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Solubility and Dissolution Improvement of Aceclofenac using Different Nanocarriers

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Abstract

The aim of the present investigation was to improve solubility and dissolution of the lipophilic drug aceclofenac using three nanocarriers namely nanoemulsion, solid lipid nanosuspension and polymeric nanosuspension. The solubility of aceclofenac in distilled water and different nanocarriers was determined using the UV spectrophotometer method at the wavelength of 274 nm. Dissolution studies of pure aceclofenac suspension and its nanocarriers were performed using USP dissolution apparatus in distilled water. The highest solubility (198.53 mg/ml) as well as % dissolution (99.5) of aceclofenac was obtained with nanoemulsion formulation as compared to lipid and polymeric nanosuspension. The results of solubility and dissolution were highly significant in nanoemulsion as compared to lipid and polymeric nanosuspension ($P<0.01$). Dissolution profile of aceclofenac in lipid and polymeric nanosuspension was significant as compared to pure aceclofenac suspension ($P<0.05$). These results indicated that nanoemulsion is a promising nanocarrier as compared to lipid and polymeric nanosuspension for solubility and dissolution enhancement of aceclofenac.

Keywords: Aceclofenac; Nanoemulsions; Lipid nanosuspensions; Polymeric nanosuspensions; Solubility; Dissolution

Introduction

The solubility and dissolution rate are very important parameters for *in vivo* performance of any dosage forms (Ahmed et al., 1993). The *in vitro* rate and extent of dissolution of the drug from dosage forms also determines the *in vivo* bioavailability of the drug (Ahmed et al., 1993). By many estimates up to 40 % of new chemical entities (NCEs) discovered by the pharmaceutical industry today and many existing drugs are poorly soluble compounds which leads to poor *in vivo* bioavailability, patients noncompliance, high intra and inter subject variability and lack of dose proportionality (Kommuru et al., 2001; Shakeel et al., 2008a, b). Relative to compounds with higher aqueous solubility, poorly soluble compounds often manifests themselves in a host of many *in vivo* consequences like decreased bioavailability, increased chance of food effect, more frequent incomplete release from the dosage form and higher intra and inter subject variability (Shakeel et al. 2008b). However, important advances have been made in improving the solubility, *in vitro* dissolution and *in vivo* bioavailability of poorly soluble compounds, so that promising drug candidates need no longer to be neglected or have their development hindered by suboptimal formulation. In addition to more conventional techniques, such as salt formation, complexation and micronization etc., novel solubility/bioavailability enhancement techniques have been developed. The recent trend for the enhancement of solubility/bioavailability of poorly soluble compounds is the lipid based systems such as microemulsions, nanoemulsions, solid dispersions, solid lipid nanoparticles/nanosuspensions, polymeric nanoparticles/nanosuspensions, niosomes and liposomes etc. This is also the most advanced commercial approach, as formulation scientists increasingly turn to a range of nanotechnology based solutions to improve solubility, dissolution and bioavailability of poorly soluble compounds (Shakeel et al., 2008a, b). The nanoemulsions, solid-lipid nanosuspensions (SLN) and polymeric nanosuspensions (PN) have been in-

vestigated successfully to improve the solubility, dissolution and *in vivo* bioavailability of poorly soluble drugs (Labhawtwar and Levy, 1997; Kommuru et al., 2001; Shafiq et al., 2007a, b; Shakeel et al., 2007; Shakeel et al., 2008a, b; Baboota et al., 2009; Jawahar et al., 2009). Aceclofenac, a nonsteroidal anti-inflammatory drug (NSAID) has been recommended for the treatment of various kinds of pains, osteoarthritis and rheumatoid arthritis (Shakeel et al., 2007). Aceclofenac is well absorbed after oral administration with hepatic first pass metabolism (Shakeel et al., 2009). Because of the poor aqueous solubility of aceclofenac poses a dissolution-related absorption problem, an attempt was made to improve the solubility as well as the dissolution of aceclofenac using different nanocarriers like nanoemulsion, SLN and PN. Nanoemulsions offer higher solubilization capacity than simple micellar solutions and other drug carriers and their thermodynamic stability presents many advantages over unstable dispersions (Shafiq et al., 2007c; Shafiq and Shakeel, 2008). The aim of the present investigation was to improve solubility and *in vitro* dissolution of the poorly soluble drug aceclofenac using different nanocarriers which would further enhance biological performance of dosage form.

