Pharmacokinetically Guided Design and Evaluation of Bilayer Tablets of Zidovudine and Lamivudine for Controlled Antiretroviral Therapy

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Abstract

Background:
Frequent dosing of Zidovudine and Lamivudine leads to fluctuating plasma concentrations and poor adherence in antiretroviral therapy. A controlled-release system integrating loading and maintenance doses may improve therapeutic consistency.

Objective:
To develop a pharmacokinetically optimized bilayer tablet delivering sustained release of Zidovudine and Lamivudine for once-daily administration.

Methods:
Pharmacokinetic parameters were used to calculate loading and maintenance doses for both drugs. Bilayer tablets were formulated by sequential compression using hydrophilic (HPMC K100M) and hydrophobic (Eudragit RLPO) polymers to modulate drug release. The formulations were evaluated for physicochemical properties, drug content using RP-HPLC, and in vitro dissolution under pH transition conditions (0.1N HCl to pH 7.4 buffer over 24 h). Swelling and erosion studies were conducted, and release kinetics were analyzed using zero-order, Higuchi, and Korsmeyer-Peppas models.

Results:
Calculated loading and maintenance doses were 56.53 mg and 354.56 mg for Zidovudine, and 26.76 mg and 176.47 mg for Lamivudine, corresponding to total daily doses of 400 mg and 200 mg, respectively. The bilayer tablets exhibited acceptable hardness (10.01-12.54 kg/cm²), friability (<0.25%), and uniform weight (0.855-0.864 g). Drug content ranged between 98.60% and 100.42%. The optimized formulation (F1B) achieved sustained release of Zidovudine (97.04%) and Lamivudine (98.52%) over 24 h. Swelling (up to 84.7%) and erosion (up to 78%) indicated a coupled matrix relaxation mechanism. Release kinetics followed zero-order ($R^2 \approx 0.995$), with Korsmeyer-Peppas exponent values (n = 0.84-0.93) confirming non-Fickian diffusion.

Conclusion:
The pharmacokinetically designed bilayer tablet achieved controlled, near zero-order drug release over 24 h through a combined swelling-erosion mechanism. This system provides a rational strategy to enhance adherence and therapeutic consistency in antiretroviral therapy.

Keywords: Bilayer tablet, Zidovudine, Lamivudine, controlled drug delivery, pharmacokinetic-based design, non-Fickian release

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1. INTRODUCTION

Human immunodeficiency virus (HIV) infection continues to impose a substantial global health burden, with an estimated 39 million people living with HIV worldwide and a significant proportion requiring lifelong antiretroviral therapy (ART) to maintain viral suppression[1,2]. Despite major advancements in ART, long-term therapeutic success remains highly dependent on strict adherence to dosing regimens. Even minor deviations from prescribed therapy can result in subtherapeutic plasma concentrations, leading to virological failure, emergence of resistant viral strains, and disease progression [3,4]. In this context, dosage form design plays a critical yet often underemphasized role in improving treatment outcomes.

Among first-line nucleoside reverse transcriptase inhibitors, Zidovudine and Lamivudine are extensively used in combination regimens due to their complementary mechanisms and established clinical efficacy [1,5]. However, their pharmacokinetic characteristics present significant formulation challenges. Zidovudine exhibits a short biological half-life (≈1 h) and rapid clearance, necessitating frequent dosing to maintain therapeutic levels, while Lamivudine, although more stable, still requires repeated administration in conventional dosage forms [6,7]. These limitations contribute to pronounced fluctuations in plasma drug concentration profiles, increasing the risk of peak-related toxicity and trough-associated therapeutic failure.

Controlled drug delivery systems have been widely explored to overcome such pharmacokinetic limitations by providing sustained and predictable drug release[8,9]. However, conventional sustained-release systems often fail to simultaneously achieve rapid establishment and prolonged maintenance of therapeutic plasma concentrations within a single delivery platform [10]. This limitation is particularly critical in antiretroviral therapy, where rapid attainment of effective drug levels is essential to suppress viral replication, followed by sustained exposure to prevent rebound viremia.

Bilayer tablet technology offers a rational and structurally adaptable platform for the development of multi-release controlled drug delivery systems by incorporating distinct matrix environments within a single dosage form [11]. Unlike conventional single-layer matrices, bilayer systems permit independent modulation of release kinetics, enabling optimization of drug release behavior through differential polymer composition and matrix architecture [12]. Despite this advantage, most reported bilayer formulations are developed using empirical approaches without integrating pharmacokinetic principles into dose selection and release design[13]. Consequently, the resulting systems often lack clinical relevance and fail to achieve optimal therapeutic performance.

A pharmacokinetically guided formulation strategy provides a more rational framework for dosage form development by linking drug release profiles to physiological parameters such as target plasma concentration, volume of distribution, clearance, and bioavailability[14]. This approach enables the calculation of loading and maintenance dose requirements and facilitates the development of controlled-release systems capable of maintaining near-constant plasma drug concentrations over extended periods. Such integration of pharmacokinetic principles into bilayer antiretroviral systems remains relatively underexplored[15].

Therefore, the present study aims to develop a pharmacokinetically optimized bilayer tablet of Zidovudine and Lamivudine capable of providing sustained release of both drugs over 24 h for once-daily administration. The formulation employs a combination of hydrophilic and hydrophobic polymers to modulate drug release through swelling, diffusion, and erosion mechanisms. The developed system is systematically evaluated to establish its physicochemical properties, release characteristics, and underlying release mechanisms, with the objective of developing a pharmacokinetically rational and patient-compliant antiretroviral delivery system.

2. MATERIALS AND METHODS

2.1 Materials

Zidovudine and Lamivudine were obtained as gift samples from a pharmaceutical industry (India). Hydroxypropyl methylcellulose (HPMC K100M) was procured from Colorcon Asia Pvt. Ltd., Goa, India. Eudragit RLPO was obtained from Evonik Industries, Darmstadt, Germany. Starch was purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Talc and magnesium stearate were obtained from SD Fine Chemicals Ltd., Mumbai, India.Acetonitrile (HPLC grade) was procured from Merck Specialities Pvt. Ltd., Mumbai, India. All other chemicals and reagents used were of analytical grade.

2.2 Instruments

FTIR analysis was carried out using an FTIR spectrophotometer (Shimadzu IR Affinity-1S, Kyoto, Japan). UV-Visible spectrophotometric analysis was performed using a UV-Visible spectrophotometer (Shimadzu UV-1800, Japan).HPLC analysis was carried out using a high-

performance liquid chromatography system (Shimadzu LC-20AT, Japan) equipped with a UV detector and LC solution software.Bilayer tablets were compressed using a rotary tablet press (Rimek Minipress-I, Karnavati Engineering Ltd., Gujarat, India).Pre-compression and post-compression parameters were evaluated using a digital weighing balance (Shimadzu AUX220, Japan), Monsanto hardness tester, Roche friabilator (Electrolab, India), and digital Vernier calipers (Mitutoyo, Japan).In vitro dissolution studies were performed using a USP Type II dissolution apparatus (Electrolab TDT-08L, Mumbai, India).

