Research Article

Formulation and Evaluation of Sustained Release Matrix Tablets of Zidovudine

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ABSTRACT

Zidovudine with all evident advantages proved to be suitable candidates for development of a controlled-release dosage form. In the present study, developing an oral sustained-release dosage form of AZT an anti-HIV drug with using HPMC, CMC, and sodium alginate, which are commonly used in hydrophilic matrix drug delivery systems. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drug is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel net work. For such drugs it becomes essential to include hydrophobic polymers in the matrix system. Hence in the present work, an attempt has been made to formulate the sustained release matrix tablets of AZT using hydrophilic matrix material in combination with hydrophobic polymers such as PVP, Eudragit and ethyl cellulose. The release of Zidovudine from the SR tablet was studied in 900 ml of phosphate buffer pH 6.8 as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37^{o} ± 0.5^{o}C. Drug content was determined by UV-visible spectrophotometer at 266 nm. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets followed non-fickian diffusion mechanism. Formulation F15 is the most successful and cost-effective formulation among the matrix tablets developed in the present study.

Keywords: Zidovudine, HPMC, CMC, Sodium alginate, Eudragit, Ethyl cellulose and Non-fickian diffusion mechanism.

INTRODUCTION

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 biological half-life, and poor bioavailability. Conventional formulations of AZT are administered multiple times a day depending on the dose (300mg twice daily or 200mg thrice daily) due to its short half-life (t112=0.5 to 3h)[1, 2]. After oral administration, AZT is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2 µg/ml at 0.8 hours[3]. In the systemic circulation, it is first converted to AZT-troposphere, which is pharmacologically active and prevents the replication of 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. Since AZT acts as a metabolic antagonist of thymidine and its antiviral effect is time dependent, an adequate zero-order delivery of AZT is desired for maintaining anti-AIDS effect and avoiding the strong side effects. These side effects are usually associated with excessive plasma level of AZT immediately after intravenous or oral administration. The oral route of drug delivery is the most popular, desirable and preferred method of administering therapeutic agents for systemic effects because it is nature, convenient for the patient, and cost effective to manufacturing process. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians Alice[4]. In the matrix devices the drug or active agent is dispersed in polymer matrix to form a homogeneous system known as a matrix system. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because they make it easier to achieve a desirable drug - release profile, they are cost - effective, and they have broad US Food and Drug Administration (US FDA) acceptance. Reports were found on usage of hydrophilic polymers such as hydroxyl propyl-cellulose (HPMC), carboxyl methyl cellulose[5], carbopols[5], sodium alginate, polyvinyl alcohol etc. for the purpose of CR formulations of different drugs. In hydrophilic polymer matrix system, Zero order or First order release kinetics can be maintained if the polymer swells at a constant rate, maintaining a constant surface area and the diffusion of the drug is comparatively rapid. In addition to matrix system, reservoir or membrane controlled and osmotic controlled release systems have also been used for prolonging and controlling the drug release rate. For successful SR of drugs, either soluble or insoluble, it is essential that polymer hydration and surface gel layer formation are quick and consistent to prevent immediate tablet disintegration and premature drug release. For this reason, polymers for hydrophilic matrices can be supplied in small particle size ranges to setter ensure rapid hydration and consistent formation of the gel layer on the surface of the tablet.

MATERIALS AND METHODS

Materials

Zidovudine was obtained as a gift sample from Aurobindo Pharma Ltd, Hyderabad. HPMC K4M, SCMC was obtained

from Colorcon Asia Pvt. Ltd. Eudragit RL 100, Ethyl Cellulose was obtained from Rohm Pharma, Germany. Sodium Alginate, Magnesium Stearate, Micro Crystalline cellulose was from SD fine chemicals. All the ingredients used were of analytical grade.

Preparation of Zidovudine matrix tablets

Fifteen different tablet formulations were prepared by wet granulation technique The composition of 300 mg Zidovodine of the drug, polymer (HPMC, CMC, NaAlg) and filler (MC) was dry mixed thoroughly and sufficient volume of granulating agent (ethanol 95%). Ethanolic solution of PVP, ERL-100, and EC) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22 meshes. The granules were dried at 55^0C for 1 hour. This granule mixture was blended with magnesium stearate (2%w/w) as lubricant; the appropriate and then compressed using a 16 station tablet compression machine round, flat-faced punches of 10-mm diameter and die set. All compressed tablets were stored in an airtight container at room temperature for the study.

