Formulation Development of Controlled Release Formulations of Lamivudine and Stavudine

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***Abstract*—The combination of Lamivudine and Stavudine is widely used in antiretroviral therapy for the management of HIV infection. However, conventional immediate-release formulations require frequent dosing, which can lead to poor patient compliance and fluctuating plasma drug levels. This study aims to develop and evaluate controlled-release formulations of Lamivudine and Stavudine to enhance therapeutic efficacy and reduce dosing frequency. Various formulation strategies, including matrix systems and release-modifying polymers, were employed to achieve sustained drug release. The formulations were characterized for physicochemical properties, in vitro drug release, and stability. Results demonstrated that the optimized controlled-release formulations maintained therapeutic drug concentrations over an extended period, showing potential for improved patient adherence and clinical outcomes. This work highlights the feasibility of developing sustained-release antiretroviral dosage forms for enhanced HIV therapy.**

***Index Terms*—Lamivudine, Stavudine, Drug delivery systems, HIV, Patient compliance**

I. INTRODUCTION

Human Immunodeficiency Virus (HIV) is a chronic viral infection that requires lifelong antiretroviral therapy (ART) to suppress viral replication and prevent progression to Acquired Immunodeficiency Syndrome (AIDS). Among the antiretroviral drugs, Lamivudine (3TC) and Stavudine (d4T) are widely used nucleoside reverse transcriptase inhibitors (NRTIs) that act by inhibiting the reverse transcriptase enzyme, thereby preventing viral DNA synthesis. Both drugs are commonly used in combination therapy due to their synergistic effects in controlling viral load.

1. However, conventional oral formulations of Lamivudine and Stavudine face several challenges:

- Frequent dosing: Both drugs have short half-lives (Lamivudine: ~5–7 hours, Stavudine: ~1–2 hours), requiring multiple daily doses, which can reduce patient adherence.
- Fluctuating plasma levels: Immediate-release formulations lead to peaks and troughs in drug concentrations, increasing the risk of side effects and subtherapeutic levels.
- Patient compliance: Lifelong therapy with multiple doses per day often leads to non-compliance, which can result in treatment failure and viral resistance.

2. Controlled Release Formulations

Controlled release (CR) drug delivery systems are designed to release the active pharmaceutical ingredient (API) at a predetermined rate, maintaining therapeutic plasma concentrations over an extended period. This approach offers several advantages:

- Reduced dosing frequency: CR formulations can potentially allow once-daily or twice-daily dosing, improving adherence.
- Stable plasma levels: Minimizes fluctuations, reducing side effects and enhancing efficacy.
- Improved patient compliance: Simplified regimens increase the likelihood of consistent therapy.
- Targeted release: Certain CR systems can release the drug at specific sites in the gastrointestinal tract, optimizing absorption.

For antiretroviral therapy, CR formulations of Lamivudine and Stavudine could significantly improve treatment outcomes by maintaining steady plasma levels and reducing pill burden.

3. Rationale for Lamivudine and Stavudine CR Formulations

Developing controlled release systems for Lamivudine and Stavudine is particularly relevant because:

1. Both drugs are highly water-soluble, which can lead to rapid absorption and elimination.
2. Their short half-lives make them ideal candidates for extended-release systems.
3. Sustained plasma levels can reduce mitochondrial toxicity (common with Stavudine) by avoiding high peak concentrations.
4. Fixed-dose combination CR tablets can improve adherence in HIV patients, especially in resource-limited settings.

4. Methods of Controlled Release

Several approaches can be used for developing CR formulations:

- Matrix systems: Drugs are embedded in a polymer matrix that controls release through diffusion or erosion.
- Coating systems: Drugs are coated with polymers that dissolve or swell at specific rates.
- Osmotic systems: Drug release is controlled by osmotic pressure through a semipermeable membrane.
- Multiparticulate systems: Drug is encapsulated in pellets or microspheres for uniform and predictable release.

II. MATERIALS AND METHODS

1. Materials

Active Pharmaceutical Ingredients (APIs):

- Lamivudine (3TC) – obtained from a certified pharmaceutical supplier (purity ≥ 99%).
- Stavudine (d4T) – obtained from a certified pharmaceutical supplier (purity ≥ 99%).

