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Effect of lyophilization and polymer compositions on solubility of aceclofenac solid dispersions

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ABSTRACT:

Aceclofenac, a non steroidal anti-inflammatory agent is BCS class II drug (highly permeable and low soluble) shows poor aqueous solubility, in order to improve solubility and dissolution rate; solid dispersions of Aceclofenac were prepared using different polymers and effect of polymer compositions on solid dispersion were also investigated. Solid dispersions of Aceclofenac were prepared using PEG 6000 and Poloxamer 407. Dissolution studies indicated significant enhancement in dissolution of Aceclofenac when dispersed in PEG 6000 and Poloxamer 407. Solid dispersions containing Aceclofenac /Poloxamer 407, 1: 4.5, showed a max. dissolution (97%) after 60 min (D60) and another dispersion containing Aceclofenac /PEG 6000, 1:6, also showed significant enhancement in dissolution rate (D60 value 94%). FT-IR study was also performed to determine the physicochemical properties of the solid dispersions in comparison with the pure drug. It was found that lyophilized solid dispersions of Poloxamer 407 had the maximum effect on the rate and extent of dissolution of Aceclofenac.

Keywords: Aceclofenac, PEG 6000, Poloxamer 407, Dissolution.

INTRODUCTION:

Poor water-solubility of drugs has been one of the major problems in drug formulation and drug absorption these drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds; several methods have been employed to improve the solubility of poorly water soluble drugs. A solid dispersion technique has been used by various researchers to enhance solubility of such drugs. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole [1-4]. Lyophilization has also been

employed largely for the preparation of lyophilized molecular dispersion [5]. Use of Aceclofenac as non steroidal anti-inflammatory agent has been limited by its low water solubility [6, 7], thus its solid dispersions were prepared using Poloxamer 407 and PEG 6000 as carrier. The results of this study suggested that lyophilization of solid dispersions is ideal for poorly water soluble drugs.

MATERIAL AND METHODS:

Apparatus and chemicals

Poloxamer 407 (Pluronic F127) was obtained from BASF (Mount Olive, NJ, USA). PEG 6000 was purchased from Sigma Aldich. Other excipients used were of analytical grade. All chemicals were used as received.

Composition of Solid Dispersion

Single component solid dispersions contained 1.5, 3, 4.5, 6 parts by weight of Poloxamer 407 or PEG 6000 and 1 part of drug (Table 1). Physical mixtures containing either Poloxamer 407 or PEG 6000 contained equal amounts of carrier and drug**.**

Table 1: Compositions of Solid dispersion

Carrier	Drug: Carrier ratio	Formulation code
Poloxamer 407	1:1.5	FE- 1
	1:3	FE- 2
	1:4.5	FE- 3
	1:6	FE- 4
PEG 6000	1:1.5	PE- 1
	1:3	PE- 2
	1:4.5	PE- 3
	1:6	PE- 4

Preparation of solid dispersions

The fusion (melt) method

Accurately weighed amounts of carrier(s) were placed in an aluminum pan on a hot plate and melted, with constant stirring, at a temperature of about 60°C. An accurately weighed amount of drug was incorporated into the melted carrier(s) with stirring to

ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The pan was then removed from the hot plate and allowed to cool at room temperature

Lyophilization of solid dispersions

The selected solid dispersions were dissolved in a minimum amount of Chloroform. This solution was rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold flask rotating in methanol bath at 50°C. After a certain layer thickness was obtained, the flask was attached to the vacuum adapter of the lyophilizer. The solvent was sublimed under pressure of 8-10 mmHg and condensed. Lyophilized preparations were stored in desiccators at room temperature.

Dissolution rate determination

An Electro-lab dissolution test apparatus type II (Paddle) at rotation speed of 50 rpm was used for the study. Dissolution of the drug and solid dispersion was carried out on an equivalent of 100 mg of the drug. The volume and temperature of the dissolution media were 900 ml and 37 ± 0.2^0C, respectively. After fixed time intervals, 5 ml of samples were withdrawn and replace with the same amount of fresh dissolution media so as to maintain sink condition. The samples were filtered through 0.2µm filter then diluted, and analyzed by HPLC (wavelength 275 nm). To increase the reliability of the observations, the dissolution studies were performed in triplicate.