Evaluation Parameters

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

To study the compatibility of various formulation excipients with AZT, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ration of 1:1 and stored in air tight containers at 30 $\pm 2^0$c/65±5%RH. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FT-IR).

Pre-compression studies Zidovudine matrix granules

Angle of Repose

The angle of repose of granules was determined by the fixed funnel and freestanding cone method, where by accurately weighed granules (3gm were carefully poured through the funnel with its tip at 2 cm height (h) until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter (r1, of the base for the powder cone was measured and angle of repose (0) was calculated using the following equation.

$\text{Tan}\theta = h/r$

$\theta = \tan^{-1} (h/r)$

Where, θ = angle of repose

h = height

r = radius

Bulk Density

Both loose bulk Density and tapped bulk density were determined, whereby a quantity (3g) of granules from each formula, previously lightly shaken to break any agglomerates cylinder. After the initial volume was observed, the cylinder was allowed to full under its own weight onto a have surface from the height of 2.5cm at 2-Second intervals. The tapping was continued until no further change in the volume was noted LBD and TBD were calculated using the following formulas

LBD = Weight of the powder/ volume of the packing

TBD = weight of the powder / tapped volume of the packing

Hauser's Ratio

It indicates the flow properties of the powder and it measured by the ratio of TBD to the LBD.

Hausner's ratio = D_t/D_b

Where, Dt is the tapped density,

Db is the bulk density.

Compressibility Index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

Carr's compressibility index (%) = $[(D_t-D_b)$ X 100] / D_t

Where,

D_t is the tapped density

D_b is the bulk density

Drug content uniformity

Standard preparation

An accurately weighed amount of pure Zidovudine (100mg) and transferred into 100ml volumetric flask. It was dissolved and made up to volume with phosphate buffer and absorbance was measured at 266 nm.

Sample preparation

An accurately weighed amount of powdered Zidovudine granules (100mg) was extracted with water and the solution was filtered through 0.45m membrane and absorbance was measured at 266nm after suitable dilution.

The amount of Zidovudine present in granules can be calculated using the formula:-

A_t / A_s X Sw / 100 x 100

A_t = Absorbance of sample preparation

A_s = Absorbance of standard preparation

S_w = Weight of Zidovudine working standard (mg)

Post compression studies Zidovudine matrix tablets

Hardness Test

For each formulation, the hardness of 5 tablets was determined using a Monsanto hardness tester.

Friability Test

For each formulation, 6 tablets were weighed. The tablets were placed in a friabilator (Roche friabilator) and subjected to 25 rpm in 4 minutes. The tablets were then declusted and reweighed. The friability was calculated as the percentages weight loss.

F = 100 (1-wo/wt)

Where,

Wo = weight of tablets before friability test

Wt = weight of tablets after friability test

Weight variation Test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Drug content uniformity

Standard preparation

An accurately weighed amount of pure Zidovudine (100mg) and transferred into 100ml volumetric flask. It was dissolved and made up to volume with pH.8 phosphate buffer and absorbance was measured at 266 nm.

Sample preparation

Five tablets were weighed individually then placed in a mortar and powdered with a pestle. An amount of powdered Zidovudine (100mg) was extracted in water. The solution was filtered through 0.45µm membrane and absorbance was measured at 266nm after suitable dilution.

$A_t/As \times S_w/100 \times 100/S_t \times A_v$

Where,

A_t = Absorbance of sample preparation

A_s = Absorbance of Standard preparation

S_w = weight at Zidovudine working standard (mg)

S_t = weight of Zidovudine tablet (mg)

Av = Average weight of tablet (mg)

In vitro dissolution

The release of Zidovudine from the SR tablet was studied in 900 ml of phosphate buffer pH 6.8 as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37° ± 0.5° C. An aliquot (1 ml) was withdrawn at specific time intervals, filtered and diluted to 10 ml with phosphate buffer pH 6.8, and drug content was determined by UV-visible spectrophotometer at 266 nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume. Dissolution studies were for a period of 12 hrs and the mean value were taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

Pre-formulation Studies

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference in the functional groups as the principle peaks of the Zidovudine were found to be unaltered in the spectra of the drug-polymer physical mixture (Figure 1 and 2).

