Dissolution behaviour of aceclofenac-PVP coprecipitates

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RESUMEN

Objetivo: El objetivo de esta investigación fue estudiar el efecto del PVP en la disolución in vitro del aceclofenaco en coprecipitados.

Material y métodos: Se prepararon diferentes coprecipitados de aceclofenaco con distintas cargas de droga y se llevaron a cabo los estudios in vitro de disolución de la droga pura, mezclas físicas y coprecipitados.

Resultados: Los coprecipitados de aceclofenaco con PVP mostraron un considerable incremento de la tasa de disolución en comparación con las mezclas físicas y la droga pura en HCl 0,1 N y tampón fosfato con pH 7,4. Los coprecipitados con proporción 1:2 mostraron una tasa máxima de disolución en comparación con otras proporciones. La naturaleza amorfa de la droga en coprecipitados fue confirmada con microscopia electrónica de barrido así cómo el descenso de la entalpia de fusión de los coprecipitados con respecto a la droga pura. Los estudios de espectrometría FT-IR y calorimetría diferencial de barrido indicaron que no hubo interacción entre el aceclofenaco y el PVP en estado sólido. La mejora de la disolución se atribuyó al descenso de la cristalinidad y humedad de la droga, la formación del eutéctico y el efecto solubilizante del soporte de los coprecipitados de aceclofenaco.

Conclusión: La disolución del aceclofenaco puede ser mejorada con el uso de los soportes hidrófílicos como el PVP.

PALABRAS CLAVE: Aceclofenaco, Disolución, PVP, Biodisponiblidad

ABSTRACT

Aim: The objective of the present investigation was to study the effect of PVP on in vitro dissolution of aceclofenac from coprecipitates.

Materials and Methods: Aceclofenac coprecipitates (CP) with different drug loadings were prepared and in vitro dissolution studies of pure drug, physical mixtures and coprecipitates were carried out.

Results: Coprecipitates of aceclofenac with PVP showed considerable increase in the dissolution rate in comparison with physical mixture and pure drug in 0.1 N HCl, pH1.2 and phosphate buffer, pH, 7.4. Coprecipitates in 1:2 ratio showed maximum dissolution rate in comparison to other ratios. Amorphous nature of the drug in coprecipitates was confirmed by scanning electron microscopy and a decrease in enthalpy of drug melting in coprecipitates compared to the pure drug. FT-IR spectroscopy and differential scanning calorimetry studies indicated no interaction between aceclofenac and PVP in coprecipitates in solid state. Dissolution enhancement was attributed to decreased crystallinity of the drug and to the wetting, eutectic formation and solubilizing effect of the carrier from the coprecipitates of aceclofenac.

Conclusion: dissolution of aceclofenac can be enhanced by the use of hydrophilic carriers like PVP.

KEY WORDS: Aceclofenac, Dissolution, PVP, Bioavailability.

INTRODUCTION

Up to 40 percent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs[1]. Poorly water-soluble drugs show unpredictable absorption, since their bioavailability depends upon dissolution in the gastrointestinal tract. The dissolution characteristics of poorly soluble drugs can be enhanced by several methods. The solid dispersions obtained by the solvent methods are called the co-precipitates[2] .Solid dispersion is one of the effective and widely used techniques for dissolution enhancement. The increase in dissolution rate for coprecipitates can be attributed to a number of factors, which include reduction in particle size, absence of agglomeration of fine crystallites of the drug, excellent wettability and dispersibility of the drug from solid dispersion and partial conversion of the drug into amorphous form.

Aceclofenac (AF), 2-[(2,6-dichlorophenyl) amino] benzene acetic acid carboxymethyl ester is a new generational non-steroidal anti-inflammatory drug showing effective anti-inflammatory and analgesic properties and a good tolerability profile in a variety of painful conditions like ankylosing spondylitis, rheumatoid arthritis and osteoarthritis. Aceclofenac is very slightly soluble in water[3] and therefore an attempt has been made to prepare coprecipitates of aceclofenac using hydrophilic carrier like polyvinylpyrrolidone (PVP) with an aim to improve its extent and rate of dissolution. A particular advantage of this carrier for the formation of coprecipitates is having good solubility in many organic solvents. Therefore, in the present study PVP was chosen as suitable polymers for the preparation of coprecipitates.

