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GEOMATRIX TECHNOLOGY: FORMULATION AND EVALUATION OF STAVUDINE EXTENDED RELEASE TABLETS

Pawankumar Rai*

CSIR-Indian Institute of Toxicology Research Lucknow, Uttar Pradesh, India.

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***Corresponding Author**
Dr. Pawankumar Rai
CSIR-Indian Institute of Toxicology Research Lucknow, Uttar Pradesh, India.

ABSTRACT

The present study was to formulate and evaluate geomatrix tablets of Stavudine. Stavudine is a nucleotide analog drug used in the treatment of acquired immune deficiency syndrome (AIDS) has been incorporated into directly compressed geomatrices where excipients like Eudragit, ethyl cellulose, HPMC, MCC, aerosil and magnesium stearate were used. Polymers are water soluble, insoluble and acid resistant polymers. Formulation was optimized on the basis of acceptable tablet properties (weight variations, drug content hardness, friability) 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 Geomatrix integrity throughout study. The drug release study was carried out at 37±0.5°C in phosphate buffer of pH 7.4 for 24 hrs. It was found that the drug release profile of these formulations were uniform and sustained throughout the study period. The drug release kinetics of prepared tablets was evaluated for different kinetic models. The regression values of the optimized formulations were found to higher (0.987) in Higuchi model indicating drug releases by diffusion. The stability studies were carried out according to ICH guidelines which indicate that the selected formulations were stable.

KEYWORDS: Controlled release, Ethyl cellulose, Eudragit RL 100, Geomatrix, Stavudine, HPMC.

INTRODUCTION

Oral ingestion has long been the most convenient for non- invasive administration and commonly employed route of drug delivery for the chronic treatment of many diseases.[1] There are many ways to design extended release dosage forms for oral administration, and

one of them is multi-layered matrixtablet. One to three layer matrix tablets is a drug delivery device, which comprises a matrix core containing the active solute and one or more barriers incorporated during tableting process.[2] The barrier layers delay the interaction of an active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate.[3,4] One of the most common approaches used for prolonging and controlling the rate of drug release is to incorporate a drug in hydrophilic colloid matrix such as hydroxyl propyl methyl cellulose (HPMC K4M).[5]

Hydrophilic polymers have been given considerable attention in the formulation of extended release drug delivery systems for various drugs. HPMC and ethyl cellulose are few representative examples of the hydrophilic polymers that have been extensively used in the formulation of controlled release systems.[6] HPMC is soluble in water; it swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse[7], and is used for the fabrication of matrices with uniform drug release characteristics.[8,9] The selection of an appropriate dosage form is critical because a dosage form with poor drug delivery can make drug ineffective. Oral delivery of drugs is frequently associated with low bioavailability, high inter subject variability and lack of dose proportionality.[10,11]

There have been different approaches to achieve zero-order drug release from dosage forms for sustained plasma concentration. Among different approaches to achieve zero-order release from hydrophilic matrix technologies, multilayer matrices have been widely evaluated and developed for commercial products under the trade name of Geomatrix.[12] The technology makes use of bilayer or trilayer tablets to modulate the release and to achieve constant release.[13]

Stavudine is a thymidine nucleoside analogue which is phosphorylated intracellularly to an active metabolite, stavudine 5'- triphosphate. Stavudine is used to treat patients with Antiretroviral HIV infection. The drug stavudine inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator into viral DNA.[14]

Stavudine is typically administered orally as a capsule and an oral solution. The virustatic drug has a very short half life (1.30 hours). However, patients receiving Stavudine develop neuropathy and lactic acidosis. The side effects of Stavudine are dose dependent and a reduction of the total administered dose reduces the severity of the toxicity.[15] To reduce the

frequency of administration and to improve patient compliance, a once daily sustained release formulation of Stavudine is desirable. The drug is freely soluble in water, commonly used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance.[16] Stavudine is eliminated quickly, with an elimination half-life was ~1.6 to 3.4hrs. The short half-life of stavudine necessitated for fabricating extended release matrix tablets to provide a therapeutic amount of drug and maintain the desired drug concentration.

