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Research Article

# Formulation and *In-Vitro* Release Kinetic Study of Stavudine from Sustained Release Matrix Tablet Containing Hydrophilic and Hydrophobic Polymers

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**ABSTRACT**

The HIV epidemic has reached an important threshold in India. India has the World's second largest burden of HIV-infected persons. The objective of the present study was to formulate and evaluate once-daily sustained release matrix tablets of Stavudine using hydrophilic hydroxypropyl methylcellulose alone, combination of two different viscosity grades of hydroxypropyl methylcellulose and combination of hydroxypropyl methylcellulose with ethyl cellulose. Stavudine (Antiviral agent) has a short half life 1.22 h and usual oral dosage regimen 30mg and 40 mg twice daily. The most commonly used method of modulating the drug release is to include it in a matrix system. The viscosity of hydroxypropyl methylcellulose polymer influences the erosion rate of matrix tablet. The rate of tablet erosion can be adjusted by the choice of hydroxypropyl methylcellulose polymer viscosity or by mixing hydroxypropyl methylcellulose polymer of varying viscosities. The drug release for extended duration using a hydrophilic matrix system is restricted because of rapid diffusion of dissolved drug through the hydrophilic gel network. For such circumstances, hydrophobic polymers are suitable, along with a hydrophilic matrix for developing sustained release dosage forms. Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications. Therefore, in this study, the hydrophilic polymer (hydroxypropyl methylcellulose) was used as matrix material and hydrophobic polymer (ethyl cellulose) was used to extend the drug release. The results of invitro dissolution study shown that the formulation F8 (HPMC K15M: Ethyl cellulose, 1:1) exhibited satisfactory drug release pattern and total drug release pattern was very close to theoretical release profile. The mechanism of the drug release from sustained release matrix tablet of formulation F8 was fickanian diffusion.



## INTRODUCTION

India has the World's second largest burden of HIV-infected persons. One of every six new HIV infections occurs in India. Two Indians become HIV-infected every minute and HIV is expected to exacerbate a number of other important public health problems in India. At least 500,000 Indians have already died of HIV-associated illnesses and most of these deaths have occurred in the past 5 yrs. Thus, India has responsibility to take important steps to reduce the number of new HIV infections and limit the public impact of this epidemic [1, 2].

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The term Sustained release is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent [3, 4]. Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained-release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products. [5, 6] HIV is the virus that causes AIDS is also known as human immuno deficiency virus (Fig-1) [7].

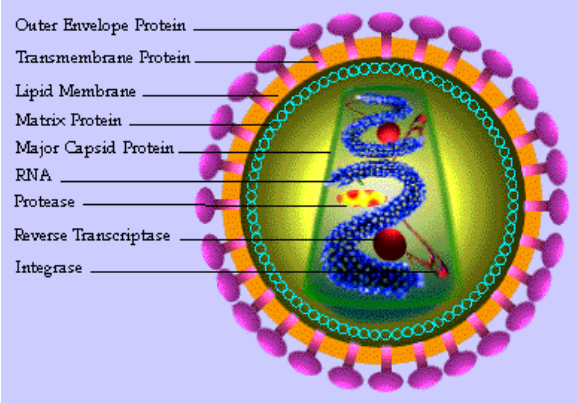


**Figure 1: HIV Virus**

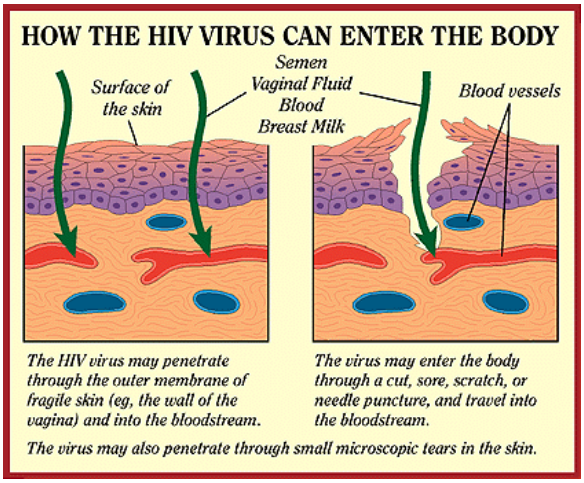


**Figure 2: Entry of HIV in the body**

According to World Health Organisation some of the major signs of HIV are weight loss greater than 10% of body weight, Fever for longer than one month, intermittent or continuous and chronic diarrhoea for longer than one month. Some of the Minor Signs include Persistent cough for longer than one month, General itchy dermatitis (skin irritation), recurrent herpes zoster (shingles).Oropharyngeal candidasis (fungus infection in the mouth/throat).

