ENHANCEMENT OF ORAL BIOAVAILABILITY AND DISSOLUTION RATE OF ACECLOFENAC USING SOLID DISPERSIONS BY DROPPING METHOD

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ABSTRACT

In the present study, the aim was to enhance the oral bioavailability and dissolution rate of aceclofenac by solid dispersions using polyethylene glycol (PEG-6000) as a carrier and to study the effect of carrier on dissolution rate. Initial studies were carried out using physical mixtures of the drug and carrier. Solid dispersions were prepared by fusion technique using dropping method. Aceclofenac was formulated as physical mixtures and solid dispersions (dropping method) using 1:2, 1:4, 1:6 and 1:8 ratios of drug and carrier (PEG 6000). Saturation solubility study for pure drug, physical mixtures and solid dispersions were carried out in water and pH 6.8 phosphate buffer solutions (PBS). The *In vitro* dissolution studies were carried in pH 6.8, higher *in vitro* dissolution of solid dispersions was recorded compared to their corresponding physical mixtures and the pure drug. The prepared solid dispersions were observed that increased in the saturation solubility and dissolution rate of aceclofenac than that of pure drug. PEG 6000 in 1: 8 drug to carrier ratio exhibited the highest drug release (98.69%) formulated as solid dispersions using dropping method. The FT-IR study shows that drug was stable in solid dispersions and there were no interactions. It is concluded that dissolution rate was improved by solid dispersion of aceclofenac: PEG 6000 prepared as 1:8 ratio by dropping method showed excellent physicochemical characteristics and was found to be described by dissolution release kinetics and was selected as the best formulation.

Keywords: Solid dispersions, Aceclofenac, Fusion technique, Dropping method & PEG-6000.

INTRODUCTION

Aceclofenac is a newer derivative of the diclofenac group of non-steroidal anti inflammatory drugs (NSAID) that exhibits analgesic and anti-inflammatory activities. It directly blocks the prostaglandin synthesis. It has less gastrointestinal complications. It is considered to be the first-line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis[1].

Aceclofenac exhibits very slight solubility in water and as consequence it exhibits low bioavailability of aceclofenac Dissolution from its oral solid dosage forms is an important issue for enhancing its bioavailability and therapeutic efficacy[2].

The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug[3, 4]. In case of poorly water soluble drug dissolution rate is rate limiting step in the process of drug absorption, potential bioavailability problem and relevant with extremely hydrophobic drug due to erratic and incomplete absorption from GIT[5]. Potential absorption problem occurs if the aqueous solubility is less than 1mg/ml. Several techniques have been developed for the solubility enhancement of poorly soluble drugs such as solid dispersion[6], inclusion complex[7, 8], ultra rapid freezing process[9], melt sonocrystallization[10], solvent change method[11], melt granulation technique[12], supercritical solvent, supercritical and cryogenic techniques as well as cosolvent approach.

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The increase in dissolution rate from solid dispersions can be attributed to one or a combination of the following factors, a reduction of particle size of the drug, solubilizing effect on the drug by the water soluble carrier, enhancement of the wettability and dispersibility of the drug by the carrier material, and the possible formation of a metastable dispersion that has a greater solubility resulting in a faster dissolution rate[13]. Among the popular carriers used in the formation of solid dispersion are polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP); both polymers are freely soluble in water and are available in various molecular weights. The molecular size of both polymers favors the formation of interstitial solid solutions[14].

A particular advantage of PEGs for the formation of solid dispersions is that they have good solubility in many organic solvents. The melting point of PEGs lies below 65 ^{0}C in all cases[15], which is advantageous for the manufacture of solid dispersions. Aceclofenac was chosen as a model candidate because of its low dissolution rate and solubility-limited bioavailability.

