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# Design and evaluation of sustained-release matrix once daily formulation of stavudine

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## Abstract

The aim of the present study was to formulate once daily sustained release matrix tablets of Stavudine to increase therapeutic efficacy, reduce frequency of administration and improve patient compliance. The sustained release tablets were prepared by direct compression and formulated using different drug: polymer ratios, formulations such as F1to F15. Hydrophilic polymers like Hydroxy propyl methyl cellulose (HPMC), Carboxymethyl cellulose (CMC) and Starch 1500 were used. Compatibility of the drug with various excipients was studied. The compressed tablets were evaluated and showed compliance with pharmacopoeial standards. Formulation containing Stavudine:HPMCK15: Na-CMC (1:2:0.5) with hardness 10-11kg/cm$^2$ showed the desired release profile which matched the theoretical release profile. SEM studies of the formulations were carried out for the confirmation of mechanism of drug release. The in vitro drug release characteristics were studied in both simulated gastric and intestinal fluids for a period of 24 hr using USP Type 2 dissolution apparatus. Mathematical analysis of the release kinetics indicated a coupling of diffusion and erosion mechanisms. The study proves that the developed sustained release tablet is capable of releasing the drug in a sustained manner for 24 hr.

**Keywords:** Sustained release; Matrix tablets; Hydroxy propyl methylcellulose; Stavudine

## Introduction

The oral route is the most common route of drug administration because of its advantages in terms of convenient administration, thus leading to increased patient compliance. Extended release formulations in many cases provide further significant advantages, including improved therapeutic effect, increased patient compliance by reducing dosing frequency and decrease in incidence and /or intensity of adverse effect by a constant blood concentration [1].

Stavudine, 2',3'-didehydro-3'-deoxythymidine (D4T) is a thymidine analog approved for the treatment of HIV infection [2] like other member of this class of antiretrovirals, its purported active metabolite, D4T-5'-triphosphate, is an inhibitor of the HIV reverse transcriptase and acts as a chain terminator during DNA synthesis [3].

Stavudine is currently approved by US-FDA for the treatment of patients who have become intolerant to or

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failed to response to zidovudine, didanosine or zalcitabine therapy. The mean serum elimination half life reported ranges between 1 to 1.67 hr in adults. It is given twice daily 40 mg. Main dose related adverse effect is peripheral neuropathy. Converting twice daily regimen of stavudine into once daily improve adherence and, therefore, enhances the effectiveness of antiretroviral therapy.

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 [4]. One of the most commonly used methods of modulating drug release is to include it in a matrix system. The classification of matrix system is based upon matrix structure, release kinetics, controlled released properties (diffusion, erosion, swelling), and the chemical nature and properties of employed materials [5].

The present research endeavour was directed towards the development of a sustained release dosage form of Stavudine in the form of tablets to be taken once daily. Theoretical release profile was calculated based on pharmacokinetic parameters. Different grades of HPMC studied include MethocelK4M and K15M in different proportions to get the desired release profile with reduced HPMC requirement. Different filler viz. starch 1500 and Avicel PH101 were used.

## Materials and methods

### Materials

Stavudine was obtained from M/s Cipla Pharmaceutical, Mumbai, India. Hydroxy propyl methyl cellulose (Methocel K4M Premium CR and K15M Premium CR) were obtained as gift samples from M/s Colorcon Asia Pvt Ltd, India. Pregelatinized Starch (Starch 1500) was obtained as a gift sample from M/s Dr reddys laboratory, India. Microcrystalline Cellulose (Avicel PH101) was obtained from M/s Signet chemicals, Mumbai. Aerosil 200 and stearic acid were obtained as a gift sample from Lupin Research Park, Pune, India.

All the other reagents and solvents used were purchased from Merck, India and were of analytical grade.

### Methods

#### *Drug–excipient interaction studies*

To study the compatibility of various formulation excipients with Stavudine, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ratio of 1:1 and then stored in airtight containers at $30^0C \pm 2^0C$/65% relative humidity (RH) ± 5% RH. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FTIR) (FTIR 8300, Shimadzu, Japan) and Differential scanning calorimetry (DSC) (DSC-60, Shimadzu).

#### *Preparation of tablets*

Tablets were made by direct compression (Formulation I-XV, table 1). All the powders were passed through ASTM (American society of testing and materials) 40 mesh. Stavudine, half of starch 1500 and aerosil were blended for 5 minutes then blend was passed through 0.4 mm sieve. HPMC and remaining half of starch 1500 were mixed to the sieved blend and mixed for 5 minutes and then finally stearic acid was added and mixed for 5 minutes. Compression was done on Cadmach multistation automatic compression machine using 10.5 mm flat face punch. Each tablet contained 100 mg Stavudine and other pharmaceutical ingredients as listed in table. Prior to compression, the powder blends were evaluated for several tests.