2.3 Methods:

2.3.1 Preformulation Studies

Preformulation studies were performed to characterize the physicochemical properties of Zidovudine and Lamivudine and to assess their compatibility with selected excipients prior to formulation development.Organoleptic characteristics (appearance, colour, and odour) were evaluated by visual inspection. The melting point of each drug was determined by the capillary method using a calibrated melting point apparatus.Solubility was assessed qualitatively in distilled water and phosphate buffer (pH 7.4) under ambient conditions to understand dissolution behaviour relevant to formulation design.Moisture content was evaluated by loss on drying (LOD) at 105 °C using a hot air oven[16]. Hygroscopicity was assessed by exposing samples to controlled relative humidity conditions (75% RH) and monitoring changes in mass.Drug-excipient compatibility was investigated using Fourier transform infrared (FTIR) spectroscopy. Spectra of pure drugs and their physical mixtures with excipients (HPMC K100M, Eudragit RLPO, and starch) were recorded over the range of 4000-400 cm^{-1} using the KBr pellet method.UV spectrophotometric scanning of drug solutions in phosphate buffer (pH 7.4) was performed over the range of 200-400 nm to establish analytical wavelengths for subsequent quantification[17,18].

2.3.2 Pharmacokinetic-Based Dose Design

A pharmacokinetically guided approach was employed to design a bilayer tablet capable of maintaining therapeutic plasma concentrations of Zidovudine and Lamivudine over a 24 h dosing interval. The formulation strategy was based on the integration of loading dose (LD) and maintenance dose (MD) concepts into a controlled-release bilayer matrix system.

The loading and maintenance doses were calculated using:

$$LD = \frac{C_{\text{target}} \cdot V_d}{F}; MD = \frac{C_{\text{target}} \cdot CL \cdot \tau}{F}$$

where C_{target}represents the desired steady-state plasma concentration, $V_d$is the apparent volume of distribution, $CL$is systemic clearance, $F$is oral bioavailability, and $\tau$is the dosing interval (24 h). Pharmacokinetic parameters were selected from reported literature values for adult populations to ensure physiological relevance.

For Lamivudine, a target plasma concentration of 0.25 mg/L was selected based on its established therapeutic window and favorable bioavailability profile. Using $V_d = 1.3$ L/kg(70 kg body weight) and $F = 0.85$, the calculated loading dose was 26.76 mg. The maintenance dose, determined using $CL = 25$ L/h, was 176.47 mg, corresponding to a total daily dose of 200 mg[19].

For Zidovudine, a higher target concentration of 0.35 mg/L was considered to compensate for its relatively rapid clearance and shorter half-life. Using $V_d = 1.5$ L/kgand $F = 0.65$, the loading dose was calculated as 56.53 mg, while the maintenance dose was 354.56 mg, yielding a total daily dose of 400 mg[19].

The calculated dose fractions were incorporated into distinct polymeric matrix layers within the bilayer tablet architecture to achieve controlled and sustained release of both drugs over 24 h. The bilayer configuration enabled independent modulation of release kinetics through differential polymer composition and matrix hydration behavior. This design establishes a mechanistic linkage between pharmacokinetic requirements and formulation architecture, facilitating near-constant drug release consistent with zero-order kinetics [20].

2.3.3 Preparation of Granules

Granules for the individual layers of Zidovudine and Lamivudine were prepared by the wet granulation method according to the compositions presented in Table 1. For the Zidovudine layer, each formulation contained 400 mg of drug, along with HPMC K100M (60-100 mg) or Eudragit RLPO (110-130 mg) as release-retarding polymers, and starch (20-90 mg) as diluent[21]. For the Lamivudine layer, each formulation contained 200 mg of drug, with HPMC K100M (30-50 mg) or Eudragit RLPO (55-65 mg), and starch (35-70 mg) as diluent. The drug and excipients were blended uniformly in a mortar to ensure homogeneity[22]. The powder mixture was granulated using 10% w/v starch mucilage as binder until a coherent wet mass was obtained. The wet mass was passed through sieve No. 16 and dried at 45 ± 2°C until constant weight. The dried granules were sieved through

sieve No. 22 to obtain uniform particle size distribution. Talc (3% w/w) and magnesium stearate (1% w/w) were added and mixed gently for 3-5 min[23]. The prepared granules were stored in airtight containers until further evaluation and compression.

2.3.4 Evaluation of Granules

Granules prepared for the individual layers of Zidovudine and Lamivudine were evaluated for flow and packing properties prior to compression. Bulk density (ρb) was determined by transferring a known mass of granules into a graduated cylinder and recording the initial volume. Tapped density (ρt) was measured after mechanically tapping the cylinder until a constant volume was obtained. Angle of repose (θ) was determined by the fixed funnel method by allowing granules to flow through a funnel onto a flat surface and measuring the height (h) and radius (r) of the formed cone, using:

$$\tan\theta = \frac{h}{r}$$

Carr's compressibility index (CI) and Hausner ratio (HR) were calculated from bulk and tapped densities using:

$$CI(\%) = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

$$HR = \frac{\rho_t}{\rho_b}$$

All measurements were performed in triplicate[24].

2.3.5 Formulation of Individual Layers

Formulations for the individual layers of Zidovudine and Lamivudine were designed as per the compositions presented in Table 1. For the Zidovudine layer, the drug and excipients-comprising the release-retarding polymer (HPMC K100M or Eudragit RLPO) and diluent (starch)-were weighed according to Table 1 and blended uniformly prior to granulation. Similarly, for the Lamivudine layer, the drug and corresponding excipients were weighed and blended as per the specified compositions. Each formulation batch (F1-F5) was prepared by varying the type and proportion of polymer to achieve different release profiles. The composition of both layers was adjusted to maintain the desired total tablet weight while ensuring uniform distribution of drug and excipients. The prepared granules for each layer were evaluated for flow properties prior to compression into bilayer tablets[16].Each layer was designed based on the calculated pharmacokinetic dose fractions described in Section 2.3.2 to achieve controlled and sustained release of both drugs over 24 h.

2.3.6 Compression of Bilayer Tablets

Bilayer tablets containing Zidovudine and Lamivudine were prepared by sequential compression using a rotary tablet press (Rimek Minipress-I) fitted with 12 mm circular concave punches.

The Zidovudine layer (sustained-release layer) was first introduced into the die cavity and subjected to light pre-compression at a compression force of approximately 2-4 kN to form a uniform base layer[24]. Subsequently, the Lamivudine layer (sustained-release layer) granules were added over the pre-compressed layer, followed by final compression at a force of 6-8 kN to obtain bilayer tablets with adequate mechanical strength. The total tablet weight was maintained at approximately 600 mg per unit, comprising 400 mg of Zidovudine layer and 200 mg of Lamivudine layer, as per the pharmacokinetic design. Care was taken to ensure minimal interlayer mixing and uniform layer distribution during compression[25]. The prepared bilayer tablets were collected and stored in airtight containers for further evaluation.

