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Formulation and Release behavior of sustained release Stavudine Hydrochloride Matrix tablet containing Hydrophilic and Hydrophobic Polymers

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Abstract

Stavudine is an antiviral drug which is used in the control of HIV and tuberculosis therapy. There are considerable inter-individual variations in serum concentration of stavudine due to short half-life. In this study, stavudine was therefore selected as the model drug and effects of different polymers (Eudragit RSPO, Eudragit RLPO and Hydroxypropyl methylcellulose) in differing combinations and ratios were studied on swelling behavior of the tablets and release pattern of stavudine from the formulations. All tablets were acceptable with regard to thickness, weight variation, hardness, and drug content. The formulation (F7) having combination of Eudragit RSPO and Eudragit RLPO (1:2) and 10% hydroxypropyl methylcellulose showed 208.21 ± 0.66 % swelling, 48.33 ± 1.49 % erosion and 90.43 ± 1.11% drug release. Maximum release was observed by increasing the content of Eudragit RLPO. Optimized formulations were subjected to stability studies for six months which showed stability with regards to release pattern.

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Key words:
Stavudine; Eudragit; Hydoxypropyl Methylcellulose; Swelling; Erosion; *In vitro* release study

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INTRODUCTION

Stavudine, an antiviral drug, has been widely used in the treatment of HIV and tuberculosis therapy [1]. Stavudine has a short half-life of 1-1.5 hr, and usually

administered orally as a capsule and an oral solution [2,3]. In clinical studies, stavudine has greater than 80% oral bioavailability, and dose limiting toxicity i.e. peripheral neuropathy[4]. Therefore the development of sustained release preparation could reduce the severity of toxicity by decreasing total administered dose .

The drug is very soluble in water, and hence judicious selection of water insoluble inert carrier is necessary to sustain the release rate of drug. Among the different approaches for obtaining sustained release systems, matrix tablets were chosen as most efficient formulation approach since their preparations involve few processing variables and they can be easily manufactured by direct compression method with conventional tableting machines. Jaber emami et. Al[5] prepared sustained release matrix tablets of lithium carbonate using different hydrophilic materials to prevent high peak blood level in man. Shoaib M. H. et. al.[6] observed respective contributions of diffusion, swelling and erosion to the release mechanism of ibuprofen through sustained release matrix tablet based on hydroxypropyl methylcellulose (HPMC).

In the present investigation sustained release tablets of stavudine were prepared by direct compression method using Eudragit (RSPO and RLPO) and HPMC. The aim of the work was to evaluate effect of different ratios of polymers on drug release characteristics of stavudine tablets.

MATERIALS AND METHODS

Stavudine (Cipla Laboratories, India), Eudragit RSPO (Rohm Pharma, Germany), Eudragit RLPO (Rohm Pharma, Germany), Hydroxypropyl Methylcellulose K4M (Colorcon, U.K.), Microcrystalline Cellulose (Asahi Kasei Chemicals Corporation, Japan), Polyvinyl pyrrolidone (Loba Chemicals, India), were used. All the solvents used were of analytical grade.

Formulation of matrix Tablets

The composition of different formulations of stavudine matrix tablets is shown in Table 1. The ingredients were weighed accurately and mixed thoroughly. Then this blend was compressed with single punch tablet machine (H/416/95, Cadmach Machinery Pvt. Ltd, Ahmedabad, India) using compression force in the range of 500-1500Kgf to produce flat faced tablets with a diameter of 8mm. Each tablet formulation was monitored for weight variation, hardness, friability, thickness and drug content.

In vitro release study

In vitro release study was done using the USP I dissolution test apparatus (Model No. DA-3, Veego Scientific Devices, Mumbai, India). The study was carried out in 900 ml of 0.1 N HCl for 2 h followed by phosphate buffer pH 6.8 for 10 h. The medium was maintained at 37° ± 0.5°C and a paddle rotation speed was 50 rpm. Aliquots of 5 ml sample solutions were analyzed for stavudine at 266 nm using a UV double beam spectrophotometer (Model no. UV 2401 PC, Schimadzu Corporation, Singpore). Cumulative percentage of drug release was calculated and the mean of three determinations was used in data analysis.

