Drug Complexation and Physicochemical Properties of Vinylpyrrolidone-*N,N′*-dimethylacrylamide Copolymers

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ABSTRACT: Solid dispersions of the nonsteriodal antiinflammatory drug (NSAID) 2′,4′-difluoro-4-hydroxy-(1,1′-biphenyl)-3-carboxylic acid (DIF) with the water-soluble random copolymer poly(*N*-vinyl-2-pyrrolidone-co-*N,N′*-dimethylacrylamide) (VP-co-DMAm) were prepared by the solvent method (coevaporates) and melting DIF/VP-co-DMAm (cofused) physical mixtures. Differential scanning calorimetry (DSC), infrared spectroscopy (FTIR), and X-ray diffraction (XRD) were used to elucidate the possible interaction between the NSAID drug and VP-co-DMAm in cofused and coevaporated polymer–drug solid dispersions. The XRD and FTIR studies suggest the presence of physical interactions with formation of a charge transfer complex between DIF and the VP-co-DMAm copolymers as a consequence of the coevaporation or cofusion processes. In solution, dynamic and equilibrium solubility studies were determined to elucidate the mechanism of interaction between DIF and VP-co-DMAm copolymers. Thermodynamics data about the DIF: VP-co-DMAm dissolution process indicate that the coevaporated systems are more stable that the cofused systems. The dissolution of the cofused and coevaporated systems was diffusion controlled and the dissolution kinetics followed the Noyes–Whitney and the Levich equations. Molecular simulations using semiempirical quantum chemical calculations reinforce the experimental results, suggesting that the improvement in the DIF solubility could be attributed to the charge transfer complex formation between the drug and VP-co-DMAm copolymers. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 93: 1337–1347, 2004

Key words: charge transfer; dispersions; diffusion

INTRODUCTION

The dispersion of several water-insoluble drugs in a hydrophilic polymeric system has been a technique commonly used to improve the biological availability of drugs whose absorption is dissolution rate-limited.

Synthetic and natural polymers have been used in the development of new drug delivery systems and have now become widespread in pharmaceutical formulations.[1–6]

The solid dispersion approach has been successfully applied to improve the solubility dissolution rates and, consequently, the bioavailability of poorly water-soluble drugs. In this sense a variety of water-soluble polymeric systems scrutinized as solid dispersion carriers have been designed molecularly.[7,8]

Nowadays poly(*N*-vinyl-pyrrolidone) (PVP) and its derivatives are playing a very important role in the formulation of poorly water-soluble drugs due to their ability to form complexes with many types of molecules.[9–15] In pharmaceutical industries PVPs can be used as hydrophilic carriers to improve the dissolution of hydrophobic drugs by preparing solid dispersions.

The 2′,4′-difluoro-4-hydroxy-(1,1′-biphenyl)-3-carboxylic acid (DIF) is a non-steroidal antiinflammatory agent with poor water solubility where the biovailability is expected to be dissolution rate-limited. Eutetic formation from the dispersion of the DIF in polyethylene glycols (PEG) and PVP with a significant increase in the dissolution rate of the drug have been reported.[16–22]

It has been pointed out that the copolymerization reactions provide an excellent method for the preparation of macromolecules with specific chemical structures and for the control of properties such as hydrophilic/hydrophobic balances, polarity, and solubility[23]. Thus, the biochemical properties of the water-soluble copolymers, such as interactions with proteins and adsorption of biological compounds, will depend upon the monomers or comonomers of which they are made.

Poly(*N*-vinyl-2-pyrrolidone) and poly(N,N′-dimethylacrylamide) (PDMAm) are two of the most frequently investigated classes of water-soluble homopolymers for use in medicine and in other applica-

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tions interfacing with biological systems.[24,25] The principal reason for the successful use of PVP and PDMAm in pharmaceutical formulations is their excellent biocompatibility with living tissues and extremely low citotoxicity.[26–28]

Despite the large number of investigations about the use of PVP and acrylic polymers to improve the solubility dissolution rates and consequently the bioavailability of poorly water-soluble drugs, there are few studies on the VP copolymers and, as far as the authors are aware, studies about the mechanisms of interaction between the water soluble copolymer poly(*N*-vinyl-2-pyrrolidone-co-*N*,*N*′-dimethylacrylamide) (Vp-co-DMAm) and 2′,4′-DIF have not been reported until now.

