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FORMULATION AND EVALUATION OF ANTIVIRAL DRUG LOADED SOLID LIPID NANOPARTICLES

Subodh A. Urkunde*, Sandeep C. Atram, Rupali P. Sable, Anuja G. Gawai
Department of pharmaceutics, Vidyabharati College of Pharmacy, Amravati – 444 602, India

*Corresponding Author's E mail: subodhurkunde17@gmail.com
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ABSTRACT
The aim of the present study was to prepare antiviral drug loaded solid lipid nanoparticles (SLNs). Antiviral drug loaded SLNs were prepared by solvent evaporation method. The nanoparticles were further characterized for particle size, zeta potential, surface morphology, drug entrapment efficiency, and in vitro drug release behavior. The results revealed that this method is reproducible, more feasible and led to the entrapment of drug with an expected sustained release. The nanoparticle precipitated was with particle size of 167.3 nm, zeta potential of −38.2 mV, and spherical in shape. The entrapment efficiency noted was 78.10%. In vitro release was about 92.34% release in 24 h. When the regression coefficient values were compared, it was observed that 'R^2' values of first order was maximum i.e. 0.9921 hence indicating drug release from formulation was found to follow first order release kinetics. Antiviral drug-loaded SLNs may be a good choice for the improvement of bioavailability and reduction in toxicity.

Keywords: Solid lipid nanoparticles (SLN), Acyclovir, SEM, Entrapment efficiency.

INTRODUCTION

The primary objective of any drug delivery system is to deliver a therapeutic dose of the drug to the appropriate site within the body, ensuring that the drug concentration at the target site is maintained at the desired level. The therapeutic effectiveness of a drug depends on four fundamental pathways of drug transport: absorption, distribution, metabolism, and elimination. Therapeutic failures can occur due to several issues, including inadequate drug concentration caused by poor absorption, rapid metabolism and elimination, poor solubility of the drug, and significant fluctuations in plasma levels resulting from unpredictable bioavailability [1].

Acyclovir (ACV) is recognized for its potent antiviral activity. In HSV-infected cells, it is converted into its monophosphate form (ACV-P) by the viral thymidine kinase (HSV-TK). ACV-P is then further phosphorylated to diphosphate and triphosphate forms by cellular kinases in the host cells. These phosphorylated forms inhibit viral DNA polymerase and terminate the elongation of viral DNA, effectively blocking DNA synthesis. However, ACV has several pharmacokinetic limitations, including high variability, poor oral bioavailability (15–30%), and a short elimination half-life of 2.5–3.3 hours [2]. These factors necessitate high doses and frequent administration (five times a day), leading to poor patient compliance and reduced therapeutic efficacy. ACV is soluble in acidic conditions, with the primary absorption site being the stomach and upper gastrointestinal tract (GIT). There is evidence of active absorption in the duodenum and jejunum regions of the GIT. Despite this, a significant portion of ACV (62–90%) is excreted unabsorbed in the feces due to its short half-life. Although newer antiviral drugs have recently become available, ACV remains the preferred treatment for most HSV infections [3].

Solid lipid nanoparticles (SLNs) are a novel class of drug delivery systems designed to improve the therapeutic performance of pharmaceuticals. Developed in the early 1990s as an alternative to traditional colloidal carriers such as liposomes, emulsions, and polymeric nanoparticles, SLNs are composed of biocompatible and biodegradable lipids that remain solid at room and body temperatures. This unique composition endows them with several advantages, including enhanced stability, controlled drug release, and the ability to encapsulate both hydrophilic and lipophilic drugs. SLNs typically range in size from 50 to 1000 nanometers. By providing sustained and targeted drug delivery, SLNs can lower the required dosage and frequency of administration, thereby enhancing patient compliance and outcomes. Additionally, their composition of physiological lipids minimizes the risk of toxicity and adverse reactions [4].

Acyclovir-loaded solid lipid nanoparticles (ACV-SLNs) represent an innovative approach in antiviral drug delivery, designed to enhance the therapeutic performance of acyclovir (ACV), a widely used antiviral agent. ACV is highly effective against herpes simplex virus (HSV) infections, but its clinical utility is limited by several pharmacokinetic challenges such as poor oral bioavailability (15–30%), high variability, and a short elimination half-life (2.5–3.3 hours). These limitations necessitate frequent dosing (up to five times daily), leading to issues with patient compliance and ultimately affecting therapeutic outcomes. To address these issues, ACV is encapsulated within solid lipid nanoparticles, which are composed of biocompatible and biodegradable lipids that remain solid at room and body temperatures. These nanoparticles provide

a stable and controlled release system that enhances the bioavailability of ACV. By protecting ACV from premature degradation and facilitating its absorption in the gastrointestinal tract, SLNs can significantly improve its pharmacokinetic profile [5].