#### *Evaluation of powder blend*

#### *Angle of repose*

The angle of repose was determined by the funnel method. The accurately weighed powder blend was 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 powder blend. The blends were allowed to flow freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [6].

$$\tan° = h/r$$

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

#### *Compressibility index*

To calculate the carr's compressibility both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerate 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 was calculated and used to calculate the carr's index and hausner's ratio.

The compressibility index of the powder blend was determined by carr's compressibility index [6].

Carr's index (%) = [(TBD-LBD) x 100]/TBD

**Table 1. Composition of various sustained release matrix formulations of stavudine**

| Ingredients (%w/w) | Sustained release matrix formulations of stavudine | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **F-I** | **F-II** | **F-III** | **F-IV** | **F-V** | **F-VI** | **F-VII** | **F-VIII** | **F-IX** | **F-X** | **F-XI** | **F-XII** | **F-XIII** | **F-XIV** | **F-XV** |
| Stavudine | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| HPMC K4MCR | 30 | 40 | 30 | 40 | 45 | 50 | 55 | 60 | - | - | - | - | - | - | - |
| HPMC K15MCR | - | - | - | - | - | - | - | - | 50 | 55 | 60 | 50 | 55 | 60 | 40 |
| Sodium CMC | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 10 |
| Starch 1500 | 43 | 38 | | | 33 | 28 | 23 | 18 | 28 | 23 | 18 | 28 | 23 | 18 | 28 |
| Avicel PH102 | - | - | 43 | 38 | - | - | - | - | - | - | - | - | - | - | - |
| Aerosol 200 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Stearic acid | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Hardness ($kg/cm^2$) | 7-8 | 7-8 | 7-8 | 7-8 | 7-8 | 7-8 | 7-8 | 7-8 | 7-8 | 7-8 | 7-8 | 11-12 | 11-12 | 11-12 | 11-12 |
| Tablet weight (mg) | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |

*HPMC is hydroxypropyl methylcellulose, Sodium CMC is sodium carboxymethylcellulose, Starch1500 is pregelatinised starch, Avicel PH101 is microcrystalline cellulose, and Aerosil 200 is colloidal silicon dioxide

***Hausner's ratio***

This value was calculated by making use of bulk and tap densities of powder samples.

Hausner's ratio = TBD/LBD

***Drug content***

An accurately weighed amount of powder blend (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane (Nunc, Delhi, India). The absorbance was measured at 266 nm after suitable dilution.

***Evaluation of tablets***

The thickness of the tablet was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used and average value were calculated.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 official method [7].To determine drug content, five tablets were weighed individually, and the drug was extracted in water. The drug content was determined by measuring absorbance at 266 nm.

The hardness and friability of 6 tablets of each formulation were determined using Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively.

***In vitro* release study**

The in vitro dissolution studies was carried out using USP apparatus type II (Tab-Machines, Mumbai, India) at 75 rpm. For the first 2 hr the dissolution medium was

0.1 N hydrochloric acid and phosphate buffer pH 7.4 from 3-24 hr (900 mL), maintained at $37^0$C±$0.5^0$C. At each time point 5 mL of sample was withdrawn and it was replaced with 5 mL of fresh medium. The drug release at different time interval was measured by UV-visible spectrophotometer (UV-1601PC, Shimadzu, Japan). It was made clear that none of the ingredient used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate (6 tablets in each set), and the mean values were plotted versus time.

