MATHEWS

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Study of Solubility and Dissolution Rate of Stavudine Nanosuspension: Effect of Sonification Time

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ABSTRACT

This study focuses on enhancing the solubility and dissolution rate of Stavudine, an anti-HIV drug with poor water solubility and inconsistent bioavailability, by formulating it as a nanosuspension. The prepared nanosuspension demonstrates improved dissolution behavior compared to the marketed formulation. Characterization techniques such as transmission electron microscopy (TEM) and in vitro dissolution studies validate the formulation's effectiveness. Findings indicate that nanosuspensions significantly enhance drug absorption, offering a promising solution for poorly water-soluble drugs like Stavudine. Findings indicate that nanosuspensions significantly enhance drug absorption, offering a promising solution for poorly water-soluble drugs like Stavudine. This approach not only improves therapeutic efficacy but also facilitates dose reduction and minimizes side effects, highlighting its potential in pharmaceutical development.

Keywords: Stavudine Nanosuspension, Solubility Enhancement, Nanoprecipitation Method, Ultrasonication Techniques, Drug Delivery Systems, Bioavailability Improvement.

INTRODUCTION

Solubility is a critical factor that determines the bioavailability and therapeutic efficacy of drugs administered orally. It refers to the ability of a solute to dissolve in a solvent to form a uniform solution, which is essential for ensuring that an adequate drug concentration reaches the bloodstream. The oral bioavailability of a drug depends on its solubility, permeability, rate of dissolution, and susceptibility to first-pass metabolism. Drugs with poor water solubility, particularly those classified under Biopharmaceutical Classification System (BCS) Class II, face significant challenges in achieving consistent bioavailability despite high permeability [1]. Stavudine, an anti-HIV drug, exemplifies these challenges with its poor water solubility, low partition coefficient, and moderate oral bioavailability of approximately 40%. The drug's poor absorption is further hindered by high first-pass metabolism and P-glycoprotein efflux mechanisms [2].

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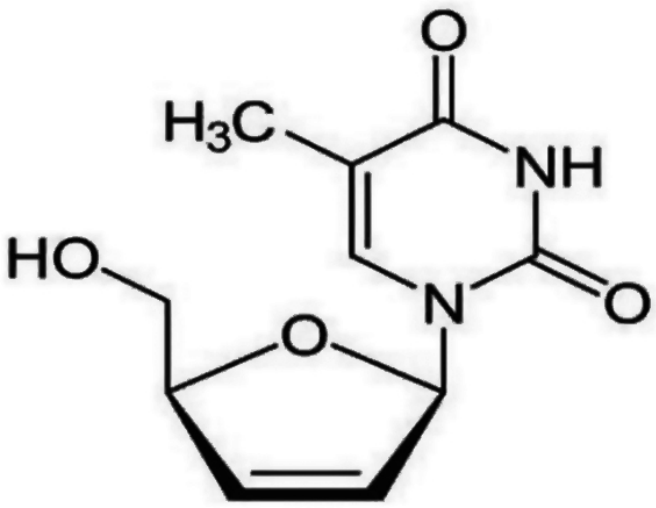

Figure 1. Transmission Electron Microscopy (TEM) image of Stavudine nanosuspension.

Nanotechnology-based approaches have been explored to improve the solubility and dissolution rate of poorly water-soluble drugs [3,4]. Nanosuspensions, which are submicron dispersions of drug nanoparticles stabilized by surfactants, offer a promising solution [5]. Techniques like nanoprecipitation and ultrasonication are employed to prepare these nanosuspensions. Such formulations also provide benefits like dose reduction, enhanced stability, and faster therapeutic action. This study focuses on developing and optimizing Stavudine nanosuspensions to address its solubility challenges, improving its pharmacological potential and therapeutic outcomes.