MATERIALS AND METHODS

Materials

Aceclofenac was a gift sample from M/S Seeko Biotech, Vijayawada, A.P, polyethylene glycol 6000 was purchased from Merck, Mumbai, potassium dihydrogen orthophosphate (Qualigens fine chemicals, Mumbai), sodium hydroxide (Finar Chemicals Ltd. Ahmedabad) and methanol (Research-Lab Fine Chemicals Industries, Mumbai). All required chemicals were of analytical grade.

Methods

Preparation of Physical Mixture

Physical mixtures of aceclofenac at four different mass ratios (1:2, 1:4, 1:6 and 1:8) with PEG 6000 was prepared in a glass mortar by light trituration for 5 minutes. The mixtures were passed through a sieve no: 60. The prepared mixtures were then filled in hard gelatin capsules, sealed and stored in a dessicator until further use. The composition of PM1, PM 2, PM 3 and PM 4 formulations and shown in Table I.

Preparation of Solid Dispersion by Dropping Method

For the preparation of the aceclofenac solid dispersions prepared by dropping method, containing different weight ratios of aceclofenac in PEG 6000. The composition of SD1, SD2, SD3 and SD4 formulations was shown in Table I. The PEG was melted in a porcelain dish at 58 ^{0}C (±1^{0}C) and a measured amount of aceclofenac was added and stirred. The melted drug–carrier mixture was pipetted and placed into an adjustable heating device to keep the temperature constant. The melted drug–carrier mixture was dropped onto a stainless steel plate, where it solidified into round particles. The temperature of the stainless steel plate was <20 ^{0}C. The round particles (equivalent to 100 mg of aceclofenac) were placed into hard gelatin capsules (size no. 2) for further investigations.

Physicochemical Characterization

Phase solubility studies

Phase and saturation solubility studies were performed according to the method described by Higuchi and Connors[16].The saturation solubility of drug and SDs with PEG 6000 (1:2, 1:4, 1:6 and 1:8 w/w) in distilled water and phosphate buffer (pH 6.8) were determined by adding an excess of drug and SDs to 50 ml distilled water or Phosphate buffer in conical flask and were rotated in a orbital shaking incubator for 96 hrs at 37 ^{0}C ±0.5 ^{0}C. The saturated solutions were filtered through a 0.45 µm membrane filter, suitably diluted with water, phosphate buffer and analyzed by UV spectrophotometer at 275nm, Lab India Double Beam UV-3000+, India.

FT-IR Spectroscopy

Fourier transmitted Infrared (FT-IR) spectroscopy was conducted using Thermo Nicolet Nexus 670 Spectrophotometer and the spectrum was recorded in the wavelength region of 4000 to 500 cm^{-1}. The procedure consisted of dispersing a sample (drug

alone or mixture of drug and excipients) in KBr and compressing into discs by applying a pressure. The pellet was placed in the light path and the spectrum was obtained.

Drug content estimation[17]

The drug content in each solid dispersions and physical mixture was determined by the UV-spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 100 mg of Aceclofenac, was transferred to a 100 mL volumetric flask containing 10 mL of methanol and dissolved. The volume was made up to 100 mL with pH 6.8. The solution was filtered and the absorbance was measured after suitable dilutions by using Lab India Double Beam UV-Spectrophotometer at 275nm.

$$\% \text{ drug content} = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

In vitro drug dissolution studies

Dissolution rate studies were performed in pH 6.8 phosphate buffer at 37 ± 0.5 ^{0}C, using USP type-II apparatus with paddle rotating at 75 rpm. Solid products, solid dispersions as well as physical mixtures, each containing 100 mg of drug were subjected to dissolution. At fixed time intervals, samples withdrawn were filtered and spectrophotometrically analyzed at 275 nm. Each test was performed in triplicate (n=3). The similarity factor (f2) was evaluated to compare Aceclofenac release profiles.

$$f2 = 50 \log \{[1+1/n \sum_{t=1}^{n} (Rt - Tt)^2]^{-0.5} \times 100\}$$

Where Rt and Tt were the cumulative percentage of drug released for reference and test assay at time t respectively, n was the number of time points. The FDA suggests that two dissolution profiles are declared to be similar if the value of *f2* is between 50 and 100[18, 19].

