

Design and Characterization of Controlled Release Matrix Tablets of Stavudine

Ranjit Kumar P*, Suresh V Kulkarni, Vinod R, Sandeep HN, Someshwara Rao B, Ashok Kumar P

Department of Pharmaceutics, Sree Siddaganga College of Pharmacy, B. H. Road, Tumkur-572102, Karnataka India

ABSTRACT

The investigation was concerned with design and characterization of oral controlled release matrix tablets of Stavudine in order to improve efficacy and better patient compliance. Tablets were prepared by wet granulation method using various proportions of polymer HPMC K 100M alone or in combination with polymer Ethyl cellulose. The granules were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index, shows satisfactory results. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, thickness, friability, hardness and *In vitro* dissolution studies. All the formulation showed compliance with Pharmacopoeial standards. The *in vitro* drug release study revealed that Eudragit preparation was able to sustain the drug release for about 9 hours (98.54 % release), but the Combination of HPMC K 100M with Ethyl cellulose sustained the drug release for 12 hours (75.32 % - 98.12 % release). The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and Zero-order to evaluate the kinetics and mechanism of the drug release was found to be diffusion coupled with erosion.

Keywords: Controlled release, Ethyl cellulose, HPMC K 100M, Matrix tablets, Stavudine.

INTRODUCTION

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy, for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. [1] Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs. [2]

AIDS is considered to be an epidemic, and according to estimates from the Joint United Nations Programmed on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) AIDS Epidemic Update 2005, 38 million adults and 2.3 million children were living with the human immunodeficiency virus (HIV) at the end of 2005. The annual number of AIDS deaths can be expected to increase for many years to come, unless more effective and patient-compliant antiretroviral medications are available at affordable prices. [3]

The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance, and their huge cost. [4-5]

Stavudine is a thymidine analogue reverse transcriptase inhibitor that is active *in vitro* against HIV-1 and HIV-2. [6] Stavudine is absorbed rapidly following oral administration producing peak plasma concentration within 1 hour with 86 % bioavailability. Elimination half life is 1 to 1.5 hours following single or multiple dose. [7] Sustained release delivery systems for oral dosing are effective in achieving optimal therapy with drugs that have a narrow therapeutic range of blood concentration which eliminate rapidly. [8]

Matrix based CR tablet formulations are the most popular and easy to formulate on a commercial scale in an industry. The matrix tablets can be prepared via wet granulation or by direct compression. [9] Different polymers have been used in the formulation of matrix based CR drug delivery systems. Reports are found on the use of hydrophilic polymers like Hydroxyl propyl methylcellulose (HPMC), Methylcellulose, Sodium carboxy methyl cellulose, [10] Carbopol [11] and Polyvinyl alcohol [12] for the preparation of CR formulations of different drug. Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. [13] The hydrophilic polymers selected for the present study were HPMC K 100M. It provides pH-independent drug release to oral dosage forms that can be

*Corresponding author: Mr. Ranjit Kumar P,
Department of Pharmaceutics, Department of Pharmaceutics,
Sree Siddaganga College of Pharmacy, B. H. Road, Tumkur-
572102, Karnataka India; Tel: +91-09886107025,
E-mail: Deptofceutics@gmail.com

used for formulating the sustained-release dosage forms. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymers in the matrix system.^[14] Hence in the present work, an attempt has been made to formulate the controlled release matrix tablets of Stavudine and tested for controlled delivery of drug using hydrophilic matrix material (HPMC K 100M) alone or in combination with hydrophobic Ethyl cellulose.

MATERIALS AND METHODS

Stavudine was obtained as a gift sample from (Strides Arcolab, Bangalore). Ethyl cellulose was procured from (S.D. Fine Chemicals, Mumbai). HPMC K 100M was obtained as a gift sample from Dr Reddy's Lab (Hyderabad, India), Micro Crystalline Cellulose and Mg. Stearate from LobaChem (Mumbai, India). All other chemicals and ingredients were used for study are of Analytical grade.

