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Original Article

Formulation and Evaluation of Didanosine Enteric Coated Sustained Release Tablet

B Arunprasath [1, *], S A Sreenivas [2], K V Subrahmanyam [1], Ashwini [1], Harika [1]

[1] Department of Pharmaceutics, Samskruti College of Pharmacy, Ghatkesar (M), Telangana, India.

[2] Sree Dattha Institute of Pharmacy, Ibhrahimpatnam, Telangana, India

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ABSTRACT

A Sustained release formulations can be utilized to avoid repetitive dosing of drugs in a day and few drugs like Didanosine incompatible with gastric juice, to avoid overcome the incompatibility of drug, tablet is coated with the enteric coat. The objective of the present study is to develop competitive enteric sustained release tablets of Didanosine for a period of 12 hrs, by preparing wet granulation method using different polymers and study the effect of polymers on their release pattern. The drug – excipients compatibility was done at accelerated temperature 25°C/55% ± 5% and 30°C/60% ± 5% relative humidity. Based on preformualation studies different formulation batches of Didanosine were prepared using selected excipient. Granules were evaluated for tests loss on drying, bulk density, tapped density, compressibility index, Hausner ratio before ring punched as tablet. Tablets were tested for weight variation, thickness, hardness, friability and in vitro drug release as per official procedure. Change in dissolution parameter study made it suitable for minute physiological variables. From the above results and discussion it is concluded that formulation of sustained release tablet of Didanosine containing 20 % of Ethyl cellulose Std 100 P, diluents MCC and with binder Povidone i.e formulation batch F6 can be taken as an ideal or optimized formulation of Enteric coated sustained release tablets for 12 hour release as it fulfills all the requirements for sustained release tablet.

Keywords: Didanosine, compatibility, enteric, preformulation, Povidone

1. INTRODUCTION

Conventional dosage form a as to be administered several times to produce therapeutic efficacy, which yields fluctuations in plasma level. Repetitive dosing of drug causes poor compliance among the patients. Sustained release formulations can be utilized to avoid repetitive dosing of drugs in a day and few drugs like

Corresponding author *
B. Arunprasath
HOD, Samskruti College of Pharmacy
E mail: arunprasad3210@gmail.com

Didanosine incompatible with gastric juice, to avoid overcome the incompatibility of drug, tablet is coated with the enteric coat. And also drug concentrations can be controlled within the narrow therapeutic range by the use of sustained release systems, which will minimize the severity of side effects. [1, 2]

2. MATERIALS AND METHODS

Since the drug has biological half-life of 1.5 hr so administration of drug 6 times per day for acute and sub-acute conditions, its having 35-54% of bioavailability. So it is selected to prepare an enteric coated sustained release tablets. The objective of the present study is to develop competitive enteric sustained release tablets of Didanosine for a period of 12 hrs, by preparing wet granulation method using different polymers and study the effect of polymers on their release pattern.

2.1 Preformulation Studies

Identification of drug: The identification of drug was done by Differential scanning Colorimetry (DSC).

DSC Studies method:

DSC studies were performed for pure drug. Accurately weighed 5-6 mg samples were hermetically sealed in aluminium pans and heated at constant rate of 10°C/min over a temperature range of 40˚C to 300˚C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50ml/min. Indium/zinc standards were used to calibrate the temperature and enthalpy scale. No changes observed from compatilibility study, so selected excipients are suitable for formulations which are shown in table no.1. [3]

2.1.1 Physical properties

For a drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug.

