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Research

Preparation, Characterization and Optimization of Famciclovir loaded Solid lipid Nanoparticle for enhancing Antiviral Therapy

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Abstract

The current study was undertaken to develop solid lipid nanoparticles (SLN) of a hydrophilic drug Famciclovir and improve the entrapment efficiency of the drug in SLN. The SLN were prepared with Compritol 888 ATO 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 and entrapment efficiency (EE) of the SLN. The maximum EE was found to be 89% with particle size of 299.4nm which was significantly higher than that reported earlier. The optimized batch was also analyzed for its morphological, physiochemical and ex vivo intestinal permeation properties. This work indicates that Famciclovir loaded in SLN could be better option for enhancing the permeability of Famciclovir in intestine as compared to existing marketed formulations.

Keywords: Solid lipid nanoparticle; Famciclovir; entrapment efficiency; particle size; Compritol 888 ATO.

INTRODUCTION

The drug delivery system using solid lipid nanoparticles (SLN) came into being about two decades ago and since then lot of work has been done in this field SLN for oral drug administration are specifically used to target the uptake of the drug by lymphatic system which prevents its first pass metabolism[1]. Lymphatic uptake of drugs follow two routes which include transcellular transport through the enterocyte and phagocytosis of the drugs by Mast cells of payer's patches lining the intestinal mucosa[2]. The production of this nano particulate system is based on the principle of solidification of lipid nano emulsion. SLN have been shown to have superior advantages over polymeric nanoparticles, fat emulsion and liposomes[3]. SLN can be produced on large scale and are also biocompatible to the body as compared to polymers, the monomeric unit of which are cytotoxic to the body. SLN exhibit sustained release effect due to the immobility of drug within lipid as compared to the emulsion formulations and also exhibit better physical and chemical stability of drug compared to liposome. This delivery system has been extensively used as carriers for proteins, protein drugs, vaccines and lipophilic

water insoluble drugs. Famciclovir is a guanine analogue antiviral drug used for the treatment of various herpes virus infections, most commonly for herpes zoster (shingles). Medically it is used to treat the herpes zoster (shingles) [4] treatment of herpes simplex virus 2 (genital herpes) [5] herpes labialis (cold sores) in immunocompetent patients [6] and for the suppression of recurring episodes of herpes simplex virus 2. It is also indicated for treatment of recurrent episodes of herpes simplex in HIV patients. Famciclovir is marketed under the trade name Famvir[9] In this present study Famciclovir 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

Famciclovir was received as a gift sample from Unison Pharmaceuticals, Baddi, INDIA, Compritol 888 ATO, Stearic acid, 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 Famciclovir loaded SLN dispersion

SLNs loaded with Famciclovir were prepared using melt emulsification and low-temperature Solidification method. Famciclovir 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

A variety of lipids were used to test for Famciclovir solubility, including stearic acid, glyceryl monostearate, Compritol 888 ATO, prerol ATO 5, & cis-cetaxanthine. Findings are summarized in the table below.

