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Design Development and *In-Vitro* Characterization of Stavudine Matrix Porous Tablets

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Abstract

The present research work was to design and develop the matrix porous tablets of Stavudine. It is having a short biological half-life (1.5 h) so it is considered as a suitable drug for the formulation of sustained release tablets to prolong its therapeutic action. Stavudine is a nucleoside analogue and reverse transcriptase inhibitor used in combination with other agents in the therapy of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). Sustained release tablets were prepared by direct compression technique, using polymers at different ratios. Powder blend was evaluated for bulk density, tapped density, angle of repose, Hausner's ratio, compressibility index. The physicochemical properties of tablets were found within the limits. The prepared tablets were evaluated for weight variation, thickness, hardness, % friability, % drug contents, and *in vitro* release. *In vitro* dissolution studies (USP dissolution rate test apparatus II, 50 rpm, 37°C±0.5°C) was carried out for 10 h using 0.1 N HCl (1.2 pH) as a dissolution medium. The optimized formulation F-3 was shown maximum drug release 98.21% in 10 h of dissolution studies. The dissolution of batch F3 can be described by zero order kinetics (R2=0.984). There was no difference observed in release profile after temperature sensitivity study at 40 °C/75% relative humidity (RH) for 1 month.

Keywords: Stavudine; Powder blend; Matrix porous tablets; Physicochemical properties; *In vitro* dissolution studies; Stability studies

Abbreviations: BD: Bulk Density; TBD: Tapped Bulk Density: RPM: Rotate Per Minute; DNA: Deoxyribonucleic Acid; HPMC: Hydroxypropyl Methylcellulose; WA: Average Weight; WI: Individual Weights; RH: Relative Humidity; SD: Standard Deviation; AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus; FTIR: Fourier-Transform Infrared Spectroscopy

Introduction

Acquired Immunodeficiency Syndrome (AIDS), which threatens to cause a great plague in the present

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generation, was first identified in California in 1981. AIDS is a disease in which the body's immune system breaks down and is unable to fight off infections caused by human immunodeficiency virus (HIV). HIV infects human cells and uses the energy and nutrients provided by those cells to grow and reproduce, so it is necessary to take many medicines for longer periods of time. This can lead to an increase in noncompliance of drugs. This problem is very serious in case of drugs having shorter biological half-life because they must be taken more number of times. It is crucial for the success of AIDS therapy to maintain systemic drug concentration consistently above its target antiretroviral concentration throughout the course of the treatment [1,2].

Traditional drug delivery system has been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this arises the need of a formulation with control release that maintain a near-constant or uniform blood level. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use [3]. Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot, and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over the extended period of time after administration of a single dose [4]. Stavudine is used as a part of highly active antiretroviral therapy. Stavudine, a nucleoside analog of thymidine, is phosphorylated using cellular kinases to the active metabolite, stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate thymidine triphosphate and by causing DNA chain termination following its incorporation into viral DNA [5]. Stavudine is typically administered orally as a capsule and an oral solution. The drug has a very short half-life (1.5 h), thus necessitating frequent administration to maintain constant therapeutic drug levels.

An attempt has been made to develop stavudine matrix porous tablet formulations which will release the drug for 12 hrs. A sustained release formulation can lead to the reduction of the number of doses administered, leading to better patient compliance and less chances of overdose.

Materials and Methods

Stavudine was obtained as a gift sample from NATCO Pharma, Hyderabad. HPMC K4, K15 & K100 and Eudragit grades were procured from SD fine chemicals Pvt Ltd, Mumbai, India, PVP-K 30, Magnesium Stearate and Talc were procured from Merck Specialties Pvt Ltd, Mumbai, India. All other reagents used were of analytical grade.

