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Formulation, Development 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 by wet granulation into the monolithic matrices whose excipients were mixtures at different ratios of Eudragit RLPO, Eudragit, RSPO, Hydroxy Propyl Methyl cellulose K4M, MCC, Mannitol, Starch and Magnesium stearate. 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 F7 was found to have good matrix integrity throughout the study. The drug release study was carried out at $37 \pm 0.5^\circ\text{C}$ in Acid buffer of pH 1.2 for 2 hrs and Phosphate buffer 6.8 for 10 hrs. It was found that the drug release profile of these formulations were uniform and sustained throughout the period of study. The other parameters like thickness, hardness, friability, weight variation and drug content uniformity for tablets was found to be within the official limits.

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Key Words

Controlled release, HPMC K4M,
Eudragit RLPO, Eudragit RSPO,
Matrix and 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 prices⁵. 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 thymidine analogue reverse transcriptase inhibitor that is active *in vitro* against HIV-1 and HIV-28. 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 dose⁹. 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 rapidly¹⁰. The objective of the present work was to evaluate the suitability of Eudragit RLPO, Eudragit RSPO and Hydroxy Propyl Methyl cellulose K4M alone or in combinations, as polymeric materials for Wet granulation matrix tablets able to adequately extend drug release using a suitable rate controlling polymer. The influence of varying the Eudragit RLPO, Eudragit RSPO – 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 was obtained as a gift sample from cipla Labs (Mumbai, India). Hydroxy Propyl Methyl cellulose K4M and Eudragit RSPO and RLPO was obtained from Loba Labs (Mumbai, India). All other reagents used were of pharmaceutical or analytical grade.

Methods

In the present work the Stavudine tablets were prepared by wet granulation method. The drug and the excipients were passed through 20# 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 wet granulation technique using 8mm punch and die. Three different polymers like Hydroxy Propyl Methyl cellulose K4M, Eudragit RLPO and Eudragit RSPO were used as retardants, and MCC, Mannitol, starch as diluents and disintegrant in different ratio. Talc and magnesium stearate is used as a lubricant to reduce die wall friction.

Table -1 Composition of stavudine tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Stavudine	50	50	50	50	50	50	50	50
Eudragit RSPO	85	85	60	60	60	85	60	85
Eudragit RLPO	00	25	25	50	50	--	30	25
HPMC K4M	--	--	--	--	20	20	20	20
MCC pH 101	50	25	50	25	5	30	25	5
Starch	35	35	35	35	35	35	35	35
Mannitol	30	30	30	30	30	30	30	30
Total weight	250	250	250	250	250	250	250	250

*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.

EVALUATION OF TABLET.

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, Sigma instrument Chennai, India). Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, and Mumbai, India). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics) for 4 minutes at 25 rpm11.

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 1.2 acid buffers and pH 6.8 phosphate buffer, maintained at 37± 0.50C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Lab India, Mumbai, India) at 266 nm. The study was performed in triplicate.

RESULTS AND DISCUSSION.

Evaluation of tablets

The tablets of different formulations were subjected to various evaluation tests, such as weight variation, friability, hardness according to the procedure specified

in Indian Pharmacopoeia. All the parameters passes the test. The parameters are shown in table no 2.

Table no-2 Evaluation parameter of tablet stavudine

Sr.No.	Evaluation	F1	F2	F3	F4	F5	F6	F7	F8
1	Weight variation (mg)	250	251	249.5	252	250	251	250	251
2	Thickness (mm)	3.97	3.98	3.97	3.96	3.97	3.96	3.99	3.97
3	Friability (%)	0.22	0.23	0.21	0.29	0.24	0.18	0.15	0.27
4	Hardness kg/cm ²	7.5	8.0	8.5	8.0	7.5	7.0	8.5	8.0
5	%Drug release (hr)	63.78	67.07	70.69	78.01	98.13	92.46	99.25	95.7

***In vitro* release studies:**

Figure-1 shows the effect of different ratios of Eudragit RLPO and RSPO on release rate of stavudine. Formulation F4 shows highest percentage release of stavudine (78.01±0.46%) as compared to formulations F1, F2, F3 (63.78±1.31%, 67.07±0.74%, 70.69±0.46%).

Figure-2 shows the effect of different ratios of Eudragit RLPO, RSPO and HPMC K4M on release rate of stavudine. Formulation F7 shows highest percentage release of stavudine (99.25±0.32) as compared to formulations F5, F6 and F8 (98.13±0.67, 92.46±1.03 and 95.73±0.56 resp.). Because of highest percentage release Formulation F7 was designated as optimized batches. The composition of different matrix tablets is summarized in table.

The successful sustained release formulation must show pH independent release. So the release of stavudine starts from upper GI tract and continues for 10 to 12 hrs. up to the lower GI tract.

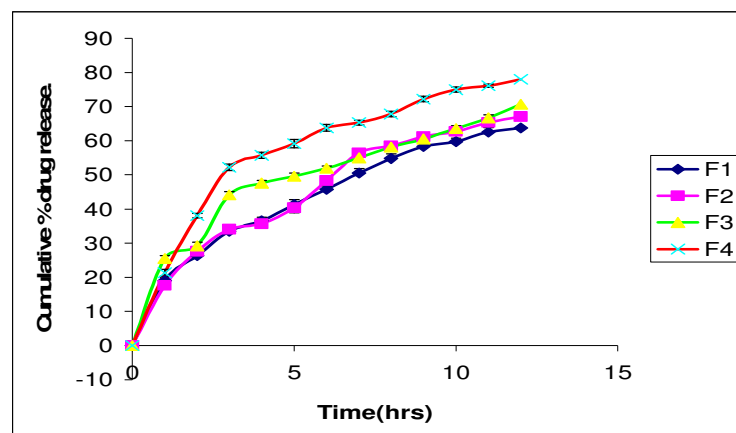


Figure -1 *In vitro* drug release profiles of formulations F1-F4 for 12 hrs

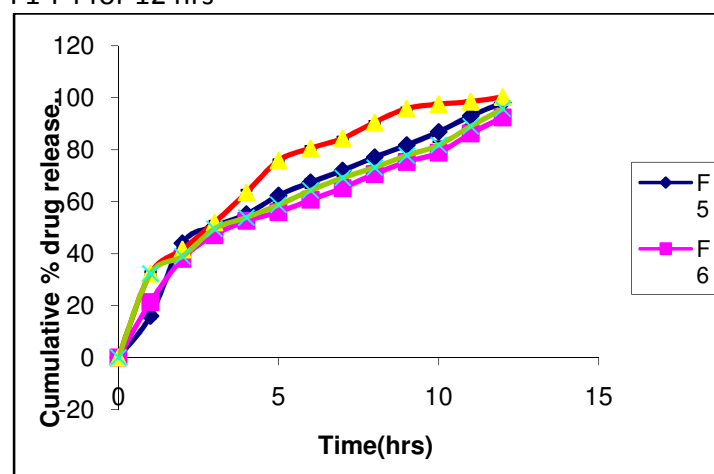


Figure -2 *In vitro* drug release profiles of formulations F5-F8 for 12 hrs

CONCLUSION

Matrix tablet containing Stavudine can be prepared successfully by using wet granulation method. The matrix tablets were found to be effective in sustaining the drug release more than 12hrs. Among all the formulation, F7 showed 99.25% 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 (F7). 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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