RESEARCH ARTICLE

FORMULATION DEVELOPMENT AND EVALUATION OF SOLID LIPID NANOPARTICLES OF ACECLOFENAC USING SOLVENT INJECTION METHOD

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ABSTRACT:

The aim of the present work is to improve solubility and bioavailability of poorly soluble drug aceclofenac by solvent injection method. Solid lipid nanoparticles (SLN) of aceclofenac were prepared by solvent injection method. Glyceryl behenate (Compritol 888 ATO) was used as lipid core, and Poloxamer 188 as the surfactant. Isopropyl alcohol (IPA) was used to dissolve both lipid and drug. The mean particle size measured by laser diffraction (LD) was 226.9 nm and the surface morphology was determined by scanning electron microscopy. The entrapment efficiency (EE) was found to be 90%. In-vitro dissolution was found to be 90.22%.

Key words: Solid lipid nanoparticles, Solvent injection method, FT-IR, Scanning electron microscopy, Aceclofenac, Glyceryl behenate, Poloxamer 188.

INTRODUCTION:

Solid lipid nanoparticles were firstly investigated in 1990 by Muller and Gasco. These submicron colloidal particles composed of physiological lipids and dispersed in aqueous surfactant solution[1]. They are new generation sub-micron sized lipid emulsion of 50-1000 nm in size and in which liquid lipid is substituted by solid lipid. They can carry both lipophilic and hydrophilic drugs.SLNs provide unique properties such as least size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals[2]. Solid lipid nanoparticles have many advantages like low cost of ingredients, ease of preparation and scale-up etc[3]. SLNs are prepared by many methods such as High pressure homogenization, Ultrasonication Technique, Solvent evaporation method, Solvent injection method (Solvent displacement method), Solvent emulsification-diffusion method, Supercritical fluid method, Microemulsion based method, Spray drying method, Double emulsion method and Precipitation technique[4,5,6].The oral route is the most preferred route for drug administration due to its convenience and good patient compliance. Drug solubility is a major challenge now days for hydrophobic drugs, 40% of all newly developed drugs are poorly soluble or insoluble in water[7]. There were much more research has done into methods for improving the solubility and dissolution rate of drugs in order to increase the bioavailability in case of hydrophobic drugs. Aceclofenac (2-[(2, 6 dichlorophenyl) amine] phenylacetoxyacetic acid) is an orally effective non-steroidal anti- inflammatory drug (NSAID) of the phenyl acetic acid group. It possesses anti-inflammatory, analgesic and anti-pyretic activity[8,9]. The solubility of aceclofenac in water is very poor and thus it shows poor bioavailability after oral administration[10,11]. There are hardly any reports on the preparation of solid lipid nanoparticles of aceclofenac and solubility enhancements of aceclofenac by solvent injection method. Solvent injection method is a straight forward method with no need of sophisticated equipment to manufacture lipid nanoparticles. The particle size can be influenced and controlled by variation of processing parameters like injected solvent, lipid concentration, injected amount and viscosity in this method.Hence the objective of the present study is to prepare and evaluate solid lipid nanoparticles of aceclofenac using solvent injection method[12,13].

MATERIALS:

Aceclofenac was a gift sample of Mankind Pharmaceuticals, Dehradun, India. Poloxamer 188 was gifted by Alcon Laboratories Pvt. Ltd, Bangalore, India. Glyceryl behenate (Compritol 888 ATO) and dialysis membrane wereprocured from HiMedia Laboratories Pvt. Ltd, Mumbai, India. Isopropyl alcohol andTween 80 were procured from Rankem, Okhla Industrial Area, New Delhi, India.

