



## FORMULATION AND *INVITRO* EVALUATION OF ACECLOFENAC SOLID DISPERSION INCORPORATED GELS

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### ABSTRACT

Aceclofenac, an analgesic and anti inflammatory drug used in treatment of Osteo arthritis, rheumatoid arthritis and ankylosing spondylitis. Various compositions of aceclofenac solid dispersions were prepared by physical mixing, fusion and solvent evaporation methods using. PVP, PEG 6000, mannitol and urea as carrier to enhance the solubility of drug. The formulations evaluated for drug content, *invitro* dissolution study and also characterized by IR and DSC studies. There is no interaction between drug and carrier. The general trend indicated that there was a increase in *invitro* drug release for solid dispersion prepared in the following order Urea > PEG 6000 > PVP > Mannitol. Based on *invitro* drug release pattern, 1:3 drug carrier ratio was selected as ideal dispersion for gels. Carbopol940 selected as ideal gel base for preparation of gels and dispersions are incorporated to gel bases by trituration. Were characterized for rheological studies, drug content estimation and *in vitro* diffusion study, IR spectroscopy. All these properties were found to be ideal. The *in vitro* release of Aceclofenac solid dispersion incorporated gel is significantly improved when compared to pure drug in incorporated gel.

**Key words:** Aceclofenac, solid dispersion incorporated gels, *in vitro*

### INTRODUCTION

Topical dermatological products are intended for localized action on one or more layers of skin. Although some medication from its topical dosage form reaches to systemic circulation, it is usually in sub therapeutic concentration, and does not produce effects of any major concern except in special situations such as pregnant or nursing patients<sup>1</sup>. Topical administration is employed to deliver a drug at or immediately beneath the point of application.

Although occasionally enough drug is absorbed in top systemic circulation to cause systemic effect. Topical administration of drugs rapidly is becoming an important route of drug administration of systemic drugs previously used only for the application of drugs to local effects in disease of skin, it is now being explored as a means of administering drugs for their systemic effects<sup>2</sup>. Cutaneous absorption of Aceclofenac with solid dispersion was significantly greater than that obtained with an intact drug<sup>3</sup>.

Solid dispersion is a unique approach which was introduced by Sekiguchi and Obi. In solid dispersion method, the drug is dispersed in extremely fine state in an inert water soluble carrier in solid state.

In order to achieve increased dissolution rate, sustained release of drugs and thus improve solubility and stability.

A number of freely water soluble materials such as citric acid, succinic acid, bile acids, sterols and related compounds and polymers like polyvinyl pyrrolidone and poly ethylene glycols are used as carrier for solid dispersions. By this approach the dissolution rate and bioavailability of poorly soluble drugs can be increased<sup>4</sup>.

Solid dispersion can be prepared by fusion process, solvent process, melting solvent method, physical mixture, kneading method, super critical fluid method<sup>5</sup>.(ref-due) Solid dispersion is an effective technique which can easily enhance the dissolution rate of drugs<sup>5</sup>.

A Aceclofenac is a novel phenyl acetic acid derivative 2-[(2,6-dichlorophenyl)amino phenyl acetoxyacetic acid] indicated for systematic treatment of pain and inflammation with reduced side effects profile, especially GI events that are frequently experienced with NSAIDs therapy<sup>6</sup>.

The continuous use of Aceclofenac through oral route causes ulcerogenic effect<sup>7</sup>. However not much attempt has been made so far for sub-cutaneous absorption, in order to enhance bioavailability, the improvement of its solubility and dissolution characteristics is considered to be very effective<sup>3</sup>.

The present study was performed to investigate the dissolution behavior and topical absorption characteristics of Aceclofenac from solid dispersion incorporated gels, tend to avoid typical side effect of NSAIDs associated with oral and systemic administration. To improve the permeability of Aceclofenac, the use of gel bases is a logical approach to increase the drug flux across the epithelium. To determine the diffusion properties of drug in semisolid vehicles especially when the release of drug at the application site is likely to be rate-limited by the diffusion of the drug, the ability of vehicle to release the drug at the local site is limited by numerous factors such as drug-vehicle, drug-skin and vehicle-skin interaction.

