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DEVELOPMENT OF SOLID DISPERSIONS OF ACECLOFENAC FOR IMPROVEMENT OF DISSOLUTION PROFILE

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ABSTRACT

Aceclofenac is a Non-Steroidal Anti-Inflammatory Drug (NSAID), mainly used for osteoarthritis, rheumatoid arthritis, and dysmenorrhea. Poor bioavailability after oral administration is the major problem with this drug which can be traced to its low solubility in biological fluids. Absorption of aceclofenac, hence, is dissolution rate limiting and enhancement of solubility would definitely improve the dissolution profile which can, hypothetically, enhance the oral bioavailability. Therefore, solid dispersions of Aceclofenac with urea, polyethylene glycol (PEG) 6000 and polyethylene glycol (PEG) 8000 were prepared by different methods and evaluated with a view to increase its water solubility and hence the dissolution profile. Solid dispersions were prepared and evaluated for solubility, melting point and % practical yield. Two solid dispersions showing maximum solubility were selected and formulated into tablet. The tablets were exposed to routine quality control tests like hardness, friability, weight variation and disintegration. The dissolution profiles of these formulations was studied in 0.1 N HCl and compared with marketed tablet. Drug release from solid dispersions was significantly higher as compared to marketed tablet and formulation TFS3 has shown the fastest drug release among the formulation under study. The present study conclusively demonstrated that solubility and dissolution profile of Aceclofenac was significantly improved by preparing solid dispersion with water soluble carriers.

INTRODUCTION

Aceclofenac is a newer derivative of the diclofenac group of non-steroidal anti inflammatory drugs (NSAIDs) that exhibits analgesic and anti-inflammatory activities. Aceclofenac is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.[1] Aceclofenac is poorly water soluble drug with poor bioavailability after oral administration.[2] Oral bioavailability depends on dissolution rate of the drug which is governed by solubility, therefore major problems associated with this drug is its very low solubility in biological fluids, which results into poor bioavailability after oral administration. Aceclofenac is having good membrane permeability (calculated log P = 2.170) and belongs to biopharmaceutics classification system (BCS) class II (low solubility, high permeability). Therefore, it shows dissolution rate limited absorption that gives rise to difficulties in pharmaceutical formulations for oral delivery, which may lead to variable bioavailability. This fact motivated the development of drug delivery technologies to overcome the obstacle to its solubilization. Besides enhancement of solubility or micronization of drug substances in order to increase the surface area and replacement of crystalline drugs by amorphous material, the solid dispersions with water soluble carriers is the promising and widely used approach to enhance the dissolution properties of water insoluble drugs.[3-7] Among numerous ways of enhancing drug dissolution, solid dispersion (SD) of drug in a hydrophilic polymer is one of the promising techniques.[8-9] Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone (PVP) and polyethylene glycols (PEGs) are used as carriers for solid dispersions.[8, 10-11] These carriers have shown very strong potential of improving dissolution of several drugs.[12-13]

The main objective of the present investigation was to explore the possibilities of improving water solubility and hence dissolution profile of Aceclofenac by preparing solid dispersions with various water-soluble carriers such as polyethylene glycol 6000, polyethylene glycol 8000 and urea by various methods. The prepared solid dispersions were extensively evaluated for solubility, melting point and % practical yield. Two solid dispersions showing promising results were selected and formulated into tablet using carbopol 940, microcrystalline cellulose, starch, mannitol, talc, sod. saccharin and SSG. The prepared tablets were exposed to routine quality control tests like hardness, % friability, weight variation, disintegration to qualify the tablets for further study. Dissolution study of tablets containing solid dispersions was conducted and compared with marketed tablet by applying suitable statistical treatment. All the tablets formulations were also evaluated for stability study.

MATERIALS

Aceclofenac was obtained as a gift sample from Sun Pharmaceuticals Industries Ltd (Baroda, India). Rofaclo 100mg conventional tablets (Sun Pharmaceuticals Industries Ltd, New Delhi) were purchased from the market. Urea, polyethylene glycol 6000 and polyethylene glycol 8000 of pharmacopoeial grades were purchased from SD Fine Chemicals Ltd, Mumbai. All reagents were of A.R. grade. All materials were used as obtained without any modification or purification. Distilled water was used for all the experiments.