METHODOLOGY:

Solid lipid nanoparticles of aceclofenac were prepared by using solvent injection method[12,13]. Aceclofenac (100 mg) and specified amount of Glyceryl behenate was dissolved in specified quantity of isopropyl alcohol (IPA) (boiling point 81°C to 83°C) with heating at melting temperature of solid lipid. Glyceryl behenate is soluble in IPA; however, it requires some heat for ease of solubilization. The resulting solution was rapidly injected into the 10 ml of aqueous phase containing specified amount of Poloxamer 188 that was continuously stirred at 400 rpm for 30 min on a magnetic stirrer; 0.1N HCl (4 ml) was added to the dispersion to decrease the pH around 1.5 - 2 to cause the aggregation of SLNs for the ease of separation.The resulted dispersion was then filtered with a filter paper in order to remove any excess lipid. Thereafter, the dispersion was centrifuged to 4,000 rpm for 30 min at in REMI cooling centrifuge, and aggregates were resuspended to 10 ml double distilled water containing 4% Poloxamer 188 (by weight) as stabilizer with stirring at 1,000 rpm for 10 min.

CHARACTERIZATION AND EVALUATION OF SLNs:

Particle size:

For the measurement of particle size photon correlation spectroscopy (PCS) and laser diffraction (LD) are important techniques.Thesurface morphology of SLNs was characterized by Scanning electron microscopy (SEM) which was conducted to characterize the surface morphology of the SLNs. The samples were mounted on alumina stubs using double adhesive tape, coated with gold in Sputter coater- Polaron SC7640. Then the sample was observed in SEM at an acceleration voltage of 20KV and a magnification of different X i.e. from 9X to 32X.

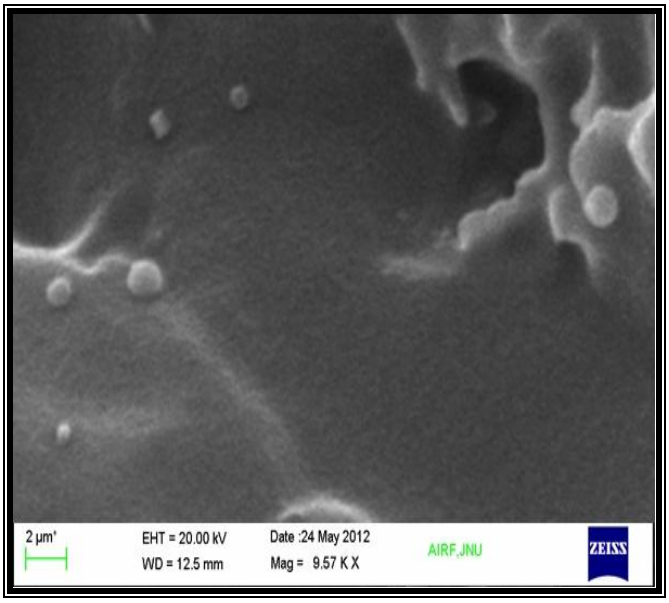

Figure 1: SEM analysis of SLNs of aceclofenac at magnification 9.57 KX

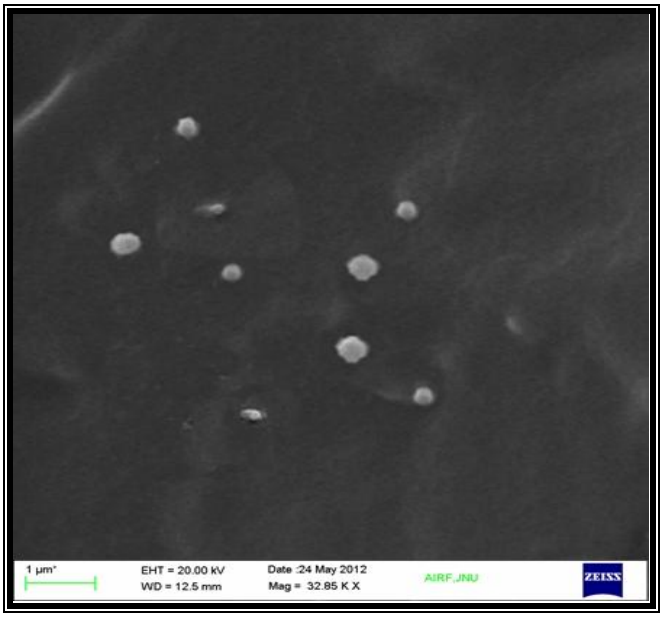

Figure 2: SEM analysis of SLNs of aceclofenac at magnification 32.85 KX

Fourier transformed infrared (FT-IR) spectroscopic analysis:

About 1–2 mg of sample of was mixed with dry potassium bromide and the samples were examined at transmission mode over wave number range of 4000 to 400 cm^{-1}. FT-IR studies were carried out on pureGlyceryl behenate and Aceclofenac as bulk materials and SLNs loaded with Aceclofenac.