MATERIAL AND METHODS

Materials

Aceclofenac was obtained as a gift sample from Ipca Laboratories, Mumbai, India. Polyvinylpyrrolidone (PVP); molecular weight: 29,000 were obtained from Merck (Germany).

Preparation of Coprecipitates and Physical mixtures of Aceclofenac

Coprecipitates of AF were prepared with PVP in different ratios such as 1:0.5, 1:1 and 1:2 (*AF-PVP-CP1, AF-PVP-CP2 and AF-PVP-CP3*) with slow evaporation of ethanolic (95%v/v) solutions of drug and carrier in a vacuum oven at 40°C. The resulting solid mass was further dried under vaccum to a constant weight and stored in dessicator [4].

The physical mixtures were prepared by mixing pre-weighed amounts of mesh. No 100-sieve fractions of aceclofenac and PVP in the same proportions as used in coprecipitates[4].

Characterisation

Percent Yield

The percent yield of CPs was calculated on the basis of dry weight (drug and carriers) and the final weight of CPs obtained[4].

Average Particle Size

The CPs were dispersed in liquid paraffin and mounted on slides. Particle size of 200 particles was measured using calibrated stage micrometer and ocular micrometer. From the data the average particle size was calculated[5].

Wettability Study

Powdered mixture of CPs (300 mg) was placed in a sintered glass funnel with 33 mm internal diameter. The funnel was plunged into beaker containing water such that the surface of water in the beaker was at the same level as the powder or granules in the funnel. Methylene blue powder (10 mg) was layered uniformly on the surface of the powder or granules in the funnel. The time required for wetting of methylene blue powder was measured. The mean of three observations was used for drawing the conclusions[5].

Hygroscopic Studies

One hundred mg each of CPs (w_1) was placed on a watch glass and exposed to ambient atmospheric conditions (70±5% RH, 30±2°C) and saturation humidity conditions (99±1% RH, 30±2°C) for 2 days. The substance was weighed again (w_2). The gain in the weight was determined and the percentage moisture gained was calculated[6].

Drug Content

The CPs (100mg) were accurately weighed and dissolved separately in 100ml of 20%v/v acetic acid. The solution was suitably diluted and the absorbance was measured at 275 nm . Drug content was calculated using the regression equation[6].

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) was carried out for 1:1 CPs. The surface morphology of the selected binary systems was studied using a Phillips 1500, scanning electron microscope[7].

Fourier Transformed Infrared Spectroscopic Studies

FTIR spectral studies were carried out for pure drug, freshly prepared and six months old 1:1 CPs and individual substances to check the compatibility between drug and carriers using Shimadzu FTIR-8400S Fourier transform infrared spectrophotometer[7].

Differential Scanning Calorimetric Studies

DSC studies were carried out for pure drug, freshly prepared and six months old 1:1 CPs. All dynamic DSC studies were carried out on a calibrated Shimadzu DSC-50 Thermal Analyzer. Calorimetric measurements were made with empty cell (high purity alpha alumina discs as reference). The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10°C/minute[7].

In Vitro **Release Studies**

In vitro release studies were carried out using basket type USP XXII dissolution test apparatus (26). Release studies were carried separately for pure drug, physical mixtures and CPs for 2h in 900 ml of 0.1 N hydrochloric acid solution, pH 1.2 and phosphate buffer, pH 7.4 separately, with a stirring speed of 50 rpm at a temperature of 37±0.5 °C. Five ml aliquots of dissolution medium were withdrawn at an interval of 5 minutes for first 15 minutes and then 15 minutes intervals, for rest of the two-hour study Absorbance of the suitably diluted solutions was measured at 275 nm. The drug content was calculated using regression equation[5, 6].

Kinetic Analysis of Drug Release

The dissolution profiles of all the CPs were subjected to dissolution efficiency and the kinetic analysis to establish the drug-release mechanism. The release data were fitted to zero order (Equation 1), first order (Equation 2), matrix and Hixson-Crowell equations (Equation 3) to ascertain the kinetic modeling of drug release[8].

$$Q_t = k_0 t \quad (1)$$

$$\ln Q_t = \ln Q_0 - k_1 t \quad (2)$$

$$Q_0^{1/3} - Q t^{1/3} = k_{HC} t \quad (3)$$

Where Q_t is the amount of drug released at time t, Q_0 is the initial amount of drug in the formulation and k_0, k_1 & k_{HC} are release rate constants for zero-order, first-order and Hixson-Crowell rate equation.

