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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF ONCE DAILY SUSTAINED RELEASE MATRIX TABLETS OF STAVUDINE

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ABSTRACT

The objective of the present study was to formulate and evaluate once-daily sustained release matrix tablets of Stavudine to increase therapeutic efficacy, reduce frequency of administration and improve patient compliance. The sustained release matrix tablets were prepared by wet granulation method and formulated using different drug:polymer ratios and combination of polymers. Matrix tablets of Stavudine were prepared by using Hydroxy Propyl Methyl Cellulose (HPMC K4M), Sodium carboxy methyl cellulose, Ethyl cellulose and natural gums like Xanthum gum, Guar gum, Gum karaya. After fixing ratio of drug and polymer for controlling the release of drug to the desired time, the release rates were modulated by combination of two different rate controlling materials. The granules were evaluated for angle of repose, bulk density, Carr's index and Hausner's ratio. The tablets were also subjected to thickness, weight variation, drug content, hardness, friability and *in vitro* drug release studies. The granules showed satisfactory flow properties, compressibility and drug content. After evaluation of physical properties of tablets the *in vitro* drug release study was performed in 0.1 N HCl for 2 hrs and in phosphate buffer pH 7.4 up to 24 hrs. Tablets having combination of HPMC K4M with ethyl cellulose / sodium CMC (F4, F5) gave more sustained release. The release data was fitted to various mathematical models such as Higuchi, korsmeyer-peppas, first order and zero order to evaluate the kinetics and the mechanism of drug release of all the formulations (F1-F8) was found to be diffusion dominated drug release.

KEYWORDS: Stavudine, hydroxy propyl methyl cellulose, ethyl cellulose, sodium CMC, Xanthum gum, Guar gum, Gum karaya, sustained release, matrix tablets.

INTRODUCTION

Stavudine (D4T, thymidine) is the Food and Drug Administration approved drug for clinical use in the treatment of HIV infection, acquired immune deficiency syndrome (AIDS) either alone or in combination with other antiviral agents. The drug has a very short half life (1.30 hrs). However, patients receiving Stavudine develop neuropathy and lactic acidosis. The side effects of Stavudine are dose dependent and a reduction of the total administered dose reduces the severity of the toxicity[1]. To reduce the frequency of administration and to improve patient compliance, a once daily sustained release formulation of Stavudine is desirable. Converting twice daily regimen of Stavudine into once daily improve adherence and, therefore enhances the effectiveness of antiretroviral therapy[2].

For many drugs, the optimal therapeutic response is observed only when adequate blood levels are achieved and maintained with minimal variation. Sustained release products have become important for the oral administration of many drugs because they give more consistent blood levels[3].

The most commonly used method of modulating the drug release is to include it in a matrix system[4]. An effort was therefore made to develop simple and effective sustained release Stavudine tablets using a polymer matrix system. The drug is freely soluble in water and hence judicious selection of matrix formers is essential for achieving constant release. HPMC is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems[5]. Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly[6]. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution[7]. As the proportion of the polymer in the formulation increases, the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix[8]. The dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer[9]. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release are found to increase with either higher levels of drug loading or with use of lower viscosity grades of HPMC[10]. However, the use of hydrophilic matrix former alone for sustaining the drug release of highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it is necessary to include hydrophobic polymers in the matrix system[11, 12].

MATERIALS AND METHODS

Materials

Stavudine was obtained as a gift sample from Hetero Labs, Hyderabad, India. Ethylcellulose, Na CMC, Xanthum gum, Guar gum and Gum karaya were procured from S.D. Fine Chemicals, Mumbai, India. HPMC was obtained as a gift sample from Dr. Reddy's Lab, Hyderabad, India. Micro Crystalline Cellulose and Mg. Stearate from Loba Chem, Mumbai, India. PVP K 30 and IPA were obtained from Nice Chemical Laboratory, Kerala,India. All other chemicals and ingredients used for study were of Analytical grade.

Methods

Preparation of Tablets

All the matrix tablets, each containing 100 mg of Stavudine, were prepared by wet granulation method. Drug and the diluent (MCC) were sifted through sieve No# 60 manually and mixed well to ensure the uniformity of premix blend.

