-15), CMC Sodium, and Eudragit-L155. Other ingredients including Starch paste as binder and Magnesium stearate as lubricant were in incorporated for matrices. The matrices were prepared by wet granulation method in different ratios and finally compressed. In each batches 50 tablets were prepared.

Table 1: The Zidovudine matrix tablets (Quantity in mg/tablets)

Sl. No.	Ingredients	Formulation batch														
		X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10}	X_{11}	X_{12}	X_{13}	X_{14}	X_{15}
1.	Zidovudine (AZT)	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300
2.	Xanthan gum	300	150	150	150	150	225	112.5	112.5	112.5	112.5	150	75	75	75	75
3.	Ethyl Cellulose	----	150	----	----	----	----	112.5	----	----	----	----	75	----	----	----
4.	HPMC- (E.LV-15)	----	----	150	----	----	----	----	112.5	----	----	----	----	75	----	----
5.	Sodium CMC	----	----	----	150	----	----	----	----	112.5	----	----	----	----	75	----
6.	Eudragit-L155	----	----	----	----	150	----	----	----	----	112.5	----	----	----	----	75
7.	Magnesium stearate (% wt/wt)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
8.	Starch paste (15%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

*q.s indicates quantity sufficient.

Table 2: The Zidovudine matrix tablets (Quantity in mg/tablet)

Sl. No.	Ingredients	Formulation Batch											
		E_1	E_2	E_3	E_4	E_5	E_6	E_7	E_8	E_9	E_{10}	E_{11}	E_{12}
1.	Zidovudine (AZT)	300	300	300	300	300	300	300	300	300	300	300	300
2.	Ethyl Cellulose	300	150	150	150	225	112.5	112.5	112.5	150	75	75	75
3.	HPMC- (E.LV-15)	----	150	----	----	----	112.5	----	----	----	75	----	----
4.	Sodium CMC	----	----	150	----	----	----	112.5	----	----	----	75	----
5.	Eudragit-L155	----	----	----	150	----	----	----	112.5	----	----	----	75
6.	Magnesium stearate (%wt/wt)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
7.	Starch paste (15%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 3: Evaluation of granules of formulation batches X_1 to X_{15}

Batch No.	Bulk Density (g/ml)	Tapped density (g/ml)	Comprssi bility (%)	Hausner Ratio	Angle of repose (°)
X_1	0.314	0.389	19.2	1.237624	25.0
X_2	0.368	0.426	13.6	1.157407	19.0
X_3	0.399	0.476	16.2	1.193317	20.0
X_4	0.421	0.512	17.7	1.215067	23.0
X_5	0.458	0.534	14.3	1.166861	20.0
X_6	0.369	0.454	18.7	1.230012	25.0
X_7	0.356	0.406	12.3	1.140251	19.0
X_8	0.358	0.424	15.5	1.183432	19.0
X_9	0.421	0.505	16.6	1.199041	22.0
X_{10}	0.465	0.536	13.2	1.152074	21.0
X_{11}	0.396	0.484	18.1	1.221001	24.0
X_{12}	0.365	0.418	12.7	1.145475	19.0
X_{13}	0.412	0.486	15.2	1.179245	20.0
X_{14}	0.389	0.464	16.1	1.191895	24.0
X_{15}	0.432	0.493	12.4	1.141553	19.0

Table 4: Evaluation of granules of formulation batches E_1 to E_{12}

Batch No.	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility (%)	Hausner Ratio	Angle of repose (°)
E_1	0.405	0.451	10.2	1.113586	19.0
E_2	0.387	0.464	16.6	1.199041	22.0
E_3	0.401	0.483	16.9	1.203369	23.0
E_4	0.421	0.476	11.5	1.129944	20.0
E_5	0.395	0.442	10.7	1.119821	20.0
E_6	0.412	0.497	17.1	1.206273	22.0
E_7	0.376	0.45	16.4	1.196172	22.0
E_8	0.366	0.416	12.1	1.137656	19.0
E_9	0.409	0.459	10.9	1.122334	21.0
E_{10}	0.425	0.515	17.4	1.210654	23.0
E_{11}	0.429	0.512	16.2	1.193317	24.0
E_{12}	0.398	0.457	12.9	1.148106	20.0

The granules of formulations prepared from Xanthan gum with different polymers (i.e. X_1 to X_{15}) showed angle of repose between 19º to 25º, whereas the granules containing ethyl cellulose with the same other polymers (i.e. E_1 to E_{12}) showed the angle of repose between 19º to 24º indicating excellent flow behavior. Compressibility index of all the formulations was found to come within the range of 13% to19% and in case of packing factor value of all formulations shown about 1.24 indicating good flow property (Table no-3 & 4).

The tablets of different batches were subjected to various evaluation tests such as weight variations, friability and hardness according to procedures specified in Indian Pharmacopoeia (Table no-5 & 6). The weight variation test revealed that the weight was within the specified limits and found to be less than 4%. The friability test of different batches were carried out and the result showed it was below 1% ranging from 0.09 to 0.43 respectively which are well under the acceptable criteria as per I.P. The hardness of the tablets compressed form in various formulations was measured by using Monsanto hardness tester. The hardness was found to be 5 to10 Kg/cm^2.

All the formulations were assayed for drug content. The drug content in formulation batches X_3, X_4, X_6, X_7, X_{12} and E_3, E_5, E_9, E_{11} were found in the range between 90 to 99%, whereas in formulation batches X_1, X_2, X_5, X_9, X_{11}, X_{14} and E_2, E_4, E_7 were found in the range between 100 to 105% (Table no-5 & 6).

