

FORMULATION AND EVALUATION OF LAMIVUDINE SUSTAINED RELEASE TABLETS

P. Udaya Chandrika ^{*1}, Neha Fatima², Ch. Sampath Reddy², Sheema Tarannum², P. Bindhu², Khazra Jameel²

1-Department of Pharmacognosy, Bhaskar Pharmacy College, Yenkapally, Moinabad, Rangareddy Dist, Telangana 500075.

2-Department of Pharmaceutics, Bhaskar Pharmacy College, Yenkapally, Moinabad, Rangareddy Dist, Telangana 500075.

ABSTRACT : *The objective of the present study was to develop sustained release matrix tablets of Lamivudine. Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS (Acquired Immunodeficiency Syndrome). The sustained release tablets were prepared by direct compression method using hydroxyl propyl methylcellulose K4M, Ethylcellulose, Sodium alginate in various concentrations. The powder showed satisfactory flow properties and compressibility. The powders for tableting were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and hausner's ratio etc. The powder blend showed satisfactory flow properties. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and in-vitro release studies. All the formulations showed good results which were compliance with Pharmacopoeial standards. All the four formulations showed acceptable pharmacopoeial standards. The result of formulation F4 sustained the release of Lamivudine up to 8 hrs.*

Key words: *Lamivudine, sustained release, matrix tablets, natural and synthetic polymers, direct compression technique, FTIR studies, in vitro rug release.*

I. INTRODUCTION

Oral administration is the most convenient, widely utilized for both conventional and novel drug delivery systems, Tablets are the most popular oral solid unit formulations available in the market and are preferred by patients and physicians alike.¹ Sustained release dosage forms may be defined as any drug or dosage form modification that prolonged but not necessarily uniform release of drug. The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period.² Sustained release tablet allowing a 2 fold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form^{3,4}. Sustained release products provide advantage over conventional dosage form by optimising biopharmaceutics and pharmacokinetics properties of drug. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady state drug plasma concentration.^{5,6} Lamivudine is a synthetic nucleoside analog that is being increasingly used as the core of an antiretroviral regimen for the treatment of HIV infection.^{7,8} Lamivudine (β -L-2', 3'-dideoxy-3'-thiacytidine) (LAM), one of the dideoxycytidine analogue NRTIs, is the first nucleoside analogue approved to treat chronic HBV infection and AIDS. Conventional oral formulations of LAM are administered multiple times a day (150 mg twice daily) because of its moderate half-life ($t_{1/2}$ = 5-7 hours). Treatment of AIDS using conventional formulations of LAM is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multi-dose therapy, poor patient compliance, and high cost. Controlled release once daily formulations of LAM can overcome some of these problems.⁹

II. MATERIALS AND METHODS

Lamivudine was collected as a gift sample from Hetero labs, Hyderabad and various excipients like HPMCK4M, ethyl cellulose, sodium alginate, were purchased from AR chemicals, Hyderabad.

2.1 Methodology

Fourier Transform Infrared Spectroscopy (FTIR)¹⁰

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a dosage form. The use of FTIR technique allows pointing out the implication of the different functional groups of drug and excipients by analyzing the significant changes in the shape and position of the absorbance bands. In this method individual samples as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a mortar and compressed into disc by applying pressure of 5 tons for 5 mins in hydraulic press. The pellet was

kept in the sample holder and scanned from 4000 to 400 cm^{-1} in FTIR spectrophotometer. Then the characteristics peaks were obtained of all sample as well as mixtures.

Evaluation Studies

Determination of bulk density and tapped density

Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

$$\text{Bulk density} = \text{weight of sample taken} / \text{volume noted}$$

Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured.

$$\text{Tapped density} = \text{weight of sample taken} / \text{tapped volume}$$

Where,

V_o = initial volume

V_f = final volume.

Compressibility index

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

$$\text{Carr's index} = \text{Tapped density} - \text{Bulk density} / \text{Tapped density} \times 100$$

Hausner's ratio

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

$$\text{Hausner's ratio} = \text{Tapped density} / \text{Bulk density}$$

Angle of repose

The flow characteristics are measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where

h = height of pile

r = radius of the base of the pile

θ = angle of repose

Table-1: Formulation table of lamivudine sustained release tablets

S.NO.	INGREDIENTS	F1	F2	F3	F4
1	Lamivudine	200	200	200	200
2	Ethylcellulose	50	-	-	-
3	HPMC K15	-	50	-	25
4	Sodium alginate	-	-	50	25
5	Micro crystalline cellulose	145	145	145	145
6	Magnesium stearate	3	3	3	3
7	Talc	2	2	2	2
8	Total Wt	400	400	400	400

Direct compression method: ^{11,12}

Pre weighed ingredients were passed through Sieve no. 40 mesh separately and collected. Ingredients were mixed in geometrical order and thoroughly mixed in a polythene bag for 15 minutes to get a uniform mixture. Talc and magnesium stearate were added to the powder mixture and compressed on a 16- station rotary tablet compression machine using 10mm round flat face punch.

Evaluation of tablet^{13,14}**Weight variation**

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage.