2.3.7 Physical Evaluation of Bilayer Tablets

Bilayer tablets containing Zidovudine and Lamivudine were evaluated for standard post-compression parameters.**Weight variation:** Twenty tablets were individually weighed using a calibrated digital balance. The average weight was calculated, and individual weights were compared with the mean.**Thickness:** Tablet thickness was measured using digital Vernier calipers, and the mean value was recorded.**Hardness:** Crushing strength was determined using a Monsanto hardness tester.**Friability:** Friability was evaluated using a Roche friabilator. Tablets were rotated for **100 revolutions at 25 rpm**, dedusted, and reweighed. Percentage friability was calculated.All measurements were performed in triplicate[26].

2.3.8 Drug Content

The drug content of bilayer tablets containing Zidovudine and Lamivudine was determined by reverse-phase high-performance liquid chromatography (RP-HPLC). Tablets were finely powdered, and an accurately weighed quantity equivalent to the labeled amount of each drug was transferred to a volumetric flask. The drugs were extracted using the mobile phase, sonicated for 10 min, and diluted to volume. The solution was filtered through a 0.45 µm membrane filter and further diluted as required. Chromatographic analysis was performed using an HPLC system (Shimadzu LC-20AT, Japan) equipped with a UV

detector and LC solution software. Separation was achieved on a C18 column (250 × 4.6 mm, 5 µm particle size) maintained at ambient temperature. The mobile phase consisted of phosphate buffer (pH 3.0) : acetonitrile (60:40 v/v), delivered at a flow rate of 1.0 mL/min under isocratic conditions. The injection volume was 20 µL. Detection was carried out at 270 nm for Zidovudine and 265 nm for Lamivudine. Quantification was performed using calibration curves constructed from standard solutions prepared in the mobile phase.All determinations were performed in triplicate[27,28].

2.3.9 In Vitro Drug Release Study

In vitro drug release studies of bilayer tablets containing Zidovudine and Lamivudine were performed using a USP Type II (paddle) dissolution apparatus (Electrolab TDT-08L, Mumbai, India). The dissolution was carried out in 900 mL of medium maintained at 37 ± 0.5 °C with a paddle rotation speed of 50 rpm. A two-stage dissolution method was employed to simulate gastrointestinal conditions. Initially, tablets were placed in 0.1 N HCl (pH 1.2) for 2 h. Thereafter, the medium was adjusted to pH 7.4 using a half-change method by replacing 450 mL of the medium with an equal volume of phosphate buffer (pH 7.8) to obtain a final pH of 7.4. At predetermined time intervals, 5 mL samples were withdrawn and replaced with an equal volume of fresh medium maintained at the same temperature to ensure constant volume and sink conditions[29]. The samples were filtered through a 0.45 µm membrane filter. The drug content in the samples was analyzed using a UV-Visible spectrophotometer (Shimadzu UV-1800, Japan) at 270 nm for Zidovudine and 265 nm for Lamivudine. The cumulative percentage drug release was calculated as a function of time[26,30]. All experiments were conducted in triplicate.

2.3.10 Swelling Study

The swelling behavior of bilayer tablets containing Zidovudine and Lamivudine was evaluated to assess matrix hydration characteristics. Pre-weighed tablets (W_0) were placed in dissolution media maintained at 37 ± 0.5 °C, initially in 0.1 N HCl (pH 1.2) for 2 h, followed by phosphate buffer (pH 7.4) for the remaining duration[26]. At predetermined time intervals (1, 2, 4, 6, 8, 12, and 24 h), tablets were withdrawn, gently blotted with filter paper to remove excess surface moisture, and reweighed (W_t).The swelling index was calculated using:

$$\text{Swelling Index (\%)} = \frac{W_t - W_0}{W_0} \times 100$$

All measurements were performed in triplicate.

2.3.11 Erosion Study

The matrix erosion behavior of bilayer tablets containing Zidovudine and Lamivudine was evaluated to assess polymer relaxation and mass loss of the hydrophilic matrix system during dissolution. Pre-weighed tablets (W_0) were placed in dissolution media maintained at 37 ± 0.5 °C, initially in 0.1 N HCl (pH 1.2) for 2 h, followed by phosphate buffer (pH 7.4). At predetermined time intervals (1, 2, 4, 6, 8, 12, and 24 h), tablets were withdrawn, gently blotted to remove surface moisture, and dried in a hot air oven at 45 ± 2 °C until constant weight (W_d) was obtained[31]. The percentage erosion was calculated using:

$$\text{Erosion (\%)} = \frac{W_0 - W_d}{W_0} \times 100$$

All measurements were performed in triplicate.

2.3.12 Drug Release Kinetics (Refined)

The in vitro drug release data of bilayer tablets containing Zidovudine and Lamivudine were analyzed using kinetic models to elucidate the release mechanism from the bilayer matrix system. The dissolution data were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models using linear regression analysis, and the goodness of fit was evaluated based on the correlation coefficient (R^2)[32].

The mathematical models applied were:

- **Zero-order:**

$$Q_t = Q_0 + k_0 t$$

- **First-order:**

$$\log Q_t = \log Q_0 - \frac{k_1 t}{2.303}$$

- **Higuchi:**

$$Q_t = k_H \sqrt{t}$$

- **Korsmeyer-Peppas:**

$$\frac{M_t}{M_\infty} = k t^n$$

where $Q_t$is the cumulative amount of drug released at time t, $M_t/M_\infty$is the fraction of drug released, $k$is the release constant, and $n$is the release exponent. The Peppas model was applied to the initial ≤60% drug release data, and the value of n

was used to characterize the mechanism of drug release from the bilayer system.

2.3.13 Stability Studies

Stability studies of bilayer tablets containing Zidovudine and Lamivudine were conducted in accordance with ICH Q1A(R2) to assess formulation stability and performance consistency. The optimized formulation was packed in airtight containers and stored under accelerated conditions (40 ± 2 °C / 75 ± 5% RH) for 3 months. Samples were withdrawn at 0, 1, 2, and 3 months and evaluated for physical appearance, hardness, friability, drug content (Section 2.3.8), and in vitro drug release profile (Section 2.3.9). All studies were performed in triplicate[33].