Swelling and erosion study

Swelling and erosion experiments were carried out on the compressed matrices using dissolution test apparatus under the standard sets of conditions as specified for determination of *in vitro* drug release. The tests were performed under the standard condition as described for *in vitro* drug release. The weight of tablet was determined before the test, and then the tablet was put into the basket and immersed in 900 of 0.1 N HCl for 2 h followed by phosphate buffer pH 6.8 for 10 h. At selected time intervals, the tablets were taken out of the dissolution medium using a small basket and placed in a vacuum oven (at 40°C). After 48 h, tablets were removed and weighed. Percent swelling and erosion was calculated according to the following formula [9-11].

$$\% \text{ Swelling} = S/R \times 100 \quad (1)$$

% Erosion = (T-R/T x 100) (2)

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.

Scanning electron microscopy

Tablet samples were removed from the dissolution apparatus at predetermined time intervals and sectioned through an undisturbed portion of the gel formed at the flat face of the tablet. The specimen was then positioned on the sample holder so as to present a cross-section of the tablet to the microscope. Samples were coated with platinum and visualized under scanning electron microscope (SEM) (JSM 6380 A, JOEL, Japan).

Kinetics of drug release

The release profiles of formulations were treated with kinetic equations to determine order of release. To elucidate the mechanism of release, profiles were treated with Korsemeyer Pappas equation [9].

Stability Studies

Stability studies were carried out on stavudine sustained release matrix tablets to assess their stability with respect to their physical appearance and *in vitro* release characteristics after 6 months storage at 40 ^{0} $\pm$ 2^{0}Cand 75 $\pm$ 5% RH.

RESULTS

Tablet properties like hardness, weight variation, and drug content of all batches were found within acceptable limits (Table 2).

The percent gain in weight of the hydrated matrices (i.e. water uptake) at various time intervals up to 12 h are shown in Figure1A and 1B. Formulations showed % swelling ranging from 170.21 $\pm$ 0.81% to 248.84 $\pm$ 1.95% whereas % erosion ranged from 28.01 $\pm$ 1.83% to 54.31 $\pm$ 1.55% (Figure 2A and 2B). Percent swelling and erosion of formulation F7 were 208.21 $\pm$ 0.66% and 48.33 $\pm$ 1.49%.

The release profiles of stavudine from the prepared formulations are shown in Figure 3A and 3B.

Cumulative percent drug release was fastest for F4 (100 % in 6 h) containing Eudragit RSPO: RLPO. Formulation F7 containing Eudragit RSPO: RLPO in the ratio 1: 2 and 10%w/w HPMC K4M showed 90.43 ± 1.11% release of stavudine in 12 h.

Various release kinetic models were applied to elucidate the mechanism of drug release from the sustained release matrix tablets. Drug release from the optimized formulations F7 (R^2= 0.992) followed the Higuchi model. To explore the release mechanism, results of the i*n vitro* dissolution data were fitted to the Korsmeyer and Peppas equation, which gave slope value of 0.58 for formulation F7.

SEM photomicrographs of optimized formulations are shown in Figure 4A, 4B and 4C. It was found that erosion of matrix increased with increase in time. SEM photomicrographs at 0, 2 and 10 h revealed pores with increasing diameter.

No significant change was found in physical appearance and *in vitro* release profiles after stability study for 6 months.

DISCUSSION

The percentage swelling and erosion was dependent on ratio of polymers in each formulation. Results showed that increasing the amount of Eudragit RLPO (Formulations F1 to F 4 containing Eudragit RLPO and RSPO) led to an increase in the erosion. This may be attributed to more hydrophilic nature of Eudragit RLPO in comparison to Eudragit RSPO which favors hydration and hence a higher water absorption capacity[12]. Formulations F5 to F6 showed better swelling behavior than F1 to F4 as they contained HPMC. HPMC is known to form gel layer in presence of aqueous medium rendering the formulations to swell.

From *in vitro* drug release study, it was observed that release of the drug increased with the increased amount of Eudragit RLPO 100 and decreased with increased amount of Eudragit RSPO 100. The release with Eudragit RLPO was due to higher water permeability of Eudragit RL PO100 which contains

10% of functional quaternary ammonium groups and lower water permeability of Eudragit RS 100 having only 5% of functional quaternary ammonium groups [13]. HPMC K4M is insoluble in water but due to its hydrophilicity it forms insoluble matrix when combined with Eudragit RLPO and RSPO. HPMC K4M forms a firm gel layer along with Eudragit RLPO and RSPO and helps in formation of pores on the tablet surface. Also because of its tendency to mask the quaternary ammonium groups of Eudragit RLPO and RSPO to some extent it modifies release rate from the matrix. This finding suggested that the swelling kinetics of the matrices were an important determinant of drug release. The presence of higher amount of Eudragit RLPO in formulation F7 lead to fast water uptake, followed by swelling owing to the presence of HPMC that could modify the drug release.