2.1.2 Determination of bulk density and tapped density

Bulk density is the ratio of the weight of a powder to the volume it occupies. It is expressed as gm/ml. Volume occupied by powder includes volume of the solid portion of the particle and voids between the particles. Bulk density is important in determining the size of the containers needed for handling and processing. An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V1) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (V2) was measured and continued operation till the two consecutive readings were equal. Results were shown in table no: 2 &3

2.1.3 Flow Properties

A glass tunnel is held in place with a clamp on ring report over a glass plate, powder (weighed) and poured in tunnel keeping the orifice of tunnel blocked. When powder is emptied from funnel, angle of heap to horizontal plane is measured with protector. Highest of pile (h) and radius of the base (r) is measured with ruler. Thus the angle of repose is measured. [4]

2.1.4 Compressibility Index

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size of a powder. The compressibility of a material can be estimated from the tap and bulk density measurements. Results were shown in table no: 4.

2.2 Manufacturing Procedure of Enteric Coated Tablets

2.2.1 Wet Granulation Method

Weighing & Sifting: Accurately weigh requires quantity of Didanosine and sifted through #40 mesh.

Mixing: Ethyl cellulose, Microcrystalline cellulose, povidone were passed through #40 mesh and added to the above granular material and blended for 5 min

and prepare damp mass and finally pass through #24 mesh and allow the granules at 40˚C. [5, 6]

Lubrication: Magnesium stearate and aerosil were passed through 60#and added to the above blended material.

Compression: compress the blend into tablets with punch size of 20 x 7mm rod shaped

Coating: Tablets are taken in a coating pan and coating has done.

Preparation of coating solution: Take required quantity of isopropyl alcohol stir with propeller stirrer to form vortex. Add quantity of Eudragit in vortex stir for 25 mins. Maintain the solution without air bubbles then use the solution for coating. Quantity of tablets to be coated is 100 Tab.

Particle Size Determination: 39, 43 A series of sieves were arranged in order of their decreasing order of pore diameter. 100gm of blend were weighed accurately and transferred through sieve no. 20, 40, 60, 80,100 and 120 which are kept on top. The sieves were shaken for 10mins. Then the blend retained on each sieve was taken. Weighed separately and expressed in terms of percentage. Results are shown in table no 5.

Evaluation Of Didanosine Enteric Coated Sustained Release Tablets1, 43, 47

Size and Shape: The size and shape of tablets can be dimensionally described, monitored, and control. The compressed tablet's shape and dimensions are determined by the tooling during compression process.

Thickness: The thickness of a tablet was the only dimensional variable related to the process.10 tablets were measured for their thickness and diameter with vernier calipers. Average thickness and diameter were calculated.

Weight variation: The USP weight variation test was run by selecting 20 tablets randomly from a particular batch and weighed individually and average weight was determined and comparing the individual tablet weights to the average. The tablets met the USP test that there were no more than 2 tablets were outside the percentage limit and no tablet differed by more than 2 times the percentage limit. [7, 8]

Hardness: 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 and the hardness should found within the range of 12-15 kg/cm².

Friability: The friability of tablets is determined by Roche fribilator 20 tablets were taken and weighed. After weighing the tablets were placed in the Roche friabilator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for 4 minutes dropping the tablets from a distance of six inches with each revolution. After operation the tablets were dedusted and reweighed. [9]

2.2.2 Assay

20 tablets were accurately weighed and crushed in a motor; a quantity of powder equivalent to label claim was transferred into in to 500ml volumetric flask and then added 250ml of water and heated in the water bath for 30 minutes with occasional stirring and removed from water bath after half an hour and kept sonication for 10 minutes and made up to the volume with D.M water amd mixed well. From the above solution, 2ml was pippeted out into 20ml volumetric flask, made up the volume with water and mix well set the absorbance the absorbance at 248nm by using UV-Visible spectroscopy. [10]

Standard preparation: Weighed and transferred 50mg of Didnosine working standard in to 100ml volumetric flask and 50ml of water and shaken well and made up the volume to 100ml with water. Shaken well and mix properly. From the above solution transfer 2ml was

pipetted out into 50ml volumetric flask and made up the volume with water. (concentration: 20 mcg/ml)