The purpose of this work was to investigate a series of random copolymers of VP-co-DMAm with selected monomer ratios and to study their interaction with the nonsteriodal anti-inflammatory drug DIF. The interaction in the solid state was investigated by differential scanning calorimetry (DSC), X-ray diffraction analysis (XRD), and Fourier-transform infrared (FTIR) spectroscopy. The interaction in solution was studied by the dissolution experiments and complemented by computer-aided molecular modeling.

EXPERIMENTAL

Materials

The NSAID DIF was obtained from Sigma. Random copolymers of *N*-vinyl-2-pyrrolidone (VP) and *N*,*N*′-dimethylacrylamide (DMAm) VP-co-DMAm, were prepared and characterized according to the method described in our previous publication.[23] Briefly, copolymerization reactions between VP and DMAm were carried out under vacuum in ethanol as the solvent using azobis(isobutyronitrile) (AIBN) (1.5×10^{-2} mol/L) as initiator, at 50°C. The resultant copolymers were precipitated from solution with diethyl ether and subsequently redissolved (in ethanol) and reprecipitated to minimize the presence of residual unreacted monomer and then dried under vacuum to constant weight. ^{1}H-NMR and ^{13}C-NMR (200 MHz, Bruker 200) spectroscopy were used to determine the precise average molar composition and purity of the synthesized copolymers.

Methods

Preparation of the DIF/VP-co-DMAm binary systems

Coevaporated solid dispersion systems. Coevaporated systems were prepared by dissolving the NSAID drug DIF and VP-co-DMAm physical mixtures in a minimum volume of absolute ethanol in the drug : VP-co-DMAm proportion of 1 : 10. The solvent was removed by lyophylization of the samples. The dispersions were then ground and sieved (75–150 μm).

Cofused solid dispersion systems. Cofused systems were prepared by heating, with constant stirring, DIF/VP-co-DMAm physical mixtures until they all melted (210°C). The melts were quickly cooled and solidified on an ice bath. The dispersions were stored 48 h in a desiccator under vacuum at room temperature before being ground in an agate mortar with a pestle and then sieved (75–150 μm).

Characterization techniques

X-ray diffraction

X-ray powder diffraction patterns were obtained with a Philips PW 1130 diffractometer (CuKα radiation), at a scan rate of 2° min^{-1} over the 5–40 20 range.

Thermal analysis

Temperature and enthalpy measurements were performed with a Mettler TA4000 apparatus equipped with a DSC 25 cell at a scanning rate of 10 K min^{-1}, on 5-to 15-mg (Mettler M3 microbalance) samples in pierced A1 pans under N_2 atmosphere. Melting enthalpies were determined following calibration with high-purity indium after integration of the areas under the melting DSC endotherms.

Infrared analysis

Fourier-transform infrared spectra (KBr disk) were obtained on a Perkin– Elmer Model 1710 apparatus using Fourier transformations of 30 scans. The instrument was internally calibrated with a laser.

Dissolution rate

The dissolution rates of free and dispersed drug (DIF) were determined in triplicate at 37°C and the required stirring rate using a USP dissolution apparatus. The dissolution medium consisted of 500 mL McIlvain buffer at the required pH and of ionic strength 0.5 adjusted with KCI. This ionic strength was used to assure the maximum swelling of the polymeric matrix. The discs in their molds were attached centrally on the surface of the top part of the USP dissolution basket apparatus leaving a lower surface of 2.00 cm^2 available for dissolution. The pH of dissolution medium was monitored throughout the experiment and was found to remain constant. A volume of 5-mL samples were withdrawn at the designated time intervals and immediately replaced with a similar volume of the fresh dissolution medium. The samples were transferred to a syringe and rapidly filtered through a 0.3-μm membrane filter unit (Millipore). The samples were then

spectrophotometrically assayed (λ = 315 nm, Shimadzu UV/VIS 1203) for the drug content. Samples were run in triplicate and the average values were taken. In all cases the standard deviation was less than 3%.