RESULTS AND DISCUSSION

The drug content in physical mixtures, solid dispersions with PEG 6000 as reported in Table II were found to be in the range of 98.56% to 101.62%. Therefore, dropping method used in this study appears applicable for the preparation of solid dispersions without affecting drug content.

When the physical mixture is added to the dissolution medium, it may simply happen that the carrier, which dissolves first, modifies the hydrophilicity/lipophilicity or wettability of the drug or it may form a weak complex with the drug at the particle surface, resulting in drug dissolution. An increase in the saturation solubility of the drug can explain the improved dissolution of solid dispersions as per the Noyes and Whitney equation[20], since the saturation solubility of a compound is dependent on the size of the particles. Since it is possible to achieve reduction in particle size with a solid dispersion system, the saturation solubility studies were performed with these systems. The results on saturation solubility indicated that the solubility was enhanced by 53 % compared to aceclofenac.

Solubility Studies

As the solid dispersion is a metastable form and tends to transform in to the stable form, the drug concentration may tend to decrease with elapse of time during the solubility test. In order to avoid this problem all the solubility test samples of the different formulations were with drawn and analyzed at established time (96hrs). This allowed readily comparing the solubility of different solid dispersions. The solubility of different concentrations of drug and carrier was observed and the prepared formulation with PEG 6000 1:8 presented higher dissolution concentration as compared with the other formulations obtained with different ratios (1:2, 1:4 and 1:6). Maximum solubility in phosphate buffer solution was observed in dropping method 1:8 (Drug: PEG 6000) ratio 103.5 ± 1.14 µg/mL, when compared with that of pure aceclofenac (55.47 ± 1.15 µg/mL).

Table I : Composition of Aceclofenac Physical Mixtures and Solid Dispersions

Ingredients (mg)	PM1	PM2	PM3	PM4	SD1	SD2	SD3	SD4
Aceclofenac	100	100	100	100	100	100	100	100
PEG-6000	200	400	600	800	200	400	600	800

Table II : Solubility studies and drug content for pure drug, physical mixtures and solid dispersions

Formulation code	Solubility (µg/mL)		Drug content (%)
	Water	PBS	
Pure drug	27.04 ± 0.56	55.47 ± 1.15	98.56±0.023
PM-1	36.45 ± 1.22	64.63 ± 1.31	98.85±0.012
PM-2	56.77 ± 1.34	73.47 ± 1.15	99.95±0.025
PM-3	62.49 ± 1.25	82.69 ± 1.21	100.69±0.022
PM-4	75.69 ± 1.22	90.73 ± 0.88	101.24±0.031
SD-1	47.32 ± 1.05	75.56 ± 1.01	100.24±0.021
SD-2	58.66 ± 1.37	81.77 ± 1.13	101.05±0.013
SD-3	67.72 ± 1.51	97.52 ± 1.16	99.97±0.026
SD-4	78.52 ± 1.05	103.5 ± 1.14	101.62±0.041

Table III : Dissolution Kinetics of ACECLOFENAC Physical Mixtures and Solid Dispersions Formulated With PEG-6000

Formulation code	Correlation Coefficient (R^2)					$T_{50\%}$	$T_{90\%}$	Slope (n)
	Zero order	First order	Higuchi	Peppas	Hixson Crowell			
PM-1	0.9415	0.9291	0.9242	0.9142	0.9242	46	>60	0.512
PM-2	0.9524	0.9456	0.9382	0.9234	0.9627	40	85	0.524
PM-3	0.9376	0.9232	0.8972	0.8945	0.9545	36.4	73	0.509
PM-4	0.9476	0.9542	0.9247	0.9252	0.9375	29.2	64	0.476
SD-1	0.9525	0.9673	0.8872	0.8749	0.9248	31.3	70.6	0.550
SD-2	0.9582	0.9756	0.9412	0.8871	0.9576	28.4	60.3	0.547
SD-3	0.9626	0.9865	0.9055	0.8783	0.9611	20.2	52.5	0.523
SD-4	0.9722	0.9897	0.8623	0.8753	0.9772	15	43.7	0.567