In this paper the influence of Aceclofenac solid dispersion on diffusion from Carbopol 940 gel base was investigated in order to develop the effective semisolid formulation of Aceclofenac for treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

### MATERIALS AND METHODS

#### Chemicals

Aceclofenac was a gift sample from Unix Biotech Pvt. Ltd., Baddi (Solani); polyvinyl pyrrolidone, polyethylene glycol 6000, Carbopol 940 were purchased from Loba Chem. Pvt. Ltd (Mumbai). Urea, mannitol, sodium hydroxide were purchased from S.D Fine chemical Pvt. Ltd, (Mumbai) All the chemicals used in the present study were of AR Grade.

#### Preparation of solid dispersions

##### a) Preparation of physical mixture<sup>8</sup>

The physical mixture of Aceclofenac prepared using PEG6000, PVP & urea in 1:1, 1:2 and 1:3 ratios were obtained by mixing pulverized powders of drugs and various carriers with the help of a spatula.

### b) Preparation by solvent evaporation method<sup>9,10</sup>

The required amount of Aceclofenac and carrier in 1:1, 1:2 & 1:3 ratio were dissolved in sufficient volume of methanol with continuous stirring. The solvent from the solution was removed at 45° with continuous stirring to obtain dry mass. The dried mass was pulverized passed through 44 mesh sieve and stored in desiccator until used for further studies.

### c) Preparation by fusion method<sup>11</sup>

Solid dispersion of Aceclofenac & carriers in ratios of 1:1, 1:2 & 1:3 were obtained by melting carrier in a porcelain dish at 80 – 85° and to this Aceclofenac added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was the pulverized passed through 44 mesh sieve and stored in a desiccator until used for further studies.

### Characterization of solid dispersions

The prepared solid dispersion were evaluated for drug carrier interaction using differential scanning calorimetry (DSC – Pyris – 6) and FTIR (Perkins Elmer 1600 series) spectral studies. For DSC studies samples were sealed in aluminium pans and the DSC thermo grams were recorded at a heating rate of 10°/min from 100°C – 300°C. FTIR spectrum was carried by KBR pellet method. The solid dispersions were also characterized for appearance. The displacement value of solid dispersions and pure drug was determined.

### In-vitro dissolution studies for solid dispersions<sup>12</sup>

The USP dissolution apparatus (Type-II) was used for evaluation of *in vitro* release profile of solid dispersions. The dissolution medium was 900ml phosphate buffer of PH 7.4 kept at 37 ± 0.1°. The drug or physical mixture or solid dispersion was filled in capsule and then kept in the basket of dissolution apparatus, which was then rotated at 50rpm. Samples of 5ml were with drawn at specified time intervals and analyzed spectro photometrically at 275nm. Withdrawn samples were replaced by fresh buffer solution.

### Preparation of solid dispersion incorporated gels<sup>13</sup>

**Carbopol 940 Gel:** Weighed quantity of Carbopol 940 soaked in 75ml water for 24 hours then glycerin, DMSO was added with stirring. The solid dispersions containing 1% drug was dissolved in ethanol and this dry solution was added to above gel with continuous stirring.

### Physical characterization of Gels

Physical characterization such as spreadability, extrudability, viscosity, PH, drug content was measured.

### Determination of spreadability<sup>14</sup>

The spreadability of the formulations was determined by an apparatus suggested by Mutimer et al, which was suitable modified in the laboratory and used for the study. It consists of a wooden block which was provided by a pulley at one end. A rectangular ground glass plate was fixed on the block. An excess of gels (about 2g) under study was placed on this ground plate.

The gel was then sandwiched between this plate and another glass plate having the dimensions of the ground plate and provided with the hook. A 300gm weight was placed on the top of two plates for five minutes to expel air and provide a uniform film of the gel between the plates. Excess of gel was scrapped off from the edges. The top plate was then subjected to a pull of 30g with the help of a string attached to the hook and the time (in sec) required by the top plate to cover a distance of 10cms was noted. The spreadability was calculated using the formula.  $S = m/l/t$  where,  $s$  = spreadability,  $m$  = weight tied to the upper glass slide,  $l$  = length of the glass side and  $t$  = time taken in seconds<sup>12</sup>.