Equilibrium solubility studies

Equilibrium solubility studies were performed by placing a 50-mg sample of the DIF/VP-co-DMAm solid dispersion in to each of a series of Erlenmeyer flasks containing 10 mL of McIlvain buffer solution adjusted to the required pH. The flasks were then placed in a water bath at 37 ± 0.1°C with continuous shaking for 24 h. Samples (3 mL) were then transferred to a syringe and rapidly filtered through a 0.3-μm Millipore filter unit (Millipore).

The amount of the dissolved drug was measured spectrophotometrically by reference to a suitable calibration curve (λ = 315 nm, Shimadzu UV/VIS 1203). Each data point is the average of three individual determinations.

Viscosity measurements

Viscosities of all solutions were determined at 37°C using an Ostwald viscometer with water as a reference.

RESULTS AND DISCUSSION

Numerous water-soluble polymers for most acrylic derivatives and vinyl-type polymers have been investigated for use as macromolecular drug carriers,[29] biomaterials for cell and islet immunoisolation,[30] protein hybrids,[31] and advanced applications in biotechnology.[32]

The random copolymers of VP-co-DMAm with selected monomer ratios exhibit a broad spectrum of physicochemical properties[23] and may be used for the preparation of controlled-release drug systems.

Composed of a lactam and amide groups, VP-co-DMAm copolymers may be able to interact with aromatic compounds by forming π–σ or π–π complexes, often called charge-transfer complexes or charge-transfer or electron donor-acceptor interactions.[23]

The molecular structures of DIF and VP-co-DMAm are shown in Figure 1. It has been known for many years that PVP exhibits a series of interactions toward small molecules in solution and forms complexes with a variety of these molecules.[33–38] These studies indicate both hydrophobic and ion-lactam ring electrostatic interactions may exist in the VP-co-DMAm random copolymers.

To evaluate the interaction mechanisms between the VP-co-DMAm matrix and DIF, the classic spectroscopic (FTIR, XRD) and thermal (DSC) techniques were used.

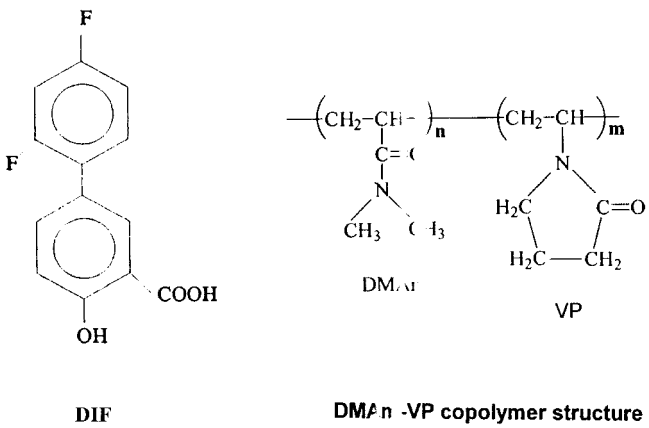

Figure 1 Molecular structures of 2′,4′-difluoro-4-hydroxy-(1,1′-biphenyl)-3-, carboxylic acid (DIF) and the VP-co-DMAm copolymer used in this work.

Interaction in the solid state

Figure 2 shows the XRD analysis of the pure DIF and coevaporated and cofused DIF/VP-co-DMAm systems. Polymer–drug XRD patterns show the typical profile of amorphous materials for both coevaporated and cofused DIF/VP-co-DMAm systems. The DIF signal completely disappeared in the studied systems, suggesting that the drug crystallization is inhibited within the VP-co-DMAm matrices, despite the VP content in the VP-co-DMAm copolymer. The pure DIF prepared in a similar manner as the dispersed samples showed the diffractographic profile of a crystalline product (Fig. 2).