Materials and Methods

Materials

Aceclofenac was obtained as a kind gift sample from Ranbaxy Research Laboratory (Haryana, India). Oleoyl macroglycerides EP (Labrafil) and diethylene glycol monoethyl ether (Transcutol-P) were kind gift samples from Gattefossé (Cedex, France). Glycerol triacetate (Triacetin) and stearic acid were purchased from E-Merck (Germany). Poloxamer-188, Tween-80 and sodium taurocholate were purchased from E-Merck (Germany). Poly-lactide coglycolide (PLGA), Pluronic F-68 and dialysis membrane were purchased from Sigma Aldrich (USA). All other chemicals used in the study were of AR grade.

Preparation of Aceclofenac Nanoemulsion

Nanoemulsion formulation of aceclofenac was prepared by the aqueous phase titration or spontaneous emulsification method (Shakeel et al., 2007). 2 % w/w of aceclofenac was dissolved in 15 % w/w combination of Labrafil and Triacetin (2:1). 53 % w/w mixture of surfactant (Tween-80) and cosurfactant (Transcutol-P) [2:1] was mixed in oily solution of drug. Distilled water was added slowly with continuous stirring to get final formulation 100 % w/w (Table 1).

Preparation of Aceclofenac-loaded Solid Lipid Nanosuspension

Acelofenac-loaded SLN was prepared using the microemulsion technique (Baboota et al. 2009). Warm o/w microemulsion was prepared using 10 % w/w of stearic acid as the oil phase, Poloxamer-188 (5 % w/w) as surfactant and a mixture of 5 % w/w of sodium taurocholate and 5 % w/w of ethanol as co-surfactants. A clear microemulsion was obtained by gentle stirring at 70°C. The prepared microemulsion was immediately dispersed in cold water, under mechanical stirring at a ratio of 1:10 (% w/w) [Table 1].

Preparation of Aceclofenac-loaded Polymeric Nanosuspension

Polymeric nanosuspension (PN) of aceclofenac was prepared by nanoprecipitation method using PLGA as polymer (Zili and Fessi 2005; Jawahar et al., 2009). The polymer PLGA was dissolved in 25 % w/w acetone. 2 % w/w of

Ingredients (% w/w)	Nanoemulsion	SLN	PN
Aceclofenac	2	2	2
Labrafil	10	-	-
Triacetin	5	-	-
Tween-80	35.66	-	-
Transcutol-P	17.33	-	-
Stearic acid	-	10	-
Poloxamer-188	-	5	-
Sodium taurocholate	-	5	-
Ethanol	-	5	-
PLGA	-	-	0.5
Pluronic F-68	-	-	0.2
Acetone	-	-	30
Distilled water (q.s.)	100	100	100

q.s. = quantity sufficient to produce final formulation 100 % w/w, PLGA = poly-lactide coglycolide

Table 1: Composition of nanoemulsion, solid lipid nanosuspension (SLN) and polymeric nanosuspension (PN).

aceclofenac was dissolved in polymer solution (organic phase). Pluronic F-68 was dissolved in sufficient quantity of distilled water (aqueous phase). Organic phase was slowly dispersed into aqueous phase with continuous stirring. Acetone was eliminated by evaporation under reduced pressure at 40°C. The final preparation was adjusted to 100 % w/w. The composition of this formulation is given in Table 1.

Characterization of Nanoemulsion, SLN and PN

Prepared nanoemulsion was characterized for particle size viscosity, surface morphology and refractive index (Shakeel et al., 2007). Prepared SLN and PN were characterized for particle size using Zetasizer and entrapment efficiency.