2.3.14 Statistical Analysis

All experimental data were expressed as mean ± standard deviation (SD) (n = 3). Statistical analysis was performed using SPSS Stata 13. Differences among formulations were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A value of $p < 0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

The physicochemical properties of Zidovudine and Lamivudine are summarized in Table 1. Both drugs exhibited narrow melting ranges, consistent with a stable crystalline phase and absence of detectable impurities or polymorphic transitions. This is relevant to downstream processing, as variability in solid-state form can directly affect compressibility and dissolution behavior in matrix-based systems[34,35]. The UV absorption maxima at 270 nm (Zidovudine) and 265 nm (Lamivudine) were distinct and well-resolved, enabling selective quantification without spectral interference. The close proximity of λmax values also supports simultaneous estimation under controlled analytical conditions. Given the high aqueous solubility of both drugs, release from the bilayer matrix system is not expected to be dissolution-limited but rather governed by polymer hydration, diffusion pathways, and matrix erosion mechanisms. Instead, release kinetics will be governed by polymer-mediated processes, including matrix hydration, diffusion pathways, and erosion dynamics[36]. This supports the selection of hydrophilic and permeability-modulating polymeric matrices to achieve controlled and sustained release of both drugs from the bilayer system. The FTIR spectra of pure drugs, excipients, and their physical mixtures and the principal absorption bands are summarized in Table 2. The FTIR spectra of pure Zidovudine, pure Lamivudine, their physical mixtures with HPMC K100M and Eudragit RLPO, and the corresponding formulations are presented in Figure 2.

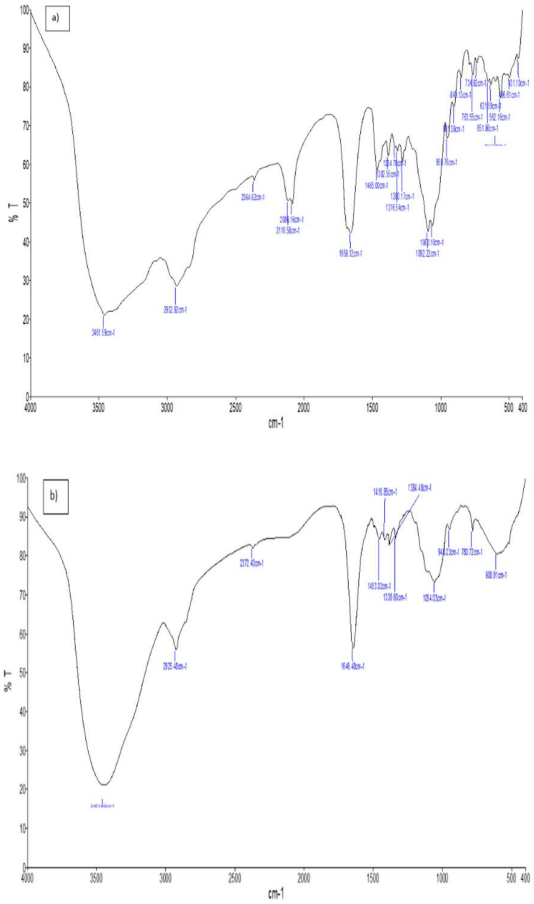
The FTIR spectrum of Zidovudine is characterized by a sharp azide stretching band (2107 cm^{-1}), a functionally sensitive group that serves as a reliable indicator of structural integrity. The persistence of this band in the physical mixture (2105 cm^{-1}) indicates that the azide moiety remains chemically unaltered in the presence of excipients. Similarly, the carbonyl stretching bands of Zidovudine (1682 cm^{-1}) and Lamivudine (1654 cm^{-1}) remained invariant within experimental limits, indicating that these functional groups are not involved in strong intermolecular interactions capable of altering bond energy. This is notable given the presence of hydroxyl-rich excipients (HPMC and starch), which are potential hydrogen bond donors. Excipients exhibited their characteristic spectral features independently-most notably the ester carbonyl band of Eudragit RLPO (1720 cm^{-1}) and the broad hydroxyl bands of hydrophilic polymers (3300-3500 cm^{-1}) - without overlapping or masking drug-specific peaks[21,24,35]. This excludes the possibility of ester-drug interaction or chemical transformation under formulation conditions. The minor peak shifts observed (≤5-10 cm^{-1}) are consistent with weak, non-specific hydrogen bonding within the polymeric matrix, which is expected in hydrated systems and does not indicate chemical incompatibility. Importantly, no peak disappearance, broadening, or emergence of new bands was observed, ruling out covalent interaction, complex formation, or solid-state instability[35]. From a formulation perspective, these findings confirm that the system is chemically inert, and that drug release behavior will be governed by physical mechanisms such as polymer swelling, diffusion, and erosion, rather than chemical degradation. This is critical for ensuring predictable and controlled release in the bilayer matrix system.

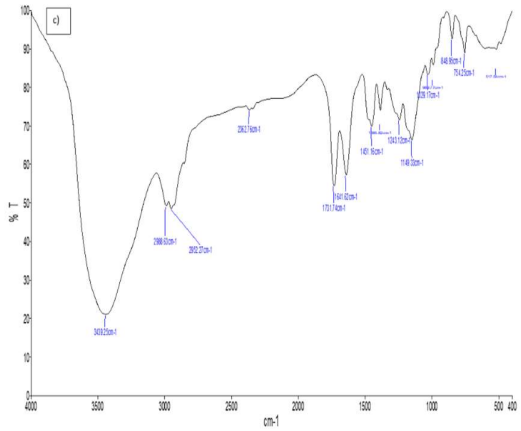
Parameter	Zidovudine	Lamivudine
Appearance	White crystalline powder	White crystalline powder
Melting point (°C)	122-124	160-162
λmax (nm)	270	265
Solubility	Freely soluble in water	Freely soluble in water

Table 1. Preformulation parameters of Zidovudine and Lamivudine

Component	Functional Group	Observed Peak (cm^{-1})	Interpretation
Zidovudine	N_3 (azide stretch)	2107	Diagnostic peak retained
	C=O stretch	1682	No perturbation observed
Lamivudine	C=O stretch	1654	Retained
	N–H/O–H stretch	3200-3400	Broad hydrogen-bonding band
HPMC K100M	O–H stretch	3400	Hydrophilic polymer band
	C–O–C stretch	1050-1150	Backbone integrity maintained
Eudragit RLPO	Ester C=O	1720	Polymer-specific peak retained
Starch	O–H stretch	3300-3500	Polysaccharide band
Physical mixture	All major peaks	2105, 1680, 1652, 3400	No new peaks; minor shifts only