**Table 2. Micromeritic properties of formulation blend.**

| Compostion | Angle of repose (°) | Carr's index (%) | Hausner ratio | Drug content |
|---|---|---|---|---|
| Stavudine | 40.12±0.138 | 18.55±0.058 | 1.700±0.012 | 99.85±0.185 |
| F-I | 24.24±0.126 | 13.21±0.046 | 1.437±0.012 | 99.25±0.101 |
| F-II | 24.18±0.116 | 12.64±0.076 | 1.263±0.025 | 98.52±0.124 |
| F-III | 23.98±0.128 | 12.10±0.056 | 1.227±0.058 | 99.10±0.298 |
| F-IV | 23.68±0.132 | 11.78±0.048 | 1.197±0.062 | 98.52±0.187 |
| F-V | 23.72±0.116 | 11.12±0.072 | 1.182±0.045 | 98.65±0.210 |
| F-VI | 23.45±0.127 | 10.88±0.056 | 1.167±0.035 | 97.85±0.234 |
| F-VII | 23.26±0.119 | 10.48±0.062 | 1.128±0.034 | 98.74±0.318 |
| F-VIII | 22.82±0.124 | 10.86±0.068 | 1.152±0.065 | 98.83±0.242 |
| F-IX | 23.68±0.118 | 11.24±0.058 | 1.144±0.023 | 98.09±0.364 |
| F-X | 23.46±0.124 | 11.36±0.066 | 1.143±0.032 | 98.86±0.235 |
| F-XI | 22.48±0.114 | 12.11±0.064 | 1.137±0.012 | 98.23±0.259 |
| F-XII | 23.68±0.118 | 11.88±0.052 | 1.133±0.020 | 97.76±0.129 |
| F-XIII | 23.46±0.124 | 11.64±0.054 | 1.152±0.032 | 98.92±0.103 |
| F-IV | 22.48±0.114 | 11.24±0.048 | 1.148±0.018 | 97.85±0.205 |
| F-XV | 23.38±0.126 | 12.12±0.060 | 1.293±0.052 | 98.78±0.264 |

*All values are expressed as Mean±SD, n=3.

### *Calculation of theoretical release profile*

Dose of Stavudine were calculated on the basis of pharmacokinetic parameters [8] as follows:

Dose of immediate release part= $Css.V_d/F$

where Css = steady state plasma concentration (228ng/mL), $V_d$ = volume of distribution (35 Litre, for 70 kg human), F= bioavilability (83%).

Dose of immediate release part= 228x35x100/83 = 9.614mg.

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

Rate of elimination = Ke.Cd.Vd= 0.4150x0.228x35 =3.3117 mg/h.

where; Ke = elimination rate constant ($0.693/t_{1/2}$), Cd = desired drug level in the body, Vd = volume of distribution. Bioavailability of Stavudine is 83% so amount required to release from dosage form to maintain the steady state of drug in plasma is 3.3117x100/83 = 3.99 mg. Hence, the formulation should release 9.614 mg in 1 hr and 3.99 mg per hr up to 24 hr.

## Results and discussion

### *Drug- excipient interaction studies*

The supplied drug passed the various tests of identification and analysis as per the certificate of analysis given by the supplier. FTIR spectra of pure Stavudine and solid admixtures of Stavudine with various excipients used in the preparation of matrix tablet formulations are shown in Figure 1.

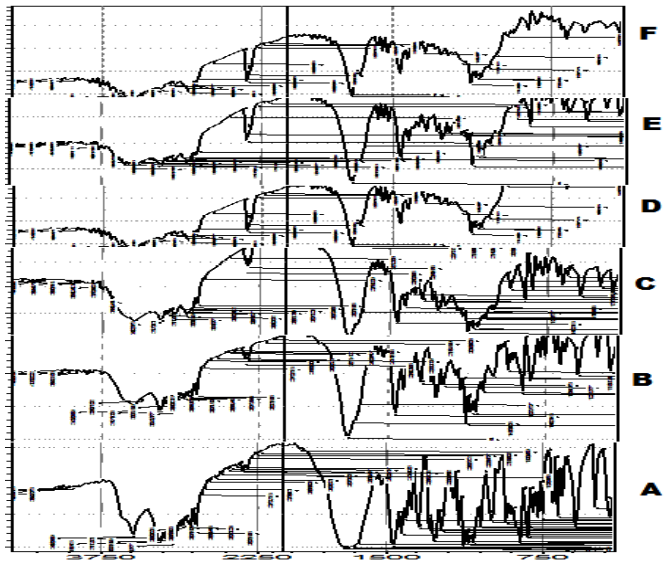


**Figure 1. IR spectra of Stavudine and Stavudine-excipient mixtures. Stavudine (A), stavudine + HPMC K4M (B), stavudine + HPMC K15 M (C), stavudine + starch 1500 (D), stavudine + avicel PH101 (E), stavudine + sodium CMC (F).**

