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Review Article

Nanoemulsion Of Lamivudine: A Review

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ABSTRACT

Lamivudine nanoemulsions, which consist of two immiscible liquids combined with emulsifying agents to form a single phase, are thermodynamically stable colloidal dispersion systems. The use of nanoemulsions as medication delivery vehicles has been thoroughly studied. The purpose of this paper is to present a comprehensive overview of the synthesis and characterisation of lamivudine nanoemulsions. Two distinct approaches are used to formulate lamivudine nanoemulsions. The nanoemulsions are characterized using a variety of methods, such as transmission electron microscopy and the assessment of entrapment efficiency, particle size, polydispersity index, and zeta potential. The stability, thermodynamic stability, viscosity, pH, osmolarity, and in vitro drug release of nanoemulsions are investigated in order to assess them further.

INTRODUCTION

Lamivudine is an antiretroviral medication primarily employed in the management of HIV and chronic hepatitis B infections. It is known by the brand names Epivir (for HIV) and Epivir-HBV (for hepatitis B). Its effectiveness can be limited by its poor solubility and bioavailability [1]. To address these issues, nanoemulsion formulations have been explored. Nanoemulsions are nanoscale emulsions, typically with droplet sizes ranging from 20 to 200 nm. They offer advantages such as improved drug solubility, stability, and bioavailability [2,3].

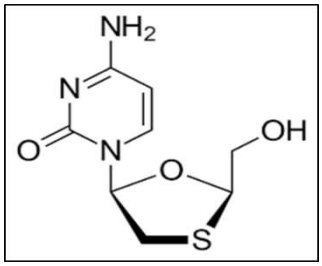

Figure 1: Structure of Lamivudine

One type of nucleoside reverse transcriptase inhibitor (NRTI) is lamivudine. It functions by preventing the reverse transcriptase enzyme, which is necessary for retroviruses like HIV to replicate. By incorporating itself into the viral DNA, it terminates the DNA chain, preventing the virus from multiplying [4].

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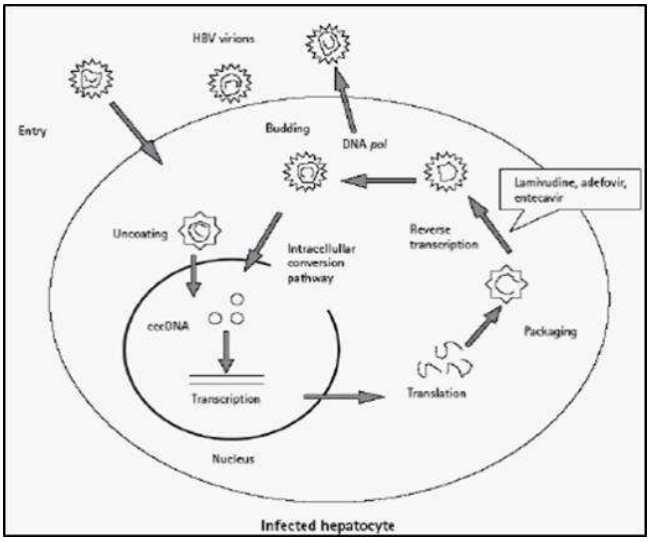

Figure 2: Mechanism of action of Lamivudine

Pharmacokinetics of Lamivudine [5-7]**:**

Nanoemulsions can significantly alter the pharmacokinetic and pharmacodynamic profiles of Lamivudine:

Absorption: Lamivudine is well absorbed with an oral bioavailability of approximately 86%. Enhanced intestinal permeability and absorption due to the small droplet size and surfactant presence.

Distribution: It distributes widely in body tissues, including the central nervous system (CNS).

Metabolism: Potential reduction in first-pass metabolism in the liver, leading to higher systemic availability.

Elimination: It is primarily excreted unchanged in the urine. The elimination half-life is approximately 5 to 7 hours.