Table 5: Evaluation of tablet of formulation batches X_1 to X_{15}

Batch no.	Weight variation (%)	Friability (%)	Hardness (kg/cm^2)	Drug content (%)
X_1	±4.0	0.12	7.8±0.13	113.026
X_2	±2.0	0.39	6.7±0.18	105.93
X_3	±3.0	0.24	7.3±0.02	95.89
X_4	±2.0	0.11	9.8±0.01	98.53
X_5	±3.0	0.43	6.8±0.07	105.12
X_6	±2.0	0.13	7.2±0.21	95.81
X_7	±4.0	0.36	6.4±0.35	92.75
X_8	±4.0	0.24	7.1±0.13	----
X_9	±2.0	0.12	8.7±0.11	100.98
X_{10}	±2.0	0.39	6.7±0.03	----
X_{11}	±3.0	0.09	7.4±0.16	105.15
X_{12}	±3.0	0.29	6.5±0.41	98.85
X_{13}	±3.0	0.18	7±0.32	----
X_{14}	±3.0	0.13	8.5±0.06	102.57
X_{15}	±4.0	0.31	6.9±0.12	----

Table 6: Evaluation of tablet of formulation batches E_1 to E_{12}

Batch no.	Weight variation (%)	Friability (%)	Hardness (kg/cm²)	Drug content (%)
E_1	±2.0	0.49	6.2±0.03	86.495
E_2	±2.0	0.21	6.9±0.37	102.00
E_3	±3.0	0.09	8.2±0.01	96.375
E_4	±2.0	0.41	5.3±0.12	107.93
E_5	±3.0	0.42	6.1±0.27	90.43
E_6	±2.0	0.20	6.5±0.35	----
E_7	±4.0	0.11	7.9±0.02	106.04
E_8	±2.0	0.37	5.2±0.11	----
E_9	±2.0	0.39	6.4±0.22	97.06
E_{10}	±4.0	0.19	6.7±0.16	----
E_{11}	±2.0	0.11	7.8±0.03	99.36
E_{12}	±3.0	0.46	5.4±0.43	----

The studies revealed that there was no significant interaction between drug and polymer in the formulations shows in Fig No-11 to 22.

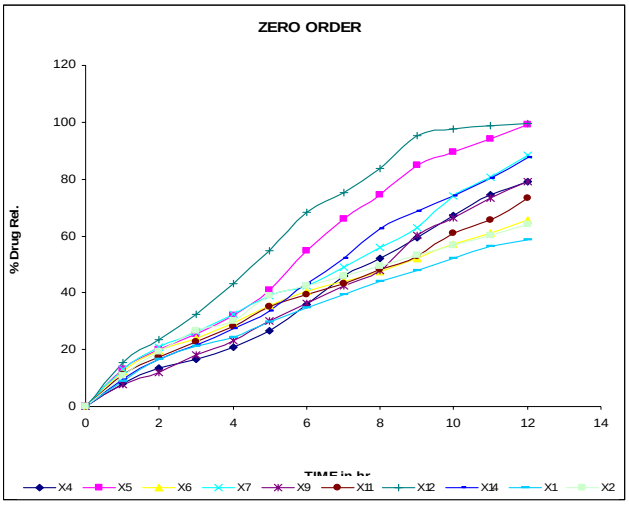

Fig. 1:

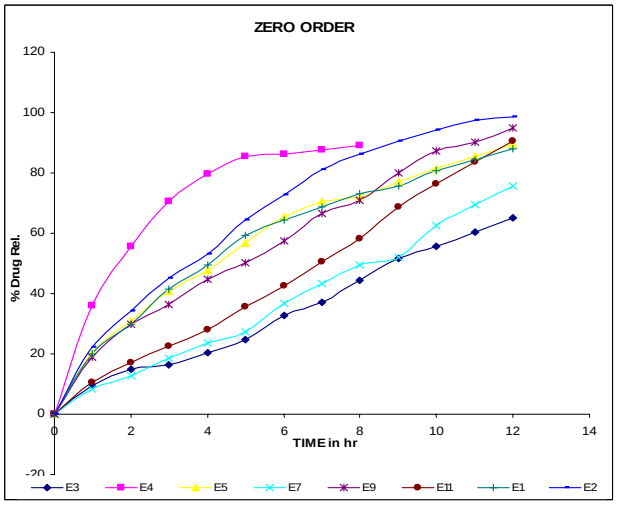

Fig. 2:

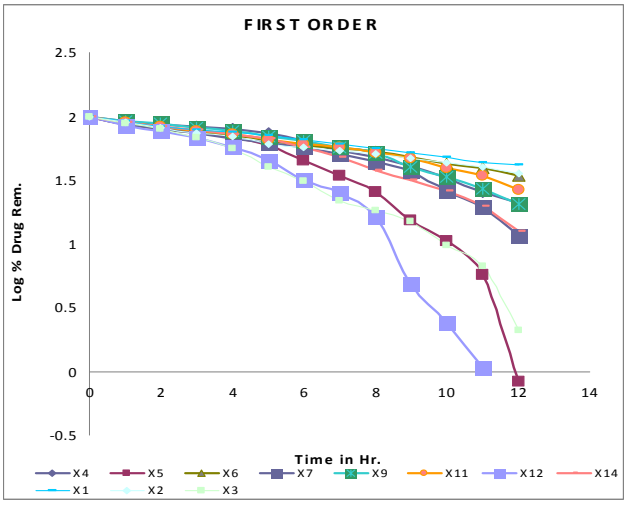

Fig. 3:

