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FORMULATION DEVELOPMENT AND EVALUATION OF DIDANOSINE SUSTAINED- RELEASE MATRIX TABLETS USING HPMC K_{15}

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ABSTRACT

The present investigation concerned with formulation design and evaluation of oral sustained release matrix tablets of Didanosine (DDI) prepared by direct compression method using various proportion of release retarding polymer viz; HPMC K_{15}. 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 II apparatus (Paddle type) at 50 rpm. Formulation F_1 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_2, F_3 and F_4 sustained release of drug for 12 hrs with 31.32%, 28.27% and 23.34% release of drug after 1hr and more than 90% at the end of 12 hrs. The release kinetics was 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: 0.985 to 0.991) when compared with those of the zero order kinetics (R^2: 0.311 to 0.897), indicating that drug release from all formulations followed first order kinetics. The mechanism of drug release from formulation F_1 to F_3 showed behavior of Fickian diffusion and remaining all formulations showed non-Fickian diffusion.

Keywords: Sustained release, Matrix tablets, Didanosine and HPMC K_{15}

INTRODUCTION

Sustained-release oral delivery systems achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, which provides better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects. Among the different approaches, matrix systems still appear as one of the most attractive from the economic as well as the process development and scale-up points of view**.** Didanosine acts by inhibiting reverse-transcriptase, an enzyme required for replication of the human immunodeficiency virus (HIV), and by blocking viral DNA synthesis, thus causing termination of the DNA molecular chain. Didanosine treatment was found to be a useful and effective alternative in patients who did not tolerate or not respond to Zidovudine, the mainstay of anti-HIV-1 drugs. Didanosine has lower and more highly variable bioavailability in comparison with other nucleoside reverse transcriptase inhibitors. In the gastric medium it is rapidly degraded due to acid hydrolysis. Such a problem, together with need for repetitive dosing, low plasma proteins binding (5%), brief plasma elimination half-life (30 min–4h), dose-related toxicity, in addition to a relatively low daily dosage (250–400 mg), make this drug a suitable candidate for incorporating into oral prolonged-release dosage forms[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 [2]. Didanosine (DDI) is a nucleoside analog reverse transcriptase inhibitor used in AIDS treatment to suppress HIV replication. DDI can be considered a suitable candidate for sustained-release formulations from both the biopharmaceutical and pharmacokinetic points of view [3].

MATERIALS AND METHODS

Materials: Didanosine was obtained as a gift sample from Aurobindo Pharmaceutical Pvt. Ltd, Hyderabad. HPMC K_{15} 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 Didanosine were prepared by direct compression technique using various concentrations of HPMC K_{15}. 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 7.96-mm punches.

Evaluation of Matrix Tablets [4, 5]

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.

In Vitro Drug Release Studies: Release rate of all the designed formulations were studied up to 12 hours using USP- type II (Paddle) dissolution apparatus at 50 rpm. The dissolution medium (900ml) consisted of phosphate buffer p^H 7.4 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 Didanosine using a double beam UV-Visible spectrophotometer at 249nm using pH 7.4 phosphate buffers. The release studies were conducted in triplicate.

Kinetic analysis of given data [6, 7, 8]

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:

$$\mathbf{W_0 - W_t = K_0 t}$$

Where $\mathbf{W_0}$ is the initial amount of drug in the pharmaceutical dosage form, $\mathbf{W_t}$ is the amount of drug in the pharmaceutical dosage form at time **t** and $\mathbf{K_0}$ is proportionality constant.

Dividing this equation by $\mathbf{W_0}$ and simplifying as:

$$\mathbf{f_t = K_0 t}$$

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

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

Where Q_t is the amount of drug released in time t, $\mathbf{Q_0}$ 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

$$\mathbf{Q_t/Q_\infty = K_k t^n}$$

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 Didanosine were formulated by using HPMC K_{15}, 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_{15}. Formulation F_1 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_2, F_3 and F_4 sustained release of drug for 12 hrs with 31.32%, 28.27% and 23.34% release of drug respectively after 1hr and more than 90% at the end of 12 hrs. It can be concluded that a stable formulation can be developed by incorporating in a definite proportion of HPMC K_{15}, 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: 0.985 to 0.991) when compared with those of the zero order kinetics (R^2: 0.311 to 0.897), 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 linearity (R^2: 0.918 to 0.990). To confirm the diffusion mechanism the data was fitted into Korsemeyer-Peppas equation. All the formulations showed good linearity (R^2: 0.947 to 0.995) with slope (n) values ranging from 0.389 to 0.691. The mechanism of drug release from formulation F_1 to F_3 showed behavior of Fickian diffusion and remaining all formulations showed non-Fickian diffusion.