Composition of Lamivudine Nanoemulsions [8-11]**:**

Table 1: Composition of Lamivudine Nanoemulsions

Oil Phase	Medium-chain triglycerides (MCT), castor oil	Dissolve Lamivudine
Surfactants	Tween 80 (polysorbate 80) or Span 80 (sorbitan monooleate)	Stabilize the emulsion and reduce surface tension
Co-surfactants	Ethanol, propylene glycol or polyethylene glycol	Enhance stability and facilitate the formation of nano-emulsions
Aqueous Phase	Purified water	As a vehicle

PREPARATION METHODS

High-Pressure Homogenization:

Because the manufacture of nanoemulsions requires a high shear force, this technique uses a high-pressure homogenizer or a piston homogenizer to produce nanoemulsions with very small particle sizes (up to 1 nm). A combination is pushed through an aperture using this technique at extremely high pressures, between 500 and 5000 psi. The end product is then exposed to hydraulic shear and high turbulence, creating an emulsion with incredibly small particles. The sole disadvantage of this technology, which has been shown to be the most effective for preparing nanoemulsions, is that it uses a lot of energy and causes the emulsion's temperature to rise while processing. Larger runs of homogenization cycles are also necessary to get lower particle sizes. Yilmaz et al. created phytosphingosine O/W nanoemulsions using the high pressure homogenization method. They discovered that after eight homogenization cycles, the droplet size of the nanoemulsion dropped and that it remained stable for more than six months [12–14].

Ultrasonication:

This method involves agitating a premixed emulsion at an ultrasonic frequency of 20 kHz, which reduces the droplets to the size of nanodroplets. After that, a high shear zone is passed through the resulting emulsion to create

droplets with a homogeneous size distribution. This method uses a water jacket to control the temperature. Sonotrodes, also called sonicator probes, used piezoelectric quartz crystals as the ultrasonic emulsification's energy sources. When an alternating electric voltage is applied, these sonotrodes dilate and contract. When the sonicator tip makes contact with the liquid, cavitation occurs, causing mechanical vibrations that eventually cause the vapour cavities that have formed inside the liquid to collapse. This method is mostly utilized when a droplet size of less than 0.2 μ is necessary. The ultrasonic emulsification approach at a frequency of 25 kHz was utilized by Shi et al. to formulate an emodin-loaded nanoemulsion. The mean diameter of the Lamivudine-loaded nanoemulsion was determined to be within the range of 10-30 nm [15,16].

Phase Inversion Temperature (PIT):

The persuasive method of creating nanoemulsions does not include the use of external forces; rather, it entails the generation of fine dispersions during phase transitions that arise by varying the temperature or composition while maintaining a constant alternative parameter. PIT can be roughly defined as follows: (i) phase transition from near-optimal state via modification of single variable, which includes adjusting one formulation variable, such as salinity or temperature, to a value close to optimal. The ideal hydrophilic-lipophilic deviation (HLD) for a system that uses a higher temperature to create microemulsion, for instance, is near to the center of the system. (ii) Phase transition from near-optimal state through modification of numerous formulation factors, i.e., more than one variable. For instance, using a greater temperature and adding more salt to a microemulsion. (iii) Catastrophic inversion, which occurs when an emulsion with low internal phase is turned into an exterior phase. (iv) Phase transition stability through liquid crystal formation, encompassing the stabilization of nanodroplets from a state nearing HLD-0 through liquid crystal formation [17–19].

Spontaneous Emulsification:

This method required three steps for the creation of the nanoemulsion. The first step involved creating an organic solution by mixing hydrophilic and lipophilic surfactants with oil in a water-miscible solvent. This organic phase was then injected into the aqueous phase while being stirred by a magnetic field to form the O/W emulsion. In the third stage, evaporation was used to eliminate the organic solvent. By using spontaneous emulsification, Sugumar et al. created a stable eucalyptus oil nanoemulsion, and it was discovered that the mean droplet size ranged from 50 to 100 nm [20, 21].

