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Research Article

Formulation and *In vitro* Release Study of Zidovudine Sustained Release Tablets

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ABSTRACT

The purpose of the present investigation was to out to formulate sustained release matrix tablets of zidovudine. The sustained release matrix tablets were prepared by wet granulation method by using hydrophilic polymers like HPMC, SCMC and Na Alginate (F1 to F9).A total of nine formulations were prepared using hydrophilic polymers. The formulation F3 was selected for further modification using different hydrophobic polymers as granulating agents, such as PVP, Eudragit RL100 and Ethylcellulose to control the drug release. The hydrophilic matrix of HPMC alone could not control the Zidovudine release effectively for 12 hours. The formulations F10 to F15 released more than 95% of AZT at the end of 12 hours.The drug polymer interaction were investigated by FTIR studies. Zidovudine tablets were evaluated for various physical tests like weight variation, hardness, friability and results showed they comply with in the limits. Kinetic treatment to the in vitro release data revealed that the drug release followed first order release and mechanism of drug release is by Non-fickian transport. Of all formulations, F15 is the most successful and cost-effective formulation among the matrix tablets developed in the present study.

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 ($t_{1/2}$=0.5 to 3h)[1,2]. Hydrophilic swell able polymers are widely utilized to sustain the release of drugs from matrix formulations. The rate of drug release from hydrophilic matrix is determined by numerous processes such as hydration of the polymer that leads to swelling, diffusion of the drug through the hydrated polymer, drug dissolution and polymer erosion.

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The hydrophilic polymers selected for the present study were hydroxylpropyl Methylcellulose (HPMC), carboxymethylcellulose (CMC), sodium Alginate (NaAlg).This polymer provides p^Hindependent drug release to oral dosage forms that can be used 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[3].Hence in the present work, an attempt has been made to formulate the extended release matrix tablets[4] of AZT using hydrophilic matrix material in combination with hydrophobic polymers such as polyvinylpyrrolidone (PVP), Eudragit RL100, and ethyl cellulose.

MATERIALS AND METHODS

Zidovudine (Aurobindo Pharma Labs. Hyderabad.) , HPMC K_4M, HPMC $K_{10}M$ and PVP K 30 (Colorcon Asia Pvt. Ltd.), Eudragit RL 100, Ethyl Cellulose,Sodiumcarboxymethylcellulose,

Sodium Alginate and Micro Crystalline cellulose (Moly Chem. Labs. Mumbai.)

Preformulation (Compatibility) studies [5]

In the present work a study was carried out by using FT-IR spectrophotometer to find out if there is any possible chemical interaction of zidovodine with hydroxypropyl methylcellulose (HPMC)[6]; carboxymethycellulose (CMC); sodium alginate (NaAlg); Polyvinypyrolidone (PVP); Eudragit RL100 (RL100); Ethycellulose (EC)[7]; Micro crystalline cellulose (MCC).The 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 ±2^{0}C/65±5%RH. The spectra's of admixtures were compared with pure Zidovudine.

Preparation of Zidovudine matrix tablets

Fifteen different tablet formulations were prepared by wet granulation technique (formulation 1-15, Tables 1 and 2). The composition of 300 mg zidovudine 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 mesh screen. The granules were dried at 55^{0}C for 1 hour. The granule mixture was blended with magnesium stearate (2%w/w) as lubricant and then compressed using a 16 station tablet compression machine round, flat-faced punches of 10-mm diameter and dies set. All compressed tablets were stored in an airtight container at room temperature.

Evaluation of physical properties of tablets

The formulated tablets were evaluated for the following parameters.

1. Thickness

The thickness and diameter of the formulated tablets were measured by using Vernier calipers.

2. Weight variation

The formulated tablets were tested for weight uniformity. 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is with in permissible limits or not.

$$\% \text{ Weight Variation} = \frac{\text{Average weight-Individual weight}}{\text{Average weight}} \times 100$$

3. Hardness

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Pfizer tablet hardness tester.

4. Friability

The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The percentage friability was calculated using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight- Final weight}}{\text{Initial weight}} \times 100$$

5. Drug content

About 100 mg of zidovudine was weighed accurately and transferred into a 100 ml volumetric flask. It was dissolved, suitably diluted and made up to volume with phosphate buffer pH 8.0.One tablet was powdered and powder equivalent to 100 mg of zidovudine was transferred to a 100 ml volumetric flask and was dissolved in phosphate buffer pH 8.0. It was sonicated for 30 min and filtered through 0.45 µm membrane filter. The absorbance after suitable dilutions was measured in a UV-visible Spectrophotometer at 266 nm using PBS pH 8.0 as blank.