The encapsulation of ACV within SLNs also allows for targeted delivery to infected cells, increasing the drug's concentration at the site of action while minimizing systemic side effects. This targeted delivery, combined with a sustained release profile, reduces the frequency of administration, thereby improving patient adherence and maximizing therapeutic efficacy [6].

MATERIALS AND METHODS

Materials:

Acyclovir was gifted by GSK pharmaceuticals, Mumbai, India. Soya lecithin was purchased from shiva biochem, khandeshwar. Other chemicals such as glyceryl monostearate, polyvinyl alcohol, polyethylene glycol 600, tween 60 were supplied by S. D. Fine Chemicals, Mumbai.

Method of preparation for antiviral drug loaded SLNs:

The Acyclovir-loaded SLNs were prepared according to a solvent evaporation method. In brief, 17.5 mg Acyclovir in 2 ml of dimethyl sulfoxide sonicate for 3min, followed by 42.5 mg soya lecithin, and 100 mg GMS were dissolved in ethanol (organic phase) at 60 ^{o}C. The aqueous phase (containing 1% PVA and 1% PEG 400, w/v) was heated to the same temperature of the organic phase. Then the organic phase was dropped into the hot aqueous phase under rapid stirring at 1200 rpm for dispersion. After that the homogeneous suspension was poured into the dispersed phase (containing 1% Tween-60 and 1% PEG 600, w/v) under stirring at 1000 rpm for 4 h at 2 ^{o}C in an ice bath to allow for the hardening of the SLNs [7].

Characterization of antiviral drug loaded SLNs:

Particle Size:

Solid lipid nanoparticles diameter can be determined using Malvern Zetasizer [8].

Zeta Potential Determination:

Charge drug loaded vesicles surface was determined using Malvern Zetasizer. Analysis time was kept for 60 s and average zeta potential and charge on the Solid Lipid Nanoparticles was determined[9].

Drug Entrapment Efficiency:

The Solid Lipid Nanoparticles suspension was ultra centrifuged at 7000 rpm for 1hr by using ultra centrifuge to separate the free drug. A clear solution of supernatant of Solid Lipid Nanoparticles were obtained. 1ml solution from the supernatant was collected and absorbance of the drug was noted at 252.8 nm. The entrapment efficiency was then calculated using following equation [10].

$$\text{Entrapment efficiency (EE)} = \frac{\text{Amount of drug in nanoparticles}}{\text{Initial amount of drug}} \text{ X 100}$$

Scanning Electron Microscopy:

A scanning electron microscope (JEOL-5400, Japan) is a type of electron microscope that produces images of a sample by scanning it with a focused beam of electrons. The electrons interact with atoms in the sample, producing various signals that can be detected and that contain information about the sample's surface topography and composition [11].

In Vitro drug Release:

In vitro release studies were performed using Franz diffusion cell. Dialysis membrane having pore size 2.4 nm, molecular weight cutoff between 12,000 –14,000, was used. Membrane was soaked in double-distilled water for 12 h before mounting in a Franz diffusion cell. ACV formulation equivalent to 10mg was placed in the donor compartment and the receptor compartment was filled with dialysis medium (0.1 N HCl). Required quantity (0.5ml) of the medium was withdrawn at specific time periods (1, 2, 3, 4, 6, 8, 24h,) and the same volume of dissolution medium was replaced in the flask to maintain a constant volume. The withdrawn samples were filtered and then 0.5ml filtrate was made up to volume with 10 ml of 0.1 N HCl. The samples were analysed for drug release by measuring the absorbance at 252.8 nm using a UV/ visible spectrophotometer (Shimadzu Corporation, Japan). The experiments for all formulations were conducted triplicate and average value recorded [12.]

In vitro diffusion has been recognized as an important element in drug development. To analysis the mechanism for the release and release rate kinetics of the formulated dosage form, the data obtained from conducted studies was fitted into Zero order, First order, Higuchi matrix, Korsmeyer-Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected [13].