The battle between the virus and the CD4 cells continues even as the infected person remains symptom-free. But after a few years, which can last up to a decade or even more, when the number of the virus in the body rises to very high levels, the body's immune mechanism finds it difficult to carry on with the battle. Opportunistic infections are caused by bacteria, virus, fungi and parasites. Some of the common opportunistic infections that affect HIV positive persons are: HIV positive persons are also prone to cancers like Kaposi's sarcoma and lymphoma [8]. Till today, there is no conclusive treatment to eliminate HIV from the body; however, timely treatment of opportunistic infections can keep one healthy for many years. The commonly available treatment for AIDS is the treatment against opportunistic infections [8].

However, during the last decade, researchers have developed powerful drugs that check the replication of the virus at various levels. However, they do not permanently cure one of HIV. This line of treatment, called HAART (Highly Active Antiretroviral Therapy) has resulted in a huge reduction or AIDS-related deaths. Though many positive persons and caregivers have welcomed these drugs, others have experienced serious side effects. They are also very expensive and are out of reach for a majority of the infected people. But of late, the prices have been steeply falling. Stavudine is nucleoside analogue Reverse Transcriptase Inhibitors (NRTIs). NRTIs were the first antiretroviral drugs to be developed. They inhibit the replication of HIV in the early stage by inhibiting an enzyme (which is necessary for viral replication) called Reverse Transcriptase [7].

## MATERIALS AND METHODS

HPMC K4M, HPMC K15M, Ethyl Cellulose obtained from Colorcon Asia and Signed polymer limited, Mumbai. The active drug Stavudine obtained from Aurobindo Pharma Ltd. other ingredients used was of analytical grade and obtained from cipla Pharmaceuticals Limited, mumbai.

### Preformulation

Prior to development of any dosage form, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined [10, 11].

### Drug-excipients interaction study

Infra red spectrophotometry is a useful analytical technique utilized to check the chemical interaction between the drug and the other excipients used in the formulations. The samples were powdered and intimately mixed with dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler and the spectra recorded by scanning in the wavelength region of 2.5 to 25 μ in a FTIR spectrophotometer (Jasco 460 plus, Japan). The IR spectrum of drug was compare with that of the physical mixture to check for any possible drug-excipents interaction [11].

### Preparation of stavudine matrix tablets by using two different HPMC grade polymers alone and in combination

With different polymer concentrations matrix tablets of stavudine were prepared by direct compression technique. Microcrystalline Cellulose was used as directly compressible vehicle. magnesium stearate was used as lubricant. stavudine matrix tablets containing 20% (F1), 35% (F2) and 50% (F3) of HPMC K4M, and HPMC K15M 20 %( F4), 35 %( F5), and F6 35 % (contains 23.33% of HPMC K4 and 11.67% of HPMC K15) were prepared the composition of different formulations in the study containing 100 mg of stavudine in each case is shown in (Table 1). All the ingredients were sieved through 40 mesh screen and mixed. After proper mixing, the powder mixture was compressed with a maximum force of compression using 8mm flat faced punches [7, 9].

**Table 1: Data indicating formulation variables for Stavudine matrix tablets**

| Ingredients Quantities (mg) | F1 (20%) | F2 (35%) | F3 (50%) | F4 (20%) | F5 (35%) | F6 (2:1)(35%) | F7 (1:0.5)(35%) | F8 (1:1)(35%) |
|---|---|---|---|---|---|---|---|---|
| Stavudine | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| HPMC K4M | 20 | 35 | 50 | - | - | 23.33 | - | - |
| HPMC K15M | - | - | - | 20 | 35 | 11.67 | 23.33 | 17.5 |
| Ethyl Cellulose | - | - | - | - | - | - | 11.67 | 17.5 |
| Avicel pH102 | 75 | 60 | 45 | 75 | 60 | 60 | 60 | 60 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Total wt.(mg) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