METHODS

Preparation of solid dispersions

Solid dispersions were prepared with three carriers i.e. PEG 6000, PEG 8000 and urea by three different methods i.e. solvent evaporation, fusion and co-grinding as shown in table 1.

a) Solvent evaporation: Solid dispersions were prepared by dissolving required amount of drug and carriers in weight ratio of 1:2, 1:3 and 1:4 into acetone:chloroform 1:1 solvent system. The solvent was evaporated at 50° C on water bath with continuous stirring to obtain dry mass. The dry mass was pulverized by passing through sieve no. 44 followed by sieve no. 60. The dried mass was stored in dessicator until further use.

b) Fusion method: Solid dispersions were prepared by melting the carriers in porcelain dish (at around 55-60° C in case of PEGs on water bath and 130-135° C in case of urea on sand bath), dispersing the drug onto the molten carrier and cooling immediately on ice bath with continuous stirring to dry mass. The dry mass was pulverized by passing through sieve no. 44 followed by sieve no. 60. The dried mass was stored in dessicator until further use.

Table 1. FORMULATION OF SOLID DISPERSIONS OF ACECLOFENAC

Carrier	Form. Code	D:C ratio	Method	Carrier	Form. Code	D:C ratio	Method	Carrier	Form. Code	D:C ratio	Method
	SE1	1:2			FS1	1:2			CG1	1:2	
PEG	SE2	1:3		PEG	FS2	1:3		PEG	CG2	1:3	
6000	SE3	1:4		6000	FS3	1:4		6000	CG3	1:4	
	SE4	1:2	SE		FS4	1:2	FS		CG4	1:2	CG
PEG	SE5	1:3		PEG	FS5	1:3		PEG	CG5	1:3	
8000	SE6	1:4		8000	FS6	1:4		8000	CG6	1:4	
	SE7	1:2			FS7	1:2			CG7	1:2	
Urea	SE8	1:3		Urea	FS8	1:3		Urea	CG8	1:3	
	SE9	1:4			FS9	1:4			CG9	1:4	

Form. Code=Formulation Code; D:C ratio=Drug:Carrier ratio; SE=Solvent Evaporation; FS=Fusion; CG=Co-grinding.

c) Co-grinding: The co-grinding mixtures were prepared blending Aceclofenac with PEG 6000, PEG 8000 and urea in 1:2, 1:3 and 1:4 weight ratios in a mortar and pestle. The dry mass was pulverized by passing through sieve no. 44 followed by sieve no. 60. The dried mass was stored in dessicator until further use.

Evaluation of solid dispersions

a)Solubility: The saturation solubility of drug, carriers and all the solid dispersions was determined by dispersing 1g of drug, carrier or solid dispersion onto 100ml of phosphate buffer saline (pH 7.4) contained in glass bottle and shaken for not less than 12 hours. Solubility was then determined in mg/ml using spectrophotometer with λ_{max} at 228nm after necessary dilutions and was recorded in table 2.

b)Melting point: Melting point of drug, polymer and all the solid dispersions was determined thrice using precision melting point apparatus and recorded in table 2.

c)Practical yield: Maximum quantity of solid dispersions were collected and weighed accurately. The percentage practical yield was calculated in %w/w using following equation:

%practical yield = (Weight of SD/total weight of all the ingredients taken initial) *100

Preparation of tablets containing solid dispersion

Tablets containing solid dispersions equivalent to 100mg of Aceclofenac were prepared by direct compression method after mixing with required amount of different ingredients as shown in table 3.