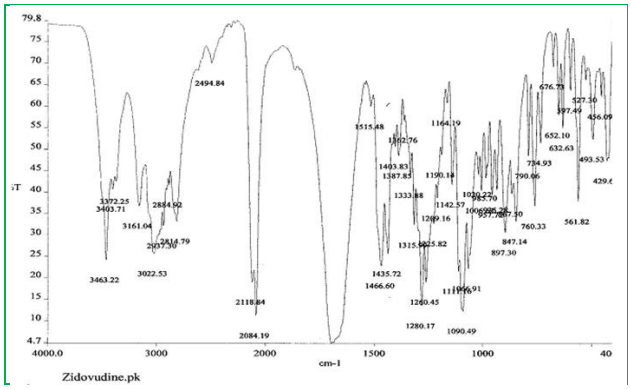

Figure 1: FT-IR spectra of pure Zidovudine

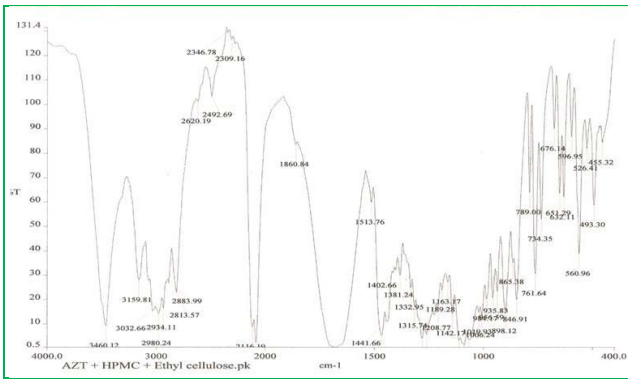

Figure 2: FT-IR spectra of pure Zidovudine+ HPMC+EC

Pre-compression studies

The granules for the tablet preparation were prepared according to the formula given in (Table 1 and 2). The granules of different formulations were evaluated for angle of repose, LBD, TBD, Compressibility index, Hauser's factor and drug content (Table No.3). The results of angle of repose range from 21.64 to 29.69 indicate good flow properties of the granules. This was further supported by lower compressibility index values (Table 3). Generally, compressibility index values from 9.61 to 16.59 (up to 16%) result in good to excellent flow properties. The bulk densities of the granules (F1, F2 and F3) granulated by ethanol 95% vol/vol were found to be quite higher than those of F10 to F15 granulated by ethanol solution of hydrophobic polymers. This indicates, as ethanol alone could not provide sufficient binding to the granules. The Hauser's ratio of granules of all formulations was <1.2

indicates free flowing. The drug content in the weighed amount of granules of all formulations was found to be uniform. All these results indicate that the granules possessed satisfactory flow-properties, compressibility and drug-content. Finally, both polymer level and polymer type did not affect the physical properties of the prepared granules.

Post-compression studies

The tablets of different formulations were subjected to various evaluations tests such as Hardness, Friability, and uniformity of weight, drug content and in vitro - dissolution. In a weight variation test, the pharmacopoeia limit for the percentage deviation from tablets of more than 250mg is ±5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percentage batches of drug content were more than 98%. The formulations (F10 to F15) showed a comparatively high hardness value of range from 7.18±0.26kg to 7.46±0.48kg indicate to the better binding properties of granules granulated by ethanol alone. In respective of polymer type, increasing polymer concentration resulted in quite a decrease in the hardness of the tablet. Another measure of tablet that loses less than 1% of their weight is generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacopoeia limit specifications for weight variation, drug content, hardness and friability (Table 4).