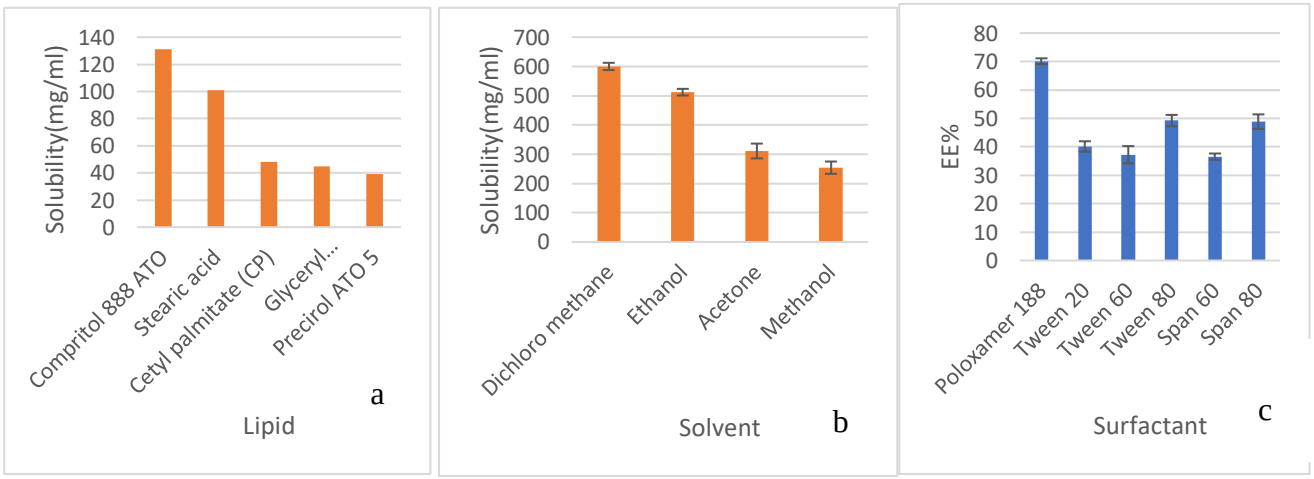


Fig 1: Selection of a)lipid b) Solvent c) Surfactant

The drug showed maximum solubility in Compritol 888 and minimum solubility in Precirol ATO 5 . Compritol 888 (Fig.1a) was selected for further investigation

Selection of solvent system

The solubility of the Drug and lipid in the different solvents was taken into consideration while selecting a solvent. Dichloromethane had the greatest solubility, as shown in Fig.1b

Selection of surfactant

ATO Compritol was utilized to create solid lipid nanoparticles, which were then examined for particle size and EE% before being selected as the surfactant. Fig 1c shows the outcomes achieved.

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[25]. 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 Sonication Time (X3) as shown in (Table 1). The dependent variables were Particle size (Y1) and EE% (Y2) The generation of experimental runs, Analysis of Variance(ANOVA)study and optimization were carried out by Design expert® software 12.

Preparation of Famciclovir loaded SLN

SLNs were prepared using the solvent evaporation technique. Briefly, Drug and Compritol 888 ATO 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 Famciclovir 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 Famciclovir encapsulated within and adsorbed on to the nanoparticles, was determined by measuring the concentration of free Famciclovir 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 Famciclovir added to the formulation and Ws is the analyzed weight of drug in supernatant (Doktorovova et al., 2010).

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

Batch Code	Lipid (mg) X1	Surfactant(mg) X2	Sonication Time(min)(X3)
F-SLN1	5	6	5
F-SLN2	15	6	3
F-SLN3	10	6	4
F-SLN4	10	6	4
F-SLN5	15	8	4
F-SLN6	5	8	4
F-SLN7	15	4	4
F-SLN8	10	8	5
F-SLN9	5	6	3
F-SLN10	10	6	4
F-SLN11	10	4	5
F-SLN12	10	4	3
F-SLN13	15	6	5
F-SLN14	5	4	4
F-SLN15	10	8	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)[7].

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

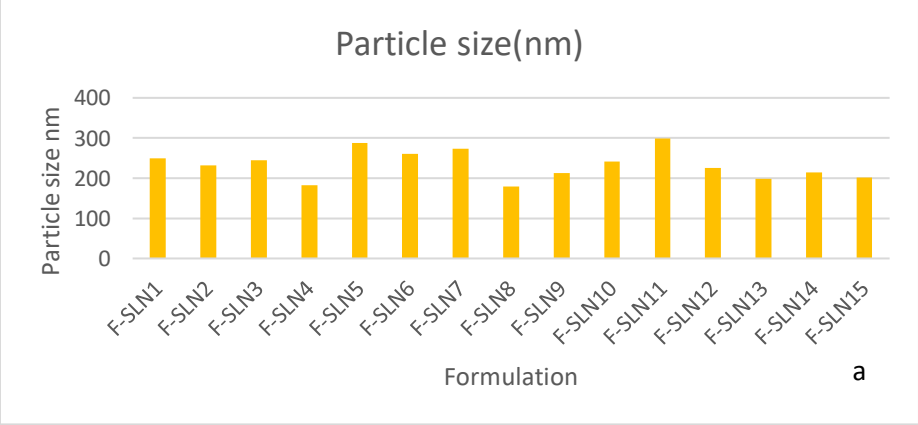
The particle size for all SLN formulation were determined using Malvern Mastersizer showed size in a range between 178.5nm to 299.4nm respectively. The particle sizes of formulations were increases as the concentration of ATO Compritol decreases as shown in table 2.