Methodology

Preformulation studies

Standard calibration curve of Stavudine: 100 mg of Stavudine was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with 0.1 N HCl (pH 1.2) to prepare stock solution. The 10 ml of stock solution was further diluted with 0.1 N HCl (pH 1.2) in 100ml to get 100µg/ml (working standard). Then 0.5,1,1.5,2,2.5 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N HCl to prepare 5µg,10µg,15µg,20µg, and 25µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer (LAB INDIA 3200 UV/Vis double beam Spectrophotometer) at 230 nm against 0.1 N HCl (pH 1.2) as blank.

The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Evaluation of pre-compression parameters

a. **Angle of Repose:** The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in the 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 blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend were measured [5].

b. **Carr's Compressibility Index:** The Carr's compressibility index was calculated from bulk density (BD) and tapped density of the blend. A quantity of 2 g of blend from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25±2/min to measure the tapped volume of the blend. The BD and tapped density were calculated by using the bulk volume and tapped volume [6,7].

c. **Bulk Density (BD):** An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The BD of powder blends was determined using the following formula [8].

Bulk density = Total weight of powder/Total volume of powder

d. Tapped Bulk Density (TBD): An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of powder blends was determined using the following formula [9].

TBD = Total weight of powder/Total volume of tapped Powder

e. Hausner's Ratio: It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Preparation of tablets: Stavudine matrix porous tablets were prepared by direct compression method. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly and the blend is compressed using rotary tablet press (using 6mm flat punch) (Table 1) [10].

Ingredient	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F10	F11	F12
Stavudine	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	40	50	-	-	-	-	-	-	-	-	-	-
HPMC K15M	-	-	40	50	-	-	-	-	-	-	-	-
HPMC K100M	-	-	-	-	40	50	-	-	-	-	-	-
Eudragit L -100	-	-	-	-	-	-	40	50	-	-	-	-
Eudragit S -100	-	-	-	-	-	-	-	-	40	50	-	-
Eudragit RSPO	-	-	-	-	-	-	-	-	-		40	50
PVP K30	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 1: Formulation composition of Stavudine sustained release tablet.

Evaluation of tablets

a. Hardness test: Hardness indicates the ability of a tablet to withstand mechanical strength while handling. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm^2. 10 tablets were randomly picked from each formulation and the mean and standard deviation values were calculated [11,12].

b. Friability test: It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed (Wt. initial) and transferred into Friabilator. The Friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (Wt. final). The percentage friability was then calculated by [12]

% F = (loss in weight/initial weight) × 100

% Friability of tablets less than 1% are considered acceptable.

c. Weight variation test: To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated by [13]

$$\% \text{ weight variation} = (WA - WI) \times 100 / WA$$

d. Drug content (Assay): Drug content of the tablets was determined by UV Spectrophotometrically.

e. Uniformity of thickness: Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using vernier caliper [14,15].

In vitro dissolution studies: *In vitro* drug release studies from the prepared Stavudine SR tablets were conducted using USP type II apparatus at 37°C at 50 rpm. Dissolution mediums used were 900 ml of 0.1 N HCl and phosphate buffer of pH 6.8. The release rates from matrix tablets were conducted in HCl solution (pH 1.2) for first 2 h and changed to phosphate buffer (pH 6.8) for next 10 h time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The samples were analyzed by UV-Visible Spectrophotometer (Lab India 3000+). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time

periods was plotted as percent release versus time curve [4].

Kinetics of drug release: To describe the stavudine release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: Zero order, first order, Higuchi, Korsmeyer–Peppas. When these models are used and analyzed in the preparation, the rate constant obtained from these models is an apparent rate constant. The release of drugs from the matrix tablets can be analyzed by release kinetic theories. To study the kinetics of drug release from matrix system, the release data were fitted into Zero order as cumulative amount of drug release versus time (Equation 3), first order as log cumulative percentage of drug remaining versus time (Equation 4), Higuchi model as cumulative percent drug release versus square root of time (Equation 5). To describe the release behavior from the polymeric systems, data were fitted according to well-known exponential Korsmeyer–Peppas equation as log cumulative percent drug release versus log of time equation [4].

