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FORMULATION AND EVALUATION OF STAVUDINE CONTROLLED RELEASE MATRIX TABLETS

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ABSTRACT
The aim of the present work is to Formulate and Evaluate controlled release of stavudine matrix tablets used for treatment of HIV infection. Development of CR stavudine is proposed considering the adverse event profile and high fluctuation index of stavudine observed with IR dosage forms. In the present work, attempts were made to formulate and evaluate controlled release of matrix tablets of stavudine. Stavudine was subjected to preformulation studies, based on the results obtained Stavudine controlled release tablets were successfully formulated. Formulations prepared by wet granulation using HPMC and carbopol 934 as control release polymers showed desired in vitro release. Set of trials were formulated for which stavudine evaluated parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) were found to lie within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in 0.1 HCL for 2 hours followed by pH 6.8 phosphate buffer. From the results of the in vitro study it appears that the release of the Stavudine was significantly influenced by the characteristics of the polymer used.

KEYWORDS: Stavudine, Natural and Synthetic Polymers, Direct Compression Technique, in Vitro Drug Release Studies.

1. INTRODUCTION
Oral route of administration have wide acceptance up to 50 to 60% of total drug form. Solid dosage forms are popular because of ease of administration, self medication, pain avoidance as compared with parenteral, and low cost.[1,2] One to three layer matrix tablets is a drug delivery device, which comprises a matrix core containing the active solute and one or more barriers incorporated during tableting process.[3] The barrier layers delay the interaction of an active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate Stavudine is used to treat patients with Antiretroviral HIV infection.[4,5] The drug stavudine inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator into viral DNA. The present research endeavour was directed towards the development of a controlled release dosage form of Stavudine in the form of tablets to be taken once daily. One of the most common approaches used for prolonging and controlling the rate of drug release is to incorporate a drug in hydrophilic colloid matrix such as hydroxyl propyl methyl cellulose and Carbopol. These tablets were prepared by using direct compression technique. After preparation of the tablets were evaluated for post compression parameters like hardness, thickness, friability, drug content, disintegration time and in vitro drug release studies.[6,7]

2. MATERIALS AND METHODS
Stavudine was collected as a gift sample from Hetero labs, Hyderabad and various excipients like hydroxyl propyl methylcellulose, carbopol 934 were purchased from AR chemicals, Hyderabed.

Methodology[8,9]
Drug excipient compatibility studies
Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 600 C and 400C/75% RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.

Formulations Table

Table. 1: Formulation of sustained release tablets of Stavudine.

S. No.	Ingredients	S1	S2	S3	S4	S5	S6
1	Stavudine	80	80	80	80	80	80
2	HPMC k $_{4M}$	25	50	75	100	175	150
3	Carbopol 934	-	15	30	45	60	75
4	Microcrystalline Cellulose	290	250	210	170	80	90
5	Magnesium stearate	3	3	3	3	3	3
6	Talc	2	2	2	2	2	2
	Total Wt	400	400	400	400	400	400

Preparation method

Drug and polymer was taken in mortar and was grind to fine powder than all other excipients were added except lubricant. This mixture was passed through 20 sieve size mesh for three times and then lubricant was added and again passed through the same sieve. The prepared powder was compressed to tablets using single punch tableting machine at an average hardness of 7 kg/cm^2.

Post compression parameters

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table No 1 and none deviate by more than twice the percentage shown.

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm. Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

% F = {1-(Wo/W)} ×100

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Stavudine. Dissolve the weighed quantity of powder into 100 ml of buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at nm using reagent blank.

***In- Vitro* Release study**

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 100 rpm. The dissolution medium consisted of 900 ml of Standard buffer 0.1 N HCL for 2 hr and followed by pH 6.8 period of time. Temperature maintained at 37±5. The sample of 1ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 1 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, and make the volume with buffer. The diluted samples were assayed at nm against reagent blank.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared Matrix tablets of Stavudine were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2^{o}c and refrigerator 2-8^{o}c for a period of 30 days.

3. RESULTS AND DISCUSSION

a) Determination of melting point

Melting point of Stavudine was found in the range of 206- 208^{0}c, which complied with the standard, indicating purity of the drug sample.

b) Solubility

Stavudine is found to soluble in ethanol, buffer pH 1.2 and 6.8 phosphate buffer very and slightly soluble in methanol and chloroform.

C) Compatibility Study

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of Stavudine were obtained at 3500 cm^{-1}, 1084 cm^{-1}, 3095cm^{-1}, 1745cm^{-1}. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

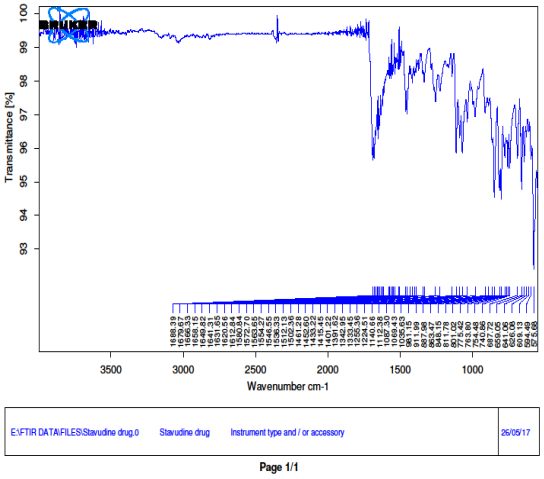

Fig. 1: FTIR Spectra of stavudine.