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 62% to 89%(table 2.)

Table 2: Characterization of Famciclovir Loaded SLN

Formulation Code	Particle size(nm)	Entrapment Efficiency%
F-SLN1	250.1	71
F-SLN2	231.4	73
F-SLN3	244.3	74
F-SLN4	182.4	86
F-SLN5	288.1	71
F-SLN6	261.2	72
F-SLN7	273.4	80
F-SLN8	178.5	88
F-SLN9	213.4	72
F-SLN10	241.6	70
F-SLN11	299.4	73
F-SLN12	225.1	70
F-SLN13	198.1	89
F-SLN14	213.7	62
F-SLN15	200.8	65



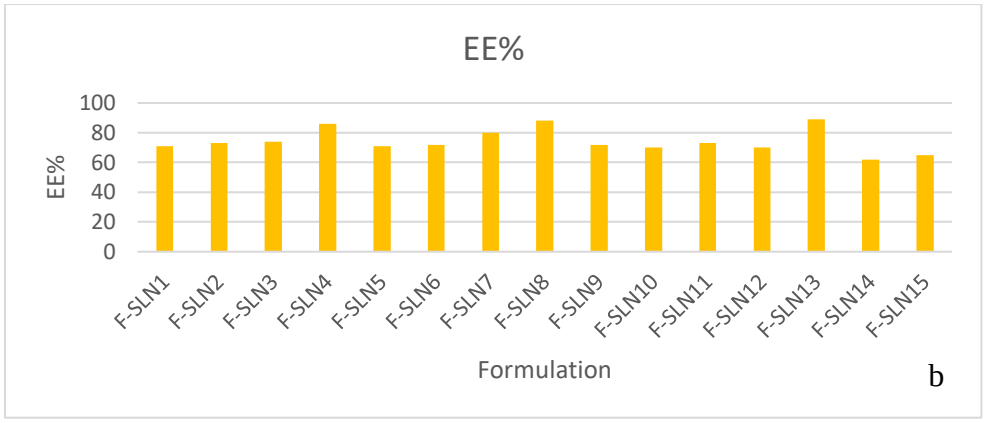


Fig 2: a) Particle size b) EE%

Optimized Formulation

The desirability function was studied using Design-Expert® software V.12 and the best formulation was found. Entrapment efficiency and particle size were both taken into account while formulating the best recipe. For this reason, a fresh batch of F-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 a 4 minute sonication period 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]