**Table 3. Physical characteristics of designed matrix tablets of stavudine.**

| Formulations | Thickness* (mm) | Hardness† ($kg/cm^2$) | Friability†* (%) | Weight variation‡ (%) | Drug content* (%) |
|---|---|---|---|---|---|
| F-1 | 4.86±0.023 | 7.2±0.080 | 0.65±0.062 | 2.10±0.056 | 98.85±0.185 |
| F-II | 4.85±0.045 | 7.1±0.088 | 0.64±0.092 | 3.12±0.059 | 98.25±0.101 |
| F-III | 4.80±0.036 | 7.2±0.095 | 0.65±0.035 | 3.02±0.135 | 98.52±0.124 |
| F-IV | 4.90±0.024 | 7.4±0.082 | 0.62±0.039 | 3.12±0.162 | 99.10±0.298 |
| F-V | 4.85±0.021 | 7.6±0.120 | 0.68±0.051 | 2.45±0.052 | 98.52±0.187 |
| F-VI | 4.90±0.080 | 7.3±0.103 | 0.61±0.039 | 3.25±0.067 | 98.65±0.210 |
| F-VII | 4.85±0.075 | 7.6±0.053 | 0.60±0.012 | 3.46±0.210 | 98.25±0.234 |
| F-VIII | 4.88±0.086 | 6.9±0.075 | 0.65±0.091 | 3.71±0.920 | 98.24±0.318 |
| F-IX | 4.95±0.069 | 7.2±0.085 | 0.65±0.078 | 2.98±0.350 | 101.2±0.242 |
| F-X | 4.75±0.063 | 7.0±0.064 | 0.50±0.089 | 3.12±0.602 | 98.09±0.364 |
| F-XI | 4.85±0.058 | 6.9±0.124 | 0.55±0.060 | 2.95±0.813 | 98.86±0.235 |
| F-XII | 4.55±0.049 | 10.2±0.161 | 0.53±0.090 | 2.65±0.510 | 98.23±0.259 |
| F-XIII | 4.60±0.064 | 10.4±0.091 | 0.58±0.039 | 3.62±0.235 | 98.76±0.129 |
| F-XIV | 4.50±0.062 | 10.4±0.082 | 0.54±0.023 | 3.05±0.263 | 98.92±0.103 |
| F-XV | 4.50±0.081 | 10.3±0.073 | 0.44±0.071 | 2.91±0.512 | 98.85±0.205 |

All values are expressed as Mean± SD; * n=5; †n=10; †*n=20; ‡n=20.

The characteristic peak of the carbonyl group (present in the cytidine nucleus) at 1691 $cm^{-1}$; a band of peaks at 3425 $cm^{-1}$ owing to amino groups; and peaks at 1286 and 1161 $cm^{-1}$ owing to asymmetrical and symmetrical stretching of the C-O-C system (present in the oxathiolane ring), respectively, in all the spectrum, indicate the stable nature of Stavudine in the solid admixtures of the drug with various excipients. This finding was further supported by DSC studies.

***Evaluation of powder blend***

The results of micromeritic properties of the drug and the composition of formulations are presented in Table 2. The method employed for compression in this study was direct compression for which the powder blend should possess good flow and compacting properties. Plain Stavudine exhibited angle of repose value of $40.12±0.138^0$ indicating extremely poor flow property. The DSC thermogram of pure Stavudine showed a sharp melting endotherm at $168^0$C with a normalized energy of 103.9 J/g, as shown in Figure 2. The thermograms of solid admixtures of Stavudine with various excipients also showed a similar peak at $168^0$C with almost the same normalized energy, indicating that Stavudine is unaffected in the presence of various excipients used in the preparation of matrix tablet formulations.

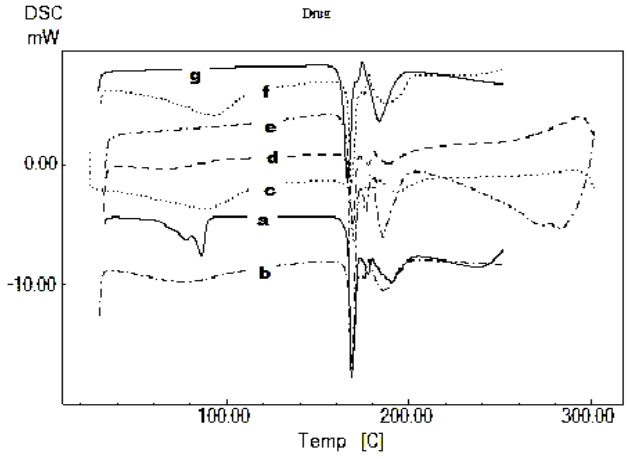


**Figure 2. Differential scanning calorimetry (DSC) thermograms of pure Stavudine (a) and its solid admixture with hydroxypropyl methylcellulose (HPMC) 4000 cps (b), HPMC 15 000 cps (c), starch 1500 (d), sodium-CMC (e), aerosil (f), and stearic acid (g), at a heating rate of $10^0$C/min using nitrogen environment.**

It was further supported by higher Carr's index value of 18.55±0.058% and Hausner's ratio of 1.700±0.012. Prepared powder blend have shown a significant increase in the flow properties as indicated by reduction in the values of angle of repose[8] (<30), Carr's index[9] (<15 %) and Hausner's ratio (<1.5). The final micromeritic values of powder blend make it suitable for direct compression.