Entrapment efficiency [14]:

The entrapment efficiencies of prepared systems were determined by measuring the concentration of free drug in the dispersion medium. The unentrapped Aceclofenac was determined by adding 0.1 ml of the nanosuspension to 9.9 ml ethanol (95%); the obtained suspension was centrifuged for 45 min at 6,000 rpm. The supernatant was separated and filtered through filter paper 0.2-µm filter. The filtrate was diluted using ethanol and measured spectrophotometrically (Systronics 2203Smart, India.). The amount of free drug was detected in the filtrate and the amount of incorporated drug was determined as a result of the initial drug minus the free drug. The entrapment efficiency was calculated using the following equation:

$$\%\,EE = \frac{W_{Inital\ Drug} - W_{Free\ Drug}}{W_{Initial\ Drug}} \times 100$$

Where "$W_{initialdrug}$" is the mass of initial drug used and the "$W_{free\ drug}$" is the mass of free drug detected in the supernatant after centrifugation of the aqueous dispersion.

The entrapment efficiency of the optimized formulations (F6, F7 and F8) was found to be maximum among all the formulations. And F7 has the most maximum entrapment of drug in the SLNs i.e. 90% which is resulted due to the high concentration of lipid and low concentration of poloxamer used in the formulation.

In-vitro drug release [15]:

In-vitro drug release of selected SLNs was performed by dialysis bag diffusion technique. Solid lipid nanosuspension equivalent to 5 mg of aceclofenac was filled in dialysis bag (Dialysis Membrane- 12–14 k Da, pore size 2.4 nm) and immersed in receptor compartment containing 150 ml of phosphate buffer pH 6.8 stirred at 100 rpm at a temperature of 37 ± 0.5°C. Five millilitre of aliquots were withdrawnat regular time intervals (4, 8, 12, 24, 28, 32, 36, 48, 52, 55 hrs.) and replenishment of receptor compartment with same volume of fresh dialyzing medium was done and the samples were analysed for % cumulative drug release at 55^{th} hr. Among the ten formulations F6, F7 and F8 were selected as the optimized formulations and F7 is considered as the best one. In these optimized formulations low amount of poloxamer 188 and slightly high amount of lipid glyceryl behenate was used. And the solvent, Isopropyl alcohol, was also used in the optimized quantity.

