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Advances in Bioresearch

ORIGINAL ARTICLE

Controlled Release Lamivudine Tablets as a Novel Anti-Retroviral for HIV and Hepatitis-B Treatment

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ABSTRACT
The aim was to produce and refine a controlled-release formulation of Lamivudine tablets to help in the long-term treatment of HIV and Hepatitis-B. A technique called Central Composite Design (CCD) was utilized to find the ideal concentrations of polymers for tablet hardness and their ability to release the drug within 24 hours. The study included a UV calibration curve (R^2 = 0.9991), solubility tests in acidic and phosphate buffer, FTIR, DSC, and a check on in-vitro drug release kinetics. The level of stability was tested using the methods recommended by the ICH Q1A(R2) guidelines under accelerated conditions. Additionally, MTT assay was performed using THP-1 cells to evaluate cytotoxicity and biocompatibility. MF9 was optimized and resulted in a hardness of 7.8 ± 0.2 kg/cm^2, and released 99.7 ± 0.8% of the drug in 24 hours. The drug was released by Zero-order kinetics (R^2 = 0.9859), which signifies prolonged and even release of the drug, regardless of its concentration. No important interaction between the drug and its excipients was observed through FTIR and DSC. Over 68% cell viability was maintained at the highest tested concentration (500 µg/mL), with an IC_{50} of 444.36 µg/mL. It was found that the properties of the tablets remained the same for 3 months under 40 ± 2°C / 75 ± 5% RH. Experimental findings that were predicted by the model had very little difference between them. Therefore, Lamivudine controlled-release provides better care by allowing for less frequent doses, proper drug levels, and compliance from patients. Because the formulation does not break down easily and continues to release medicine slowly, it could be used in future drug studies. The formulation shows promising potential for clinical translation, and additional animal studies should be performed to confirm the results obtained for this drug.
KEYWORDS: Lamivudine, Controlled-release tablet, HIV, Hepatitis-B, Central Composite Design, Zero-order kinetics, Optimization, Stability, Cytotoxicity study.

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INTRODUCTION

The spread of HIV and HBV remains a big public health problem around the world. An estimated 39 million people have HIV and approximately 1.3 million people become infected every year [1]. On top of that, HBV infection adversely affects approximately 296 million individuals worldwide and adds to the rate of liver diseases and deaths [2]. Progress made in treating viral diseases is still challenged by patients failing to use their medicine, the virus adapting to drugs and experiencing negative effects, mainly with dosing regimens that are repeated frequently [3]. They interfere with the quality of care and escalate spending on health, putting pressure on both individuals and the health system, mostly in the developing world. Presently, experts are calling for long-acting antiviral medicines to make it easier for patients to adhere to treatment and manage their health outcomes [4]. Nevertheless, because most first-line cards depend on basic, immediate-release tablets, major trouble areas are still left unaddressed [5]. Therefore, new techniques are essential to help medicines against viruses reach patients and be used as instructed [6].

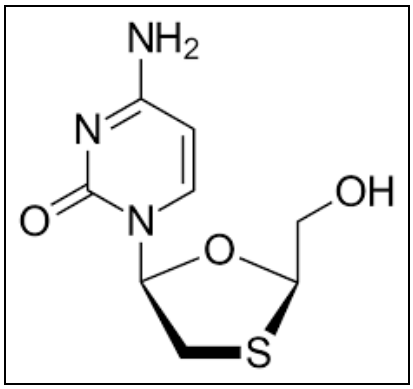

Figure 1: Structure of lamivudine

The target treatment for both HIV and chronic HBV infections often includes lamivudine (3TC) [7]. Its chemical structure is (−)-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine and it has a molecular weight of 229.26. The drug absorbs quickly through the mouth, but because it clears the blood fast, it has to be given often in the day [8]. Lamivudine interferes with reverse transcriptase which prevents viral DNA synthesis. Many studies have shown that it can both reduce the amount of HIV and prevent HBV from replicating [9]. Due to problems with development of drug resistance and patient adherence, it is still necessary to improve the way medicines are given [10]. According to current studies, medicines released slowly in the body can maintain normal levels of the drug for a longer time and therefore improve treatment outcomes while reducing any negative side effects. This proof indicates that other research should be conducted on delivering Lamivudine in modified ways [11].

With controlled-release, there is hope to handle the limitations associated with traditional ways of giving Lamivudine. In this case, a matrix-type tablet is suggested whose drug release is managed by hydrophilic polymers such as HPMC for an extended time [12]. With this approach, the blood plasma level of drugs does not increase, patients take antibiotics less frequently and chances for resistance might lessen. Instead of regular formulations, controlled-release tablets are helpful since they increase adherence, cause fewer unwanted effects and ensure better medical outcomes [13]. Following this way is based on making sure there are always higher levels of the drugs than the minimum they need to inhibit HIV and HBV. Thanks to the progress made in both polymer field and drug device technology, it is now possible to accurately control the phase where the drug is released [14]. Furthermore, controlled-release drug systems for other antiviral drugs have worked well in clinical practice, so Lamivudine-controlled-release formulations also look promising [15].

This research work is designed to prepare and optimize an extended-release Lamivudine tablet to help treat HIV and HBV infections. The specific goals in the program are to develop formulations, examine them in a test tube, test how fast they release and determine their stability. It focuses on providing a new, user-friendly therapy that helps achieve better results and eases the problem of patients having to take medicines frequently.

MATERIAL AND METHODS

MATERIALS

Lamivudine was obtained as a gift sample from Cipla Ltd., Oune, India. Hydroxypropyl methylcellulose K100M (HPMC K100M) and Eudragit RS 100 were procured from Loba Chemie Pvt. Ltd., Mumbai. Polyvinylpyrrolidone K30 (PVP K30), lactose monohydrate, talc, magnesium stearate, and Aerosil were purchased from SD Fine-Chem Ltd., Mumbai. Analytical grade solvents including ethanol, methanol, acetone, dimethyl sulfoxide (DMSO), and phosphate buffer components were used throughout the study. All chemicals and reagents used were of analytical grade and used without further purification. Double-distilled water was used in all experimental procedures.

METHODS

Calibration curve determination

A calibration curve for Lamivudine was prepared to test the accuracy of quantitative analysis. Lamivudine was dissolved in 100 mL of phosphate buffer (pH 6.8) to reach a final concentration of 1000 µg/mL. Solutions containing 5, 10, 15, 20, 25 and 30 µg/mL were made by step-by-step diluting the main solution. Clear quartz cuvettes were placed in the UV-1800 Shimadzu, Japan spectrophotometer and absorbance values were recorded at 270 nm. The buffer used for the blank was phosphate. All concentrations of the standards were replicated 3 times (n=3) and the mean absorbance for every concentration was used to

draw the calibration curve. Analysis of linear regression was used to find the equation and the correlation coefficient, showing the data were linear [16].

Solubility study

Using the solvent saturation method, Lamivudine was measured for solubility in water, methanol, ethanol, acetone, DMSO and phosphate buffer (pH 6.8). For each solvent, 10 mL was mixed with a slightly higher amount of Lamivudine and put into a sealed vial; the solution was shaken with a shaker on the CIS-24BL (Remi, India) for 24 hours at 25 ± 2°C. Filtered the mixtures through Whatman No. 1 filter paper after being in equilibrium and diluted them with the proper solvents. The absorbance was determined by UV-Visible spectrophotometry (UV-1800, Shimadzu, Japan) at wavelength 270 nm. Each solubility experiment was repeated three times (each group had n=3) and then the average concentration was measured for the solvent [17].

Differential scanning colorimetry

To check the compatibility and thermal properties of Lamivudine with some excipients, we performed differential scanning calorimetry (DSC). For each of the samples, pure Lamivudine and physical mixtures were accurately weighed (between 2 and 5 mg) and sealed in standard aluminum pans. A DSC instrument (DSC-60 Plus from Shimadzu, Japan) was used to analyze heat flow and temperatures in an atmosphere of nitrogen flowing at a rate of 50 mL/min. Temperature was raised from 30°C to 300°C at a steady pace of 10°C per minute. A pan made of aluminum was prepared to serve as a comparison. To ensure accuracy, all the measurements were made three times (n=3). The thermograms were checked for any distinctive peaks, melting points and possible ways drug and excipients can connect [18].