2.3 Dissolution Test

Dissolution studies were performed using USP standard dissolution apparatus at 37 ± 0.5ºC. Using one tablet at a time in a vessel. The basket was immersed in 900ml of dissolution medium and rotated at 50 rpm. The dissolution Media used was initially 0.1N HCl up to 2hrs, then continuation with fasted buffer having pH 6.8. During the test 10ml of the sample was withdrawn at specific time intervals 1, 2, 4, 6, 8, 10, 12 hrs after each withdrawal, same volume of fresh dissolution medium was added to maintained sink conditions. Different aliquots were suitably diluted. The absorbance was measured in the UV spectrophotometer at λmax 248nm. [11, 12]

Standard Curve of Didanosine:

Preparation of 0.1N HCl: 8.5 ml of concentrated hydrochloric acid was diluted upto 1000 ml with distilled water.

Preparation of phosphate buffer pH 6.8 : Accurately weighted quantity of 6.8 g of potassium dihydrogen phosphate and 0.89 gms of sodium hydroxide pellets were dissolved in distilled water and diluted with distilled water upto 1000 ml.

Preparation of standard curve in 0.1 N HCl: One hundred mg equivalent weight of didanosine was dissolved in 100 ml of 0.1N HCl. The 10 ml of above solution was further diluted upto 100ml with 0.1 N HCl. The resulting solution was serially diluted with 0.1 N HCl to get drug concentration 5, 10, 20, 40, 50 and 60, µg/ml. The absorbance of the solutions were measured against 0.1 N HCl (distilled water) as a blank at 248 nm using double beam UV visible spectrophotometer. Results were shown in table no:6 and graph no.1

Preparation of standard curve in 6.8 pH buffer

One hundred mg equivalent weight of didanosine was dissolved in 100 ml of phosphate buffer pH 6.8. The 10 ml of above solution was further diluted upto 10ml with phosphate buffer pH 6.8. The resulting solution was serially diluted with phosphate buffer pH 6.8 to get drug concentration 5, 10, 20, 30, 40, 50 and 60 µg/ml. The absorbance of the solutions were measured against phosphate buffer pH 6.8 (distilled water) as a blank at 248nm using double beam UV visible spectrophotometer. Results were shown in table no:7 and graph no.2

Stability Studies: Ten tablets were individually wrapped using aluminum foil and packed in amber coloured screw cap bottle and put at above specified condition in incubator for 2 months. After two months, tablets were evaluated for content uniformity and invitro drug release.

3. RESULTS AND DISCUSSION

The drug – excipients compatibility was done at accelerated temperature 25°C/55% ± 5% and 30°C/60% ± 5% relative humidity. Opened and closed vial methods were used. The result doesn't show any physical change to the mixture after 30 days. This fact concluded that the drug and excipients are compatible with each other. Results were shown in table no:1

The Enteric coated sustained release tablet of Dedanosine were prepared by wet granulation method, They were evaluated for weight variation, drug content, friability, hardness, and thickness for all batches (F1 to F9).

No significant difference was observed in the weight of individual tablets from the average weight. Tablet weights of all bathes were found within recommended pharmacopoeia limits. The data of uniformity of content indicated that tablets of all batches had drug content within pharmacopoeia limits. The hardness of tablets of all batches are in acceptable limits, which is shown in the literature. All the

formulation showed percentage friability less than 1% that indicates ability of tablets of withstands shocks, which may encounter. No significant difference was observed in the thickness of individual tablet from the average weight.

Table 1: Drug and Excipients compatibility Study

S.No	Drug+excipient	Initial colour	Storage Conditions 25 C/55% RH At the end of 60 days	Storage Conditions 30 C/60% RH At the end of 60 days
1.	D+Ethylcellulose	White to dull White powder	White to dull White powder	White to dull White powder
2.	D+MCC	White to dull White powder	White to dull White powder	White to dull White powder
3.	D+Povidone	White to dull White powder	White to dull White powder	White to dull White powder
4.	D+Aerosil	White to dull White powder	White to dull White powder	White to dull White powder
5.	D+Eudrajit	White to dull White powder	White to dull White powder	White to dull White powder
6.	D+Diethylpthalate	White to dull White powder	White to dull White powder	White to dull White powder
7.	D+Mg Stearate	White to dull White powder	White to dull White powder	White to dull White powder