***In vitro* release studies**

The *in vitro* drug release characteristics were studied in 900ml of phosphate buffer ph 6.8 for a period of 12 hours using USP. XXIII dissolution apparatus type II (paddle). The results of dissolution studies indicated that F1, F2 & FIII released 99.37%, 99.59% and 99.42% of AZT at the end of 4.5 hours, 5 hours, and 7 hours, respectively. The results of dissolution studies indicated that F4, F5 and F6 released 99.57%, 99.64% and 99.85% of AZT at the end of 2.5 hours, 4 hours and 5.5 hours respectively. The result at dissolution studies indicated that F7, F8 and F9 released 99.43%, 99.92% and 99.11% at AZT at the end of 2 hours, 3.5 hours and 5 hours. Among these formulations the release rate was increased in the following polymer order: Sodium alginate > CMC > HPMC. Sodium alginate and CMC released the drug at a faster rate than did HPMC. The formulation F3, which exhibited the slowest dissolution profile than other formulation. However formulation F3 were selected for further modified using different granulating agents, such as PVP, Eudragit and Ethyl cellulose (Table 5 and 6) to control the drug release. The formulations F10 to F15 released more than 95% of AZT at the end of 12 hours. The formulation F13 (ERL 8%) and F15 (EC 4%) exhibited the slowest dissolution than formulation F10 (PVP 5%), F11 (PVP 10%), F12 (ERL 4%) and F14 (EC 2%). The formulation F10, F11, F12 & F14 released 36.23%, 34.78%, 27.185% and 24.38% of drug at the end of 2 hour, and 98.60%, 97.79%, 97.79%, 97.8% and 97.13% of drug at the end at 12 hours respectively.

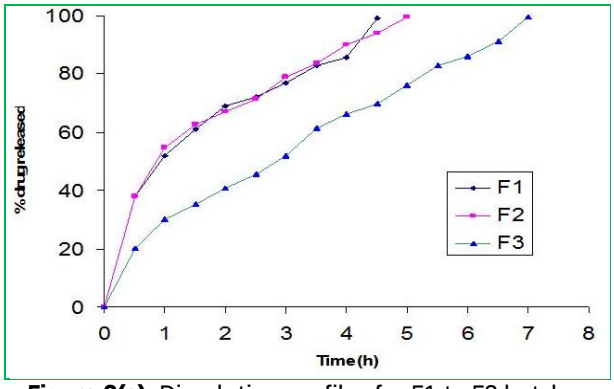

Figure 3(a): Dissolution profiles for F1 to F3 batches

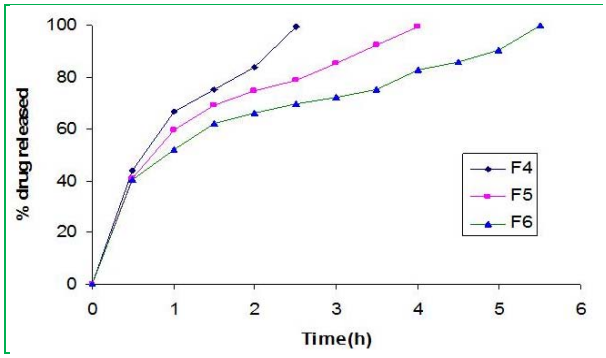

Figure 3(b): Dissolution profiles for F4 to F6 batches

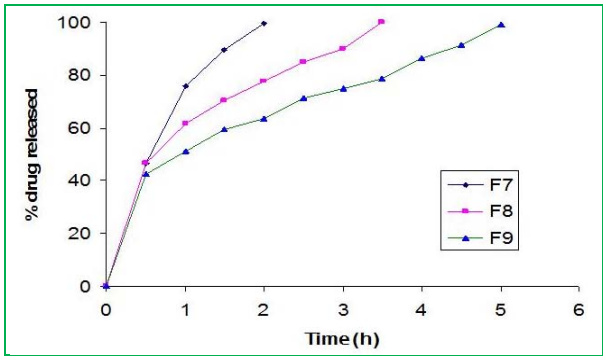

Figure 4(a): Dissolution profiles for F7 to F9 batches

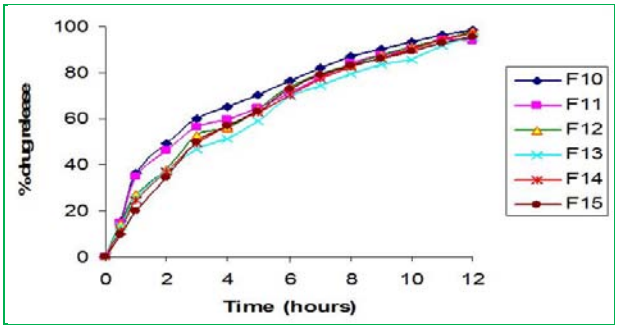

Figure 4(b): Dissolution profiles for F10 to F15 batches

These formulations showed a high release in the initial Hours. The formulation F13 and F14 released 25.69% and 20.93% of drug at the end of 2 hours and 95.32% and 95.38% of 12 hours respectively. From a commercial point

of view, EC is more economical than Eudragit. Hence, F15 is the most successful and cost-effective formulation among the matrix tablets developed in the present study.