Fourier Transform Infrared Spectroscopy

FTIR was used to determine if Lamivudine and the other ingredients in the compound interact chemically. A mixture of pure drug, each individual excipient and their mix was finely ground and combined with potassium bromide (KBr) in a ratio of 1:100. This was then shaped into a transparent pellet under hydraulic pressure. Recording was done using an FTIR spectrometer (IRAffinity-1S from Shimadzu in Japan) and the measurements were made between 4000 and 400 cm-1, with a resolution of 4 cm^{-1}. For each sample, the process was performed 32 times to collect an average spectrum. Each set of samples was measured three times (n=3) to confirm the experiment's repeatability. Changing, new or missing peaks in the spectra were observed and noted to detect possible interactions between the drug and its ingredients [19].

Experimental design

A Central Composite Design (CCD) was utilized to optimize the formulation of Lamivudine-controlled release tablets using Design-Expert® software (Version 13.0, Stat-Ease Inc., USA). The design included a total of 10 experimental runs, incorporating factorial points, axial points, and 2 center points to ensure adequate estimation of experimental error and model predictability. Two independent formulation variables were selected: HPMC K100M (X_1), varied at 20% and 30% w/w, and Eudragit RS 100 (X_2), varied at 10% and 15% w/w. These polymers were chosen for their hydrophilic and hydrophobic matrix-forming properties, respectively, which help regulate drug release and tablet integrity. The influence of these variables was studied on two critical dependent responses tablet hardness (Y_1) and percent drug release at 24 hours (Y_2) to achieve a sustained and controlled drug delivery profile. The selected levels of independent and dependent variables are summarized in Table 1. The relationship between the factors and responses was modeled using a second-order polynomial regression equation:

$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_{12}X_1X_2 + \beta_{11}{X_1}^2 + \beta_{22}{X_2}^2$,

where Y is the predicted response, X_1 is the HPMC K100M concentration, and X_2 is the Eudragit RS 100 concentration [20–23].

Table 1: Variables and their levels in Central Composite Design

Variables	**Levels**	
Independent variables	**Low**	**Medium High**
(A) = HPMC K100M (%w/w)	10	20
(B) = Eudragit RS 100 (%w/w)	10	15
Dependent variables	**Goals**	
(R_1) = Tablet hardness (kg/cm^2)	Maximize	
(R_2) = Drug release at 24 h (%)	Target	

Table 2: Composition of Lamivudine Controlled Release Tablets

Ingredients	MF 1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9	MF10
Lamivudine	300	300	300	300	300	300	300	300	**300**	300
HPMC K 100 M	175	175	140	210	224.49	140	175	210	**175**	125.50
Eudragit RS 100	87.5	62.75	70	105	87.5	105	112.24	70	**87.5**	87.5
PVP K 30	14	14	14	14	14	14	14	14	**14**	14
Aerosil	7	7	7	7	7	7	7	7	**7**	7
Lactose (q.s to 700 mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	**q.s**	q.s
Talc	14	14	14	14	14	14	14	14	**14**	14
Magnesium sterate	7	7	7	7	7	7	7	7	**7**	7

Micromeritics study

Before compression, each powder blend was examined with micromeritics to find out about its flow and ease of compression. Bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose were measured using standard techniques. Quantities of powder were added to 100 mL graduated cylinders and the initial and final volumes were recorded after the powder was tapped. Carr's index and Hausner's ratio were determined using the actual densities measured. To find the angle of repose, we used a fixed funnel technique, setting the funnel vertically above the surface and measuring the height and width of the cone as the powder came out. Experiments were performed three times on every batch for the study to be reliable and consistent [24,25].

Formulation of Controlled Release Lamivudine tablets

The controlled release Lamivudine tablets were created using a matrix-based approach to direct compression. The pharmacists prepared each tablet so that it would have 300 mg of Lamivudine and total weight of 700 mg. To find the best concentrations of matrix-forming polymers, scientists used a 10-run central composite design. In designing various batches, the main polymers chosen for retardant function were HPMC K100M and Eudragit RS 100 which were used at different concentrations as indicated in Table 2. All materials such as Lamivudine, HPMC K100M, Eudragit RS 100, PVP K30 (binder), Aerosil (glidant), Talc (lubricant) and Magnesium stearate (lubricant) were weighed in the proper amounts and passed through a 40# sieve to obtain particles of the same size. They used geometric dilution to blend the sieved compounds in a mortar and pestle until all parts were uniform. 700 mg of tablets were created by using lactose as a filler. The resulting blend was compressed into tablets with a rotary tablet compression machine that had flat-faced punches [26,27].

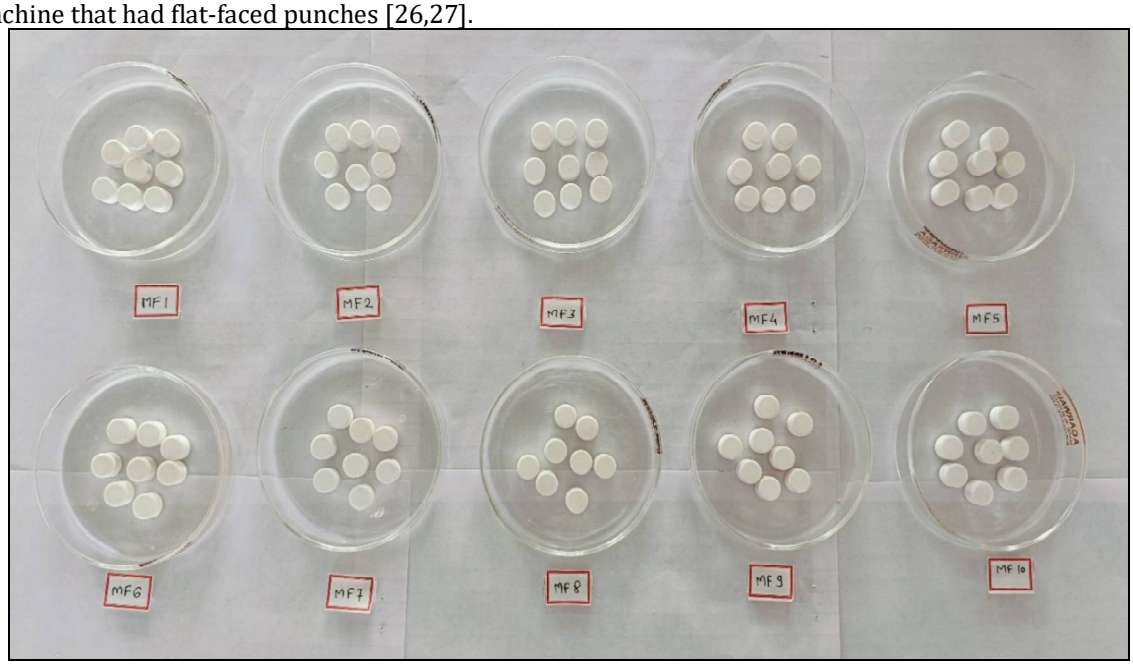

Figure 2: All formulated batches of Lamivudine Controlled Release Tablets

Evaluation of formulated batches of Lamivudine Controlled Release Tablets

Organoleptic evaluation

The organoleptic evaluation of the formulated controlled release Lamivudine tablets was carried out through visual and sensory inspection. Each batch was examined for color, shape, texture, and odor

immediately after compression. The tablets were assessed under adequate lighting conditions to ensure consistency in appearance. Observations were made manually without the use of any instruments, and parameters such as uniformity of surface, presence of any physical defects (e.g., cracks, capping), and overall aesthetic quality were recorded. This evaluation was performed as a routine quality control check to ensure the formulations met acceptable pharmaceutical standards [28].

Weight Variation

Twenty tablets from every batch of Lamivudine controlled release were chosen randomly to check their weight uniformity. Each tablet was checked using a Shimadzu BL-220H digital analytical balance from Japan with a sensitivity of 0.1 mg while in the laboratory. An average weight was calculated for every batch and the difference between this and each individual tablet was measured. Experts ensured that the results matched the limits set by the Indian Pharmacopoeia for accuracy in preparing the medicine [29].

