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Research Article

FORMULATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF STAVUDINE

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ABSTRACT

The investigation was concerned with Formulation and *in vitro* evaluation of sustained release matrix tablet of Stavudine. Stavudine a nucleoside analog drug used in the treatment of acquired immune deficiency syndrome (AIDS) has been incorporated into directly compressed monolithic matrices whose excipients were mixtures at different ratios of Eudragit RL 100, Ethylcellulose, Talc and Magnesium sterate. Both polymers are water insoluble and acid resistant polymers. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations) and in-vitro drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and low friability. The optimized formulation F4 was found to have good matrix integrity throughout the study. The drug release study was carried out at 37± 0.5ºC in phosphate buffer of pH 7.4 for 12 hrs. It was found that the drug release profile of these formulations were uniform and sustained throughout the period of study. The release mechanism of Stavudine from matrix tablets was evaluated on the basis of Higuchi model. The regression values of the optimized formulations was found to be 0.987 (close to 1) which indicates that the diffusion was the of drug release from the matrix. The other parameters like thickness, hardness, friability, weight variation and drug content uniformity for tablets was found to be within the official limits. The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable.

Key words: Controlled release**,** Ethylcellulose, Eudragit RL 100, Matrix, 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]. Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects [2]. Among the different approaches studied with this aim, matrix systems still appear as one of the most attractive from both the economic as well as the process development and scale-up points of view [3]. Moreover, it has been shown that the suitable combination of more types of polymers as matrix-forming materials enables appropriate modifications of the release characteristics of the drug from the dosage form [4].

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[5]. 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 [6, 7].

Stavudine is a thymide analogue reverse transcriptase inhibitor that is active *in vitro* against HIV-1 and HIV-2[8]. 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[9]. 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[10].

The objective of the present work was to evaluate the suitability of Eudragit RL 100 and Ethylcellulose, alone or in combinations, as polymeric materials for directly-compressed matrix tablets able to adequately extend drug release using a suitable rate controlling polymer. The influence of varying the Eudragit RL 100–Ethyl cellulose ratio and/ or the drug polymeric matrix ratio on drug release behavior has been investigated. The technological properties of the tablets obtained with the different formulations were also examined

MATERIALS AND METHODS

Materials

Stavudine and Eudragit were obtained as a gift sample from Strides Arco Labs (Bangalore, India). Ethyl cellulose was obtained from Micro Labs (Bangalore, India). All other reagents used were of pharmaceutical or analytical grade.

Methods

In the present work the Stavudine tablets were prepared by direct compression method. The drug and the excipients were passed through 72# size mesh prior to the preparation of dosage form. The entire ingredients were weighed separately and mixed thoroughly for 10 minutes in double cone blender to ensure uniform mixing in geometric ratio. The tablets were prepared by direct compression technique using 12mm punch. Two different polymers like Ethylcellulose and Eudragit RL 100 were used as retardants as well as diluents in different ratio. Talc and magnesium state is used as a lubricant to reduce die wall friction (Table 1).

Evaluation of tablets

Physical characterization of the designed tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods .The weight variation was determined by taking 20 tablets using an electronic balance (type ER182A, Afcoset, Mumbai, India). Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics) for 4 minutes at 25 rpm[11].

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.

Table 1: Composition of different formulations

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6
Stavudine	80	80	80	80	80	80
Eudragit RL 100	30	48	60	84	120	----
Ethyl cellulose	90	72	60	36	----	120
Micro crystalline cellulose	94	94	94	94	94	94
Magnesium Stearate	03	03	03	03	03	03
Talc	03	03	03	03	03	03

Table 2: Granules properties of formulations F1 to F3 of Stavudine sustained release tablets

Parameters	Formulations		
	F1	F2	F3
Angle of repose	27.52 ± 1.14	25.15 ± 1.58	28.22 ± 1.21
Loose bulk density (LBD) (g/ml)	0.278 ± 0.002	0.292 ±0.008	0.262 ± 0.003
Tapped bulk density (TBD) (g/ml)	0.285 ± 0.016	0.312 ± 0.011	0.287 ± 0.018
Compressibility index (%)	9.21 ± 0.93	11.45 ± 1.73	8.71 ± 1.49

Table 3: Granules properties of formulations F4 to F6 of Stavudine sustained release tablets

