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FORMULATION AND EVALUATION OF STAVUDINE ORAL DISINTEGRATION TABLETS

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ABSTRACT

Stavudine an anti-retroviral drug is used for treating HIV now-a-days. The present approach aims to formulate an orally disintegrating tablet of stavudine for better patient compliance and bypassing the hepatic metabolism. In order to have an orally disintegrating tablet of stavudine, there is a need to mask the bitter taste. For the masking of bitter taste mannitol is used as taste masking agent. In the formulation of ODTs, a semi-synthetic super disintegrant sodium starch glycolate and a natural disintegrant, sodium alginate was used. Formulations F_1, F_2, F_3, S_1, S_2 and S_3 were evaluated for the required quality control tests.F_3 and S_3 were found to have a disintegration time of 7secs and 6secs, respectively. Upon observing the dissolution profiles and disintegration time of formulations, F_3 and S_3 showed good results.

INTRODUCTION: Stavudine (d4T), a synthetic thymidine nucleoside analogue, active against the human immunodeficiency virus type 1 (HIV-1). The chemical name for stavudine is 2', 3'-didehydro-3'-deoxythymidine.It comes under the category of nucleoside analogue reverse transcriptase inhibitor (anti-viral drug).Conventionally it is used for treatment of HIV infection in combination with other anti-retro viral drugs. Presently drug is formulated in the form of oral disintegrating tablets.

Pharmaceutical technologies have developed a novel dosage form known as orally disintegrating tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take it with water. ODTs are distinguished from conventional sublingual tablets, buccal tablets and lozenges, which require more than a minute to dissolve in oral cavity. This tablet dissolves within 60seconds when placed in the mouth.

The active ingredients are absorbed through mucous membranes in the mouth and GIT and enter the blood stream. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms. In general, the tablets are physically robust and can be packed in multi dosage containers.

The technology incorporated in the formulation of stavudine ODTs is wet granulation technique. In this technique the tablets were prepared by using natural disintegrant sodium alginate and a semi synthetic disintegrant sodium starch glycolate. The taste masking agent used in the formulation was mannitol. Stavudine ODTs are formulated to minimize the bitter taste and bypass the first pass hepatic metabolism. The taste masking effect of mannitol was done by granulation technique which was evaluated with the drug substance.

The main objective is to check the quality control parameters of the formulated granules and tablets.

MATERIALS AND METHODS: The active pharmaceutical ingredient stavudine was obtained from CIPLA Pharmaceuticals Limited, Bangalore. The excipients camphor, talc, sodium alginate and sodium starch glycolate are obtained from Loba Chemi, starch from N.R. Chemic and mannitol from Rankem.

PREPARATION OF GRANULES: Stavudine (30mg) was dry blended with appropriate quantity of excipients and wet massing of powder blend was done using 10% starch solution. The wet mass was subjected to coarse screening using a suitable sieve (no. 22) and semi dried at 50°C – 55°C for 15 min. Dried granules were again passed through sieve no.44.

FORMULATION OF TABLETS: Tablets were prepared using a natural disintegrant sodium alginate and a semi synthetic disintegrant sodium starch glycolate. The granules were prepared by using wet granulation technique. The obtained granule mixture was blended with appropriate quantity of talc and other excipients, compressed using semi-automatic tablet punching machine.

TABLE 1: OFFICIAL FORMULA FOR PREPARATION OF DIFFERENT STRENGTHS OF STAVUDINE TABLETS

Ingredients	Official formula for one tablet					
	F_1	F_2	F_3	S_1	S_2	S_3
Stavudine	30mg	30mg	30mg	30mg	30mg	30mg
Starch (10%)	q.s	q.s	q.s	q.s	q.s	q.s
Mannitol	60mg	60mg	60mg	60mg	60mg	60mg
Camphor	30mg	30mg	30mg	30mg	30mg	30mg
Talc	4mg	4mg	4mg	4mg	4mg	4mg
Lactose	85mg	75mg	65mg	85mg	75mg	45mg
Sodium Alginate	10mg	20mg	30mg	-	-	-
Sodium Starch Glycolate	-	-	-	10mg	20mg	50mg

RESULTS:

GRANULE PARAMETERS:

TABLE 2: PHYSICAL PARAMETERS OF STAVUDINE GRANULES

PARAMETERS	F_1	F_2	F_3	S_1	S_2	S_3
Angle of repose	20°25′	21°14′	21°25′	20°45′	21°44′	22°34′
Bulk density (g/cc)	0.38	0.40	0.42	0.3957	0.4057	0.4275
Tapped density (g/cc)	0.40	0.45	0.48	0.4534	0.4799	0.4939
Compressibility index	12.32%	13.37%	14.37%	10.05%	12.51%	13.15%
Hausner's ratio (g/cc)	1.082	1.124	1.208	1.0120	1.1220	1.2120

TABLET PARAMETERS:

TABLE 3: PHYSICAL PARAMETERS OF STAVUDINE TABLETS

PARAMETERS	F_1	F_2	F_3	S_1	S_2	S_3
Weight variation	Not more than two tablets deviated from average weight (±5%)	Not more than two tablets deviated from average weight (±5%)	Not more than two tablets deviated from average weight (±5%)	Not more than two tablets deviated from average weight (±5%)	Not more than two tablets deviated from average weight (±5%)	Not more than two tablets deviated from average weight (±5%)
Friability	0.48%	0.55%	0.58%	2.0%	2.5%	2.8%
Hardness (kg/cm^2)	2.20	2.50	2.80	2.72	2.75	2.76
Disintegration (secs)	6.5	6.8	7	5.2	5.5	6
Wetting time (secs)	40	43	45	30	33	35
Water absorption ratio	14.90%	14.95%	14.98%	8%	9%	9%

Calibration curve of Stavudine: In standard graph, linearity was obtained between 5-40µg/ml concentration of stavudine and the regression value was found to be R^2=1.

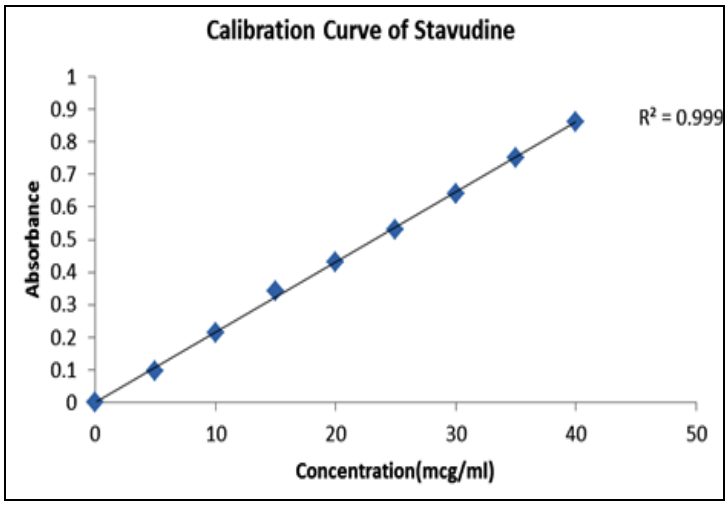

FIG. 1: CALIBRATION CURVE OF STAVUDINE

DISSOLUTION STUDIES:

TABLE 4: DISSOLUTION DATA FOR STAVUDINE TABLETS WITH SODIUM ALGINATE AS DISINTEGRANT

Time (min)	CUMULATIVE % DRUG RELEASE		
	F_1	F_2	F_3
0	0.00	0.00	0.00
5	70.16	81.83	89.91
10	89.96	92.10	98.99
15	90.10	93.11	98.81
30	95.11	96.41	97.98
45	95.11	96.41	97.81