Thickness

Twenty tablets were randomly selected from each batch and their thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

The percentage friability was measured using the formula,

$$\% F = \{1 - (W_o/W)\} \times 100$$

Where,

% F = friability in percentage

W_o = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Lamivudine. Dissolve the weighed quantity of powder into 100 ml of 6.8 phosphate buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at suitable wavelength using reagent blank.

In- Vitro Release study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time. Temperature maintained at 37±1. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, to it add 6.8 phosphate buffer solution. The diluted samples were assayed at suitable wavelength against reagent blank.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared Matrix tablets of lamivudine were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°C and refrigerator 2-8°C for a period of 30 days.

III.RESULTS & DISCUSSION**Drug - excipient compatibility studies (FT-IR)**

The compatibility between the drug and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

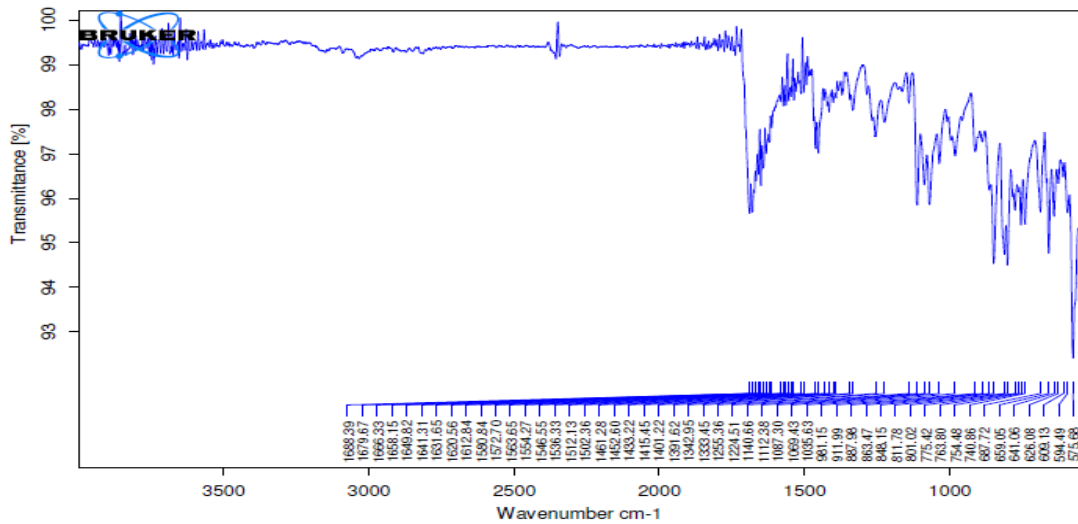


Fig-1 : FTIR Studies of Pure Drug

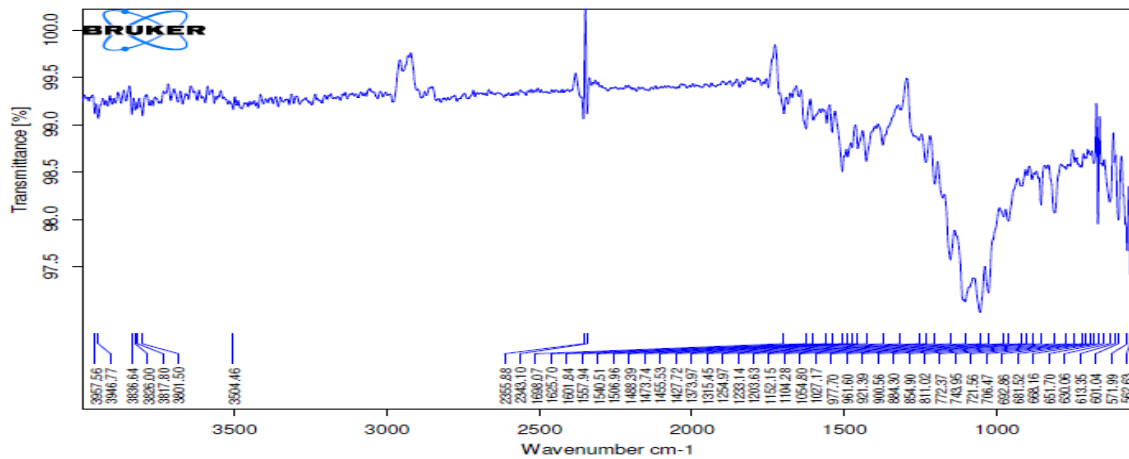


Fig -2: FTIR Studies of optimized formulation

Evaluation studies

Pre compression parameters

Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.419-0.432.

Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.521-0.543.

Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 27⁰ to 30⁰

Compressibility index: Compressibility index was carried out, it found between 10% to 20.70% indicating the powder blend have the required flow property for compression.

Table-2: Results for pre compression parameters

S. n o	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(0)
F1	0.425	0.536	20.70	1.26	28 ⁰
F2	0.432	0.543	20.44	1.25	30 ⁰
F3	0.419	0.521	19.57	1.24	27 ⁰
F4	0.422	0.526	19.77	1.24	29 ⁰

Post compression parameters**Weight variation:**

All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of $\pm 7.5\%$ of the weight. The weights of all the tablets were found to be uniform with low standard deviation values

Thickness:

Tablets mean thickness were uniform in F1 to F4 formulations and were found to be in the range of 3.25mm to 3.46mm.

