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ONCE DAILY TABLET FORMULATION AND *IN VITRO* EVALUATION OF DIDANOSINE USING ETHYL CELLULOSE

V. Rajasekhar Reddy*[1]

[1*]Department of Pharmaceutics, Seven Hills College of Pharmacy, Tirupati, Andhra Pradesh, 517561, India.

ABSTRACT

The objective of the study is to formulate and evaluate enteric coated sustained release tablets of didanosine. Tablets were formulated by wet granulation technique using different ratio of polymers such as ethyl cellulose std 100 FP, ethyl cellulose med 70 P, ethyl cellulose med 50 P. Different ratios of polymers were selected to achieve suitable lag time for the treatment of AIDS. Tablets were evaluated for physical characteristics, thickness, friability, weight variation, hardness, drug content uniformity and *in vitro* drug release for 24 hrs. Among all formulations, the formulation of enteric coated sustained release of didanosine (FESRTD-1) has been showed better sustained release of dosage forms.

KEYWORDS

Didanosine, Enteric coated sustained release tablets, Ethyl cellulose, Wet granulation and *In vitro* studies.

Author for Correspondence:

V. Rajasekhar Reddy,

Department of Pharmaceutics,

Seven Hills College of Pharmacy, Tirupati,

Andhra Pradesh, 517561, India.

Email: rajasekharreddy.vr@gmail.com

INTRODUCTION

This enteric coated tablets should not dissolve in stomach should be released in intestine. Release of drug in intestine is depend on site pH, which polymers are dissolved in only intestinal pH, that will be used in enteric coated tablet preparation[1-3]. So an attempt was made to formulate a dosage form of enteric coated sustained release tablets of didanosine.

Didanosine is antiretroviral agent. Mainly used for treatment of AIDS. Didanosine (2′,3′di deoxyinosine) is a purine nucleoside analog active against HIV-1, HIV-2, and other retroviruses

including HTLV-1. Didanosine is required for 60kg weight adult is 400mg, required for below 60 kg weight adult is 250mg and 100 mg once daily for child patients. This drug is incompatible with gastric juice (55% acidity)[4], So that enteric coating is need for the formulation.

MATERIAL AND METHOD

Material

Didanosine was obtained from Alkem Pharmaceuticals Ltd, India. Ethyl cellulose and Polyvinyl pyrrolidone K_{30} was a Gift sample from Apex Laboratories Pvt. Ltd, Chennai. Microcrystalline cellulose, Talc and Magnesium Stearate were purchased from Qualigens fine chemicals, Mumbai, India. All other chemicals and ingredients were used for study are of Analytical grade.

Method[5-7]

Preparation of Didanosine enteric coated sustained release tablets

Didanosine enteric coated sustained release tablets were prepared by wet granulation technique. Weigh the required quantity of pure drug and different ratios of polymers were mixed thoroughly and add all these formulations required quantity of micro crystalline cellulose and mix it. Then add sufficient volume of polyvinyl pyrrolidone K_{30} solution for making good mass. The mass is sieved by sieve no.180. The dried granules are passed through the sieve no.120 for getting uniform size of granules. Talc and magnesium stearate were finally added as a glidant and lubricant respectively. The blend was directly compressed using multiple punch tablet compression machine (Table No.1 and 2).

EVALUATION PARAMETERS[5-10]

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The Fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BOMEN MB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR spectroscopy.

Pre-compression studies of granules

Bulk density

3gm of granules were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated bulk density according to the formula

Formula

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the granules bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

Formula

Tapped density = Weight of granules/ Tapped volume of granules

Angle of Repose

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

Formula

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

Where,

θ = Angle of repose,

h = Height of the granules cone,

r = Radius of the granules cone.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density.

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where,

TD = Tapped density**,** BD = Bulk density.

Hausner's Ratio

It indicates the flow properties of the granules and ratio of Tapped density to the Bulk density of the granules.

Formula

Hausner's Ratio = Tapped density/Bulk density

Post compression studies of Didanosine enteric coated sustained release tablets

Hardness or Crushing strength Test

Hardness of the tablets was determined by breaking it between the second and third fingers with thumb being as a fulcrum. There was "sharp" snap, the tablet was deemed to have acceptable strength. Hardness of the tablets is also determined by Stokes Monsanto hardness tester.

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Venire caliper and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight

F - Final weight

Weight variation test

The USP weight variation test was run by selecting 20 tablets randomly from a particular batch. The tablets met the USP test that there were not more than 2 tablets were outside the percentage limit and no tablet differed by more than 2 times the percentage limit.

Average weight

Weigh accurately 20 tablets and calculate the average weight by using following formula.