Several drug-diluent premixes were then mixed with the selected ratio of polymer(s), previously sifted through sieve No# 60. Premix blend was wet granulated with 1.5% w/v solution of PVP K-30 in Iso Propyl Alcohol (IPA) in a mortar. The wet mass was passed through No#16 sieve. The wet granules were dried at 55°C ± 5°C for 1 hour in a hot-air oven and the dried granules were sieved through No# 18 sieve.

These granules were blended with lubrication mixture (1% w/w magnesium stearate and 1% w/w talc) and compressed using 16 station rotary tableting machine, equipped with flat-faced, round punches of 12 mm diameter[13, 14].

The drug polymer ratio was altered to adjust the drug release as per theoretical release profile and total weight of tablet was kept constant for all the fabricated batches. The total weight of the matrix tablets was 500 mg. Matrix tablets were prepared with different drug polymer ratios like 1:2, 1:3, 1:3.5 and drug with different combinations of polymers in the ratios like 1:2.5:1 .

Table 1 Formulation of Matrix Tablets

Materials	F1	F2	F3	F4	F5	F6	F7	F8
Drug (mg)	100	100	100	100	100	100	100	100
HPMCK4M (mg)	200	300	350	250	250	250	250	250
EC (mg)	-	-	-	100	-	-	-	-
Na CMC (mg)	-	-	-	-	100	-	-	-
Xanthum gum (mg)	-	-	-	-	-	100	-	-
Guar gum (mg)	-	-	-	-	-	-	100	-
Gumkaraya (mg)	-	-	-	-	-	-	-	100
MCC (mg)	182.35	82.35	32.35	32.35	32.35	32.35	32.35	32.35
PVP- K30 (mg)	7.65	7.65	7.65	7.65	7.65	7.65	7.65	7.65
IPA (ml)	qs	qs	Qs	qs	qs	qs	qs	qs
MS (mg)	5	5	5	5	5	5	5	5
Talc (mg)	5	5	5	5	5	5	5	5
Total (mg)	500	500	500	500	500	500	500	500

Calculation of Sustained Release Dose and Theoretical Release Profile of Stavudine

Dose of Stavudine was calculated on the basis of Pharmacokinetic parameters as follows[1]:

Dose of immediate release part = $C_{SS}.V_d/F$

Where

C_{SS} = Steady state plasma concentration (228 ng/ml)

V_d = Volume of distribution (35 Liter, for 70 Kg human)

F = bioavilability (83%)

Dose of immediate release part =228×35×100/83 =9.614 mg

To maintain the drug concentration in the blood, rate of elimination of drug should be equal to rate of drug release from the dosage form.

Rate of elimination = $K_e \times C_d \times V_d$

= 0.415×0.228×35

= 3.3117 mg/h

Where

Ke (elimination rate constant) = $0.693/t_{1/2}$

C_d= desired drug level in the body

V_d = Volume of distribution

Bioavailability of Stavudine is 83%, so amount of drug to be released from dosage form to maintain the steady state in plasma is

= 3.3117×100/83

= 3.99 mg.

The formulation should release 9.614 mg in first 1 hr and 3.99 mg per hr up to 24hrs.

Total dose required = $D_T = D_L + D_M$

=9.614 +90.306

= 99.92 mg

=100 mg

Where

D_L= Loading dose

D_M = maintenance dose

Hence, an oral controlled release formulation of Stavudine should contain a total dose of 100 mg and should release 9.614 mg in first 1 hr like conventional tablets, and 3.99 mg/h up to 24 hrs thereafter.

Evaluation of Granules

Angle of Repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation[15].

$$\tan \theta = h/r$$

Where h and r are the height and radius of the powder cone.

Bulk Density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any ag-glomerates formed, was introduced into a 10-ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas[16].

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

Carr's Index:

The Carr's index of the granules was determined by using the following formula

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Hausner's Ratio:

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties[16]. Generally a value less than 1.25 indicates good flow prop

Evaluation of Tablets

Thickness:

The thickness of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Ten tablets from each batch were used, and average values were calculated[17, 18].

Weight Variation Test:

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado), and the test was performed according to the official method[17, 18].

Drug Content:

Ten tablets were weighed individually, an accurately weighed portion of the drug powder equivalent to about 100 mg of Stavudine was extracted in 0.1N HCl and the mixture was filtered through a Whatman filter paper (No.1). From this resulted solution 1 ml was taken, suitably diluted with 0.1N HCl and absorbance was measured against blank at 266 nm [19].