Tablet Thickness and Diameter

To ensure uniformity in tablet dose and successful packaging, the product's thickness and diameter need to be controlled. Ten tablets from every batch of controlled release Lamivudine were chosen at random and their dimensions were assessed. Both the center-based diameter and the thickness of every tablet were measured with a digital Mitutoyo 500-196-30 caliper with a precision of 0.01 mm. Placing each tablet between the calipers guaranteed that all the readings were correct. After getting the data, I noted them down and expressed the results by reporting the mean ± standard deviation for each significant value (n = 10). Using this process, it was possible to measure consistency across all batches which plays a big role in both maintaining the quality of manufacturing and what patients prefer [30].

Tablet Hardness (Crushing Strength)

To check the mechanical strength, the hardness of the tablets was measured for every batch of the controlled release Lamivudine. These ten tablets were chosen and their hardness was tested using a Monsanto-type hardness tester (Campbell Electronics, India). A tablet was allowed to rest on the anvils and then pressed evenly until it was broken apart. The hardness was measured using the unit of kg/cm^2. Each batch was tested in a laboratory with controlled conditions and both the mean hardness and standard deviation (based on 10 values) were worked out. As a result of this assessment, it was decided that the tablets were strong enough to face stresses from handling, putting them in packages and shipping without breaking apart [31].

Tablet Friability

Using a Roche friabilator (Electrolab EF-2, India), the resistance to mechanical handling was evaluated for the controlled release Lamivudine tablets. Each batch, 6.5 grams of tablets were carefully weighed and treated to 100 rotations at a speed of 25 rpm for 4 minutes. After taking the measurements, the tablets were thoroughly cleaned of dust and their weight was written down. The tablets' friability was assessed by looking at the percentage weight loss they experienced. If the tablet surpasses 1% in terms of friability, according to pharmacopeial standards, it is believed that mechanical stress will not cause any significant weight or surface loss during use and transportation [32].

Drug Content Uniformity

The controlled release Lamivudine tablets were checked to ensure that each unit contains the same drug amount. For each batch prepared, ten tablets were randomly selected, one was accurately weighed using a mortar and pestle and the powder was formed. One hundred milligrams of Lamivudine powder was weighed and dissolved in 100 mL of phosphate buffer, setting the pH to 6.8. For 15 minutes, the solution was sonicated so that the drug was dissolved completely and it was then filtered using Whatman No. 1 filter paper. An appropriate dilution was performed and then the absorbance was measured at 270 nm with the Shimadzu UV-1800 spectrophotometer. Lamivudine was measured using the standard curve based on the tests performed. The findings were presented as mean ± standard deviation (based on ten samples) and the amounts were compared to what the pharmacopeia accepts for drug content uniformity [33].

***In-vitro* Drug Release Studies**

The drug release from the controlled release Lamivudine tablets was studied using a USP Type II (paddle) dissolution apparatus (Electrolab TDT-08L in Mumbai, India). The experiment was performed in 900 mL of buffer (pH 6.8) kept at 37 ± 0.5 °C and the paddle rotated at 50 rpm. Each dissolution group's batch tablet was introduced to the medium and 5 mL samples were taken every hour for 1, 2, 4, 6, 8, 12 and 24 hours. Just after each sampling, the same amount (equal to the sample) of prewarmed fresh medium was added to keep the sink at the proper temperature. Samples without dye were filtered using a 0.45 µm membrane and then measured at 270 nm with a Shimadzu UV-1800 UV-Visible spectrophotometer (made in Japan). The percentage of drug release was calculated for all time points, the data was reported as

mean plus standard deviation for replicate batches (n = 3) and values were analyzed through graphical reporting [34].

Drug Release Kinetics Study

Release data for the optimized controlled release tablet of Lamivudine were evaluated to understand the release pattern and process involved. The drug release data were adjusted to Zero-order, First-order, Higuchi and Korsmeyer–Peppas models. While the Zero-order model says the rate of drug release remains constant regardless of concentration, the First-order model indicates that release depends on the drug concentration. Higuchi proposes that drugs are released from a matrix based on diffusion and the Korsmeyer–Peppas model defines the type of release based on how the release exponent (n) describes whether it is Fickian or anomalous transport. The correlation coefficient (R^2) was worked out in Microsoft Excel for every model, to decide on the most accurate one. It was decided that the best model to describe the drug release from the optimum formulation is the one with the maximum R^2 [35].

Biocompatibility study using MTT assay

For the biocompatibility evaluation, an MTT assay was performed on the THP-1 human monocytic cell line to assess the cytotoxic potential of Lamivudine. THP-1 cells were cultured in DMEM supplemented with 10% fetal bovine serum and maintained at 37°C with 5% CO_2. Cells were seeded at a density of 1×10^5 cells per well in 96-well plates and incubated for 24 hours. After achieving a half-confluent monolayer, the cells were treated with nine different concentrations of Lamivudine using a double dilution method in MEM with FBS. Untreated cells served as the control. After 48 hours of incubation, the culture medium was replaced with fresh medium and 10 µL of MTT reagent was added to each well, followed by a 4-hour incubation. Subsequently, a solubilization solution was added and incubated for 1 hour to dissolve the formazan crystals. Absorbance was recorded at 570 nm using a microplate reader, and percent cell viability was calculated. The IC50 value of Lamivudine was found to be 444.36 µg/mL, indicating low cytotoxicity and suggesting its biocompatibility with THP-1 cells.

Formula used for calculating percentage cell viability

$$Percent\ Cell\ Viability\ (\%) = \frac{Absorbance\ of\ Test}{Absorbance\ of\ control} \times 100$$

Stability Study

Lamivudine tablet formulation with controlled release was examined by accelerating temperature and humidity to see how it changed the tablet over a certain period. ICH guidelines were used for the study, so the tablets were packed in aluminum blister packs and then kept stored in the ThermoLab stability chamber at 40 ± 2 °C and 75 ± 5% RH for a total of three months. Every 0, 30, 60 and 90 days, samples were taken. For each assessment, three measurements were made to check appearance, amount of drug, disintegration time and rate of drug release in the lab. The assessments of the formulation's characteristics over time were made by expressing all data as mean ± standard deviation [36].

Statistical Analysis

Results from the experiments were analyzed with Design Expert® (Version 13.0) and GraphPad Prism® (Version 10.1.2). Based on the sequence of p-values, adjusted R^2 and predicted R^2 values, a quadratic model was chosen. ANOVA was introduced to check the effects that formulation variables had on the time taken for disintegration, the release of the drug and wetting. Release of the drug was modeled in GraphPad Prism, with Design Expert® creating both contour and 3D surface plots to show how the factors interact. The formula used in the model produced accurate predictions with very little error [37].

RESULTS

Results of micromeritics study

The study found that each formulation showed good flow, having bulk density between 0.73 and 0.76 g/mL and Carr's index between 8.87% and 10.5%. Since the Hausner ratio was between the given limits (1.09–1.15) and the angle of repose was steady (25.68°–26.10°), the drug is suitable for direct compression, as shown in Table 3.

Table 3: Micromeritics Evaluation of Pre-Compression Powder Blend for All Formulated Batches of Lamivudine Tablets

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose
MF1	0.74±0.004	0.81±0.054	8.91±0.055	1.09±0.05	25.92±0.50
MF2	0.75±0.021	0.82±0.043	9.16±0.042	1.10±0.06	25.95±0.33
MF3	0.74±0.03	0.83±0.057	10.5±0.064	1.11±0.07	26.02±0.27
MF4	0.76±0.044	0.84±0.065	8.87±0.077	1.09±0.08	26.02±0.44
MF5	0.74±0.32	0.82±0.012	10.02±0.098	1.12±0.09	25.95±0.71
MF6	0.75±0.007	0.83±0.034	8.87±0.045	1.09±0.08	26.02±0.52
MF7	0.75±0.003	0.83±0.068	9.98±0.044	1.15±0.07	26.05±0.34
MF8	0.76±0.005	0.84±0.034	10.4±0.046	1.11±0.05	26.09±0.12
MF9	0.76±0.048	0.85±0.044	10.5±0.022	1.11±0.04	26.10±0.23
MF10	0.73±0.035	0.81±0.065	10.1±0.082	1.09±0.08	25.68±0.42

All values are expressed as mean ± SD (where n=3)

Calibration curve determination

Lamivudine showed a good trend of increasingly linear concentrations over the range 5–30 µg/mL in phosphate buffer (pH 6.8), fitted by y = 0.0395x + 0.0118 with an R^2 of 0.9988, meaning the accuracy and precision were both high. A UV-Visible spectrophotometer was used to test absorbance at 270 nm and the findings are shown in Figure 3.

