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Research

Development Optimization Characterization of Penciclovir Loaded Solid Lipid Nanoparticle for Enhancement of Oral Bioavailability

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Abstract

The current study was undertaken to develop solid lipid nanoparticles (SLN) of a hydrophilic drug Penciclovir and improve the entrapment efficiency of the drug in SLN. The SLN were prepared with Precirol ATO 5 as lipid using solvent-evaporation technique by Box Behnken design. Three operating variables lipid concentration, Surfactant and Sonication time were found to have significant effect on the particle size, entrapment efficiency (EE) and zeta potential of the SLN. The maximum EE was found to be 87.43% with particle size of 167.3nm and zeta potential of -22.77. The optimized batch was also analyzed for its morphological, physiochemical and ex vivo intestinal permeation properties. This work indicates that Penciclovir loaded in SLN could be better option for enhancing the permeability of Penciclovir in intestine as compared to existing marketed formulations.

Keywords: solid lipid nanoparticle; Penciclovir; entrapment efficiency; particle size; Precirol ATO 5.

INTRODUCTION

Solid lipid nanoparticles (SLNs) are worthy carriers for oral delivery of lipophilic and to some extent for hydrophilic drug candidates [1]. SLNs, important colloidal carriers for lipophilic drugs are composed of a solid lipid (i.e. those lipids which are solid at room temperature and at the body temperature too) core in which drug is entrapped to target it to a specific organ or system of the human body [2], [3]. Recently, SLNs have been used orally aiming at targeted delivery and enhancing oral bioavailability.

SLN not only has combine advantages of colloidal drug carrier systems such as liposomes, polymeric nanoparticles and emulsions but also avoid the drawbacks associated with respective carrier system [5], [6]. Proposed advantages include compatible degradation in in vivo, possibility of controlled drug release and drug targeting, and avoidance of organic solvents. Polymeric nanoparticles have disadvantages like residual contamination, possible toxicity, lack of suitable sterilisation method and stability, which can be avoided by

SLNs. The mechanism of bioavailability enhancement by SLNs is attributed to adhesive properties that make them adhere to gut wall and release the drug exactly where it should be absorbed [7]. Lymphatic uptake was found to be the major absorption mechanism for drugs encapsulated in SLN [8]. One of the prominent advantages of SLNs prepared by high pressure homogenisation is its ability for production at industrial scale up [9].

Penciclovir is a synthetic acyclic guanine derivative with antiviral activity used for the treatment of various herpes simplex virus (HSV) infections. Displaying low toxicity and good selectivity, penciclovir is a nucleoside analogue. Penciclovir is a Herpesvirus Nucleoside Analog DNA Polymerase Inhibitor. The mechanism of action of penciclovir is as a DNA Polymerase Inhibitor.

In this present study Penciclovir is loaded in SLN and evaluated for various characterization study like particle size , EE% .The optimized Formulation is evaluated for Scanning Electron microscopy and ex vivo intestinal permeation study

MATERIALS AND METHODS

Penciclovir was received as a gift sample from Unison Pharmaceuticals, Baddi, INDIA, Compritol 888 ATO, Precirol ATO 5, Stearic acid, Glyceryl monostearate, Cetyl palmitate (CP)Isopropyl Myristate, Poloxamer 188 , Tween 20,60 & 80 were purchased from Fizmerk Chemicals, U.P., INDIA, All the reagents and solvents were of analytical reagent (AR) grade.

Preparation of Penciclovir loaded SLN dispersion

SLNs loaded with Penciclovir were prepared using melt emulsification and low-temperature Solidification method. Penciclovir was dissolved in methanol and mixed with acetone solution containing stearic acid. The mixtures were sonicated for 15 minute, and then added drop wise to Tween 80 solution, stirred at 3000 rpm for 0.5 h at 70 °C temperature. The mixed solution was transferred to icy water bath and stirring for four hour at 3000 rpm. Different formulations of drug loaded SLN were prepared by varying concentrations of stearic acid as shown in the below [Table 1] and these SLN dispersions used for further study [10]

Selection of Lipid

Penciclovir's solubility in several lipids, including Stearic acid, Glyceryl monostearate, Compritol 888 ATO, Precirol ATO 5, and Cetyl palmitate, was determined.