Table 2: Physical properties of pure drug

S.No	Parameter	Observation
1.	Bulk Density (w/v1)	0.471 -- 0.478 g/cc
2.	Tapped Density (w/v2).	0.661 -- 0.668 g/cc
3.	Compressibility Index.	20.74 -- 21.52%
4.	Hausner Ratio.	0.903 -- 1.018
5.	Angle of Repose	29°.2'– 31°.5'

Standard calibration curve of Didanosine tablets were prepared in two media i.e 0.1N HCl and phosphate buffer 6.8 pH. Correlation coefficient values indicate the linear correlation between concentration and absorbance and following lamberts beers law.

The release of Didanosine from enteric coated sustained release tablet of various formulations varied according to the ratio and degree of the polymer.

Table 3: Physical Characterization of all formulation Blends

B.No	Bulk density	Tapped density	Loss on Drying in %	Compressibility Index %	Hausner Ratio	Angle of Repose
F1	0.49	0.57	1.1 0.010	12.8	1.19	28 .3"
F2	0.44	0.56	1.0 0.09	13.6	1.13	26 .1"
F3	0.47	0.53	1.2 0.015	12.2	1.16	26 .8"
F4	0.50	0.59	1.4 0.016	13.1	1.15	26 .2"
F5	0.51	0.59	1.4 0.013	14.9	1.12	27 .4"
F6	0.49	0.61	1.7 0.016	15.1	1.19	28 .6"
F7	0.48	0.55	0.9 0.021	12.5	1.17	23 .9"
F8	0.46	0.62	2.1 0.014	13.9	1.15	25 .9"
F9	0.50	0.58	1.6 0.016	14.2	1.20	27 .5"

Table 4: Compressibility Index Std Range

S. No.	% Compressibility index	Flow Property
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair-passable
4	23-35	Poor
5	33-38	Very poor
6	<40	Very very Poor

Table 5: Particle Size Distribution

Formulation batch No.	Percent blend retain 20#	40#	60#	80#	100#	120#	Pan
F1	20	27	20	13	13	5	2
F2	22	24	22	9	17	5	2
F3	27	21	20	11	15	5	2
F4	25	20	19	14	15	6	1
F5	17	30	21	18	11	6	1
F6	25	23	16	14	15	6	1
F7	20	23	25	11	15	5	2
F8	30	26	24	10	8	2	0
F9	22	28	23	12	10	4	1

Table 6: Standard curve of Didanosine in 0.1N HCl at 248nm

Sample No.	Concentration (µg/ml)	Absorbance
1	0	0
2.	5	0.256
3.	10	0.501
4.	20	1.045
5.	30	1.523
6.	40	2.089
7.	50	2.562
8	60	3.014

Table 7: Standard Curve of Didanosine in 6.8 pH Buffer at 248nm

Sample No.	Concentration (µg/ml)	Absorbance *
1	0	0
2.	5	0.259
3.	10	0.511
4.	20	1.015
5.	30	1.538
6.	40	2.052
7.	50	2.562
8.	60	3.191

Table 8: Comparative Dissolution study of Formulations F1 to F9

Time in Hours	% Cumulative Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0
4	27.55	29.65	31.12	25.61	25.85	24.17	28.92	31.29	30.48
6	65.65	72.26	63.56	61.2	59.13	57.65	63.98	67.44	62.98
8	91.28	96.23	74.54	81.54	87.65	75.28	72.41	78.86	85.95
10	-	-	95.85	96.91	92.23	86.89	95.62	97.91	92.69
12	-	-	-	-	-	99.28	-	-	-