### Determination of extrudability<sup>15</sup>

The apparatus used for extrudability was suitably fabricated in the laboratory. It consist of a wooden block inclined at an angle of 45° fitted with a thin, ling metal strip (tin) at one end. While the other end was free. The aluminium tube containing 10gm of gel was positioned on inclined surface of wooden block 30gm weight was placed on free end of the aluminium strip and was just touched for 10 seconds. The quantity of gel extruded from each tube was noted.

### Determination of viscosity<sup>16</sup>

Viscosity of prepared gels was determined by Brook field programmable DV-II viscometer.

### Determination of pH<sup>16</sup>

pH of formulation determined by dispersing 0.5gm of gel in 50ml of water. Checked using digital pH meter at constant temperature prior to this, the P<sup>H</sup> meter was calibrated using buffer solution of pH 4.0 and 9.2, and then electrode was washed with demineralised water. The electrode was then directly dipped in to gel formulation and constant reading as noted.

### Determination of drug content<sup>17</sup>

One gm of solid dispersion incorporated gel was mixed with methanol, diluted to 100ml then after filtering the stock solution, filtrate was diluted suitably and absorbance was measured against blank at 275nm.

### *In vitro* diffusion studies for solid dispersion incorporated gels<sup>18</sup>

The *in-vitro* diffusion studies for the gels were carried out by apparatus consist of cylindrical glass tube which was opened at both the ends 1gm of gel formulation equivalent to 10gm of Aceclofenac was spread uniformly on the surface of cellophane membrane (previously soaked in water for overnight). Whole assembly was fixed in such a way that the lower end of tube containing gel was just touched the surface of diffusion medium i.e. 100ml PH 7.4 phosphate buffer contained in 150ml beaker which was placed in water bath and maintained at 37 ± 2°C, the contents were stirred using magnetic stirrer at 5 ± 5 rpm. The sampling was done at different time intervals over a period of 6 hours and absorbance was measured at 275nm using Shimadzu UV-visible spectrophotometer.

## RESULTS & DISCUSSION

### Dissolution profile

The *in vitro* release studies of different batches of solid dispersions are shown in figure 1, 2 and 3 the solid dispersion prepared by fusion method showed improved dissolution when compared with solvent evaporation & physical mixtures and pure drug. Among the solid dispersions prepared 1:3 ratio showed greater solubility than the others.

Because of enhanced / greater release solid dispersion prepared with 1:3 drug carrier ratios was selected as ideal batch for incorporation into gels.

Physical characteristics of Aceclofenac solid dispersion incorporated gels were measured according to the methods describe above. The pH of all formulations was found between 6.8 to 7.2 which is lies in normal pH range of the skin. The pH of all the formulations was found between 5.2 to 7.2 thus indicating suitability for application along with good extrudability and spreadability. The release of tretinoin from the Carbopol gels was affected by the pH of Carbopol gels, showing the best release at pH 8. As the concentration of drug increased, the release of drug from the gel increased, showing concentration dependency<sup>19</sup>. The results in present study correlates pH of Carbopol gel formulations.

All the prepared gel formulations showed uniformity in drug content and were within permissible range indicating the uniformity of drug dispersion in the gels.