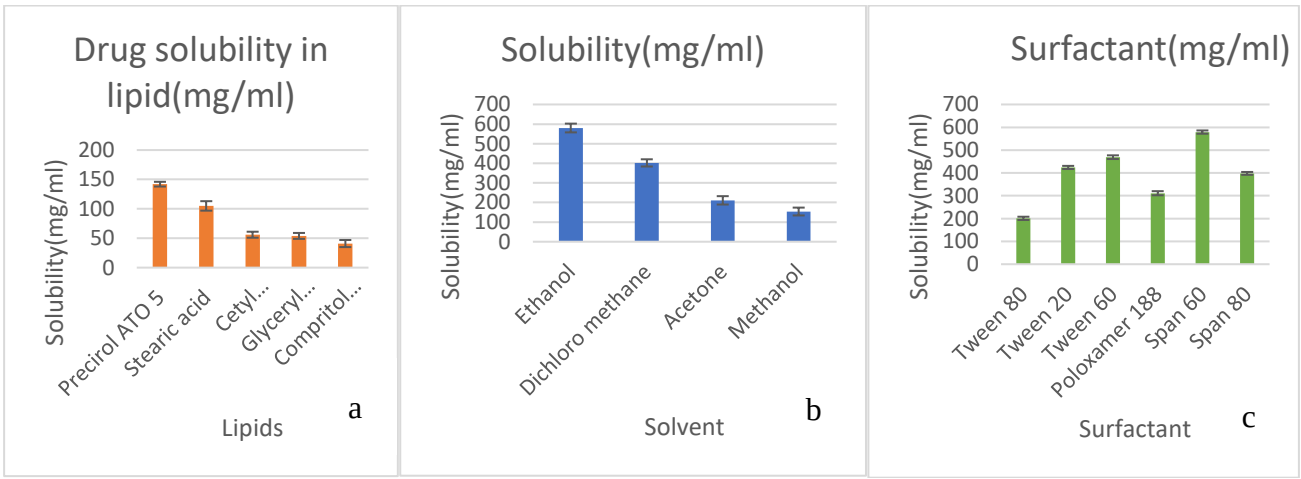


Fig 1: Selection of a)lipid b) Solvent c) Surfactant

The drug showed maximum solubility in Precirol ATO 5 (142±4.01mg/ml) and minimum solubility in Compritol 888(41±6.04). Precirol ATO 5 was selected for further investigation

Selection of solvent system

Solvent was selected with reference to solubility of the Drug and lipid in the different solvents. Ethanol exhibited the highest solubility ($P < 0.05$) (Mean ±SD, n=3)

Selection of surfactant

With Precirol ATO 5, six different surfactants were used to make solid lipid nanoparticles, which were then tested for particle size distribution and the efficacy of encapsulation.

Experimental Design

Response Surface Methodology aims to establish the relative importance of two or more factors and also to indicate whether or not interaction occurs between the factors and thereby affects the magnitude of the response. Box Behnken design .A 3-level, 3-factor, 15 run experimental design was adopted to optimize levels of variables in the nano formulations. The selected independent variables were amount of Lipid i.e (X1), Surfactant(X2), and Co-Surfactant (X3) as shown in (Table 1). The dependent variables were Particle size (Y1) and EE% (Y2) Zeta potential(Y3).The generation of experimental runs, Analysis of Variance(ANOVA)study and optimization were carried out by Design expert® software 12.

Preparation of Penciclovir loaded SLN

SLNs were prepared using the solvent evaporation technique. Briefly, Drug and Precirol ATO 5 were dis-solved in Dichloro methane . This organic phase was added drop wise to an aqueous solution containing surface active agent (Poloxamer 188) and co surfactant(Propylene glycol). The obtained pre-emulsion was subsequently subjected to ultrasonication using probe sonicator (Ultrasonic processor model VCX 750) to decrease the globules size to the required nanometer range. The formed emulsion was stirred at the room temperature using a magnetic stirrer at 400 rpm to allow the organic solvent to evaporate and SLNs to be formed.