$T_{50\%}$ and $T_{90\%}$ in min

In Vitro drug release

The dissolution profiles of aceclofenac for solid dispersion and physical mixture performed in 6.8 phosphate buffer were studied. The comparative cumulative release of aceclofenac at various time intervals from the physical mixtures and solid dispersions made by using various concentrations of PEG 6000 are shown in Fig. 1&2. Dissolution of the pure drug, aceclofenac, in PBS (pH 6.8) was only 47.12%. Prepared physical mixtures and solid dispersions showed improvement in dissolution characteristics. In the first 30 minutes, physical mixtures of PEG 6000 (1:2, 1:4, 1:6 and 1:8) showed 34.5, 40.1, 43.2 and 51.5 % drug released 48.3, 52.5, 61.2 and 70.5 % drug released from solid dispersions (1:2, 1:4, 1:6 and 1:8). After 50 min, physical mixtures with PEG 6000 showed 61.8, 67.6, 75.6 and 83.5 % drug released, whereas solid dispersions with PEG 6000 showed 71.2, 78.8, 86.8 and 98.8 % drug release, respectively.

Dissolution of the pure drug was found to be 47.12 % in 50 minutes. Almost half of the drug was dissolved from physical mixtures and solid dispersions in the first 30 minutes. After 50 min, physical mixture with PEG 6000 (1:8) showed 83.5 % release whereas maximum release was obtained solid dispersion with PEG 6000 (1:8) and was 98.87%.

Possible mechanisms of increased dissolution rates of solid dispersions have been proposed by Ford[21]. A reduction of crystallite size, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of the drug from the dispersion, dissolution of the drug in the hydrophilic carrier, drug conversion to amorphous state and finally, a combination of the mentioned mechanisms. The increased dissolution rate in these cases can thus be attributed to several factors, such as the solubilization effect of the carrier, conversion to amorphous state, and improved wettability of aceclofenac. In general, dissolution may be described by two processes: the rate of the interfacial or solid solvent reaction leading to solubilization of the molecule, and the rate associated with the diffusional

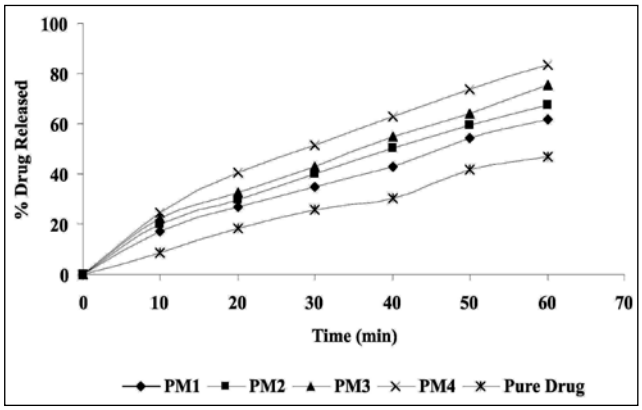

Fig. 1: Comparison of Dissolution Profiles Using PEG-6000 by Physical Mixtures with Pure Drug

