Available online at www.ijpsdr.com
International Journal of Pharmaceutical Sciences and Drug Research 2009; 1(1): 32-35

Research Article

Preparation and Evaluation of Solid Dispersions of Aceclofenac

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ABSTRACT
Aceclofenac is a potent anti-inflammatory analgesic agent indicated for acute and chronic treatment of rheumatoid arthritis, ostio arthritis, and onkylosing spondylytis. Aceclofenac is poorly water soluble and may show dissolution limited absorption. Solid dispersions (SDs) of Aceclofenac in PEG-6000, PVP were prepared by solvent evaporation method. The solid dispersion was characterized for physical appearance, solubility and IR. FTIR study reveled that drug was stable in SDs. Solubility of Aceclofenac from SDs increased in distilled water. The drug content was found to be high and uniformly distributed in the all formulation. Dissolution of drug increased from all the solid dispersion. Dissolution of Aceclofenac increased with increase in the proportion of carriers (1:1, 1:5, and 1:9). Of both the carriers used, dissolution of the drug was more in PEG 6000 based SDs. It is concluded that dissolution of the Aceclofenac could be improved by solid dispersion and PEG 6000 based solid dispersions were more effective in the enhancing the dissolution.

Keywords: Aceclofenac, solid dispersion, PEG 6000, PVP-K30, *In vitro* release.

INTRODUCTION

Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole and chloramphenicol come immediately to mind. The formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. Although salt formation, solubilization, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs [1-3], there is practical limitation of these techniques. In 1961, Sekiguchi and Obi [4] developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be over come. This method, which was later termed solid dispersion, involved the formation of eutectic mixture of drugs with water-soluble carriers by the melting of their physical mixtures.

MATERIALS AND METHODS

Aceclofenac was obtained from Zydus-Cadila, Ahmedabad, as a gift sample.PEG 6000, PVP K30, Dichloromethane, Methanol, Sodium hydroxide (NaOH), Potassium di-hydrogen phosphate and Hydrochloric acid were purchased from S. D. fine chemicals limited, Mumbai. Magnetic stirrer and vacuums pump were purchased from Remi Equipments, Bangalore. All the carriers and solvent used were of analytical grade.

Preparation of solid dispersion: [9-12]

Solvent evaporation method was used for the preparation of solid dispersions. Briefly appropriate amount of aceclofenac was taken in china dish and minimum amount of solvent system (combination of methanol and dichloromethane 1:1) was added to dissolve the drug. Required amount of carrier (PEG 600 and PVP) was added to prepare required drug to carrier ratio for formulations as shown in above Table 1. Excess of solvent system was added if required to dissolve drug and carriers. The solvent was then removed by evaporation at 40°C under vacuum. The solid dispersions prepared were pulverized and sifted (80#) and stored in a desiccator.

Preparation of physical mixture and drug content uniformity

Drug and carriers physical mixture were prepared by lightly grinding drug aceclofenac and carriers (PEG 6000,PVP) in mortar for 2 min at the required drug/ carriers level (as shown in above table). Then the powder was passed through the sieve no- 80. Product was stored in desiccator to carry out further analysis. The drug content uniformity was estimated using solid dispersion of 100 mg equivalent of aceclofenac in 0.1 M, 7.4 pH buffer as solvent. The estimation was done in a UV/Vis spectrophotometer.

Evaluation of solid dispersion

FT-IR study of pure drug and all preparations [13]

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For FT-IR study, the pellets have been prepared of all the formulation and Aceclofenac using KBr. The pellets were subjected to FT-IR instrument 'Perkin Elmer FTIR spectrometer, spectrum 1000 Germany' for the collection of IR spectra.