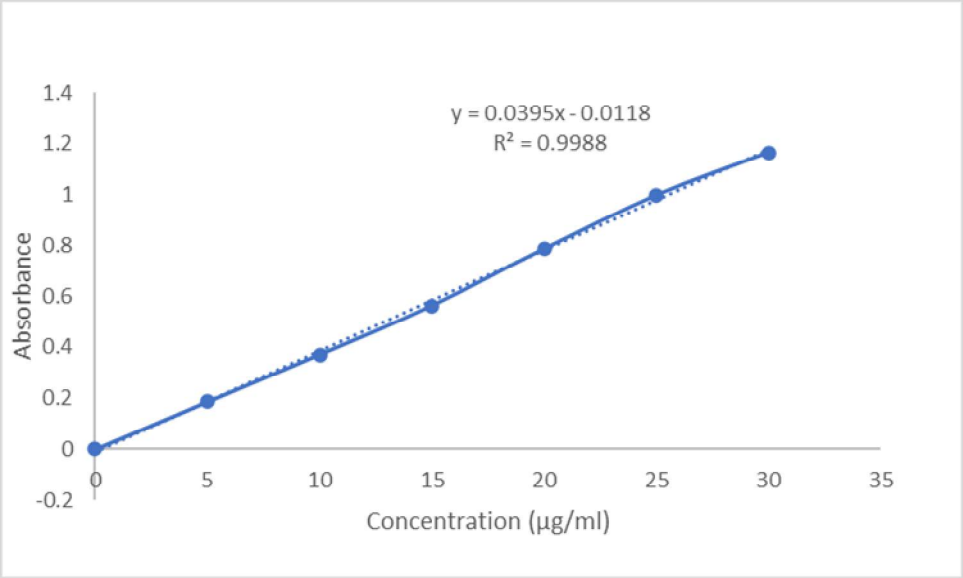

Figure 3: Calibration curve determination in phosphate buffer (pH 6.8)

Determination of solubility in various solvents

The saturation method was used to determine that Lamivudine's solubility varied greatly due to the solvent system used. The drug's solubility was the greatest in acidic 0.01 N HCl (276.08 ± 2.61 mg/mL), second greatest in DMSO (20.114 ± 0.731 mg/mL) and weaker in phosphate buffer pH 6.8 (3.037 ± 0.095 mg/mL). However, it was very hard to dissolve Aquilon in water (0.065 ± 0.004 mg/mL) or methanol (0.089 ± 0.006 mg/mL). It is, therefore, suitable to use pH 6.8 buffer for dissolution studies. Solubility information for each compound is supplied in Table 4.

Table 4: Solubility of Lamivudine in Various Solvents

Sr. No.	Solvent	Solubility (mg/mL)	Result
1	Water	0.065 ± 0.004	Practically insoluble
2	Methanol	0.089 ± 0.006	Practically insoluble
3	Ethanol	0.502 ± 0.013	Very slightly soluble
4	Acetone	1.128 ± 0.022	Slightly soluble
5	Dimethyl sulfoxide (DMSO)	20.114 ± 0.731	Sparingly soluble
6	Phosphate buffer (pH 6.8)	3.037 ± 0.095	Slightly soluble
7	0.01 N HCl	276.08 ± 2.61	Freely soluble

All values are expressed as mean± SD (Where n=3)

Differential scanning colorimetry

DSC was used to study how Lamivudine and the excipients reacted to changes in temperature. Lamivudine was confirmed to be a crystal since the thermogram indicated melting and had a peak at 176.85°C. No new drug-excipient interaction was seen, because there were no other peaks in the

absorbance. According to these results, Lamivudine can be combined with the selected excipients at high temperatures. You can see the thermograms in Figure 4.

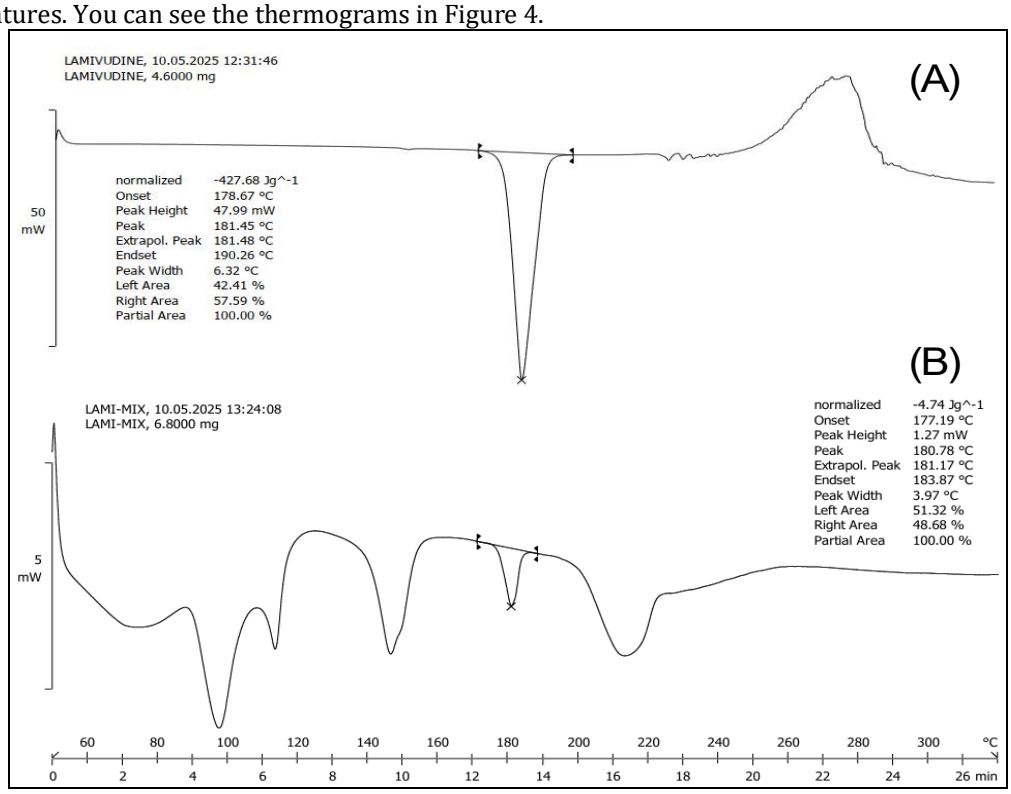

Figure 4: Differential Scanning Calorimetry (DSC) thermograms of (A) pure Lamivudine and (B) physical mixture of Lamivudine with excipients.

Fourier Transform Infrared spectroscopy

The study looked into the possible reactions between Lamivudine and various excipients by using FTIR spectroscopy. In the IR spectra of the physical mixture, the important characteristics of Lamivudine at –OH/–NH stretch (3329.55 cm^{-1}), C=N stretch (1648.84 cm^{-1}) and C–N/C–O stretch (1276.47 cm^{-1}) remained and did not move or vanish. It is a sign that there is no chance of the drug reacting badly with the excipients. The overlapping spectra of FTIR and a table explaining the functional groups are given in Figure 5 and Table 5.

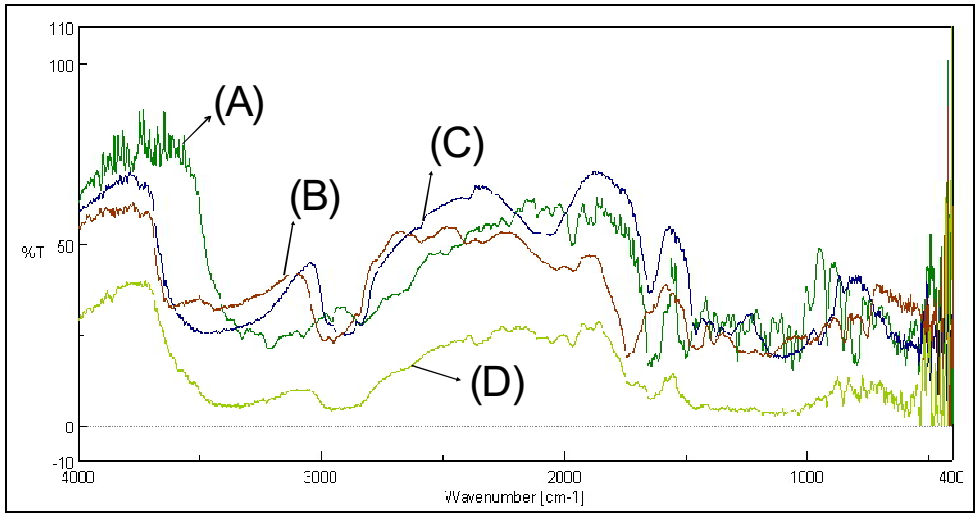

Figure 5: FTIR overlay spectra of (A) Lamivudine (pure drug), (B) HPMC K100M, (C) Eudragit RS 100, and (D) physical mixture

Results of Organoleptic evaluation

All ten batches of Lamivudine tablets had the same look after the organoleptic evaluation. Consistent formulation and compression were shown in white and odorless round and flat pills. The product had a

clean and smooth finish which indicates it is easy to handle and attractive in appearance. Details from the observations are included in Table 6.