### *Evaluation of tablets*

The physical appearance, tablet hardness, friability, weight variation, and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in table 3. Tablet hardness was found to be good (6.9±0.124 to 10.4 ± 0.091 kg/cm$^2$) depending on the compression force applied. In the present study, the percentage friability for all the formulations was found below 1% indicating that friability (%) is within the acceptable limits[9]. In a weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of more than 250 mg is ±5%. The average percentage deviation of all tablet formulations was found to be within above limit, and hence all formulations passed the test for uniformity of weight as per official requirement. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 98 %, which indicates that by direct compression we can get a good quality of stavudine matrix tablets.

### *In vitro release study*

The in vitro drug release characteristics were studied in simulated gastric and intestinal fluids for a period of 24 hr using USP XXIII dissolution apparatus 2. The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in a predetermined manner [10]. According to the theoretical release pattern, a once-daily Stavudine sustained-release formulation should release 9.614 mg in 1 hr and 3.99 mg per hr up to 24 hr. The results of dissolution studies indicated that F-I, F-II, F-III, F-IV and F-IV released 18.62, 17.64, 23.15, 23.07 and 17.13% of Stavudine at the end of 1 hr; and 76.83, 72.84, 79.38, 76.86 and 70.16 at the end of 12 hr respectively (Figure 3).

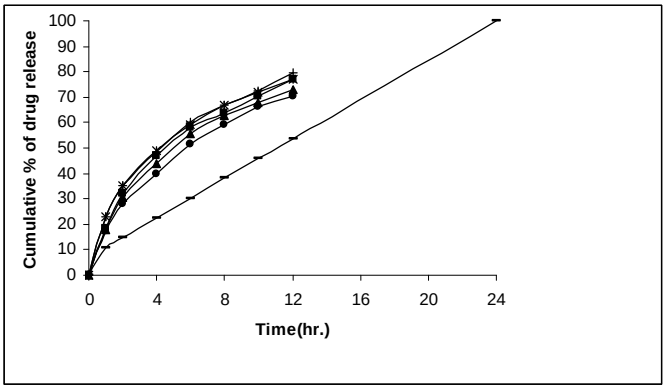


**Figure 3. The In vitro release profiles of Stavudine from F-I, FII, F-III, F-IV and F-V formulations. n=3.Theoretical (—), F-I (—■—), F-II ( —▲— ), F-III (—+—),F-IV (—✳—) and F-IV(' —●—).**

Among these formulations, F-I and F-II contain pregelatinized starch as filler and F-III and F-IV contain microcrystalline cellulose as filler. Drug: polymer ratio in F-I and F-III (1:1.5) and F-II and F-IV (1:2).

**Table 4. Kinetic values obtained from different plots of formulations, F-I to F-Xv.**

| Formulations | First Order Plots * | Higuchi's Plot † | Korsmeyer et al's Plot‡ | |
|---|---|---|---|---|
| | Regression coefficient I | Regression coefficient I | Slope (n) | Regression coefficient I |
| F-I | 0.9858 | 0.9945 | 0.5535 | 0.9837 |
| F-II | 0.9859 | 0.9944 | 0.5581 | 0.9865 |
| F-III | 0.9851 | 0.9963 | 0.4881 | 0.9944 |
| F-IV | 0.9787 | 0.9942 | 0.4813 | 0.9925 |
| F-V | 0.9872 | 0.9963 | 0.5671 | 0.9943 |
| F-VI | 0.9772 | 0.9955 | 0.5536 | 0.9967 |
| F-VII | 0.9796 | 0.9949 | 0.5566 | 0.9963 |
| F-VIII | 0.9753 | 0.9943 | 0.5484 | 0.9971 |
| F-IX | 0.9921 | 0.9804 | 0.6256 | 0.9939 |
| F-X | 0.8955 | 0.9785 | 0.6276 | 0.9924 |
| F-XI | 0.9085 | 0.9787 | 0.6273 | 0.9927 |
| F-XII | 0.9228 | 0.9741 | 0.6113 | 0.9934 |
| F-XIII | 0.9541 | 0.9810 | 0.6067 | 0.9952 |
| F-XIV | 0.9639 | 0.9878 | 0.5955 | 0.9954 |
| F-XV | 0.9019 | 0.9728 | 0.6572 | 0.9913 |

*First order equation, Log C = log C – Kt/2.303. † Higuchi's equation, Q = $Kt^{1/2}$. ‡ Korsmeyer et al's equation, Mt/Ma = $Kt^n$

The release results showed that pregelatinized starch is better release retarding than microcrystalline cellulose.

