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Enhancement of Dissolution Rate of Aceclofenac by Solid Dispersion Technique

Sachin R. Patil*[1], RaviKumar[1], M.B. Patil[2], Mahesh S.Paschapur[3] and V.S.N.Malleswara Rao[4]

[1]Department of Pharmaceutics, K.L.E.S's College of Pharmacy, Ankola 581314,India,
[2]Department of Pharmacognosy, K.L.E.S's College of Pharmacy,Ankola 581314,India,
[3]Department of Pharmacology, K.L.E.S's College of Pharmacy,Ankola 581314,India.
[4]Research Scholar, Riddet Institute, Massey University, Private Bag 11 222, Palmerston North, New Zealand 4442
Corres. Author: srpatil78@gmail.com

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 were 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 SD 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 also due to reduction in drug crystallinity. The prepared SDs was subjected for percent practical yield, drug content and infrared (I.R) spectroscopic studies. Absence of significant drug-carrier interaction was confirmed by I.R data.
Key words: Aceclofenac, solid dispersion, lactose, mannitol, urea.

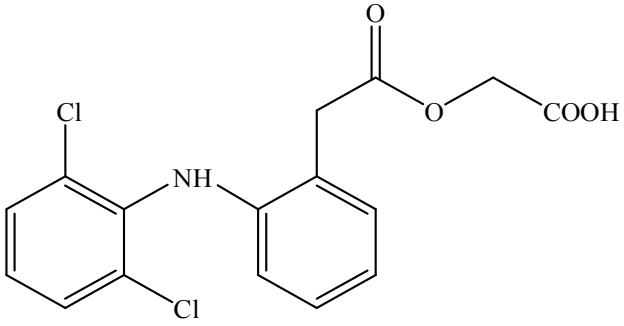
INTRODUCTION

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, therefore efforts to increase dissolution of drugs with limited water solubility is often needed. Many methods are available to improve these characteristics including salt formation, micronization and addition of solvent or surface-active agents. Solid dispersion (SD) 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 SD was introduced by Sekiguchi and Obi[1], in which the drug is dispersed in an inert water-soluble carrier at solid state. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone (PVP) and polyethylene glycols (PEGs) are used as carriers for SDs[2-4].

Aceclofenac is a new generation NSAID used in the treatment of osteoarthritis, rheumatoid arthritis and other joint diseases. Aceclofenac (chemically designated as 2-[2-[2-(2,6-dichlorophenyl)aminophenyl]acetyl]oxyacetic acid).Aceclofenac was developed in order to provide a highly effective pain relieving therapy with a reduced side effect profile, especially gastrointestinal tract events that are frequently experienced with NSAID therapy. Aceclofenac is practically insoluble in water leading to poor dissolution and variable bioavailability upon oral administration[5-10]. The chemical structure of aceclofenac is presented in figure 1.

The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of aceclofenac by preparing SD 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.

Figure 1: Chemical structure of aceclofenac



MATERIALS AND METHODS

Materials

Aceclofenac was a generous gift from Ipca Laboratories, Mumbai. Mannitol, Lactose and Urea of I.P grade were purchased from SD Fine Chemicals Ltd, Mumbai. All reagents were of analytical grade. Double distilled water was used for all the experiments.

Methods

Estimation of Aceclofenac

Aceclofenac contents were estimated by U.V. 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 SDs

Aceclofenac SDs were prepared by using carriers (i.e.mannitol, lactose and urea) in proportions 4:1, 7:3 and 9:1 (drug: carrier) (Table 1). 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 SDs was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and passed through a sieve number # 60 before packing in an airtight container[11].

Percent Practical Yield (PY)

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.