Table 5: Interpretation of FTIR Spectra of Pure Drug, Excipients, and Physical Mixture

Functional Group	Standard Wavenumber (cm^{-1})	Pure Drug (cm^{-1})	HPMC K100M (cm^{-1})	Eudragit RS 100 (cm^{-1})	Physical Mixture (cm^{-1})
–OH / –NH Stretch	3200–3600	3329.55, 3213.79	3613.95	2965.02	3362.72, 3377.71
C–H Stretch (Aliphatic)	2850–2950	2835.81	2957.3	2911.99	2911.99
C=O Stretch (Carbonyl)	1700–1750	—	1739.48	1731.76	—
C=N / C=C Stretch	1600–1650	1648.84	—	1640.16	1640.16
C–H Bending	1400–1500	1494.56	1452.14	1457.94	1457.92
C–N / C–O Stretch	1000–1300	1276.47, 1062.59	1150–1250 range	1250.81, 1150–1000	949.49, 526.41
Out-of-plane Ring Deformation	<1000	—	852.75, 758.29	849.49, 750.17	949.49, 526.41

Table 6: Organoleptic Evaluation of Formulated Lamivudine Tablets

Batch Code	Color	Shape	Surface Appearance	Odor
MF1	White	Round flat	Smooth	Odorless
MF2	White	Round flat	Smooth	Odorless
MF3	White	Round flat	Smooth	Odorless
MF4	White	Round flat	Smooth	Odorless
MF5	White	Round flat	Smooth	Odorless
MF6	White	Round flat	Smooth	Odorless
MF7	White	Round flat	Smooth	Odorless
MF8	White	Round flat	Smooth	Odorless
MF9	White	Round flat	Smooth	Odorless
MF10	White	Round flat	Smooth	Odorless

Results of Thickness, Diameter, Weight Variation, and Hardness of Formulated Batches

All Lamivudine tablets from formulations MF1 to MF10 were within the necessary size and weight ranges. While the thickness of the tablets was 7.03 ± 0.03 mm to 7.15 ± 0.03 mm, their diameter did not change, staying close to 11.1 ± 0.02 mm. The average weight of tablets was almost within the target (700 mg) and the variation was relatively small (±2.5 mg). The hardness of the panels varied between 6.3 ± 0.3 kg/cm^2 and 7.8 ± 0.2 kg/cm^2, so they are strong enough for common handling and packaging. All the data reported here are summarized in Table 7.

Table 7: Evaluation of Thickness, Diameter, Weight Variation, and Hardness of Formulated Batches

Batch Code	Thickness (mm) ± SD	Diameter (mm) ± SD	Average Weight (mg) ± SD	Hardness (kg/cm^2) ± SD
MF1	7.10 ± 0.03	11.10 ± 0.02	701.2 ± 2.5	7.8 ± 0.2
MF2	7.08 ± 0.02	11.12 ± 0.03	700.8 ± 2.3	7.2 ± 0.2
MF3	7.06 ± 0.04	11.08 ± 0.02	700.3 ± 2.1	6.8 ± 0.3
MF4	7.12 ± 0.02	11.14 ± 0.03	701.7 ± 2.4	7.1 ± 0.2
MF5	7.15 ± 0.03	11.16 ± 0.02	702.1 ± 2.6	6.5 ± 0.1
MF6	7.04 ± 0.03	11.11 ± 0.03	700.1 ± 2.0	6.6 ± 0.2
MF7	7.10 ± 0.02	11.13 ± 0.02	701.5 ± 2.2	7.3 ± 0.2
MF8	7.14 ± 0.04	11.10 ± 0.03	702.3 ± 2.5	6.8 ± 0.2
MF9	7.11 ± 0.03	11.09 ± 0.02	701.6 ± 2.3	7.8 ± 0.2
MF10	7.03 ± 0.03	11.07 ± 0.02	699.9 ± 2.4	6.3 ± 0.3

All values are expressed as mean ± SD (where n=3)

Results of Tablet Friability and Drug Content Uniformity

All batches of Lamivudine tablets met the requirement for friability, as their values were all below 1% and ranged from 0.38 ± 0.02% to 0.51 ± 0.03%. The results demonstrated that uniformity between batches of the drugs was acceptable since the content ranged from 98.3 ± 0.6% to 99.7 ± 0.3%. They prove that the process for making each composition is dependable and similar. A summary of the detailed values is given in Table 8.

Table 8: Evaluation of Tablet Friability and Drug Content Uniformity.

Batch Code	Friability (%) ± SD	Drug Content (%) ± SD
MF1	0.48 ± 0.02	98.6 ± 0.5
MF2	0.46 ± 0.03	99.1 ± 0.6
MF3	0.50 ± 0.02	98.4 ± 0.7
MF4	0.42 ± 0.01	99.3 ± 0.4
MF5	0.38 ± 0.02	99.7 ± 0.3
MF6	0.44 ± 0.02	98.9 ± 0.5
MF7	0.41 ± 0.03	99.0 ± 0.6
MF8	0.45 ± 0.02	98.7 ± 0.4
MF9	0.47 ± 0.02	99.2 ± 0.5
MF10	0.51 ± 0.03	98.3 ± 0.6

All values are expressed as mean ± SD (where n=3)

***In-Vitro* Cumulative Drug Release Profile of Lamivudine Controlled-Release Tablets**

The study found that the Lamivudine tablets all have a sustained release pattern lasting at least 24 hours. At the start, insulin release was 4.0 ± 0.4% to 4.7 ± 0.4% and this amount slowly increased until it reached 94.3 ± 1.0% to 99.7 ± 0.8% at the 24th hour. Among all of the batches, MF9 exhibited the most cumulative release (99.7% ± 0.8%), suggesting that it has the optimal amount of polymer for controlled release. All the release profiles for each batch are collected in Table 9 and shown graphically in Figure 6.

Table 9*: In-Vitro* Cumulative Drug Release Profile of Lamivudine Controlled-Release Tablets

Time (h)	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9	MF10
1	4.3 ± 0.4	4.6 ± 0.4	4.2 ± 0.4	4.1 ± 0.4	4.0 ±0.4	4.5 ±0.4	4.3 ± 0.4	4.1 ± 0.4	4.5 ± 0.4	4.7 ± 0.4
2	8.4 ± 0.4	9.0 ± 0.4	8.3 ± 0.4	8.0 ± 0.4	7.8 ±0.4	8.7 ±0.4	8.3 ± 0.4	7.9 ± 0.4	8.6 ± 0.4	9.1 ± 0.4
4	16.7 ± 0.5	17.6 ± 0.5	16.4 ±0.5	15.9±0.5	15.5 ±0.5	17.3 ±0.5	16.4 ± 0.5	15.7 ± 0.5	16.9 ± 0.5	18.0 ± 0.5
6	25.1 ± 0.5	26.2 ± 0.5	24.7 ±0.5	24.0 ±0.5	23.3±0.5	26.0± 0.5	24. ± 0.5	23.6 ± 0.5	25.2 ± 0.5	26.8 ± 0.5
8	33.4 ± 0.6	34.8 ± 0.6	33.0±0.6	32.0± 0.6	31.0± 0.6	34.6± 0.6	32.8± 0.6	31.4 ± 0.6	33.5 ± 0.6	35.7 ± 0.6
12	50.1 ± 0.7	52.3 ± 0.7	49.6±0.7	48.0± 0.7	46.5± 0.7	52.0± 0.7	49.3± 0.7	47.1 ± 0.7	50.4 ± 0.7	53.7 ± 0.7
24	99.6 ± 0.8	98.4 ± 0.7	97.1±0.6	96.0± 0.7	94.3± 1.0	98.1± 0.6	96.9± 0.7	95.1 ± 0.6	99.7 ± 0.8	98.6 ± 0.7