**Preparation of Stavudine matrix tablets with combination of hydrophilic and hydrophobic polymers**

Matrix tablets of stavudine were prepared by direct compression technique by using HPMC K15 and ethyl cellulose in combination of 1:0.5(F7) and 1:1(F8) shown in (Table 1). Microcrystalline cellulose was used as directly compressible vehicle [10, 13, 14, 15]. Magnesium stearate was used as lubricant. The composition of different formulations in the study, contain 100 mg of Stavudine in each case. All the ingredients were sieved through the 40 mesh screen and mixed. After proper mixing, the powder mixture was compressed with a maximum force of compression using 8mm flat faced punches [15, 16].

**Evaluation of prepared powder mixture and tablets**

The physical mixture of drug and excipients were evaluated for angle of repose, bulk density, tap density, Carr's index and Hausner's ratio. The tablets were evaluated for following characteristics such as uniformity of weight, thickness variation, hardness, friability, drug content [11, 18]. (Table 2)

***In vitro* Drug release Study**

Dissolution studies were performed using USP standard dissolution apparatus at 37±0.5°c using one tablet at a time in a vessel. The basket was immersed in 900 ml of dissolution medium and the paddle rotates at 100 rpm. The dissolution media used was 0.1 N HCl for the first 2 h and Phosphate Buffer pH 7.4 from 3 h to 24 h. The absorbance was measured in the UV –VIS spectrophometer at 266 nm [13, 18]. (Table 3)

**Scanning electron microscopy (SEM) of the optimized formulation**

The SEM analysis was conducted using Jeol, Japan (Model - JSM 5610LV) scanning electron microscope for the optimized formulation in the following states [9, 10], tablets after swelling of 2, 6, 12 and 16 h. As with SEM high vacuum is required for image formation and samples must be thoroughly desiccated before entering the vacuum chamber, therefore samples were thoroughly dried after swelling for analysis. The dried samples were mounted on sample holder using double sided adhesive carbon tape. The SEM was operated at 15 KV. The condenser lens position was maintained at a constant level [19].

**RESULT AND DISCUSSION**

The FTIR study was carried out to know the compatibility of the excipients with stavudine, the active constituent of the formulation. The FTIR spectrum of Stavudine (Fig. 3a) mixture of Stavudine with HPMC (K4 and K15) (Fig. 3b) and Stavudine with HPMC (K15) and Ethyl cellulose (Fig. 3c) are shown. The above study confirms that the drug and other excipients in the formulation are compatible with each other.