Table 2. FTIR characteristic peaks and compatibility assessment




c)
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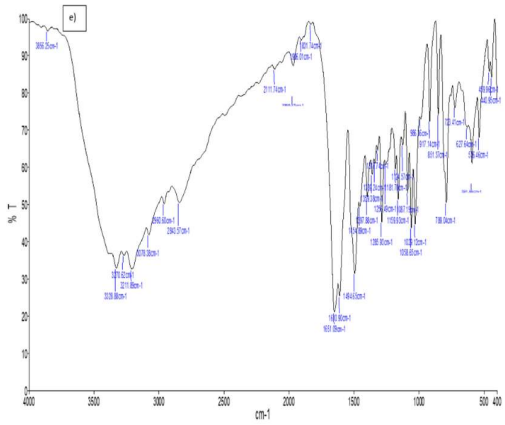
e)
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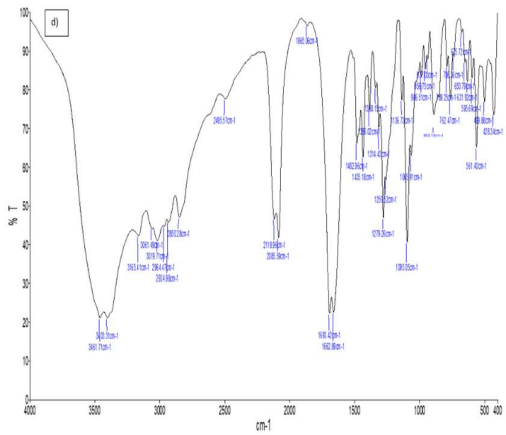
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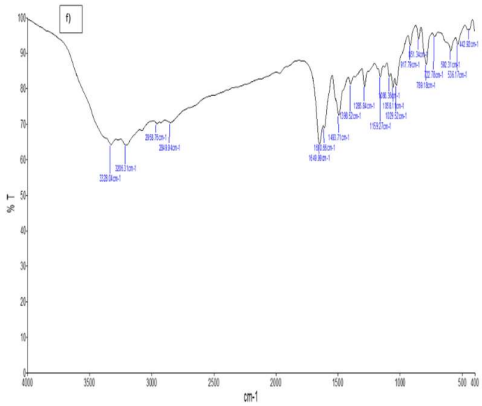
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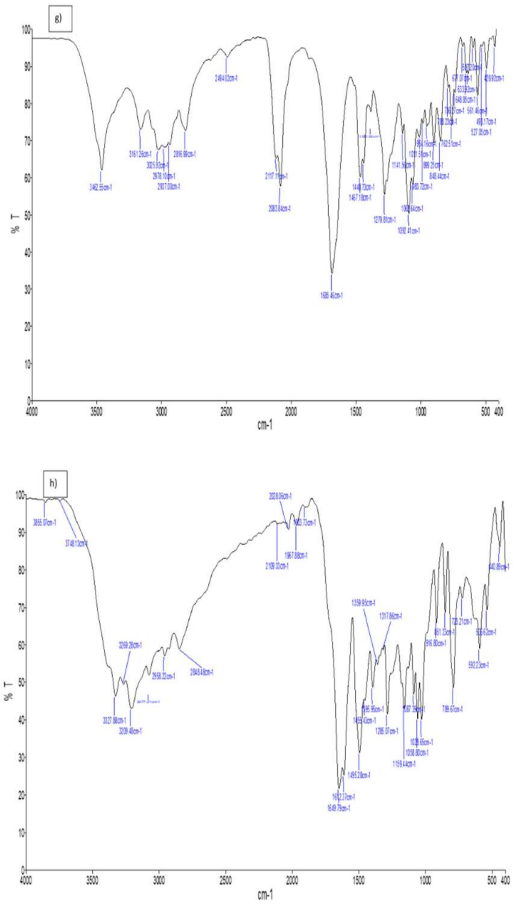

Figure 2. Fourier transform infrared (FTIR) spectra of (A) Zidovudine with HPMC K100M physical mixture, (B) Zidovudine formulation, (C) Zidovudine with Eudragit RLPO physical mixture, (D) pure Zidovudine, (E) Lamivudine formulation, (F) Lamivudine with HPMC K100M physical mixture, (G) Zidovudine with Eudragit RLPO formulation, and (H) Lamivudine with Eudragit RLPO physical mixture, illustrating the characteristic functional group absorption bands used for drug–excipient compatibility assessment.

3.2 Pharmacokinetic-Based Dose Design

The bilayer tablet was designed to achieve pharmacokinetically optimized controlled delivery of Zidovudine and Lamivudine through independently modulated sustained-release matrix layers within a single dosage form. The key pharmacokinetic parameters guiding the formulation design are summarized in Table 2. The formulation strategy was primarily driven by the elimination characteristics of the two drugs. Zidovudine exhibits a short biological half-life (1 h), resulting in rapid decline in plasma concentration following administration. Without controlled delivery, this necessitates frequent dosing and leads to pronounced peak–trough fluctuations. Incorporation into a controlled-release matrix was therefore essential to prolong drug release and maintain therapeutic plasma levels over an extended duration [37].

Although Lamivudine possesses a comparatively longer half-life, sustained release was also considered advantageous to minimize fluctuations in plasma concentration and improve dosing convenience during long-term antiretroviral therapy. Accordingly, both drugs were incorporated into polymeric matrix layers designed to provide prolonged and controlled release over 24 h.The bilayer configuration enabled independent modulation of release kinetics through differential polymer composition and matrix architecture, thereby overcoming formulation limitations associated with conventional single-layer systems [38,39]. This approach is particularly relevant in antiretroviral therapy, where maintenance of consistent plasma drug concentrations is critical for therapeutic effectiveness and suppression of resistant viral populations.The selected dose distribution (200 mg Lamivudine and 400 mg Zidovudine, Table 3) was consistent with established therapeutic dosing while allowing controlled drug release through matrix hydration, diffusion, and erosion mechanisms [40].

Overall, the pharmacokinetic-based design established a mechanistically rational foundation for the bilayer matrix system, ensuring that subsequent in vitro performance reflected pharmacokinetic requirements rather than empirical formulation optimization alone.

Parameter	Zidovudine	Lamivudine
Biological half-life (t½)	1 h	5-7 h
Elimination behavior	Rapid clearance	Moderate clearance
Clinical implication	Frequent dosing required	Sustained plasma maintenance desirable
Formulation approach	Sustained-release matrix	Sustained-release layer

Table 2. Pharmacokinetic parameters and formulation rationale

Layer	Drug	Dose (mg)	Functional Role
Layer I	Lamivudine	200	Controlled and prolonged drug release

Layer II	Zidovudine	400	Controlled and sustained plasma drug maintenance

Table 3. Dose allocation in bilayer tablet

3.3 Evaluation of Granules

The pre-compression properties of granules intended for the bilayer tablet of Zidovudine and Lamivudine are summarized in Table 4. All formulations exhibited angle of repose values between 25.8° and 27.5°, indicative of good flowability according to established micromeritic criteria (<30°). This ensures efficient die filling during compression, which is particularly critical for bilayer systems where layer uniformity directly influences dose accuracy and interfacial integrity. The Carr's index values (11.8-12.8%) fall within the range associated with good compressibility (10-15%), while Hausner ratios (1.13-1.15) remain well below the critical limit of 1.25, confirming low interparticulate friction. These parameters collectively indicate that the granules possess suitable packing and flow characteristics for reproducible compression[41]. The close agreement between bulk and tapped densities across formulations suggests consistent granule structure and minimal densification variability, reflecting a controlled granulation process. No evidence of segregation-prone behavior or density heterogeneity was observed. Formulation-dependent variations were minimal but systematic. Granules containing higher proportions of HPMC K100M showed marginally increased cohesiveness, attributable to its hydrophilic and gel-forming nature, which promotes interparticle adhesion[42]. In contrast, Eudragit RLPO-based formulations exhibited slightly improved flow characteristics due to their relatively lower moisture affinity and particulate morphology. From a manufacturing perspective, these micromeritic properties are critical for bilayer compression, where inadequate flow or compressibility can result in layer weight variation, poor interlayer adhesion, and tablet defects such as capping or lamination[41]. The observed parameters across all formulations fall within acceptable limits, indicating that the granules are suitable for sequential compression without compromising layer integrity or uniformity.