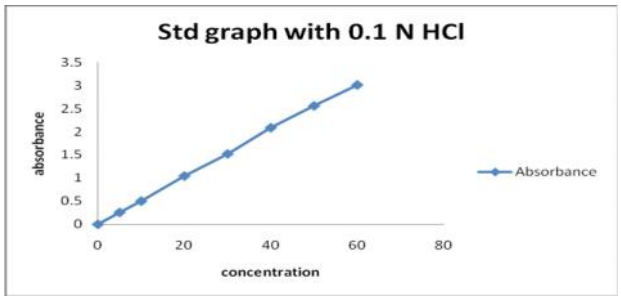

Fig 1: Std graph with 0.1N HCl

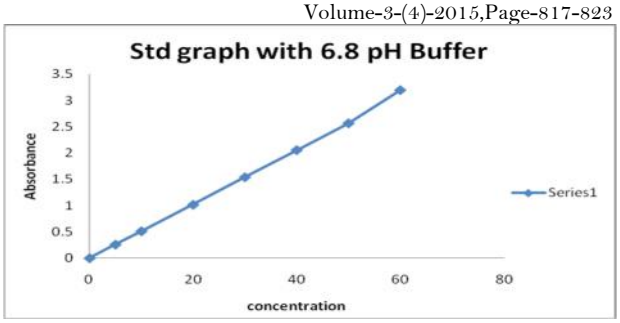

Fig 2: Std graph with 6.8 Phosphate Buffer

In case of tablet of F1 containing Drug and 10% Ethyl cellulose Med 70p, with povidone and MCC shows the 91% of drug release with in 8hrs, In case of Formulation F2 containing Drug and 15%Ethyl cellulose Med 70 P with povidone, MCC shows maximum release in 8hrs only.

In case of tablet of F3 containing Drug and 20% Ethyl cellulose Med 70p, with povidone and MCC shows the 95% of drug release with in 10hrs, In case of Formulation F4 containing Drug and 10%Ethyl cellulose Std 100 P with povidone, MCC shows maximum release in 10hrs only, In case of tablet of F5 containing Drug and 15% Ethyl cellulose Std 100 P, with povidone and MCC shows the 96% of drug release with in 10hrs, In case of Formulation F6 containing Drug & Ethyl cellulose Std 100FP 20%, povidone, MCC, shows accurate results that is drug release up to 12hrs. In case of Formulation F7 containing Drug and 10%Ethyl cellulose Med 50 P with povidone, MCC shows maximum release in 10hrs only, In case of Formulation F8 containing Drug and 15%Ethyl cellulose Med 50 P with povidone, MCC shows maximum release in 10hrs only, In case of Formulation F9 containing Drug and 12%Ethyl cellulose Med 50 P with povidone, MCC shows maximum release in 10hrs only, from the above data In case of tablet of F6 containing Drug & Ethyl cellulose Std 100FP 20%, povidone, MCC, shows accurate results that is drug release up to 12hrs. No significant change was observed in Formulation- 6

from the stability study of all physical test, assay and dissolution test. Results were shown in table no:8

4. CONCLUSION

The project was undertaken with an aim to formulate and evaluate Didanosine Enteric coated sustained release tablet using different polymers as release retarding agent and overcome the gastric juice incompatability, Preformualtion study was done initially and results were directed for the further course of formulation . Based on preformualation studies different formulation batches of Didanosine was prepared using selected excipient. Granules were evaluated for tests loss on drying, bulk density, tapped density, compressibility index, Hausner ratio before ring punched as tablet . Tablets were tested for weight variation, thickness, hardness, friability and in vitro drug release as per official procedure. Change in dissolution parameter study made it suitable for minute physiological variables.

From the above results and discussion it is concluded that formulation of sustained release tablet of Didanosine containing 20 % of Ethyl cellulose Std 100 P, diluents MCC and with binder Povidone i.e formulation batch F6 can be taken as an ideal or optimized formulation of Enteric coated sustained release tablets for 12 hour release as it fulfills all the requirements for sustained release tablet.

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