From the photomicrograph it was seen that erosion of matrix increased with increase in time. SEM photomicrographs at 0, 2 and 10 h revealed pores with increased diameter. It also suggested formation of gelling structure indicating the possibility of swelling of matrix tablet.

The value of release exponent (*n*) for the optimized formulation F7 was 0.58 (Fickian diffusion mechanism), indicating drug release occurred by the usual molecular diffusion of the drug due to a chemical potential gradient.

Table 1: Composition of stavudine tablets

Ingredients (mg)	Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
Stavudine	50	50	50	50	50	50	50	50
Eudragit RSPO	50	50	25	25	25	50	25	50
Eudragit RLPO	--	25	25	50	25	--	50	25
HPMC K4M	--	--	--	--	20	20	20	20

Microcrystalline cellulose added as diluent in quantity sufficient to prepare 200mg tablet.
Weights are given for one tablet.
Polyvinyl pyrrolidone and Talc were added in concentrations 5% w/w and 1% w/w respectively as binder and lubricant.

Table 2 Physical properties of stavudine tablets

Formulations	Hardness* (kg/cm²)	Friability* (%w/w)	Thickness* (mm)	Diameter* (mm)
F1	6.23 ± 0.14	0.58±0.05	3.30 ± 0.02	8.03 ± 0.01
F2	6.47 ± 0.09	0.70±0.04	3.29 ± 0.03	8.02 ± 0.02
F3	6.36 ± 0.10	0.50±0.03	3.30 ± 0.03	8.03 ± 0.01
F4	6.54 ± 0.13	0.59±0.03	3.31 ± 0.01	8.04 ± 0.03
F5	6.57 ± 0.11	0.61±0.04	3.31 ± 0.05	8.02 ± 0.04
F6	6.67 ± 0.08	0.61±0.04	3.28 ± 0.05	8.03 ± 0.02
F7	6.75 ± 0.08	0.63±0.04	3.31 ± 0.03	8.03 ± 0.01
F8	6.74 ±0.16	0.59±0.05	3.29 ± 0.05	8.04 ± 0.03

*Results are mean of 5 observations ± S.D.

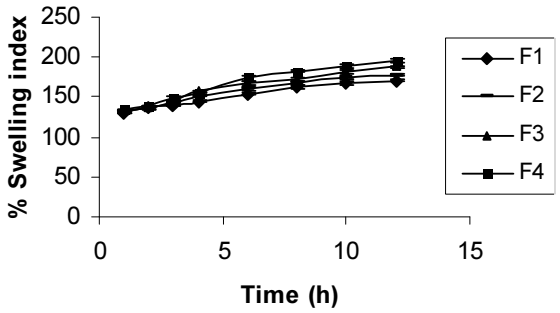


Figure 1A: Percentage swelling indices of formulations F1-F4

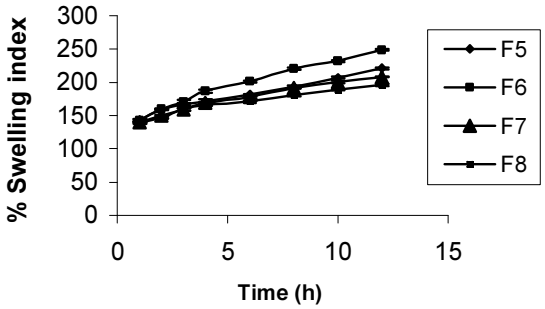


Figure 1B: Percentage swelling indices of formulations F5-F8.

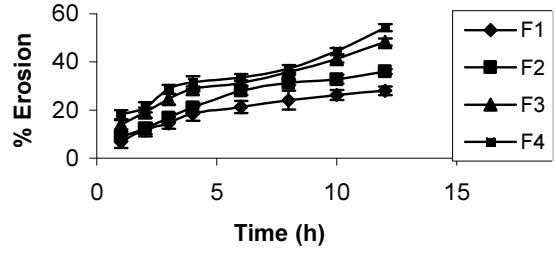


Figure 2A: Percentage erosion of formulations F1-F4.