Release mechanism

To know the mechanism of drug release from these formulations, the data were treated according to first-order release, Higuchi's, and Korsmeyer equation / Peppa's model et al's equation along with zero order release pattern. The release rate kinetic data for all the other equations can be seen in (Table 7). When the data were plotted according to the first-order equation, the formulations showed a fair linearity, with regression values between 0.9503 and 0.9845 in our experiments, the in vitro release profiles of drug from all the formulations could be best expressed by Higuch's equation, as the plots showed high linearity R^2-0.9682 to 0.9948. To confirm the diffusion mechanism, the data were fit into Korsmeyer, et al's equation, with slope (n) values ranging from 0.58 to 0.82. This indicates that the release of drug follows Non-Fickian transport. It means in release of drug from the tablet dissolution and diffusion both mechanisms are used.

Table 1: General composition of 300mg Zidovudine tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hyroxy propyl methyl cellulose (%)	10	20	30	-	-	-	-	-	-
Carboxy methyl cellulose (%)	-	-	-	10	20	30	-	-	-
Sodium alginate (%)	-	-	-	-	-	-	10	20	30
Microcrystalline cellulose (%)	28	18	8	28	18	8	28	18	8
Ethanol (95%)	qs	qs	qs	qs	qs	qs	qs	qs	qs
Magnesium stearate (%wt\wt)	2	2	2	2	2	2	2	2	2

Table 2: General composition of 300mg Zidovudine tablet

Ingredients	F10	F11	F12	F13	F14	F15
Hyroxypropylmethylcellulose (%)	30	30	30	30	30	30
Polyvinylpyrrolidone (PVP5%)	qs	-	-	-	-	-
PVP (10%)	-	qs	-	-	-	-
Eudragit RL100 (4%)	-	-	qs	-	-	-
Eudragit RL100 (8%)	-	-	-	qs	-	-
Ethylcellulose (2%)	-	-	-	-	Qs	-
Ethylcellulose (4%)	-	-	-	-	-	Qs
Microcrystalline cellulose (%)	8	8	8	8	8	8
Magnesium stearate (%w\w)	2	2	2	2	2	2

Table 3: Results of Pre-compression Studies of sustained release matrix tablets of Zidovudine (F1 to F15)

Formulation code	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index	Hauser's ratio	% Drug content
F1	24.2	0.2762	0.3250	15.02	1.177	99.36
F2	24.38	0.2738	0.3220	14.92	1.175	99.19
F3	29.20	0.2622	0.3145	16.59	1.199	99.21
F4	26.36	0.2287	0.2591	11.71	1.133	99.27
F5	27.35	0.2154	0.2467	12.67	1.145	99.15
F6	28.64	0.2119	0.2407	11.98	1.136	99.36
F7	29.18	0.2959	0.3234	8.51	1.093	98.99
F8	21.64	0.2993	0.3310	12.43	1.106	99.11
F9	22.84	0.3109	0.3483	10.71	1.120	99.56
F10	27.63	0.268	0.3136	14.57	1.171	99.64
F11	26.94	0.2657	0.3097	14.18	1.165	99.07
F12	25.94	0.2657	0.3037	16.46	1.14	99.23
F13	26.23	0.2617	0.3067	14.52	1.17	99.24
F14	29.69	0.2550	0.2932	13.03	1.15	99.68
F15	29.80	0.2696	0.3227	12.43	1.14	99.60

Table 4: Results of post-compression Studies of sustained release matrix tablets of Zidovudine (F1 to F15)

Formulation code	Hardness (kg/cm^3)	Friability (%)	Weight Variation (mg)	% Drug content
F1	7.02	0.12	500.94	99.11
F2	6.82	0.039	500.21	99.15
F3	6.88	0.08	500.45	99.07
F4	7.34	0.079	500.81	99.19
F5	7.22	0.099	500.04	98.95
F6	7.16	0.139	500.5	99.19
F7	7.92	0.199	500.69	98.87
F8	7.64	0.079	500.78	98.95
F9	7.5	0.159	500.55	99.76
F10	7.34	0.059	501.11	99.56
F11	7.18	0.099	500.43	98.95
F12	7.46	0.139	501.2	99.11
F13	7.16	0.06	500.76	99.15
F14	7.24	0.099	500.9	99.36
F15	7.02	0.12	500.94	99.11