Hardness and Friability:

For each formulation, the hardness of 6 tablets and friability of 10 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Camp-bell Electronics, Mumbai, India), respectively [17, 18].

***In Vitro* Release Studies:**

The *in vitro* dissolution studies were carried out using USP apparatus type I (Tab-Machines, Mumbai, India) at 50 rpm. The dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hrs and the phosphate buffer pH 7.4 from 3 to 24 hrs (900 ml), maintained at 37°C ± 0.5°C [16]. The drug release at different time intervals was measured by diode array UV-visible spectrophotometer (Elico SL-164, New Delhi, India) at 260 nm.

RESULTS AND DISCUSSION

The granules of different formulations were evaluated for angle of repose, LBD, TBD, Carr's index and Hausner's ratio and the results are given in **Table 2**. The results of angle of repose and Carr's index (%) were found to be in the range of 25.49 ± 0.72 to 33.65 ± 0.22 and 12.11 ± 0.33 to 19.39 ± 0.68, respectively. The results of LBD and TBD ranged from 0.214 ± 0.01 to 0.521 ± 0.04 and 0.251 ± 0.01 to 0.629 ± 0.04 respectively. The results of Hausner's were found to be in the range of 1.13 ± 0.01 to 1.24 ± 0.03.

Angle of repose was less than 35° and Carr's index values were less than 21 for the granules of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

The results of the uniformity of weight, hardness, thickness, friability and drug content of the tablets are given in **Table 3**. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 499.9 ± 0.67 and 520.6 ± 1.14 mg. The hardness of the tablets ranged from 5.0 ± 0.30 to 7.50 ± 0.31 kg/cm^2 and the friability values were less than 1.0% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 5.14 ± 0.80 to 5.38 ± 0.66 mm. All the formulations satisfied the content of the drug as they contained 95.28 ± 0.80 to 101.22 ± 0.88 % of Stavudine and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically with in control.

Table. 2 Properties of the Granulation

Formulation Code	Angle of repose (°) ±S.D	Bulk Density (g/ml)±S.D	Tapped Density (g/ml)±S.D	Carr's Index (%)±S.D	Hausner's ratio ±S.D
F1	25.49±0.72	0.214±0.01	0.251±0.01	14.74±0.42	1.17±0.01
F2	26.24±0.71	0.308±0.01	0.364±0.02	15.38±0.67	1.18±0.04
F3	29.05±0.73	0.276±0.04	0.322±0.02	14.28±0.56	1.16±0.02
F4	26.97±0.81	0.341±0.03	0.388±0.02	12.11±0.33	1.13±0.01
F5	29.25±0.11	0.324±0.02	0.376±0.05	13.82±0.28	1.16±0.11
F6	32.27±0.21	0.320±0.06	0.397±0.04	19.39±0.68	1.24±0.03
F7	33.65±0.22	0.521±0.04	0.629±0.04	17.17±0.44	1.20±0.03
F8	33.21±0.81	0.518±0.04	0.627±0.02	17.38±0.71	1.21±0.02

Table 3. Physical Evaluation of Matrix Tablets

Formulation Code	Hardness (kg/cm^2)±S.D	Thickness (mm) ±S.D	Weight variation (mg)±S.D	Friability (%) ±S.D	Drug content (%) ±S.D
F1	5.50 ±0.44	5.22±0.17	519.8±1.48	0.36±0.01	98.25±1.37
F2	7.50±0.31	5.37±0.25	500.4±0.54	0.39±0.01	95.28±0.80
F3	6.58±0.40	5.14±0.80	506±0.41	0.43±0.03	99.12±2.47
F4	5.66±0.55	5.20±0.20	518.8±1.64	0.12±0.01	101.22±0.88
F5	7.25±0.57	5.38±0.66	520.6±1.14	0.44±0.02	100.24±1.25
F6	5.0±0.30	5.33±0.25	511.2±0.83	0.48±0.03	99.53±1.87
F7	7.5±0.57	5.24±0.71	499.9±0.67	0.34±0.01	98.8±1.99
F8	6.41±0.60	5.32±0.89	515.0±0.43	0.37±0.02	95.35±1.14

