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Research Article

STUDIES ON ACECLOFENAC SOLID DISPERSION IN CORPORATED GELS: DEVELOPMENT, CHARACTERIZATION AND *IN VITRO* EVALUATION

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ABSTRACT

Aceclofenac, an analgesic and anti inflammatory drug is 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 *invtiro* drug release pattern, 1:3 drug carrier ratio was selected as ideal dispersion for gels. HPMC selected as ideal gel base for preparation of gels and dispersions are incorporated to gel bases by trituration. Formulations were characterized for rheological studies, drug content estimation and *invitro* diffusion study, IR spectro scopy. 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 corporated gel.

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

INTRODUCTION

Aceclofenac is an analgesic, anti pyretic and antiflammatory drug. The major drawback of Aceclofenac is its poor aqeous solubility[1]. The continuous use of Aceclofenac through oral route cuases ulcerogenic effect[2]. However no much attempt has been made so far for subcutaneous absorption. In order to enhance bioavailability, the improvement of its solubility and dissolution characteristics is considered to be very effective. Solid dispersion is an effective technique which can easily enhance the dissolution rate of drugs[3]. Subcutaneous absorption of Aceclofenac with solid dispersion was significantly greater than that obtained with an intact drug[4]. 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 drugs in semisolid vehicles especially when the release of drug is 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 HPMC 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 (Solan). Polyvinyl pyrrolidone, polyethylene glycol 6000, HPMC was 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

Preparation of physical mixture[5]

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.

Preparation by solvent evaporation method[6,7]

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.

Preparation by fusion method[8]

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 (Perkin Elmer 1600 series) spectral studies. For DSC studies samples were sealed in aluminium pans and the DSC thermograms 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[9]

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 50 rpm. Samples of 5ml were with drawn at specified time intervals and analyzed spectrophotometrically at 275 nm. Withdrawn samples were replaced by fresh buffer solution.

Preparation of solid dispersion incorporated gels[10]

HPMC-Gel: Weighed quantity of HPMC 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 spreadibility[11]

The spreadibility 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 2 g) 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 the 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 spreadibility was calculated using the formula. S = m l/t where, s = spreadibility, m = weight tied to the upper glass slide, l= length of the glass side and t = time taken in seconds.[9]

Determination of Extrudability[12]

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[13]

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

Determination of pH[13]

pH of formulation determined by dispersing 0.5 gm of gel in 50 ml of water. It was checked using digital pH meter at constant temperature. Prior to this, the pH 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[14]

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**[15]

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 275 nm using shimadzu UV-visible spectrophotometer.

RESULTS AND 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 solvent evaporation showed improved dissolution when compared with physical mixtures, fusion method 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: Physical characteristics were measured according to the methods describe above. The results and listen in Table 3.

The *in vitro* diffusion studies were performed by over a period of 6 hours and results are shown in figure 4.

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. Solvent evaporation followed by physical mixture. IR studies indicated that no chemical interaction between drug and carrier took place during preparation of solid dispersion of Aceclofenac.

Table 1: Formulation of Aceclofenac dispersion

Formulation code	Drug carrier ratio	Method	Carrier	Formulation code	Drug carrier ratio	Method	Carrier	Formulation code	Drug carrier ratio	Method
GP_1	1:1	Physical mixture	Mannitol	MF_1	1:1	Fusion method	PVP	VS_1	1:1	Solvent Evaporation method
GP_2	1:2			MF_2	1:2			VS_2	1:2	
GP_3	1:3			MF_3	1:3			VS_3	1:3	
VP_1	1:1		PEG 6000	GF_1	1:1		PEG 6000	GS_1	1:1	
VP_2	1:2			GF_2	1:2			GS_2	1:2	
VP_3	1:3			GF_3	1:3			GS_3	1:3	
UP_1	1:1		Urea	UF_1	1:1					
UP_2	1:2			UF_2	1:2					
UP_3	1:3			UF_3	1:3					