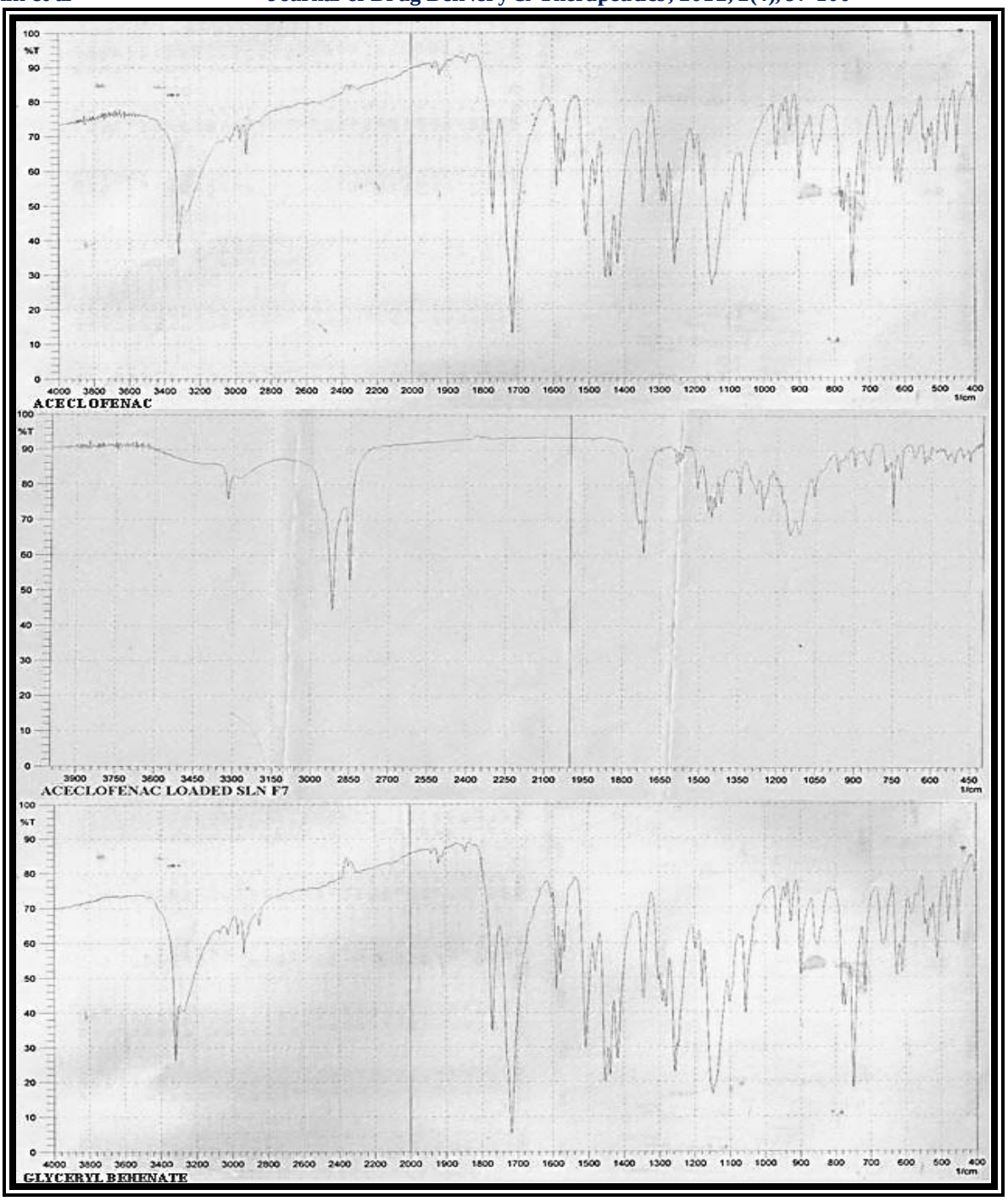

Figure 3: FTIR spectra of aceclofenac, glyceryl behenate and formulation.