Characterization of Nanoemulsions

Key parameters for the characterization of Lamivudine nanoemulsions include:

Calculating the polydispersity index (PDI) and particle size:

Using a Malvern Zetasizer, photon correlation spectroscopy (PCS) is used to analyze the particle size and part-defect index (PDI) of nanoemulsions. PCS measures the variation in light scattering caused by the Brownian motion of particles over time. The foundation of PCS is the idea that smaller particles move faster than larger ones. These sub-micron particles in solution cause the laser beam to diffract. Particle size determines how quickly the laser scattering intensity fluctuates around a mean value at a fixed angle due to particle diffusion. A histogram of the line width distribution is produced by the computed photoelectron time correlation function and can be connected to the particle size. In order to get a uniform dispersion and quantify particle size and PDI, a weighed amount of formulation is mixed with double-distilled water. This mixture must be used right away. A monodisperse system is represented by a 0 (zero) PDI, whereas a polydisperse particle dispersion is represented by

a 1 PDI [22, 23]. Using this method, Dordevic et al. assessed the PDI and mean particle size of risperidone nanoemulsion, reporting a mean particle size of around 160 nm with a mean size distribution of less than 0.15 [24]. Using the same methodology, Singh et al. have discovered primaquine nanoemulsion particle sizes in the 20–200 nm range [25].

Measurements of pH and osmolarity:

A microosmometer, which uses the freezing point method, is used to calculate the osmolarity of an emulsion, while a pH meter is used to measure the pH of a nanoemulsion. Measurements are made after transferring 100 µl of nanoemulsion into a microtube [26]. Morsi et al. claimed that the acetazolamide nanoemulsion was suitable and non-irritating for application to the eye after measuring its pH using a pH meter and finding a range of 4.9 to 5.5 [27].

Viscosity determination:

Viscosity evaluation is a crucial metric for the physicochemical characterization of nanoemulsions. A variety of equipment, including the Ostwald viscometer, Hoeppler falling ball viscometer, Stormer viscometer, Brookfield viscometer, and Ferranti-Shirley viscometer, are used to measure viscosity. The Brookfield viscometer is the recommended model for determining the viscosity of nanoemulsion among all of these viscometers. Viscosity determination confirms if the system is an O/W or W/O emulsion. Systems with low viscosity indicate they are O/W type, whereas those with high viscosity indicate they are water in oil type [28]. Since it measures the particle size, hydrodynamic volumes, contact angle, dipole moment, interfacial tension, surface tension, and viscosity of the nanoemulsions, the survismeter has, nevertheless, become the most commonly used piece of equipment [29, 30].

Zeta potential determination:

When a particle is submerged in a liquid, its surface charge can be measured using the zeta potential. Zeta potential is a useful tool for forecasting dispersion stability; its value is influenced by the physicochemical characteristics of the medication, polymer, and medium as well as the presence and adsorption of electrolytes. The Malvern Zetasizer equipment is used to measure it. Zeta potential is measured by diluting the nanoemulsion and estimating its value based on the oil droplets' electrophoretic mobility. It is thought that a zeta potential of ±30 mV is adequate to guarantee the physical stability of the nanoemulsion. Using the Malvern Zetasizer, Dordevic et al. found a zeta potential of around –50 mV for their risperidone nanoemulsion [31].

Drug Loading and Encapsulation Efficiency:

A weighed quantity of the formulation is ultrasonically dispersed in an organic solvent to release the drug, which is then extracted into an appropriate buffer to ascertain the amount of drug entrapped in the formulation. The extraction is subjected to spectrophotometric analysis at the drug's λmax after appropriate dilutions are made in comparison to a suitable blank to estimate the drug content. The following formulas can be used to determine the drug's loading efficiency (LE) and entrapment efficiency (EE):

drug LE = drug content in the product obtained (mg)/total product weight (mg)×100, and

drug EE = drug content in the product obtained (mg)/total amount of drug added (mg)×100.

High-performance liquid chromatography (HPLC) techniques in the reverse phase could also be used to determine the drug content. This method was used by Singh et al. to determine the concentration of primaquine, and they found a 95% encapsulation effectiveness of the prepared nanoemulsion [34].