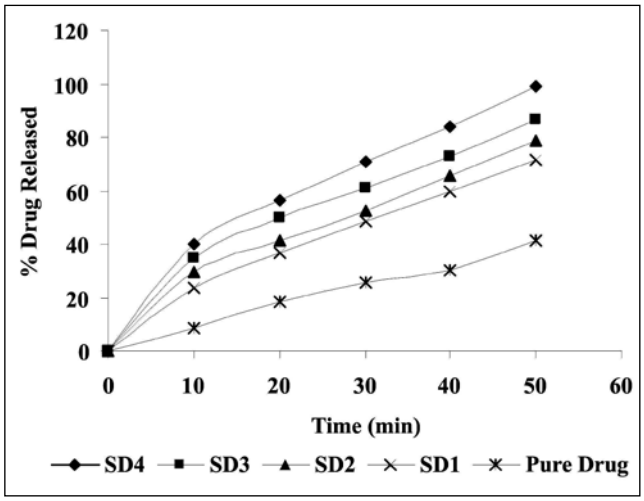

Fig. 2 : Comparison of Dissolution Profiles Using PEG-6000 by solid dispersions with Pure Drug

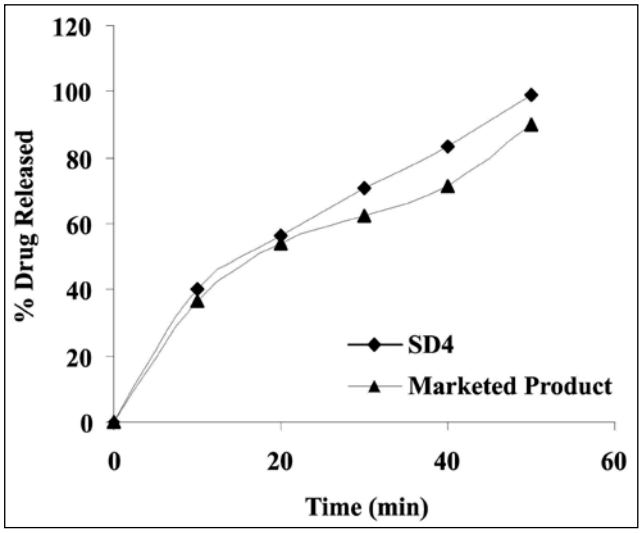

Fig. 3 : *In-vitro* Dissolution Profiles of Aceclofenac Solid Dispersion (SD4) And Marketed product (Lessen)