Results and Discussions

Drug- excipient compatibility studies using FTIR

Drug-excipient compatibility studies by FTIR revealed no interaction between drug and the polymers used in the formulation thus showing compatibility [Figures 1&2].

Figure 1: FTIR spectrum of pure drug.

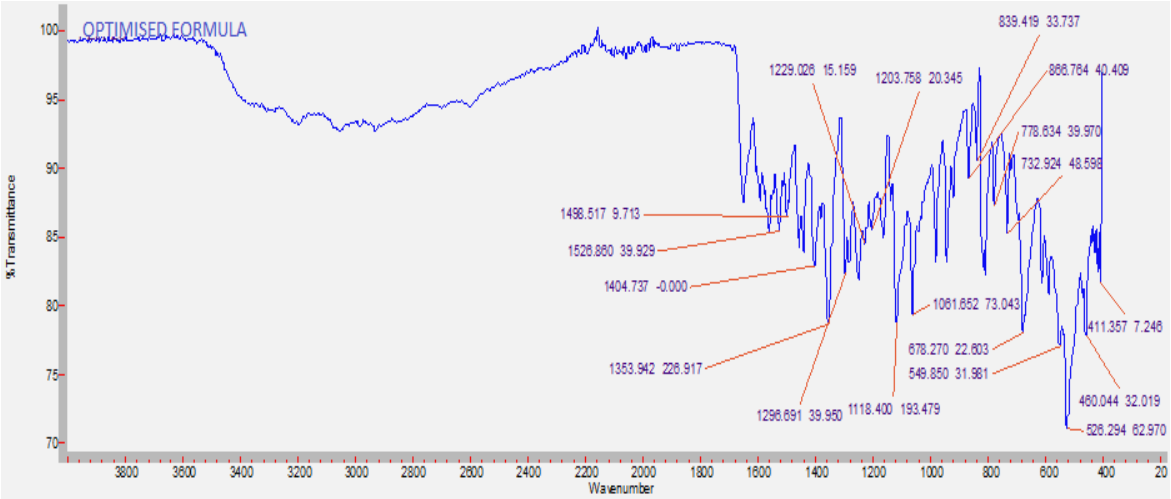

Figure 2: FTIR spectrum of optimized formulation.

Evaluation of pre-compression parameters

The Pre compression parameters such as Bulk density, Tapped density, Carr's index, Hausner ratio and Angle of repose of the all formulations (F1-F9) were found to be in between the range of 0.41±0.10 to 0.51±0.15 g/ml., 0.50±0.13 to 0.58±0.40 g/ml., 12.78±0.24 to 19.18±0.45, 1.16±0.08 to 1.32±0.24 and 26.68±0.42 to 30.72±0.12 respectively (Table 2).

Pre-compression Parameters					
Formulations	**Bulk Density (gm/ml)**	**Tap Density (gm/ml)**	**Carr's Index (%)**	**Hausner's ratio**	**Angle Of Repose(Θ)**
F_1	0.45 ±0.18	0.56 ±0.23	19.18 ±0.45	1.32 ±0.24	30.72 ±0.12
F_2	0.46 ±0.26	0.55 ±0.32	14.54 ±0.37	1.17 ±0.31	28.23 ±0.41
F_3	0.51 ±0.15	0.58 ±0.40	12.78 ±0.42	1.16 ±0.21	29.34 ±0.64
F_4	0.46 ±0.11	0.55 ±0.24	16.16 ±0.29	1.19 ±0.29	26.71 ±0.23
F_5	0.50 ±0.24	0.56 ±0.37	13.58 ±0.35	1.16 ±0.08	29.34 ±0.22
F_6	0.47 ±0.23	0.55 ±0.12	14.54 ±0.09	1.17 ±0.52	28.23 ±0.10
F_7	0.50 ±0.29	0.57 ±0.08	13.79 ±0.24	1.16 ±0.23	29.34 ±0.54
F_8	0.41 ±0.16	0.50 ±0.15	18.0 ±0.12	1.21 ±0.39	26.78 ±0.29
F_9	0.41 ±0.10	0.50 ±0.13	18.0±0.37	1.21 ±0.51	26.68 ±0.42

Table 2: Pre-compression parameters.
The data are presented as mean value ±SD (*n*=3). SD: Standard deviation.