In vitro drug release study:

This type of research aids in determining how well a drug formulation works in vivo. A USP

dissolving equipment is typically used to study a drug's in vitro release rate. After being dissolved in buffer, dried nanoparticles or nanoemulsion containing 10 mg of medication was added to dialysis membrane pouches and put in a flask with buffer. This investigation is conducted at 37±0.5° with 50 rpm of stirring. Samples are taken out on a regular basis and replaced with an identical volume of brand-new dissolving media each time. After samples have been appropriately diluted, their absorbance is measured at a certain wavelength using spectrophotometry. Using a calibration curve, the absorbance of the sample is used to determine the percentage of drug release at various time periods [35]. Using a dissolving apparatus type-II, Kotta et al. investigated the in vitro drug release profile of an anti-HIV medication nanoemulsion and found that 80% of the drug was released after six hours [36].

Stability Studies:

Conducted to evaluate the drug substance's stability in the presence of several environmental conditions, such as light, humidity, and temperature. According to the standards of the International Conference on Harmonization, the nanoemulsion stability experiments are conducted after the formulation has been stored for 24 months in a dispersed and freeze-dried state. The three storage conditions that are used are freeze (–20±5°), refrigeration (5±3°), and ambient (25±2°/60±5% RH). The required amount of nanoemulsion is kept in hermetically sealed glass vials. At certain intervals, samples are taken out and examined for traits such loading, EE, and particle size as well as the in vitro drug release profile [37]. After conducting stability studies on nanoemulsion, Singh et al. found that after three months at 25°/60% RH and 30°/65% RH, there was no change in viscosity, drug content, or particle size [38].

Clinical Implications [39-41]**:**

HIV Treatment:

Lamivudine is used in combination with other antiretroviral agents for the treatment of HIV-1 infection. It helps reduce the viral load, increase $CD4^+$ cell counts, and slow the progression of the disease. Enhanced bioavailability and absorption lead to more effective viral suppression and improved patient outcomes.

Adults and Adolescents: 300 mg once daily or 150 mg twice daily.

Pediatric Patients: Dosage is based on body weight, typically 4 mg/kg twice daily, up to a maximum of 150 mg twice daily.

Hepatitis B Treatment:

Lamivudine is also used to treat chronic hepatitis B virus (HBV) infection. It reduces HBV DNA levels, improves liver enzyme levels, and slows the progression of liver disease. Improved therapeutic efficacy with the potential for reduced dosing frequency, making it easier for patients to adhere to their treatment regimens.

Adults: 100 mg once daily.

Pediatric Patients: Dosage is based on body weight, typically 3 mg/kg once daily, up to a maximum of 100 mg once daily.

Patient Compliance:

Nanoemulsions can reduce the frequency of dosing and minimize side effects, improving overall patient compliance and quality of life.

Challenges and Future Directions

Despite the promising benefits, several challenges remain in the development and commercialization of Lamivudine nanoemulsions:

Scalability: Producing nanoemulsions on a large scale while maintaining consistency and quality can be challenging.

Regulatory Approval: New formulations must meet stringent regulatory requirements, including comprehensive safety and efficacy evaluations.

Long-term Stability: Ensuring the nanoemulsion remains stable and effective over extended periods is crucial.

Clinical Trials: Extensive clinical trials are necessary to confirm the safety and effectiveness of nanoemulsion formulations in diverse patient populations.

CONCLUSION

Lamivudine is a crucial medication in the management of HIV and chronic hepatitis B infections. Its efficacy, combined with its generally favourable safety profile, makes it a staple in antiviral therapy. However, the development of resistance and potential side effects require careful monitoring and management by healthcare providers. Nanoemulsion formulations of Lamivudine represent a significant advancement in drug delivery technology. They offer the potential to overcome the limitations of poor solubility and bioavailability, leading to better therapeutic outcomes for patients with HIV and hepatitis B. Continued research and development are essential to address the existing challenges and fully realize the potential of this innovative drug delivery system.

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