FT-IR Studies

FT-IR spectra of prepared Lyophilized solid dispersion were recorded on Shimadzu FT IR – 8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm^{-1}.

RESULTS AND DISCUSSION:

In Vitro Dissolution Study of Solid Dispersion

The dissolution rate of Aceclofenac from all the physical mixtures was significantly higher than Aceclofenac alone. The dissolution profiles of solid dispersions prepared using Poloxamer 407 exhibited significant increase in rate of dissolution. The dispersion prepared with 6 parts of PEG 6000 had the highest dissolution at 60 min (D60) of 94% (Fig. 1), which is significantly greater than the other dispersions. Dispersions containing 4.5 parts of Poloxamer 407 appear to be the best preparation, showing a D60 value of

97% (Fig. 2), which is about 18-fold increase, compared with Aceclofenac alone. Solid dispersions prepared with 6 parts of PEG 6000 and 4.5 parts of Poloxamer 407 were chosen for lyophilization because these dispersions provided the best dissolution profiles. The rate and extent of dissolution increased with all the lyophilized solid dispersions (Fig. 3). Dissolution of solid dispersions at 60 min (D60) is shown in Fig. 1, 2 and 3.

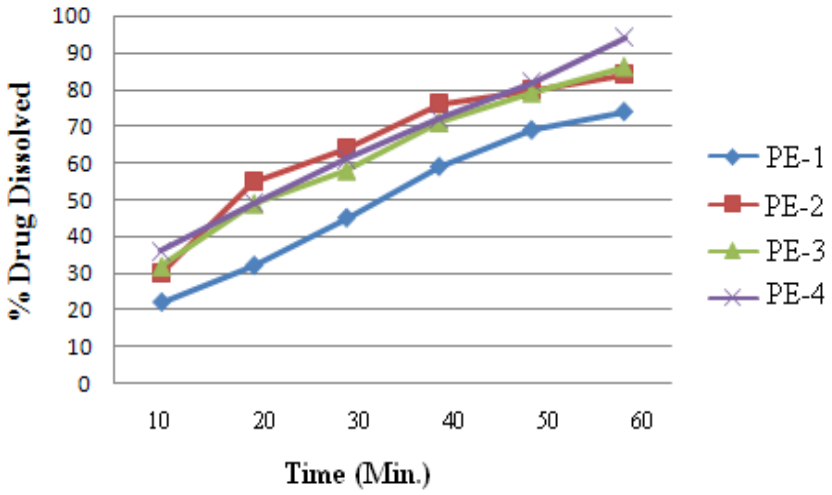

Fig. 1. In vitro dissolution of Aceclofenac solid dispersions (PEG 6000) at 60 min

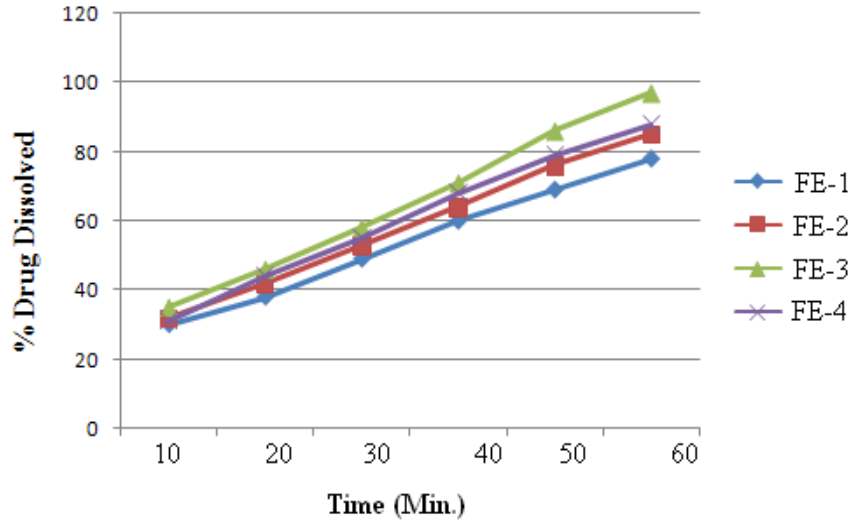

Fig. 2. In vitro dissolution of Aceclofenac solid dispersions (Poloxamer 407) at 60 min