Hence, the objective of the present study was aimed to develop once daily controlled release multi-layered matrix tablets of stavudine with different hydrophobic and hydrophilic polymers to achieve zero-order drug release. The results indicate the optimized multi-layer Stavudine tablet can be successfully used for the treatment of HIV infection.

MATERIALS

Stavudine gift sample from Mylan, ethyl cellulose, Hydroxy propyl methyl cellulose and microcrystalline cellulose were purchased from Sigma Aldrich, USA. Other solvents and chemicals used for the study were of analytical grade.

METHODOLOGY

Analytical method development by UV-visible spectroscopy: Preparation stock solution of drug: of 100mg of the drug was weighed and dissolved in acidic medium. The volume was made up to 100ml to get stock solution of the concentration of 1000µg/ml. From this 1ml was pipetted and was made up to 100ml solution to get a concentration of 100 µg/ml solution. Out of this 10ml solution was transferred to a volumetric flask (100ml) and the volume was made up to mark with 0.1N HCl acid solution.

Determination of λmax of Stavudine: The standard drug solution (10µg/ml) was scanned between 200 to 400 nm using UV spectrophotometer. The λmax was found to be 266nm.

Formulation of controlled release stavudine trilayer matrix tablets

The trilayered matrix tablets of stavudine were prepared by direct compression method. The first step in the formulation was to develop the active middle layer so as to give atleast 90% drug release during 12 hrs. The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate time. This layer would be then sandwiched

between barrier layers (upper and lower layers) so as to continue the drug release for 24 hrs.

Preparation of active middle layer: The prepared formulations, active layer were prepared by direct compression method using polymers HPMC K15M and pure drug. After passing through sieve 60, mixed uniformly and compressed to form a core material.

Preparation of polymeric coat: The required quantities of HPMC K100M and ethyl cellulose were passed through the sieve 60. Then appropriate amounts of diluent, glident and lubricants were added. All this mixture mixed uniformly to get a homogenous blend (coating material).

Preparation of stavudine controlled release tablet geomatrix technology: Required tablet weight (500mg) was prepared by varying the concentration of coating material as in Table 1. The prepared core material was embedded in the coating material in and around then compressed into the tablet by using tableting machine.

Table No. 1: Composition of stavudine controlled release formulations from F1 to F9.

Sr.No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Stavudine	80	80	80	80	80	80	80	80	80
2	HPMCK15M (core)	100	100	100	120	120	120	160	160	160
3	Ethyl cellulose (coating)	50	60	80	50	60	80	50	60	80
4	HPMCK100 (coating)	50	60	80	50	60	80	50	60	80
5	Microcrystalline cellulose102	212.5	192.5	152.5	192.5	172.5	132.5	152.5	132.5	92.5
6	Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7	Magnesium stearate	5	5	5	5	5	5	5	5	5
8	Total weight	500	500	500	500	500	500	500	500	500

Evaluation parameters

Pre Compression parameters:

Bulk density (D_B): An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and measure the bulk volume. Bulk density is the ratio between a given mass of the powder and its bulk volume.

Bulk density = Mass of Powder / Bulk volume of the powder Bulk density (D_B) = W /V_0

Tapped Density (D_T): An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and the cylinder was tapped on a wooden surface from the height of 2.5 cm at two

second intervals. The tapping was continued until no further change in volume (until a constant volume) was obtained (V_f). The tapped density was calculated by using the formula. Tapped density[11] is the ratio between a given mass of powder (or) granules and the constant (or) fixed volume of powder or granules after tapping.