All values are expressed as mean ± SD (where n=3)

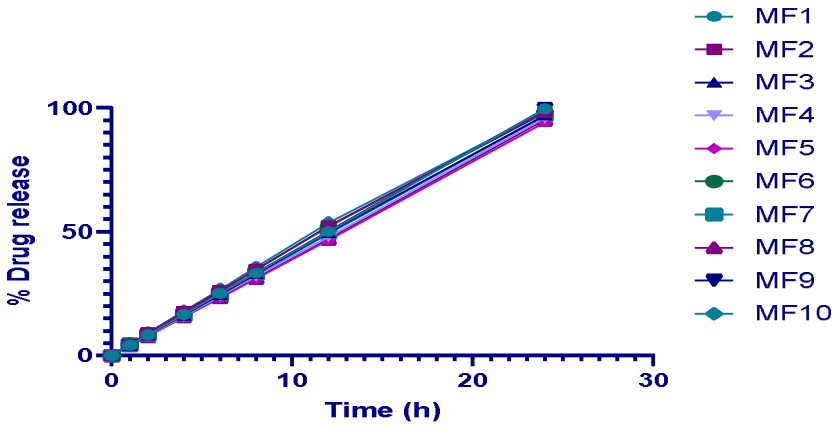

Figure 6: In vitro cumulative drug release profile of Lamivudine controlled-release matrix tablets (MF1–MF10) over a 24-hour period.

Optimization of formulations

Hardness (Y_1)

The quadratic model for hardness demonstrated high statistical significance with a sequential p-value of < 0.0001, and showed excellent goodness of fit, with Adjusted R^2 = 0.9819 and Predicted R^2 = 0.9739 (Table 10). As per ANOVA results (Table 11), the model was significant (F = 312.96, p < 0.0001), confirming that the selected variables contributed meaningfully to the response. The linear term for HPMC K100M (A) showed a significant effect (F = 50.16, p = 0.0021), whereas Polymer B (B) was not statistically significant (F = 4.77, p = 0.0943). However, the interaction term AB was statistically

significant (F = 40.92, p = 0.0031). Both quadratic terms A^2 (F = 1466.66, p < 0.0001) and B^2 (F = 226.36, p = 0.0001) had strong curvature effects on hardness.

The final regression equation in terms of coded factors was:

Hardness (Y_1) = 7.8 + 0.0979A + 0.0302B + 0.125AB − 0.7A^2 − 0.275B^2

As shown in the response surface and contour plots (Figures 7 A and B), a non-linear trend was evident, where increasing HPMC K100M led to an increase in hardness until an optimal point, beyond which a decline occurred. Polymer B exhibited a relatively weaker individual effect, but its quadratic term contributed meaningfully to the curvature. The combination of mid-range A and B levels produced a synergistic effect, resulting in maximal hardness. These results confirm a well-defined optimum zone with a convex topology in the design space, primarily governed by strong quadratic influences.

Drug Release at 24 Hours (Y_2)

The drug release at 24 hours followed a quadratic model that was statistically significant with a sequential p-value of < 0.0001, and demonstrated a strong fit as evident from Adjusted R^2 = 0.9916 and Predicted R^2 = 0.9739 (Table 10). ANOVA results (Table 11) confirmed overall model significance (F = 212.84, p < 0.0001). Among the model terms, HPMC K100M (A) had a highly significant influence on drug release (F = 599.49, p < 0.0001), while Polymer B (B) was not statistically significant (F = 1.09, p = 0.3550). The interaction term AB also showed no statistical significance (F = 5.44, p = 0.0801). However, the quadratic terms were both highly significant A^2 (F = 397.60, p < 0.0001) and B^2 (F = 242.68, p < 0.0001) highlighting the dominant role of curvature in the model.

The final regression equation in terms of coded factors was:

Drug Release (Y_2) = 99.65 − 1.4851A − 0.0634B + 0.2AB − 1.6A^2 − 1.25B^2

The 3D response surface and contour plots (Figures 7 C and D) depicted a dome-shaped profile with optimal release at mid-level concentrations of HPMC K100M and Polymer B. A marked decline in drug release was observed at higher levels of HPMC K100M, attributed to formation of a denser gel barrier. The significant negative coefficients of both A^2 and B^2 confirmed a downward curvature. The non-significant AB interaction resulted in a flatter transition zone along the interaction axis. The visual and statistical trends collectively confirmed that polymer concentration must be balanced within a narrow range to achieve optimal extended drug release.

Table 10: Model Fit Summary for Response Variables of Lamivudine Controlled-Release Tablets

Response Variable	Model	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	Model Status
Hardness (Y_1)	Linear	0.8827	—	-0.2407	-0.7090	Not adequate
	2FI	0.6972	—	-0.4084	-0.8987	Not adequate
	Quadratic	< 0.0001	—	0.9943	0.9819	**Suggested**
Drug Release at 24 hr (Y_2)	Linear	0.0555	0.0357	0.4372	0.3385	Not adequate
	2FI	0.7994	0.0325	0.3510	0.1831	Not adequate
	Quadratic	< 0.0001	0.2605	0.9916	0.9739	**Suggested**
	Cubic	0.0425	1.0000	0.9993	0.9994	Aliased

Table 11: ANOVA Results for Quadratic Models of Lamivudine Controlled-Release Tablets

Source	Sum of Squares	df	Mean Square	F-value	p-value	Significance
Hardness (Y_1)						
Model	2.3899	5	0.4780	312.96	< 0.0001	Significant
A – HPMC K100M	0.0766	1	0.0766	50.16	0.0021	Significant
B – Polymer B	0.0073	1	0.0073	4.77	0.0943	Not Significant
AB	0.0625	1	0.0625	40.92	0.0031	Significant
A^2	2.2400	1	2.2400	1466.66	< 0.0001	Significant
B^2	0.3457	1	0.3457	226.36	0.0001	Significant
Residual	0.0061	4	0.0015			
Lack of Fit	0.0061	3	0.0020			Not Significant
Pure Error	0.0000	1	0.0000			
Cor Total	2.3960	9				
Drug Release at 24 h (Y_2)						
Model	31.3233	5	6.2647	212.84	< 0.0001	Significant
A – HPMC K100M	17.6451	1	17.6451	599.49	< 0.0001	Significant
B – Polymer B	0.0321	1	0.0321	1.09	0.3550	Not Significant
AB	0.1600	1	0.1600	5.44	0.0801	Not Significant
A^2	11.7029	1	11.7029	397.60	< 0.0001	Significant
B^2	7.1429	1	7.1429	242.68	< 0.0001	Significant
Residual	0.1177	4	0.0294			
Lack of Fit	0.1127	3	0.0376	7.52	0.2605	Not Significant
Pure Error	0.0050	1	0.0050			
Cor Total	31.4410	9				

Statistical optimization of formulation

According to statistical optimization, MF9 was chosen as the best combination due to having the most hardness and releasing the proper concentration of drug within 24 hours. There was very little variation between the experimental and predicted findings, demonstrating that the model was accurate. This proves the model is effective and the formulation depends on solid reasoning. The details of optimization can be found in Table 12.

Drug Release Kinetics Study

The MF9 formulation's data on drug release rate in the laboratory were best described by the Zero-order kinetics, as the correlation coefficient was high (R^2 = 0.9859). The models of First-order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas showed R^2 values lower than 0.9, indicating that therapeutic levels of this formulation are maintained by a Zero-order mechanism. Figure 8 shows the kinetic modeling graphs.