6. In vitro drug release studies

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. 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.

RESULTS AND DISCUSSION

Preformulation Studies

The IR Spectrum of pure zidovudine drug was compared with the IR spectrum of physical mixture of Zidovudine (Fig. 1).

Table 1: Composition of formulations (Formulations F1 to F9)

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Zidovudine	300	300	300	300	300	300	300	300	300
HydroxyPropylMethylCellulose (HPMC)	50	75	125	-	-	-	-	-	-
CarboxyMethyl Cellulose(CMC)	-	-	-	50	75	125	-	-	-
SodiumAlginate	-	-	-	-	-	-	50	75	125
Microcrystalline cellulose	140	115	65	140	115	65	140	115	65
Magnesium Stearate	10	10	10	10	10	10	10	10	10

Table 2: Composition of formulations (Formulations F10 to F15)

Ingredients	F10(mg)	F11(mg)	F12(mg)	F13(mg)	F14(mg)	F15(mg)
Zidovudine	300	300	300	300	300	300
HPMC	125	125	125	125	125	125
PolyVinylPyrrolidine	5%	10%	-	-	-	-
EUDRAGIT L100	-	-	4%	8%	-	-
EthylCellulose	-	-	-	-	2%	4%
Microcrystalline cellulose	65	65	65	65	65	65
MagnesiumStearate	10	10	10	10	10	10

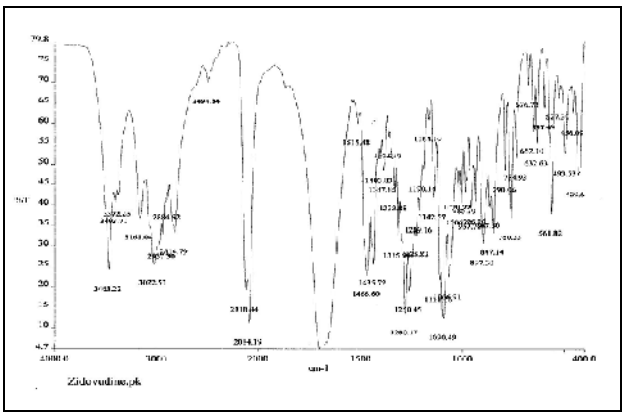

Figure 1.1: FTIR spectra of pure zidovudine.

