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Formulation and Evaluation of Aceclofenac Solid Dispersions for Dissolution Rate Enhancement

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ABSTRACT
Aceclofenac is a novel non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties, and is widely used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersions (SDs) of Aceclofenac were prepared using lactose, mannitol and urea to increase its aqueous solubility. Aceclofenac SDs was prepared in 9:1, 7:3 and 4:1 ratios of the drug to polymer (by weight). *In vitro* release profiles of all SDs (F-1 to F-9) were comparatively evaluated and also studied against pure Aceclofenac. Faster dissolution was exhibited by solid dispersion containing 9:1 ratio of drug: lactose. The increase in dissolution rate of the drug may be due to increase in wettability, hydrophilic nature of the carrier and due to reduction in drug crystallinity. The prepared solid dispersion was subjected for % practical yield, drug content and infrared (IR) spectroscopic studies. Absence of significant drug-carrier interaction was confirmed by infrared spectroscopic (IR) data.

Keywords: Aceclofenac, Lactose, Mannitol, Urea, Carriers, Solid dispersion.

INTRODUCTION

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration. Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization, and addition of solvent or surface-active agents. SDs is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The concept of solid dispersions (SDs) was introduced in 1961 by Sekiguchi and Obi [1], in which the drug is dispersed in inert water - soluble carrier at solid state. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone (PVP) and polyethylene glycols are used as carriers for SDs. [2-5] Aceclofenac is a new generation NSAID used in the treatment of osteoarthritis, rheumatoid arthritis and other joint diseases. It is chemically designated as 2-[[2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid. Solid dispersions of aceclofenac were formulated to overcome problems like gastric irritation and other side effects that are frequently experienced with NSAID drug therapy. Aceclofenac is practically insoluble in water leading to poor dissolution and variable bioavailability upon oral administration. [6-9] The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Aceclofenac by preparing SDs with various water-soluble polymers such as mannitol, lactose and urea. The prepared SDs were evaluated for % practical yield, drug content, *in vitro* dissolution rate studies and interactions between the drug and polymer using IR spectral studies.

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MATERIALS AND METHODS

Aceclofenac having purity of 99.3 % was a generous gift from Ipca Laboratories, Mumbai. Mannitol, Lactose and Urea of pharmacopoeial grade were purchased from SD Fine Chemicals Ltd, Mumbai. All reagents were of A.R. grade. Double distilled water was used for all the experiments.

Estimation of aceclofenac

Aceclofenac contents were estimated by UV Spectrophotometric method by measuring the absorbance at 275 nm. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beers law in the concentration range of 2-10 µg/ml (r = 0.9985). When a

standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variation were found to be 0.90 % and 1.2 % respectively.

Preparation of solid dispersions (SDs)

Aceclofenac solid dispersions were prepared by using carriers (i.e. mannitol, lactose and urea) in proportions viz. 4:1, 7:3 and 9:1 (drug: carrier). The drug and carrier was dissolved in dichloromethane and triturated in dry mortar until the solvent evaporated and a clear film of drug and carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and passed through a 250µm sieve before packing in an airtight container. [10]

% Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation. [11]

$$PY\ (\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + carrier)}} \times 100$$

Drug content

Solid dispersions equivalent to 10 mg of Aceclofenac were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 275 nm by UV spectrophotometer. [12] The Actual Drug Content was calculated using the following equation as follows:

$$\%\ \text{Drug content} = \frac{M_{act}}{M_{ss}} \times 100$$

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

Infrared spectroscopy

IR spectra of pure Aceclofenac, mannitol, urea, lactose and Aceclofenac with its solid dispersions were obtained by a Perkin-Elmer Fourier transform infrared spectrophotometer using KBr pellets. KBr pellets were prepared by gently mixing the sample with KBr (1:100). The scanning range used was 4000 to 400cm^{-1}.

***In vitro* drug release studies**

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its *in vivo* behavior. *In vitro* release profile for each solid dispersion as well as pure drug were performed using USP XXII type 2 dissolution apparatus (TDP-06P, Electro lab, Mumbai, India). Sample equivalent to 100 mg of Aceclofenac was added to 900 ml phosphate buffer pH 6.8 at 37± 0.5ºC and stirred at 50 rpm. Aliquot of 5ml was withdrawn at time intervals of 5, 10, 15, 20, 30, 45, 60 and 90 min. The withdrawn volume was replaced with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at λ_{max} 275 nm after suitable dilution if necessary, using appropriate blank.