RESULTS AND DISCUSSION:

Antiviral drug loaded SLNs were prepared by solvent evaporation method. Particle size was measured using malvern zetasizer having a mean diameter 167.3 ± 1.2 nm (n = 5), and the zeta potential was measured to be −38.2 mV [Figures 1 and 2]. The SLNs shows percentage entrapment of 78.2% and this may be due to the higher intactness of the lipid. The SEM photograph of ACV SLNs is shown in Figure 3. It can be seen that nanoparticles are almost spherical with a smooth surface. From the In vitro drug Release study SLNs release around 92.34 % of drug at the end of 24 hours for a sustained release is shown in figure 4. The rate at which nanoparticles release their contents is influenced by several factors: 1) the desorption of surface-bound or adsorbed drugs, 2) diffusion through the nanoparticle matrix, 3) diffusion through the polymer wall, 4) the erosion of the nanoparticle matrix, and 5) a combination of erosion and diffusion processes. Consequently, the mechanisms of diffusion and biodegradation are key determinants in the drug release process.

Drug release study shows that the release of drug from the SLNs by first order (0.9921) followed by higuchi model (0.9768) and hixson model (0.9557) as shown in table No. 1

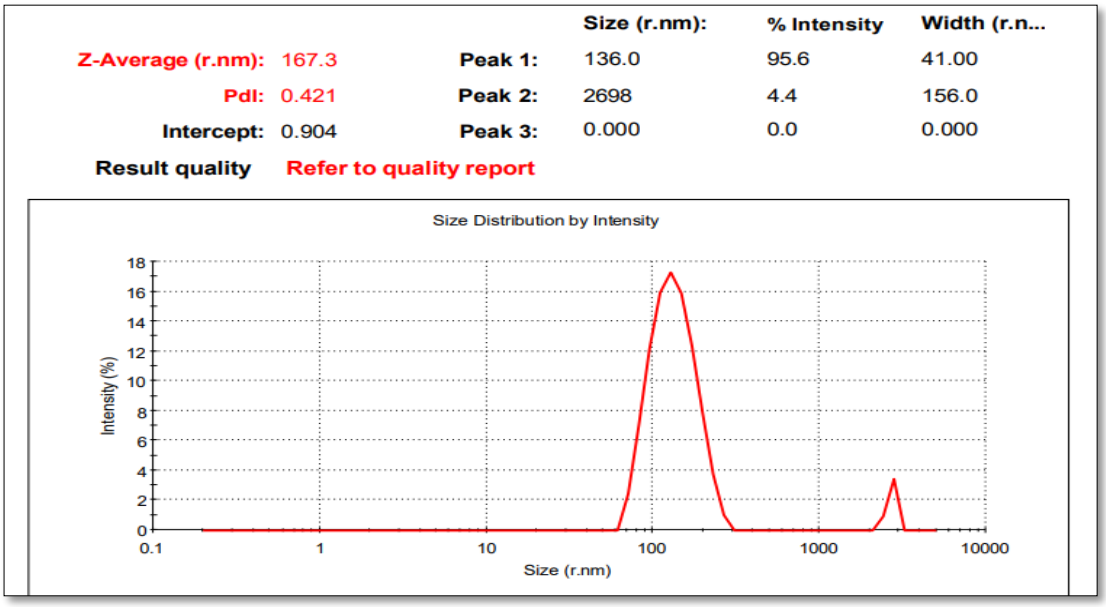

Figure No. 01: Particle size of antiviral drug loaded Solid Lipid Nanoparticles

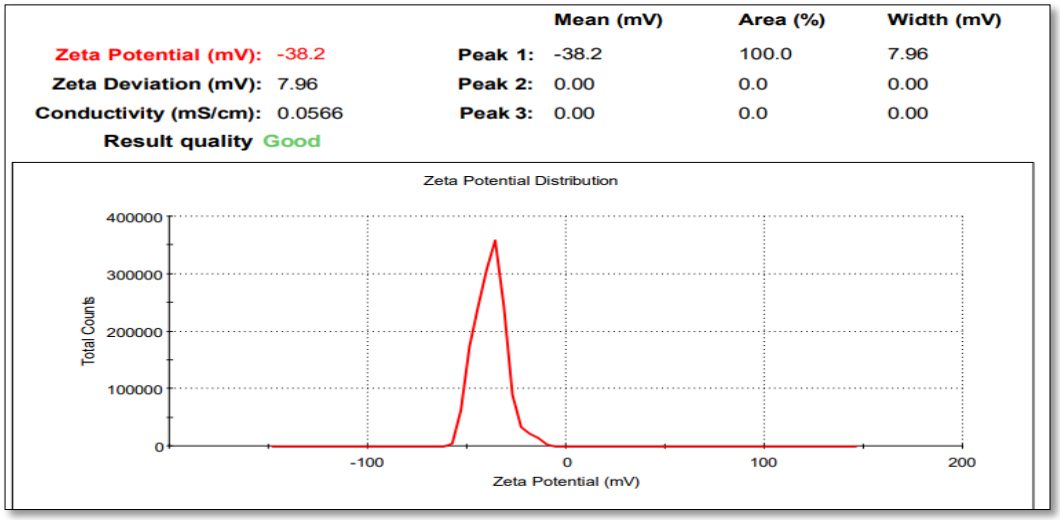

Figure No. 02: Zeta potential of antiviral drug loaded Solid Lipid Nanoparticles

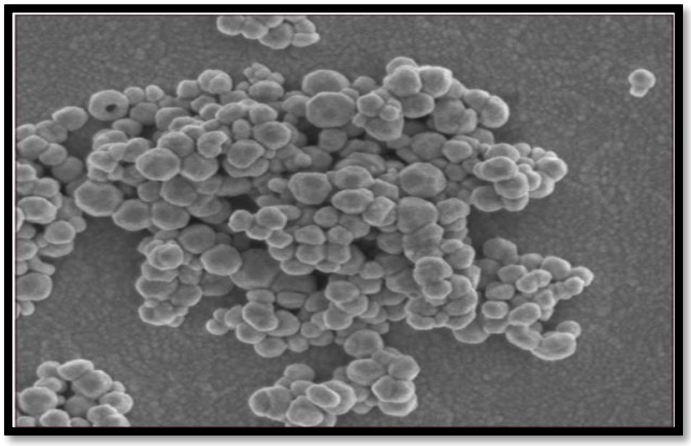

