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FORMULATION DESIGN AND EVALUATION OF SUSTAINED RELEASE TABLETS OF ZIDOVUDINE CONTAINING HPMC K_{100}

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ABSTRACT

The present investigation concerned with formulation design and evaluation of oral sustained release matrix tablets of Zidovudine (AZT) prepared by direct compression method using various proportion of release retarding polymer viz; HPMC K_{100}. The prepared tablets were evaluated for weight variation, percentage friability, hardness and *In Vitro* dissolution studies and all the formulations showed compliance with pharmacopeia standards. *In Vitro* release studies were performed using USP type I apparatus (rotary basket type). Formulation F_1 and F_2 failed to sustain release beyond 10 hours and the cumulative percentage of drug release is not more than 85% at the end of 12 hour in formulation F_5. The formulations F_3 and F_4 sustained release of drug for 12 hrs with 26.7%, and 21.12% release of drug respectively after 1hr and more than 90% at the end of 12 hrs. The release kinetics were analyzed using Zero-order model equation, Higuchi's square root equation and Korsmeyer and Peppas' empirical equation. The regression coefficient obtained for first order kinetics were found to be higher (R^2: 0.897 to 0.971) when compared with those of the zero order kinetics (R^2: 0.673 to 0.920), indicating that drug release from all formulations followed first order kinetics. The mechanism of drug release from formulation F_1 and F_2 showed behavior of Fickian diffusion and remaining all formulations showed non-Fickian diffusion.

INTRODUCTION

Tablets are the most popular oral dosage form available in the market preferred by patients and physicians alike. Conventional formulations are required to be administered in multiple doses in long term therapy for chronic disease condition, which leads to several limitations. To overcome this problem sustained release tablets are preferred; because they provide better patient compliance, maintain uniform drug level, reduce dose and side effects, and increase the potency of the drug [1].HIV (Human Immunodeficiency Virus) is a virus which causes AIDS (Acquired Immuno Deficiency Syndrome) in which a portion is affected by a series of diseases due to poor immunity. Zidovudine is the first anti HIV compound approved clinical use for treatment of AIDS, either alone or with other antiviral drug [2]. Zidovudine (AZT) is a potent antiviral agent used in the treatment of AIDS. Conventional formulation of AZT is administered multiple times in a day depending upon the dose (300mg twice a day or 200mg thrice a day) due to its short half life [3]. 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. After oral administration, it is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2 µg/mL at 0.8 hours.5 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**.** AZT is absorbed throughout the GIT [4]. In recent years hydrophilic polymers have attracted considerable attention in sustaining the drug release of water soluble and water insoluble agents. A number of natural and number of polysaccharides such as Xanthan gum, Guar gum, Sodium alginate etc have been shown for controlling the release due to their hydrophilic properties [5].

MATERIALS AND METHODS

Materials

AZT was obtained as a gift sample from Mecleod's Pharm (Mumbai, India), HPMC K_{100} was obtained from Dr Reddy's Lab (Hyderabad, India), Micro Crystalline 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 concentrations of HPMC K_{100}. All ingredients except magnesium stearate and aerosil were blended in glass mortar uniformly. After the sufficient mixing of drug as well as other components, magnesium stearate and aerosil were added and mixed for additional 5 minutes and finally compressed on a rotary tableting machine using 13-mm punches.

Table 1: Preparation of Matrix Tablets of Zidovudine

Formulation ingedients	**Formulation batch**				
	F_1	**F_2**	**F_3**	**F_4**	**F_5**
Zidovudine(mg)	300	300	300	300	300
HPMC K_{100}(mg)	(6%) 30	(8%) 40	(10%) 50	(12%) 60	(15%) 75
MCC(mg)	160	150	140	130	115
Aerosil(mg)	5	5	5	5	5
Magnesium stearate(mg)	5	5	5	5	5
Total wt(mg)	500	500	500	500	500

Evaluation of Matrix Tablets [6, 7]

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. 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 (Sartorius Electronic Balance, BT-2245). The drug content of the manufactured tablets of each batch was determined in triplicate. For each batch 10 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved and analyzed after making appropriate dilutions.