Table 2. EVALUATION OF SOLID DISPERSION OF ACECLOFENAC

Form. code	S	M.P ºC	PPY	Form. code	S	M.P. ºC	PPY	Form. code	S	M.P. ºC	PPY
SE1	0.236	85.9	97.11	FS1	0.122	80.3	94.59	CG1	0.172	132.5	98.11
SE2	0.413	77.3	96.74	FS2	0.587	73.1	95.02	CG2	0.188	114.1	96.30
SE3	0.949	73.1	95.58	FS3	1.113	71.3	94.38	CG3	0.210	97.0	97.18
SE4	0.205	92.6	98.11	FS4	0.212	90.2	99.10	CG4	0.170	151.6	98.11
SE5	0.381	89.1	98.53	FS5	0.394	86.5	97.23	CG5	0.187	146.1	98.53
SE6	0.554	81.9	97.89	FS6	0.614	80.1	97.71	CG6	0.206	135.2	97.89
SE7	0.197	86.1	97.13	FS7	0.187	82.0	96.27	CG7	0.175	142.4	94.56
SE8	0.243	79.8	95.28	FS8	0.238	75.8	98.50	CG8	0.189	126.3	95.22
SE9	0.278	71.5	96.66	FS9	0.288	70.1	96.81	CG9	0.212	110.5	95.51
Drug	0.150	149.4		PEG6	sol.	57		PEG8	sol.	61	
Urea	sol.	131									

n=3; %RSD (% Relative standard deviation) was found to be less than 4% for all the observations; S=Saturation solubility (mg/ml); M.P=Melting point; PPY=Percentage practical yield; sol.=soluble – all the carriers were found to be soluble in the proportions they were used in preparation of solid dispersion.

Table 3. FORMULATION OF TABLET CONTAINING SOLID DISPERSIONS

Tablet ingredients	Formulations of tablet containing solid dispersions	
	TSE3	TFS3
SD equivalent to 100 mg of drug	400	400
Carbopol 974	22.0	22.0
Mannitol	50.0	50.0
Starch	25.0	25.0
SSG	25.0	25.0
Sod. Saccharin	3.0	3.0
Micro Crystalline Cellulose	50.0	50.0
Talc	5.0	5.0
Total tablet weight	580	580

SD= Solid dispersion; TSE3 and TFS3 =Tablets of batch SE3 and FS3. All the weights shown above are in mg.

3.3 Evaluation of tablet

Tablets containing solid dispersion as well as marketed tablets were passed through routine quality control tests like hardness, friability, weight variation and disintegration, as recorded in table 4, to qualify for further testing of dissolution study. The dissolution study was performed on 8 vessel USP type II dissolution test apparatus in 0.1N HCl with constant temperature and speed at 37±2 °C and 50rpm respectively. Aliquots were withdrawn at different time intervals, analyzed by UV-visible spectrophotometric method and cumulative percentage release of drug was recorded and presented as chart in figure 1.