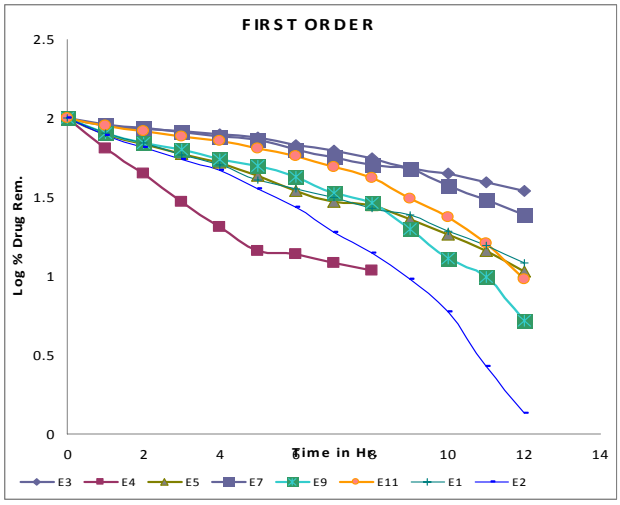

Fig. 4:

Comparative Dissolution Study of formulation- X_1 to X_{14} & E_1 to E_{11}

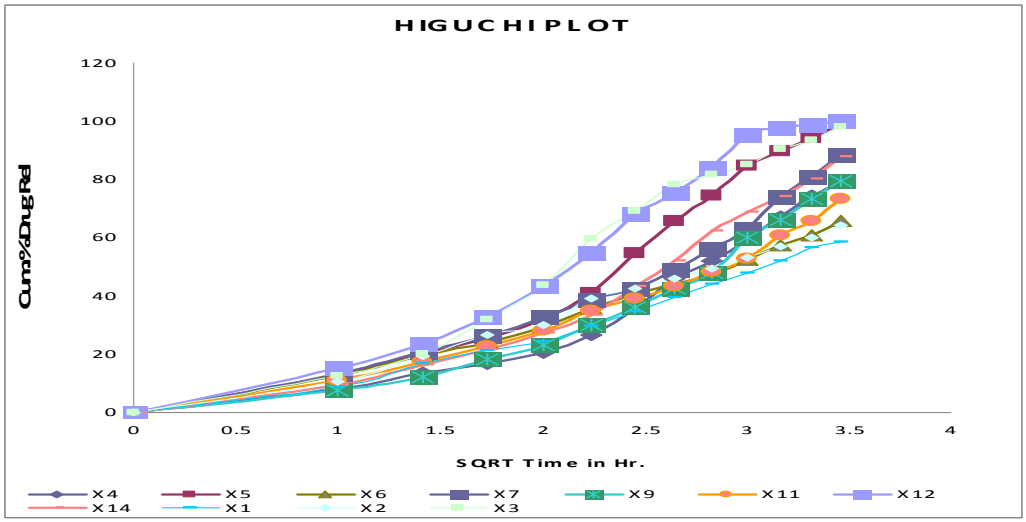

Fig. 5: Comparative dissolution study of formulation- X_1 to X_{14}

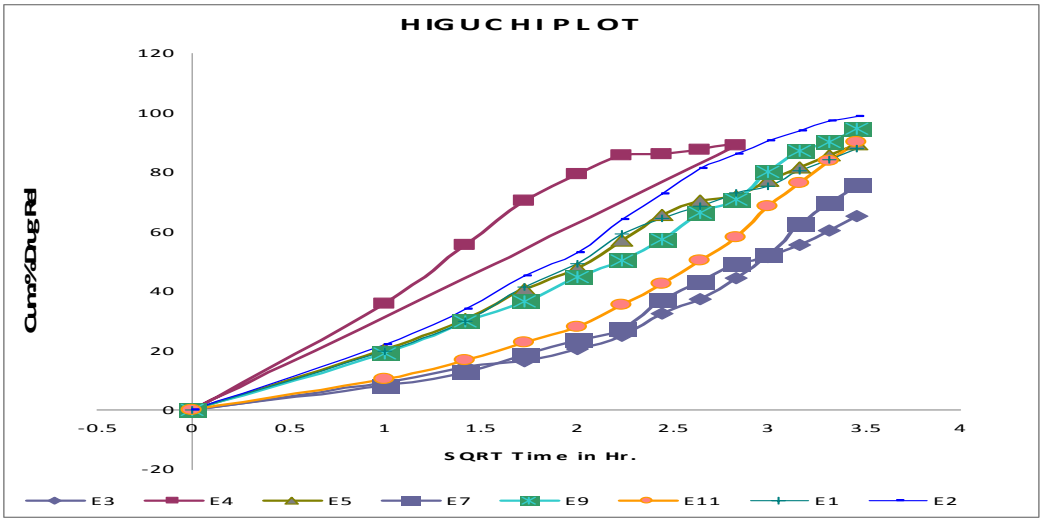

Fig. 6: Comparative dissolution study of formulation- E_1 to E_{11}

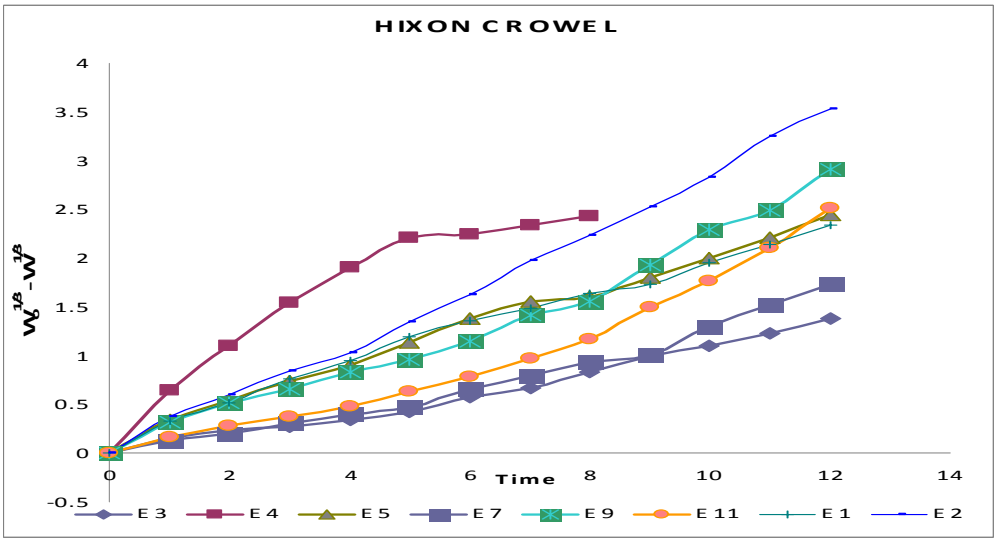

Fig. 7: Comparative Dissolution Study of Formulation- E_1 to E_{11}

