RESEARCH ARTICLE

Extended release matrix tablets of Stavudine: Formulation and *in vitro* evaluation

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During the past two decades, there has been a steady increase in both the number of antiretroviral medications and the number of possible regimens available to manage human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS). But still, regimen fails due to some reasons such as toxicity, adverse effects, and consequent difficulties with patient adherence. Stavudine is the Food and Drug Administration approved drug for clinical use for the treatment of HIV infection, AIDS, and AIDS related conditions, either alone or in combination with other antiviral agents. The side effects of Stavudine are dose dependent and a reduction of the total administered dose reduces the severity of the toxicity. To reduce the frequency of administration and to improve patient compliance, a once daily sustained release formulation of Stavudine is desirable. Hence, in the present work, an attempt has been made to develop once daily sustained release matrix tablets of Stavudine using putative hydrophilic matrix materials such as hydroxyl propyl methyl cellulose (HPMC) K4M and Carbopol 974P. The prepared extended release tablets were then evaluated for various physical tests like diameter, thickness, weight variation, hardness, friability, and drug content uniformity. The results of all these tests were found to be satisfactory. Formulation F9 extended the drug release till the end of 24 hours and showed higher r values for zero order plot, indicating that drug release followed zero order kinetics. This finding reveals that above a particular concentration, HPMC K4M and Carbopol 974P are capable of providing almost zero order drug release.

Key words: *Carbopol 974P, Extended release, HPMC K4M, Stavudine*

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] 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 (HPMC K4M) and Carbopol[2] Currently available anti - human immunodeficiency virus(HIV) drugs can be classified into the following three categories: nucleoside reverse transcriptase inhibitors, non nucleoside reverse transcriptase inhibitors, and protease inhibitors. Most of these drugs bear some significant drawbacks such as relatively short half life, low bioavailability, poor permeability and undesirable side effects. Efforts have been made to design drug delivery systems for antiHIV agents to: (a) reduce the dosing frequency, (b) increase the bioavailability and decrease the degradation/metabolism in the gastrointestinal tract, (c) improve the central nervous system (CNS) penetration and inhibit the CNS efflux, and (d) deliver them to the target cells selectively with minimal side.[3] Stavudine (D4T, thymidine) is the Food and Drug Administration approved drug for clinical use for the treatment of HIV infection, acquired immune deficiency syndrome (AIDS) and AIDS related conditions, either alone or in combination with other antiviral agents. Stavudine is typically administered orally as a capsule and an oral solution. The virustatic drug has a very short half life (1.30 hours). 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.[4] To reduce the frequency of administration and to improve patient compliance, a once daily sustained release formulation of Stavudine is desirable. The drug is freely soluble in water, and hence judicious selection of release retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug. The most commonly

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used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance.[5] Hence, in the present work, an attempt has been made to develop once daily sustained release matrix tablets of Stavudine using putative hydrophilic matrix materials such as HPMC K4M and Carbopol 974P.

MATERIALS AND METHODS

Stavudine was received as a gift sample from Aurobindo Pharma Lab (Hyderabad, India): Carbopol 974P and HPMC K4M Premium were obtained from Colorcon, (Goa, India) talc and magnesium stearate were obtained from Loba Chemie Pvt. Ltd. (Mumbai, India); PVP K30 were obtained from Nice Chemicals Laboratory (Kerala, India); all other reagents used were of analytical grade.

Differential scanning calorimetry

The differential scanning calorimetry (DSC) analysis of pure drug and drug loaded microcapsules were carried out using a DSC Shimadzu (DSC 60) to evaluate any possible drug polymer interaction. The analysis was performed at the rate 5°C/min from 10 to 300°C temperature range under nitrogen flow of 25 ml/min [Figure 1].

Wet granulation

Weighed quantity of drug, polymer were passed through sieve No. 80 and mixed uniformly for 10 minutes. The PVP K 30 was dissolved in sufficient quantity of ethanolic solution (95%) resulting PVP solution. The ethanol solution was added to the above mixture and mixed thoroughly with sufficient volume of granulating agent; after enough cohesiveness was obtained, the mass was passed through a No.10 sieve and dried at 40°C for 30 minutes. The dried granules were passed through sieve No. 16 to get uniform granules and again were dried at 40°C for 2 hours. The granules were sieved (No.16/22 sieve).The oversized granules (retained on No.16 sieve) were kept aside. The undersized granules (passed from No.22 sieve) were mixed with granules retained on No.16 sieve in a ratio of 1:9 as fines this granules mixture was blended with talc and magnesium stearate which already passed through a No.60 sieve The granules were compressed by single punch tablet machine using 12 mm standard concave punch.[6-8] The composition of various formulations is shown in Table 1.