Figure 3 shows representative FTIR spectra of VP-co-DMAm at VP content of 62.7% (w/w) and their 50 : 50 w/w coevaporated and cofused systems. The IR spectra of both coevaporated and cofused mixtures show the presence of the characteristic DIF and VP-co-DMAm peaks. The carbonyl and lactam groups of the DIF and VP-co-DMAm are visible at 1,680 and 2,900–3,200 cm^{-1}, respectively (Fig. 3).

A strong modification in the characteristic of amide frequency bands in the carboxyl stretching region (2,900–3,200 cm^{-1}) and a decrease of the DIF carbonyl band intensity at 1,680 cm^{-1} were observed by comparing the spectra of the VP-co-DMAm copolymer with those of corresponding coevaporated and cofused systems. The decrease in intensity of the amide and carbonyl bands give evidence that some interaction between the DIF and the VP-co-DMAm copolymer may exist.

The DSC curves of the DIF : VP-co-DMAm cofused and coevaporated systems are presented in Figure 4. In the DSC analysis, the pure DIF exhibits a endother-

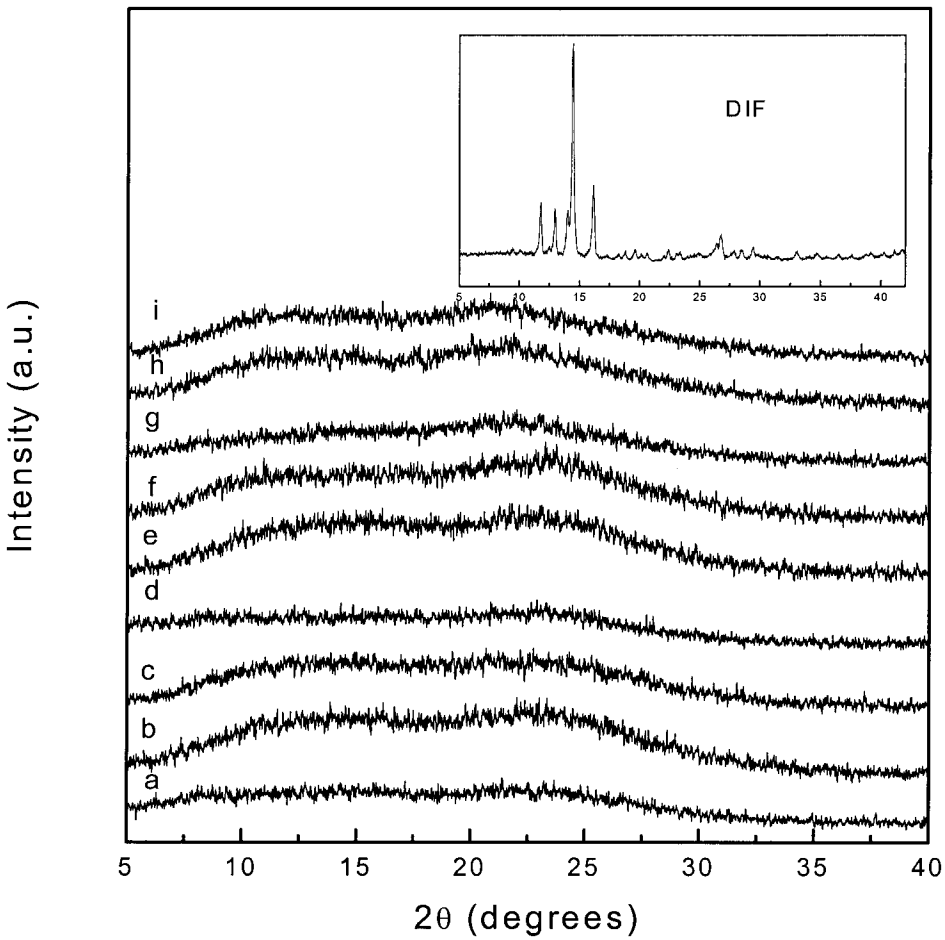

Figure 2 X-ray powder diffraction patterns of 2′,4′-difluoro-4-hydroxy-(1,1′-biphenyl)-3-carboxylic acid (DIF) and their coevaporated (a–e) and cofused (f–i) systems. The VP weight percentage (wt %) in VP-co-DMAm copolymers is (a) 0, (b) 8, (c) 29.3, (d) 62.7, (e) 100, (f) 0, (g) 29.3, (h) 62.7, and (i) 100. Drug : polymer (w/w) ratio, 1 : 1.

mic peak around 214.8°C (melting point of the drug). A blend of the drug with VP-co-DMAm copolymer resulted in a sensible decreasing of the DIF endothermic peak and the disappearance of the fusion temperature of the copolymer in both cofused and coevaporated systems (Fig. 4). This fact may be indicative of an eutetic mixture formation between DIF and VP-co-DMAm copolymers.[39] The presence of the weak endotherm signals in VP-co-DMAm cofused or coevaporated systems may be indicative that DIF crystals still exist in solid dispersions.