Statistical analysis

All the data were expressed as mean ± SD and the data was analyzed by one-way analysis of variance (ANOVA) followed by post hoc Tukey test for multiple comparisons using Jandel Sigma Stat statistical software, version 2.0. In all the analysis $p < 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

All the CPs prepared was found to be fine and free flowing powders. Percentage yield ranged from 87.2 to 92.5% (Table 1). Low coefficient of variance (CV) values (< 1.0 %) in percentage yield indicates the reproducibility of the technique employed for the preparation of CPs. Average particle size was found to be within the range of 51.53 μm to 63.17μm (Table 1). This narrow range of particle size was satisfactory from the point of improving the aqueous solubility.

The wetting time ranged from 22.11 to 23.32 sec .The maximum wetting time was observed with AF-PVP-CP1 (23.32 sec). The percentage entrapment of the drug in CPs was found to be approximately nearer to the theoretical values. Low value for CV (<1.0) indicates uniformity of drug content in the product. The obtained results implied that the drug remained stable during preparation.

Hygroscopic Studies

The hygroscopicity of binary system containing AF-PVP (1:2-*AF-PVP-CP3*) was found to be more in comparison to other under ambient as well as saturation humidity conditions. Similar results were reported by Sethia and Squilante[9] with carbamazepine. At saturation humidity conditions the weight gain was higher, compared to ambient conditions.

Scanning Electron Microscopy

AF appeared as irregular shaped crystals. The original morphology of all other binary systems (CPs) had disappeared and it was not possible to differentiate between the two components. All the binary systems appeared as agglomerates exhibiting the presence of a homogeneous solid phase of amorphous nature. Existence of a single phase is also responsible for the enhanced drug dissolution in comparison to pure AF (Figure 1).

Table 1. Physical characteristics of coprecipitates of aceclofenac.

Carrier	Product	Drug : carrier	Percent yield	Particle size range (μm)	Average particle size (μm)	Drug content (mg)	Percent drug content	Wetting Time (sec)
PVP	*AF-PVP-CP3*	*1 : 2*	87.2 (0.79)	6.3-152.4	63.11 (0.91)	30.4 (33)*	95.7 (0.78)	22.11 (0.22)
	AF-PVP-CP 2	*1 : 1*	91.7 (0.83)	7.3-133.9	51.53 (0.92)	44.7 (50)*	96.8 (0.94)	22.16 (0.19)
	AF-PVP-CP1	*1 : 0.5*	92.5 (0.77)	6.1-153.9	63.17 (0.89)	67.2 (66.7)*	98.8 (0.91)	23.32 (0.27)

Values in parenthesis indicates the standard deviation (n=3) and values given in the parenthesis marked with * indicates theoretical values of drug content.

Figure 1. Scanning electron photomicrographs of aceclofenac (A); aceclofenac-PVP (1:2) coprecipitate (B).
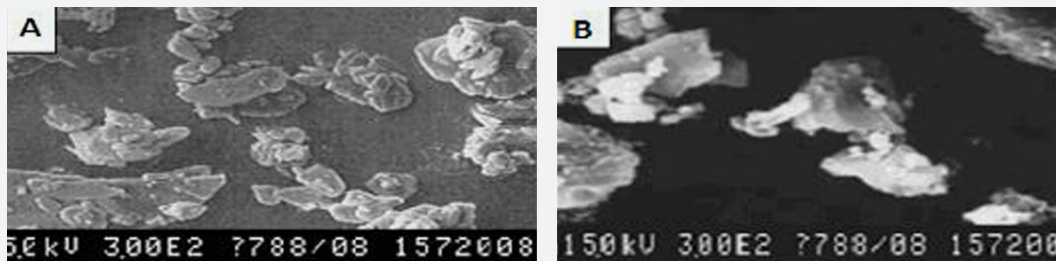