Tapped density = mass of the powder/ tapped volume Tapped density (D_T) =W/V_f

Hausner's ratio: Hausner's ratio is an indirect index of ease of powder flow and was calculated by the formula,

Hausner's ratio = D_T/D_B

Where, DT is the tapped density**;** DB is the bulk density

Compressibility index: Compressibility index (CI) was determined by measuring the initial volume (V_o) and final volume (V_f) after hundred tapping's of a sample in a measuring cylinder.

Angle of repose: Angle of repose was measured by fixed funnel method. It determines flow property of the powder. It is defined as maximum angle formed between the surface of the pile of powder and the horizontal plane.

Evaluation of post compression parameters for prepared Tablets

The designed formulation floating tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

Twenty tablets were randomly selected and weighed, to estimate the average weight and that were compared with individual tablet weight. The percentage weight variation was calculated as per Indian Pharmacopoeial Specification. Tablets with an average weight 250 mg so the % deviation was ± 5%.

Friability test

Twenty tablets were weighed and subjected to drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The friabilator was operated for 4 minutes and reweighed the tablets. % loss (F) was calculated by the following formula.

F =100 (W_0-W)/W_0

Where W0 = Initial weight, W = Final weight

Hardness test

The hardness of tablets was measured by using Monsanto hardness tester. The results were complies with IP specification.

Thickness test

The rule of physical dimension of the tablets such as sizes and thickness is necessary for consumer acceptance and maintain tablet uniformity. The dimensional specifications were measured by using screw gauge. The thickness of the tablet is mostly related to the tablet hardness can be used as initial control parameter.

Drug content

The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch were weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml of volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.

In-Vitro Drug Release Study

In-vitro dissolution study was carried out using USP II (basket) apparatus in 900ml of 7.4pH phosphate buffer for 24 hrs. The temperature of the dissolution medium was kept at 37±0.5°C and the basket was set at 75rpm. 5ml of sample solution was withdrawn at specified interval of time and filtered through 0.45µm whatmann filters. The absorbance of the withdrawn samples was measured at λmax 266nm using UV visible spectrophotometer. The concentration was determined from the standard curve of Stavudine drug prepared in pH 7.45 buffer at λmax 266nm.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release models.

Stability results

The optimized formulation was subjected to stability at 40±2 and 75±5% RH for period of 4 weeks. After 4 weeks tablet were analyzed for physical characteristics and drug release

profile.

RESULTS AND DISCUSSION

The present study was undertaken to formulate a geomatrix tablet dosage form containing an extended release layers on both sides.

Analytical method of Stavudine

By using UV spectrophotometer the maximum absorption of stavudine was found to be at 266 nm as shown in Figure 1. The remaining studies such as drug content and drug release were done at 266 nm for the accurate drug determination by using UV spectrophotometer.

Table 2 shows the drug linearity at concentrations from o to 15µg/mL. Stavudine of different concentrations obeyed beer's lamberts law at a concentration from 3 – 15 15µg/mL. The standard linearity plot of stavudine as shown in Figure 2.

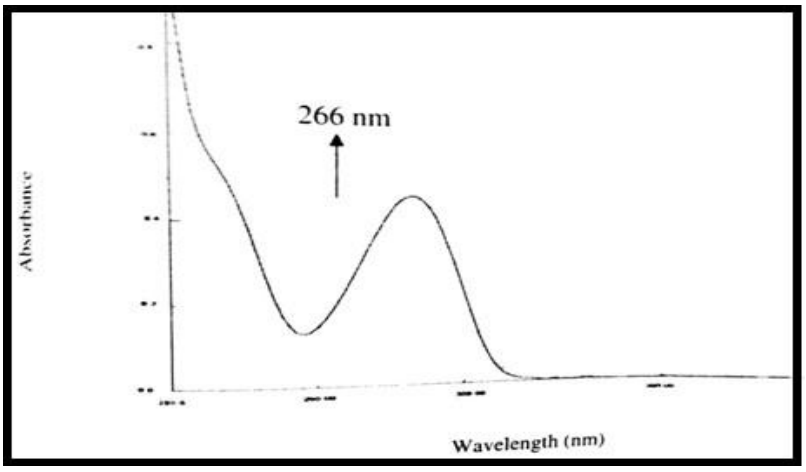

Fig. 1: Maximum absorption peak of stavudine by using UV Spectrophotometer.