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

Drug Content

SDs 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:

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

$$= \frac{\text{Actual Aceclofenac content in weight quantity of solid dispersion}}{\text{Theoretical amount of aceclofenac in solid dispersion}} \times 100$$

Table 1: Formulation ingredients of aceclofenac solid dispersions

Formulation	Composition	Drug: Polymer
F-1	Aceclofenac + Mannitol	4: 1
F-2	Aceclofenac + Lactose	4: 1
F-3	Aceclofenac + Urea	4: 1
F-4	Aceclofenac + Mannitol	9: 1
F-5	Aceclofenac + Lactose	9: 1
F-6	Aceclofenac + Urea	9: 1
F-7	Aceclofenac + Mannitol	7: 3
F-8	Aceclofenac + Lactose	7: 3
F-9	Aceclofenac + Urea	7: 3

Infrared Spectroscopy

IR spectra of pure aceclofenac, mannitol, urea, lactose and aceclofenac with its SDs 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 400 cm^{-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* behaviour. *In vitro* release profile for each SD 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 of pH 6.8 at 37±0.5ºC and stirred at 50 rpm. Aliquot of 5 ml 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 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 √time), 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 total nine formulations were prepared. All the SDs prepared was found to be fine and free flowing powders. The results of % practical yield studies are shown in Figure 2. Percent practical yield increased as the amount of drug added to each formulation increased (4:1 and 9:1 ratio of drug: carrier). But as the amount of carrier is increased (7:3 ratio of drug: carrier) the percentage practical yield was decreased. Maximum yield was found to be 97.92%.

Actual drug content of all nine formulations are shown in Figure 3. 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). IR spectroscopic studies were conducted to determine 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 SDs; thus indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its SD. The results of IR studies are shown in Figure 4 and 5.

In vitro drug release data obtained for formulations F-1 to F-9 are tabulated in Table 2. 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. *In vitro* release studies reveal that there was marked increase in the dissolution rate of aceclofenac from all the SDs 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 *in vitro* drug release data's (percentage cumulative drug released vs time) of pure drug and formulations (F 1 to F 9) were analyzed by one way ANOVA followed by Dunnett's test at significance level. Comparison of formulations (F 1 to F 9) with control group (pure drug) by Dunnett's multiple comparison test revealed that the formulations F 1 and F 4 to F 9 were statistically significant whereas formulations F 2 and F3 were statistically not significant.

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 than those in the zero order model with all the SDs indicating that the dissolution of aceclofenac as such and from all the SDs followed first order kinetics. Based on 'r' values it was also observed that all the SDs followed Higuchi matrix suggesting the drug release by diffusion. The '*n*' values (less than 0.5) of Peppas suggest Fickian release and Hixson Crowell regression data showed that formulations also appear to release drug by erosion mechanism and the release is drug dissolution limited.

Table 2: *In vitro* dissolution profile of pure drug and different formulations of aceclofenac solid dispersions

Time (min)	Percentage cumulative drug released (average of three experiments)									
	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 dispersions (Using regression coefficient (r) and 'n' value)

Formulations	Regression coefficient (r) values					'n' value
	Zero order	**First order**	**Hixson-Crowell**	**Higuchi**	**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	0.3199	0.9719	0.963	0.9866	0.1682
F7	0.9809	0.647	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

Figure 2: Percent Practical Yield of Different Formulations of Aceclofenac Solid Dispersions

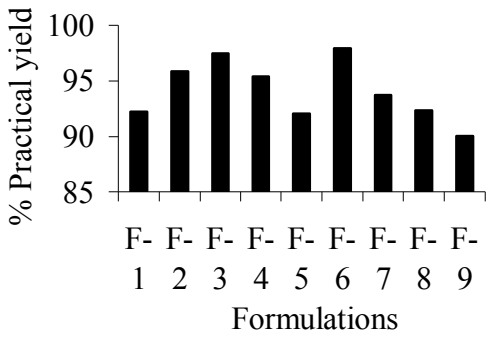


Figure 3: Percent Drug Content of Different Formulations of Aceclofenac Solid Dispersions