Drug release pattern from SDs

In order to understand the mechanism and kinetics of drug release, the results of the *in vitro* drug release study were fitted with various kinetic equations like zero order (cumulative percent drug released vs. Time), first order (Log cumulative percent drug retained vs. Time), Higuchi (cumulative percent released vs. √T), Peppas (log of cumulative percent drug released Vs. log Time) and Hixson-Crowell's cube root model ((Percentage Retained) $^{1/3}$ Vs. Time). The kinetic model that best fits the dissolution data was evaluated by comparing the regression coefficient (r) values obtained in various models. Peppas model used 'n' value to characterize different release mechanisms. The values of n = 0.5 for Fickian diffusion, between 0.5 to 1.0 for non-Fickian diffusion and n = 1 for zero order. [13]

RESULTS AND DISCUSSION

SDs of aceclofenac was prepared by using carriers like mannitol, lactose and urea. In the present work, nine formulations were prepared and their complete composition is shown in Table 1. All the SDs prepared was found to be fine and free flowing powders. The results of % practical yield studies are shown in Fig. 1. Percent practical yield for all formulations of solid dispersions found to be 90.06-97.92 %. The results of % practical yield studies are shown in Fig. 3. Maximum yield was found to be 97.92 % in F6. Actual drug content of all nine formulations are shown in Fig. 2.

The drug content of the prepared SDs was found to be in the range of 48.39- 83.63 %. Maximum % drug content was found in the formulation F-8 (7:3). Percent drug content decreased as the amount of drug added to each formulation increased (4:1 and 9:1 ratio of drug: carrier). The release data obtained for formulations F-1 to F-9 are tabulated in

Table 1: Formulation Plan of Aceclofenac Solid Dispersions

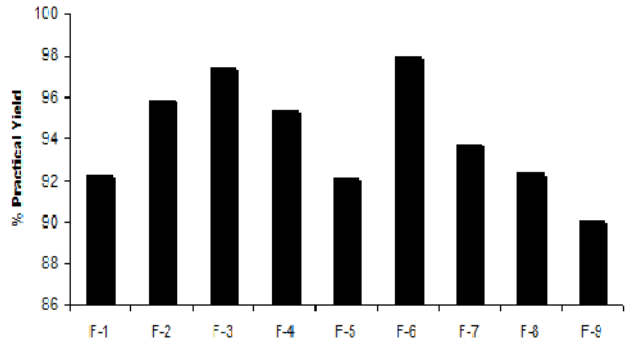
S. No	Formulation	Composition	Drug: polymer
1	F-1	Aceclofenac + Mannitol	4: 1
2	F-2	Aceclofenac + Lactose	4: 1
3	F-3	Aceclofenac + Urea	4: 1
4	F-4	Aceclofenac + Mannitol	9: 1
5	F-5	Aceclofenac + Lactose	9: 1
6	F-6	Aceclofenac + Urea	9: 1
7	F-7	Aceclofenac + Mannitol	7: 3
8	F-8	Aceclofenac + Lactose	7: 3
9	F-9	Aceclofenac + Urea	7: 3

Table 2: *In Vitro* Dissolution Profile of Pure Drug and Different Formulations of Aceclofenac Solid Dispersions

Time (min)	Cumulative percentage drug released									
	Pure drug	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0	0
5	4.72	42.15	31.40	36.04	40.08	46.35	56.06	36.04	37.30	44.26
10	10.57	45.73	33.30	37.72	52.90	56.48	66.60	44.47	42.78	46.79
15	12.13	50.16	33.93	38.99	55.01	64.28	73.76	48.89	45.94	50.37
20	14.12	54.80	35.62	40.46	58.38	70.39	75.24	51.00	49.10	54.37
25	17.69	55.64	35.83	42.15	59.64	72.50	77.98	55.43	53.11	56.69
30	25.66	57.32	36.67	43.62	62.38	81.35	79.03	56.27	54.37	57.75
45	29.71	72.50	40.67	47.63	70.81	87.89	84.09	65.33	59.43	60.91
60	33.56	72.50	43.20	50.16	76.93	95.60	88.10	72.92	62.59	67.23
90	37.52	72.92	44.89	53.53	80.09	99.23	94.00	83.88	68.71	72.50