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

Estimation of Drug Content

An accurately weighed amount of powdered Didanosine (100 mg) was extracted with water and solution was filtered through 0.45µ membrane filter paper. The absorbance was measured at 248 nm after suitable dilution.

Calculation

The amount of Didanosine present in tablet can be calculated using the formula

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

Where,

A_t = Absorbance of sample preparation

A_s = Absorbance of Standard preparation

S_w = weight at Didanosine working standard (mg).

***In vitro* drug release studies**

The dissolution was carried out using rotating basket method (USP dissolution testing apparatus I); freshly prepared 0.1N Hcl (pH 1.2) (900 ml) was placed in dissolution flask and allowed to obtain temperature at 37±0.5°C and 100 rpm for first 2 h. Then replaced with 6.8 pH phosphate buffer and continued for 24 h. Aliquot volume of 10 ml was withdrawn at regular intervals and replaced with fresh buffer diluted. The samples were replaced with fresh dissolution medium. After filtration, the sample is measured the absorbance at 248 nm by using UV Spectrometer. The dissolution data obtained were plotted as percentage drug release versus time.

RESULTS AND DISCUSSION

Pre formulation studies

Compatability studies (Fourier Transform Infrared Spectroscopic studies)

The fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the formulated tablets, pure drug and different polymers was recorded. The tablets were taken in a KBr pellet by using BOMEN MB SERIES FTIR instrument. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the different polymers and pure drug. Then all the functional groups are found in the IR spectrum of pure drug and different polymers.

Precompression studies

The precompression studies are evaluated in terms of their bulk density, tapped density, angle of repose,

compressibility index and hausner's ratio. All the batches showed good to satisfactory of free flowing properties and the values are within the pharmacopeia limit (Table No.3).

Postcompression studies

The enteric coated sustained release tablets of Didanosine is physically evaluated and show the acceptable results with hardness, thickness, weight variation, estimation of drug content uniformity and friability, for all batches no significant difference was observed (Table No.4).

***In vitro* drug release study**

The release of Didanosine from enteric coated sustained release tablet of various formulations varied according to the ratio and degree of the polymer. In case of all formulations containing 20% Eudragit L100. So that first 2 hrs there is no release observed. Among all the batches FESRTD-1 formulation showed the better *invitro* release of drug (Table No.5 and Figure No.1).

Table No.1: Different formulation of enteric coated sustained release tablets of Didanosine

S.No	Ingredients	FESRTD-1	FESRTD-2	FESRTD-3	FESRTD-4	FESRTD-5	FESRTD-6	FESRTD-7
1	Didanosine	250 mg	250 mg	250 mg	200 mg	250 mg	250 mg	250 mg
2	Ethyl cellulose Std 100P	90 mg	-	-	45 mg	-	45 mg	30 mg
3	Ethyl cellulose Med 70P	-	90 mg	-	45 mg	45 mg	-	30 mg
4	Ethyl cellulose Med 50P	-	-	90 mg	-	45 mg	45 mg	30 mg
5	Microcrystalline cellulose	95mg	95mg	95mg	95mg	95mg	95mg	95mg
6	PVP K_{30}	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
7	Talc	10mg	10mg	10mg	10mg	10mg	10mg	10mg
8	Magnesium stearate	5mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg

Total tablet weight – 450mg

FESRTD - Formulation of Enteric coated Sustained Release Tablets of Didanosine

Table No.2: Coating solution composition and Parameters

S.No	Coating solution composition	% Used	Parameters	
			Atomization Air	2 kg/cm²
1	Eudragit L100	40%	Pan RPM	5
2	Diethylpthalate	12%	Inlet temperature	65 ºC
3	Isopropyl alcohol	Q.s	Exhaust temperature	48-50 ºC

Table No.3: Precompression studies of granules

S.No	Formulations	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio
1	FESRTD-1	0.659	0.705	26.45	6.52	1.069
2	FESRTD-2	0.645	0.697	28.26	7.46	1.080
3	FESRTD-3	0.643	0.689	26.92	6.67	1.071
4	FESRTD-4	0.639	0.684	27.21	6.57	1.070
5	FESRTD-5	0.632	0.678	27.68	6.78	1.072
6	FESRTD-6	0.625	0.674	28.12	7.27	1.078
7	FESRTD-7	0.618	0.666	26.57	7.20	1.077

Table No.4: Postcompression studies of enteric coated sustained release tablets of Didanosine

S.No	Formulations	Hardness Test (kg/cm)	Thickness Test (cm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content
1	FESRTD-1	14.24	0.45	0.8	99.5	99.6
2	FESRTD-2	13.15	0.45	0.8	99.5	99.6
3	FESRTD-3	11.86	0.45	0.8	99.5	99.6
4	FESRTD-4	12.55	0.45	0.6	99.2	99.5
5	FESRTD-5	12.05	0.45	0.6	98.6	99.5
6	FESRTD-6	12.25	0.45	0.6	98.8	99.5
7	FESRTD-7	11.75	0.45	0.4	98.5	99.4