Characterization of Penciclovir Loaded SLN Dispersion

The SLNs characterization parameter like Particle size and size distribution, zeta potential, drug entrapment efficiency (EE), scanning electron microscopy (SEM), FTIR, differential scanning calorimeter analysis (DSC) are described below:

Particle size, Particle size Distribution & Zeta potential

The mean particle size and polydispersity index of SLN for size distribution was measured using Malvern Mastersizer 2000MU (Malvern instrument UK)[6].

Drug entrapment efficiency

The entrapment efficiency (EE), which corresponds to the percentage of Penciclovir encapsulated within and adsorbed on to the nanoparticles, was determined by measuring the concentration of free Penciclovir in the dispersion medium A volume of 2.0 ml of each drug-loaded sample was centrifuged at 5300 rpm for 70 min to separate the lipid and aqueous phase. The supernatant was then diluted with methanol and analyzed by UV-visible spectrophotometer at 233 nm using a Model- 1371, Electronics India. The entrapment efficacy of nanoparticle was calculated as follows:

$$EE = \left(\frac{Wa - Ws}{Wa}\right) \times 100$$

Where,

EE is entrapment efficiency, Wa stands for the mass of Penciclovir added to the formulation and Ws is the analyzed weight of drug in supernatant

Table 1: Formulation Table of Penciclovir loaded SLN using Box-Behnken Design

Formulation code	Lipid(X1)m	Surfactant(X2)ml	Cosurfactant(X3)ml
PSLN1	12	10	2
PSLN2	12	4	2
PSLN3	8	7	3
PSLN4	10	10	1
PSLN5	8	4	2
PSLN6	10	7	2
PSLN7	10	10	3
PSLN8	12	7	1
PSLN9	8	7	1
PSLN10	10	7	2
PSLN11	12	7	3
PSLN12	8	10	2

PSLN13	10	7	2
PSLN14	0	4	1
PSLN15	0	4	3

Scanning Electron Microscopy

The morphological characteristic of SLN was determined by scanning electron microscope (JEOL-JSM-6360 JAPAN). One drop of sample was placed on a slide and excess water was left to dry at room temperature. then the slide was attached to the specimen holder using a double coated adhesive tape and gold coated under vacuum using a sputter coater (Model JFC-1100, Jeol, JAPAN)for 10 minute and investigated at 20kV (Nasr et al., 2008).

Infrared spectroscopy (FTIR)

Physicochemical characterization was performed using Fourier transform infrared (FTIR) spectroscopy. For this purpose, sample were analysed as KBr pellets by using a FTIR spectrometer (Shimadzu Corporation, Japan).

RESULTS AND DISCUSSIONS

Particle size, Particle size distribution & Zeta potential

The particle size for all SLN formulation were determined using Malvern Mastersizer showed size in a range between 127.3nm to 211.4nmrespectively and zeta potential ranges from -33.11mv to -18.19mv The particle sizes of formulations were increases as the concentration of ATO Compritol decreases as shown in table 2.