Formulation	**Bulk Density (g/cm³)**	**Tapped Density (g/cm³)**	**Angle of Repose (°)**	**Carr's Index (%)**	**Hausner Ratio**
F1B	0.42 ± 0.02	0.48 ± 0.01	26.5 ± 0.5	12.5 ± 0.6	1.14 ± 0.02
F2B	0.44 ± 0.01	0.50 ± 0.02	27.2 ± 0.4	12.0 ± 0.5	1.13 ± 0.01
F3B	0.41 ± 0.02	0.47 ± 0.01	25.8 ± 0.6	12.8 ± 0.7	1.15 ± 0.02
F4B	0.43 ± 0.01	0.49 ± 0.02	26.9 ± 0.5	12.2 ± 0.6	1.14 ± 0.01
F5B	0.45 ± 0.02	0.51 ± 0.01	27.5 ± 0.4	11.8 ± 0.5	1.13 ± 0.02

Table 4. Pre-compression parameters of granules

3.4 Physical Evaluation of Bilayer Tablets

The distinct bilayer structure with clear interfacial separation was visually confirmed (Figure 1), indicating successful sequential compression without layer mixing.The post-compression parameters of bilayer tablets containing Zidovudine and Lamivudine are summarized in Table 5. All formulations complied with pharmacopeial requirements for post-compression quality attributes. The average tablet weight (600 mg) showed deviations well within the acceptable limit of ±5% for tablets ≥250 mg (IP/USP), confirming consistent die filling and uniform mass distribution between layers. Tablet thickness exhibited minimal variability (5.5-5.7 mm), indicating stable compression parameters and reproducible layer stacking[39]. This is critical in bilayer systems to ensure dimensional consistency and avoid interfacial stress during handling. The measured hardness values (10.8-12.1 kg/cm²) indicate sufficient mechanical strength to withstand handling, packaging, and transportation. At the same time, this range remains compatible with matrix hydration requirements, ensuring that excessive compaction does not impede liquid penetration during dissolution. Friability values for all batches were <1% (0.19-0.24%), satisfying IP/USP criteria and confirming the mechanical robustness of the tablets. The low friability reflects effective interparticle bonding and adequate compression force[43].

From a bilayer perspective, the simultaneous achievement of adequate hardness and low friability is particularly significant. Excessive hardness can promote layer separation, while insufficient strength can lead to capping or lamination. The balanced mechanical profile observed across all formulations indicates optimal compression conditions, ensuring structural

integrity without compromising functional performance[44]. Minor variations among formulations can be attributed to differences in polymer composition. HPMC-rich formulations exhibited slightly higher hardness due to enhanced binding and gel-forming capacity, whereas Eudragit-based systems showed marginally lower but acceptable hardness values, reflecting their comparatively lower plastic deformation behavior[21].

Overall, the tablets met all pharmacopeial specifications, demonstrating that the compression process was well controlled and suitable for producing mechanically stable bilayer dosage forms.

Formulation	Weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)
F1B	598 ± 6	5.6 ± 0.1	11.2 ± 0.3	0.21
F2B	602 ± 5	5.7 ± 0.1	10.8 ± 0.4	0.24
F3B	596 ± 4	5.5 ± 0.1	12.1 ± 0.2	0.19
F4B	600 ± 5	5.6 ± 0.1	11.5 ± 0.3	0.22
F5B	604 ± 6	5.7 ± 0.1	10.9 ± 0.4	0.23

Table 5. Physical evaluation parameters of bilayer tablets

Figure 1. Photograph of the bilayer tablet showing distinct separation between the sustained-release matrix layer of Lamivudine and the sustained-release matrix layer of Zidovudine,confirming successful sequential compression and layer integrity.

3.5 Drug Content

The assay of bilayer tablets containing Zidovudine and Lamivudine was determined using the validated RP-HPLC method described in Section 2.3.8. The results are summarized in **Table 6**.All formulations exhibited drug content within the acceptable pharmacopeial range of 95-105% of the labeled claim (IP/USP), confirming adequate content uniformity across both layers. The low standard deviation values (<1%) indicate high precision and uniform distribution of drug within the matrix, reflecting effective mixing and granulation processes. This is particularly critical in bilayer systems, where segregation or non-uniform distribution can lead to dose imbalance between layers and compromise therapeutic performance. No systematic variation in drug content was observed across formulations, suggesting that polymer composition and concentration did not adversely affect drug distribution or extraction efficiency during analysis[27]. This indicates that both drugs were uniformly incorporated and remained stable during processing. The consistency of assay values across batches also confirms the robustness of the manufacturing process, ensuring reproducibility and reliability of the bilayer system[45,46]. From a regulatory perspective, compliance with content uniformity requirements is essential to guarantee dose accuracy and patient safety, particularly for antiretroviral therapy where precise dosing is critical.

Formulation	Zidovudine (% of label claim)	Lamivudine (% of label claim)
F1B	99.2 ± 0.8	98.9 ± 0.7
F2B	98.7 ± 0.9	99.1 ± 0.6
F3B	99.5 ± 0.7	98.6 ± 0.8
F4B	98.9 ± 0.8	99.3 ± 0.5
F5B	99.1 ± 0.6	98.8 ± 0.7

Table 6. Drug content of bilayer tablet formulations

3.6 In Vitro Drug Release Study

The dissolution profiles of bilayer tablets containing Zidovudine and Lamivudine are presented in Figure 2 and Figure 3, respectively. The cumulative percentage drug release at key time points is summarized in Table 7.All formulations exhibited controlled and extended drug release behavior over 24 h, with formulation-dependent variation governed primarily by polymer composition and matrix characteristics. [39,46]. Formulations containing higher proportions of HPMC K100M (F3B) demonstrated comparatively

slower release profiles due to the formation of a highly viscous gel barrier that restricted penetration of dissolution medium and reduced drug diffusion rates. In contrast, formulations containing Eudragit RLPO (F5B) exhibited relatively faster release, attributable to its permeability-enhancing and comparatively less hydrophilic nature, facilitating drug diffusion through the polymeric matrix[47]. Among all formulations, F1B achieved the most balanced release profile, exhibiting approximately 97% release of Zidovudine and 98% release of Lamivudine over 24 h. This indicates an optimal interplay between diffusion resistance, matrix swelling, and polymer erosion, enabling controlled drug delivery without excessive retardation or premature release.The observed release behavior is consistent with a matrix-controlled release mechanism, where hydration of hydrophilic polymers leads to gel layer formation followed by gradual diffusion of drug molecules and progressive matrix erosion. The absence of abrupt release or dose dumping indicates uniform matrix integrity, effective polymer distribution, and robust bilayer compression characteristics.Importantly, the bilayer configuration enabled independent modulation of release kinetics for both drugs through differential polymer composition and matrix architecture. This represents a significant advantage over conventional single-layer systems, where simultaneous optimization of release behavior for multiple drugs may be difficult to achieve [48].