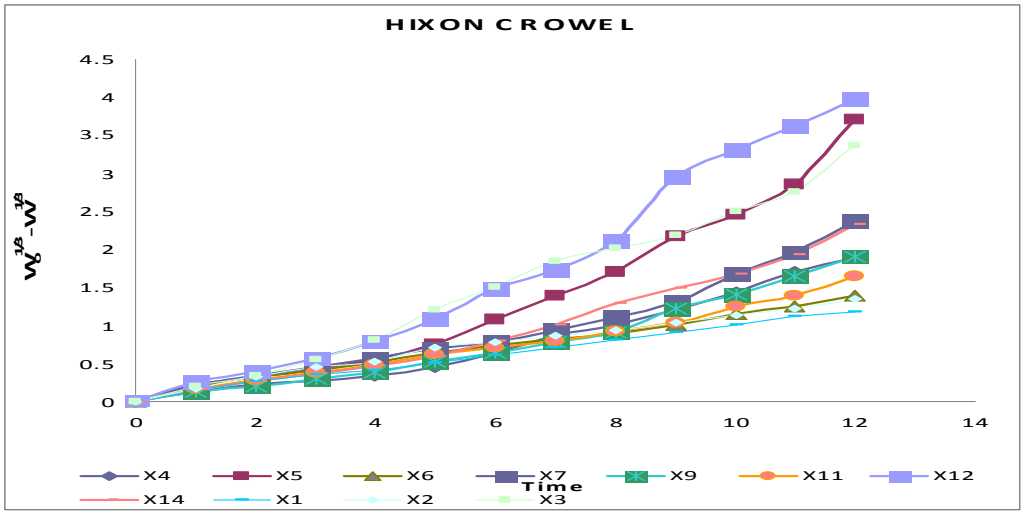

Fig. 8: Comparative dissolution study of formulation- X_1 to X_{14}

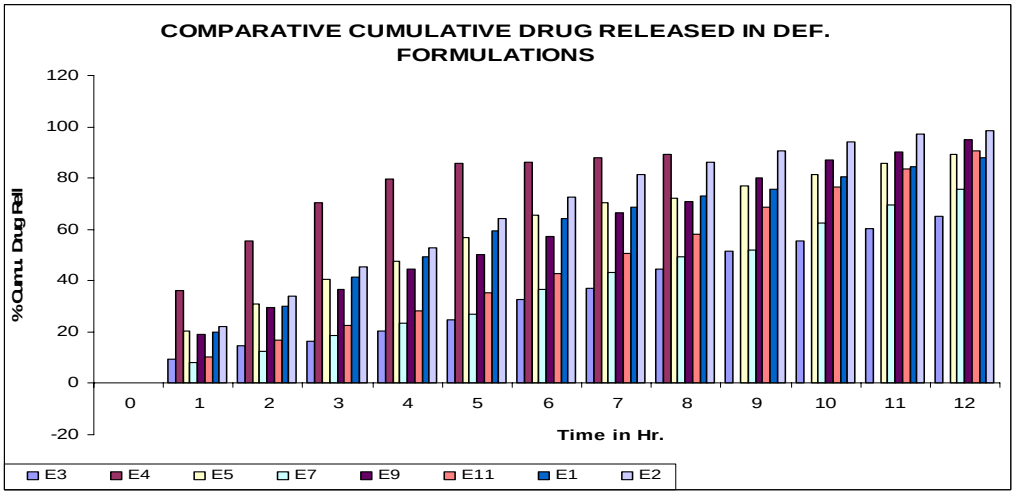

Fig. 9: Comparative cumulative drug release study of formulation E_1 to E_{11}

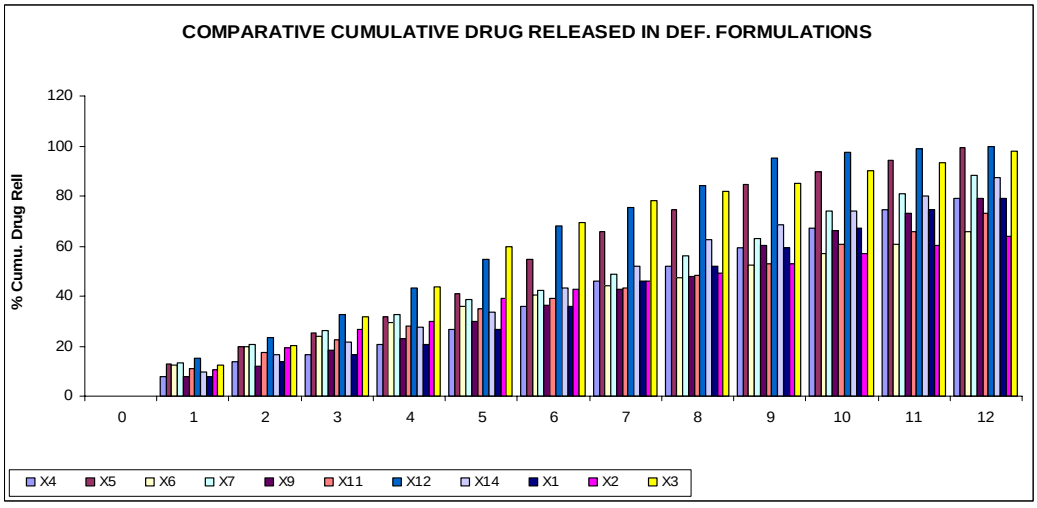

Fig. 10: Comparative Cumulative Drug Release Study of Formulation X_1 to X_{14}

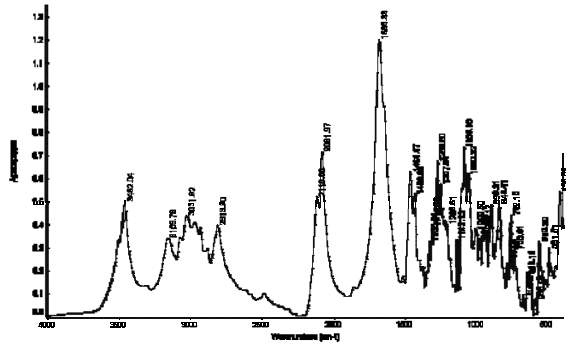

Fig. 11: FTIR Study of Zidovudine (AZT)