Table 1. Details of formulations

Formulation Codes	Carrier	Drug: Carrier	Method
PMPEG	PEG 6000	1:1	Physical mixture
SDPEG1		1:1	Solid dispersions
SDPEG2		1:5	(Solvent method)
SDPEG3		1:9	
PMPVP	PVP	1:1	Physical mixture
SDPVP1		1:1	Solid dispersions
SDPVP2		1:5	(Solvent method)
SDPVP3		1:9	
PMM	Mannitol	1:1	Physical mixture
SDMS1		1:1	Solid dispersions
SDMS2		1:5	(Solvent method)
SDMS3		1:9	
SDMF1		1:1	Solid dispersions
SDMF2		1:5	(Fusion method)
SDMF3		1:9	

Table 2: Physical Characters and Solubility of formulations (PMs and SDs) in distilled water

Formulations	Nature of the formulation	Drug solubility in water mg/ml (±SD ,n=3)
PURE DRUG	White crystalline powder	0.088±0.015
PMPEG	Off white sticky particles	0.152±0.012
SDPEG1	Off white sticky, soft particles	0.318±0.011
SDPEG2	Solid sticky lumps	-
SDPEG3	Solid sticky lumps	-
PMPVP	White free flowing powder	0.126±0.011
SDPVP1	White free flowing powder	0.293±0.010
SDPVP2	White free flowing powder	0.244±0.010
SDPVP3	White free flowing powder	0.206±0.011

Physical characterization and saturation solubility study [8]

Excess amount of the formulations (PMs and SDs) was added to conical flask containing 10 ml of distilled water and subjected to shaking on a rotary shaker for 48 hours at 37°C. Then the flasks were removed and filtered. Suitable aliquots were withdrawn from the filtered solution and analyzed for the drug content after appropriate dilution with distilled water and compared with pure drug solubility.

Drug content analysis

Preparations equivalent to 20 mg was weighed accurately and transferred to 100 ml volumetric flask and dissolved in phosphate buffer pH 7.4. The volume was made up with phosphate buffer pH 7.4 up to the mark. After suitable dilution, the absorbance of the above solution was measured at 274 nm using appropriate blank solution. The drug content of Aceclofenac was calculated using calibration curve.

In vitro Release studies [5-7]

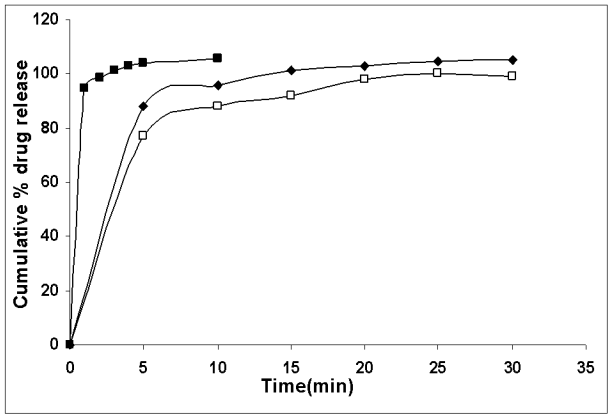
Accurately weighted amount of sample was taken for dissolution studies. An aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 273.5 nm (distilled water was used as dissolution medium) or 274 nm (phosphate buffer pH 6.8 was used as dissolution medium). The volume withdrawn at each time intervals replaced with same amount of fresh quantity of dissolution medium.

Stability studies

Stability studies of selected formulations were carried out by keeping them at ambient room temperature conditions for 3 months. All the formulations were subjected to physical examination and drug content analysis before and after stability studies.

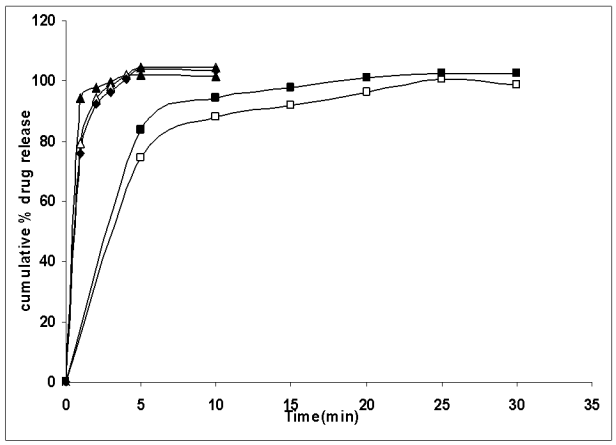
Statistical analysis

Each tablet formulation was prepared in duplicate, and each analysis was duplicated. Effect of formulation variables on disintegration time and release parameters ($t_{50\%}$ and $t_{80\%}$) were tested for significance by using analysis of variance (ANOVA: single factor) with the aid of Microsoft® Excel 2002. Difference was considered significant when P <0.05.