The Post compression parameters such as Weight variation, Hardness, Thickness, Friability, Drug content of the all formulations (F1-F9) results was found to be Within the Pharmacopoeial specifications (Table 3).

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F_1	105±0.89	4.2±0.18	3.50±0.13	0.43±0.12	97.23±1.21
F_2	104±0.81	4.4±0.21	3.57±0.15	0.34±0.14	98.55±1.05
F_3	110±0.87	4.5±0.32	3.42±0.14	0.49±0.09	98.16±0.98
F_4	109±0.85	4.7±0.25	3.58±0.21	0.47±0.22	99.34±0.92
F_5	99.4±1.02	4.6±0.15	3.38±0.25	0.49±0.12	98.16±1.09
F_6	102±0.98	4.4±0.19	3.44±0.52	0.34±0.16	98.55±1.03
F_7	101±0.97	4.2±0.21	3.59±0.28	0.49±0.19	98.16±1.11
F_8	107±0.87	4.6±0.18	3.56±0.32	0.34±0.28	99.25±2.12
F_9	102±0.89	4.3±0.24	3.66±0.29	0.34±0.26	99.25±1.76
	n=20	n=5	n=10	n=10	n=5

Table 3: Evaluation of Post-compression parameters.

In vitro dissolution studies

The tablets were evaluated for *in vitro* dissolution studies in acid buffer (pH-1.2) for 2 hours followed by pH 6.8 buffers for 8 hours. The results of in-vitro drug release revealed that the Stavudine was released in a controlled manner from all the formulations where formulation F3 showed maximum drug release i.e. 98.21±1.35 % at the end of 10th hour (Table 4), (Figure 3-5).

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	12.20±0.65	13.26±0.86	15.02±1.12	17.21±0.69	14.66±0.54	16.22±0.54	21.10±0.65	19.50±0.69	23.54±0.96
2	22.65±0.98	22.58±1.23	22.55±1.02	29.53±0.78	28.44±0.68	25.45±0.28	32.86±0.96	31.88±0.36	38.33±0.89
3	34.72±0.32	31.62±1.21	40.89±1.24	40.12±0.59	43.85±0.78	36.89±0.32	43.24±1.10	49.28±1.23	44.25±0.29

4	46.24±1.21	49.55±1.18	48.22±0.95	56.84±1.69	65.88±0.59	42.83±0.41	66.49±1.21	61.11±1.35	51.01±0.36
5	60.35±0.96	65.58±1.25	54.48±0.68	66.85±0.78	79.25±0.87	58.46±0.26	74.85±1.14	78.96±1.57	66.86±0.56
6	74.24±0.89	80.65±0.96	59.77±1.12	76.63±1.21	96.12±0.69	62.70±0.45	84.25±1.30	82.58±1.42	78.98±0.68
7	88.28±1.12	98.63±1.14	66.62±1.42	85.12±1.35		75.23±0.62	95.57±1.28	94.66±1.15	84.26±0.65
8	97.01±1.25		74.35±0.98	97.70±1.29		84.26±0.85			96.99±0.29
9			88.99±1.14			97.99±1.12			
10			98.21±1.35						

Table 4: Dissolution profiles of formulations (F1-F9).