The results of drug release studies of formulations F1 to F8 composed of HPMC and its combination with EC/ Na CMC/ Xanthum gum/ Guar gum/ Gum karaya are shown in Figure 1, 2. All the formulations retained their shape up to 24 hrs of dissolution testing. As the percentage of polymer increased, the drug release was decreased. Formulations F1, F2 composed of drug polymer ratios of 1:2, 1:3 provided sustain release up to 20 hrs, where as the formulation with drug polymer ratio 1:3.5 (F3) extended the drug release for 24 hrs. In the first 2 hrs 50.4 ± 1.22%, 45.8 ± 0.78% and 36.09 ± 1.03% of drug released from F1, F2, F3 formulations respectively. The initial release was more in all the formulations indicating burst release. Formulations containing combination of HPMC K4M and ethyl cellulose/ Na CMC (F4 & F5) have shown better release profiles. There was no burst release observed with formulations F4 & F5, and release was extended up to 24 hrs. F4 & F5 released 22.9 ± 1.2 5% and 25.5 ± 0.87% of Stavudine respectively at the end of 2 hrs and they released 94.3 ± 0.87% and 98.5 ± 1.88% of Stavudine respectively at the end of 24 hrs. Formulations containing combination of HPMC K4M and Xanthum gum/Gum karaya (F6, F8) provided sustain release up to 20 hrs, they released 38.7 ± 1.23% and 43.1 ± 0.89% of Stavudine respectively at the end of 2 hrs. Formulations

containing combination of HPMC K4M and Guar gum (F7) extended the drug release for 24 hrs. It released 36.2 ± 0.66% at the end of 2 hrs and 97.4 ± 0.99% of Stavudine respectively at the end of 24 hrs.

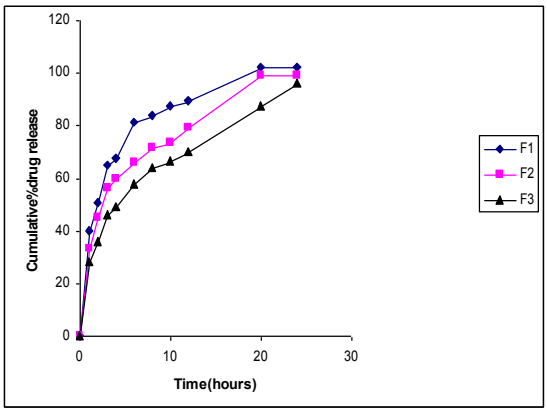

Figure 1. Release Profiles of Stavudine from matrix tablets containing HPMC K4 M

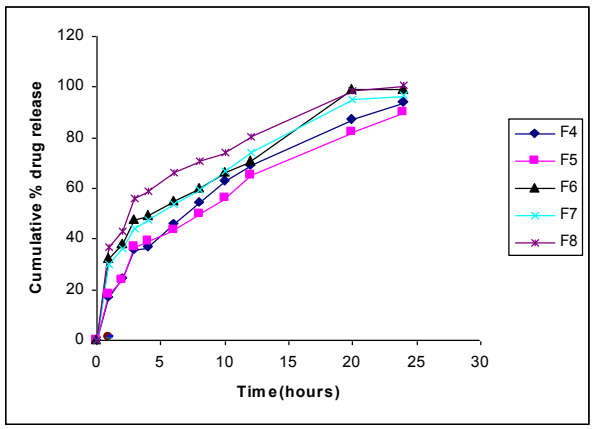

Fig 2. Release Profiles of Stavudine from matrix tablets containing combination of HPMC K4M and EC/ Na CMC/ Xanthum gum/ Guar gum/ Gum karaya

Among these Formulations the drug release rate was increased in the following polymer order HPMC K4M > HPMC K4M+Gum karaya> HPMC K4M+Guar gum > HPMC K4M+Xanthum gum> HPMC K4M+Na CMC> HPMC K4M+E C.