Key: - Pure drug (□); PMPEG1 (◆); SDPEG (■)

Fig.1: Dissolution profiles in phosphate buffer pH 6.8 of ACL: PEG



Keys: - Pure drug (□); PMPVP (■); SDPVP1 (▲); SDPVP2 (△); SDPVP3 (◆)

Fig. 2: Dissolution profiles in phosphate buffer pH 6.8 of ACL: PVP formulations

RESULTS AND DISCUSSION

Aceclofenac is practically insoluble in water as the intrinsic solubility of ACL in pure water at room temperature is found to be 0.088 mg/ml.

Physical characterization and Saturation Solubility study

Among PMs and SDs (1:1) containing both the carriers, PEG containing PM and SD showed highest saturation solubility. This may be due to the inherent differences between the carriers in terms of hydration, dissolution and possible Complexation of drug with different carriers.

Fig. 3: IR Spectra of PVP and its solid dispersion

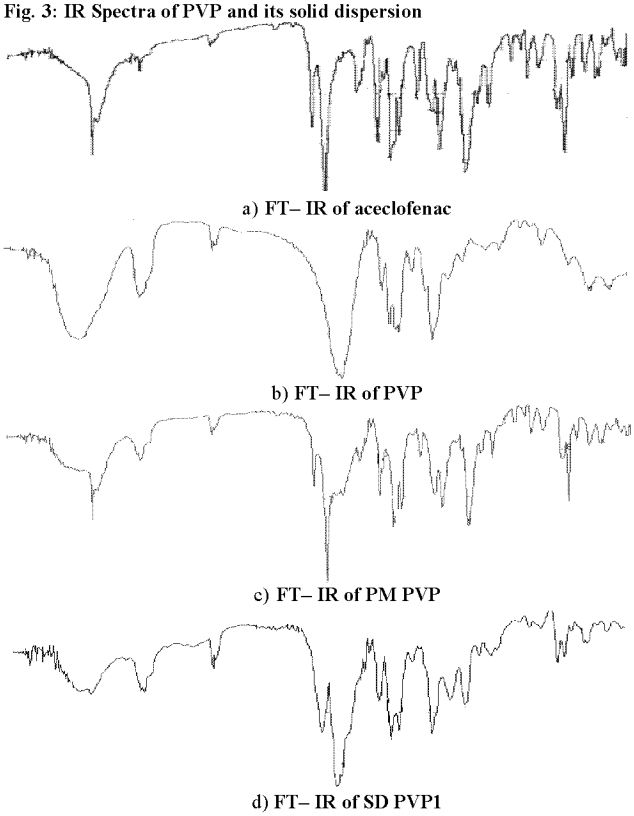
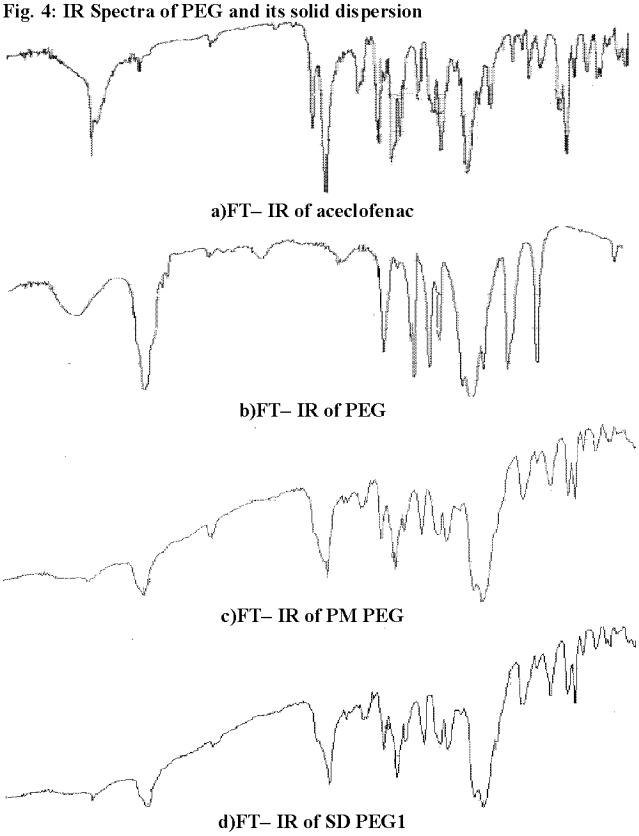


