Formulation and Evaluation of Didanosine Enteric Coated Sustained Release Tablet

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Abstract:
Enteric coated tablets of Didanosine were developed to get resistance from Gastric juice when it presents in stomach, because Didanosine is incompatible with gastric juice. The tablets are prepared by using wet granulation technique using polymer Ethyl Cellulose std 100 FP, Ethyl Cellulose Med 70 P, Ethyl Cellulose Med 50 P and other excipients are Povidone Micro crystalline Cellulose in different ratios. These polymers and excipients are used for sustained the drug release. And 20% solution of Eudragit L 100 with Iso propyl alcohol used for enteric coat. And Di Ethyl Phthalate added as polishing agent in enteric coat solution.
Tablets were evaluated for physical characteristics, weight variation, hardness, drug content, and further tablets were evaluated for invitro drug release for 12 hrs i.e. first 2 hrs no drug release was observed and gradually drug release was increased up to 12 hrs by using Ethyl Cellulose std 100 P 20% with other excipients.
Key words: *Didanosine, Enteric coated, Eudragit, Ethyl Cellulose*

Introduction:

Convenience of administration and patient compliance are the aim of the formulation of sustained release dosage form preparations. 400 mg of Didanosine is required for 60kg weight adult, 250 mg of Didanosine is required for below 60 kg weight adult and 100 mg once daily for child patients**.** Didanosine is antiretroviral agent. Mainly used for treatment of AIDS. Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxyadenosine in which the 3'-hydroxyl group is replaced by hydrogen. Intracellular, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5'-triphosphate. Dideoxyadenosine 5'-triphosphate inhibits the activity of HIV-1 reverse transcriptase. This drug is incompatible with gastric juice enteric coating is need for the formulation.

To prepare a sustained release dosage form Ethyl Cellulose with binder and diluents are used. And also lipophillic polymer used for enteric coat. 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 intestine pH, that will be used in enteric coated tablet preparation. After administration of enteric coated tablet, it must be no release in stomach, drug release only intestine,

Materials used:

Didanosine, Ethyl Cellulose STD 100p, Eudragit L 100, Ethyl Cellulose STD 70p, Ethyl Cellulose STD 50p, were used along with diluents, binding agents and polishing agent are microcrystalline cellulose, Povidone and diethyl phthalate. These all polymers are used in different ratios for different formulations. Isopropyl alcohol is used as solvent.

Formulation composition details:

Formulation F1 containing ethyl cellulose Med 70 P for 10% with different excipients ratios, Formulation F2 containing ethyl cellulose Med 70 P for 15%, Formulation F3 containing ethyl cellulose Med 70 P for 20%, Formulation F4 containing ethyl cellulose Std 100 FP for 10%, Formulation F5 containing ethyl cellulose Std 100 FP for 15%, Formulation F6 containing ethyl cellulose Std 100 FP for 20%, Formulation F7 containing ethyl cellulose Med 50 P for 10%, Formulation F8 containing ethyl cellulose Med 50 P for 15% and Formulation F9 containing ethyl cellulose Med 50 P for 20% in all these formulations having diluents micro crystalline e cellulose and binder Povidone are used in different ratios. Eudragit L100 used as coating polymer. And diethyl phthalate used as polishing agent. Isopropyl alcohol is used as solvent. 20% Eudragit L100 solution used for coating.

Table 1: Formulation of enteric coated sustained release tablets using different polymer ratios

S.No	Ingredients	Quantity per Tab (mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Didanosine	100	100	100	100	100	100	100	100	100
2.	Ethocel Std 100FP	-	-	-	16	24	32	-	-	-
3.	Ethocel Med 70P	16	24	32	-	-	-	-	-	-
4.	Ethocel Med 50P	-	-	-	-	-	-	16	24	32
5.	MCC	26	18	10	26	18	10	26	18	10
6.	Povidone	10	10	10	10	10	10	10	10	10
7.	Aerosil	6	6	6	6	6	6	6	6	6
8.	Mg Stearate	2	2	2	2	2	2	2	2	2

Table 2: Coating solution composition

Ingredients	%Used
Eudragit L100	20%
Diethylpthalate	6%
Isopropyl alcohol	q.s.

Method of preparation:

Accurately weigh required quantity of Didanosine and excipients sifted pass to make as uniform powder through #40 meshes**.** 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 to prepare granules and allow the granules at 40˚C. For lubrication purpose Magnesium Stearate and Aerosil were passed through 60#and added to the above blended material. Compress the blend into tablets with punch size of 20 x 7mm shaped. 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. Then Tablets are taken in a coating pan and coating has done.