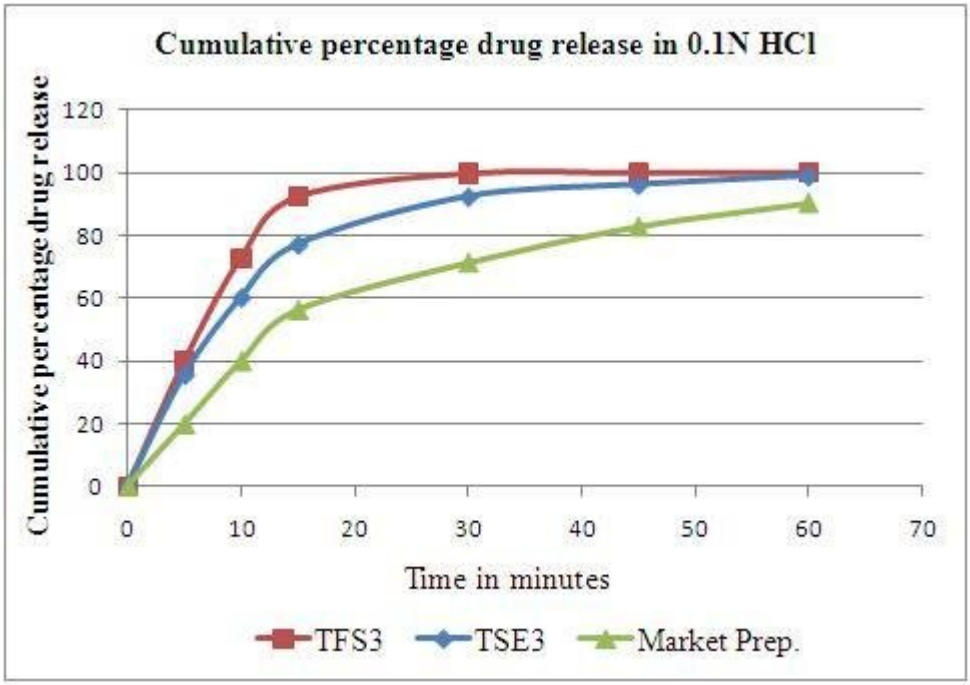

Figure 1. CUMILATIVE PERCENTAGE DRUG RELEASE FROM DIFFERENT FORMULATIONS

The tablets were also evaluated for routine quality control tests (table 4) as well as stability study by accelerated stability testing method (table 5). Tablets were stored at 45° C with 65% RH in incubator for about 8 weeks where all the five tablet formulations were found stable without any significant difference.

Table 4. EVALUATION OF MATRIX TABLETS

Formulation	Evaluation parameters of matrix tablets			
	Hardness Kg/cm^2	% Friability	Weight variation	Disintegration time in seconds
TSG3	4.5	0.62	250 ± 7.3	35
TFG3	4.8	0.51	250 ± 8.1	41
MP	5.1	0.33	105 ± 2.5	112

n=3; %RSD (% Relative standard deviation) was found to be less than 5% for all the observations

Table 5. STABILITY STUDY OF TABLETS AND PLAIN DRUG

Time in Weeks	CPR of drug at the end of 30 minutes			
	TSE3	TFS3	MP	Plain drug
1	90.29	99.10	71.18	24.15
3	89.98	99.08	71.55	24.14
5	89.60	99.15	71.89	24.11
7	90.12	98.57	71.22	24.13
9	89.56	99.11	70.85	23.97
12	89.88	98.49	70.77	23.92

n=3; %RSD was found to be less than 3.3% for all the observations
CPR=Cumulative percentage release; MP=Market preparation;

RESULTS AND DISCUSSION

Solid dispersions of Aceclofenac were prepared successfully by solvent evaporation, fusion and co-grinding method with three hydrophilic carriers i.e. PEG 6000, PEG 8000 and urea. The solubility of drug was found to be 0.150 mg/ml, agrees well with literature (Garala Kevin et al., 2009), which was increased significantly by formulating the drug into solid dispersion. Table 2 shows highest solubility was obtained with FS3 (1.113mg/ml) followed by SE3, FS6, FS2, SE6, etc. It is also reflecting from table 2 that there is significant reduction in melting point of solid dispersion as compared to pure drug. The % practical yield was determined to understand the recoverability of the formulation. All formulations show more than 94% practical yield, as per table 2, reflecting feasibility of the methods.

After the preliminary study of all the Solid dispersions, three solid dispersions i.e. FS3 and SE3 were selected and formulated into tablet as shown into table 3. The tablets prepared with

solid dispersions were compared with conventional marketed tablet by dissolution test.

The results of dissolution study, as in Figure 1, reveals that dissolution profile of Aceclofenac is improved significantly, which can be justified by applying one way ANOVA to the data of dissolution study, by incorporating into solid dispersion. This data suggests that formulating the drug into solid dispersion using hydrophilic carrier enhances water solubility which may be traced to conversion of crystalline powder into amorphous form, which is reflected as decrease in melting point of solid dispersions as compared to pure drug.

CONCLUSION

The solubility and dissolution profile of Aceclofenac was significantly improved by preparing solid dispersion with water soluble carrier like PEG 6000, PEG 8000 and urea by solvent evaporation, fusion and co-grinding techniques. The techniques explored are relatively easy, simple, quick, inexpensive and reproducible; and the carrier used are of GRAS grade suggesting that solid dispersion is trustworthy alternative for solubility enhancement of poorly water soluble drugs. The outcome of this investigation is very encouraging and author suggest further study with more number of carriers with detail analysis to establish strong evidence for the conclusion drawn in present study.

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