Table No. 2: Standard plot of drug in 0.1 N HCl acid.

Concentration (µg/ml)	Absorbance
0	0.00 ± 0.00
3	0.158 ± 0.002
6	0.302 ± 0.007
9	0.401 ± 0.012
12	0.536 ± 0.004
15	0.654 ± 0.021

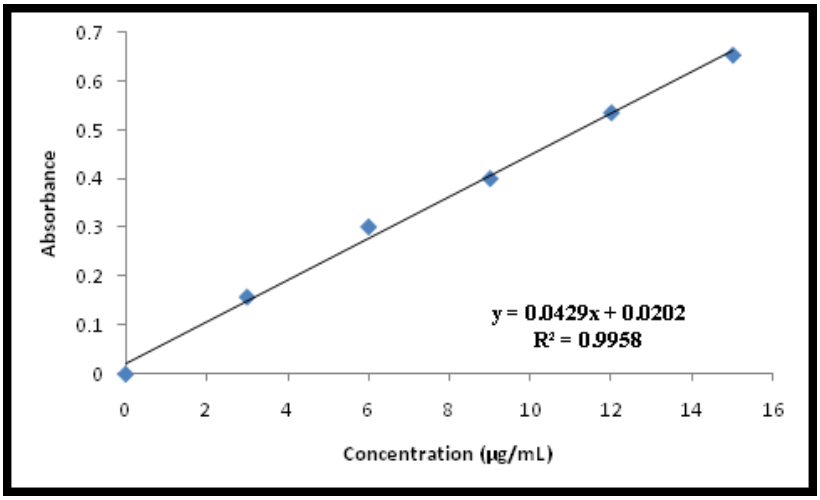

Fig. 2: Linearity plot of drug in 0.1 N HCl acid.

Flow properties of stavudine

The pure drug powder showed book and acceptable flow properties as mentioned below.

Table No. 3: Flow properties of Stavudine.

Parameter	Observation
Bulk density (g/ml)	0.282
Tapped density(g/ml)	0.341
Compressability index (%)	17.5
Hausner's ratio	1.212

Precompression parameters

The study involves Pre-formulation studies of drug excipients, formulation and processing development along with evaluation of dosage form made with the optimized formulation. It exhibited the angle of repose value of 17.66 – 30.12°C, good Carr's index value of 14.73 – 20.17% and Hausner's ratio of 1.19 – 1.29 for all pre- compressional mixtures as given in Table 4. Hence powder mixture was found suitable for direct compression method.

Table No. 4: Micromeritic properties of pre compressional powder blend.

Formulation code	Angle of repose	Carr's index	Hausner's ratio
F1	42.22 ± 0.16	31.19 ± 0.14	1.45 ± 0.07
F2	17.66 ± 0.32	18.25 ± 0.09	1.22 ± 0.02
F3	18.41 ± 0.15	19.37 ± 0.02	1.24 ± 0.01
F4	19.33 ± 0.87	18.05 ± 0.14	1.22 ± 0.02
F5	21.32 ± 0.41	17.90 ± 0.11	1.21 ± 0.03
F6	23.31 ± 1.27	19.12 ± 0.30	1.23 ± 0.01
F7	24.56 ± 3.01	17.46 ± 0.21	1.21 ± 0.03
F8	26.10 ± 0.94	19.72 ± 0.18	1.24 ± 0.01
F9	30.12 ± 2.19	18.14 ± 0.22	1.25 ± 0.03