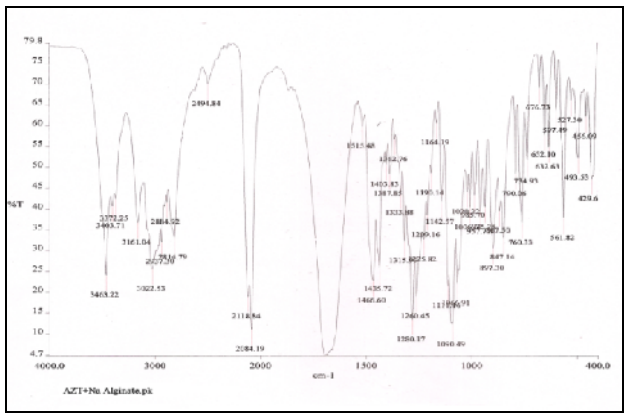

Figure 1.2: FTIR spectra of zidovudine and sodium alginate

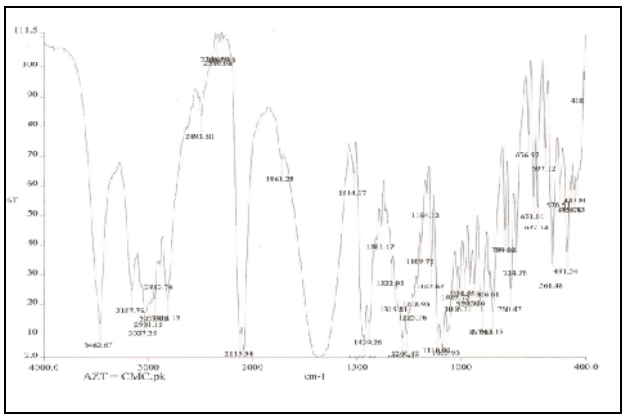

Figure 1.3: FTIR spectra zidovudine and carboxy methyl cellulose

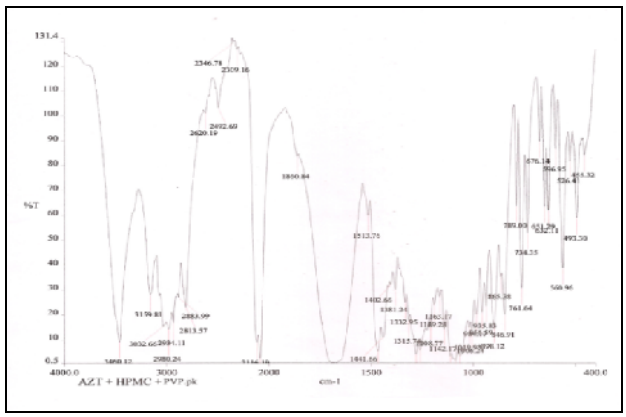

Figure 1.4: FTIR spectra of AZT+HPMC+PVP

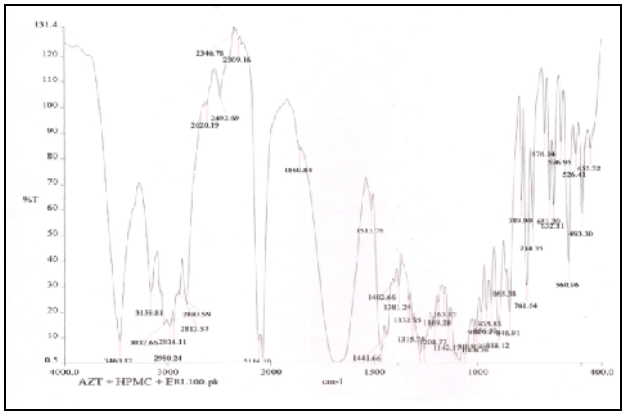

Figure 1.5: FTIR spectra of AZT+HPMC+ERL 100

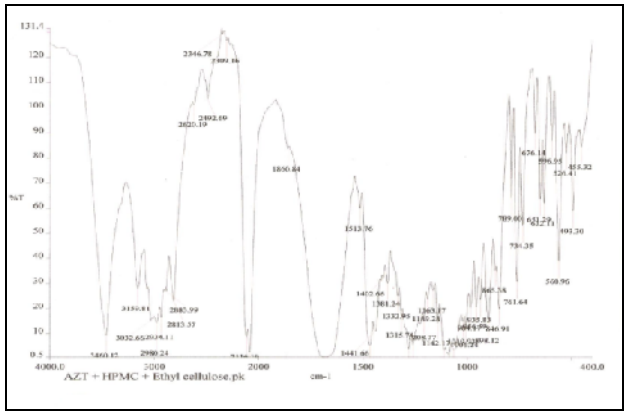

Figure 1.6: FTIR spectra of AZT+HPMC+EC

Table 3: Characterization of granules

Formulation code	Angle of Repose (°)	Bulk Density (gm/ml)	TappedDensity (gm/ml)	Compressibility index	Hauser's ratio
F1	24.29±1.29	0.2762±0.008	0.3250±.008	15.02±0.81	1.177±0.011
F2	24.38±1.52	0.2738±0.011	0.3220±0.017	14.92±1.12	1.175±0.015
F3	29.20±1.86	0.2622±0.015	0.3145±0.021	16.59±0.97	1.199±0.014
F4	26.36±1.73	0.2287±0.009	0.2591±0.014	11.71±1.56	1.133±0.020
F5	27.35±1.32	0.2154±0.006	0.2467±0.007	12.67±0.58	1.145±0.008
F6	28.64±1.58	0.2119±0.006	0.2407±0.005	11.98±1.58	1.136±0.021
F7	21.80±1.19	0.2959±0.019	0.3234±0.020	8.51±0.71	1.093±0.009
F8	21.64±1.47	0.2993±0.012	0.3310±0.009	9.61±1.19	1.106±0.014
F9	22.84±1.64	0.3109±0.016	0.3483±0.020	10.71±0.84	1.120±0.010
F10	27.63±1.56	0.268±0.007	0.3136±0.005	14.57±0.98	1.171±0.013
F11	26.94±1.82	0.2657±.009	0.3097±0.015	14.18±1.24	1.165±0.017
F12	25.94±1.35	0.2696±0.006	0.3227±0.006	16.46±0.78	1.020±0.011
F13	26.23±1.24	0.2617±0.004	0.3067±0.003	14.52±1.85	1.17±0.02
F14	29.69±1.65	0.2550±0.003	0.2932±0.004	13.03±0.49	1.15±0.006
F15	29.18±1.57	0.2657±0.009	0.3037±0.017	12.43±1.96	1.14±0.03