Solubility Determination

The solubility of aceclofenac in distilled water, nanoemulsion, SLN and PN was determined by UV spectrophotometer at the wavelength of 274 nm (Shakeel et al., 2007). Excess amount of aceclofenac in all sample matrices were added in conical flasks in triplicate. These conical flasks were kept in a mechanical water shaker bath (Memmert, Germany) at the temperature of 25 ± 1°C for 72 h to reach equilibrium. After 72 h, solutions were filtered and diluted suitably with distilled water and subjected for quantification of aceclofenac by UV spectrophotometric method at the wavelength of 274 nm (Shakeel et al., 2007).

In Vitro Dissolution Studies

In vitro dissolution studies (drug release studies) were performed in 900 ml of distilled water using USP XXIV dissolution apparatus 2 at 50 rpm. 5 ml of each formulation (nanoemulsion, SLN and PN containing 100 mg of aceclofenac) and pure drug suspension were placed in dialysis bag (MWCO 12000 g/mol, Sigma Aldrich, USA). Samples (3 ml) were withdrawn at regular intervals (0, 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 h) and replaced with drug free distilled water. The drug content was determined by UV spectrophotometer method at the wavelength of 274 nm (Shakeel et al., 2007).

Statistical Analysis

The results of solubility and in vitro dissolution were compared for statistical significance by applying one-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test using GraphPad Instat software (GraphPad Software Inc., CA, USA).

Results and Discussion

All the formulations like nanoemulsion, SLN and PN were prepared and characterized successfully. The particle size, viscosity and refractive index of nanoemulsion were found 35.20 ± 1.24 nm, 92.20 ± 1.41 cps and 1.40 ± 0.05 respectively (Table 2). The shape of nanoemulsion was found spherical by TEM experiments (Shakeel et al., 2007). The particle size and entrapment efficiency of SLN and PN were found 171.32 ± 5.42 nm & 96.40 ± 3.51 % and 212.25 ± 9.76 nm & 84.41 ± 3.85 % respectively as shown in Table 2. All characterization parameters of nanoemulsion, SLN and PN were satisfactory. The solubility of aceclofenac in nanoemulsion, SLN and PN was determined and compared with aqueous solubility of aceclofenac. The solubility of aceclofenac in distilled water and different nanocarriers is given in Table 3.

The solubility of aceclofenac in distilled water at 25°C was found 0.015 ± 0.002 mg/ml. The solubility of aceclofenac in nanoemulsion, SLN and PN was found 198.53 ± 4.21,

Parameters	Nanoemulsion	SLN	PN
Particle size (nm)[a]	35.20±1.24	171.32±5.42	212.25±9.76
Viscosity (cps)[a]	92.20±1.41	-	-
RI[a]	1.40±0.05	-	-
EE (%)[a]	-	96.40±3.51	84.41±3.85

[a]mean ± SD, n = 3, RI = refractive index, EE = entrapement efficiency

Table 2: Characterization parameters of nanoemulsion, SLN, and PN.

Sample matrices	Solubility (mg/ml)[a]	Enhancement in solubility
Distilled water*	0.015±0.002	-
Nanoemulsion	198.53±4.21	13235 folds
SLN	104.23±3.05	6948 folds
PN	83.73±2.89	5582 folds

[a]mean ± SD, n = 3, * Distilled water was used as control

Table 3: Solubility of aceclofenac in distilled water, nanoemulsion, SLN, and PN at 25°C.