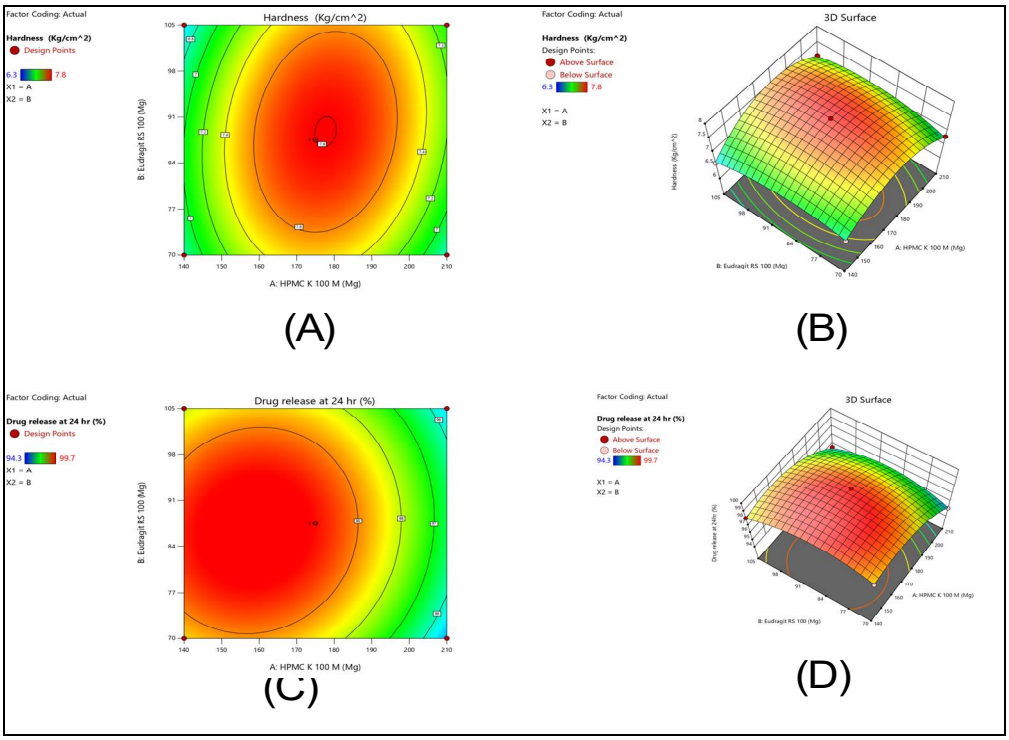

Figure 7. Contour and 3D surface response plots showing the effect of HPMC K100M (X1) and Eudragit RS 100 (X2) on tablet hardness (Y_1) and drug release at 24 hours (Y_2). (A) Contour plot for hardness showing central region with maximum hardness (7.8 kg/cm^2); (B) 3D surface plot illustrating a convex curvature in hardness response with peak values at moderate polymer levels; (C) Contour plot for drug release depicting a dome-shaped profile with highest release (99.7%) at mid-levels of both polymers; (D) 3D surface plot confirming quadratic curvature in drug release response, with decline at extreme concentrations of X1 and X2.

Table 12: Statistical optimization of formulation

F. Code	Composition	Amount (mg)	Response	Predicted Value	Experimental Value	Relative Error (%)
MF9	HPMC K100M	175	Hardness	7.79	7.8	0.128%
	Eudragit RS 100	87.5	In-vitro Drug Release at 24 hr (%)	99.7	99.7	0%

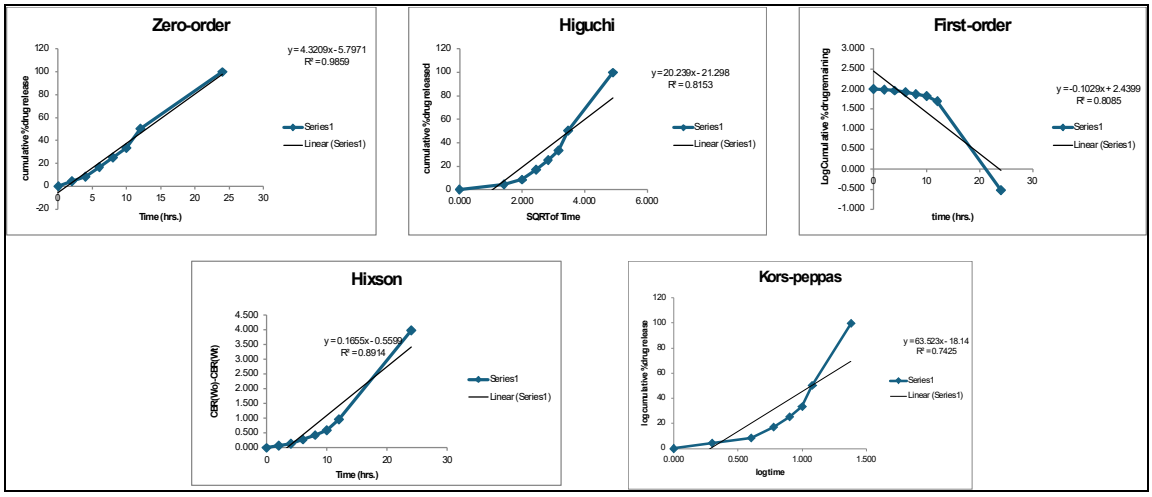

Figure 8. Kinetic modeling of in vitro drug release profile of the optimized Lamivudine formulation fitted to various mathematical models: (a) Zero-order (R^2 = 0.9859), indicating a constant rate of drug release over time; (b) Higuchi model (R^2 = 0.8153), describing diffusion-based release; (c) First-order kinetics (R^2 = 0.8085), suggesting concentration-dependent release; (d) Hixson-Crowell model (R^2 = 0.8914), reflecting changes in surface area and diameter during release; and (e) Korsmeyer–Peppas model (R^2 = 0.7425), used to interpret release mechanisms based on the release exponent (n). Highest correlation was observed with the zero-order model, indicating release was independent of drug concentration.

Results of MTT assay

The MTT assay revealed that Lamivudine exhibited low cytotoxicity across all tested concentrations. Cell viability remained above 68% even at the highest dose of 500 µg/mL, with minimal reduction compared to control. The IC_{50} was determined to be 444.36 µg/mL, indicating good biocompatibility with THP-1 cells after 24 hours of exposure (Table 13; Figures 9 and 10).

Table 13. Effect of Test Sample on Cell Viability Assessed by MTT Assay at Various Concentrations

Concentration (µg/ml)	Average % Cell Survival
CTRL	100.00 ± 8.7817
1	88.83 ± 1.99
5	81.98 ± 4.4277
25	89.46 ± 2.5847
50	80.05 ± 2.5847
100	80.73 ± 1.7976
250	73.95 ± 2.1405
500	68.96 ± 2.7278

All values are expressed as mean± SD (n=3)

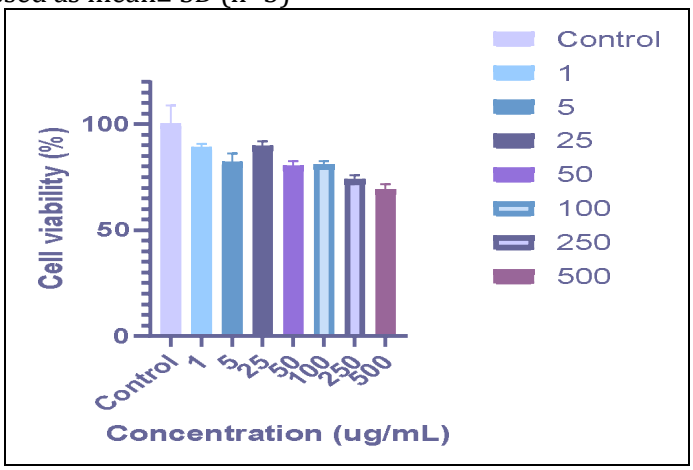

Figure 9. Effect of Lamivudine on THP-1 Cell Viability at Varying Concentrations Assessed by MTT Assay