Parameters	Formulation code		
	F4	F5	F6
Angle of repose	26.54 ± 1.86	30.05 ± 1.69	29.53 ± 1.45
Loose bulk density (LBD) (g/ml)	0.264 ± 0.008	0.294 ±0.004	0.275± 0.003
Tapped bulk density (TBD)(g/ml)	0.261 ± 0.011	0.293 ± 0.015	0.297± 0.013
Compressibility index (%)	9.45± 0.65	9.63 ± 1.63	10.51 ± 1.45

Table 4: Tablet properties of formulations F1 to F3 of Stavudine sustained release matrix tablets

Parameters	Formulation code		
	F1	F2	F3
Thickness (mm)	3.45 ± 0.12	3.79 ± 0.15	3.82 ± 0.26
Hardness (kg/cm^2)	6.2 ± 0.16	6.8 ± 0.19	6.3 ± 0.14
Friability (%)	0.31 ± 0.14	0.33 ± 0.27	0.32 ± 0.20
Drug content (%)	97.81 ± 0.29	99.52 ± 0.13	98.83 ± 0.17

Table 5: Tablet properties of formulations F4 to F6 of Stavudine sustained release matrix tablets

Parameters	Formulation code		
	F4	F5	F6
Thickness (mm)	3.51 ± 0.18	3.49 ± 0.11	3.69 ± 0.35
Hardness (kg/cm^2)	6.4 ± 0.18	6.7 ± 0.24	6.8 ± 0.14
Friability (%)	0.29 ± 0.11	0.30± 0.23	0.28± 0.21
Drug content (%)	98.76 ± 0.27	97.54 ± 0.16	96.19 ± 0.14

Table 6: Kinetic values obtained from different plots of formulations F1 to F6

Formulation	First order plots*	Zero order plots$^{\square}$	Higuchi's plots•	Korsmeyer et al's plots$^{\square}$	
	R^2	R^2	R^2	Slope(n)	R^2
F1	0.968	0.918	0.994	0.481	0.985
F2	0.912	0.955	0.985	0.547	0.918
F3	0.982	0.968	0.992	0.565	0.969
F4	0.972	0.957	0.987	0.598	0.982
F5	0.953	0.971	0.989	0.621	0.956
F6	0.937	0.948	0.995	0.645	0.921

*First order equation, Log C=log $C_{\square}$-K_t/2.303, $^{\square}$Zero order equation, C=K_0 t, •Higuchi's equation, Q= $Kt^{½}$, $^{\square}$Korsmeyer et al's equation, M_t/M_α= Kt^n.