Table 3: Kinetics of *In vitro* Release from Different Formulations of Aceclofenac Solid Dispersion (Using regression coefficient(r) and 'n' value)

Formulations	'r' values					'n' value
	Zero order	First order	Hixson-Crowell	Highuchi	Peppas	
Pure drug	0.9390	0.9406	0.9580	0.9760	0.9823	0.2360
F1	0.9036	0.9123	0.9104	0.9527	0.9686	0.2205
F2	0.9723	0.9764	0.9758	0.9885	0.9681	0.1316
F3	0.9791	0.9866	0.9854	0.9955	0.9749	0.1459
F4	0.9340	0.9738	0.9703	0.9787	0.9878	0.2283
F5	0.9605	0.9900	0.9950	0.9919	0.9978	0.2971
F6	0.9045	0.9199	0.9719	0.963	0.9866	0.1682
F7	0.9809	0.9912	0.9969	0.9975	0.9936	0.2848
F8	0.9515	0.9786	0.9667	0.9915	0.9984	0.2152
F9	0.9682	0.9876	0.9823	0.9940	0.9878	0.1769



Figurel :Plot of % Practical Yield for Different Formulations of Aceclofenac Solid Dispersions

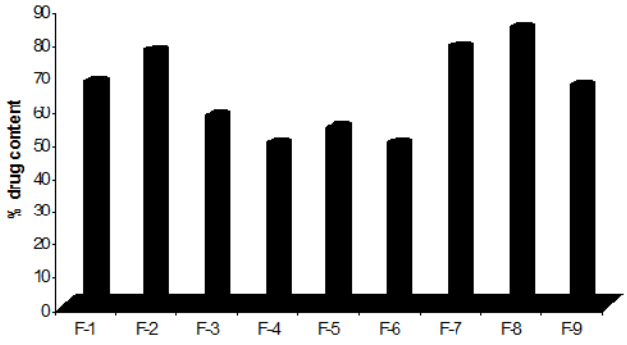


Figure2: % Drug Content of Different Formulations of Aceclofenac Solid Dispersions

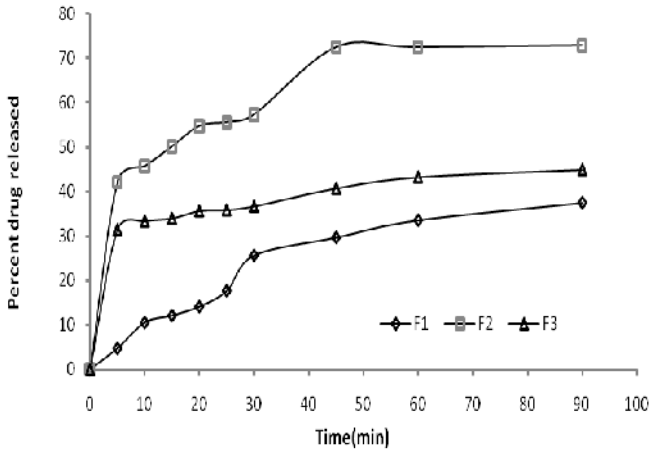


Fig. 3: *In vitro* Dissolution Profile of Solid Dispersion of Aceclofenac in Phosphate Buffer pH 6.8 (F-1 to F-3) (4:1 ratio)

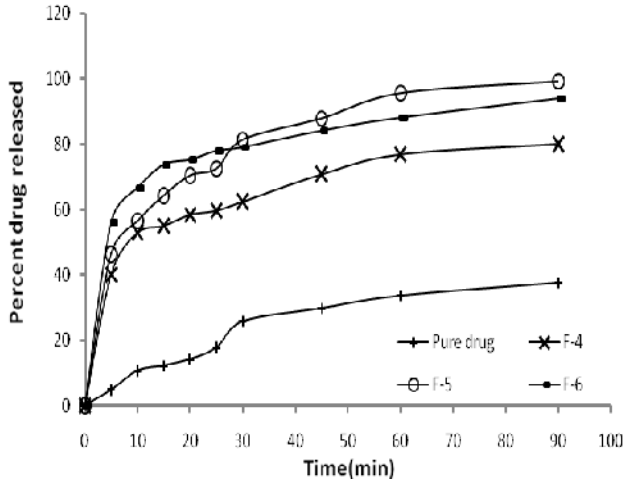


Fig. 4: *In vitro* Dissolution Profile of Solid Dispersion of Aceclofenac in Phosphate Buffer pH 6.8 (F-4 to F-6) (9:1 ratio)