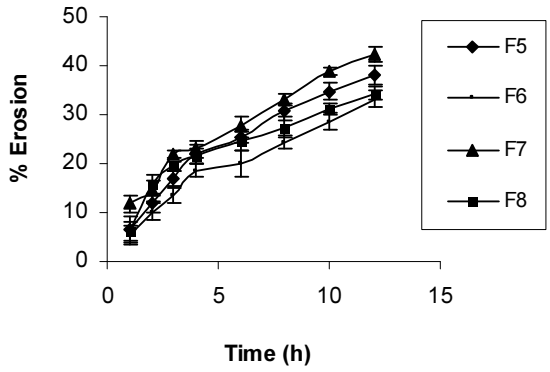


Figure 2B: Percentage erosion of formulations F5-F8.

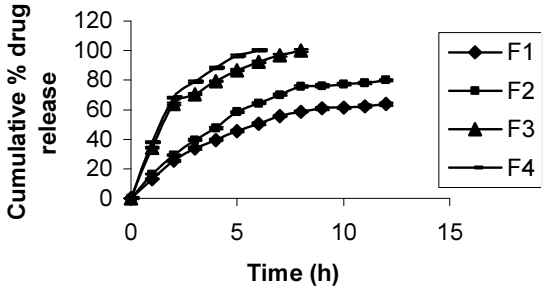


Figure 3 A: *In vitro* drug release profiles of formulations F1-F4 for 12 h.

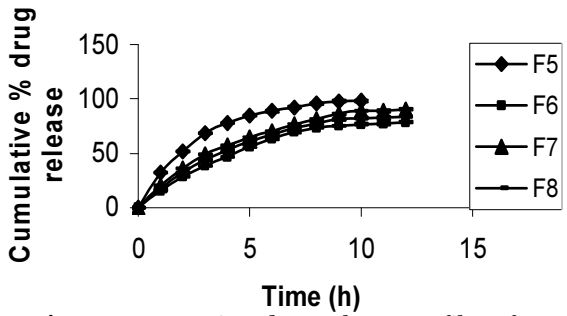
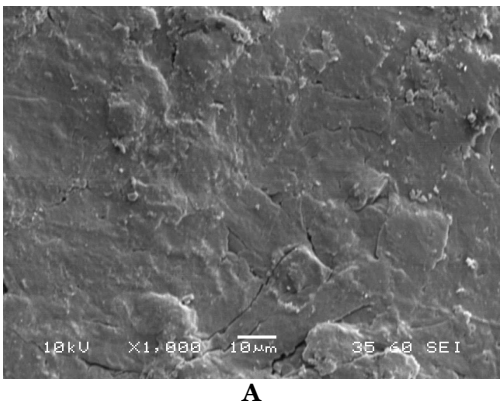
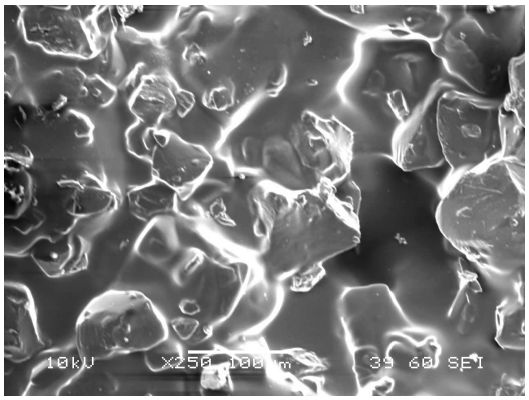


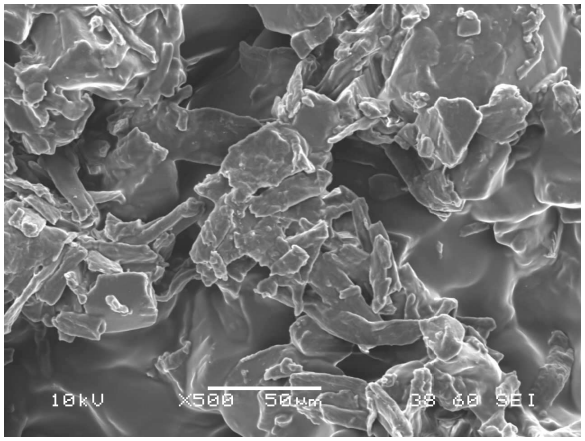
Figure 3B: *In vitro* drug release profiles of formulations F5-F8 for 12 h.



A



B



C

Figure 4: SEM photomicrographs of optimized matrix tablet (batch F7) showing surface morphology after 0 (A), 2(B) and 10 (C) hours of dissolution study.

CONCLUSION

The investigated formulation (F7) comprising Eudragit RSPO and Eudragit RLPO (1:2) and 10% HPMC was capable of sustaining release up to 12 h. 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.

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