Preparation of matrix tablets

Tablet formulations were prepared by wet granulation method. A non-aqueous granulation process was adopted to prepare Stavudine tablets. Granules were prepared as follows. Proportion of excipients with drug was as given in Table 1. All ingredients were sifted through # 40. HPMC K 100M and Ethyl cellulose were mixed with Stavudine manually and the obtained blend were mixed with Micro crystalline cellulose to form final blend. PVP K 30 was dissolved in PVA (5 % w/v) and used for wet granulation of the final blend. The wet mass was passed through sieve no. 20 and wet granules were dried at 50°C in an oven for 30 minutes. Dried granules were sized by passing it through # 40 and mixed with magnesium stearate and talc for 1 min. Tablets was compressed using Rotary tablet machine with 10 mm standard concave punch. Tablet weight was (300 mg) kept constant as shown in Table 1.

Table 1: Composition of different formulations

| Ingredients (mg/tablet) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|-----------------------------|-----|----|----|----|----|----|----|----|-----|
| Stavudine | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 |
| Ethyl Cellulose | 120 | 90 | 84 | 72 | 60 | 48 | 36 | 30 | --- |
| HPMC K 100M | --- | 30 | 36 | 48 | 60 | 72 | 84 | 90 | 120 |
| PVP K 30 (5%) | 06 | 06 | 06 | 06 | 06 | 06 | 06 | 06 | 06 |
| Micro crystalline cellulose | 88 | 88 | 88 | 88 | 88 | 88 | 88 | 88 | 88 |
| Magnesium Stearate | 03 | 03 | 03 | 03 | 03 | 03 | 03 | 03 | 03 |
| Talc | 03 | 03 | 03 | 03 | 03 | 03 | 03 | 03 | 03 |

Evaluation of granules

The angle of repose was measured by using funnel method^[15] which indicates the flow ability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD)^[16] were measured using the formula: LBD= weight of the powder / volume of the packing. TBD= weight of the powder / tapped volume of the packing. Compressibility index^[17] of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] × 100. The physical properties of granules were shown in Table 2.

Evaluation of tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods^[18] shown in Table 4.

Drug content

Five tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100 mg) was extracted with pH 7.4 buffer and the solution was filtered through 0.45 µ membranes. The absorbance was measured at 266 nm after suitable dilution.

In vitro drug release studies

In vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of pH 7.4 phosphate buffer, maintained at 37± 0.5°C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 266 nm. The study was performed in triplicate.

Characterization of Release Kinetics

Drug release kinetics

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug release vs time, first order (Equation 2) as log cumulative percentage of drug remaining vs time, and Higuchi's model (Equation 3) as cumulative percentage of drug released vs square root of time.

$$C = K_0 t \dots \dots \dots (1)$$

Where K_0 is the zero order rate constant expressed in units of concentration / time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.^[19]

$$\log C = \log C_0 - Kt/2.303 \dots \dots \dots (2)$$

Where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.^[20]

$$Q = kt^{1/2} \dots \dots \dots (3)$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.^[21]

Mechanism of drug release

To evaluate the mechanism of drug release from Stavudine controlled release tablets, data of drug release were plotted in korsmeyer et al's equation (Equation 4) as log cumulative percentage of drug release vs log time and the exponent n was calculated through the slope of the straight line.

$$Mt/M_\infty = kt^n \dots \dots \dots (4)$$

Where Mt/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristics of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers.^[22] For cylindrical matrix tablets, if the exponent $n=0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent's value of 0.89 is indicative of case-II Transport or typical zero-order release.^[23]

Swelling and Erosion Study

Swelling and erosion studies were carried out according to the method reported by Al-Taani and Tashtoush to understand the influence of swelling and erosion behaviour on drug release and also to determine the effect of polymer viscosity on the swelling and erosion. Matrix tablets were introduced into the dissolution apparatus under the standard set of conditions as specified for release rate studies. The tablets were removed using a small basket and swollen

Table 2: Granules properties of formulations F1 to F9 of Stavudine controlled release tablets