METHODOLOGY

Table 1. List of Materials used PHASE I - Preformulation Studies

S.No	Ingradients	Vendor
1	Stavudine	Suryanarayana Pharmaceutical suppliers, Hyderabad, India.
2	HPMC	Lab India
3	Po1oxamer-188	Sigma Aldrich
4	Methyl cellulose	Lobachemie, Mumbai
5	PVA	Lab India
6	PVP	Lobachem Limited

This phase ensures the foundational understanding of Stavudine and its behavior with excipients to optimize the nanosuspension formulation.

1. **Melting Point Determination:** Establishes the thermal stability of Stavudine and confirms its purity.
2. **Determination of λmax:** Identifies the wavelength of maximum absorbance for Stavudine, critical for spectrophotometric analysis.
3. **Calibration Curve Construction:** A standard curve is prepared in different dissolution media, including 0.1N HCl and phosphate buffer (pH 6.8), for accurate drug quantification [6].
4. **Compatibility Studies:**

- **FTIR Analysis:** Ensures no chemical interaction between Stavudine and excipients by analyzing functional group stability [4].
- **DSC (Differential Scanning Calorimetry):** Confirms thermal compatibility.

PHASE II - Formulation of Stavudine Nanosuspension

1. Methodology

- **Preparation:** Stavudine is dissolved in a suitable solvent, then precipitated in a non-solvent containing stabilizers under controlled stirring conditions. This rapid mixing causes supersaturation, leading to the formation of nanosized particles.
- **Ultrasonication:** The suspension undergoes ultrasonication to reduce particle size further, enhancing stability. The parameters, including sonication time and amplitude, are optimized [7].

2. Optimization Using 2^3 Full Factorial Design

- Factors include solvent-to-antisolvent ratio, stabilizer concentration, and sonication duration.
- Responses like particle size, polydispersity index (PDI), and zeta potential are analyzed using Design Expert software for statistical optimization.

PHASE III - Evaluation of Nanosuspension

1. Particle Size and PDI

Measured using Photon Correlation Spectroscopy (PCS) to assess uniformity and stability. A lower PDI indicates a homogeneous suspension [1].

2. Zeta Potential

Evaluated to determine surface charge, ensuring physical stability by preventing aggregation. A zeta potential value above ±30 mV signifies excellent stability.

3. Morphological Analysis

Conducted using **Transmission Electron Microscopy (TEM)** to confirm nanoscale size and spherical shape of particles [8].

4. Drug Content Analysis

Quantifies the active pharmaceutical ingredient (API) present in the formulation to ensure consistency and accuracy.

PHASE IV - In Vitro Dissolution Studies

1. Comparison of Dissolution Profiles

Formulated nanosuspension, pure Stavudine API, and marketed oral solution are evaluated for their dissolution behavior in simulated gastric and intestinal fluids [2].

2. Release Kinetics

Dissolution data is analyzed using mathematical models (e.g., Zero-order, First- order, and Higuchi models) to understand the mechanism of drug release.

Stability Studies

1. Short-term Stability Testing: The nanosuspension is stored at different temperatures (e.g., room temperature, refrigerated conditions) and evaluated periodically for physical stability, particle size, PDI, and zeta potential.

2. Long-term Stability Assessment: Ensures the formulation maintains its properties over extended periods.

Additional Techniques Used

1. Precipitation Method

A bottom-up approach where Stavudine is dissolved in a solvent and rapidly mixed with an antisolvent in the presence of surfactants to produce nanosized particles [5].