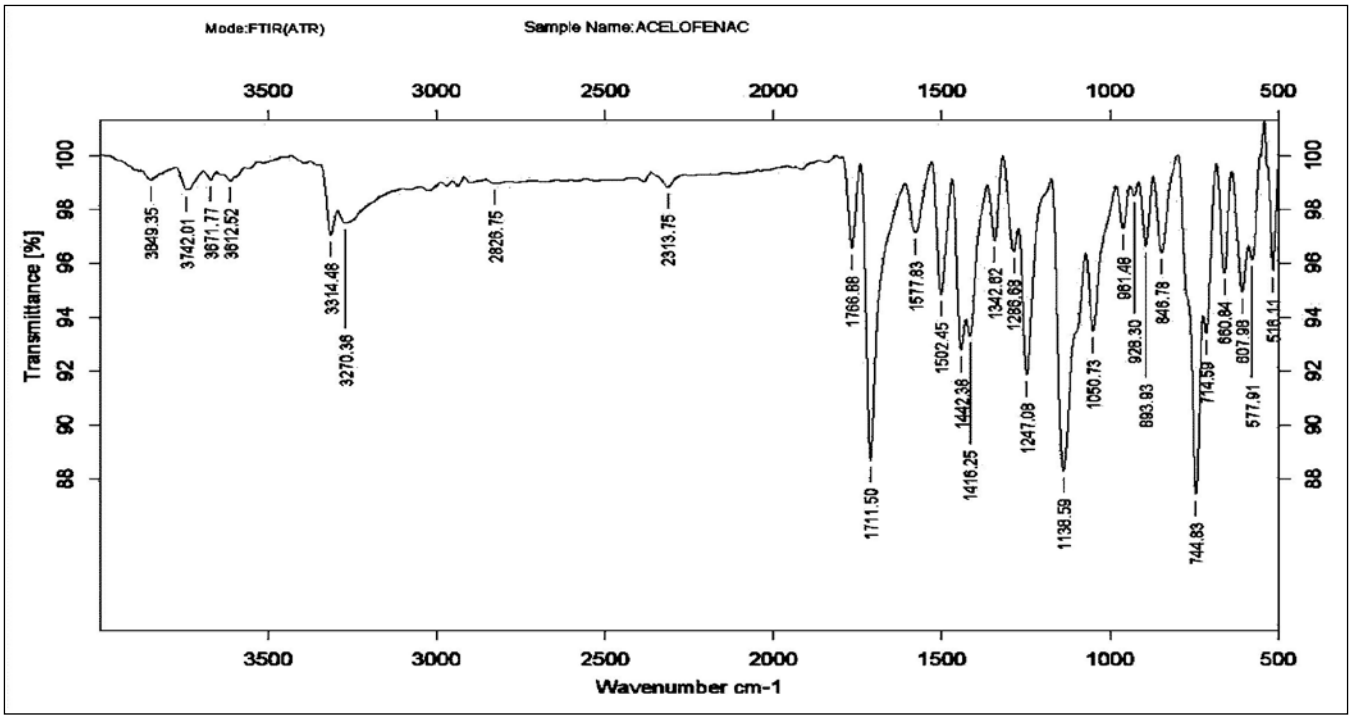

Fig. 4 : FT-IR Spectra of Aceclofenac

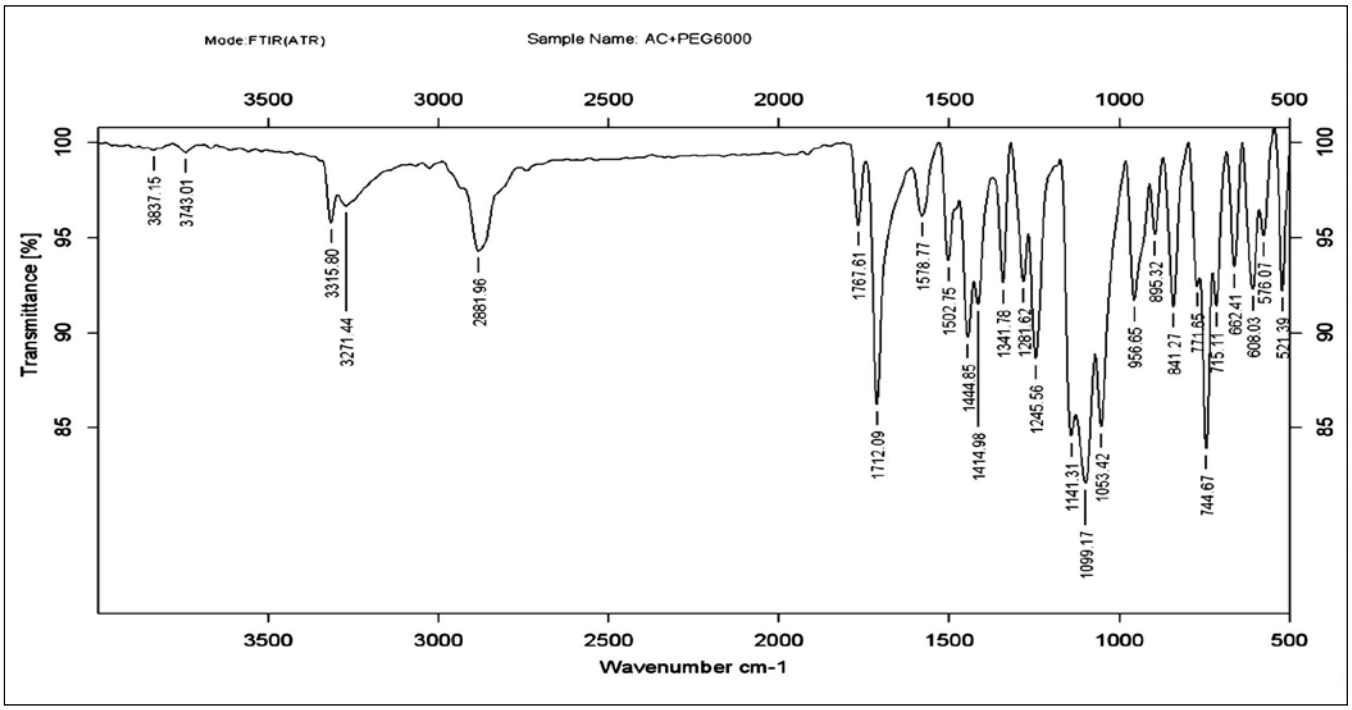

Fig. 5 : FT-IR Spectra of ACECLOFENAC & PEG-6000 Mixture

or transport process of the solvated molecule to the bulk part of the dissolution medium. The strength of bonds between water and PEG and water and drug molecules may be stronger than or comparable with that between the molecules of the solid dispersions[22]. Upon contact, water molecules solvate the carriers

and aceclofenac molecules, either in the crystalline or in amorphous form, and break the hydrogen bonds in the drug-carrier complexes.

The drug release from all the formulations followed first order kinetics, as the plot observed in between log% of undrug released Vs time was found to be linear. The corresponding release rate constant values were shown in Table III. To analyze the mechanism of drug release from these formulations, the data followed Hixson Crowell equation ({fraction unreleased} $^{1/3}$ vs. time). The release rate kinetic data, $T_{50\%}$ & $T_{90\%}$ for these formulations were given in Table III. The slope values (n) obtained show decline between 0.476 to 0.567 for all formulations for the release of aceclofenac, indicating non-fickian diffusion. The dissolutions profile showed in (fig. 3) and similarity factor (f_2), these two formulations were found to be 89.34% indicating the significant differences in between the selected (SD4) and marketed tablet (Lessen). The above results indicated that the increasing concentration of PEG-6000 content enhanced the drug release. The release kinetics of aceclofenac prepared from different methods of solid dispersions was observed and tabulated.

Spectroscopy studies