**Table 1: Formulation of Aceclofenac dispersion**

Carrier	Formulation code	Drug carrier ratio	Method	Carrier	Formulation code	Drug carrier ratio	Method	Carrier	Formulation code	Drug carrier ratio	Method
PEG 6000	GP <sub>1</sub>	1:1	Physical mixture	Mannitol	MF <sub>1</sub>	1:1	Fusion method	PVP	VS <sub>1</sub>	1:1	Solvent Evaporation method
	GP <sub>2</sub>	1:2			MF <sub>2</sub>	1:2			VS <sub>2</sub>	1:2	
	GP <sub>3</sub>	1:3			MF <sub>3</sub>	1:3			VS <sub>3</sub>	1:3	
PVP	VP <sub>1</sub>	1:1	Physical mixture	PEG 6000	GF <sub>1</sub>	1:1	Fusion method	PEG 6000	GS <sub>1</sub>	1:1	Solvent Evaporation method
	VP <sub>2</sub>	1:2			GF <sub>2</sub>	1:2			GS <sub>2</sub>	1:2	
	VP <sub>3</sub>	1:3			GF <sub>3</sub>	1:3			GS <sub>3</sub>	1:3	
Urea	UP <sub>1</sub>	1:1	Physical mixture	Urea	UF <sub>1</sub>	1:1	Fusion method	PEG 6000	GS <sub>1</sub>	1:1	Solvent Evaporation method
	UP <sub>2</sub>	1:2			UF <sub>2</sub>	1:2			GS <sub>2</sub>	1:2	
	UP <sub>3</sub>	1:3			UF <sub>3</sub>	1:3			GS <sub>3</sub>	1:3	

**Table 2: Formulation of Aceclofenac solid dispersion**

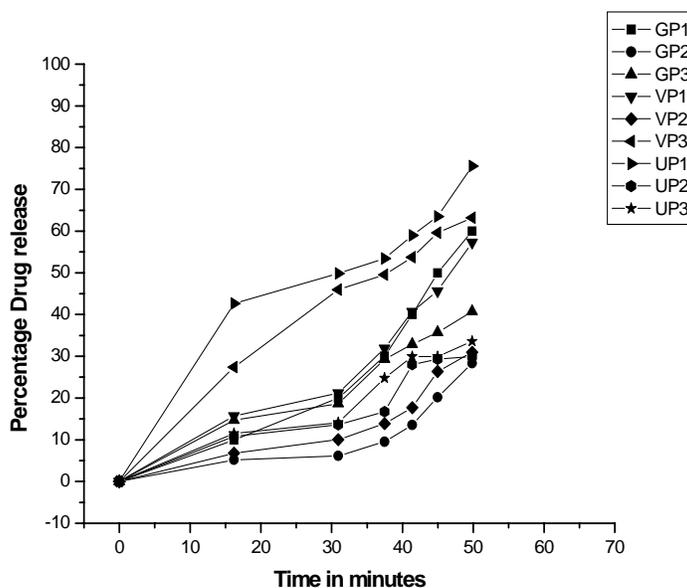
Ingredients	CGP3	CGF3	CGS3	CVP3	CUF3	CVS3
SD equivalent to 1gm of Aceclofenac	4.0	4.0	4.0	4.0	4.0	4.0
Carbopol 940 (gm)	0.6	0.8	1.0	0.6	0.8	1.0
Triethanolamine(ml)	Qs	qs	qs	Qs	qs	qs
Ethanol (ml)	8.0	8.0	8.0	8.0	8.0	8.0
SLS (gm)	0.25	0.25	0.25	0.25	0.25	0.25
Glycerol (ml)	5.0	5.0	5.0	5.0	5.0	5.0
Dist water (ml)	100.00	100.00	100.00	100.00	100.00	100.00

**Table 3: Physical characteristics of Aceclofenac solid dispersion incorporated gels**

Formulation code	PH	Drug content (%)	Viscosity (Cp)	Spreadability (gm/s)	Extrudability
CAG	6.9	98.15	Viscous	9.15	++
CGP <sub>3</sub>	6.8	97.78	Viscous	9.12	++
CGF <sub>3</sub>	7.1	98.52	Viscous	8.13	++
CGS <sub>3</sub>	6.9	98.89	More viscous	7.33	+
CVP <sub>3</sub>	7.0	95.94	Viscous	9.25	++
CUF <sub>3</sub>	7.2	98.52	Viscous	8.51	++
CVS <sub>3</sub>	6.8	99.26	More	7.15	+

+ → Satisfactory

++ → Good



**Fig. 1: Percent release of Aceclofenac from (GP<sub>1</sub>, GP<sub>2</sub> & GP<sub>3</sub>), (VP<sub>1</sub>, VP<sub>2</sub> & VP<sub>3</sub>) & (UP<sub>1</sub>, UP<sub>2</sub> & UP<sub>3</sub>) prepared by physical mixing.**