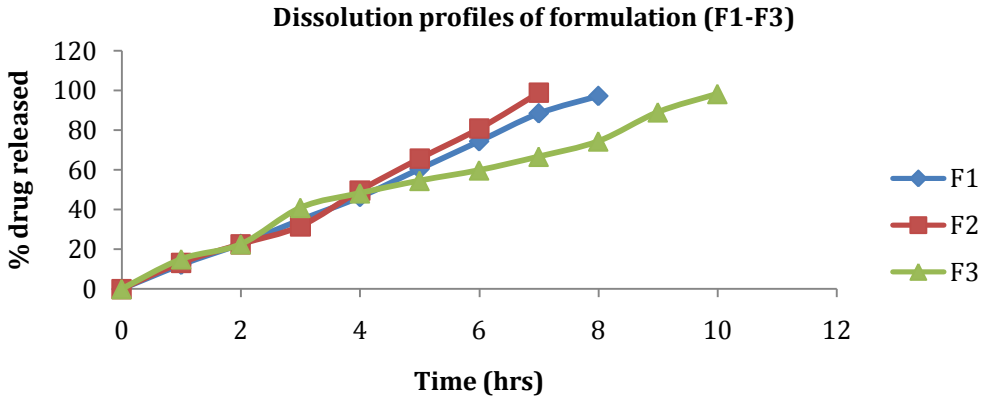

Figure 3: Dissolution profile of formulation F1-F3.

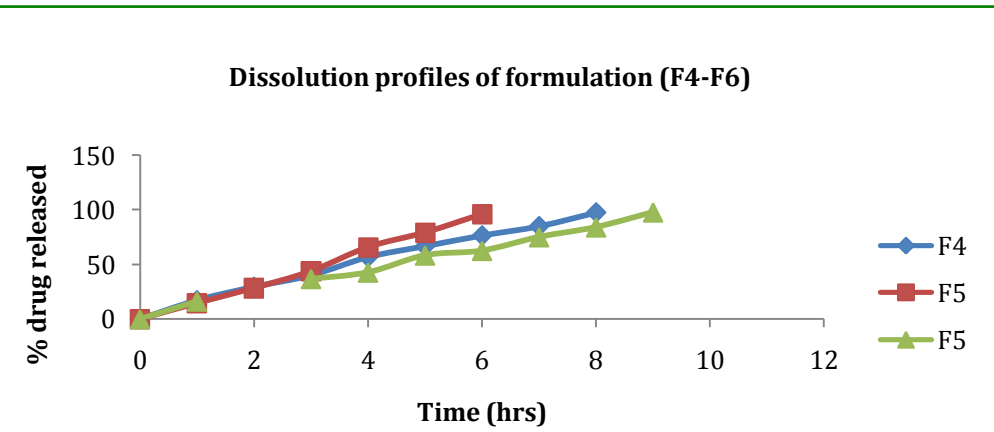

Figure 4: Dissolution profile of formulation F4-F6.

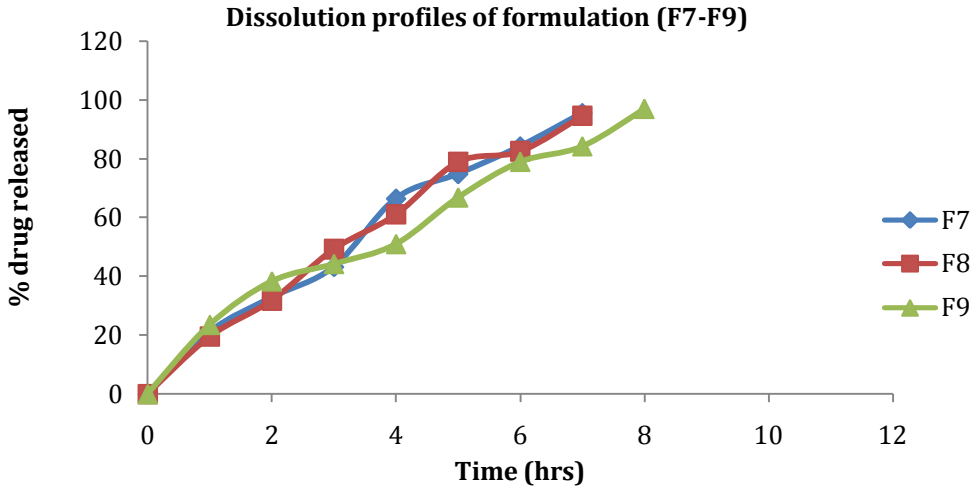

Figure 5: Dissolution profile of formulation F7-F9.