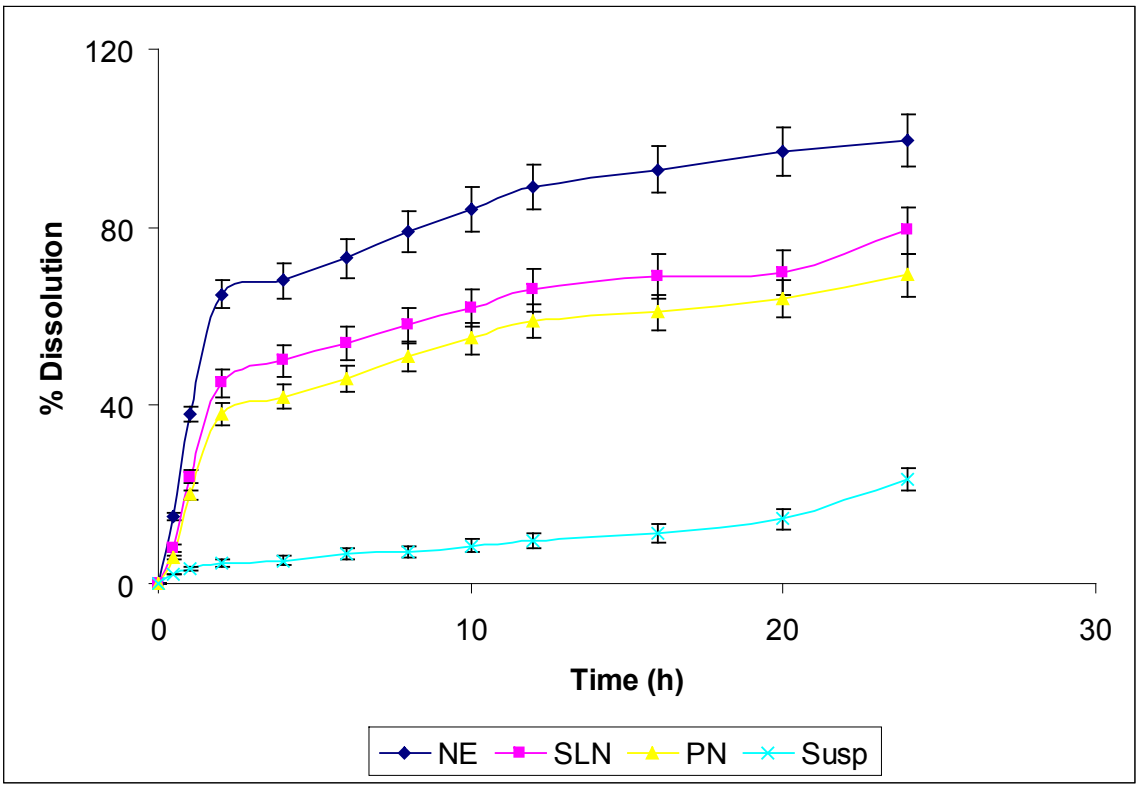

Figure 1: In vitro dissolution profile of aceclofenac from pure drug suspension (Susp), nanoemulsion (NE), solid lipid nanosuspension (SLN) and polymeric nanosuspension through sigma membrane.

104.23 ± 3.05 and 83.73 ± 2.89 mg/ml, respectively as shown in Table 3. The solubility of aceclofenac in all three nanocarriers was extremely significant as compared to its aqueous solubility ($P<0.001$). Highest solubility of aceclofenac was found in nanoemulsion formulation as compared to SLN and PN (Table 3). The solubility of aceclofenac in nanoemulsion was significant as compared to its solubility in SLN and PN ($P<0.05$). The enhancement in solubility was 13235, 6948 and 5582 folds in nanoemulsion, SLN and PN, respectively as compared to its solubility in distilled water. The highest solubility of aceclofenac in nanoemulsion could be due to the presence of surfactant (Tween-80) and co-surfactant (Transcutol-P). The dissolution studies of aceclofenac from pure drug suspension and different nanocarriers were performed in distilled water. The % dissolution of aceclofenac through dialysis membrane was lowest in pure drug suspension (23.5) and highest in nanoemulsion (99.5) after 24 h as shown in Figure 1. The % dissolution of aceclofenac in all three formulations was extremely significant as compared to pure suspension ($P<0.001$). This indicated that the presence of nanocarriers can significantly enhance the dissolution of a poorly soluble drug aceclofenac. The most interesting results with nanoemulsion were that around 65 % of drug was released within 2 h of study. The % dissolution of aceclofenac in nanoemulsion was significant as compared to SLN and PN ($P<0.05$). These results indicated that nanoemulsion can be successfully used as nanocarrier for solubility and dissolution enhancement of aceclofenac.

Conclusion

The results of these studies indicated that nanoemulsions are promising nanocarriers for solubility and dissolution enhancement of a poorly soluble drug like aceclofenac as compared to SLN and PN.

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