Table 2: Formulation of Aceclofenac solid dispersion

Ingredients	HGP3	HGF3	HGS3	HVP3	HUF3	HVS3
SD equivalent to 1gm of Aceclofenac	4.0	4.0	4.0	4.0	4.0	4.0
HPMC (gm)	4.0	5.0	6.0	4.0	5.0	6.0
Ethanol (ml)	8.0	8.0	8.0	8.0	8.0	8.0
DMSO (ml)	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)	Spreadibility (gcm/s)	Extrudability
HAG	6.5	98.52	291.1	15.53	++
HGP_3	6.9	97.78	292.4	15.69	++
HGF_3	6.7	96.30	384.4	11.40	++
HVP_3	7.1	95.57	832.8	8.55	+
HVP_3	6.4	98.15	292.4	16.87	++
HUF_3	6.6	98.89	384.4	12.05	++
HVS_3	6.8	97.04	832.8	8.61	+

+ → Satisfactory ++ → Good

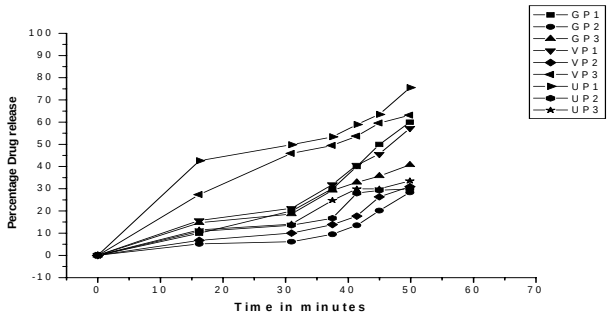

Fig. 1: Percent release of Aceclofenac from (GP_1, GP_2 & GP_3), (VP_1, VP_2 & VP_3) & (UP_1, UP_2 & UP_3) prepared by physical mixing.

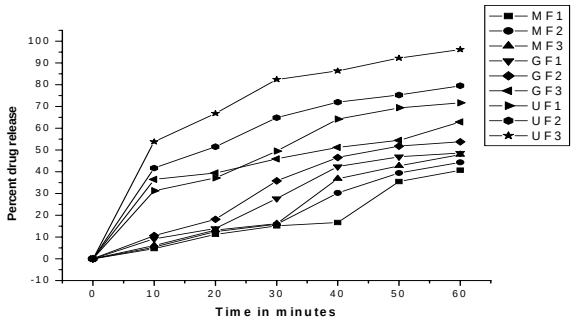

Fig. 2: Percent release of Aceclofenac from (MF_1, MF_2 & MF_3), (GF_1, GF_2 & GF_3) & (UF_1, UF_2 & UF_3) prepared by fusion method

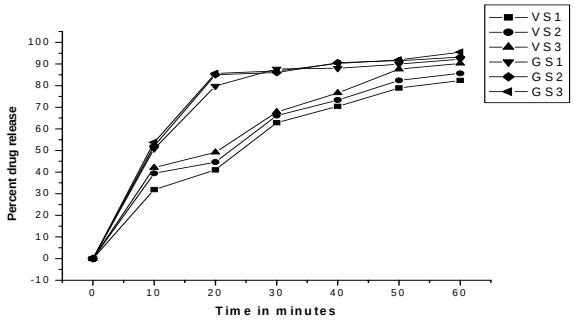

Fig. 3: Percent release of Aceclofenac from (VS1, VS2 & VS3) & (GS1, GS2 & GS3) solid dispersions prepared by solvent evaporation method

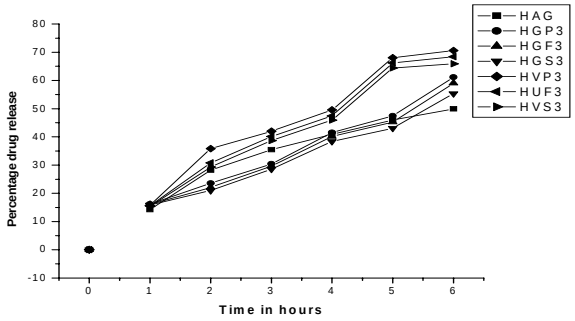

Fig. 4: Diffusion profile of Aceclofenac solid dispersion incorporated gels from various formulations

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 HVP_3 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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