Excipients:

- Polymers for matrix formulation: Hydroxypropyl methylcellulose Plasticizers and release modifiers: Polyethylene glycol, Propylene glycol.
- Diluents and fillers: Microcrystalline cellulose , Lactose monohydrate.
- Lubricants: Magnesium stearate, Talc.
- Disintegrants: Sodium starch glycolate, Crosscarmellose sodium.
- Solvents: Distilled water, Ethanol (analytical grade).

Analytical reagents:

- Phosphate buffer solutions (pH 1.2 and 6.8)
- Methanol and other HPLC-grade solvents

2. Methods

2.1 Preformulation Studies

Preformulation studies were performed to assess the physicochemical properties of Lamivudine and Stavudine before formulation development:

- Drug-excipient compatibility: Using Fourier Transform Infrared Spectroscopy (FTIR) to detect potential interactions.
- Melting point determination: To check the purity and thermal stability of drugs.
- Solubility studies: Solubility in water, phosphate buffer pH 1.2, pH 6.8, and ethanol to guide polymer selection.
- Partition coefficient and stability: To understand the drug's lipophilicity and degradation profile.

2.2 Formulation of Controlled Release Tablets

Method: Direct compression

1. Preparation of granules:
   - APIs and polymer(s) were accurately weighed and mixed uniformly.
   - Granulating agent isopropyl alcohol was added to form a wet mass.
   - The mass was passed through a sieve to form granules, then dried at 40–50°C until constant weight.
2. Blending and lubrication:
   - Dried granules were blended with lubricants (magnesium stearate, talc) to ensure uniform flow and prevent sticking during compression.
3. Compression into tablets:
   - Tablets were compressed using a rotary tablet press with appropriate die and punch size.
   - Target weight, hardness, and thickness were maintained for uniformity.

2.3 Evaluation of Pre-Compression Parameters

Before compression, the granules were evaluated for:

- Angle of repose: To determine flow properties.
- Bulk and tapped density: For compressibility index and Hausner ratio calculation.
- Moisture content: Using a moisture analyzer.

2.4 Evaluation of Post-Compression Parameters

The compressed tablets were evaluated for:

- Physical appearance: Shape, color, and surface characteristics.
- Weight variation: Using 20 tablets according to pharmacopeial standards.
- Hardness: Using a hardness tester to ensure mechanical strength.
- Friability: Using a friabilator; tablets with <1% weight loss were acceptable.
- Drug content uniformity: By dissolving powdered tablets in suitable solvent and analyzing using UV-visible spectrophotometry or HPLC.
- Swelling index: To assess the polymer hydration and matrix expansion.

2.5 In Vitro Drug Release Studies

- Dissolution testing:
  - Apparatus: USP Type II (paddle method).
  - Medium: 900 mL of phosphate buffer pH 1.2 (2 hours) followed by pH 6.8 (up to 12 hours).
  - Rotation speed: 50–75 rpm.
  - Temperature: 37 ± 0.5°C.
  - Sample collection: Aliquots withdrawn at predetermined intervals, filtered, and analyzed for drug content using UV spectrophotometry or HPLC.
- Release kinetics: Data were fitted to models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas to determine the mechanism of drug release.

III. RESULTS AND DISCUSSION

Solubility analysis

The available literature on solubility profile of Lamivudine and Stavudine indicated thatthe drugisvery soluble indichloro methane,ethanol,acetone and slightly soluble in methanol, aceto nitrile, practically insoluble in water. Lamivudine and Stavudine are found to be freely soluble in dichloromethane, ethanol, acetone, slightly soluble in methanol and acetonitrile, practically insoluble in water.The study was carried out to select suitable dissolution medium for *in vitro* release studies. The solubility of Lamivudine and Stavudine in acid buffer of pH 1.2 was highest. Hence, media containing acid buffer of pH 1.2 for first 2 h, then phosphate buffer of pH 7.4 for next 10 h are selected for dissolution studies.