The process of drug absorption takes place in an aqueous environment. The rate of drug dissolution depends on the interactions between the polymeric material and on the ability of the polymer to swell and the number of ionizable groups in the system.

It is well documented in the literature that, in the presence of hydrogen donors, the mesomerism of the peptide linkage in VP may be significantly shifted and hydrophobic interactions and electrostatic in VP- VP-co-DMAm may contribute to the formation of a charge-transfer complex with DIF.[37,38]

To understand the interactions between DIF and VP-co-DMAm random copolymers in cofused and coevaporated systems, the dissolution assay was considered in a macroscopic sense.

Interaction in aqueous phase

In a diffusion-controlled dissolution process, dissolution rate per unit surface area, J, of a dissolving solid, A, may be calculated by the graphical methods of the Noyes– Whithney equation:[40]

$$J = KA(C_s - C) \quad (1)$$

where J is the dissolution rate per unit surface area of the dissolving solid A, K is the dissolution rate constant, C_s is the saturation solubility of the drug, and C is its concentration in the dissolution medium at particular time.

The constant K may be calculated in according to the diffusion layer theory as:[41]

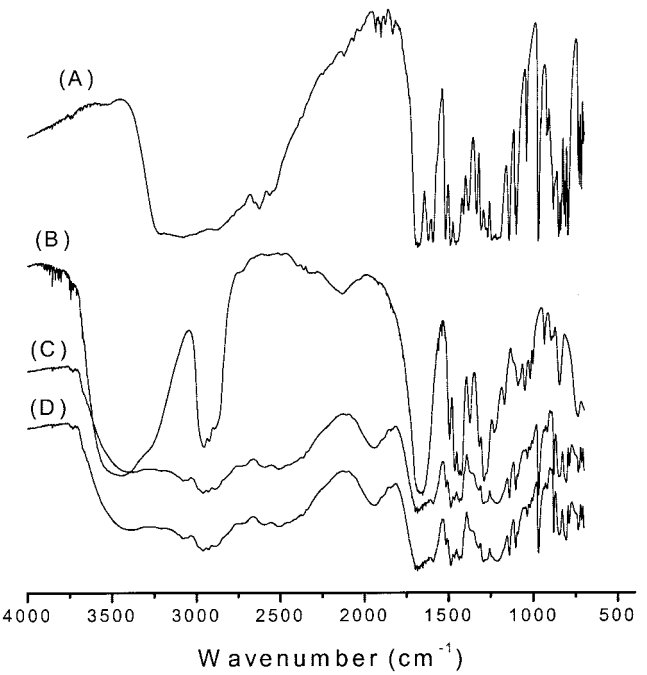

Figure 3 FTIR spectra of DIF (A), VP-co-DMAm copolymer at VP content of 62.9% w/w (B), and DIF:VP-co-DMAm coevaporated (C) and cofused (D) systems. DIF : VP-co-DMAm ratio, 1 : 10.