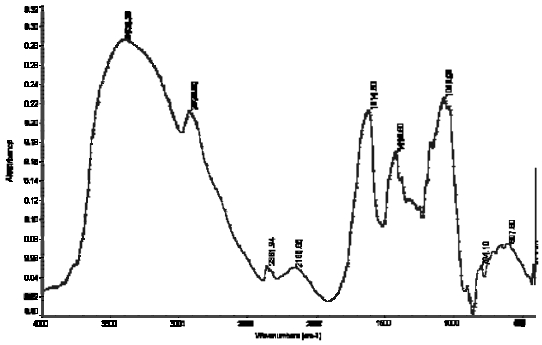

Fig. 12: FTIR Study of Xanthan gum

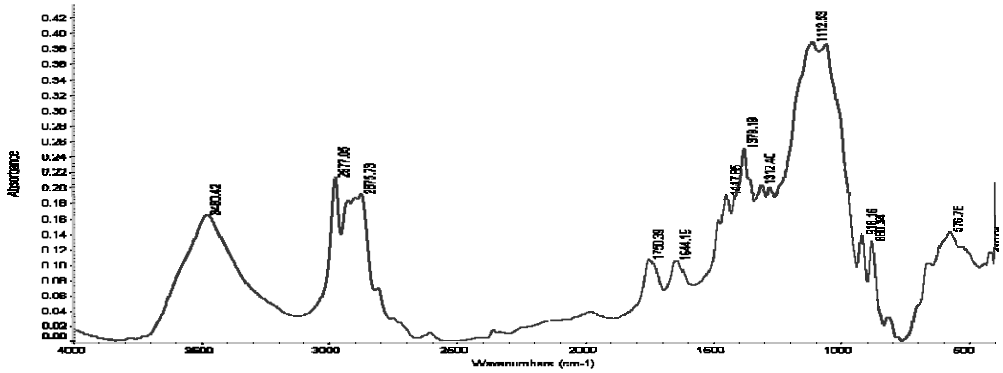

Fig. 13: FTIR study of Ethyl Cellulose

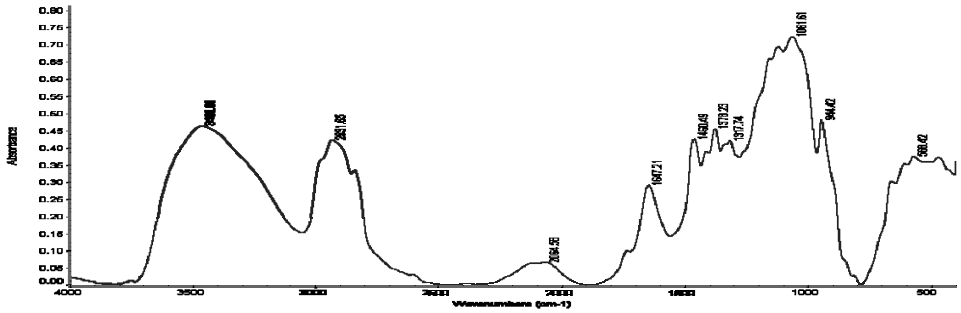

Fig. 14: FTIR study of HPMC E.LV-15

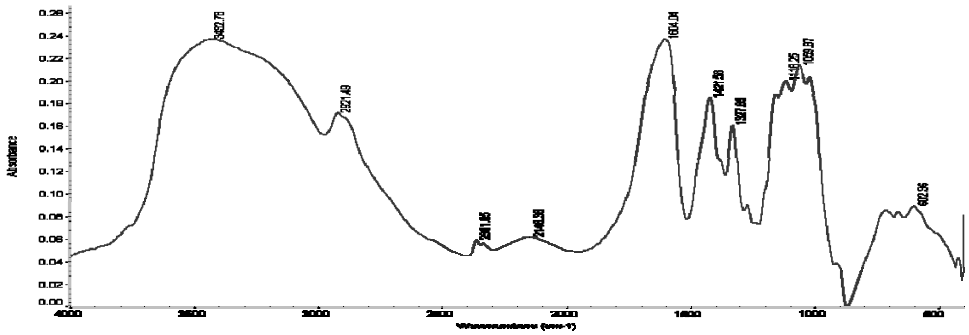

Fig. 15: FTIR study of Sodium CMC