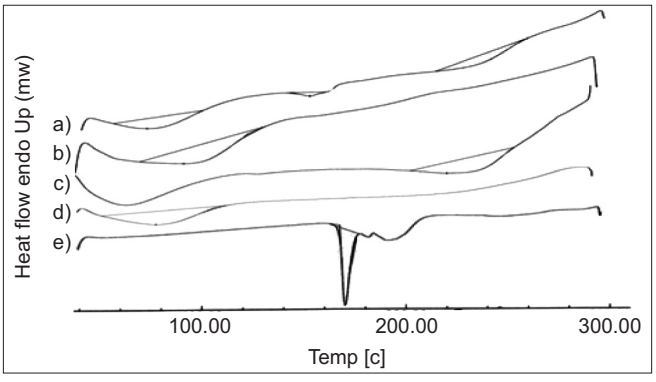

Figure 1: Differential scanning calorimetry diagrams curve of (a) physical mixture (b) PVP (c) Carbopol 974P (d) HPMC K4M (e) Stavudine

In vitro dissolution study

All dissolution studies were carried out for extended release of Stavudine formulations in 900 ml water in USP dissolution paddle assembly (Electrolab, Mumbai) at 50 rpm and 37±0.5°C for 24 hours.[9,10] The amount of drug dissolved in the medium was determined by ultra violet (UV) spectrophotometer (UV–1601 PC Shimadzu, Japan) at 266 nm.

Drug release kinetics

For finding out the mechanism of drug release from tablets, the dissolution data obtained from the above experiments were treated with the different release kinetic equations.

Zero order release equation:

$$Q = K0\ t \quad (1)$$

First order equation:

$$\ln Q = Kf\ t \quad (2)$$

Higuchi's square root of time equation:

$$Q = KH\ t^{1/2} \quad (3)$$

Korsmeyer and Peppas equation:

$$F = (Mt/M) = Km\ tn \quad (4)$$

RESULTS AND DISCUSSION

Preformulation studies (compatibility studies)

Differential scanning calorimetry

The DSC thermogram of pure Stavudine showed sharp melting endothearm at 175.05°C [Figure 1]. The thermogram of solid admixtures of Stavudine with various excipients also had shown slight earlier shift peak at 166.42°C, indicating that solublizing characteristic of PVP may result in formation of solid dispersion in the preparation of extended release tablet formulations.

Table 1: Formulation of Stavudine extended release matrix tablets Quantity of raw materials per tablet (in mg)

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	100	100	100	100	100	100	100	100	100
HPMC K4M	150	180	210	-	-	-	175	150	125
Carbopol 974P	-	-	-	150	180	210	15	40	60
Pvp (1.5%)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Talc (1%)	3	3	3	3	3	3	3	3	3
Magnesium sterate (1.5%)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total tablet weight	260	290	320	260	290	320	300	300	300

HPMC K4M - hydroxyl propyl methyl cellulose K4M; PVP - poly vinyl pyrolidine

Evaluation of physical characteristics of Stavudine granules

The granules were prepared by wet granulation method and physicochemical characteristics of prepared granules were evaluated. The granules of all the batches exhibited good flow characteristics evident from the results of these physicochemical evaluations in Table 2. The angle of repose value ranged from 26°09′ ± 0.03 to 29°76′ ± 0.02. The results were found to be below 30^0 and hence the blend was found to have good flow ability. Bulk and tapped densities are used for the measurement of Compressibility index. The low bulk density and tapped bulk density ranged from 0.477±0.04 to 0.536±0.05 and 0.542±0.02 to 0.625±0.03, respectively. The blend was found to have free flowing property as the result was found to be below 18%. The Hausner's ratio ranged from 1.1± 0.02 to 1.18± 0.02 [Table 2]. The result indicates the free flowing properties of the granules as the value was below 1.2.