$$J = \frac{D}{h} \tag{2}$$

where D is the coefficient of diffusion of the drug through the diffusion layer and h is the thickness of such layer. If $C_s \gg C$, eq. (1) becomes:

$$J = \frac{DAC_s}{h} \tag{3}$$

Equation (3) indicates that, for diffusion-controlled dissolution processes, J is directly proportional to D and inversely related to h.

The coefficient of diffusion, D, and the thickness of the diffusion layer have been fitted to the Levich equations:[42]

$$J = \frac{0.62\sqrt[3]{D^2}}{\sqrt[6]{\nu}}\sqrt{\omega}C_s \tag{4}$$

$$h = \frac{1.612\sqrt[3]{D^2}}{\sqrt{\omega}}\sqrt[6]{\nu} \tag{5}$$

where ν is the kinematical viscosity of the dissolution medium and ω is the angular speed of rotation.

To gain information on the nature of a possible interaction in solution between DIF and VP-co-DMAm copolymers, solubility experiments were performed at 37°C. The drug solubility linearly increased as the VP content in the copolymer increased, in all cases showing the features that a soluble complex between VP-co-DMAm copolymers and DIF may have occurred (Fig. 5). The coevaporated DIF/VP-co-DMAm systems exhibited faster drug dissolution rates than cofused DIF/VP-co-DMAm systems, possibly due to an increase in the wettability of the drug particles and a local solubilization effect by the carrier at the DIF layer caused by a major interaction between the drug and the macromolecule.

Figures 6 and 7 show the dissolution rates of DIF per unit area, J, plotted as a function of the square root of the angular speed of rotation. The linearity of the plots suggests that the dissolution kinetics followed both Noyes–Whitney and Levich equations.

The slopes of the Levich plot (Figs. 6 and 7) were used to calculate the diffusion coefficient, D of coevaporated and cofused DIF : VP-co-DMAm systems according to eq. (6). As is evident from Figure 8 there is a significant increase in the diffusion coefficient with the VP content, and saturation is attained at a VP content of 100% w/w. An increase in the diffusion coefficient may be due to the high proportion of undissociated relative to the noionized DIF molecules in the hydrodynamic layer.[43]

Figure 9 shows the variation of the diffusion coefficient of DIF with pH. As can be seen, an increase in pH

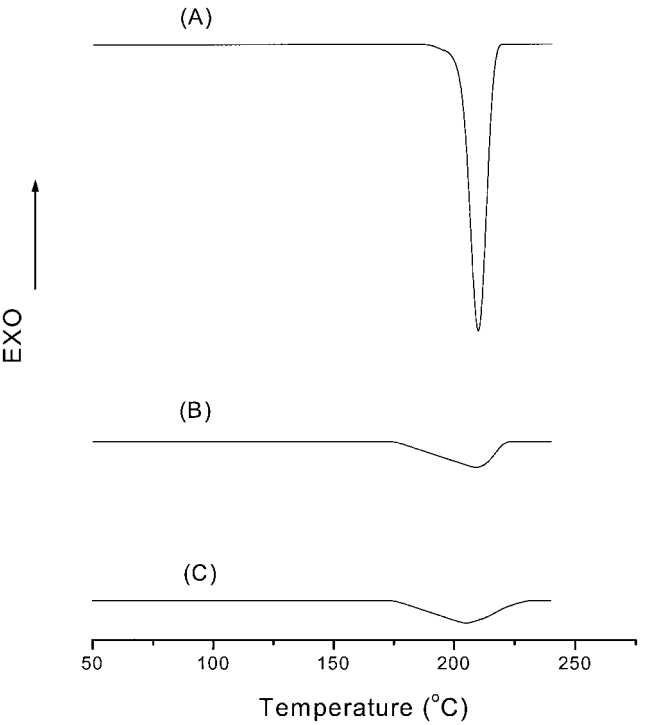

Figure 4 DSC curves of 2′,4′-difluoro-4-hydroxy-(1,1′-biphenyl)-3-carboxylic acid (DIF) (A) and DIF : VP-co-DMAm coevaporated (B) and cofused (C) systems. Drug : polymer (w / w) ratio, 1 : 10. VP content in the copolymer (w/w), 62.7%; melting point of the pure VP-co-DMAm copolymer, 150°C.