Initially tablets were prepared with a drug to polymer ratio of 1:2 using PVP K30 in isopropyl alcohol as a granulating agent. But the tablets released 99.8% of Stavudine with in 20 hrs. In an attempt to prolong the release of drug, the concentration of polymer was increased. The tablets prepared with drug to polymer ratio of 1:3, 1:3.5 using PVP K30 in isopropyl alcohol as a granulating agent released 96.8% of Stavudine with in 20 hrs and 96% of Stavudine with in 24 hrs respectively with burst release of Stavudine in the initial hours, which is probably due to faster dissolution of the highly water soluble drug from the core and its diffusion out of the matrix forming the pores for the entry of solvent molecules.

A suitable sustained release formulation should release required amount of drug in the initial hrs followed by slow release. Hence, initial burst release and high deviations in the release profile from the theoretical release pattern demonstrated the need for further development to find a suitable formulation to mimic the theoretical pattern. The formulation F3, which exhibited the slowest dissolution profile of the initial series, was modified using different combinations of polymers, HPMC K4M with EC/ Na CMC/ Xanthum gum/ Guar gum/ Gum karaya in the ratio of 1:2.5:1 to control the drug release in the initial hours. The formulations F4, F5, F6, F7, F8 released 22.9%, 22.5%, 38.7%, 36%, 43.1% of Stavudine respectively at the end of 2 hrs and 94.3%, 98.5%, and 99.8%, 97.7%, 98.4% of Stavudine respectively at the end of 24 hrs. *In vitro* release profiles of all the Stavudine matrix formulations were compared with the theoretical release profile which was calculated earlier. The data were analyzed and the similarity factor (f_2) values of all the Stavudine matrix formulations were determined. Formulations with f_2 values > 50 were selected as best formulations.

Table 4. Drug Release Kinetics of Stavudine Matrix Formulations

Formulations	Zero order		First order		Korsmeyer-peppas		Higuchi
	R^2	K_0	R^2	K_1	R^2	N	R^2
F1	0.589	2.87	0.9471	0.139	0.931	0.28	0.847
F2	0.756	3.10	0.929	0.193	0.979	0.331	0.944
F3	0.823	3.15	0.948	0.112	0.993	0.376	0.9767
F4	0.944	3.55	0.931	0.11	0.968	0.52	0.964
F5	0.955	3.72	0.904	0.149	0.976	0.53	0.969
F6	0.860	3.38	0.897	0.196	0.971	0.360	0.975
F7	0.862	3.36	0.960	0.139	0.989	0.381	0.986
F8	0.755	3.16	0.945	0.182	0.986	0.316	0.948

So formulations F4 & F5 were considered as optimized formulations (F_2 > 50), as these tablets did not show any burst release and extended the release for 24 hrs with similar release pattern to that of theoretical release profile. These formulations showed comparatively less deviation from the theoretical release profile. Therefore both these formulations can be considered as successful formulations.

To know the mechanism of drug release from the formulations, the data obtained from *in vitro* dissolution studies of formulations (F1 to F8) were fitted to Zero order, First order, Higuchi[20] and Korsmeyer - peppas equations[21, 22]. From the regression coefficients, the *in vitro* drug release from matrix formulations F1 to F3 and F6 to F8 was best explained by First order kinetics as the plots showed highest linearity when compared to Zero order plots, where as the *in vitro* drug release from formulations F4 & F5 was best explained by zero order kinetics as the plots showed highest linearity when compared to first order plots. All the formulations (F1 to F8) showed good correlation in Higuchi kinetics, clearly indicating that the drug release mechanism was predominantly diffusion controlled. To confirm the exact mechanism of drug release from the formulations (F1 to F8), the data were fitted to Korsmeyer-peppas equation[21, 22]. The diffusional exponent values (n) obtaintied for formulations

F1-F3 & F6-F8 ranging from 0.28- 0.38, indicating that stavudine release from these formulations followed fickian diffusion, Where as the n values of formulations F4, F5 were found to be 0.52 and 0.53 respectively indicating that stavudine release from these formulations followed Non-fickian diffusion.

CONCLUSION

The hydrophilic matrix of HPMC alone could not control the Stavudine release effectively for 24 hrs. It is evident from the results that a matrix tablet prepared with a combination of HPMC K4 M with EC/Na CMC is a better system for once-daily sustained release of a highly water-soluble drug like Stavudine. The optimized formulations F4 and F5 exhibited diffusion-dominated drug release. The relative complexity of these formulations and its components may indicate that the drug release is controlled by more than one process.

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