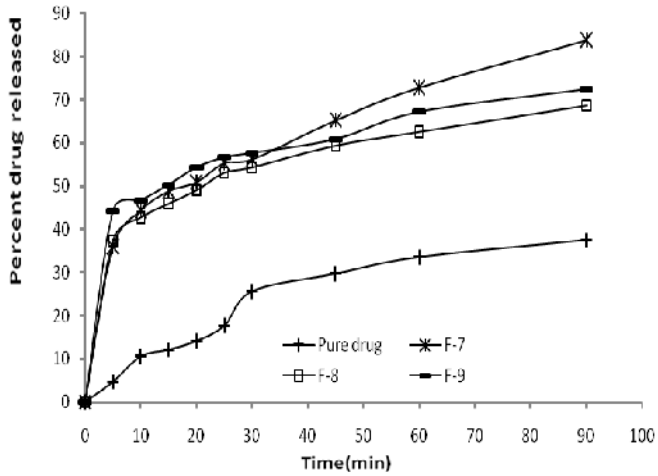


Fig. 5: *In vitro* Dissolution Profile of Solid Dispersion of Aceclofenac in Phosphate Buffer pH 6.8 (F-7 to F-9) (7:3 ratio)

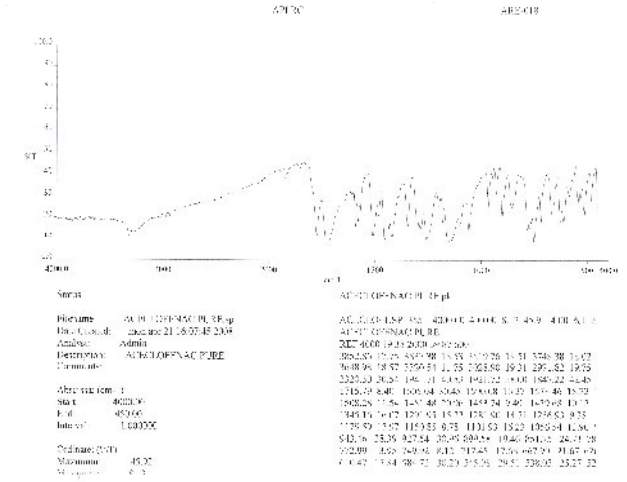


Fig. 6: IR Spectra of solid dispersions of pure Aceclofenac

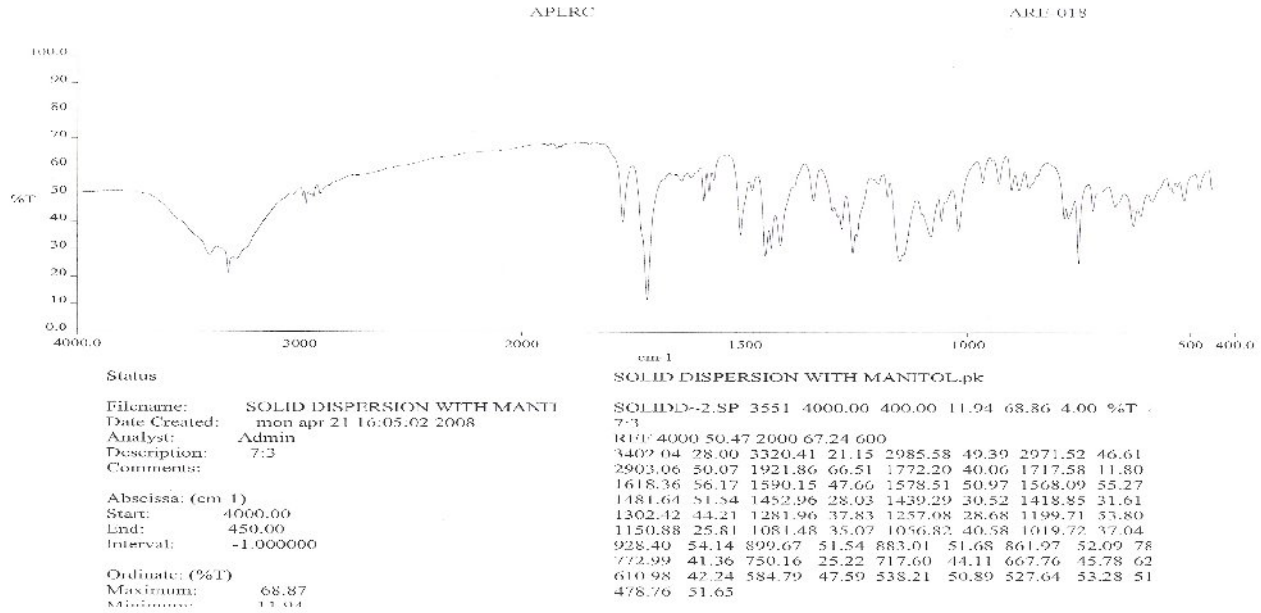


Fig. 7: IR Spectra of solid dispersions of Aceclofenac with mannitol

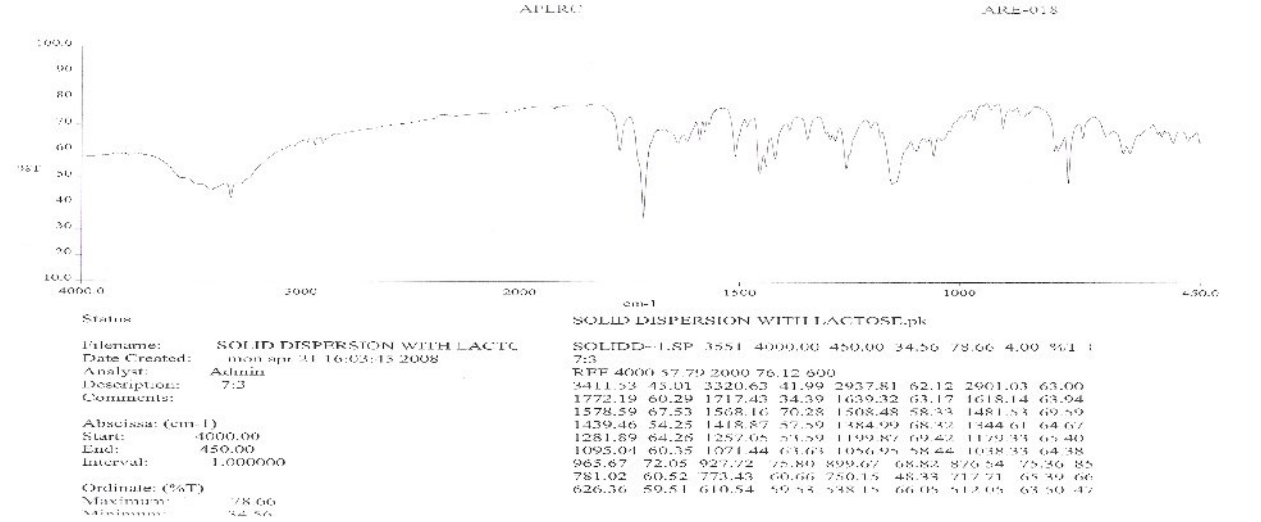


Fig. 8: IR Spectra of solid dispersions of Aceclofenac with lactose

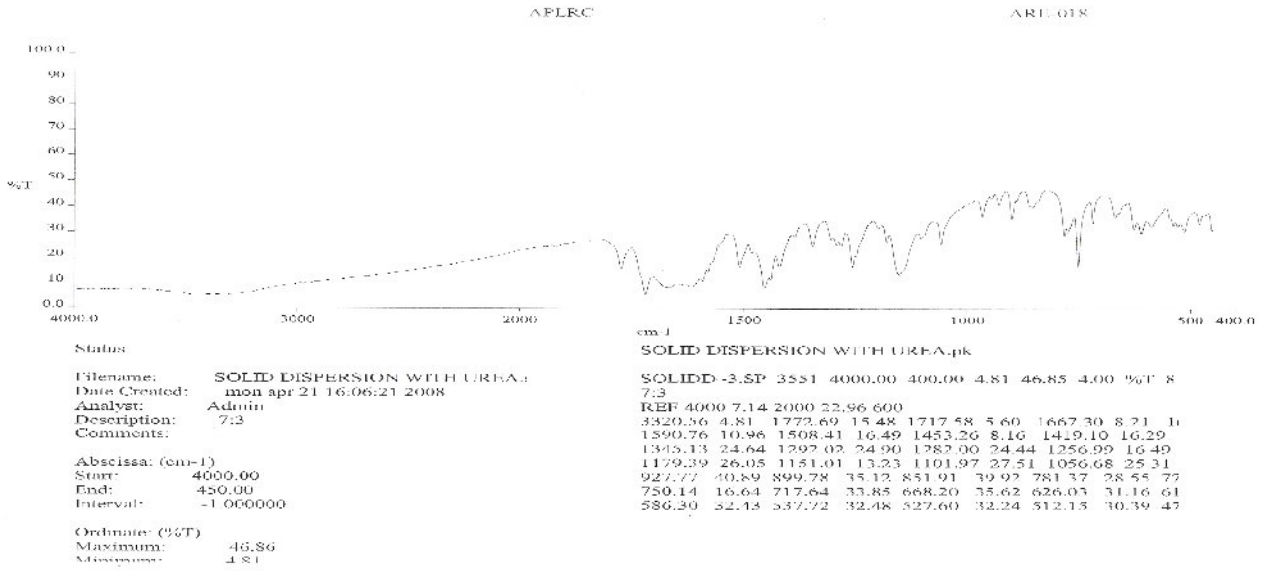


Fig. 9: IR Spectra of solid dispersions of Aceclofenac with urea

Table 2, shows the cumulative percent drug released as a function of time for all formulations. Cumulative percent drug released after 90 min was 72.92 %, 44.89 %, 53.53 %, 80.09 %, 99.23 %, 94.00 %, 83.88 %, 68.71 % and 72.5 % for F-1 to F-9 respectively and was 37.52% in 90 min for pure drug (Fig. 3-5).

In vitro release studies reveal that there is marked increase in the dissolution rate of aceclofenac from all the solid dispersions when compared to pure aceclofenac itself. From the *in vitro* drug release profile, it can be seen that formulation F-5 containing lactose (9:1 ratio of drug: lactose) shows higher dissolution rate compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. The increase in dissolution rate is in the order