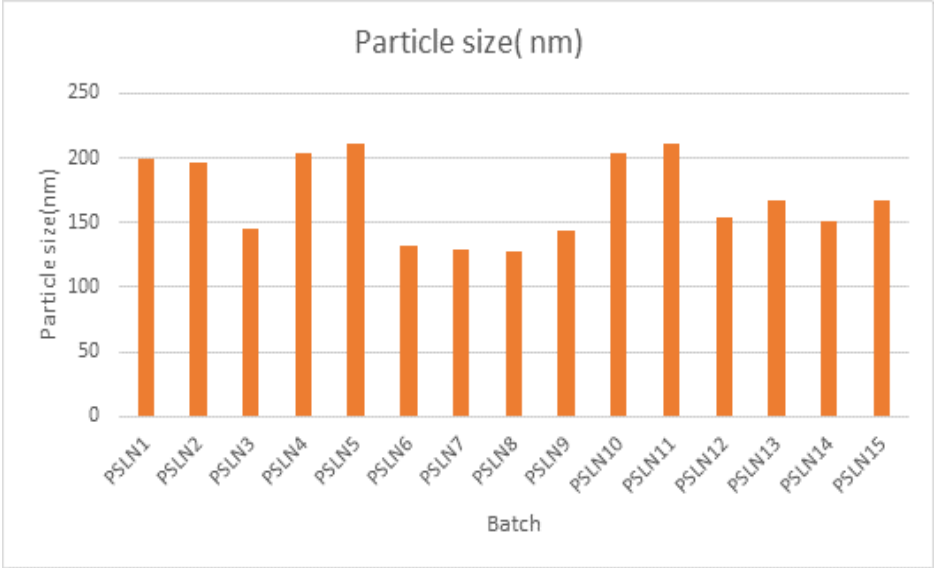
Drug entrapment efficiency

From the results given in table 2, it has been observed that, the high lipid concentration containing formulation have higher entrapment as compare to other formulations. The developed SLN dispersion has shown an EE% in between 54.33% to 87.43% (table 2.)

Table 2: Characterization of penciclovir Loaded SLN

Batch	Particle size(nm)	Entrapment Efficiency(%)	Zeta Potential(mV)
PSLN1	200.1	63.44	-23.42
PSLN2	197.2	71.32	-33.11
PSLN3	145.3	68.31	-24.61
PSLN4	203.2	62.21	-22.17
PSLN5	211.3	76.98	-18.19
PSLN6	132.7	81.02	-22.11
PSLN7	129.3	82.32	-28.03
PSLN8	127.3	87.31	-29.47
PSLN9	144.3	76.22	-31.42
PSLN10	204.4	54.33	-20.47
PSLN11	211.4	61.09	-23.08
PSLN12	154.3	84.43	-20.12
PSLN13	167.3	87.43	-22.77
PSLN14	151.3	84.44	-22.17
PSLN15	167.8	78.03	-27.41

a



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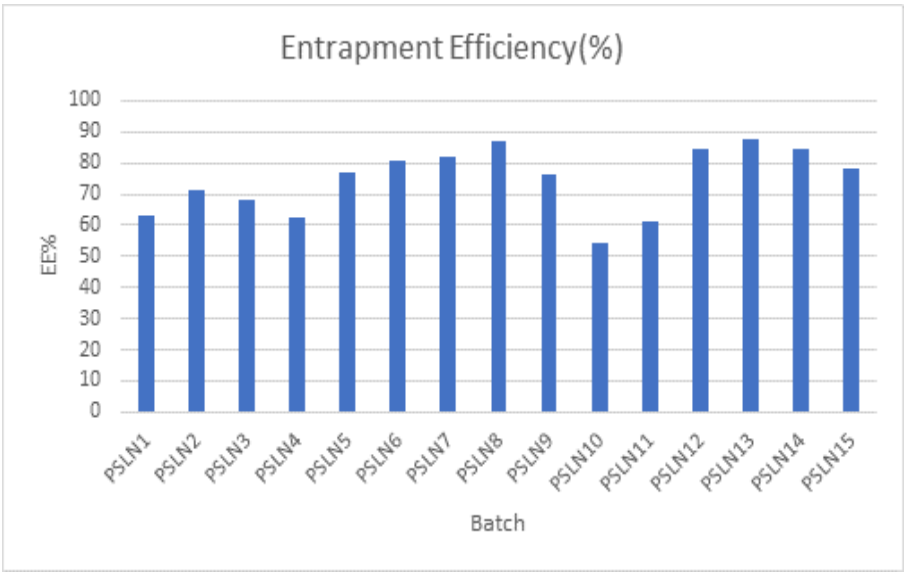