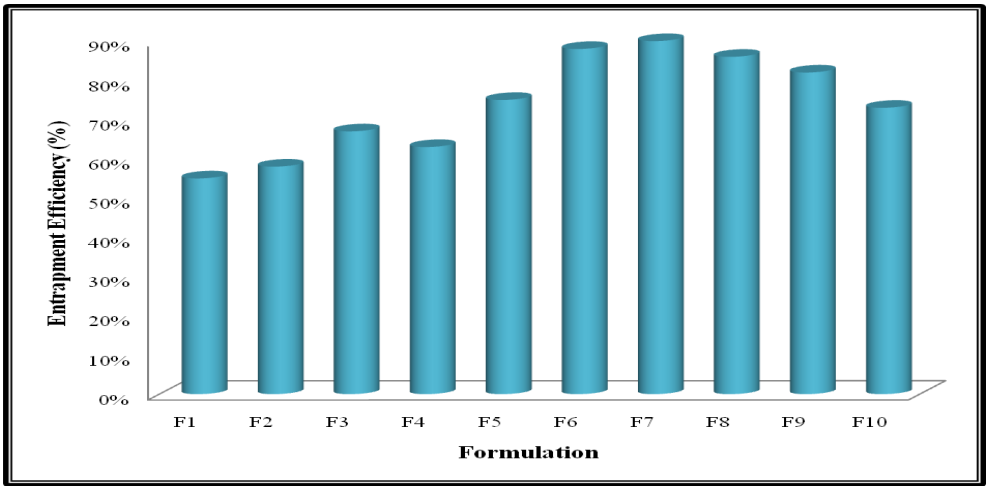

Figure 4: % Drug entrapment efficiency of formulation F1 to F10

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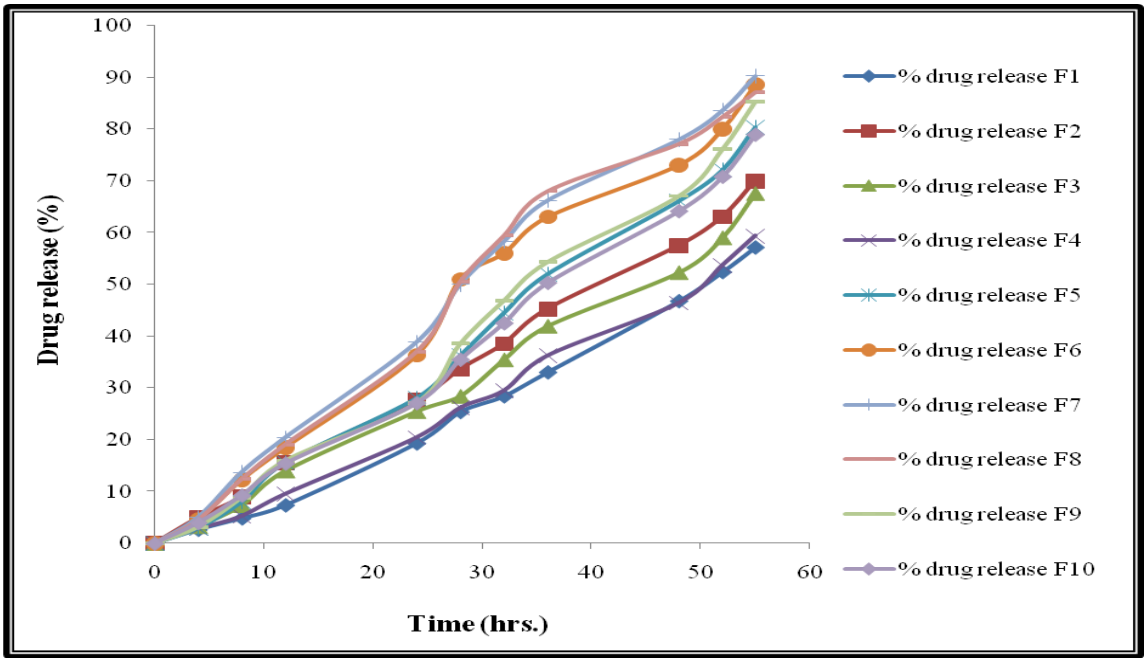

Figure 5: % Drug Release of formulation F1 to F10

RESULT AND DISCUSSION:

In the present work an attempt was made to prepare solid lipid nanoparticles of aceclofenac using glyceryl behenate as solid lipid, poloxamer 188 as surfactant and isopropyl alcohol as solvent. The FTIR spectroscopy showed positive results for the API. The IR spectrum was performed in percentage transmission (%T) versus wave number. The melting point of aceclofenac was determined by melting point apparatus, which was found to be 145^0C-155^0C and compared to the literature value 149^0C-153^0C. Drug compatibility was performed by Cartension method and FT-IR spectroscopic studies which showed that excipients were compatible with API. The SLNs were prepared using solvent injection method. Ten formulations were prepared successfully which exhibit the particle size of the prepared formulations was found in the range between 226.9 nm to 451.2 nm. Surface charge of the formulations was found to be -12.89 kV to -35.22 kV. Entrapment efficiency of the formulations was found to be from 55% to 90%. Aceclofenac loaded SLNs show in-vitro percentage drug release from 57.12% to 90.22%.

CONCLUSION:

Aceclofenac solid lipid nanoparticles are prepared by solvent injection method using glyceryl behenate as solid lipid core and poloxamer 188 as surfactant. Effect of the process parameters such as particle size, entrapment efficiency and drug release from SLNs were studied.The results indicated that SLNs which have least particle size can release properly from nanoparticles. FT-IR spectra studies indicated that there was no interaction of lipid and poloxamer with drug. Further studies can be performed as in-vivo drug release in animals in future.

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