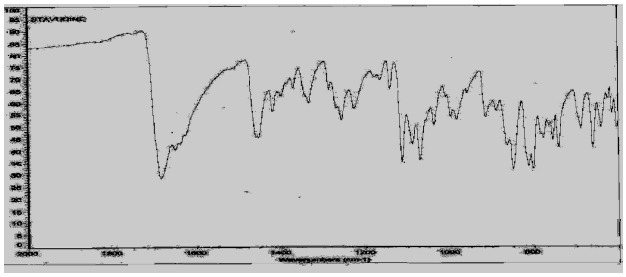

**Figure 3 (a): FTIR Spectra of Stavudine**

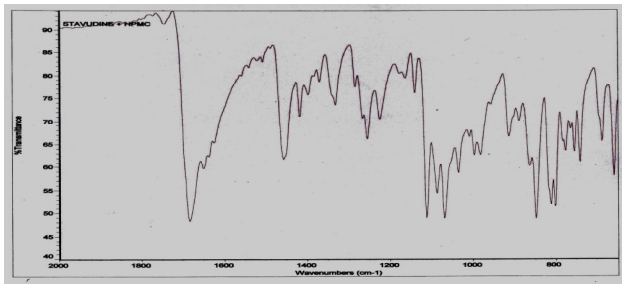


**Figure 3 (b): FTIR Spectra of Stavudine + HPMC K4M AND K15M**

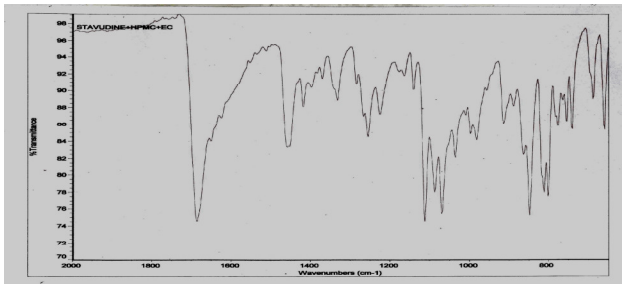


**Figure 3 (c): FTIR Spectra of Stavudine + HPMC K15 + EC**

**Table 2: Data indicating results of evaluation of Stavudine matrix tablets**

| Tablet Properties | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| Angle of repose* | 25°48′±1.06 | 26°58′±1.51 | 26°86′±1.51 | 25°81′±0.65 | 25°80′±0.34 | 23°33′±1.93 | 24°36′±2.43 | 24°63′±1.38 |
| Uniformity of weight*(mg) | 200.7±0.81 | 199.93±2.43 | 201.76±2.13 | 201.83±1.72 | 201.46±2.84 | 199.97±1.45 | 202.13±2.15 | 199.86±1.47 |
| Thickness variation**(mm) | 3.21±0.01 | 3.23±0.05 | 3.23±0.03 | 3.21±0.02 | 3.23±0.035 | 3.23±0.03 | 3.25±0.015 | 3.27±0.01 |
| Hardness**(kg/cm$^2$) | 5.9±0.74 | 5.2±0.9 | 6.6±0.41 | 5.6±1.08 | 5.9±0.65 | 6.2±0.9 | 6.4±0.41 | 6.0±0.61 |
| Friability*(%) | 0.433±0.12 | 0.500±0.17 | 0.466 ±0.15 | 0.400 ±0.10 | 0.500±0.30 | 0.600±0.20 | 0.266±0.12 | 0.500 ±0.17 |
| Bulk Density*(gm/ml) | 0.495±0.014 | 0.455±0.031 | 0.508±0.019 | 0.290±0.002 | 0.286±0.002 | 0.304±0.005 | 0.292±0.005 | 0.297±0.014 |
| Tapped Density*(gm/ml) | 0.571±0.16 | 0.528±0.42 | 0.6±0.027 | 0.344±0.006 | 0.331±0.003 | 0.350±0.006 | 0.346±0.009 | 0.344±0.01 |
| Carr's index*(%) | 12.59±0.294 | 13.7±0.99 | 15.23±0.56 | 15.49±0.86 | 13.89±0.9 | 13.3±0.9 | 15.99±1.05 | 13.36±1.087 |
| Hausner's ratio* | 1.06±0.16 | 1.15±0.015 | 1.18±0.01 | 1.18±0.01 | 1.15±0.01 | 1.15±0.011 | 1.18±0.015 | 1.16±0.026 |
| Drug content* (%) | 97.23±0.16 | 102.2±0.17 | 96.2±0.58 | 96.17±0.78 | 99.21±0.47 | 100.24±0.75 | 99.02±0.42 | 92.23±0.32 |