Figure 2. In vitro dissolution profile of aceclofenac-PVP coprecipitates and their physical mixtures in 0.1N HCl, pH 1.2.
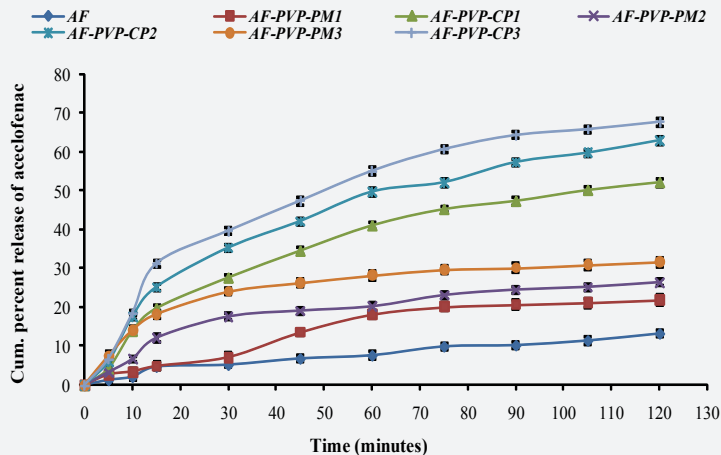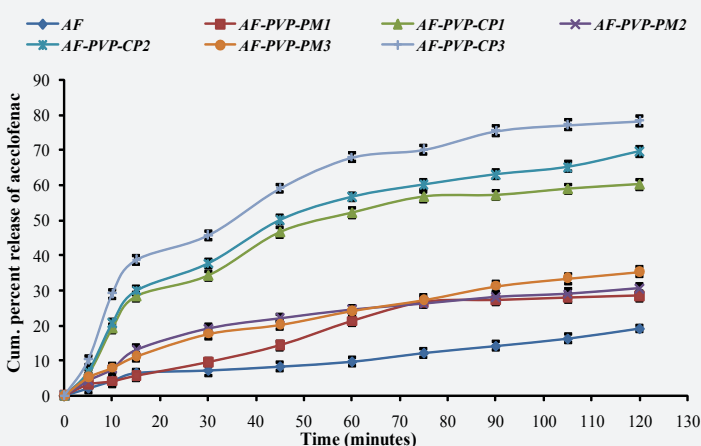

Figure 3. In vitro dissolution profile of aceclofenac-PVP coprecipitates and their physical mixtures in phosphate buffer, pH 7.4.

Fourier Transformed Infrared Spectroscopic Studies

All the characteristic bands of AF were observed in the binary mixtures. Broadening of bands was observed to a large extent. The characteristic bands of PVP were observed at 2970, 1452, 1417, 1716 and 1270 cm^{-1}. The FTIR spectra of physical mixtures and coprecipitates indicate reduction in the intensity of several peaks like O-H (s) and C-H (s). The absence of any significant change in the IR spectral pattern in the formulations containing the drug and carriers indicated the absence of interaction between the drug and carriers employed for the solubility enhancement.

Differential Scanning Calorimetric Studies

The pure AF exhibited endothermic peaks at 152.48°C which represents melting of AF and in accordance with the literature value[3]. Another endothermic peak was observed at 102 °C. This broad melting transition is due to water, because PVP is very hygroscopic product.

The DSC curve of AF with various carriers physical mixtures show peaks resulting from the superposition of their separated component DSC curves. The drug endothermic peak was suppressed in the thermograms of the CPs suggesting that the drug was able to dissolve partially in the carrier to form a solid-solid solution. The appearance of low intensity endothermic peak also indicated some of the drug still managed to crystallize out from the matrix of carrier. In addition, PVP due to its amorphous nature

also aids in retarding the crystallization of the drug. These phenomena could also be attributed to the amorphous form of the drug in prepared coprecipitates.

DSC thermograms indicate the existence of the new solid phase and confirm FTIR spectral data concerning the presence of AF in an amorphous and homogenously dispersed state in carriers employed. No additional or shift in endothermic peaks were observed which indicated the compatibility between the drug and PVP.

In Vitro Release Studies

In, 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4), the physical mixtures and CPs with all drug: carrier ratios exhibited faster dissolution rates than that of pure AF at all time points (Figure 2 and 3). The dissolution rate of CPs was faster as compared to their corresponding physical mixtures at all the time intervals. With the increase in the proportion of carrier, rate of dissolution of CPs also increases. The order of dissolution shown by the CPs was found to be 1:2 > 1:1 > 1:0.5.