CONCLUSION

It can be concluded that stable formulation can be developed by incorporating in a definite proportion of hydrophilic release retarding polymer like HPMC K_{15}, So that sustained released profile is maintained for an extended periods of time.

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Table 1: Preparation of matrix tablets of Didanosine

Formulation ingredients	Formulation batch				
	F_1	F_2	F_3	F_4	F_5
Didanosine(mg)	50	50	50	50	50
HPMC K_{15}(mg)	(10%) 30	(15%) 45	(20%) 60	(25%) 75	(30%) 90
MCC(mg)	214	199	184	169	154
Aerosil(mg)	3	3	3	3	3
Magnesium stearate(mg)	3	3	3	3	3
Total wt(mg)	300	300	300	300	300

Table 2: Physical Characterization of Prepared Matrix Tablets of Didanosine

Formulation batch	Avg. Wt. (mg)	Hardness (kg/cm^2)	Drug Content (%)	Friability (%)
F_1	295.25±6.257	5.12±0.337	97.292±2.282	0.587
F_2	298.79±6.63	5.24±0.288	97.654±2.246	0.571
F_3	307.79±6.63	5.09±0.265	97.932±2.064	0.582
F_4	307.55±6.634	5.13±0.188	99.051±2.102	0.566
F_5	305.768±5.491	5.22±0.219	98.83±2.21	0.549

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

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	0.389	0.440	0.477	0.576	0.691
	R^2	0.947	0.977	0.983	0.995	0.989
	K_1	40.45	34.35	30.61	23.01	16.03
Higuchi Model	R^2	0.918	0.972	0.984	0.990	0.970
	K_2	32.18	30.34	29.09	26.91	23.61
Zero- Order	R^2	0.311	0.535	0.608	0.819	0.897
	K_3	10.71	10.19	9.80	9.18	8.11
First- Order	R^2	0.989	0.991	0.985	0.985	0.990
	K_4	0.290	0.260	0.223	0.207	0.151

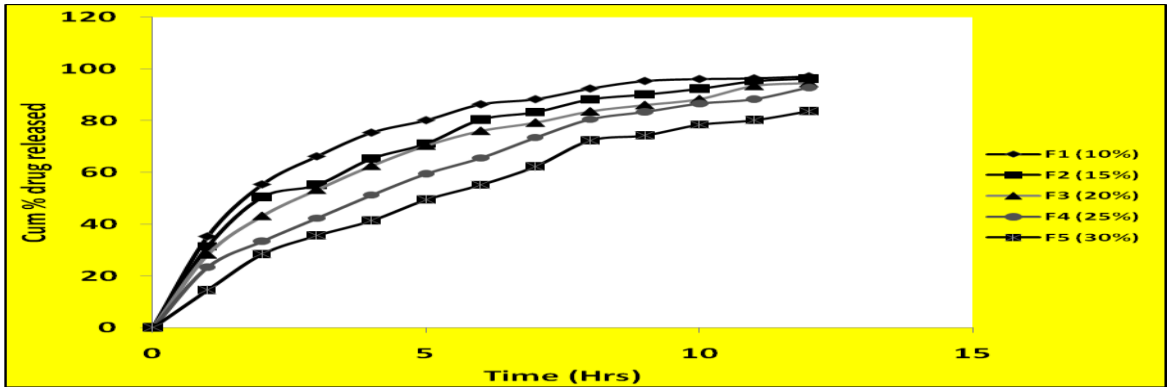

Fig.1: In-vitro drug release profile of sustained release matrix tablets of Didanosine using HPMC K_{15}

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