| Parameters | Formulation code | | | | | | | | |
|----------------------------------|------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Angle of repose | 25.22 ± 1.32 | 27.15 ± 1.41 | 26.22 ± 1.78 | 29.45 ± 1.52 | 28.12 ± 1.57 | 26.12 ± 1.73 | 31.15 ± 1.38 | 30.26 ± 1.34 | 32.35 ± 1.81 |
| Loose bulk density (LBD) (g/ml) | 0.254 ± 0.005 | 0.284 ± 0.004 | 0.262 ± 0.003 | 0.294 ± 0.009 | 0.279 ± 0.006 | 0.314 ± 0.006 | 0.301 ± 0.001 | 0.268 ± 0.007 | 0.297 ± 0.003 |
| Tapped bulk density (TBD) (g/ml) | 0.273 ± 0.013 | 0.322 ± 0.011 | 0.289 ± 0.014 | 0.235 ± 0.012 | 0.295 ± 0.016 | 0.282 ± 0.015 | 0.317 ± 0.018 | 0.291 ± 0.019 | 0.325 ± 0.011 |
| Compressibility index (%) | 8.54 ± 0.75 | 11.63 ± 1.63 | 9.71 ± 1.33 | 10.20 ± 1.48 | 11.56 ± 0.78 | 8.94 ± 0.61 | 9.87 ± 1.41 | 10.71 ± 1.76 | 11.40 ± 1.58 |

Table 3: Release kinetics parameters of designed controlled release matrix tablets of Stavudine

| Formulations | Zero order plots ^a | First order plots ^b | Higuchi's plots ^c | Korsmeyer et al's plots ^d |
|--------------|-------------------------------|--------------------------------|------------------------------|--------------------------------------|
| F1 | 0.966 | 0.983 | 0.978 | 0.931 |
| F2 | 0.9754 | 0.938 | 0.985 | 0.944 |
| F3 | 0.9546 | 0.984 | 0.995 | 0.916 |
| F4 | 0.9633 | 0.9829 | 0.989 | 0.920 |
| F5 | 0.9526 | 0.969 | 0.993 | 0.907 |
| F6 | 0.962 | 0.9686 | 0.991 | 0.906 |
| F7 | 0.977 | 0.949 | 0.978 | 0.915 |
| F8 | 0.951 | 0.901 | 0.992 | 0.902 |
| F9 | 0.934 | 0.9649 | 0.987 | 0.901 |

^aZero order equation, $C=K_0 t$.^bFirst order equation, $\log C = \log C_0 - K_1/2.303 t$.^cHiguchi's equation, $Q = Kt^{1/2}$.^dKorsmeyer et al's equation, $M_t/M_\infty = Kt^n$.

weight of each tablet was determined. To determine matrix erosion, swollen tablets were dried in a vacuum oven at 45°C to a constant weight. Swelling (%) and Erosion (%) were calculated according to the following formula: % Swelling = $S/R \times 100$, % Erosion = $(T-R)/T \times 100$; Where, S is the weight of the matrix after swelling; R is the weight of the eroded matrix; and T is the initial weight of the matrix. [24]

Stability Studies

The optimized formulation was subjected to stability at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for period of six months. After each month tablet sample was analyzed for physical characteristics and drug release profile. [25]

RESULT & DISCUSSION

The supplied drug passed the various tests of identification and analysis. The pure drug (Stavudine) and the solid admixture of drug and various excipients used in the preparation of CR tablet formulations were characterized by FTIR spectroscopy to know the compatibility, Fig. 5-7.

Granules of the different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, and compressibility index. The results of angle of repose and compressibility index (%) ranged from $(25.22^\circ \pm 1.32)$ to $(32.35^\circ \pm 1.81)$ and (8.54 ± 0.75) to (11.63 ± 1.63) , respectively. The results of loose bulk density and tapped bulk density ranged from (0.254 ± 0.005) to (0.314 ± 0.006) and (0.235 ± 0.012) to (0.325 ± 0.011) , respectively. The results of angle of repose (< 30) indicate good flow properties of granules. [26-27] This was further supported by lower compressibility index values. [26] The lowest compressibility index is 5-15 % which indicates excellent flow properties in Table 2. The physical properties of different batches of developed matrix tablets are given in Table 4. The thickness of the tablets ranged from (3.38 ± 0.16) to (3.88 ± 0.36) mm. All the batches showed uniform thickness. The average percentage deviation of 20 tablets of each formulation was less than (5 %), and hence all formulations passed the test for uniformity of weight as per

official requirements (Pharmacopoeia of India 1996). The hardness of all the formulation ranged from (6.1 ± 0.14) to (6.83 ± 0.35) kg/cm². Tablets hardness is, however, not an absolute indicator of strength. The percentage friability of the tablets of all the formulations ranged from (0.28 % to 0.34 %). In the present study, the percentage friability for all formulations was below 1 % w/w, indicating that the friability is within the prescribed limits. Drug content was found to be uniform among different formulations of the tablets and ranged from (95.71 ± 0.241) to (99.52 ± 0.131) . The results of the dissolution studies for formulations F1 to F9 are shown in the Fig. 1 and 2.