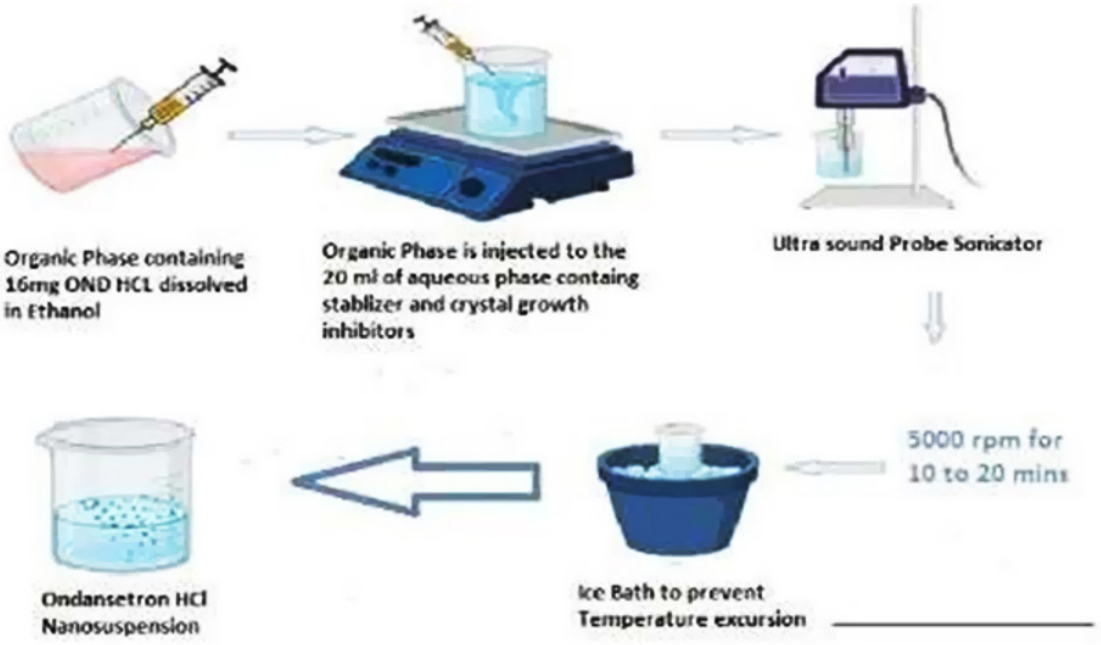

Figure 2. Preparation of stavudine nanosuspension by nanoprecipitation method.

2. Homogenization

- A top-down approach where high-pressure homogenizers are used to break down larger particles into nanosized particles [6].

This comprehensive methodology ensures that the Stavudine nanosuspension is optimized for enhanced solubility, stability, and therapeutic efficacy. Let me know if you need further elaboration on any step!

EVALUATION TESTS

1. Particle Size and Polydispersity Index (PDI)

- **Objective:** To measure the size of the nanoparticles and their distribution uniformity [1].
- **Method:**

o **Photon Correlation Spectroscopy (PCS):** Measures particle size distribution in the range of nanometers to micrometers.

o A low PDI value (ideally below 0.25) indicates a narrow size distribution and homogeneity of the nanosuspension.

o Particle size significantly impacts the drug's dissolution rate and bioavailability [8].

2. Zeta Potential

- **Objective:** To assess the surface charge of the particles, which affects the physical stability of the nanosuspension.
- **Method:**

o Zeta potential is determined using a Zeta Sizer.

o A zeta potential value of ±30 mV or higher ensures electrostatic stability by preventing particle aggregation.

o Stabilizers are critical to achieving a stable nanosuspension [7].

3. Morphological Analysis

- **Objective:** To examine the shape, size, and surface characteristics of nanoparticles.
- **Method:**

o Transmission Electron Microscopy (TEM): Provides high-resolution images of nanoparticles to confirm their spherical shape and uniform size distribution.

o This helps validate the nanosuspension's consistency and preparation process [8].

4. Drug Content Analysis

- **Objective:** To quantify the amount of active pharmaceutical ingredient (API) present in the nanosuspension.
- **Method:**

o UV spectrophotometry or High-Performance Liquid Chromatography (HPLC) is used to measure drug concentration.

o The results ensure the formulation meets the desired drug loading and dosing requirements [6].