Post compression parameters

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits as shown in Table 5. The average tablet weight of all the formulations was found to be between 1.22 ± 0.11 to 2.37 ± 0.12%**.** The maximum allowed percentage weight variation for tablets weighing >250 mg is 5% and no formulations are not exceeding this limit. And thickness of all the formulations was also complying with the standards that were found to be between 4.44 ± 0.08 to 4.53 ± 0.05mm. The average hardness for all the formulations was found to be from 5.46 ± 0.18 to 7.20 ± 0.38 Kg/cm^2 which were found to be acceptable. The average percentage friability for all the formulations was between 0.05 ± 0.08 and 0.34 ± 0.07, which was found to be within the limit. The drug content values for all the formulations were found to be in the range of 98.21 ± 0.33 to 99.91 ± 0.56**.** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Hence, all the parameters are within acceptable range pharmacopeias.

Table No. 5: Post compression parameters of Stavudine Geomatrix Tablets.

Formulation code	Hardness test (kg/cm^3)	Friability (%)	Weight Variation (%)	Thickness (mm)	Drug Content (%)
F1	5.46 ± 0.18	0.31 ± 0.09	2.33 ± 0.01	4.47 ± 0.08	98.21 ± 0.33
F2	5.48 ± 0.06	0.28 ± 0.08	1.72 ± 0.32	4.52 ± 0.04	98.01 ± 0.26
F3	5.71 ± 0.48	0.2 ± 0.05	1.38 ± 0.16	4.47 ± 0.05	98.45 ±0.14
F4	5.64 ± 0.38	0.34 ± 0.07	1.22 ± 0.11	4.44 ± 0.08	98.32 ± 0.17
F5	5.71 ± 0.32	0.32 ± 0.06	1.71 ± 0.37	4.55 ± 0.04	98.41 ± 0.11
F6	5.63 ± 0.44	0.29 ± 0.03	2.37 ± 0.12	4.48 ± 0.06	98.11 ± 0.24
F7	6.06 ± 0.32	0.05 ± 0.08	1.62 ± 0.43	4.53 ± 0.05	99.32 ± 0.14
F8	7.2 ± 0.38	0.21 ± 0.06	1.53 ± 0.41	4.52 ± 0.07	99.91 ± 0.56
F9	6.56 ± 0.53	0.29 ± 0.04	1.73 ± 0.69	4.50 ± 0.04	98.53 ± 0.13

***In vitro* drug release**

In vitro dissolution profile of stavudine matrix tablets of different formulations were carried out in phosphate buffer pH 7.4 for 24 hrs. The highest drug release was found in the formulation F4 showed 99.35% at the end of 24hrs. F4 was found to be optimized formulation based on the dissolution and other evaluation parameters the results were shown in the Figure 3. These results revealed that the geomatrix tablets were found to be effective in sustaining the drug release more than 24hrs when compared to available conventional matrix formulations. This sustained release formulations thus may reduce dose frequency and side effects as well as improved patient compliance.

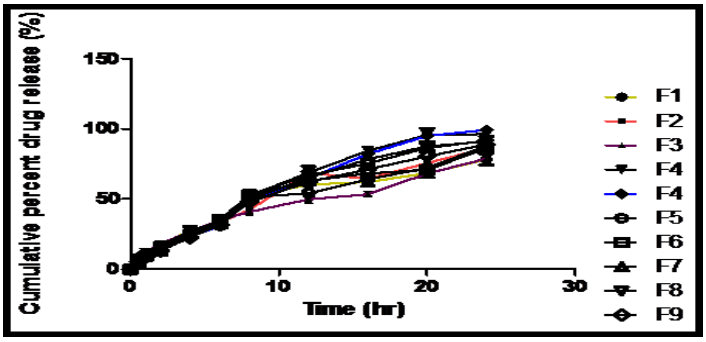

Fig. 3: Drug release profiles of prepared tablets.