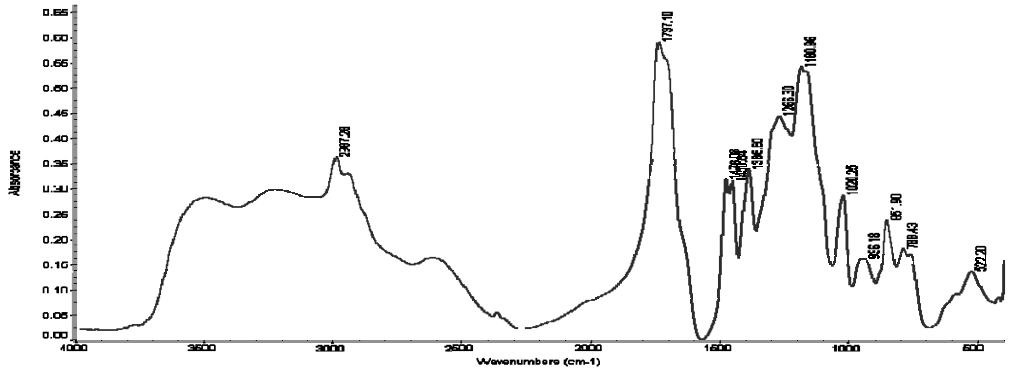

Fig. 16: FTIR study of Eudragit-L155

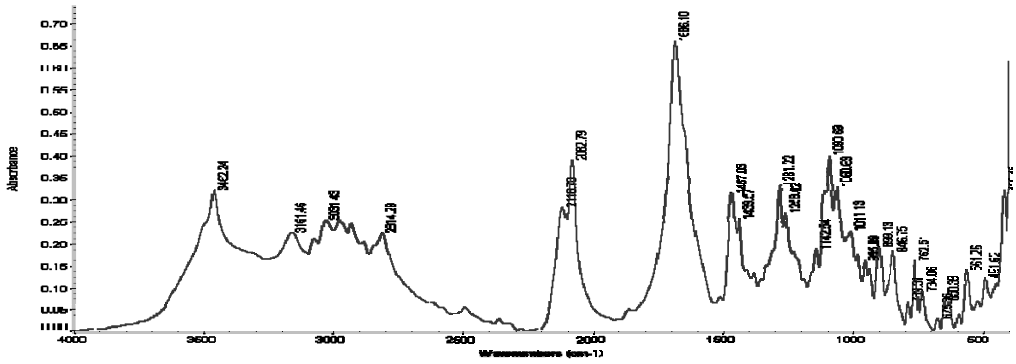

Fig. 17: FTIR study of AZT: (Xanthan: EC)

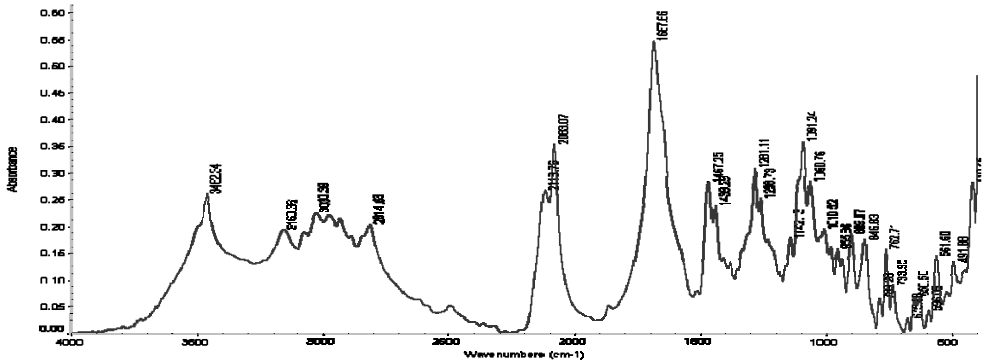

Fig. 18: FTIR study of AZT: (EC: Sodium CMC)

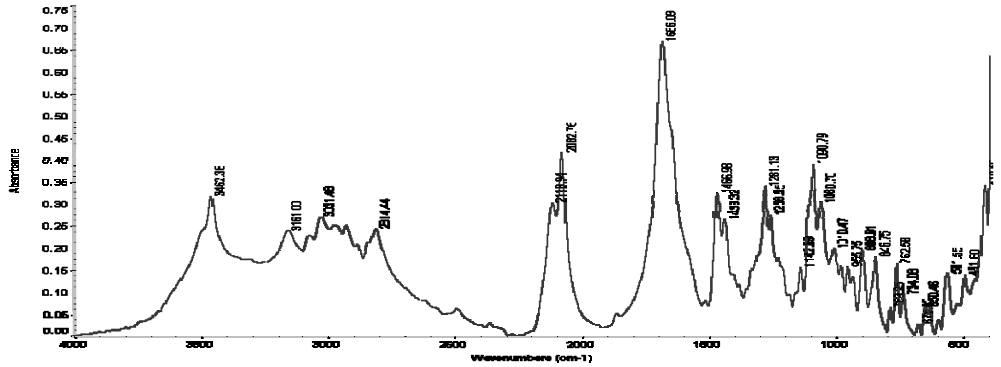

Fig. 19: FTIR study of AZT: (Xanthan gum: Sodium CMC)