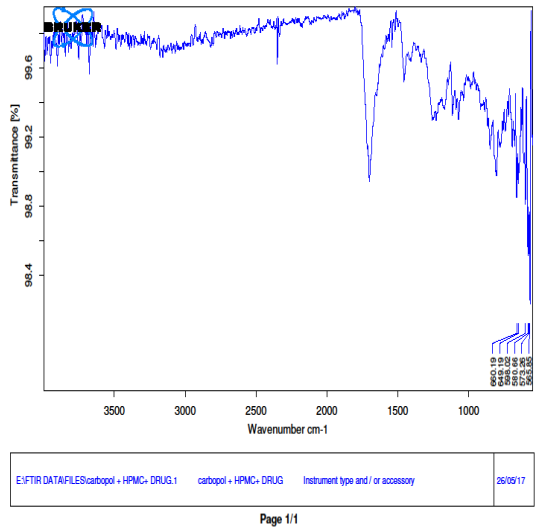

Fig. 2: FTIR Spectra of Pure drug + HPMC + Carbopol 934.

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

EVALUATION STUDIES

Pre compression Parameters

a) Bulk Density

The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.619-0.628.

b) Tapped density

The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.711-0.729.

c) Angle of repose

The angle of repose for the formulated blend was carried out and the results were shown in Table No 6. It concludes that all the formulations blend was found to be in the range of 290 to35^0.

d) Compressibility index

Compressibility index was carried out, it found between 10% to 14.28% indicating the powder blend have the required flow property for compression.

Table 2: Results of Pre compression parameters of tablets.

B. No	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(0)
S1	0.620	0.711	12.79	1.14	30^0
S2	0.627	0.715	12.30	1.14	31^0
S3	0.619	0.725	14.62	1.17	32^0
S4	0.628	0.723	13.13	1.15	35^0
S5	0.624	0.728	14.28	1.16	30^0
S6	0.626	0.729	14.12	1.16	31^0

Post compression parameters

Weight variation: All the formulated (S1 to S6) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness: The thickness determined for formulated tablets. Tablets mean thickness (n=3) were uniform in S1 to S6 formulations and were found to be in the range of 3.20 mm to 3.30 mm.

Hardness: The measured hardness of tablets of each batch ranged between 6.5 to 7 kg/cm^2. This ensures good handling characteristics of all batches.

Friability: The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity: The percentage of drug content for S1 to S6 was found to be between 95.10% and 98.80% of Stavudine it complies with official specifications.

Table. 3: Results of Evaluation parameters of tablets.

B. No.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drug content (%)
S1	400	3.21	6.50	0.42	95.10
S2	399	3.28	6.52	0.45	96.41
S3	400	3.20	6.81	0.43	96.51
S4	438	3.23	6.19	0.49	98.80
S5	400	3.29	6.56	0.45	95.56
S6	399	3.30	6.59	0.50	96.90

In-vitro Dissolution Study

Table. 4: *In vitro* release data of tablet F_1 to F_6.

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6
0	0	0	0	0	0	0
1	28.22	27.84	28.30	27.50	29.31	26.65
2	33.55	32.30	31.55	32.56	34.80	35.15
3	42.80	40.61	42.85	46.25	48.70	45.30
4	51.65	52.65	53.69	59.75	56.50	54.65
5	62.18	65.68	67.50	64.80	61.40	66.13
6	70.35	73.80	79.45	75.82	76.50	72.55
7	81.2	84.59	86.80	89.51	84.56	87.15
8	90.3	92.50	95.25	97.75	96.55	94.74

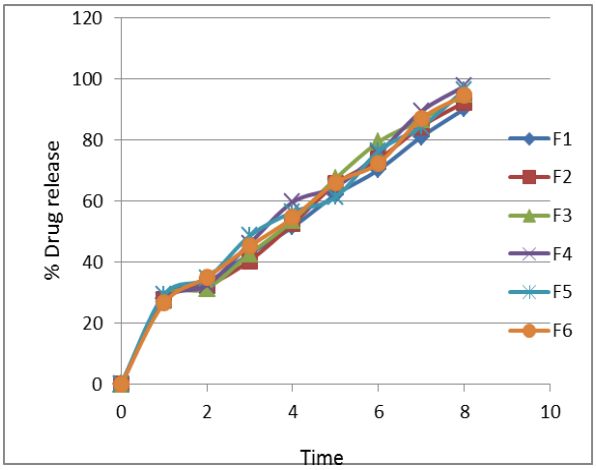

Fig. In vitro drug release studies.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-4 after 30 days. Parameters quantified at various time intervals were shown.

Table. Results of stability studies of optimized formulation F-4.

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-4	25^0C/60%RH % Release	97.75	97.74	Not less than 85%
F-4	30^0C/75% RH % Release	97.75	97.73	Not less than 85%
F-4	40^0C/75% RH % Release	97.75	97.74	Not less than 85%

4. CONCLUSION

In the present work, attempts were made to formulate and evaluate controlled release stavudine matrix tablets. Stavudine was subjected to preformulation studies; based on the results obtained Stavudine controlled release tablets were successfully formulated. Formulations prepared by direct compression technique using HPMC and carbopol 934 as control release polymers. Set of trials were formulated for which physical parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) were found to lie within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in 0.1 HCL for 2 hours followed by pH 6.8 phosphate buffer upto 8hr. From the results of the in vitro study it appears that the release of the stavudine was significantly influenced by the characteristics of the polymer used.

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