All values expressed as mean± S.D, n=3

Table 4: Physical Evaluation Of SR tablets of Zidovudine

Formulation code	Thickness(mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Drug content (%)
F1	2.5±0.02	7.02±0.05	0.120±0.03	2.95±0.03	99.11±0.04
F2	2.5±0.02	6.82±0.06	0.039±0.03	3.52±0.02	99.15±0.05
F3	2.44±0.03	6.88±0.03	0.080±0.06	2.46±0.03	99.07±0.06
F4	2.38±0.04	7.34±0.01	0.079±0.05	3.09±0.04	99.19±0.06
F5	2.56±0.02	7.22±0.06	0.099±0.06	2.24±0.06	98.95±0.08
F6	2.5±0.03	7.16±0.04	0.139±0.05	2.75±0.09	99.19±0.07
F7	2.4±0.04	7.92±0.04	0.199±0.04	2.92±0.05	98.87±0.05
F8	2.52±0.03	7.64±0.05	0.079±0.03	2.48±0.07	98.95±0.05

..... Continue

Formulation code	Thickness(mm)	Hardness (kg/cm²)	Friability (%)	Weight variation (%)	Drug content (%)
F9	2.48±0.02	7.5±0.05	0.159±0.01	2.99±0.05	99.76±0.06
F10	2.60±0.02	7.34±0.05	0.059±0.06	3.12±0.06	99.56±0.04
F11	2.36±0.04	7.18±0.08	0.099±0.02	3.24±0.06	98.95±0.03
F12	2.44±0.05	7.46±0.06	0.139±0.06	2.96±0.02	99.11±0.03
F13	2.39±0.06	7.16±0.06	0.060±0.05	2.68±0.04	99.15±0.02
F14	2.65±0.04	7.5±0.05	0.059±0.05	2.79±0.05	99.6±0.06
F15	2.50±0.03	7.24±0.02	0.099±0.02	3.38±0.06	99.36±0.02