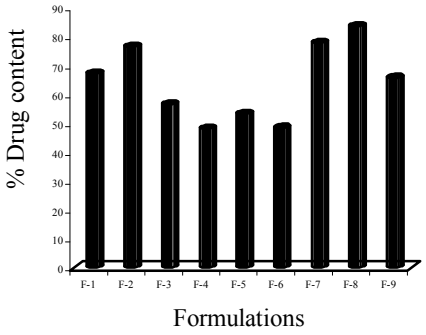


Figure 4: FTIR Spectra of (a) Aceclofenac (b) Urea (c) lactose (d) mannitol

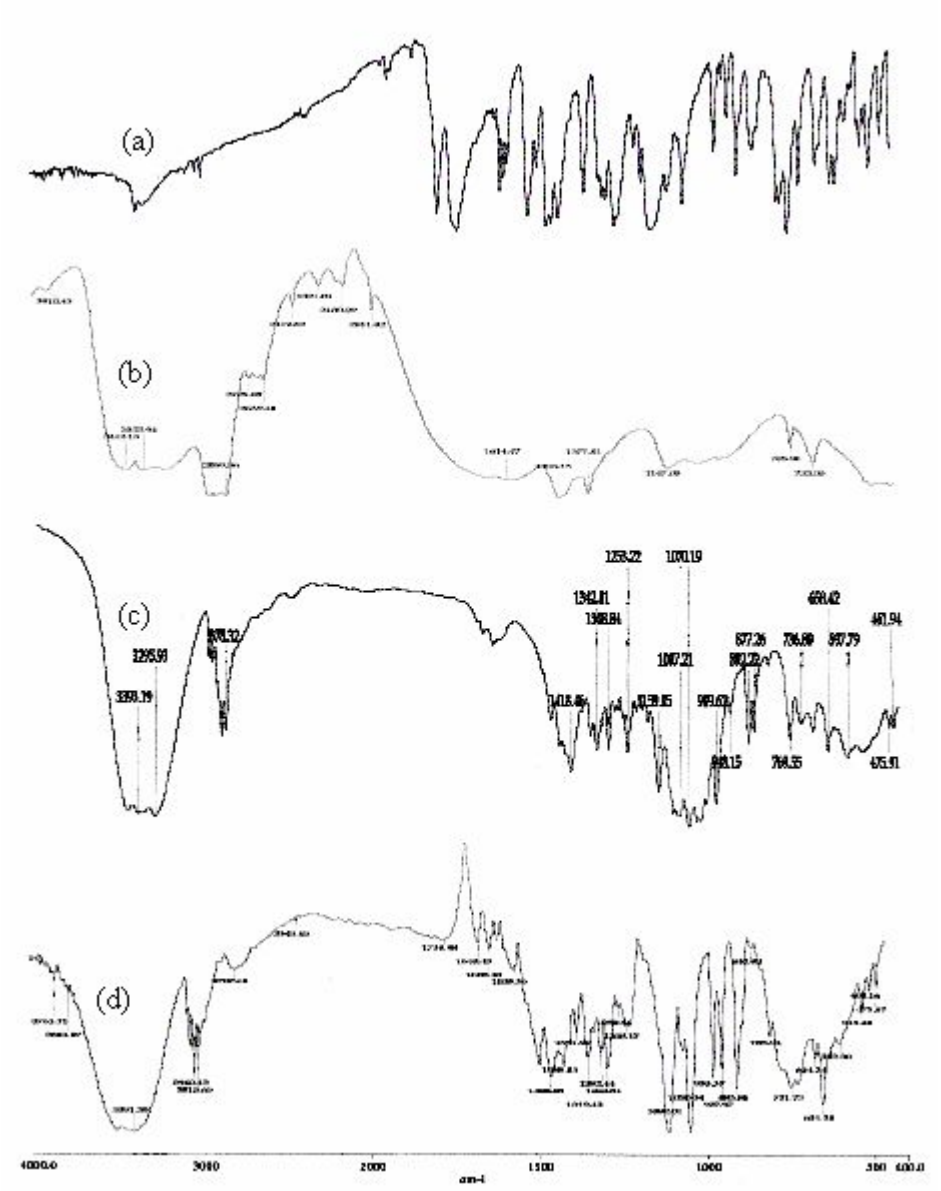
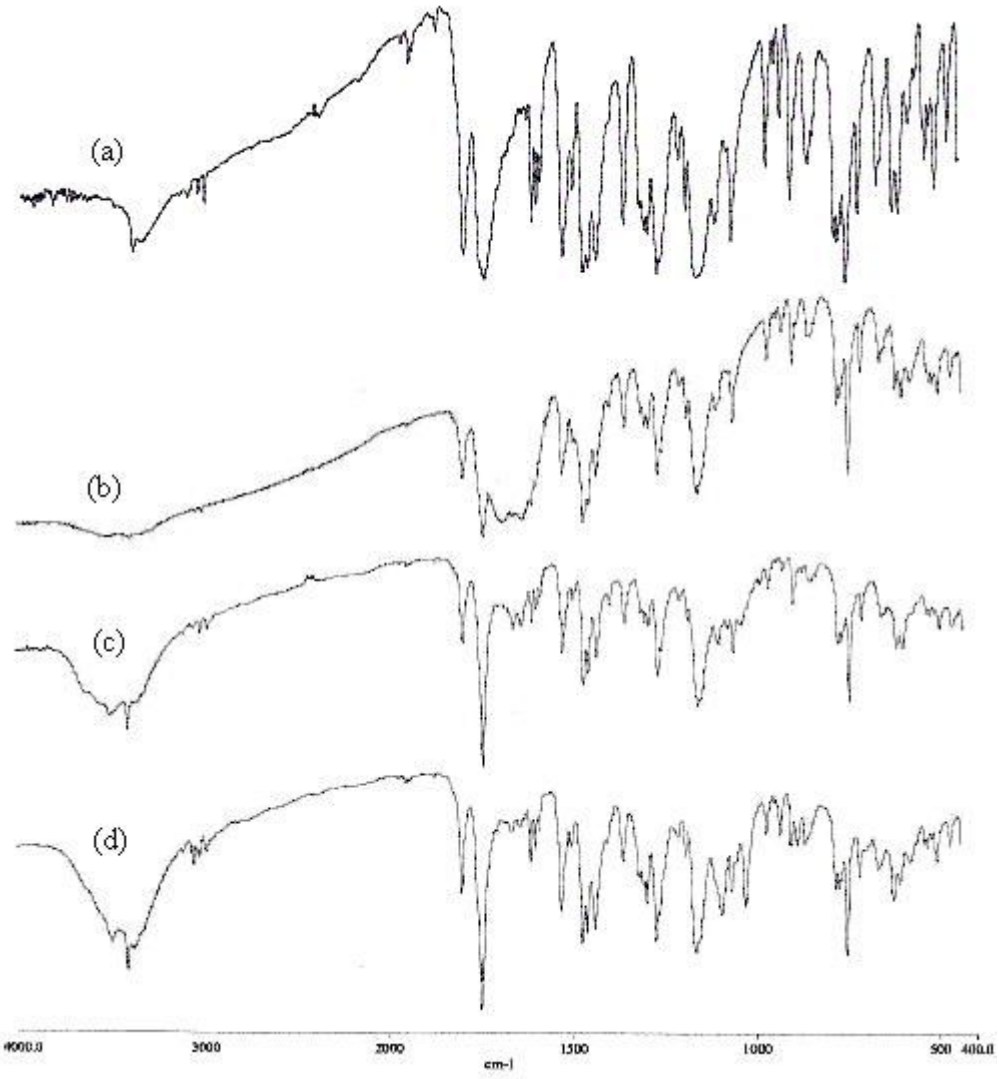


Figure 5: Comparison of FTIR spectrum of (a) aceclofenac with SD (b) aceclofenac with urea (c) aceclofenac with lactose (d) aceclofenac with mannitol



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