Evaluation of physical characteristics of extended release matrix tablets of Stavudine

The prepared extended release tablets were then evaluated for various physical tests like diameter, thickness, weight variation, hardness, friability, and drug content uniformity. The results of all these tests were found to be satisfactory. The diameter of the tablets was uniform in all formulations and ranged from 8.00±0.024 to 8.03±0.043 mm. The thickness of the tablets was uniform in all formulations and ranged from 3.78±0.010 to 3.80±0.059mm [Table 2]. The hardness of tablets in all batches ranged from 4.25±0.1 to 7.21±0.5 kg/cm^2 [Table 2]. All the formulations (F_1 - F_9) passed weight variation test as per the pharmacopoeia limit of 7.5% [Table 3]. The friability of all batches ranged from 0.265 to 0.634 [Table 2], which was well below the pharmacopeia limit of 0.1%. Drug content was also found to be uniform among the all formulations and ranged from 95.53±0.04 to 98.55±0.03 [Table 3].

***In vitro* drug release studies for extended release matrix tablets of Stavudine**

The prepared tablets were subjected to dissolution test for evaluating the *in vitro* drug release. The dissolution studies were carried out in 900 ml water in USP dissolution paddle assembly (Electrolab) at 50 rpm and 37±0.5°C. The results of the dissolution studies indicate that the polymer concentration have a substantial effect on the drug release from the tablets. Formulations containing HPMC K4M alone (F_1 - F_3) released the total drug before 18 hours. However, the formulations containing (F_4 - F_6) extended the drug releases till the end of 20 hours. The concentration of Carbopol 974P had a greater effect on the drug release than concentration of HPMC K4M, which may be due to lesser permeability of the former. This finding is in favor of the investigation done on the effects of levels of HPMC K4M and Carbopol 974P on the release of Stavudine from the swellable matrices. Formulations

Table 2: Blend characteristics of Stavudine granules

F code	*Angle of repose ± S.D	*Loose bulk density (g/ml) ± S.D	*Tapped bulk density (g/ml) ± S.D	*Carr's index (%) ± S.D	*Hausner's ratio ± S.D
F_1	29° 09′±0.02	0.536±0.02	0.625±0.02	14.24±0.04	1.16±0.05
F_2	28° 33′±0.01	0.516±0.03	0.614±0.01	14.8±0.02	1.17±0.04
F_3	26° 09′±0.03	0.505±0.03	0.625±0.03	14.2±0.02	1.16±0.04
F_4	26°14′±0.03	0.477±0.04	0.542±0.02	11.99±0.01	1.13±0.02
F_5	27° 01′±0.02	0.498±0.03	0.549±0.02	9.22±0.02	1.1±0.06
F_6	27° 09′±0.03	0.528±0.02	0.586±0.06	9.89±0.04	1.1±0.02
F_7	28° 63′±0.02	0.521±0.03	0.596±0.02	12.5±0.03	1.14±0.03
F_8	26° 49′±0.01	0.492±0.06	0.542±0.04	9.22±0.06	1.1±0.02
F_9	29° 76′±0.02	0.536±0.05	0.593±0.03	15.96±0.01	1.18±0.02

*Each reading is an average of three determinations±S.D - standard deviation; ER - Extended release

Table 3: Physical characteristics of Stavudine ER tablets

F code	*Diameter (mm) ± S.D	*Thickness (mm) ± S.D	*Weight variation (mg) ± S.D	*Hardness (kg/cm^2) ± S.D	Friability (%)	*Drug content (%) ± S.D
F_1	8.02±0.049	3.79±0.007	260.73±0.85	5.21±0.5	0.399	95.53±0.04
F_2	8.01±0.043	3.80±0.059	290.62±0.63	5.00±0.1	0.395	96.51±0.03
F_3	8.03±0.043	3.80±0.006	320.96±0.77	6.31±0.1	0.335	97.54±0.02
F_4	8.01±0.036	3.80±0.011	260.74±0.92	6.18±0.3	0.332	96.79±0.04
F_5	8.01±0.043	3.78±0.010	290.26±0.84	7.21±0.5	0.265	98.55±0.02
F_6	8.00±0.024	3.79±0.008	320.42±0.63	5.23±0.3	0.634	97.62±0.04
F_7	8.01±0.041	3.79±0.007	300.87±1.83	6.34±0.2	0.199	95.60±0.03
F_8	8.00±0.033	3.80±0.009	300.33±2.46	4.25±0.1	0.265	95.53±0.04
F_9	8.01±0.048	3.79±0.009	300.63±0.99	5.31±0.2	0.295	98.55±0.03

*Each reading is an average of three determinations±S.D- standard deviation; ER- Extended release

Table 4: Drug release kinetic parameters for extended release matrix tablets of Stavudine