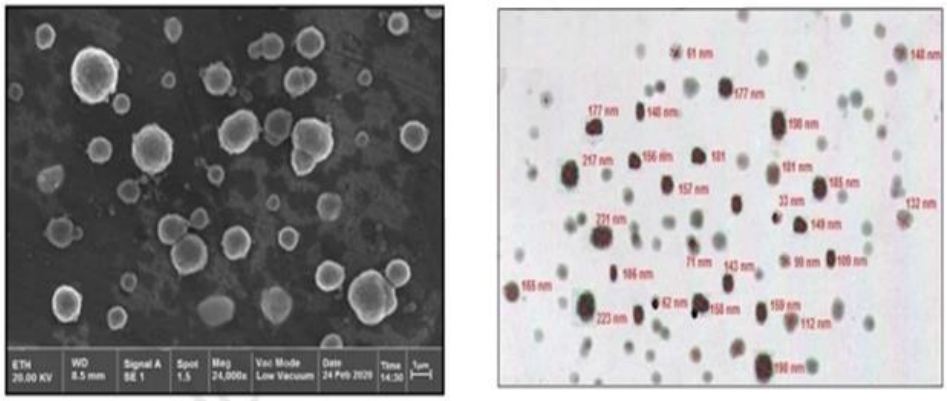


Fig 3: SEM image of Opt-Famciclovir Loaded SLN Dispersion

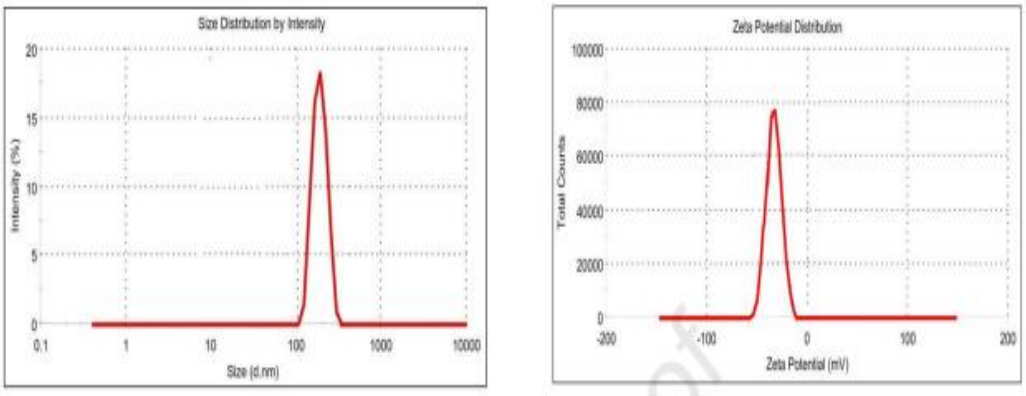


Fig 4: a) Particle size b) zeta potential

Ex-vivo Permeation Study

Permeability of Opt-F-SLN in the intestinal sac was shown in Fig:5 It was shown that Opt-F-SLN had a substantially higher permeation (500 µg/ml) than F-dispersion(90 µg/ml) in 24 hr.

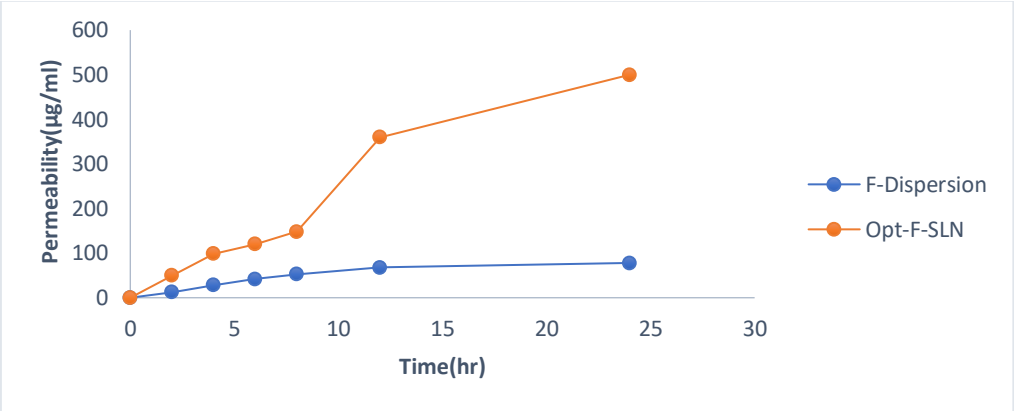


Fig 5: Ex-vivo permeation study

CONCLUSION

The Solid lipid nanoparticles were successfully developed for oral delivery of Famciclovir. SLN dispersions were prepared by solvent evaporation method. Physicochemical characterization including particle size, particle size distribution, EE%, scanning electron microscopy, crystallinity study by DSC and Ex vivo release profile were carried out. It was found that Famciclovir loaded in SLN could be better option for enhancing the permeability and bioavailability of Famciclovir in intestine as compared to existing marketed formulations

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