Release of Stavudine at the end of 1 hr and at the end of 12 hr in all the five formulations was more than the theoretical. Further optimization of release was done by taking higher concentration of HPMC and pregelatinized starch was taken as filler for further formulation development. As the release rate of first five formulations in first 12 hr was high, proportion of HPMC was increased to decrease the release rate [11] have reported that by increasing the concentration of HPMC the release rate of drug decreases. This was because an increase in polymer concentration caused an increase in the viscosity of the gel (by making it more resistant to drug diffusion and erosion) as well as the formation of a gel layer with a longer diffusional path.Formulations F-VI, F-VII and F-VIII contain drug : polymer ratio 1:2.5, 1:2.75 and 1:3 respectively while the tablet was kept constant at 500 mg. The results of dissolution studies showed that F-VI, F-VII and F-VIII released 16.12, 15.88 and 16.28 % of Stavudine at the end of 1 hr and 64.12, 63.02 and 62.06 % of Stavudine at the end of 12 hr; and 98.88, 98.1 and 97.68 % of Stavudine at the end of 24 hr (Figure 4). When the profile was compared with theoretical release profile the release was found to be more at each time point. Hence, initial burst release and high deviation 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.

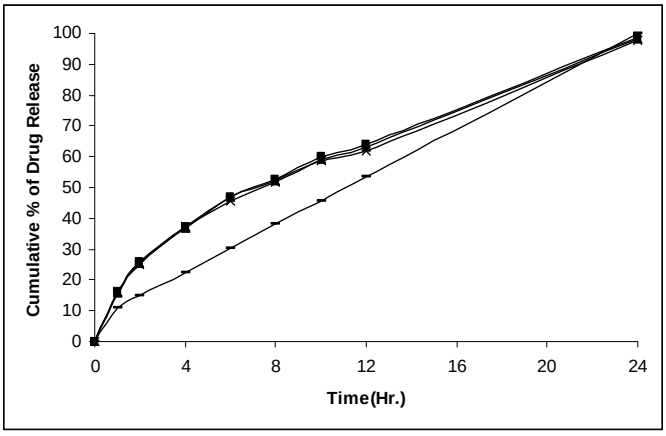


**Figure 4. The in vitro release profiles of Stavudine from F-VI, F-VII, and F-VIII formulations. n=3. Theoretical (—), F-VI (—■—), F-VII( —▲— ),F-VII (—✳—).**

In the further formulation development process, HPMC K15M CR instead of K4M CR grade in the ratio 2.5, 2.75 and 3.0 with drug was taken for formulations F-IX, F-X and F-XI respectively. The higher viscosity grade was chosen to decrease the release rate because the diffusion co-efficient is inversely proportional to viscosity. The tablets were compressed at hardness of 7 kg/cm$^2$ (with similar hardness as previous eight formulations). The result of dissolution studies showed that F-IX, F-X and F-XI released 14.76, 14.09 and 14.02 % of Stavudine at the end of 1 hr and 63.24, 61.85 and 60.49 % of Stavudine at the end of 12 hr; and 98.22, 98.24 and 97.49 % of stavudine at the end of 24 hr (Figure 5).

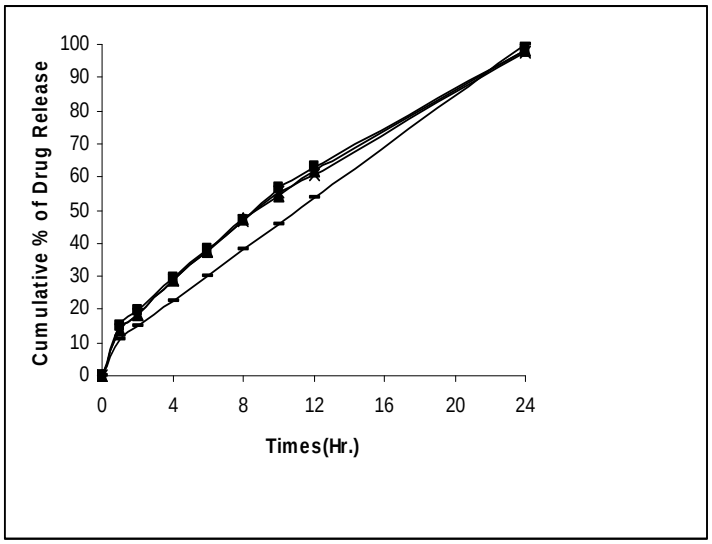


**Figure 5. The in vitro release profiles of Stavudine from F-IX, F-X, and F-XI formulations. n=3. Theoretical (—), F-IX (—■—), F-X ( —▲— ) and F-XI (—✳—).**