The IR spectra of pure Aceclofenac and solid dispersions are shown in Fig. 4 and 5. The IR spectra of pure Aceclofenac showed characteristic peaks at C-H-(bending) 1342.62cm^{-1}, 1442.38cm^{-1}, 1502.45cm^{-1}.

C-O-(stretching) 1050.73 cm^{-1}, 1138.53 cm^{-1}.

C=O-(stretching) 1711.50cm^{-1}.

C-N (Amine) 1286.68cm^{-1}.

N-H-(stretching) 3314.48cm^{-1}.

There might be a possibility of intermolecular hydrogen bonding between adjunct aceclofenac molecules. The spectrum of pure aceclofenac was equivalent to the spectra obtained by the addition of carrier. This indicated that no interaction occurred with a solid dispersion of drug and lipid carriers. The results revealed no considerable changes in the IR peaks of aceclofenac, when mixed with carrier PEG-6000. These observations indicated the compatibility of PEG-6000 with aceclofenac.

CONCLUSION

The prepared solid dispersions were examined to various characterizations. The solubility and dissolution studies showed there is a possibility of improved solubility of aceclofenac through solid dispersion with Poly ethylene glycol 6000. The dissolution rate of aceclofenac from solid dispersions with PEG 6000 improved to more than 57.5 % compared to the pure drug. Further, all the solid dispersions performed better than the corresponding physical mixtures. Also, the saturation solubility of the drug when formulated into solid dispersion with the carrier was higher than that of phase solubility achieved in the presence of the carrier (physical mixture). IR spectra indicated no well-defined interaction between the drug and carrier. A maximum increase in dissolution rate was obtained with aceclofenac: PEG 6000 solid dispersion with a weight ratio of 1:8. PEG 6000 dispersion by dropping method showed faster dissolution rate when compared with that of physical mixtures of various concentrations and pure drug.

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