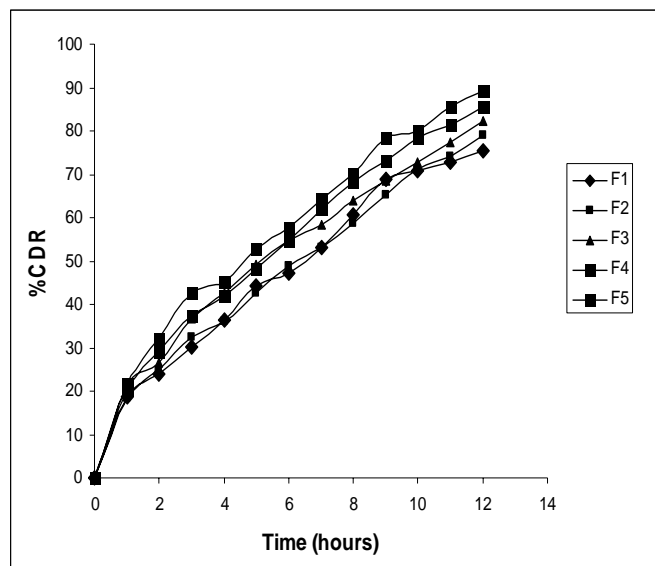
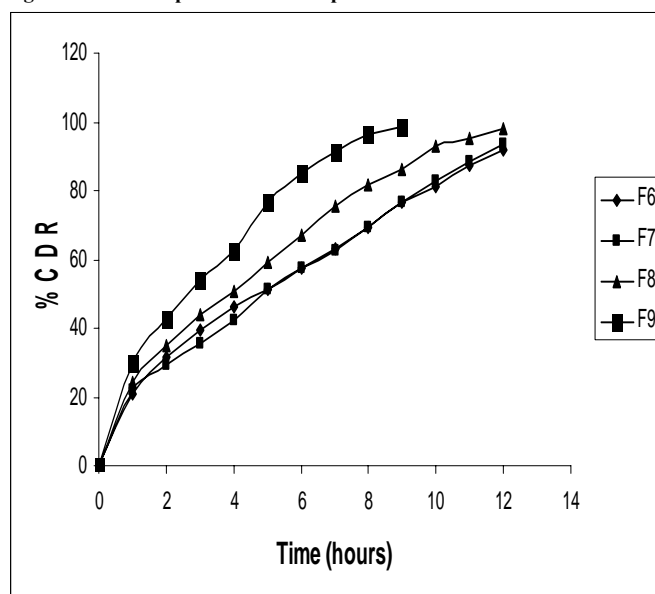
**Fig. 1: Dissolution profiles of developed matrix tablets F1 to F5****Fig. 2: Dissolution profiles of developed matrix tablets F6 to F9**

Table 4: Tablet properties of formulations F1 to F9 of Stavudine controlled release matrix tablets

| Parameters | Formulation code | | | | | | | | |
|--------------------------------|------------------|-------------|-------------|-------------|-------------|-------------|-------------|---------------|---------------|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Thickness (mm) | 3.38 ± 0.16 | 3.48 ± 0.18 | 3.72 ± 0.32 | 3.85 ± 0.03 | 3.61 ± 0.16 | 3.41 ± 0.14 | 3.56 ± 0.12 | 3.88 ± 0.36 | 3.75 ± 0.03 |
| Hardness (kg/cm ²) | 6.2 ± 0.10 | 6.7 ± 0.24 | 6.1 ± 0.14 | 6.4 ± 0.12 | 6.83 ± 0.35 | 6.3 ± 0.13 | 6.5 ± 0.34 | 6.1 ± 0.25 | 6.6 ± 0.12 |
| Friability (%) | 0.29 ± 0.13 | 0.32 ± 0.41 | 0.34 ± 0.21 | 0.28 ± 0.12 | 0.28 ± 0.35 | 0.31 ± 0.21 | 0.33 ± 0.61 | 0.32 ± 0.41 | 0.29 ± 0.12 |
| Drug content (%) | 97.76 ± | 99.52 ± | 96.19 ± | 98.45 ± | 97.89 ± | 95.71 ± | 98.62 ± | 97.11 ± 0.172 | 99.45 ± 0.154 |
| | 0.235 | 0.13 | 0.132 | 0.136 | 0.214 | 0.241 | 0.14 | | |