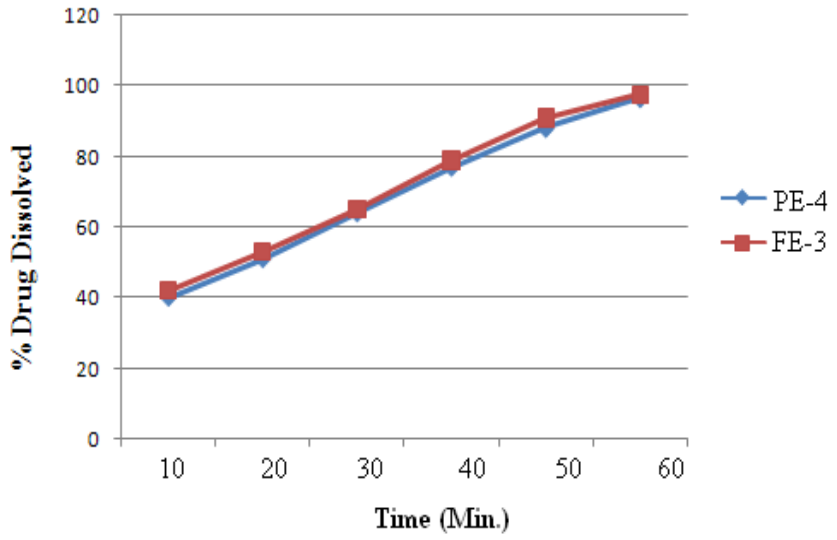

Fig. 3. In vitro dissolution of lyophilized solid dispersions of Aceclofenac at 60 min

All the lyophilized solid dispersions showed significant increase in D60 values compared with their respective non- lyophilized solid dispersions. The dissolution of the drug from the solid dispersion is also affected by the method of preparation of the solid dispersion. It also depends on the proportion and properties of the polymer carrier used in the composition of solid dispersion [8].

Solid dispersions containing Poloxamer 407 and PEG 6000 showed higher dissolution rates compared with Aceclofenac alone. Physical mixtures also exhibited higher dissolution rates as compared with Aceclofenac alone. The process of lyophilization occurs in three stages: freezing, primary drying (ice sublimation) and secondary drying (water desorption) [9]. The freezing process largely determines the physical traits of the dried solid product [10]. The resultant dried mixture was porous and fluffy this is expected to increases the surface area and surface free energy; resulting in enhancement of dissolution rate. The faster dissolution rate merely based on the particle size without anything to do with energy changes. The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and drug; and thus enhance dissolution rates. The presence of carrier polymers was also expected to inhibit crystal growth of the drug which may facilitates faster dissolution [11].

FT-IR Study

State of drug molecule with the different polymers and surfactants was determined using FT-IR. IR-spectra of Aceclofenac and solid dispersion are exactly same, and there is no shift of peaks after absorption of drug onto polymer and surfactants surface; indicating that there is no change in chemical structure of drug after preparing it into melt granules.

CONCLUSION:

In conclusion, physical mixtures, solid dispersions and lyophilized solid dispersions increase dissolution of Aceclofenac. Lyophilized solid dispersions of Poloxamer 407 had the maximum effect on the rate and extent of dissolution of Aceclofenac. The adsorption of Aceclofenac does not leave any residual solvent in the final formulation because of elimination of use of solvent from the preparation of solid dispersion. The results of this study clearly suggest that lyophilization of solid dispersions is ideal for poorly water soluble drugs.

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