Figure No. 03: Scanning Electron Microscope Photographs of The Solid Lipid Nanoparticles In 10000 X

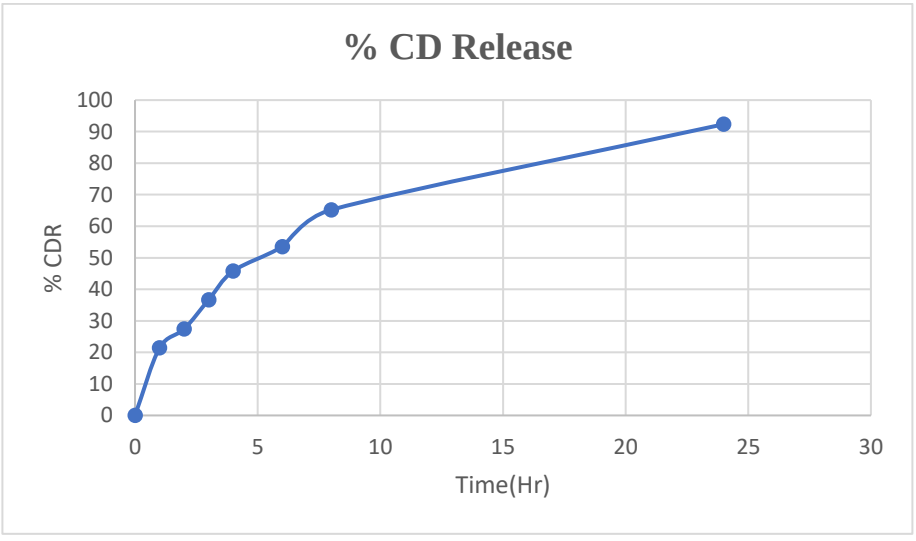

Figure No. 04: % Cumulative Drug Release of antiviral drug loaded solid lipid nanoparticles at Different Time Intervals

Table No. 01: Regression Coefficient of SLNs

SLNs Formulation	Regression Coefficient (R^2) values				
	Zero order	First Order	Higuchi Model	Korsemeyer-peppas	Hixson Model
F-1	0.8006	0.9921	0.9768	0.5408	0.9557

CONCLUSION:

Antiviral drug-loaded solid lipid nanoparticles were prepared by solvent evaporation method. The formulated Solid Lipid Nanoparticles shows the particle size of 167.3nm. Zeta potential of solid lipid nanoparticles was -38.2mV indicating presence of optimum charge on the surface of formulations to prevent aggregation during their shelf life. The SLNs shows percentage entrapment of 78.2%. SEM studies shows the morphology of Solid Lipid Nanoparticles also shows the spherical shape of the solid lipid nanoparticles with smooth surface. In vitro drug release were performed in Franz diffusion cell apparatus and cumulative drug release was found to be 92.34%. emulsifier concentration showed effect on release of solid lipid nanoparticles formulation. Drug release study shows that the release of drug from the SLNs by first order (0.9921) followed by higuchi model (0.9768) and hixson model (0.9557). The results demonstrated the effective use of ACV-loaded SLNs as a controlled release preparation for the treatment of viral infections.

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