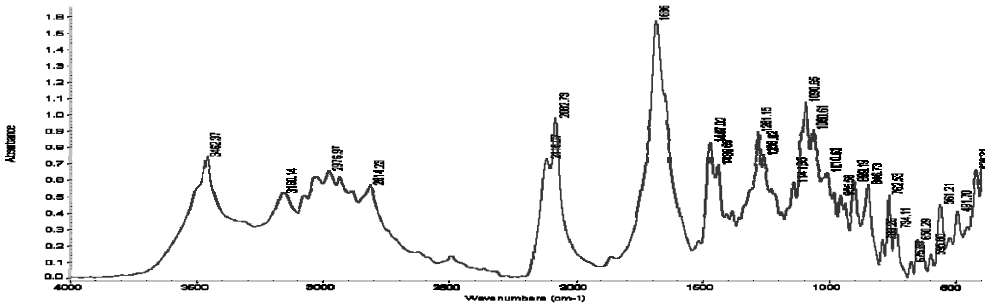

Fig. 20: FTIR study of AZT: EC

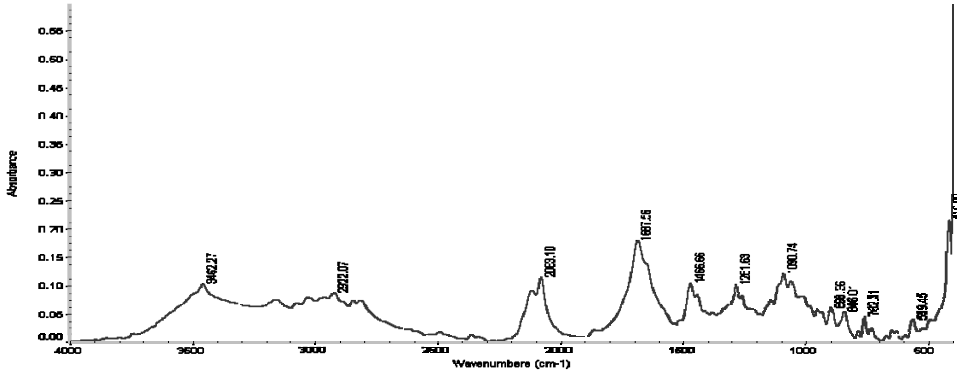

Fig. 21: FTIR study of AZT: (Xanthan gum: HPMC E.LV-15)

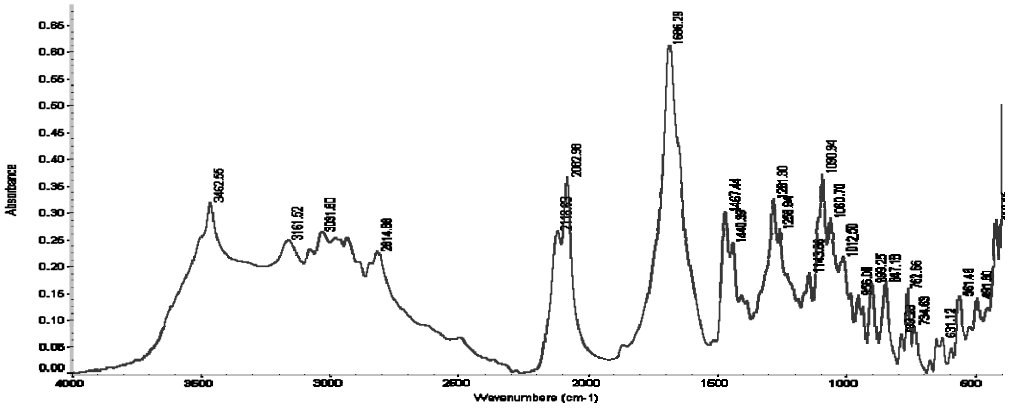

Fig. 22: FTIR study of AZT: (Xanthan gum: Eudragit L-155)

Dissolution study

In this study formulation X_1, X_2, X_4 and X_6, the drug release was found in the range between 58 to 79% within 12hrs.Whereas in formulation E_3 and E_7 it was in the range between 65 to 75%, it is due to the nature of polymer's characteristics. The formulation X_1, X_6 and X_{11} containing only Xanthan gum were found only swelling of polymer without erosion throughout the study. Due to non erosion effect the total drug could not released and showed fast order release kinetics. But in case of X_{11} the release kinetics is zero-order with correlation factor 0.99272.

The formulation X_3, X_4, X_5, X_7, X_9, X_{12} and X_{14} shows zero-order kinetic of release with 80% to 97% of drug released. As these formulations containing a combination of two polymer i.e. Xanthan gum, combine with E.C, Sodium CMC, HPMC in the different ratios, which helps to erosion of the polymer network. But in presence of sodium CMC in the formulation X_4, X_9, X_{14}, E_3, E_7 and E_{11}, the drug released in 12 hour was in the range of 75% to 85% and shows zero-order kinetics. The drug release was depends on the concentration of Na CMC i.e. by increasing the concentration of Na CMC the formulation gives more sustaining action. The formulation X_4 & E_3 containing Na CMC with Xanthan gum and EC respectively in the ratio 1:1 gave more sustaining action i.e. 79.16% and 65.21% respectively in 12 hour which was independent of initial drug concentration.