**Table 3: Percentage drug release of F1-F8 with standard deviation**

| Time (h) | $F_1$ Mean* %dissolution | $F_2$ Mean* %dissolution | $F_3$ Mean* %dissolution | $F_4$ Mean* %dissolution | $F_5$ Mean* %dissolution | $F_6$ Mean* %dissolution | $F_7$ Mean* %dissolution | $F_8$ Mean* %dissolution |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | 31.80 ± 0.13 | 23.06 ± 0.35 | 23.66 ± 0.13 | 18.46 ± 0.47 | 6.55 ± 0.35 | 4.44 ± 0.35 | 4.97 ± 0.47 | 9.49 ± 0.26 |
| 1 | 58.36 ±0.23 | 49.64 ± 0.47 | 38.57 ± 0.35 | 28.51 ± 0.13 | 9.53 ± 0.26 | 9.97 ± 0.13 | 8.24 ± 0.45 | 12.63 ± 0.26 |
| 2 | 69.92 ± 0.34 | 67.48 ± 0.47 | 52.5 ± 0.35 | 40.20 ± 0.35 | 13.12 ± 0.34 | 16.73 ± 0.47 | 14.39 ± 0.46 | 17.68 ± 0.34 |
| 4 | 83.02 ± 0.12 | 75.07 ± 0.24 | 57.83 ± 0.32 | 46.59 ± 0.12 | 17.37 ± 0.33 | 20.89 ± 0.21 | 18.42 ± 0.33 | 22.05 ± 0.21 |
| 6 | 97.17 ± 0.33 | 83.76 ± 0.32 | 65.31 ± 0.12 | 54.43 ± 0.21 | 22.49 ± 0.25 | 26.71 ± 0.12 | 23.67 ± 0.12 | 27.58 ± 0.12 |
| 8 | - | 95.4 ± 0.33 | 73.9 ± 0.32 | 62.81 ± 0.33 | 29.13 ± 0.44 | 33.84 ± 0.12 | 30.58 ± 0.22 | 34.42± 0.12 |
| 10 | - | - | 83.66± 0.21 | 72.58 ± 0.32 | 37.22 ± 0.32 | 41.86 ± 0.33 | 38.52 ± 0.11 | 42.57 ± 0.13 |
| 12 | - | - | 95.18 ± 0.21 | 84.53 ± 0.24 | 46.49 ± 0.32 | 51.55 ± 0.12 | 47.92 ± 0.25 | 51.90 ± 0.25 |
| 16 | - | - | - | 98.25 ± 0.33 | 57.80 ± 0.43 | 63.21 ± 0.12 | 60.00 ± 0.25 | 63.81 ± 0.12 |
| 20 | - | - | - | - | 72.00 ± 0.45 | 76.85 ± 1.05 | 74.95 ± 0.12 | 78.86 ± 0.11 |
| 24 | - | - | - | - | 89.97 ± 0.25 | 91.63 ± 0.12 | 92.36 ± 0.38 | 97.82± 0.22 |

*n=3

The matrix tablets were prepared by direct compression method using micro crystalline cellulose as directly compressible vehicle. The angle of repose of the powder mixture was found to have 23°33′ to 26°86′. The matrix tablets were compressed by applying maximum force of compression and the hardness of tablets was found to be in the range of 5.2 to 6.4kg/cm$^2$.

The flow property of the powder was excellent that was confirmed by the determination of angle of repose which indicates better uniformity of weight. Good hardness of the matrix tablets with less standard deviation indicated retardation in the release as observed in dissolution profile.

On performing the friability for all the formulations the % weight loss falls between the range 0.26% and 0.60% indicates that it falls within the limit showing good compressibility and non defective tabletting.

After performing *in-vitro* drug dissolution study, (Fig. 4) showed the effect of different concentrations of HPMC K4M 20%(F1), 35% (F2) and 50% wt/wt (F3) on release rate 97.17% ± 0.33, 95.40% ± 0.33 and 95.18% ± 0.21 within 6h, 8h and 12h of dissolution study, respectively of Stavudine.

By observing the dissolution data, it is clear that HPMC K4M retards the release of drug up to 12h in 50% w/w. So, to sustain the drug release for more hours other derivative of HPMC with higher viscosity is used (HPMC K15M).As observed, the release of F4 (HPMC K15M 20%) sustained the release of the drug up to 16 h (98.25 ± 0.33), which indicates that by increasing the concentration of HPMCK15M the drug release may be sustained.

The formulation F5 (35% w/w, HPMC K15M) showed the drug release 89.97% ± 0.25 for 24 h, so in order to minimize the retardation of drug release HPMCK4M is added, in formulation F6 (35%) {HPMC K4M: HPMC K15M (2:1)}, because it has less viscosity than HPMC K15M. The dissolution profile of F6 does not show any significant improvement in the drug release (91.63 ± 0.12) (Fig. 5).

Then in order to achieve better release hydrophobic polymer (Ethyl Cellulose) is used. Addition of ethyl cellulose with HPMC K15M in the ratio 0.5:1 in F7 does not added any significance in the drug release (92.36 ± 0.38).