Overall, the dissolution profiles confirm that the bilayer matrix system successfully achieved prolonged and controlled release of both drugs over 24 h, consistent with the pharmacokinetic objectives of the formulation.

Time (h)	F1B (ZDV)	F2B (ZDV)	F3B (ZDV)	F4B (ZDV)	F5B (ZDV)	F1B (LMV)	F2B (LMV)	F3B (LMV)	F4B (LMV)	F5B (LMV)
1	18	15	12	20	22	20	18	15	24	26
2	28	24	20	32	35	32	28	25	36	38
4	42	38	32	48	52	48	44	40	54	58
6	55	50	45	60	65	60	55	50	66	70
8	65	60	55	70	75	70	66	60	76	80
12	80	75	70	85	88	84	80	75	88	92
24	97	92	88	98	99	98	95	90	99	99

Table 7. Cumulative percentage drug release of bilayer formulations

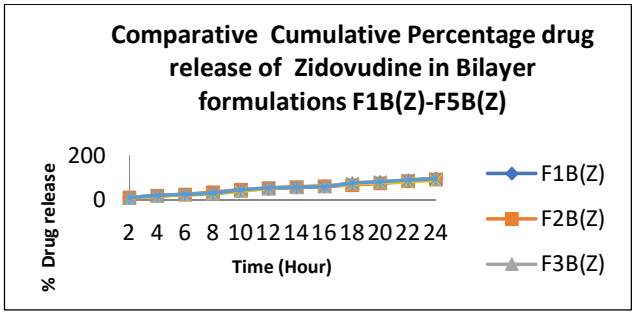

Figure 2. In vitro release profile of Zidovudine from bilayer tablets.

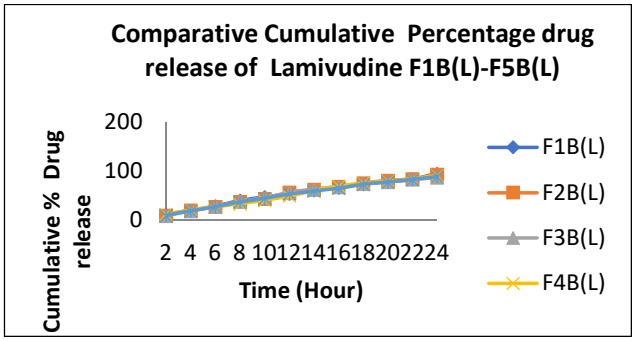

Figure 3. In vitro release profile of Lamivudine from bilayer tablets.

3.7 Swelling and Erosion Studies

The swelling and erosion behavior of bilayer tablets containing Zidovudine and Lamivudine are presented in Figure 4 and Figure 5, respectively. The corresponding values at selected time points are summarized in Table 8. All formulations exhibited progressive swelling with time, indicating rapid hydration of the polymeric matrix upon contact with dissolution medium. The increase in swelling index reflects the formation of a gel layer, which acts as a diffusion barrier controlling drug release[48]. Formulation F3B, containing a higher proportion of HPMC K100M, showed the highest swelling index throughout the study. This is attributable to the high water uptake capacity and gel-forming nature of HPMC, resulting in a thicker and more viscous diffusion barrier. Consequently, this formulation exhibited slower drug release, consistent with dissolution data. In contrast, formulation F5B showed

comparatively lower swelling but higher erosion rates[46,47]. This behavior is associated with the presence of Eudragit RLPO, which exhibits limited swelling and allows greater matrix permeability, leading to enhanced erosion and faster drug release. Erosion profiles demonstrated a gradual increase in mass loss over time, indicating polymer relaxation and structural breakdown of the matrix. The simultaneous occurrence of swelling and erosion suggests that drug release is governed by a coupled mechanism, rather than a single dominant process[39].

Notably, formulation F1B exhibited a balanced swelling-erosion profile, where sufficient gel formation was achieved to control diffusion, while gradual erosion prevented excessive retardation of drug release. This balance is critical for achieving sustained and predictable release kinetics[47]. The interplay between swelling and erosion confirms that the system operates through non-Fickian (anomalous) transport, where drug release is controlled by both diffusion through the hydrated matrix and polymer relaxation/erosion. This mechanistic behavior directly supports the kinetic modeling results discussed in the subsequent section.

Time (h)	Swelling Index (%) F1B	Swelling F3B	Swelling F5B	Erosion (%) F1B	Erosion F3B	Erosion F5B
1	45 ± 2	55 ± 3	38 ± 2	8 ± 1	5 ± 1	10 ± 1
2	65 ± 3	78 ± 4	55 ± 3	12 ± 1	8 ± 1	15 ± 2
4	90 ± 4	110 ± 5	75 ± 4	18 ± 2	12 ± 2	22 ± 2
6	115 ± 5	135 ± 6	95 ± 5	25 ± 2	18 ± 2	30 ± 3
8	135 ± 6	155 ± 7	110 ± 6	32 ± 3	24 ± 3	38 ± 3
12	150 ± 7	175 ± 8	125 ± 6	45 ± 3	32 ± 3	50 ± 4
24	165 ± 8	190 ± 9	140 ± 7	60 ± 4	45 ± 4	65 ± 5

Table 8. Swelling index and erosion (%) of bilayer formulations

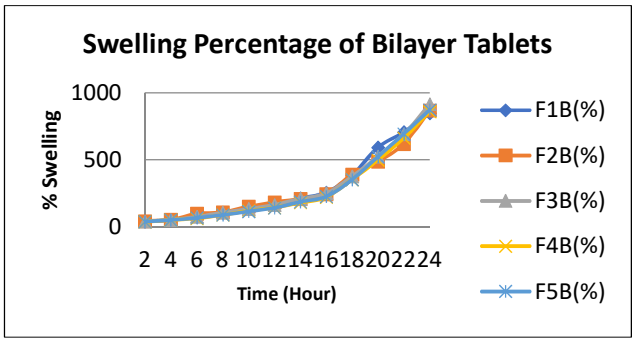

Figure 4. Swelling behavior of bilayer formulations as a function of time.