PXRD STUDIES

PXRD FOR LAMIVUDINE

The solid state crystallinity of Lamivudine drug, HPMC, EC, Eudragit RS100 Microspheres are prepared with different ratios by Solvent Evaporation method. The developed formulations are studied by PXRD technique. The reduction in crystallinity of Lamivudine in the formulations (SolventEvaporationmethod) was observed. and it was also noted that the crystallinity was decreased after the formulation of microspheres, meaning the drug was converted crystalline to amorphous then the total drug was entrapped in all the formulations with different polymers

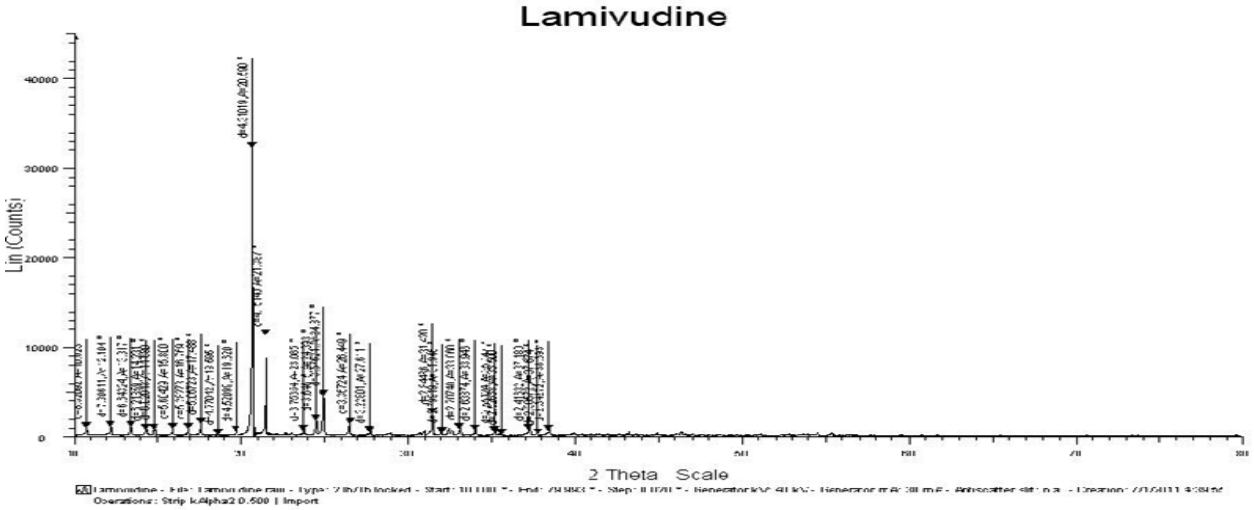


Fig 1.1 XRD of Lamivudine

PXRDFORSTAVUDINE

The solid state crystallinity of Stavudine, HPMC, EC, and Eudragit RS100Microspheres are prepared with different ratios by Solvent Evaporation method. The developed formulations are studied by PXRD technique. The reduction in crystallinity of lamivudine in the formulations (SolventEvaporationmethod)was observed. it was also noted that the crystallinity was decreased after the formulation of microspheres, meaning the drug was converted crystalline to amorphous then the total drug was entrapped in all the formulations with different polymers.