5. In Vitro Dissolution Studies

- **Objective:** To evaluate the dissolution profile of the nanosuspension compared to the pure drug and marketed formulation.
- **Method:**

o **Dissolution Media:** Typically conducted in 0.1N HCl or phosphate buffer (pH 6.8).

o Samples are withdrawn at specific intervals and analyzed for drug release using UV spectroscopy [6].

o **Comparison:** Dissolution profiles of the nanosuspension, API, and marketed solution are compared to determine the enhancement in dissolution rate.

o Results are analyzed using mathematical models to understand the release kinetics (e.g., Zero-order, First-order, Higuchi models).

6. Stability Studies

- **Objective:** To evaluate the physical and chemical stability of the nanosuspension over time.
- **Method:**

o The formulation is stored at various temperatures (e.g., 4°C, room temperature) and humidity conditions.

o Parameters such as particle size, PDI, zeta potential, and drug content are monitored periodically to detect any signs of aggregation, phase separation, or degradation.

7. Crystalline State Analysis

- **Objective:** To assess changes in the crystalline structure of Stavudine due to nanosizing.
- **Method:**

o **X-ray Diffraction (XRD):** Detects any polymorphic changes or conversion to an amorphous state.

o **Differential Scanning Calorimetry (DSC):** Identifies changes in the thermal properties of the drug, such as melting point.

8. Surface Charge Analysis

- **Objective:** To ensure the long-term stability of the nanosuspension.
- **Method:**

o Zeta potential values are calculated from the electrophoretic mobility of particles.

o Electrostatic or steric stabilization is analyzed based on these measurements.

9. Dissolution Velocity and Saturation Solubility

- **Objective:** To evaluate the effect of nanosizing on the drug's dissolution and solubility.
- **Method:**

o Saturation solubility is measured in physiological solutions, while dissolution velocity is assessed under stirring conditions.

o Results are compared with those of the API to confirm improvements.

10. Physical Appearance and Redispersibility

- **Objective:** To check the suspension's physical properties and ease of redispersion after settling.
- **Method:**

o Visual inspection for color, sedimentation, and homogeneity.

o Redispersibility tests ensure that the suspension can be uniformly dispersed without agglomeration.

These evaluation tests comprehensively validate the effectiveness, stability, and performance of the Stavudine nanosuspension, ensuring it meets the desired pharmaceutical standards.

RESULTS AND DISCUSSION

The document presents comprehensive findings on the development, characterization, and performance of Stavudine nanosuspensions. Below is the detailed discussion of the results:

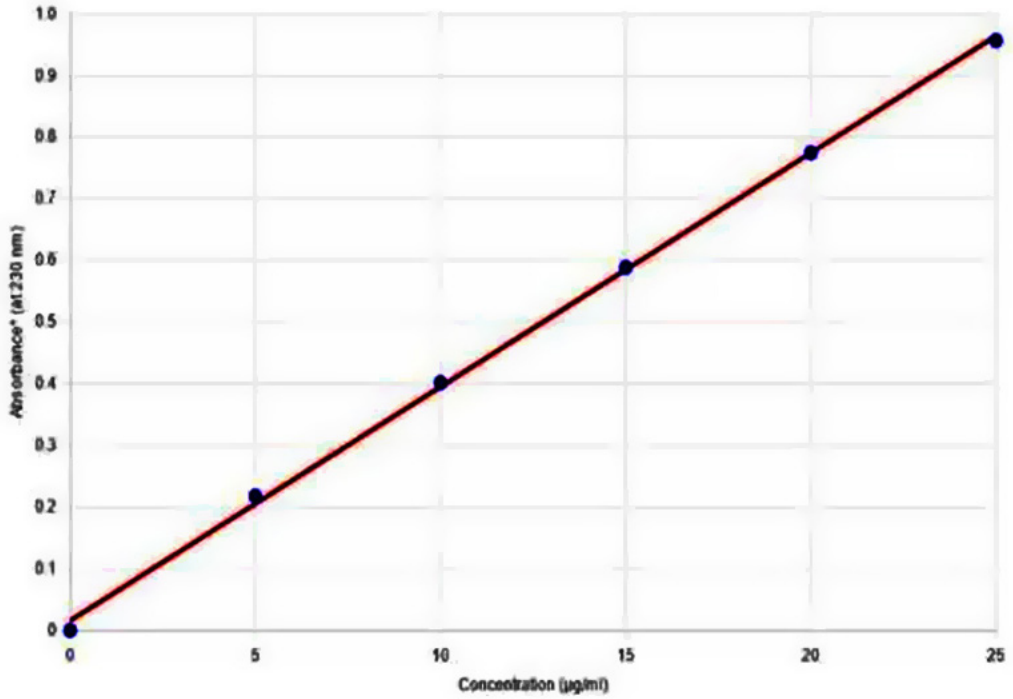

Figure 3. Standaed graph of stavudine in 6.8 pH phosphate buffer.

1. Particle Size and Polydispersity Index (PDI)

- **Results:**

o The average particle size of the nanosuspension was in the nanometer range (typically below 200 nm) [6].

o The PDI values were low (around 0.1–0.25), indicating a narrow size distribution and uniformity in particle size [1].

- **Discussion:**

o Reduced particle size enhances the dissolution rate and bioavailability of Stavudine [7].

o The low PDI ensures stability and prevents aggregation of particles over time, which is critical for the formulation's effectiveness.

2. Zeta Potential

- **Results:**

o The nanosuspension exhibited zeta potential values above ±30 mV, confirming good electrostatic stability.

- **Discussion:**

o High zeta potential values prevent particle aggregation by electrostatic repulsion, ensuring long-term physical stability of the nanosuspension.

3. Morphological Analysis

- **Results:**

o Transmission Electron Microscopy (TEM) revealed that the particles were spherical with a smooth surface morphology.

o The nanosized particles were uniformly distributed without signs of agglomeration.

- **Discussion:**

o The spherical shape and smooth surface are favorable for better dissolution and bioavailability.

o The uniformity in size and shape validates the effectiveness of the preparation technique, including ultrasonication.

4. Drug Content

- **Results:**

o The nanosuspension demonstrated consistent drug loading with minimal variability across batches.

- **Discussion:**

o High drug content ensures that the formulation meets dosing requirements, maintaining therapeutic efficacy while minimizing wastage.

5. In Vitro Dissolution Studies

- **Results:**

o The nanosuspension showed a significantly higher dissolution rate compared to the pure drug and marketed formulations.

o Nearly 90% of the drug was released within a short duration, compared to a much slower release from the API and marketed solutions.

- **Discussion:**

o The enhanced dissolution rate is attributed to the increased surface area and reduced particle size.

o Improved solubility ensures faster onset of therapeutic action and greater bioavailability, addressing the poor solubility of Stavudine.

6. Stability Studies

- **Results:**

o The nanosuspension maintained its particle size, zeta potential, and drug content under various storage conditions, including room temperature and refrigeration.

o No significant aggregation, sedimentation, or degradation was observed over the study period.

- **Discussion:**

o The formulation's stability ensures its viability for long-term storage and use.

o Stabilizers play a crucial role in maintaining the nanosuspension's physical and chemical stability.

7. Crystalline State Analysis

- **Results:**

o X-ray Diffraction (XRD) and Differential Scanning Calorimetry (DSC) analyses indicated partial amorphization of Stavudine in the nanosuspension.

o This amorphous state contributed to enhanced solubility.

- **Discussion:**

o Amorphous forms typically have higher dissolution rates than crystalline forms, which aligns with the observed results.

o The process of nanosizing and ultrasonication alters the drug's crystalline structure, improving its solubility and dissolution behavior.

8. Release Kinetics

- **Results:**

o The drug release followed a sustained release profile and was best described by the Higuchi and First-order kinetic models.

o The release mechanism involved a combination of diffusion and erosion.