Release kinetics for optimized formulation F3

From the below graphs it was evident that the formulation F3 was followed Zero order release kinetics. (Table 5), (Figure 6-9).

Cumulative (%) Release Q	Time (T)	Log (%) release	Log (%) remain	Release rate (Cumulative % Release / t)	1/CUM% Release	PEPPAS log Q/100	% Drug Remaining
0	0		2.000				100
14.62	0.5	1.165	1.931	29.240	0.0684	-0.835	85.38
19.86	1	1.298	1.904	19.860	0.0504	-0.702	80.14
22.35	2	1.349	1.890	11.175	0.0447	-0.651	77.65
31.45	3	1.498	1.836	10.483	0.0318	-0.502	68.55
39.8	4	1.600	1.780	9.950	0.0251	-0.400	60.2
45.25	5	1.656	1.738	9.050	0.0221	-0.344	54.75
58.24	6	1.765	1.621	9.707	0.0172	-0.235	41.76
66.73	7	1.824	1.522	9.533	0.0150	-0.176	33.27
71.34	8	1.853	1.457	8.918	0.0140	-0.147	28.66
75.52	9	1.878	1.389	8.391	0.0132	-0.122	24.48
82.17	10	1.915	1.251	8.217	0.0122	-0.085	17.83
87.1	11	1.940	1.111	7.918	0.0115	-0.060	12.9
96.1	12	1.983	0.591	8.008	0.0104	-0.017	3.9

Table 5: Release kinetics data for optimised formulation.

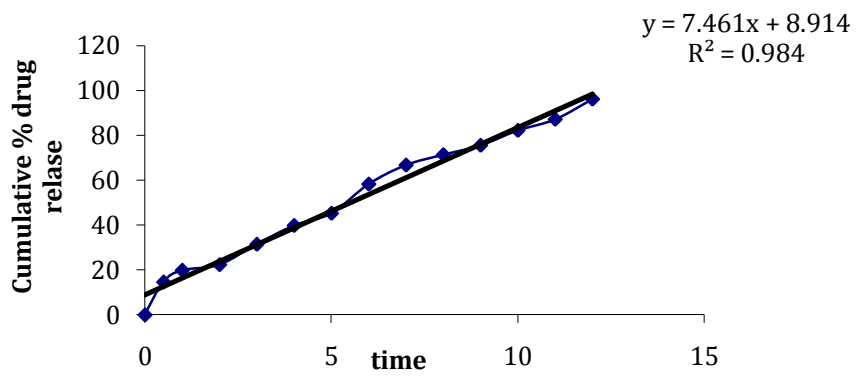

Figure 6: Zero order release kinetics graph.

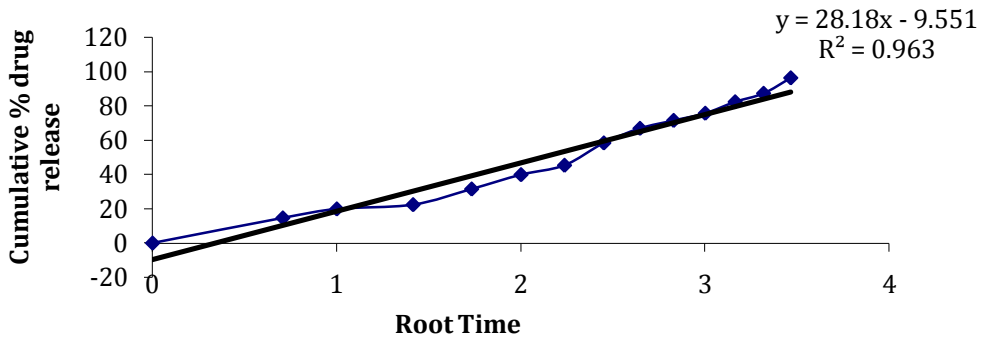

Figure 7: Higuchi release kinetics graph.