In these formulations the release rate decreased but the burst effect continued and was more than the desired theoretical release. Hence the formulation had to be developed further to minimize the burst effect. To control the burst effect and release rate, further formulations (F-XII, F-XIII and F-XIV) were prepared with same composition of polymer as (F-IX, F-X and F-XI) but the tablet hardness was increased from 7-8 kg/cm$^2$ to 10-11 kg/cm$^2$. The results of dissolution studies showed that F-XII, F-XIII and F-XIV released 13.68, 13.62 and 13.64 % of Stavudine at the end of 1 hr; 56.16, 56.08 and 55.68 at the end of 12 hr; 94.89, 91.84 and 89.74 at the end of 24 hr (Figure 6). The results indicated that by increasing the hardness the burst effect decreases but not significantly as supported

by previous studies [13,14]. The release rate decreased which resulted into less release at the end of 24 hr. F-XII released 94.89 % of Stavudine at the end of 24 hr and its release profile was similar to the theoretical profile but it showed a burst effect in 1st hr. Hence formulation F-XII was chosen for further development.

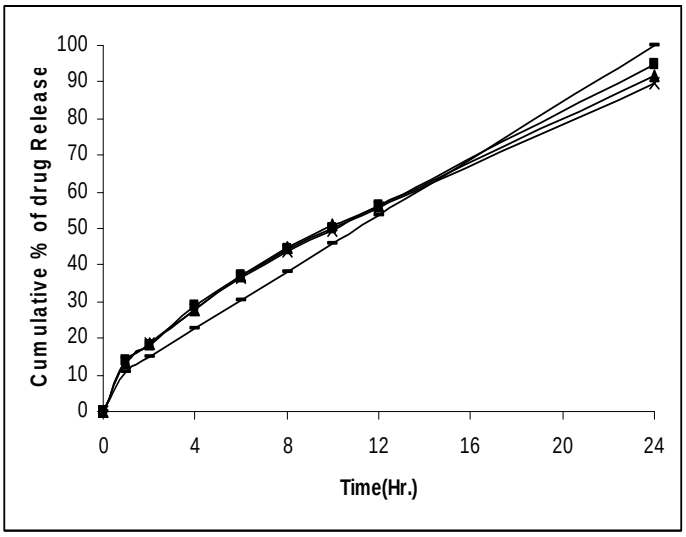


**Figure 6. The in vitro release profiles of Stavudine from F-XII, F-XIII, and F-XIV formulations. n=3. Theoretical (—), F-XII (—■—), F-XIII ( —▲— ) and F-XIV(—✳—).**

The burst effect of formulation F-XII was reduced by adding a polymer that hydrated quickly. As reported addition of Na-CMC with HPMC minimizes the initial release of soluble drug during initial phase of release profile [11,12]. So in F-XII 10%wt/wt of Na-CMC was added and F-XV was compressed with Drug:HPMC:Na-CMC (1:2:0.5). The tablets were compressed with hardness value of 10-11 Kg/cm$^2$. The result of dissolution studies showed that the burst effect was decreased (10.98%) and the release profile was similar to the desired theoretical pattern (Figure 7). To know the mechanism of drug release from these formulations, the data was treated according to first-order (log cumulative percentage of drug remaining versus time), Higuchi's (cumulative percentage of drug released vs square root of time), and Korsmeyer et al's [15, 16] log cumulative percentage of drug released versus log time) equations along with zero order (cumulative amount of drug released versus time) pattern.