- **Discussion:**

o Sustained release profiles ensure prolonged therapeutic effects and reduce dosing frequency, improving patient compliance.

o The release mechanism demonstrates the nanosuspension's ability to provide controlled and consistent drug release.

9. Comparative Analysis

- **Results:**

o The nanosuspension outperformed the pure drug and marketed solutions in all parameters, including dissolution rate, bioavailability, and stability.

- **Discussion:**

o These results validate the superiority of nanosuspension technology for enhancing the performance of poorly soluble drugs like Stavudine.

CONCLUSION

This study marks a significant breakthrough in the development of effective drug delivery systems for poorly water-soluble drugs. The successful formulation of Stavudine nanosuspension using nanoprecipitation and ultrasonication techniques demonstrates the vast potential of nanotechnology in overcoming solubility challenges. The optimized nanosuspension exhibited substantially improved dissolution rates and sustained drug release, outperforming both the pure API and marketed formulations [2,6]. These findings have profound implications for the treatment of HIV, as enhanced bioavailability and therapeutic efficacy can lead to improved patient outcomes and reduced mortality rates. Furthermore, this approach can be readily applied to other poorly soluble drugs, revolutionizing the field of pharmaceuticals and transforming the lives of millions worldwide [9].

Future Directions and Clinical Implications

Nanosuspensions present a promising future in pharmaceutical applications by addressing the challenges of poorly water-soluble drugs. They improve drug solubility and dissolution rates, significantly enhancing bioavailability and therapeutic efficacy. Their adaptability across multiple administration routes, including oral, parenteral, pulmonary, ocular, and dermal, makes them versatile for diverse medical needs. Nanosuspensions enable targeted drug delivery, particularly beneficial for intracellular infections and site-specific treatments like cancer therapy, while also reducing dosing requirements and systemic side effects, thereby improving patient compliance. Innovations such as sustained-release formulations, like in-situ gels, ensure prolonged therapeutic effects, making them suitable for chronic disease management. Customizable properties, including particle size and surface characteristics, pave the way for personalized medicine approaches. Additionally, their effectiveness in sensitive applications, such as ocular and pulmonary drug delivery, highlights their potential in specialized treatments. Advances in formulation techniques and stabilization methods further enhance their stability and performance, ensuring reliable therapeutic outcomes. With continued research and technological progress, nanosuspensions are poised to revolutionize drug delivery systems and expand their clinical utility.

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None.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Muller RH, Gohla S, Dingler A, Schneppe T, Wise D. (2000). Handbook of pharmaceutical controlled release technology. Marcel Dekker. pp. 359-375.
2. Nagaraju P, Krishnachaithanya K, Srinivas VD, Padma SV. (2010). Nanosuspensions: A promising drug delivery system. International Journal of Pharmaceutical Sciences and Nanotechnology. 2(1):679-684.
3. Rabinow BE. (2004). Nanosuspensions in drug delivery. Nat Rev Drug Discov. 3(9):785-796.
4. Grau MJ, Kayser O, Müller RH. (2000). Nanosuspensions of poorly soluble drugs--reproducibility of small scale production. Int J Pharm. 196(2):155-159.
5. Lakshmi P, Ashwini GK. (2010). Nanosuspension technology: A review. International Journal of Pharmaceutical Sciences. 2(1):35-40.
6. Liversidge GG, Cundy KC. (1995). Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. International Journal of Pharmaceutics.125(1):91-97.
7. Verma S, Lan Y, Gokhale R, Burgess DJ. (2009). Quality by design approach to understand the process of nanosuspension preparation. Int J Pharm. 377(1-2):185-198.
8. Sharma P, Denny WA, Garg S. (2009). Effect of wet milling process on the solid state of indomethacin and simvastatin. Int J Pharm. 380(1-2):40-48.
9. Kakran M, Sahoo NG, Li L, Judeh Z, Wang Y, Chong K, Loh L. (2010). Fabrication of drug nanoparticles by evaporative precipitation of nanosuspension. Int J Pharm. 383(1-2):285-292.