of Lactose> Mannitol> Urea. In the case of SDs of Aceclofenac with urea, lactose and mannitol ratio of 9:1, the dissolution rate of drug increased while in the case of those prepared in the ratio of 4:1 and 7:3 the dissolution rate of drug was decreased. This might be due to formation of viscous layer around the drug particles leading to decrease in the dissolution rate. The increase in dissolution rate is in the order of F5 >F6>F4 >F7>F1>F9>F8 >F3>F2. The regression coefficient (r) values for formulations F-1 to F-9 are tabulated in Table 3. The model that gave higher 'r' value was considered as best fit model. The 'r' values were found to be higher in the first order model (0.9406, 0.9123, 0.9764, 0.9866, 0.9738, 0.9900, 0.9199, 0.9912, 0.9786, 0.9876) than those in the zero order models (0.9390, 0.9036, 0.9723, 0.9791, 0.9340, 0.9605, 0.9045, 0.9809, 0.9515, 0.9682) with all the SDs(pure aceclofenac , F1, F2, F3, F4, F5, F6, F7, F8 and F9 respectively) indicating that the dissolution of aceclofenac as such and from all the SDs followed first order kinetics. Based on 'r' values (greater than 0.9527) it was also observed that all the SDs followed Higuchi matrix suggesting the drug release by diffusion. The '*n*' values (less than 0.2971) of Peppas suggest Fickian diffusion release and Hixson Crowell regression data ('r' values greater than 0.9104) show that formulations also appear to release drug by erosion mechanism and the release is drug dissolution limited. IR spectroscopic studies conducted for possible drug: carrier interactions IR spectra of pure drug aceclofenac, mannitol, lactose, urea and aceclofenac with its SDs were obtained which shows all the characteristic peaks of aceclofenac and carriers were present in the solid dispersions; thus indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion (Fig. 6-9).

The solid dispersions of the water- insoluble drug aceclofenac were successfully prepared by solvent evaporation technique using hydrophilic carriers. The *in vitro* dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure aceclofenac. Mechanisms involved are solubilization and improved wetting of the drug in the hydrophilic carriers rich microenvironment formed at the surface of drug crystals after dissolution rate. The crystallinity of the drug was reduced in solid dispersion formulation with polymers i.e. urea. Results from IR spectroscopy concluded that there was no well-defined interaction between aceclofenac and carriers. Finally it could be concluded that solid dispersion of aceclofenac using hydrophilic polymers would improved the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.

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