F code	Zero order plot		First order plot		Higuchi plot	Korsemeyer Peppa's plot		Mechanism of drug release
	K_0	R	K_1	R	r	n	r	
F_1	6.6282	0.8970	0.2312	0.9866	0.0358	0.3226	0.9954	First order fickian diffusion
F_2	4.9176	0.9041	0.1865	0.9806	0.0417	0.3358	0.9963	First order fickian diffusion
F_3	4.5089	0.9294	0.2264	0.9243	0.0442	0.3660	0.9969	First order fickian diffusion
F_4	5.6891	0.9901	0.2237	0.8508	0.0389	0.5822	0.9696	First order fickian diffusion
F_5	5.2348	0.9923	0.2148	0.8459	0.0397	0.6201	0.9750	First order non fickian diffusion
F_6	4.8438	0.9941	0.2005	0.8558	0.0407	0.6540	0.9786	First order non fickian diffusion
F_7	5.6853	0.9919	0.2214	0.7864	0.0383	0.7123	0.9810	First order non fickian diffusion
F_8	4.5625	0.9955	0.1719	0.9444	0.0413	0.7456	0.9923	Zero order non fickian diffusion
F_9	4.3154	0.9931	0.1670	0.8966	0.0417	0.8862	0.9989	Zero order non fickian diffusion

K_0 zero order rate constant; r - regression; K_1 - first order rate constant; n - release exponent

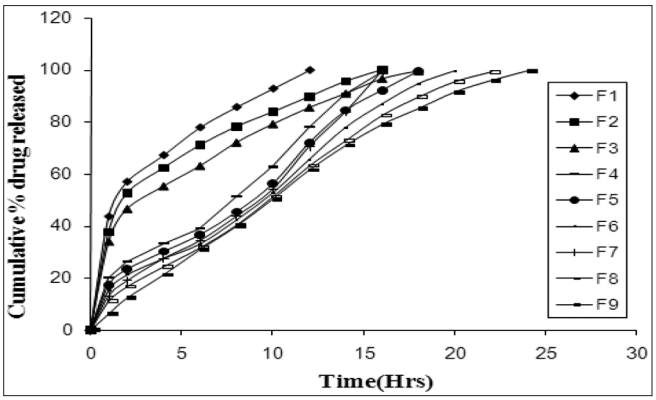

Figure 2: Drug release profile for extended release matrix tablets of Stavudine

containing combination of HPMC K4M and Carbopol 974P F_7 - F_9 polymer concentration extended the drug release till the end of 24 hours [Figure 2], which indicates that these formulations were capable of achieving the objective. This is probably due to the stronger hydrogen bonding between the carboxyl groups of Carbopol and hydroxyl groups of HPMC, leading to stronger cross linking between two polymers and diminishes the release fluctuation.[11]

In order to understand the complex mechanism of drug release from the extended tablets, the *in vitro* Stavudine release data were fitted to Korsemeyer Peppa's release model, and interpretation of release exponent values (n) enlightens us in understanding the release mechanism from the dosage form. The release exponent values thus obtained were from 0.5829 to 0.7827. Based on these values, we can say that the formulations F_1 to F_4 exhibited fickian transport. However, the formulations F_5 to F_9 exhibited anomalous (non fickian transport) diffusion mechanism.

The drug release was diffusion controlled, as the plot of Higuchi's model was found to be linear (r >0.9683) for all formulations. The formulations F_1 to F_7 showed higher r values for first order plot, indicating that the drug release from these formulations was concentration dependent and followed first order kinetics. However, the formulations F_8 to

Table 5: Dissolution data of percentage cumulative drug release for formulation F_9

Time in hours	Cumulative percentage drug release		
	First month	Second month	Third month
24	99.52	99.27	98.14

F_9 showed higher r values for zero order plot, indicating that drug release followed zero order kinetics and drug release from these extended release tablets were by both diffusion and erosion. This finding reveals that above a particular concentration, HPMC K4M and Carbopol 974P are capable of providing almost zero order drug release [Table 4].

Stability studies

The stability studies were carried out for F_9 batch at 45°C with 75% RH for 3 months.[12] Data revealed that there was no considerable difference in dissolution rate [Table 5].

CONCLUSION

The objective of this study was to develop an extended release matrix tablet of Stavudine for once daily therapy. It has been observed in this investigation that using HPM K4M and Carbopol 974P in combination retarded the drug release than using alone. It may be concluded from the study that, formulation F_9 (containing 125 mg of HPMC K4 M and 60 mg of Carbopol 974P) has showed Stavudine release over a period of 24 hours. The mechanism of drug release from F_9 was diffusion coupled with erosion. So, formulation F_9 is a better system for once daily therapy of Stavudine.

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