Table 2: Physical Characterization of Prepared Matrix Tablets

Formulation batch	Avg. Wt. (mg)	Hardness (kg/cm^2)	Drug Content (%)	Friability (%)
F_1	497.25±6.257	5.12±0.337	97.292±2.282	0.587
F_2	508.79±6.63	5.21±0.288	97.654±2.246	0.571
F_3	504.79±6.63	5.09±0.265	97.932±2.064	0.582
F_4	507.55±6.634	5.15±0.188	99.051±2.102	0.566
F_5	501.768±5.491	5.22±0.219	98.83±2.21	0.549

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

***In Vitro* Drug Release Studies**

Release rate of all the designed formulations were studied up to 12 hours using USP- type I dissolution apparatus at 50 rpm. The dissolution medium (900ml) consisted of 0.1N hydrochloric acid for first 2 hours and the phosphate buffer p^H 7.4 from 3 to 12 hours, maintained at 37°C ± 0.5°C. Sample of 5 ml was withdrawn at specific time intervals throughout 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 at 266nm for 0.1N HCl and 267nm for phosphate buffer. The release studies were conducted in triplicate.

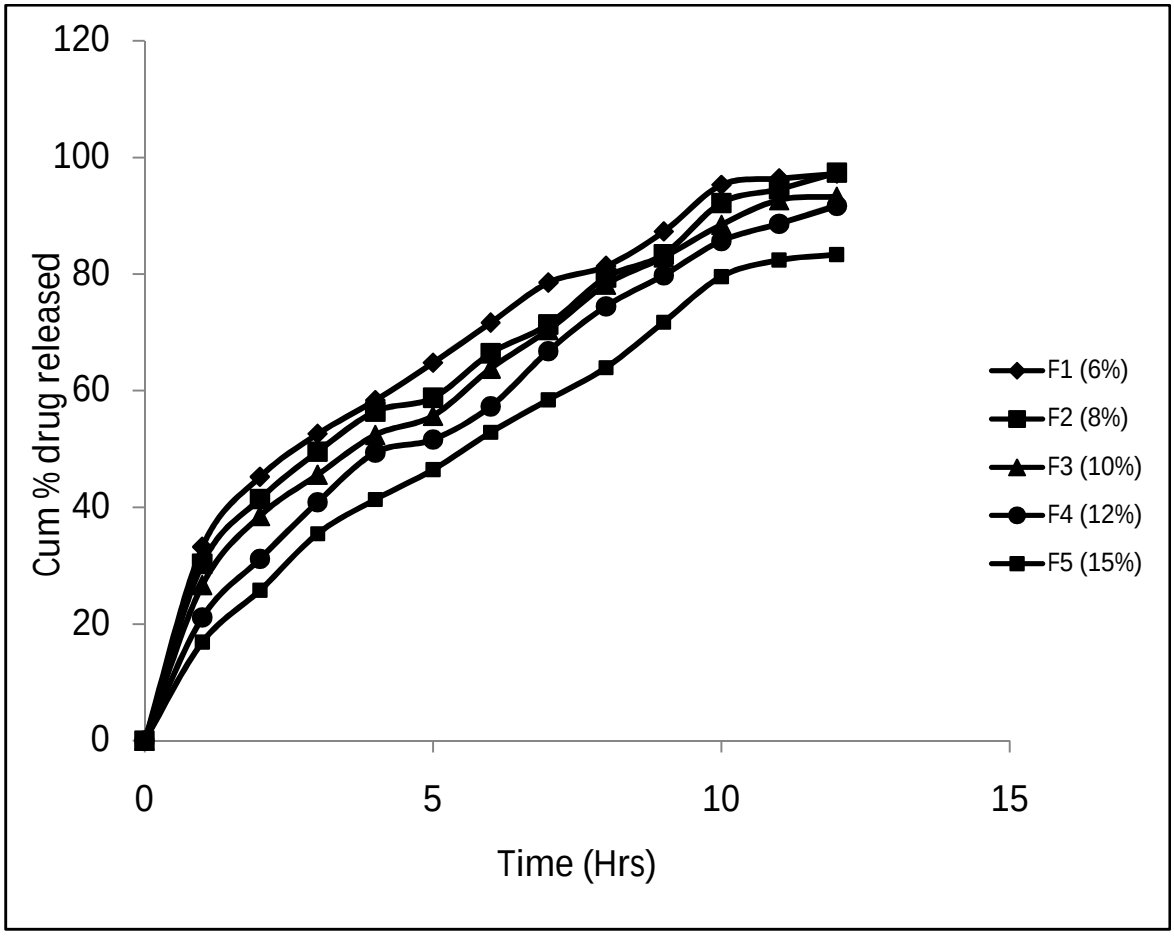

Fig.1: *In-Vitro* Drug Release Profile of Sustained Release Matrix Tablets of Zidovudine Using HPMC K_{100}