All the AF formulations showed a better dissolution profile in phosphate buffer, pH 7.4 in comparison to 0.1N HCl, pH 1.2. Similar results were reported by Soni *et al.*[10] in their saturation solubility studies of AF carried out in different dissolution media. Furthermore, this may be due to the weakly acidic nature of AF. With reference to pH-solubility profile, the dissolution rate of AF has been shown to increase on increasing pH of the medium[11]. This supports higher drug release in phosphate buffer, pH 7.4 in the present study.

Among all the coprecipitates, AF-PVP-CP3 showed the maximum dissolution in 0.1N HCl, pH 1.2 (67.7±0.96%) and phosphate buffer pH 7.4 (78.2±1.30%) respectively. Due to the hydrophilic nature, PVP enhances the wetting of hydrophobic drugs in CPs. Since, wetting is prerequisite for dissolution, this effect contributed to the faster drug release as reported by Simonelli *et al*[12].

Another mechanism for this preferential enhancement of dissolution rate from CPs may be due to the formation of a eutectic mixture, or a solid solution. Enhancement of dissolution rate from CPs can also be attributed to the amorphization of drug and the particle size reduction. The particle size reduction results in increased surface area available and thus, acceleration of dissolution. In CPs , the presence of the water soluble carrier (PVP) results in improvement of wetting characteristics of poorly soluble drug like AF.

Kinetic Analysis of Drug Release

The release of drug from all formulations was observed to follow the first order release kinetics (Table 2) and have shown the maximum dissolution efficiency with AF-PVP-CP3in both 0.1N HCl, pH 1.2 and phosphate buffer, pH 7.4 (Table 3). AF-PVP-CP3 showed significantly higher release as compared to other formulations ($P<0.05$).

Table 2. Comparison of different kinetic models applied on the in vitro dissolution profile of selected formulations of aceclofenac in 0.1N HCl, pH 1.2 and phosphate buffer, pH 7.4.	*Formulation*		*Regression equations*			
			Zero order	*First order*	*Higuchi*	*Hixson Crowell*
	0.1N HCl, pH 1.2	*AF-PVP-CP3 (1:2)*	y = -0.5337t + 85.353 R^2 = 0.8630	y = -0.0041t + 1.9393 R^2 = 0.9426	y = 6.7205√t - 0.3088 R^2 = 0.9704	y = 0.012x + 0.2247 R^2 = 0.9194
	Phosphate buffer, pH 7.4	*AF-PVP-CP3 (1:2)*	y = -0.595t + 79.886 R^2 = 0.8343	y = -0.0055t + 1.9153 R^2 = 0.9445	y = 7.5872√t + 2.8538 R^2 = 0.9618	y = 0.015x + 0.3155 R^2 = 0.9139

Table 3. Dissolution parameters of aceclofenac coprecipitates

	Sample	DP_{15}	DS_{60}
	AF	8.12±0.91	43.12
0.1 N HCl, pH 1.2	*AF-PVP-CP1*	22.01±0.12	51.23
	AF-PVP-CP2	32.11±1.21	63.21
	AF-PVP-CP3	38.12±0.34	65.32
Phosphate buffer, pH 7.4	*AF-PVP-CP1*	29.23±1.23	58.34
	AF-PVP-CP2	30.01±1.21	59.12
	AF-PVP-CP3	39.11±1.34	83.44

DP15= Percent drug dissolved in 15 min; DS60= Dissolution efficiency at t=60 min (calculated from the area under the dissolution curve at t=60 min and expressed as % of the area of the rectangle described by 100% dissolution in the same time). Each value is the determination of three values.

CONCLUSION

This study clearly shows that addition of hydrophillic carrier like PVP to aceclofenac improves its dissolution rate. DSC thermograms of physical mixture and coprecipitates indicated complete miscibility of the drug in melted carrier. Amorphous nature of the drug in coprecipitates was confirmed by scanning electron microscopy and a decrease in enthalpy of drug melting in coprecipitates compared to the pure drug. Results from FT-IR spectroscopy concluded that there was no well-defined interaction between aceclofenac and carriers employed in the preparation of coprecipitates. The coprecipitates of aceclofenac with PVP lend an ample credence for better therapeutic efficacy.

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