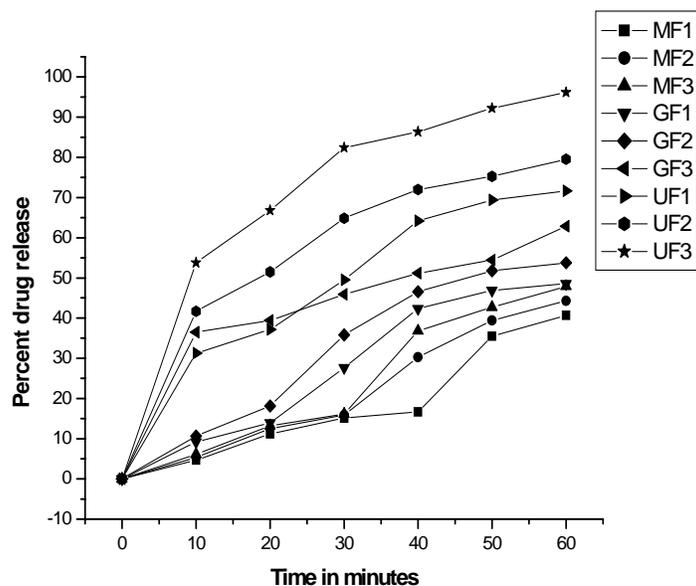


Fig. 2: Percent release of Aceclofenac from (MF<sub>1</sub>, MF<sub>2</sub> & MF<sub>3</sub>), (GF<sub>1</sub>, GF<sub>2</sub> & GF<sub>3</sub>) & (UF<sub>1</sub>, UF<sub>2</sub> & UF<sub>3</sub>) prepared by fusion method.

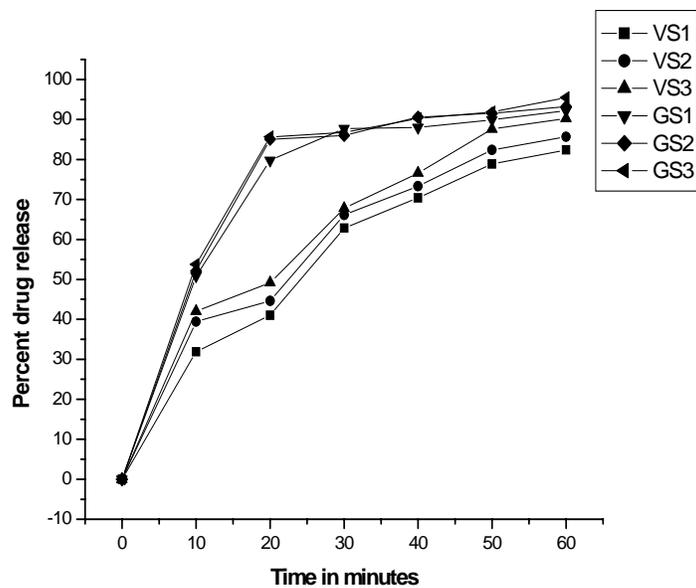
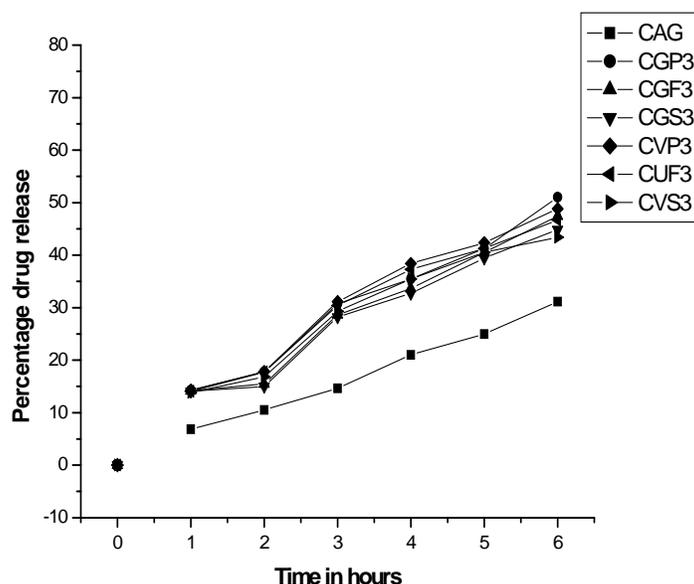