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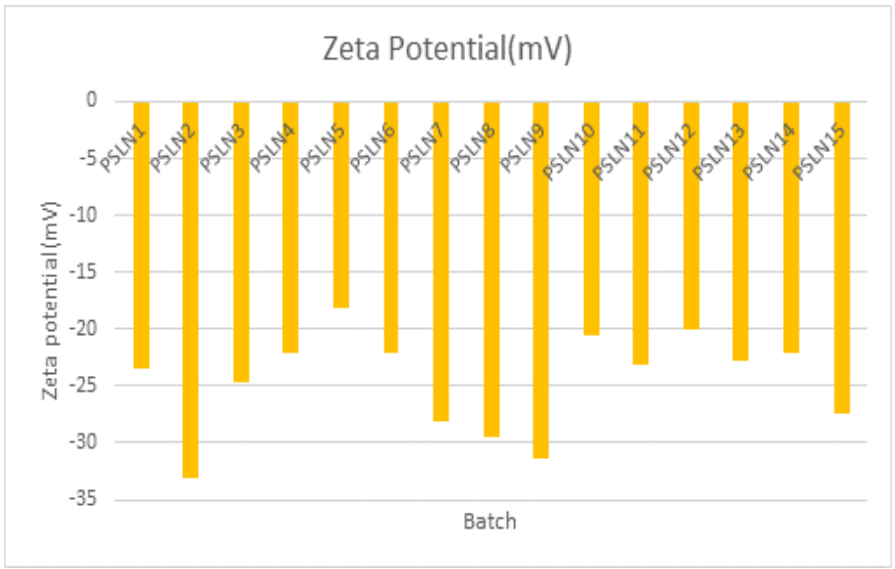

Fig 2: a) Particle size b) EE% c)Zeta Potential

Optimized Formulation

The desirability function was studied using Design-Expert® software V.12 and the best formulation was found. Entrapment efficiency, particle size and zeta potential were taken into account while formulating the best recipe. For this reason, a fresh batch of P-SLNs was made with projected formulation factor concentrations to verify the optimization procedure's accuracy. The formulation factor including 10 mg of lipid, 6mg of surfactant, and 3ml Co-Surfactant resulted in the optimal formulation. As expected, the improved formulation's particle size and entrapment effectiveness were 222nm and 76.66 %, respectively. This formulation was predicted to have 180.36 nm particle size and 72% entrapment efficiency. [8]