Release Kinetics

The release data were analyzed as per zero order, first order, Higuchi and Peppas equation models. The correlation coefficient (r) values in the analysis of release data as per various models are given Table 6. Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from gastroretentive tablets formulated followed zero order kinetics. The correlation coefficient (r) values were higher in zero order model when compared to first order model as shown in Figure 4&5. The r-values were also more than 0.977 in the Higuchi and Peppas equation models indicating that the drug release from these tablets prepared also obeyed these two models. When the release date were analyzed as per Peppas equation the release exponent 'n' was found in the range 0.482-0.913. In the present study drug release data obtained is found to be zero order and best fitted to Higuchi model because regression coefficient was seen closest to 1 (R^2 =0.977 to 0.988) showing highest linearity. It confers the drug is released by diffusion assisted mechanism of release.

Table No. 6: Kinetics of formulation.

Formulation	Zero order	First order	Higuchi Plots	Hixon and crowell	Korsemeyer-Peppas plots	
					R^2	n
F1	0.965	0.897	0.979	0.964	0.549	0.913
F2	0.962	0.954	0.978	0.982	0.662	0.761
F3	0.975	0.878	0.977	0.976	0.543	0.909
F4	0.968	0.954	0.988	0.984	0.657	0.674
F5	0.967	0.955	0.980	0.989	0.658	0.678
F6	0.967	0.988	0.988	0.988	0.688	0.675
F7	0.965	0.977	0.985	0.988	0.698	0.604
F8	0.949	0.99	0.988	0.992	0.750	0.559
F9	0.964	0.988	0.987	0.995	0.742	0.482

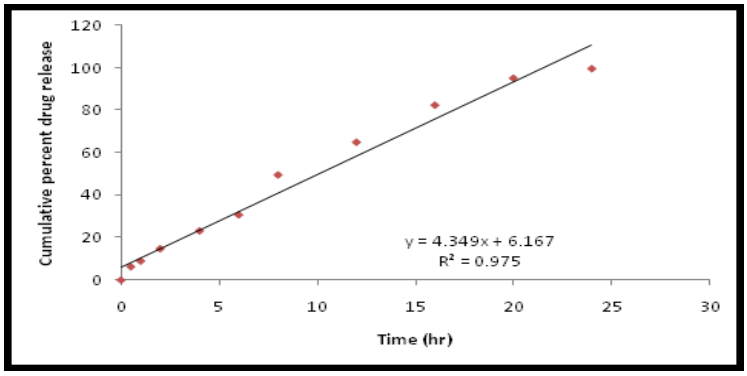

Fig. 4: Zero order kinetics plot of selected formulation.

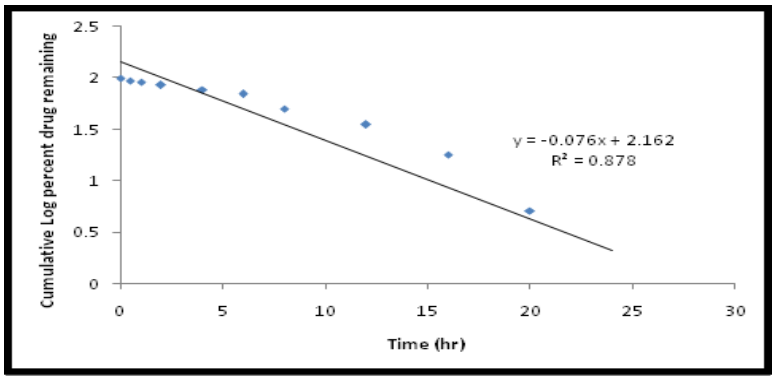

Fig. 5: First order kinetics plot of selected formulation.

CONCLUSION

Based on the results and discussion we can conclude that, geomatrix trilayer tablets can be successfully prepared by using direct compression technique using different concentration of polymers. Based on the evaluation parameters, drug dissolution profile and release drug kinetics F4 was found to be optimized formulation. The drug release from F4 was found to be zero order and best fitted to Higuchi's model confirming to be the diffusion assisted mechanism. Sustained release without initial peak level achieved with these formulations mat reduce dose frequency and side effects as well as improved patient compliance in the treatment of antiretroviral HIV infection.

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