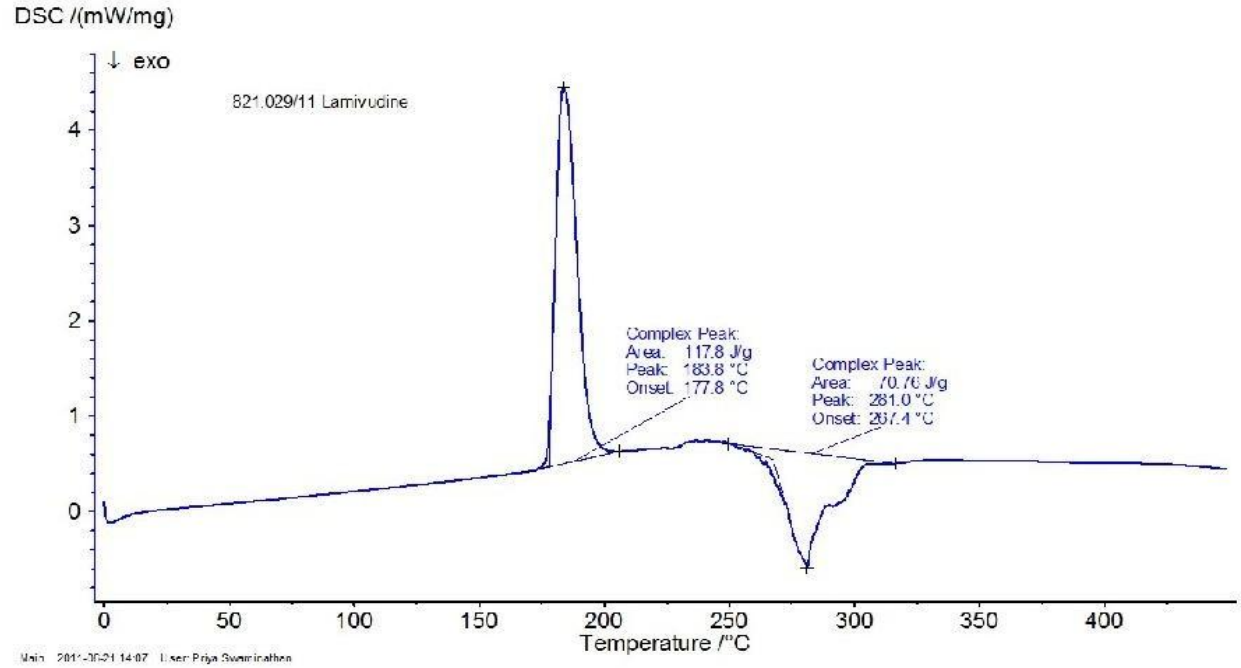


Fig 1.2 DSC of Lamivudine

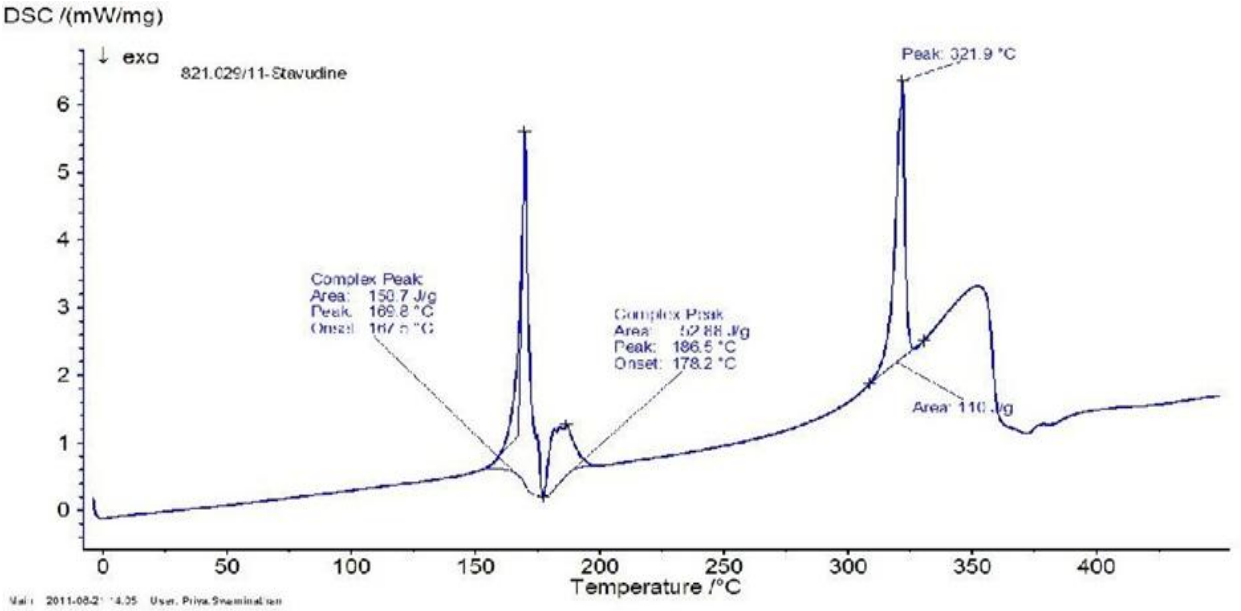


Fig 1.3 DSC Curve of Stavudine

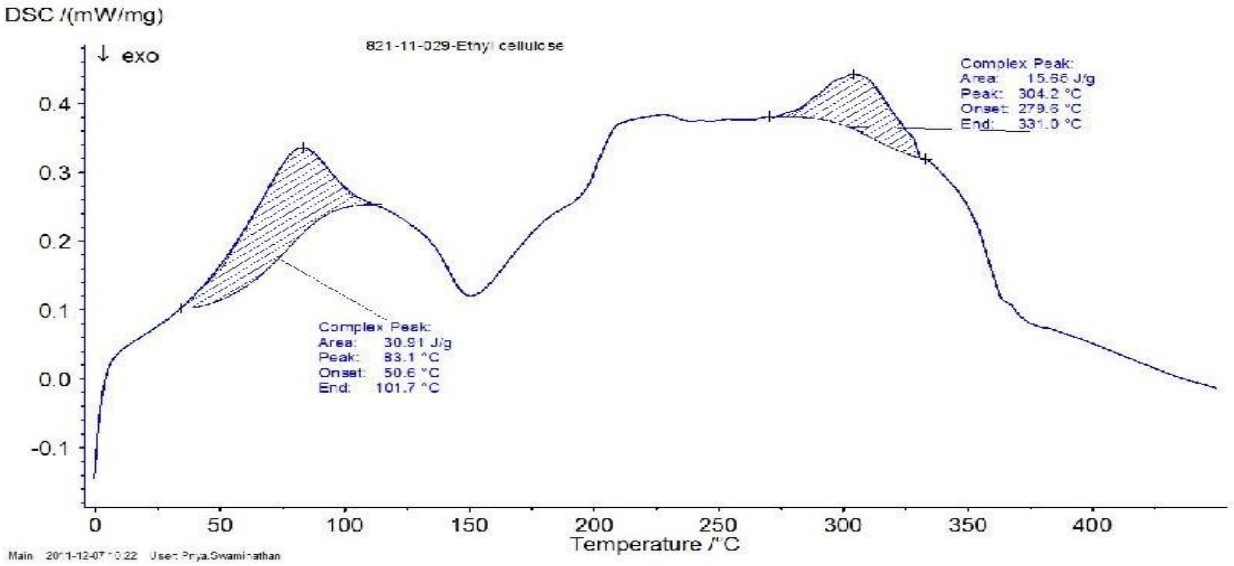


Fig 1.4 DSC of Microsphere

Micro meritic properties of LAM and STA microspheres:

BulkandT appeddensity :Bulk density and Tapped densities showed good pack ability of the microspheres. The values are given in Table 1.1