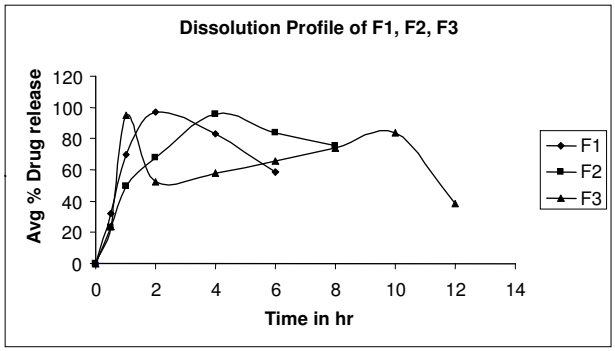


**Figure 4: Dissolution Profiles of F1, F2, F3**

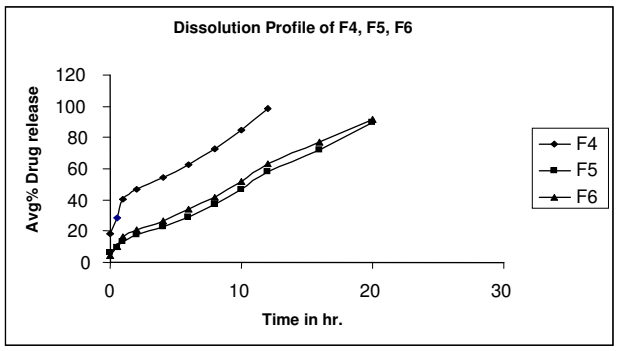


**Figure 5: Dissolution Profiles of F4, F5, F6**

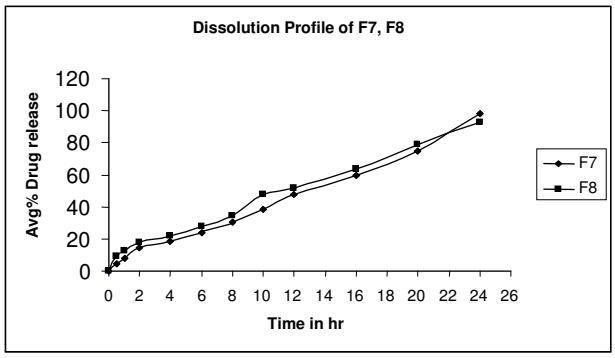


**Figure 6: Dissolution Profiles of F7, F8**

For formulation F8 {HPMC K15K: Ethyl Cellulose (1:1)} optimum release (97.82 ± 0.22%). Inclusion of ethyl cellulose in the matrix optimized the drug release for 24 h. This may be due to the less viscosity of formulation F8 as compared to F5 and more viscosity as compared to F6 and F7 (Fig. 6).

The formulation F8 best suited with first (Fig.7a) order releases kinetics (correlation coefficient =0.9583). The formulation F8 follows Huguchi model (Fig.7b) of drug release kinetic correlation coefficient (0.9961). The Koresmyer peppas (Fig.7c) drug release kinetics showed correlation coefficient (0.9895) and release exponent (n) 0.4497 which indicates that the drug release mechanism is fickanian diffusion. The Hixon-crowel (Fig. 7d) cube root law for F8 (correlation- coefficient 0.9898). The mechanism of the drug release from sustained release matrix tablet of formulation F8 was fickanian diffusion.

SEM study further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of matrix tablet (F8). SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact and pores had formed throughout the matrix (Fig. 8d).