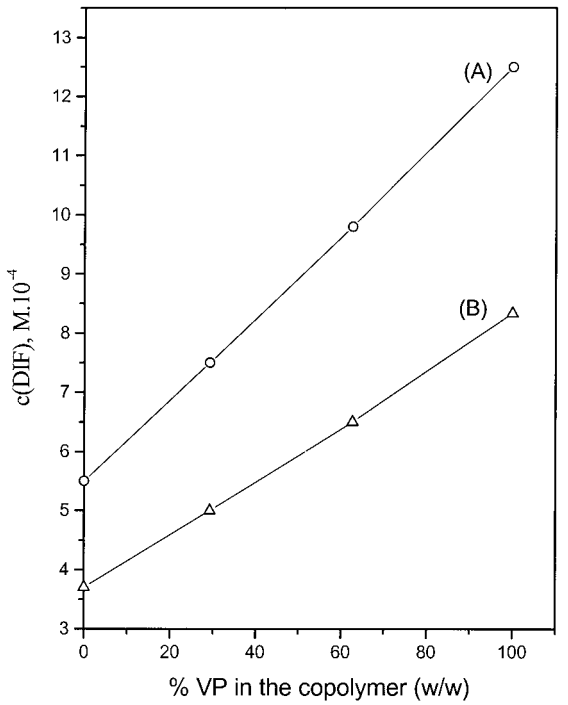

Figure 5 Aqueous solubility of the 2′,4′-difluoro-4-hydroxy-(1,1′-biphenyl)-3 carboxylic acid (DIF) in the presence of VP-co-DMAm copolymers at 50 : 50 w/w coevaporated (A) and cofused (B) systems. McIlvein buffer and 37°C. Samples were run in triplicate and the average values were were taken. In all cases the standard deviation was less than 3%, $p < 0.032$.

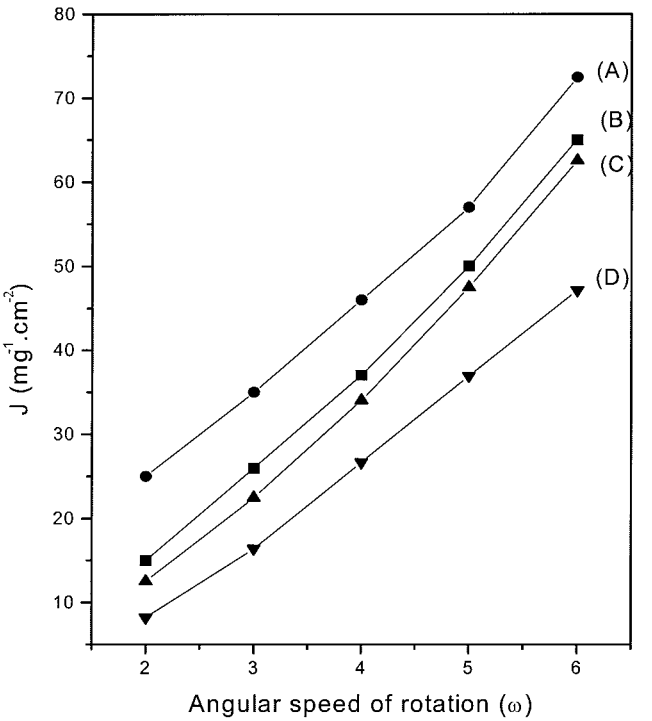

Figure 7 Flux *J* of DIF dispersed in VP-co-DMAm cofused systems as a function of the angular speed of rotation. VP content in the copolymer (% w/w) : 62.7 (A), 29.3 (B), 100 (C), and 0 (D).