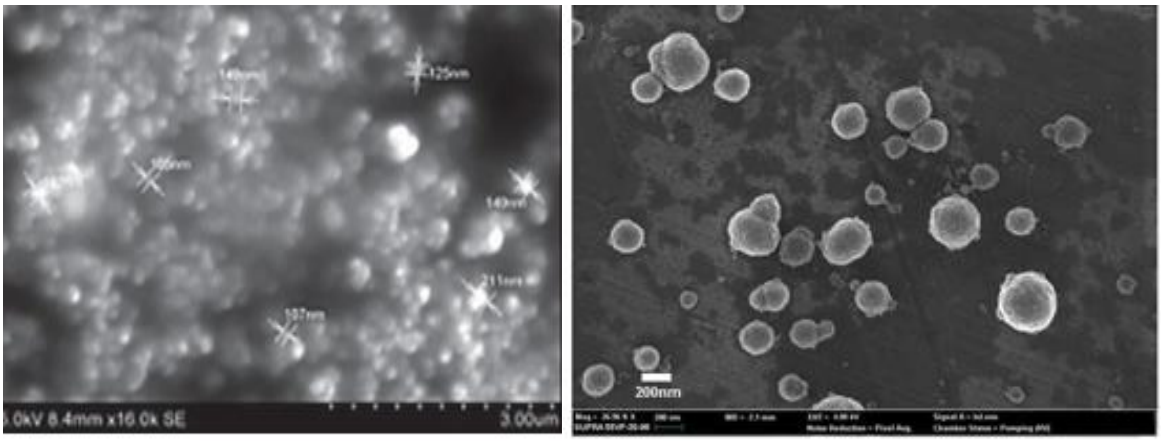

Fig 3: SEM image of Opt-Penciclovir Loaded SLN Dispersion

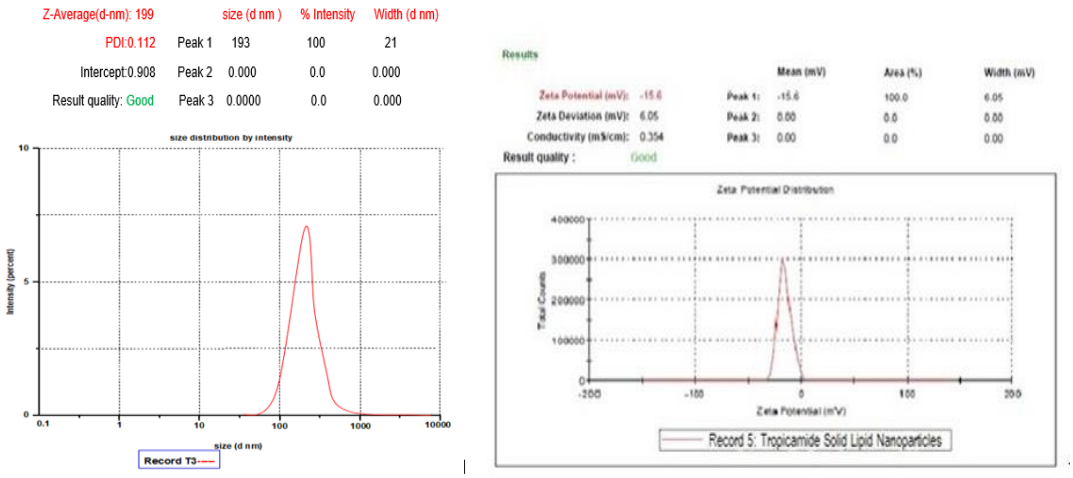

Fig 4: a) particle size b) zeta potential

Ex-vivo Permeation Study

Fig 5 depicted OPT-P-SLN and P-dispersion permeability and dispersion in the intestinal sac ex vivo. Permeation of OPT-P-SLN was substantially higher than P-dispersion (300 g/cm) (p 0.05). Flux was calculated using a time-dependent slop plot of the drug permeation quantity. Over the course of an hour, OPT-P-SLN has a flux four times greater than that of P-dispersion (0.2683 g/cm2/h).

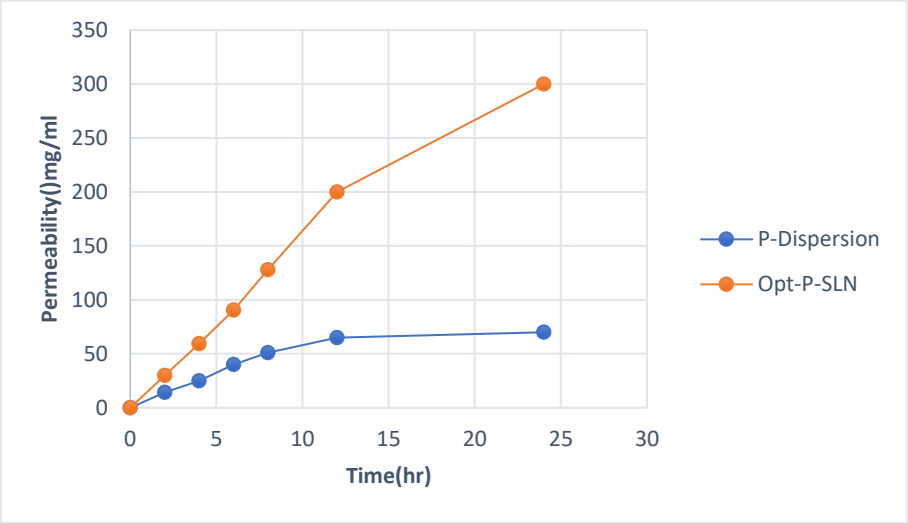

Fig 5: Ex-vivo permeation study

CONCLUSION

We have developed successful solid lipid nanoparticles (SLNs) for delivering Penciclovir orally. These nanoparticles were created using a solvent evaporation method. To assess their properties, factors like particle size, distribution, and encapsulation efficiency (EE%) and Zeta potential were measured. Techniques like scanning electron microscopy (SEM) to visualize the particles, differential scanning calorimetry (DSC) to study their crystallinity, and ex vivo studies to analyze drug release. The findings suggest that Penciclovir encapsulated in SLNs could significantly improve its permeability and bioavailability in the intestine compared to existing medications on the market.

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