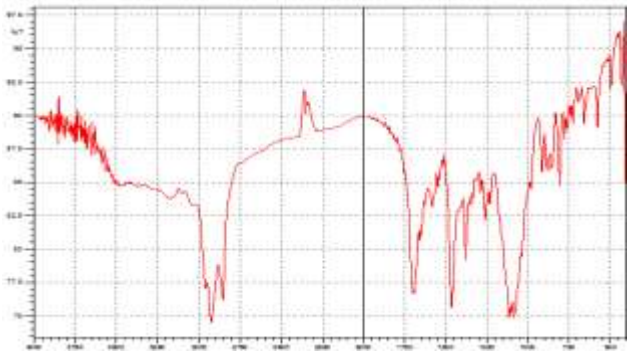

Figure 1: FTIR spectra of Stavudine

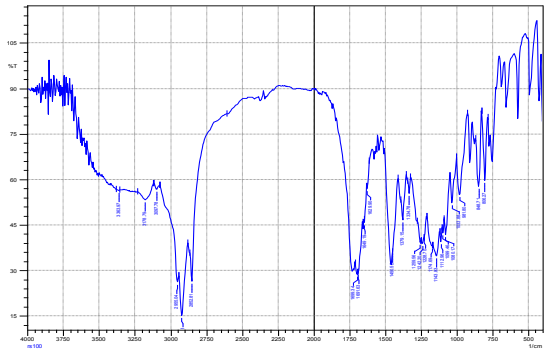

Figure 2: FTIR spectra of Stavudine with eudragit RL 100

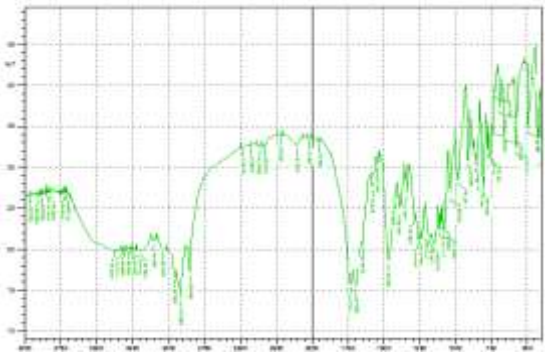

Figure 3: FTIR spectra of Stavudine with ethyl cellulose

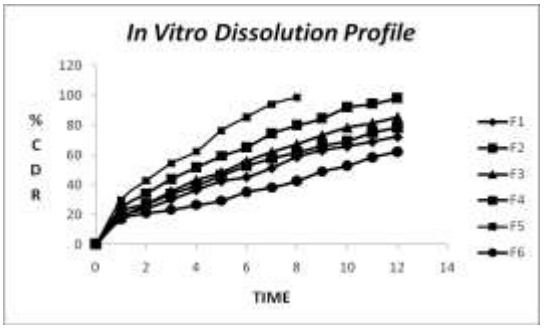

Figure 4: Dissolution profiles of developed matrix tablets F1 to F6

***In vitro* drug release studies**

In vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electro lab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of pH 7.4 phosphate buffer, maintained at 37± 0.5^{0}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.

Stability studies

The optimized formulation was subjected to stability at 40 ± 2^{0}C and 75 ± 5 % RH for period of six months. After each month tablet sample was analyzed for physical characteristics and drug release profile [12].

RESULTS AND 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 SR tablet formulations were characterized by FTIR spectroscopy to know the compatibility. As shown in the Figure 1-3, there was no significant difference in the FT-IR spectra of pure Stavudine and drug along with polymers (Both Eudragit RL and Ethyl cellulose). The characteristic OH stretching, NH stretching of secondary amine, C-H

stretching and C=O stretching of pure drug was unchanged in all the spectrum, indicate the stable nature of Stavudine in the solid admixtures of the drug with various excipients, as shown in Figure 1-3.

The results of angle of repose and compressibility index (%) ranged from (25.15^0 ± 1.58 to 30.05^0 ± 1.69) and (8.71 ± 1.49 to 11.45 ± 1.73), respectively. The results of loose bulk density and tapped bulk density ranged from (0.262 ± 0.003 to 0.294 ± 0.004) and (0.261 ± 0.011 to 0.312 ± 0.011), respectively. The results of angle of repose (< 30) indicate good flow properties of granules. This was further supported by lower compressibility index values. The lowest compressibility index is 5-15% which indicates excellent flow properties in Table 2-3.

The physical appearance, thickness, 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 4-5. Tablet thickness and hardness were found to be good (between 3.45±0.12 to 3.82±0.26 mm and 6.2±0.16 to 6.8±0.19 kg/cm2) depending on the compression force applied, and the percentage friability of the tablets of all the formulations ranged from (0.28% to 0.33%), which is less than 0.5% (wt/wt) indicating that the friability is within the prescribed limits. Weight variation results of matrix tablets ranged from 298±1.12 to 301± 1.29mg.For weight variation test, the pharmacopoeial deviation for tablets of more than 250 mg is ± 5%.The average percentage deviation of all tablet formulation was found to be within the above limit, incompliance with official standards. Drug content was found to be uniform among different formulations of the tablets and ranged from (96.19 ± 0.14 to 99.52 ± 0.13) indicating that direct compression is an acceptable method for preparing good-quality matrix tablets of Stavudine.

The results of the dissolution studies for formulations F1 to F6 are shown in the Figure 4 .The cumulative percentage drug release for F1, F2, F3, F4, F5, and F6 (72.21%, 78.34%, 85.44%, 98.12, 98.2349% and 62.21%) at the end of 12hrs respectively. Among all the formulation F9 shows highest drug release (98.49%) in 8 hrs, where as the drug release from other formulations was slow; this shows that Ethyl cellulose is less permeable. The release rate of Eudragit RL 100 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.

In order to describe the kinetics of release process of drug in all formulations, various equations were used, such as the zero-order rate equation, which describes the systems where the release rate is independent of concentration of dissolved species[13]. The first-order equation describes the release from systems where dissolution rate is dependent on concentration of the dissolving species[14]. The higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to rate of drug diffusion[15]. The Korsmeyer-peppas equation is used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved[16]. The applicability of all these equations was tested in this work. The kinetic data for all the formulations is shown in Table 6.