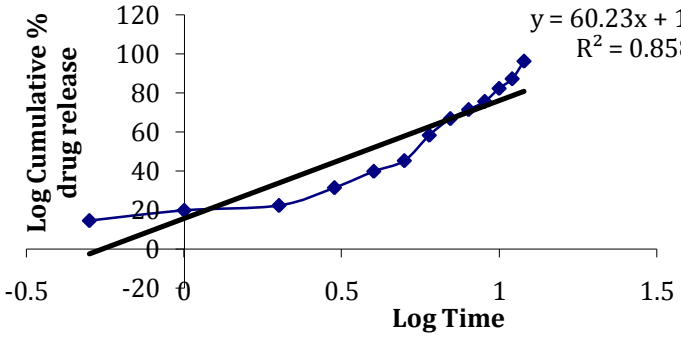

Figure 8: Korsemeyer peppas graph.

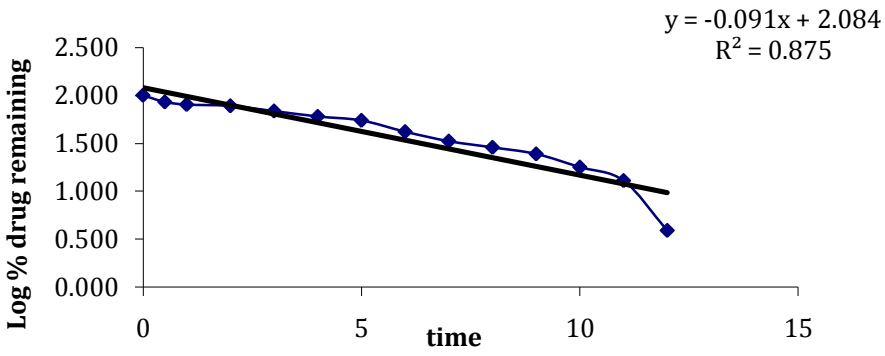

Figure 9: First order release kinetics graph.

From short term stability studies (40^{0}C±2°C/75%±5% RH for 30 days) of optimized formulation F3, it was confirmed that there was no significance change in hardness, %friability and drug content. It is shown in (Table 6).

Condition	Parameters	Initial Data	After 30 days
Accelerated(40°C ± 2°C/75% RH ± 5 % RH)	Hardness(kg/cm^2)	4.5±0.32	4.41±0.63
	Friability (%)	0.49±0.09	0.47±0.12
	Assay (%)	98.16±0.98	97.54±1.12

Table 6: Results of Stability Studies for optimized formulation (F3).

Conclusion

The Sustained Release matrix tablets of Stavudine were prepared by direct compression technique [16]. FTIR spectra indicated the absence of probable chemical interaction between the drug and polymers; hence these polymers were selected in the present investigation. The peaks obtained in the spectrum of each formulation correlates with the peaks of drug's spectrum. This indicates that the drug is compatible with the formulation components.

The tablets were formulated with different grades of HPMC (HPMC-K4M, HPMC-K15M, HPMC-K100M), Eudragit (Eudragit L-100, S-100, RSPO) other Polymers like PVP K-30, Microcrystalline cellulose, Magnesium Stearate. Among 12 formulations, F-3 is optimized based on the cumulative % drug release is 98.21±1.35 % at the end of 10th hour. The *in vitro* drug release data was plotted for various kinetic models. The R^2 value for optimized formulation F3 for zero order was found to be 0.9902 [17].

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