Table 5: Results of *in vitro* % drug release of sustained release matrix tablets of Zidovudine (F1 to F9)

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	38.21	38.28	20.04	44.17	41.04	40.47	46.44	46.5	42.26
1	52.05	54.92	29.99	66.83	59.83	51.93	76.02	61.52	51.26
1.5	61.16	62.66	35.28	75.23	68.96	62.33	89.6	70.1	59.16
2	69.18	67.24	40.95	83.71	74.89	66.05	99.43	77.75	63.31
2.5	72.04	71.54	45.63	99.57	78.56	69.71	-	85.13	71.45
3	77.12	78.96	52.14	-	85.53	72.16	-	90.12	74.84
3.5	82.77	83.71	61.43	-	92.45	75.02	-	99.92	78.53
4	85.55	90.08	66.13	-	99.64	82.65	-	-	86.22
4.5	99.37	94.01	69.87	-	-	86.04	-	-	91.16
5	-	99.59	76.05	-	-	90.27	-	-	99.11
5.5	-	-	82.95	-	-	99.85	-	-	-
6	-	-	86.18	-	-	-	-	-	-
6.5	-	-	91.36	-	-	-	-	-	-

Table 6: Results of *in vitro* percentage drug release of sustained release matrix tablets of Zidovudine (F10 to F15)

Time (hrs)	F10	F11	F12	F13	F14	F15
0.5	15.13	14.97	14.49	13.43	11.05	9.87
1	36.23	34.78	27.18	25.69	24.38	19.93
2	49.16	46.14	38.2	34.26	37.09	37.64
3	60.11	56.23	52.59	48.94	49.26	46.81
4	65.21	59.39	58.92	57.13	56.83	51.08
5	70.19	64.4	64.33	63.26	62.82	58.72
6	76.55	71.32	73.91	72.91	70.20	69.79
7	82.23	78.11	79.43	78.74	77.27	74.41
8	86.95	84.14	83.28	82.84	82.39	79.3
9	90.33	87.47	87.61	86.10	86.34	83.66
10	93.16	90.35	91.23	89.42	90.24	85.46
11	96.34	92.07	94.39	92.7	94.2	91.8
12	98.60	93.79	97.80	95.38	97.13	95.32

Table 7: Results of *in vitro* kinetic data for F10 to F15

Formula code	Zero order	First order	Higuchi's	Korsmeyer-Peppa's	
	r	r	r	n	r
F10	0.9198	0.9550	0.9860	0.58	0.9834
F11	0.9388	0.9503	0.9948	0.59	0.9933
F12	0.9470	0.9517	0.9796	0.71	0.9801
F13	0.9582	0.9646	0.9837	0.67	0.9790
F14	0.9552	0.9601	0.9845	0.77	0.9817
F15	0.9431	0.9845	0.9682	0.82	0.9657

CONCLUSION

The hydrophilic matrix of HPMC alone could not control the Zidovudine release effectively for 12 hours. It is evident from the results that a matrix tablet prepared with HPMC and a granulating agent of a hydrophobic polymer (EC, 4% wt/vol) is a better system for sustained release of a highly water-soluble drug like Zidovudine. Formulations F10 to F15 exhibited diffusion - coupled with erosion drug release.

REFERENCES

1. Anthony S F, Clifford H L. "Human Immuno deficiency virus (HIV) Disease: AIDS and Related Disorclers", 15th edition, 1996, 1297-1305.
2. Betty J D, "Human immunodeficiency virus (HIV) - Antiretroviral Therapy". Section 15, 7th edition.
3. Chien Y W. "Novel Drug Delivery systems", 1992, 139-136.
4. Brahmankar D M, Jaiswal S B." Bio pharmaceutics and pharmacokinetics a treatise", *Vallabh prakashan, New Delhi*, 1st edition, 1995, 64-70.
5. Parojcic J, Duric Z, Jovanovic M, Ibrics. "An investigation into the factors influencing drug release from hydrophilic matrix tablets - based on novel carbomer polymers", *Drug Delivery*, 11(1), 2004, 59 - 65.

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