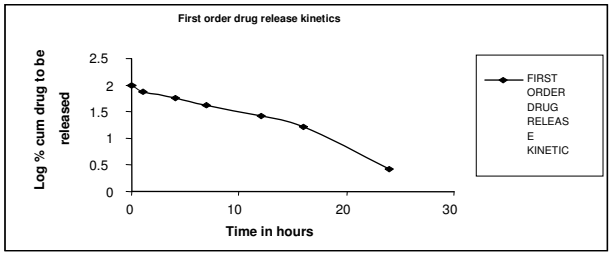


**Figure 7a: First order release kinetics of formulation F8**

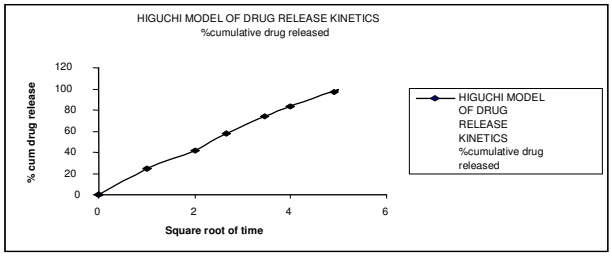


**Figure 7b: Higuchi release kinetics of formulation F8**

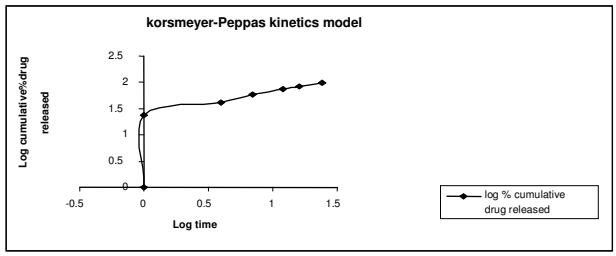


**Figure 7c: Korsmeyer -Peppas release kinetics of formulation F8**

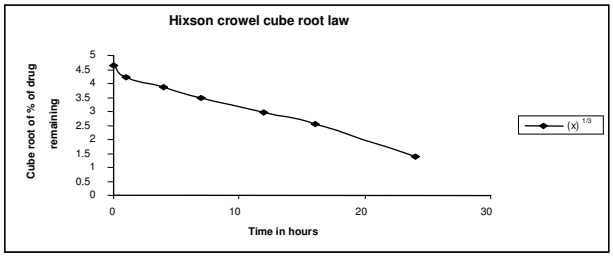


**Figure 7d: Hixon-Crowel (Release) cube root law of F8**

SEM photomicrographs of tablet surface at different time intervals also showed that erosion of matrix increased with respect to time indicated by the photomicrographs at 2, 6, 10 and 16 h revealing pores with increasing diameter. These photomicrographs also revealed formation of gelling structure indicating the possibility of swelling of polymer (Fig. 8a, 8b, 8c and 8d.)

Hence, the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of stavudine from formulated matrix tablets.

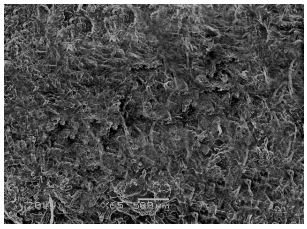

**Figure 8 (a): SEM (2 h)**

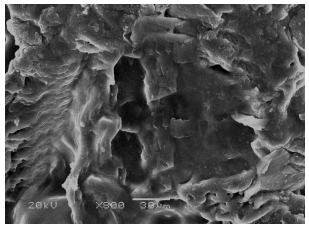

**Figure 8 (b): SEM (6 h)**

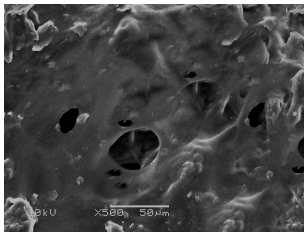

**Figure 8 (c): SEM (10 h)**

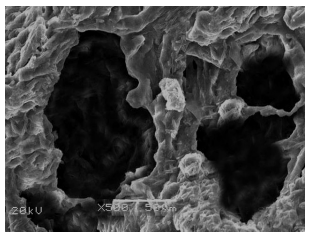

**Figure 8 (d): SEM (16 h)**

## CONCLUSION

The present study was carried out to develop sustained release matrix tablets of stavudine for safe and effective action. Matrix tablets with HPMC K4M were prepared and evaluated. The matrix tablets were failed to control the drug release for extended period of time. In another study matrix tablets are prepared by using derivative of HPMC of higher viscosity i.e.HPMCK15M and matrix combination of two hydrophilic polymers is also done in order to achieve the release of drug as per expectation. But, this approach also does not given the required drug release. Hence it was planned to control the drug release by using combination of hydrophilic and hydrophobic polymers. Matrix tablets with HPMC K15M and Ethyl Cellulose in 1:0.5 and 1:1 ratios (F7 and F8) were prepared and evaluated. The results showed that F8 formulation was able to sustain the drug release up to 24h. Hence the above study demonstrated that combination of hydrophilic and hydrophobic polymers in equal ratios could be successfully employed for formulating sustained release matrix tablets of Stavudine. This can be expected to reduce the frequency of administration and decrease the dose – dependent side effects associated with repeated administration of conventional Stavudine tablets. The sustained release matrix tablet was found to be beneficial in terms of reduction in frequency of administration.

Hence it can be concluded that once daily sustain release matrix tablet of stavudine having short half life, was found to exert a satisfactory sustained release profile which may provide an increased therapeutic efficacy.

## ACKNOWLEDGMENT

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