Fig. 3: Percent release of Aceclofenac from (VS<sub>1</sub>, VS<sub>2</sub> & VS<sub>3</sub>) & (GS<sub>1</sub>, GS<sub>2</sub> & GS<sub>3</sub>) solid dispersions prepared by solvent evaporation method



**Fig. 4: Diffusion profile of Aceclofenac solid dispersion incorporated gels from various formulations**

Viscosity is an important parameter for characterizing the gels as it affects the spreadability, extrudability and release of the drug. All the gels showed increase in viscosity as the concentration of gelling agent was increased. The gels with high viscosity may not extrude from tube easily, where as low viscosity gels may flow quickly. Hence, there should be an optimum viscosity.

The extrusion of gel from the tube is important during application and for the patient compliance. Extrudibility of gel formulations with high concentration of gelling agent was found satisfactory while with low concentration of gelling agents good extrudability was observed. Spreadability plays an important role in patient compliance and help in uniform application of gel to the skin. Good gel takes less time to spreads and will have high spreadability. Here the spreadability of formulation was decreased as concentration of gelling agent was increased as given in Table 3

The dissolution rate of Aceclofenac from solid dispersion is significantly higher than that of pure drug. Solid dispersion prepared by fusion method showed faster drug release than prepared by. Solid dispersion incorporated suppositories were prepared by the fusion method. The rectal bioavailability of lemidipine from solid dispersion incorporated oleaginous suppositories in dogs was approximately 14-times higher than that from intact bulk incorporated oleaginous suppositories<sup>20</sup>. Findings showed that incorporated delivery systems are promising for improved results. Solvent evaporation followed by physical mixture. The addition of PEG-6000 to Terbinafine HCL improved its dissolution rate. Mechanisms involved are solubilisation and improved wetting of the drug in the polyethylene glycol rich micro-environment formed at the surface of drug crystals after dissolution rate compared with physical mixtures<sup>21</sup>, hence the results in present study ,the PEG 6000 may responsible for improved dissolution rate. IR studies indicated that no chemical interaction between drug and carrier took place during preparation of solid dispersion of Aceclofenac.

DSC studies indicted that Aceclofenac was homogenously distributed within the carrier in an amorphous state and no drug crystallized out of the dispersion suggesting that drug and carrier exist in the form of a mixture rather than the reaction product *in vitro* release was decreased when concentration of gallant was increased. The addition

of PEG-6000 to Terbinafine HCL improved its dissolution rate. Mechanisms involved are solubilisation and improved wetting of the drug in the polyethylene glycol rich micro-environment formed at the surface of drug crystals after dissolution rate compared with physical mixtures<sup>21</sup>. For this reason PEG -600 is selected for our study.

The decrease in *in vitro* release may be due to increase in viscosity of gels. The *in vitro* diffusion studies were performed by over a period of 6 hours and results are shown in figure 4.

At the end of 6 hours Aceclofenac solid dispersion incorporated gel (CGP<sub>3</sub>) released 51.04% drug as compare the pure drug incorporated gel released 31.13 % of drug after 6 hours. Ointment and gel bases containing 1% Aceclofenac were prepared and evaluated for pH, drug content, rheological properties and *in vitro* drug release rate. *in vitro* release was found to be better with the gel base in comparison to ointment bases. The results showed that Carbopol gel bases were the most suitable bases for Aceclofenac formulations<sup>22</sup>. The results proved that the Aceclofenac solid dispersion incorporated gels. Were better in releasing /diffusing the drug than the pure drug incorporated gels.

#### CONCLUSION

The *in vitro* diffusion study of Aceclofenac solid dispersion incorporated gels was greatly improved when compared with those of intact Aceclofenac incorporated gels. From overall formulations CGP<sub>3</sub> was found to be the best formulations. From the above results, it may be concluded that solid dispersion incorporated. Gels were better for improvement of dissolution and diffusion of Aceclofenac and also to overcome gastric side effect of the drug.

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