Hardness:

The measured hardness of tablets of each batch ranged between 5.72 to 5.85 kg/cm². This ensures good handling characteristics of all batches.

Friability:

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F4 was found to be between 95.90% and 98.55 % of Lamivudine, it complies with official specifications.

Table-3: Physical parameters of tablets of each batch

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)
F1	400	3.25	5.15	0.45	90.90
F2	300	3.34	5.21	0.50	89.55
F3	398	3.50	5.28	0.48	93.50
F4	400	3.46	5.24	0.51	96.50

In-vitro Dissolution Study

All the four formulation of prepared matrix tablets of Lamivudine were subjected to in-vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for the 8 hrs.

Table-4: Dissolution Profile of F1 to F4

Time (hrs.)	F ₁	F ₂	F ₃	F ₄
0	0	0	0	0
1	19.12	18.20	17.11	20.10
2	22.45	25.30	23.11	31.45
3	32.80	35.32	33.76	49.90
4	42.63	44.65	43.23	56.70
5	58.21	59.28	52.11	65.16
6	63.35	68.55	65.22	72.22
7	78.26	80.10	75.16	82.26
8	82.25	92.11	85.12	94.50

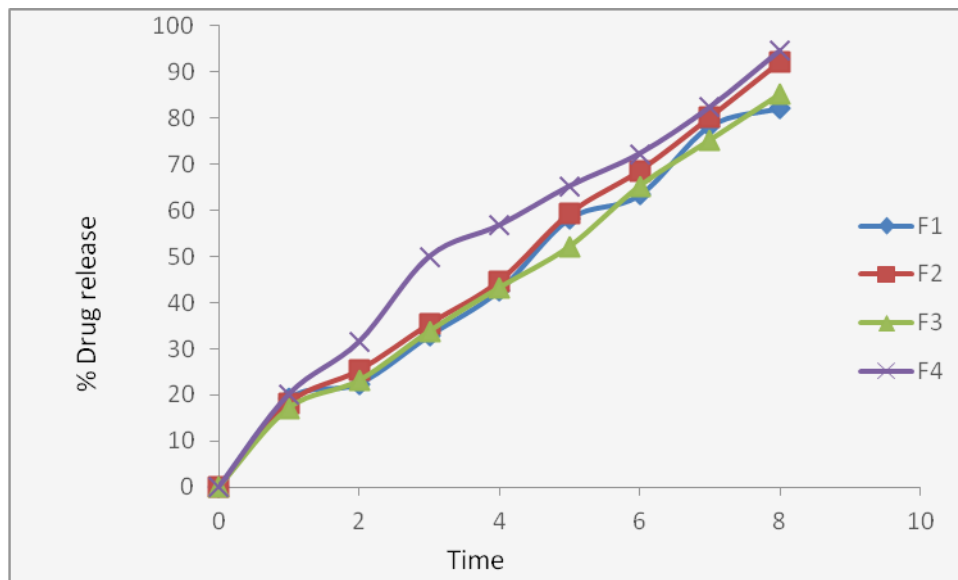


Fig-3: Dissolution profile of Formulations

Stability studies

Sustained release matrix tablets of Lamivudine formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40°C and 2-8°C for a period up to 30 days. The samples were withdrawn after periods of 15 days, and 30 days and were analyzed for its appearance, hardness, friability, drug content and in vitro release. The results revealed that no significant changes in appearance, drug content, hardness, friability, and in vitro release for F4 formulation. When it was stored at the three storage conditions. However there was slight variation in invitro release when it is stored at 2-8°C, there was no change when it is stored at 40°C and room temperature.

Table-5s: Results of stability studies of optimized formulation F-4

Formulation Code	Parameters	Initial	1 st Month	Limits as per Specifications
F-4	25 ⁰ C/60%RH % Release	94.50	94.29	Not less than 85 %
F-4	30 ⁰ C/75% RH % Release	94.50	94.05	Not less than 85 %
F-4	40 ⁰ C/75% RH % Release	94.50	93.99	Not less than 85 %

CONCLUSION

The present study was undertaken with an aim to formulate and evaluate Lamivudine sustained release tablets using different polymers as release retarding agents. Preformulation study was carried out and all the parameters were found within the specification. Hence different batches of Lamivudine were prepared using selected excipients. Powders were evaluated for Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets. Various formulations of sustained release tablets of Lamivudine were prepared by using different polymers in different proportions by direct compression technique. The tablets were evaluated for physical parameters, *in vitro* release study and stability studies. In-vitro release indicated that the formulation F4 had better dissolution profile along with sustained action as compare to other formulations. Stability study was conducted on tablets of Batch F4 stored at room temperature, 40°C, and 2-8°C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. No significant changes were observed in any of the studied parameters during the study period (30days), thus it could be concluded that formulation was stable.

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