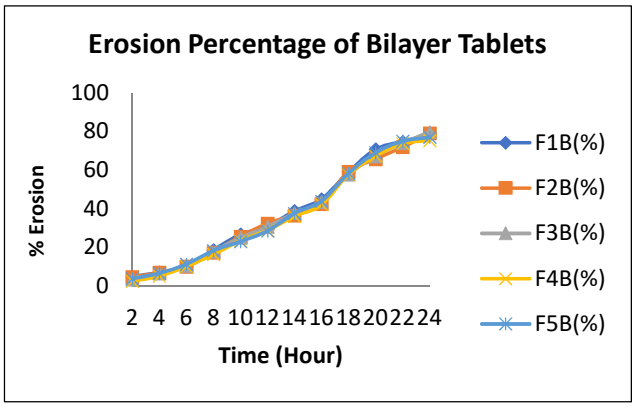

Figure 5. Matrix erosion profile of bilayer formulations over time.

3.8 Drug Release Kinetics

The in vitro release data of Zidovudine and Lamivudine from the bilayer formulations were fitted to various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. The corresponding regression coefficients (R^2) and release exponent (n) values are presented in Table 9.

The release profiles of Zidovudine from all formulations exhibited the highest correlation with the zero-order model (R^2 = 0.985-0.993), indicating that drug release occurred at a nearly constant rate, independent of concentration [39]. This behavior is desirable for controlled-release systems, as it enables maintenance of steady plasma drug levels. In contrast, the lower correlation observed with the first-order model confirms that the release is not governed by concentration-dependent kinetics, further supporting a controlled matrix-based release mechanism.The good fit to the Higuchi model (R^2 > 0.97) indicates that diffusion plays a significant role in drug release. However, the simultaneous high correlation with zero-order kinetics suggests that diffusion alone does not fully explain the release behavior. The Korsmeyer-Peppas model yielded release exponent (n) values in the range of 0.82-0.91, indicating a non-Fickian (anomalous)

transport mechanism[26,47]. This implies that drug release is governed by a combination of diffusion and polymer relaxation/erosion processes.This interpretation is consistent with the swelling and erosion results (Section 3.7), where both matrix hydration and gradual polymer erosion were observed. The interplay between these mechanisms leads to a controlled and sustained release profile. Although kinetic modeling was primarily emphasized for Zidovudine due to its shorter biological half-life and greater requirement for controlled-release modulation, Lamivudine also exhibited sustained-release behavior consistent with matrix-controlled diffusion.Among all formulations, F1B demonstrated optimal kinetic behavior, exhibiting near zero-order release with an n value of 0.87, reflecting a balanced contribution of diffusion and matrix relaxation. This aligns with its dissolution profile and swelling-erosion characteristics, confirming its suitability as the optimized formulation[49].

Overall, the kinetic analysis confirms that the bilayer system achieves controlled drug delivery through a synergistic mechanism, rather than a single dominant process, validating the formulation design.

Formulation	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Peppas (R^2)	n value
F1B	0.992	0.945	0.978	0.989	0.87
F2B	0.988	0.950	0.975	0.985	0.84
F3B	0.985	0.952	0.973	0.983	0.91
F4B	0.993	0.940	0.980	0.990	0.85
F5B	0.991	0.947	0.977	0.987	0.82

Table 9. Kinetic modeling parameters of Zidovudine release

3.9 Stability Studies

The stability of the optimized bilayer formulation (F1B) containing Zidovudine and Lamivudine was evaluated under accelerated conditions (40 ± 2 °C / 75 ± 5% RH) for a period of 3 months, as per ICH Q1A(R2). The results are summarized in Table 10.The optimized formulation (F1B) remained physically stable throughout the study period, with no observable changes in appearance, indicating absence of moisture-induced degradation or structural instability. Mechanical properties showed minimal variation over time[26,50]. The slight reduction in hardness and marginal increase in friability remained within acceptable pharmacopeial limits, indicating that the tablets retained their mechanical integrity under accelerated conditions. Drug content values for both Zidovudine and Lamivudine remained within the acceptable range (95-105%), with only minor reductions observed over time. These changes are within experimental variability and do not indicate significant degradation. The dissolution profiles of both Zidovudine and Lamivudine remained largely unchanged throughout the stability period, with sustained drug release maintained over 24 h. The absence of significant deviation in release behavior suggests that the polymeric matrix structure remained intact during storage[51].

Overall, the stability data indicate that the bilayer formulation is physically and chemically stable under accelerated conditions, with no significant impact on drug content or release characteristics. This supports the suitability of the formulation for further development and long-term stability evaluation.

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	No change	No change	No change	No change
Hardness (kg/cm²)	11.2 ± 0.3	11.1 ± 0.2	11.0 ± 0.3	10.9 ± 0.3
Friability (%)	0.21	0.22	0.23	0.24
Drug Content (%) (ZDV)	99.2 ± 0.8	98.9 ± 0.7	98.7 ± 0.9	98.5 ± 0.8
Drug Content (%) (LMV)	98.9 ± 0.7	98.7 ± 0.6	98.5 ± 0.7	98.3 ± 0.8
% Drug Release (24 h, ZDV)	97	96	96	95
% Drug Release (2 h, LMV)	98	97	96	96

Table 10. Stability data of optimized formulation (F1B)

4. Conclusion

A pharmacokinetically guided bilayer tablet of Zidovudine and Lamivudine was successfully developed to achieve coordinated and sustained drug delivery within a single dosage form. The formulation strategy, based on the distinct elimination profiles of the two drugs, enabled prolonged and controlled release of both drugs over 24 h through independently modulated polymeric matrix layers.The optimized formulation (F1B) demonstrated desirable pre-compression and post-compression characteristics, complying with pharmacopeial requirements and ensuring mechanical integrity of the bilayer system. Dissolution studies confirmed that the system achieved sustained and controlled drug release consistent with the intended pharmacokinetic objectives. The release mechanism was identified as non-Fickian (anomalous) transport, governed by a combination of diffusion, polymer swelling, and matrix erosion, as supported by kinetic modeling and swelling-erosion analysis.The absence of drug-excipient incompatibility, along with stable performance under accelerated conditions, indicates that the formulation is chemically and physically robust. Importantly, the bilayer architecture enabled independent modulation of release kinetics for both drugs, overcoming formulation limitations associated with conventional single-layer systems.

Overall, the developed bilayer matrix tablet represents a mechanistically rational and therapeutically relevant controlled drug delivery system, with potential to improve dosing convenience and maintain consistent plasma drug concentrations. The formulation provides a scalable platform for further optimization and warrants evaluation through in vivo pharmacokinetic and bioavailability studies to establish clinical relevance.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Statement

This article does not contain any studies with human participants or animals performed by the authors. Therefore, ethical approval and informed consent were not required.

Author Contributions

Conceptualization: [Name]

Methodology: [Name]

Investigation: [Name]

Data curation: [Name]

Writing – original draft: [Name]

Writing – review & editing: [Name]

Visualization: [Name]

Supervision: [Name]

Project administration: [Name]

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Data Availability

The datasets generated and analyzed during the current study are included within the article. Additional data supporting the findings of this study are available from the corresponding author upon reasonable request.

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