The regression coefficients obtained for first order kinetics were found to be (R^2: 0.912 to 0.982), and with those of zero order kinetics (R^2: 0.918 to 0.971), indicating that drug released from all formulation followed mixed zero order and first order kinetics (Table 6). All the formulations in this investigation could be best expressed by higuchi's classical diffusion equation, as the plots showed high linearity (R^2: 0.985 to 0.995). The linearity of the plots indicates that the release process is diffusion-controlled. To confirm the diffusion mechanism the data were fit in to Korsmeyer-peppas model. All the formulations showed good linearity (R^2: 0.918 to 0.985), with slope (n) values ranging from 0.481 to 0.645, anomalous (non-Fickian) diffusion ($0.45 < n < 0.89$) is the dominant mechanism of drug release with all the formulations.

CONCLUSION

Matrix tablet containing Stavudine can be prepared successfully by using direct compression method. The matrix tablets were found to be effective in sustaining the drug release more than 12hrs. Among all the formulation, F4 showed 98.12% release at the end of 12 hours. Drug release was diffusion controlled and followed mixed zero order and first order kinetics. Stability studies revealed that there was no significant change in hardness, friability, and drug content of selected formulation (F4). FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between Stavudine and other ingredients used. Sustained release without initial peak level achieved with these formulations may reduce dose frequency and side effects as well as improved patient compliance.

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REFERENCES

1. Y W Chien. "Novel drug delivery systems," ed. by Chien Y W; Marcel Dekker, Inc; New York, U.S.A; 1992, pp 139-196.
2. Vergnaud J M,. Controlled drug release from oral dosage forms. Ellis Horwood Limited, London, 1993.
3. Lordi N, Sustained release dosage forms. In: Lachman L, Lieberman H A, Kanig J L. The theory and practice of Industrial Pharmacy. Lea and Febiger, Philadelphia, pp. 430–478.
4. Rodriguez L, Caputo O, Cini M, Cavallari C, Grecchi R. In vitro release of theophylline from directlycompressed matrices containing methacrylic acid copolymers and/or dicalcium posphate dihydrate. II Farmaco. 1993;48: 1597–1604.
5. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). "AIDS Epidemic Update2005," Geneva, Switzerland: UNAIDS. Available at: http://www.unaids.org/epi/2005/ doc/EPIupdate2005_pdf_en/epi-update 2005_en.pdf. Accessed: December 10, 2006.
6. Zhou J, Paton N I, Ditangco R. Experience with the use of a first-line regimen of Stavudine, lamivudine and nevirapine in patients in the TREAT Asia HIV Observational Database. HIV Med. 2007; 8: 8-16.
7. Castillo S A, Hernandez J E, Brothers C H. Long-term safety and tolerability of the lamivudine/abacavir combination as components of highly active antiretroviral therapy. Drug Saf. 2006; 29: 811-826.
8. Hardman J G, Limbird L E, Molinoff P B, Ruddeon R W, Gilman A G. Goodman & Gilman's the Pharmacological Basis of Therapeutics. McGraw–Hill, New York, 2001, 1357.
9. Sweetman S C, Martindale. In: The complete reference. Pharmaceutical Press, London, 33rd Ed, 2002, 641.
10. Welling P G, Dobrinska M R. Sustained and controlled release drug delivery systems, Marcel Dekker Inc, New York, 1978.
11. Chang R, Robinson J R. Sustained release from tablets and particles through coating. In Phamaceuticls Dosage form Tablets, Vol. III, Marcel Dekker, New York, 1990, pp 199-302.
12. Cartensen J T. Drug Stability: Principle and Practices, Marcel Dakker, New Work, 2nd Ed, 1995, pp 538-550.
13. Shan-yang L. Effect of excipients on tablet properties and dissolution behavior of theophylene –tableted microcapsules under different compression forces. J Pharm Sci 1988; 77: 229-32.
14. Ranga KV, Padmalatha DK, Buri P. Cellulose matrices for zero-order release of soluble drugs. Drug Dev. Ind Pharm. 1988;14: 2299-320.
15. Higuchi T. Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963; 52: 1145-1149.
16. Koesmeyer R W, Gurny R, Doelker E, Buri P, Peppas N A. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm. 1983; 15: 25-35.