Fig. 4: IR Spectra of PEG and its solid dispersion



IR spectroscopy

These significant changes indicate the possibility of intermolecular hydrogen bonding between the –NH group of Aceclofenac and –OH group of PEG 6000. Comparison of spectra of PMPEG and SDPEG1 with drug and carrier indicated significant changes. However, although little shifts in the stretching vibration due to –CH2 groups (of PEG 6000) appeared at two different wave numbers 2879.5 cm-1, and 2875.75 cm-1 respectively Suggesting possible difference in the degree of interaction between drug and carrier in PM and SD.

A decrease in the intensity of peak of –NH group of Aceclofenac (at 3319.3 cm-1) or ternary amide peak of PVP (at 1642.3 cm -1) may support intermolecular hydrogen bonding between drug and carrier in both physical mixture and solid dispersion. A decrease in the intensity of bands may also be due to the amount of compounds. Thus it can be concluded with some reservation, the absences of interaction between two compounds by FTIR

Drug content analysis

Drug content is found to be between 94.52 % and 104.83 %. All the PMs and SDs shows presence of high drug content and low standard deviations of results. It indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for the preparation of SDs.

In vitro dissolution study

Dissolution rate of Aceclofenac did not increase with the increase in the concentration of carriers when the dissolution test was carried in phosphate buffer pH 6.8. This may be due to high solubility (5.236 mg/ml) of Aceclofenac in phosphate buffer pH 6.8. Therefore, dissolution tests were carried out in distilled water. Dissolution of the Aceclofenac increased with increasing proportions of carriers and $T_{50\%}$ and $T_{70\%}$ values were least with the SDs of PVP (i.e.1:1-1:9). These observations indicate the enhanced dissolution of SDs with increase in the concentration of carriers possibly due to the increased wettability of the drug by the carrier, drug particle size reduction in the course of the solid dispersion preparation, polymorphic transformation of drug crystals and chemical interactions between drug and carrier.

Stability studies

Formulation (SDPEG1, SDPVP3) which showed promising results, were subjected to stability studies at ambient room conditions for 3 months. After 3 months, SDs did not show any change in physical appearance or drug content. It indicates that the drug was stable in SDs even after three months of short term storage.

Initially solubility studies were conducted to analyze the solubility of Aceclofenac in different solvents/buffers. Formulation studies included the preparation of physical mixtures (PMs) and solid dispersion (SDs) of Aceclofenac with different carrier (PVP, PEG 6000) with solvent method and their physico-chemical characterization using FT-IR spectroscopy, solubility studies, drug content analysis, dissolution studies and stability studies. All the PMs and SDs show high drug content (>94 %). The dissolution of Aceclofenac from the PMs was higher than pure drug. The formulations of Aceclofenac in SDs significantly improved the dissolution of Aceclofenac. SDs of Aceclofenac with the same proportion of PEG 6000 as a carrier was superior in dissolving Aceclofenac compared with PVP. The dissolution of Aceclofenac from SDs of PVP increased with increasing

proportion of carrier from 1:1 to 1:9. Three months stability studies of selected formulations at ambient room conditions showed no change in the physical character and drug content. It is concluded that dissolution of the Aceclofenac could be improved by solid dispersions and PEG 6000 based solid dispersions are more effective in the enhancing the dissolution.

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