Kinetic analysis of given data [8, 9, 10]

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$W_0 - W_t = K_0 t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time **t** and **K** is proportionality constant. Dividing this equation by W_0 and simplifying:

$$f_t = K_0 t$$

Where $f_t = 1 - (w_t / w_0)$ and f_t represents the fraction of drug dissolved in time t and k_0 the apparent dissolution rate constant or zero order release constant.

First order kinetics:

The relation expressing this model:

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t / 2.303$$

Where Q_t is the amount of drug released in time t, Q_0 is initial amount of drug in the solution and K_1 is the first order release rate constant.

Korsmeyer Peppas model:

It can be represented by the following equation:

$$Q_t / Q_\infty = K_k t^n$$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and *n* is the release exponent, indicative of the drug release mechanism. For matrix tablets, an *n* value of ~0.5 indicates diffusion-controlled mechanism while an *n* value of ~1.0 indicates erosion-controlled release. Intermediate values suggest dual mechanism of both diffusion and erosion.

Higuchi Model:

It can be represented by the following equation:

$$\mathbf{Qt = K_H t^{1/2}}$$

Where Q_t = the amount of drug released at time t and

K_H= the Higuchi release rate;

RESULTS AND DISCUSSION

The oral sustained release matrix tablets of Zidovudine were formulated by using HPMC K_{100} as the retardant polymers. Matrix tablets were prepared by direct compression method and prepared tablets were evaluated for weight variation, percentage friability, hardness and *In Vitro* dissolution studies. All the formulations showed compliance with pharmacopeia standards. *In Vitro* release studies revealed that the release rate decreased with increase polymer proportion of HPMC K_{100}. Formulation F_1 and F_2 failed to sustain release beyond 10 hours and the cumulative percentage of drug release is not more than 85% at the end of 12 hour in formulation F_5. The formulations F_3 and F_4 sustained release of drug for 12 hrs with 26.7%, and 21.12% release of drug respectively after 1hr and more than 90% at the end of 12 hrs. It can be concluded that stable formulation could be developed by incorporating in a definite proportion of HPMC K_{100}, So that sustained released profile is maintained for an extended periods of time. Further the release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The regression coefficient obtained for first order kinetics were found to be higher (R^2: 0.897 to 0.971) when compared with those of the zero order kinetics (R^2: 0.673 to 0.920), indicating that drug release from all formulations followed first order kinetics. In this experiment, the *In-Vitro* release profiles of drug from all these formulations can be best expressed by Higuchi equation as the plots showed the highest linearity(R^2: 0.967 to 0.994). To confirm the diffusion mechanism the data was fitted into Korsemeyer-Peppas equation. All the formulations showed good linearity (R^2: 0.991 to 0.997) with slope (n) values ranging from 0.445 to 0.656. The mechanism of drug release from formulation F_1 and F_2 showed behavior of Fickian diffusion and remaining all formulations showed non-Fickian diffusion.

Table 3: Release exponent and drug transport mechanism

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.5<*n*<1.0	Anomalous transport
1.0	Case-II transport
Higher than 1.0	Super Case-II transport

Table 4: Kinetic Analysis of Dissolution profile from batches F_1 to F_5

Models		F_1	F_2	F_3	F_4	F_5
Peppas Model	**n**	0.445	0.474	0.515	0.601	0.656
	R^2	0.995	0.991	0.993	0.995	0.997
	K_1	32.58	29.37	26.12	20.74	16.63
Higuchi Model	**R^2**	0.993	0.994	0.993	0.981	0.967
	K_2	29.27	28.05	27.08	25.64	23.02
Zero- Order	**R^2**	0.673	0.752	0.800	0.880	0.920
	K_3	9.90	9.53	9.23	8.8	7.94
First- Order	**R^2**	0.924	0.897	0.954	0.963	0.971
	K_4	0.292	0.271	0.221	0.200	0.151

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