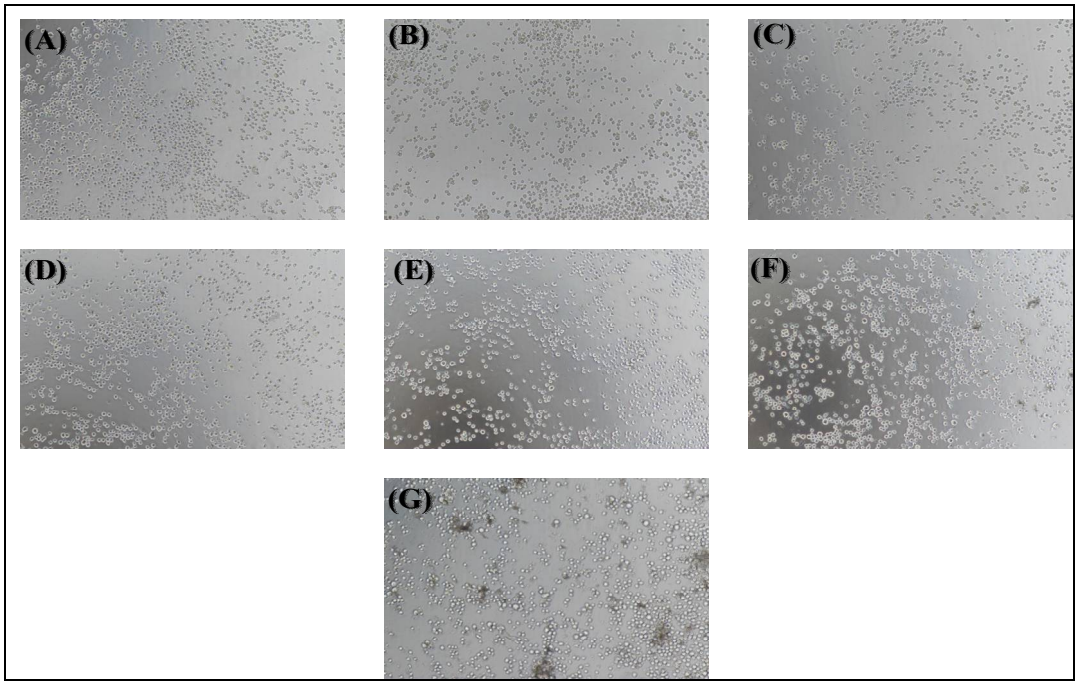

Figure 10. Microscopic images of THP-1 cells treated with Lamivudine at various concentrations after 24 hours of incubation (A) 1 µg/mL, (B) 5 µg/mL, (C) 25 µg/mL, (D) 50 µg/mL, (E) 100 µg/mL, (F) 250 µg/mL, (G) 500 µg/mL.

Accelerated stability study

The studies of batch MF9 were performed for three months under the ICH-recommended conditions (temperature 40 ± 2 °C and relative humidity 75 ± 5%). During the study, there were no changes to their bodies or physiques. After three months, the hardness of the tablets decreased from 7.8 kg/cm^2 to 7.6 kg/cm^2, while their drug content still stayed within the acceptable range and slightly went down from 99.1% to 98.5%. Testing the drugs in vitro still yielded stable results, falling very slightly from 99.7 ± 0.8% to 99.1 ± 0.6%. The findings suggest that the optimized formula is stable when exposed to harsh conditions. All the relevant information is shown in Table 14.

Table 14: Accelerated Stability Study of Optimized Batch MF9 (40 ± 2 °C / 75 ± 5% RH)

Study Duration	Appearance	Hardness (kg/cm^2)	Drug Content (%)	In-vitro Drug Release at 24 h (%)
Initial	White, smooth tablet	7.8 ± 0.05	99.1 ± 0.4	99.7 ± 0.8
1 Month	No change	7.7 ± 0.06	98.9 ± 0.5	99.5 ± 0.6
2 Months	No change	7.7 ± 0.04	98.7 ± 0.3	99.3 ± 0.7
3 Months	No change	7.6 ± 0.05	98.5 ± 0.5	99.1 ± 0.6

All values are expressed as mean ± SD (where n =3)

DISCUSSION

The goal behind controlled-release Lamivudine was to improve on the flaws of normal immediate-release Lamivudine which include daily dosing and poor adherence by patients. At the beginning of the experiment, the researchers tested to be sure they could precisely quantify Lamivudine [38]. By looking at the calibration curve (Figure 3) with a correlation coefficient value of 0.9991, it can certainly be concluded that drug content could be determined correctly and consistently using UV-Visible spectrophotometry. Both acidic and phosphate solutions were investigated (Table 4) and it was found that Lamivudine dissolves well in acid and poorly in phosphate, so the acidic dissolution medium was selected for in vitro testing [39]. Micromeritic tests indicated that all of the pre-compression batches were easy to flow and compress, with bulks densities ranging from 0.73 to 0.76 g/mL, Carr's index between 8.87% and 10.5%, Hausner's ratio between 1.09 and 1.15 and angles of repose within 25.68° to 26.10°, confirming that they could be directly compressed [40]. Suitable interaction between the compounds was ensured by carrying out thermal and spectral analyses. No interaction between Lamivudine and the carrier system could be observed on the DSC graph, as verified by a single endothermic peak at 176.85°C

for pure Lamivudine (Figure 4). Figure 5 and Table 5 prove that Lamivudine's characteristic peaks in FTIR indicate that the physical mixture has no chemical reaction with other ingredients [41].
All batches of tablets had the same smooth, white, round appearance and had no smell (Table 6). Thickness, diameter and mechanical strength were found to be the same for all these cases, ranging from 7.03 to 7.15 mm, 11.07 to 11.16 mm and 6.3 to 7.8 kg/cm^2 respectively (Table 7). The chemical values found in the tablets are acceptable and do not interfere with their handling or proper administration [42]. Robustness of the mechanical properties was found, as the tablet friability was consistently below 1%, staying in the range of 0.38% to 0.51%. There was consistency in the uniformity of drugs in all batches, proving that the drugs were evenly distributed in the matrix (Table 8). All of these findings prove that the rules used in the formulation process are consistent and reliable [43].
It was observed that all the MFs gradually discharged Lamivudine for 24 hours, but MF9 was the most effective, releasing 99.7 ± 0.8%. During the first hours, the medicine was released slowly and the cumulative calculations showed that the matrix was managing the release well. Statistics were used to identify the optimal batch of MF9 by applying a Central Composite Design [44]. Both the model prediction and conductive measurement of hardness (7.79 vs. 7.8 kg/cm^2) were close, proving that the model is effective (Table 12). The results of drug release kinetics analysis point to the optimized batch following Zero-order kinetics (the R^2 value being 0.9859), making it possible for prolonged effects of the therapeutic drug (Figure 8). There is also evidence from the First-order, Higuchi and Korsmeyer–Peppas models that the Zero-order model is the best fit since it gave the best results [45].
Lamivudine showed little cytotoxicity at all the concentrations tested and the cells kept their viability above 68% even after being treated with 500 µg/mL of Lamivudine. An IC_{50} value of 444.36 µg/mL was recorded, showing that the drug is compatible with THP-1 cells. Examining cells under a microscope proved little variation at lower doses, confirming that it is safe for use in therapies (Table 13; Figures 9 and 10) [46].The results of the accelerated stability study (Table 14) indicate that after three months, the improved formulation did not change significantly in appearance, feel, drug content or in-vitro release. According to the data, the formulation can maintain stability and last for a suitable period as suggested by the ICH [47]. Overall, each result points to the success of creating a controlled-release Lamivudine tablet that is strong enough, slowly releases its contents over time, is stable and might help patients improve their treatment attendance and outcomes in HIV and HBV treatment.

CONCLUSION

The present research successfully designed and improved a Lamivudine formulation for a controlled release using HPMC K100M and Eudragit RS 100 in a matrix system. The results from MF9 (this formulation) showed the highest strength, distributed drugs evenly and kept releasing them steadily according to Zero-order kinetics for 24 hours. It was concluded from micromeritics that the microparticles have good flow for direct compression. No apparent interactions between the drug and excipients were found during compatibility studies by FTIR and DSC. Notably, the composition under study was highly biocompatible, showing 68% cell viability at its maximum tested concentration and an IC_{50} of 444.36 µg/mL. Additionally, the accelerated stability study found that the formula maintained its physicochemical and release features for three months under ICH conditions. All things considered, Lamivudine tablets that release slowly over time give patients a useful way to stick to their treatment, need fewer doses and achieve better outcomes in HIV and Hepatitis-B diseases.

ABBREVIATIONS

ANOVA: Analysis of Variance; FTIR: Fourier-transform infrared spectroscopy; UV: Ultra-violet spectroscopy; DSC: Differential Scanning Calorimetry; HPMC: Hydroxypropyl Methylcellulose; PVP: Polyvinylpyrrolidone; DMSO: Dimethyl Sulfoxide; RH: Relative Humidity; RPM: Revolutions Per Minute; SD: Standard Deviation; IP: Indian Pharmacopoeia; R^2: Correlation Coefficient; CCD: Central Composite Design.

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Authors contribution

All authors contributed equally.

Conflict of interest
The authors declare no conflict of interest.

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