Table 3: Coating parameters

Atomization Air	2 kg/cm²
Pan RPM	5
Inlet temperature	65 ºC
Exhaust temperature	48-50 ºC

In process evaluation study:

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.

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_1) 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 (V_2) was measured and continued operation till the two consecutive readings were equal.

Table 4: Reports of in process evaluation

B.No	Bulk density	Tapped density	Compressibility Index %	Hausner Ratio	Angle of Repose
F1	0.49	0.57	12.8	1.19	28°.3”
F2	0.44	0.56	13.6	1.13	26°.1”
F3	0.47	0.53	12.2	1.16	26°.8”
F4	0.50	0.59	13.1	1.15	26°.2”
F5	0.51	0.59	14.9	1.12	27°.4”
F6	0.49	0.61	15.1	1.19	28°.6”
F7	0.48	0.55	12.5	1.17	23°.9”
F8	0.46	0.62	13.9	1.15	25°.9”
F9	0.50	0.58	14.2	1.20	27°.5”

The bulk density, and tapped density were calculated using the following formulas:

Bulk density $= W / V_1$

Tapped density $= W / V_2$

Where, W = weight of the powder

V_1 = before tapped volume

V_2 = after tapped volume

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.

$$\tan \Theta = \frac{h}{r}$$

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

Compressibility index = T.D-B.D/T.D*100

Hauser ratio: It indicates the flow property of the powder and

Measured by the ratio of tapped density to bulk density

Evaluation of didanosine enteric coated sustained release tablets:

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 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.

Average weight:

Weigh accurately 20 tablets and calculate the average weight.

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

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.

Friability:

The friability of tablets is determined by Roche friabilator 10 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.

Table 5: Evaluation Reports

S.No	Formulation Batches	Weight variation (%) ±5	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Assay (%)
1	Formulation-1	162.25	7.6	4.16	0.15	93.3
2	Formulation-2	160.65	7.5	4.19	0.28	96.8
3	Formulation-3	164.19	7.7	4.21	0.32	97.6
4	Formulation-4	161.27	7.4	4.19	0.40	98.5
5	Formulation-5	159.92	7.5	4.12	0.41	98.6
6	Formulation-6	161.85	7.4	4.13	0.39	99.5
7	Formulation-7	162.42	7.5	4.14	0.36	98.6
8	Formulation-8	160.95	7.5	4.20	0.41	99.8
9	Formulation-9	165.15	7.7	4.13	0.45	100.1