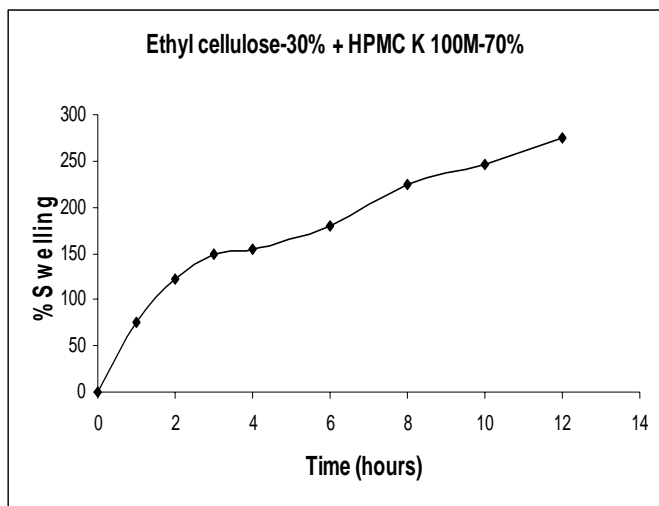


Fig. 3: Swelling behaviour of optimized batch of matrix tablets (Formulations F8). Data are represented as mean ± SD (n=3).

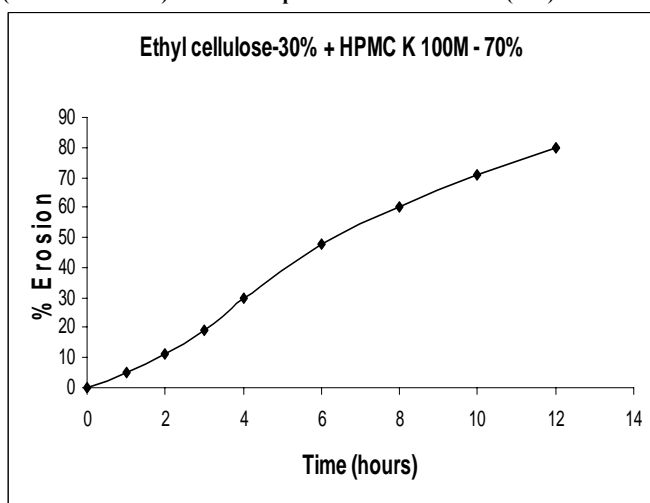


Fig. 4: Erosion behaviour of optimized batch of matrix tablets (Formulations F8). Data are represented as mean ± SD (n=3).