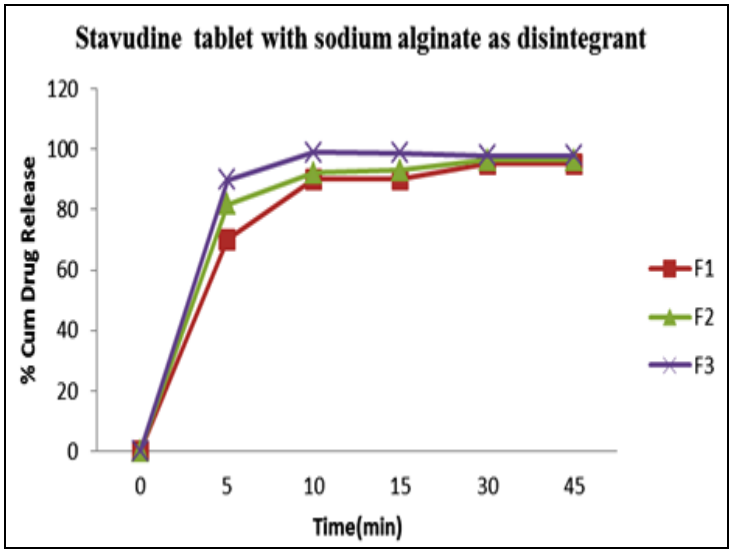

FIG. 2: DISSOLUTION PROFILES FOR STAVUDINE WITH SODIUM ALGINATE AS DISINTEGRANT

TABLE 5: DISSOLUTION DATA FOR STAVUDINE TABLETS WITH SODIUM STARCH GLYCOLATE AS DISINTEGRANT

Time (min)	CUMULATIVE % DRUG RELEASE		
	S_1	S_2	S_3
0	0.00	0.00	0.00
5	72.12	83.38	92.34
10	90.41	96.69	99.67
15	90.52	96.89	99.70
45	92.45	95.58	98.67

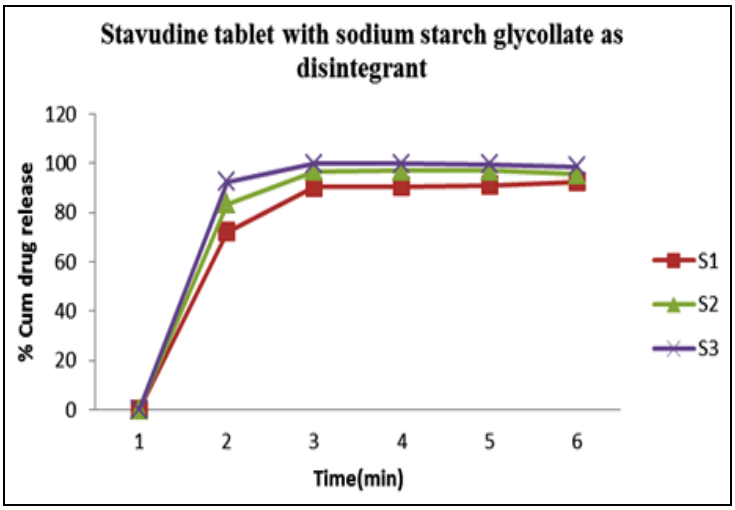

FIG. 3: DISSOLUTION PROFILES FOR STAVUDINE WITH SODIUM STARCH GLYCOLATE AS DISINTEGRANT

DISCUSSION: Formulation and Physical evaluation of granules and tablets of stavudine was done. Evaluation of physical parameters was done. The parameters of the granules were within the standard limits. All the tablets had a friability of less than 1%. The content of stavudine in each tablet brand was within the limits prescribed by the U.S.P. All the tablets with different disintegrants passed the weight variation test. As all the brands passed the weight variation test, it is concluded that all the tablets are uniform in drug content also. All the tablets passed the U.S.P disintegration test indicating that they will completely disintegrate in the buccal cavity within 60 seconds.

All the tablets passed the dissolution test as prescribed by U.S.P. Even though all the tablets passed the dissolution test as prescribed by U.S.P., there was variation in stavudine wetting time and water absorption ratio due to the difference in the difference in the disintegrant. The formulated stavudine tablet was masked by mannitol to prevent the bitter taste. The quality control parameters of the formulated granules and tablets were evaluated. The effect of disintegrants such as sodium alginate and sodium glycolate in the formulation was studied.

CONCLUSION: Stavudine oral disintegration tablets were formulated by compression technique to bypass the hepatic metabolism. The hepatic bypass effect and bioavailability have been studied. The inclusion of camphor and mannitol in the tablets will help to minimize the bitter taste. The semi-synthetic disintegrant, sodium starch glycolate containing stavudine tablets complies with the standard limits for the granule and tablet parameters when compared with the directly compressible and natural disintegrant sodium alginate containing tablets.

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