Table 4: 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**	-	-	-

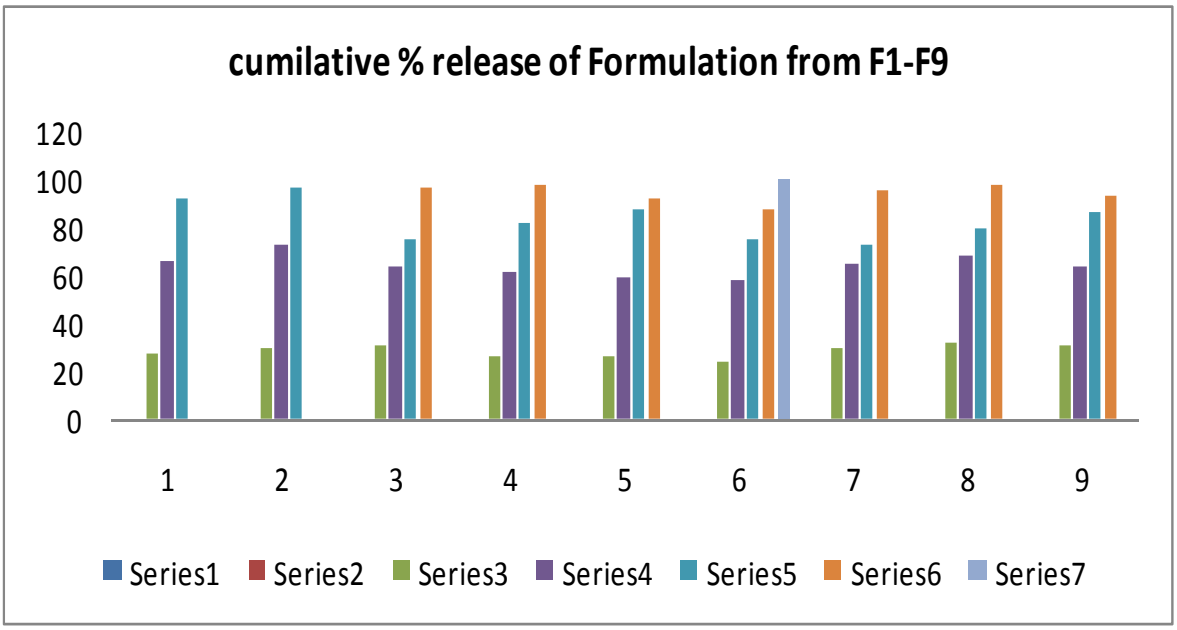

Fig 1: Cumulative % drug release of all formulations from F1-F9

Friability is determined by

$$F=100\ (1-W_0/W_t)$$

Where,

W_0 = Weight of tablets before friability test.

W_t = Weight of tablets after friability test.

Assay:

20 tablets were accurately weighed and crushed in a motor, quantity of powder equivalent to 100mg 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 and mixed well and drug content was analyzed by UV-spectrophotometrically at 248nm

Dissolution Studies

Dissolution studies were performed using USP standard dissolution apparatus at 37 ± 0.5ºC. 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. And finally obtained eliquotes are checked by UV spectrophotometer at 248nm.

Where,

Numbers 1 to 9 indicates Formulation F1 to F9 batches and

Series1: 0hrs, Series2: 2hrs, Series3: 4hrs, Series4: 6hrs, Series5: 8hrs, Series6: 10hrs, Series7: 12hrs

Results and discussion:

The Enteric coated sustained release tablet of Didanosine is physically evaluated and show the acceptable results with 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

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 first 2 hrs there is no release observed. 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 FP with Povidone, MCC shows maximum release in 10hrs only, In case of tablet of F5 containing Drug and 15% Ethyl cellulose Std 100 FP, 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.

Conclusion: By the use of Eudragit L100 polymer prevents the release of drug for first 2hrs. And then drug was released in pH6.8 buffer for up to 12hrs by the use of Ethyl cellulose STD 100FP and other excipients s like microcrystalline cellulose, Povidone and diethyl phthalate

Refference:

[1] Rubinstein, M. H. Tablets. In Pharmaceutics: The Science of dosage form Design. Aulton, M. E. Ed.; Churchill Livingstone: New York, 2000, pp. 305.

[2] Chien, Y. W. Rate control drug delivery systems: controlled release vs. Sustained release. Med. Prog. Techn. 1989, 15, pp. 21-46.

[3] Chein, Y. W. Novel Drug Delivery System Vol. 14, Marcel Dekker Inc. New York, 1992, pp. 139-196.

[4] Grass, G. M.; Robinson, J. R. Sustained and Controlled release drug Delivery systems. In Modern Pharmaceutics. Vol. 40; 2nd ed., Banker, G. S.; Rhodes, C. T.; Eds.; Marcel Dekker Inc: New York. 1990, pp. 635-638.

[5] Robinson, R.; Lee, V. H. Influence of Drug Properties and route of Drug Administration on the design of sustained and controlled release drug delivery system. In Controlled Drug Delivery Fundamentals and Applications. Vol. 29; 3rd ed., Robinson, R.; Lee, V. H.; Eds.; Marcel Dekker Inc: New York, 1995, pp. 3-35.

[6] Lee, V. H. L.; Yang, J. J. Oral Drug Delivery. In Drug Delivery and argeting. Hillery, A. M.; Llyod, A.W.; Swarbrick, J.; Eds. Taylor and Francis: London and New York, 2001, pp.165-168.

[7] Lordi, N. G. Sustained release dosage forms. In The Theory and Practice of Industrial Pharmacy. 3rd ed., Lachman, L.; Lieberman, H. A.; Kanig J. L. Eds.; Lea and Febiger: Philadelphia, 1991, pp. 430-435.

[8] Lachman and Liebermann, Joseph B.Schwartz, Pharmaceutical Dosage Forms Tablets Vol-I. , 2nd edition 2005, Page No: 13-14, 136.

[9] United States Pharmacopoeia Edition. 23rd pp. 943.

[10] Aulton, M. E. Pharmaceutics The Science of Dosage Form Design. Churchill Livingstone. 2002, 2nd, pp. 113 -118.

[11] Leon Lachman, Herbert A. Lieberman, Joseph L.Kanig. Theory and Practice of Industrial pharmacy 3rd edition pp. 293 – 313, 354 - 356.