From the above study it was concluded that presence of sodium CMC gives zero-order release kinetics and the linearity ranges from 0.990 to 0.996. It has also good drug entrapment efficiency ranges from 96 to 106% of drug. . The release kinetics of formulations X_1 to X_{14} was shown in table no-7 and for formulations E_1 to E_{11} shown in table no-8.

Table 7: Kinetic values obtained from different plots of formulation x_1 to x_{14}

Formulations	Correlation coefficient			
	Zero order	First order	higuchi'plot	Hixson- crowel plot
X_1	0.98794277	0.99655081	0.966274422	0.997200541
X_2	0.961519923	0.994518117	0.985052755	0.988134552
X_3	0.950749432	0.930232387	0.954837715	0.988425871
X4	0.990353116	0.936309347	0.884786845	0.962661314
X_5	0.988712076	0.803764053	0.920952362	0.938299617
X_6	0.97974623	0.993735945	0.978419418	0.994620801
X_7	0.991189284	0.891966258	0.926575406	0.944478336
X_9	0.99402494	0.931597371	0.893318875	0.961409396
X_{11}	0.992712221	0.963677891	0.963677891	0.982143961
X_{12}	0.966360705	0.866387688	0.952479763	0.966456077
X_{14}	0.990353116	0.931953782	0.914691193	0.969073451

Table 8: Kinetic values obtained from different plots of formulation $e_1$to e_{11}

Formulations	Correlation Coefficient			
	Zero order	First order	higuchi'plot	Hixson- crowel plot
E_1	0.925304937	0.994105359	0.992383022	0.989546995
E_2	0.932950765	0.939081943	0.988152236	0.995945802
E_3	0.992099977	0.969597392	0.910797572	0.981054711
E_4	0.782894464	0.940362299	0.980779641	0.898852318
E_5	0.935799366	0.990150473	0.992698695	0.992777298
E_7	0.994803028	0.943876608	0.904527566	0.969005957
E_9	0.97817746	0.92866615	0.977666115	0.979009559
E_{11}	0.996335215	0.894334511	0.894334511	0.948371114

From the above discussion it was concluded that the formulation containing sodium CMC with Xanthan gum and EC gives sustained release of drug more than 12hrs.

CONCLUSION

In the present investigation, Zidovudine matrix tablets were successfully fabricated using selected polymers as detailed in the formulation table and evaluated for its sustained release properties. From the results obtained, it can be concluded that stable formulation could be developed by incorporating both hydrophilic and hydrophobic polymers in a definite proportion so that sustained release profile is maintained for an extended periods of time. A total number of twenty seven formulations were prepared with varying proportions of the polymers. It can be concluded form the research study that among the prepared formulations, X4 and E3 are the best.

REFERENCES

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. Controlled Drug Delivery Concepts and Advances; S.P. Vyas, Roop K. Khar; First Edition; Vallabh Prakashan; 2002; P.155-195.
3. 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 .
4. Lewis L D, Amin S., Civin C I, Lietman P S, Hum. Exp. Toxicol., 2004; 23, 173—185.
5. 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 Syndrome. 1992; 5:60Y64.
6. Chitnis S, Mondal D, Agrawal K C, Life Sci., 2002:12; 967— 978.
7. 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.
8. Re M. C., Bon I., Monari P., Gorini R., Schiavone P., Gibellini D., La Placa M., New Microbial., 2003;26: 405—413.
9. 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.
10. Vargas C L, Ghaly E S, Drug Dev. Ind. Pharm., 1999;25: 1045—1050 .
11. Ranga R K V, Padmalatha D K, Buri B, Drug Dev. Ind. Pharm., 1988;14: 2299—2320.
12. Parojcic J, Duric Z, Jovanovic M, Ibric S, Drug Delivery, 2004;11: 59— 65.
13. 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.
14. Meshali MM, El Sayed GM, Syed EL. Preparation and evaluation of theophylline sustained release tablets. Drug Develop Ind Pharm 1996; 22:373-6.
15. Nath BS, Venkatesh, Hiremath D. Formulation and evaluation of sustained release dosage form of theophylline using a combined hydrophobic and hydrophilic matrix. Indian J Pharm Sci 2000; 62:33-6.
16. Hajare AA, More HN, Dsouza JI. Design and evaluation of sustained release tablets of diltiazem hydrochloride. Indian Drugs 2004; 41:175-6.
17. Behl AK, Dhake AS. Formulation and release characteristics of sustained release ofloxacin Tablets. Indian Drugs 2005; 42:316-8.
18. Holte O, Onsogen E, Myrvold R. Sustained release of water soluble drug from directly compressed alginate tablets. Eur J Pharm Sci 2003; 20:403-7.
19. 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.
20. Atul Kuksal,Ashok K. Tiwary, Narendra K. Jain, and Subheet Jain "Formulation and In Vitro, In Vivo Evaluation of Extended-release Matrix Tablet of Zidovudine: Influence of Combination of Hydrophilic and Hydrophobic Matrix Formers" AAPS PharmSciTech 2006; 7 (1) Article1
21. 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.
22. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, editors. Tutorial pharmacy. New Delhi: CBS publisher and Distributors; 1986. P.211-33.
23. Aulton ME, Wells TI. Pharmaceutics: The science of dosage form design. London, England: Churchill Livingstone; 1998. p. 647-9.
24. Government of India Ministry of Health and Family Welfare. The Pharmacopoeia of India. Delhi, India: Controller of Publication; 1996.