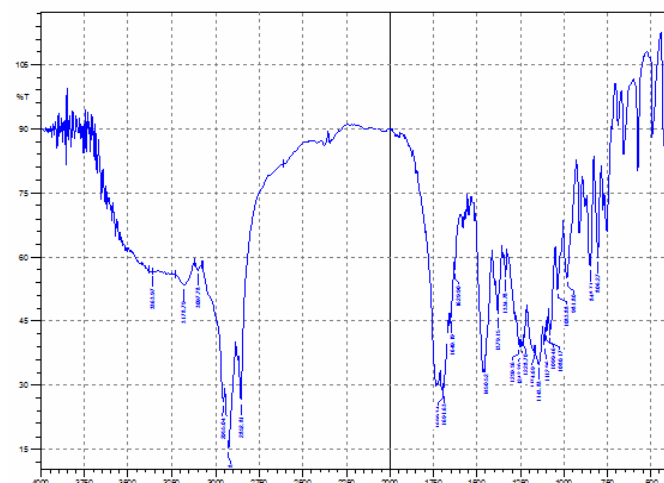


Fig. 6: FTIR Spectra of Stavudine with HPMC K 100M

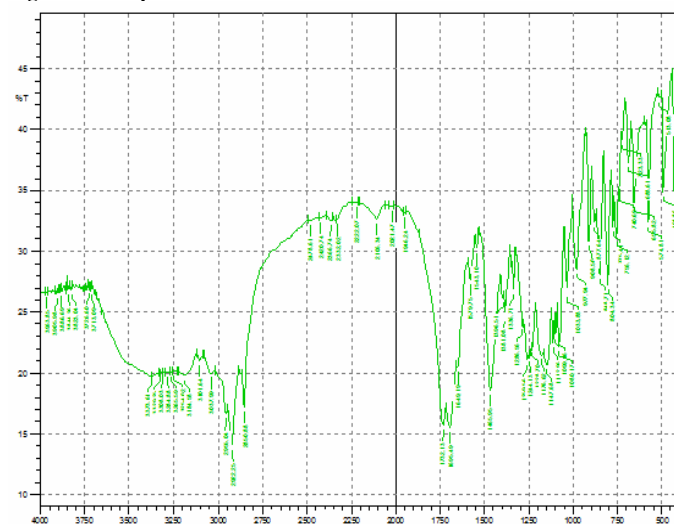


Fig. 7: FTIR spectra of Stavudine with Ethyl cellulose

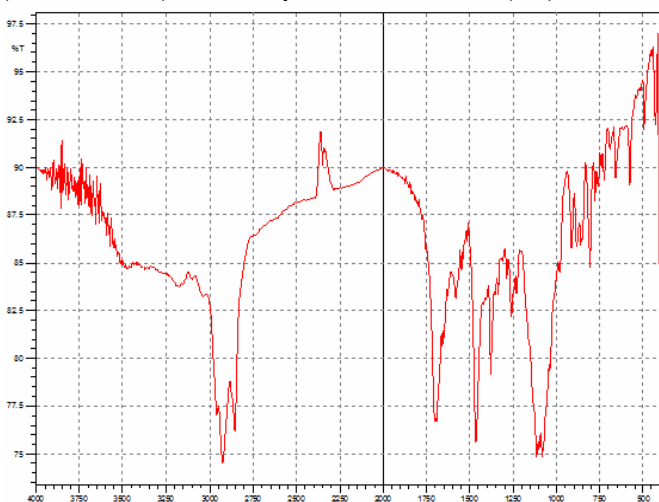


Fig. 5: FTIR spectra of pure Stavudine

The cumulative percentage drug release for F1, F2, F3, F4, F5, F6, F7, F8 and F9 (75.32 %, 79.13 %, 82.29 %, 85.44 %, 89.23 %, 91.95 %, 93.62 %, 98.12 % and 98.54 %) at the end of 12 h respectively. Among all the formulation F9 shows highest drug release (98.54 %) in 9 h, where as the drug release from other formulations was slow; this shows that Ethyl cellulose is less permeable. The release rate of HPMC K 100M was extended by adding Ethyl cellulose in combination. The data clearly indicate the drug release can be effectively controlled by varying the polymer and its ratio. The regression coefficients obtained for first order kinetics were found to be (R^2 : 0.901 to 0.984), and with those of zero order kinetics (R^2 : 0.934 to 0.977), indicating that drug released from all formulation followed mixed zero order and first order kinetics (Table 3). To evaluate drug release mechanism from the matrix tablets, plots of cumulative percentage release vs square root of time as per Higuchi's equation were constructed. These plots were found to be linear with all the formulations (R^2 : 0.978 to 0.995)

indicating that the drug release from the matrix tablets was diffusion controlled. To confirm the diffusion mechanism the data were fit into korsmeyer et al's equation. All the formulation shows good linearity (R^2 : 0.901 to 0.944), with the slope (n) values 0.493 to 0.623, indicating release mechanism was anomalous non-Fickian or anomalous release ($0.45 < n < 0.89$). But it cannot be concluded that release was totally based on diffusion, which generally in the case in Higuchi's square root equation. Based on swelling and erosion studies, it was concluded that matrix tablets undergo swelling (Fig. 3) as well as erosion (Fig. 4) during the dissolution study, which indicates that polymer relaxation had a role in drug release mechanism. However, it can be concluded that effect of release kinetics was found to be diffusion coupled with erosion.

CONCLUSION

The matrix tablets were found to be effective in sustaining the drug release more than 12 h. Drug release was found to be diffusion coupled with erosion. Stability studies revealed that there was no significant change in drug content and dissolution profile of matrix tablets. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between Stavudine and other ingredients used. It can be concluded that stable formulation could be developed by incorporating both hydrophilic and hydrophobic polymer in a definite proportion. So that the sustained released profile is maintained for an extended period of time.

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