All values expressed as mean± S.D, n=3

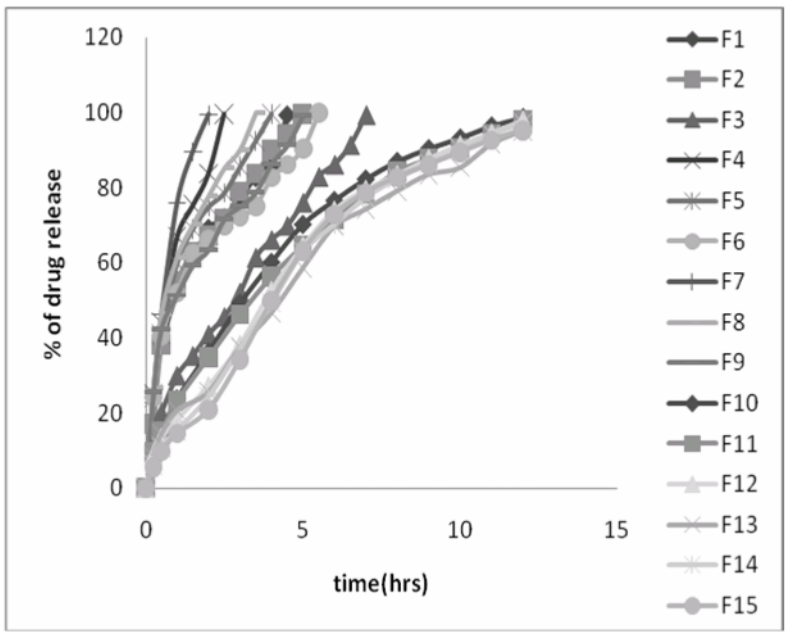

Figure 2: Dissolution Profiles of Zidovudine SR Tablets

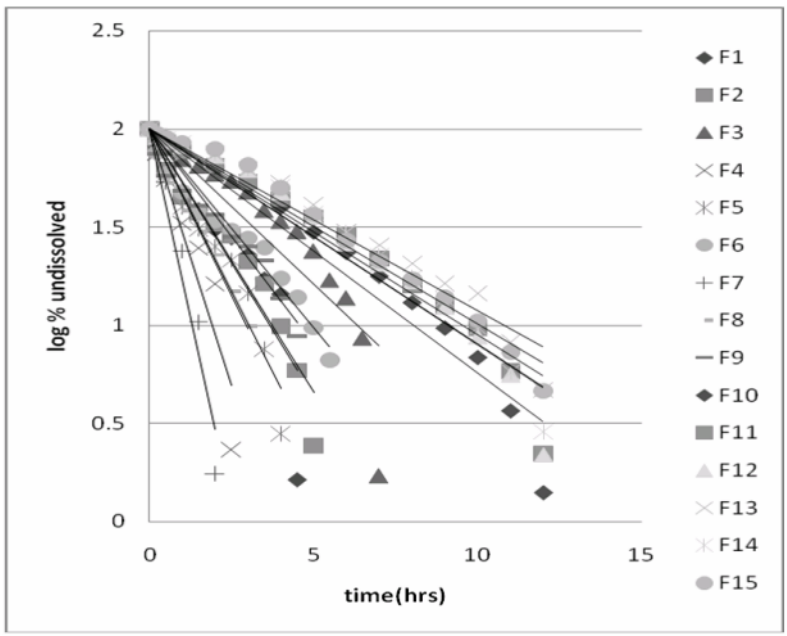

Figure 3: First order plots for zidovudine SR formulations.(F1-F15)

Table 5: Kinetic values obtained from different plots of Formulation (F1 – F15)

Formulation code	Zero-order		First-order		Higuchi	Korsmeyer-peppas	
	Zero order rate constant K_0 (mg.h^{-1})	Regression Coefficient (R^2)	First order rate constant K (h^{-1})	Regression Coefficient (R^2)	Regression coefficient (R^2)	Slope (n)	Regression coefficient (R^2)
F1	88.48	0.9365	0.7385	0.8373	0.9924	0.4544	0.9921
F2	84.723	0.9345	0.6236	0.9699	0.9904	0.5435	0.9731
F3	63.495	0.9898	0.4117	0.9056	0.9905	0.5921	0.9964
F4	179.18	0.9539	1.2786	0.9440	0.9950	0.5682	0.9982
F5	105.25	0.9302	0.7546	0.9705	0.9919	0.4724	0.9856
F6	69.39	0.9223	0.4173	0.9820	0.9860	0.4811	0.9847
F7	242.19	0.9603	1.9271	0.9793	0.9922	0.6539	0.9896
F8	120.77	0.9315	0.9838	0.9312	0.9930	0.4614	0.9850
F9	76.05	0.9214	0.5432	0.8788	0.9918	0.4845	0.9860
F10	7.9954	0.9198	0.2454	0.9550	0.9860	0.5822	0.9834
F11	7.8502	0.9388	0.2639	0.9503	0.9948	0.5945	0.9933
F12	8.2163	0.9470	0.2254	0.9517	0.9796	0.7122	0.9801
F13	7.8209	0.9582	0.2761	0.9646	0.9837	0.6721	0.9790
F14	8.3404	0.9552	0.2666	0.9601	0.9845	0.7717	0.9817
F15	8.3804	0.9431	0.3044	0.9845	0.9682	0.8245	0.9657

The characteristic functional groups of the pure zidovudine and physical mixtures of zidovudine and polymers showed the peaks at the following wave number region .C-N(amine) stretching – 1000-1250 cm^{-1};NH stretching-3400-3500 cm^{-1};C=O stretching-1600-1700 cm^{-1};Azide group stretching- 2100-2270 cm^{-1}.

The quality control tests adopted for the tablets were depicted in the table 4. The thickness of the tablets ranged between 2.36±0.04 mm to 2.65±0.04mm. The hardness of the tablets ranged between 6.82±0.06 Kg/cm^2 to 7.92±0.04Kg/cm^2.The percent friability of the prepared tablets were within acceptable limit. There was no significant weight variation observed between average weight and individual weight.The drug content in all the formulations was within the range of 98.87±0.05 % to 99.76±0.06 %, ensuring uniformity of drug content in the formulations.

The dissolution data was showed in Fig. 2. The drug release followed first order kinetics (table 5) and the graph was drawn in between the log % undissolved verses time were found to be linear (Fig. 3). To ascertain the mechanism of drug release [8] the data was subjected to Higuchi & Korsmeyer Peppas equation. Application of Korsmeyer Peppas[9] equation to the data showed that the mechanism of drug release of Zidovudine from the matrix tablets is governed by non fickian diffusion (slope > 0.45), and the release rate of drug is governed by the hydrophobic polymers employed.

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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% w/v) is a better system for sustained release of a highly water-soluble drug like zidovudine. Formulations F1 to F15 exhibited diffusion – coupled with erosion drug release.

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