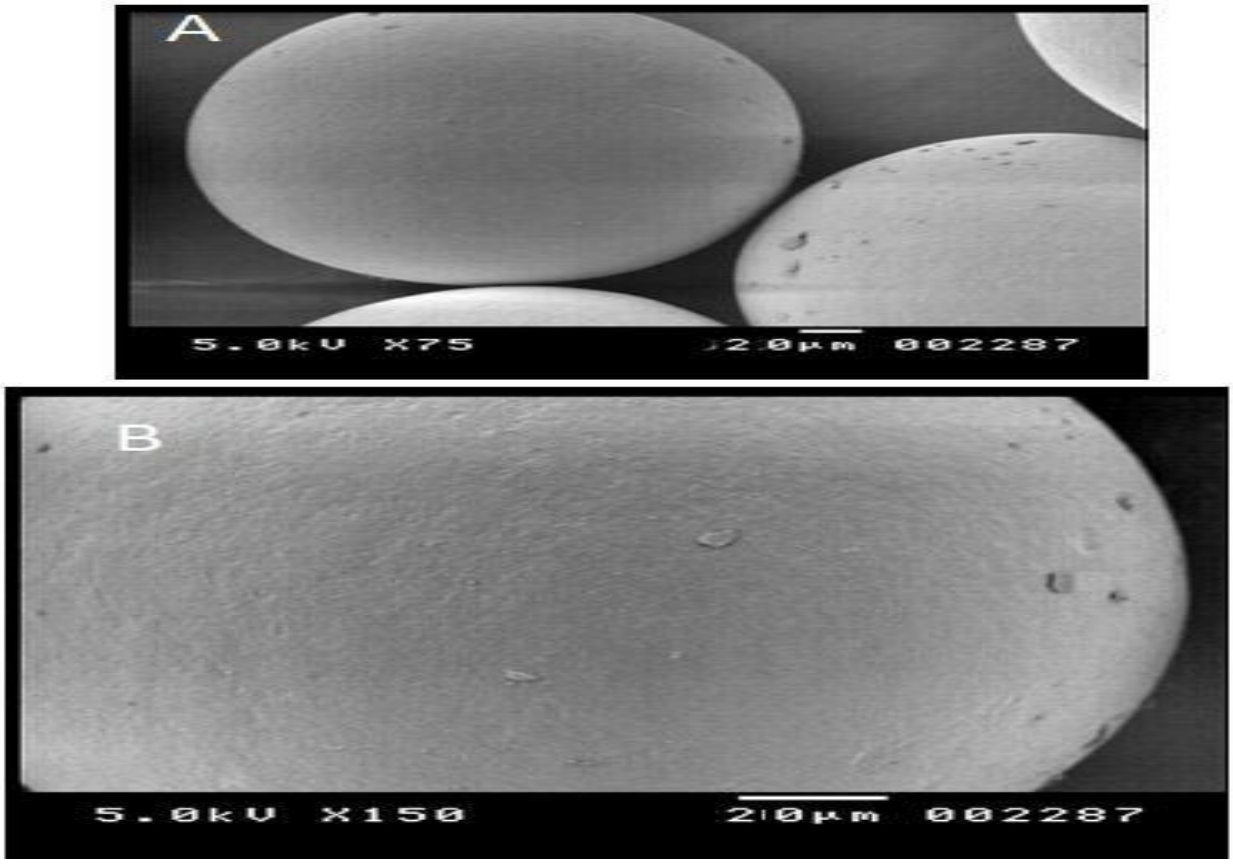
Table1.1 Flow properties of LAM and STA loaded microspheres

S.No	Formulationcode	Bulkdensity±S.D (gm/mL)	Tappeddensity±S.D
1	LSF1	0.462±0.006	0.528±0.008
2	LSF2	0.502±0.007	0.581±0.010
3	LSF3	0.463±0.011	0.527±0.014
4	LSF4	0.614±0.012	0.714±0.017
5	LSF5	0.494±0.007	0.583±0.010
6	LSF6	0.450±0.006	0.538±0.008
7	LSF7	0.581±0.011	0.695±0.015
8	LSF8	0.660±0.014	0.745±0.017
9	LSF9	0.599±0.006	0.698±0.008
10	LSF10	0.598±0.006	0.697±0.008
11	LSF11	0.582±0.005	0.680±0.008
12	LSF12	0.576±0.011	0.668±0.014
13	LSF13	0.580±0.006	0.667±0.008
14	LSF14	0.583±0.006	0.670±0.008
15	LSF15	0.601±0.017	0.686±0.014
16	LSF16	0.596±0.006	0.682±0.008
17	LSF17	0.593±0.006	0.682±0.008

SEMAnalysis:

SEM analysis was performed on the prepared Lamivudine and Stavudine loaded micro spheres to access their surface morphological characteristicsas

The micrographs do not show any pores on microspheres. Smooth surface reveals complete removal of Dichloromethane from microspheres.



IV. CONCLUSION

In this study, controlled release formulations of Lamivudine and Stavudine were successfully developed with the objective of improving patient compliance and achieving sustained therapeutic drug levels. Various formulation strategies, including the use of polymers and matrix systems, were evaluated for their ability to control drug release over an extended period. The optimized formulations demonstrated desirable physicochemical properties, uniform drug content, and consistent in vitro drug release profiles, indicating effective modulation of release kinetics. Stability studies confirmed that the formulations maintained their integrity and drug release characteristics over time.

Overall, the research highlights that controlled release formulations of Lamivudine and Stavudine can offer significant therapeutic advantages, including reduced dosing frequency and improved adherence in HIV treatment. These findings provide a strong foundation for further in vivo studies and potential clinical application of sustained-release antiretroviral therapy.

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