Table No.5: Comparative *invitro* dissolution study of enteric coated sustained release tablets of Didanosine

S.No	Time (hrs)	% of drug release (FESRTD-1)	% of drug release (FESRTD-2)	% of drug release (FESRTD-3)	% of drug release (FESRTD-4)	% of drug release (FESRTD-5)	% of drug release (FESRTD-6)	% of drug release (FESRTD-7)
1	0	00.00	00.00	00.00	00.00	00.00	00.00	00.00
2	1	00.00	00.00	00.00	00.00	00.00	00.00	00.00
3	2	08.23	06.64	05.92	7.52	06.15	06.42	06.14
4	3	18.12	16.82	15.27	17.25	16.52	16.70	15.27
5	6	32.54	28.64	24.18	30.12	26.48	31.08	26.34
6	9	45.32	42.85	37.32	43.26	40.25	42.02	39.21
7	12	58.96	54.18	49.12	56.73	52.27	53.25	51.15
8	15	69.15	65.98	60.42	67.45	63.02	64.68	62.54
9	18	78.96	72.45	70.24	74.42	71.13	72.02	72.46
10	21	89.14	83.64	79.92	85.41	80.42	81.73	80.95
11	24	99.64	95.16	90.72	97.23	92.28	93.12	91.14

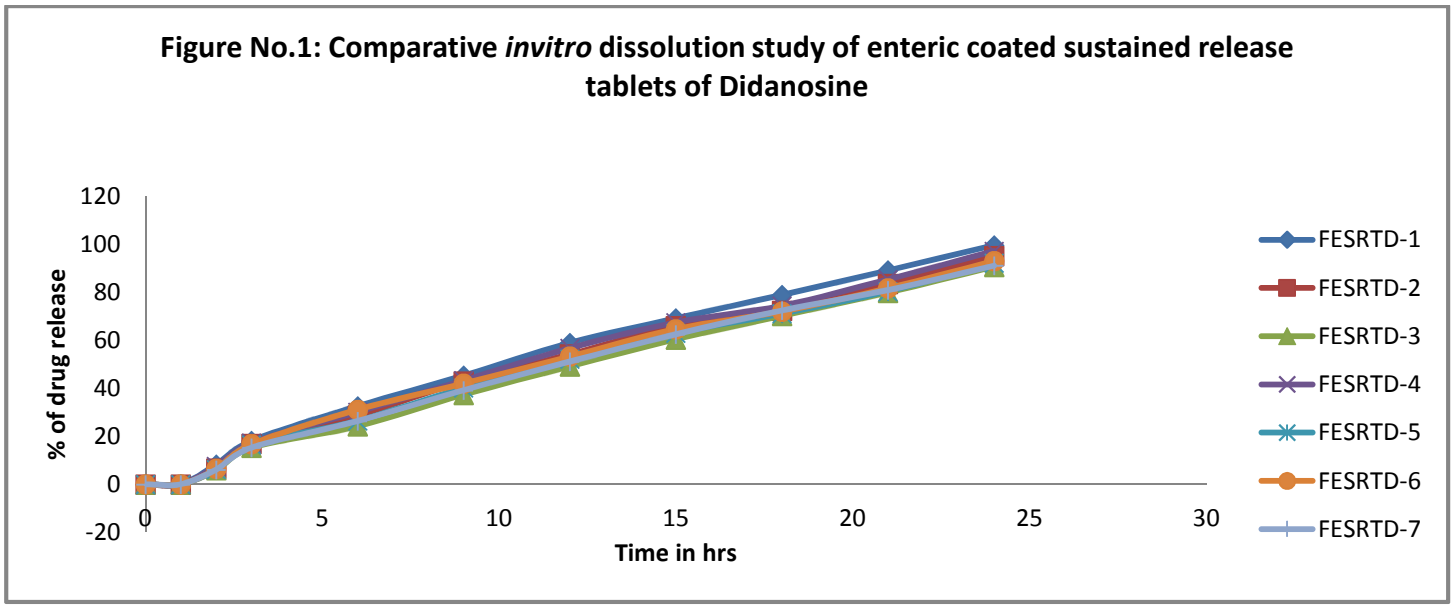

Figure No.1: Comparative *invitro* dissolution study of enteric coated sustained release tablets of Didanosine

CONCLUSION

The present study demonstrates that the Didanosine compression coated tablet could be successfully prepared and evaluated. Form the above results, the formulation FESRTD-1 has been showed better sustained release of dosage forms. So that, it can be used for treatment of AIDS.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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