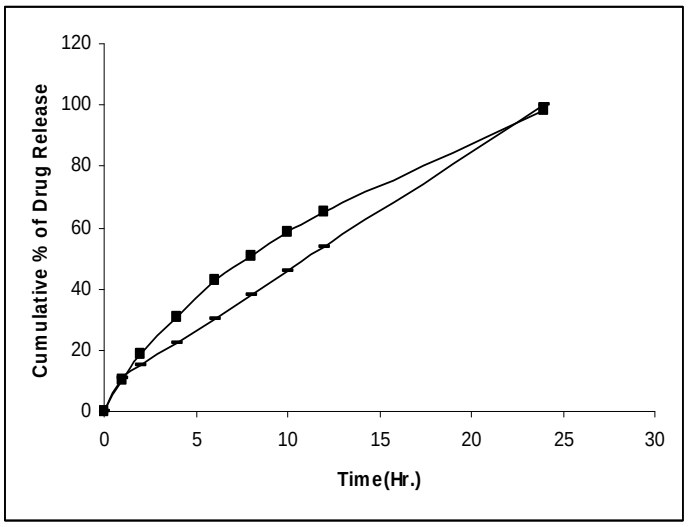


**Figure 7. The in vitro release profiles of Stavudine from F-XV formulation. Theoretical (—), F-XV (—■—). n=3.**

As clearly indicated in Figure 1, the formulation F-I to F-V did not follow a zero order release pattern. The release rate kinetics data for all the other equation can be seen in table 4. When the data was plotted according to the first-order equation, the formulation showed a fair linearity. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the in vitro study fluid depending on the concentration. As gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square-root kinetics or Higuchi's kinetics [15]. In our experiments, the in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity ($R^2$: 0.9728 to 0.9963). To confirm the diffusion mechanism, the data were fit into Korsmeyer et al's [16] equation. The formulations F-I to F-XV showed good linearity ($R^2$: 0.9837 to 0.9971), with slope (*n*) values ranging from 0.4813 to 0.6572, indicating that diffusion is the dominant mechanism of drug release with these formulations.

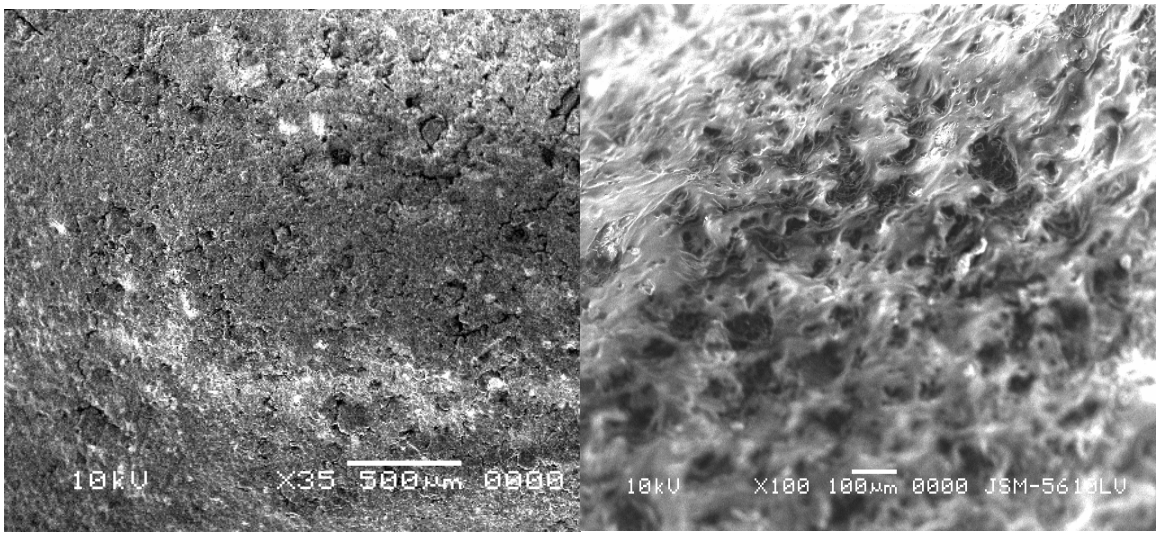


**Figure 8. SEM photomicrographs of optimized matrix tablet (Formulation XV) showing surface morphology after 0 hours (A, 35X), and 24 hours (B, 100X) of dissolution study. (Arrow indicates the formation of pores on matrix surface).**

When plotted according to Korsmeyer et al's equation, formulation F-XV also showed high linearity ($R^2$: 0.9913), with a comparatively high slope (*n*) value of 0.6572. This *n* value, however, appears to indicate a coupling of diffusion and erosion mechanisms so-called anomalous diffusion. The relative complexity of this formulation and its components may indicate that the drug release is controlled by more than one process. Similar results were observed by Fassihi and Ritschel with matrix tablets of theophylline containing EC; they considered the *n* value of about 0.7 to be indicative of an anomalous release mechanism [17]. Hence, diffusion coupled with erosion may be the mechanism for the drug release from F-XV. Further the SEM of tablet indicates the formation of pores and sign of erosion which support the finding of release mechanism.

## Conclusions

Sustained release matrix tablets of Stavudine were prepared by direct compression. Drug content was found to be uniform with all the formulations. Formulations containing HPMC, Starch 1500 did not show satisfactory release due to burst effect. The formulation containing Stavudine:HPMC (K15):NaCMC (1:2:0.5) with hardness 10-11kg/cm2 showed the desired release profile with reduced burst effect. SEM studies of the formulation revealed that the formation of both pores and gelling structure on tablet surface. Drug release was found to follow anomalous diffusion. In conclusion the present study demonstrated the successful preparation of stable once daily extended release matrix tablet of Stavudine.

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