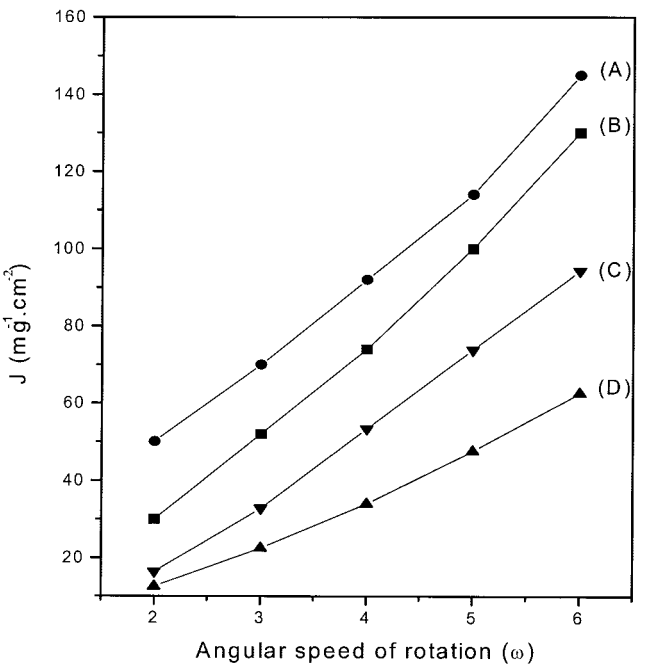

Figure 6 Flux *J* of DIF dispersed in VP-co-DMAm coevaporated systems as a function of the angular speed of rotation. VP content in the copolymer (% w/w) : 62.7 (A), 29.3 (B), 100 (C), and 0 (D). The standard deviation was less than 1.8%, $p < 0.0018$.

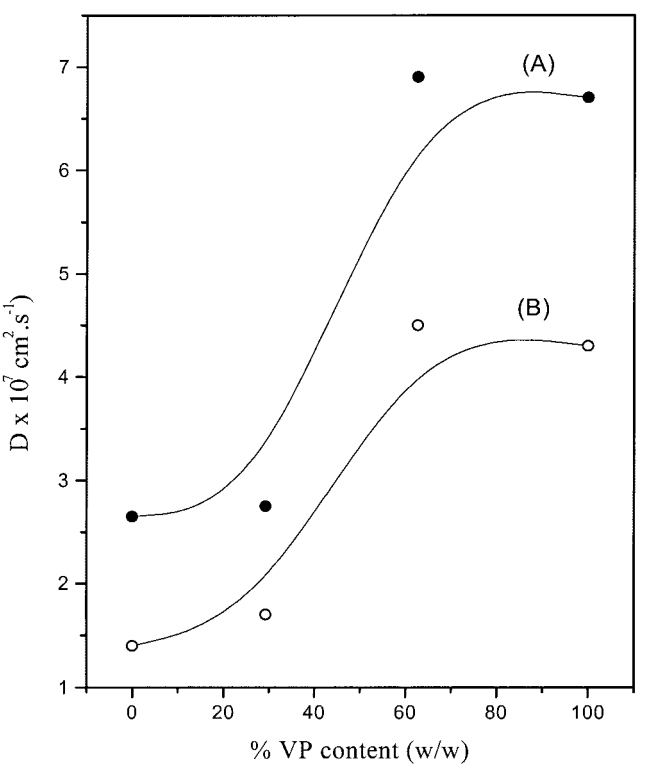

Figure 8 Relationship between the diffusion coefficient of DIF and the amount of VP present if the VP-co-DMAm copolymers. Coevaporated DIF : VP-co-DMAm (A) and cofused DIF : DMAm (B) systems. The standard deviation was less than 3%, $p < 0.0028$.

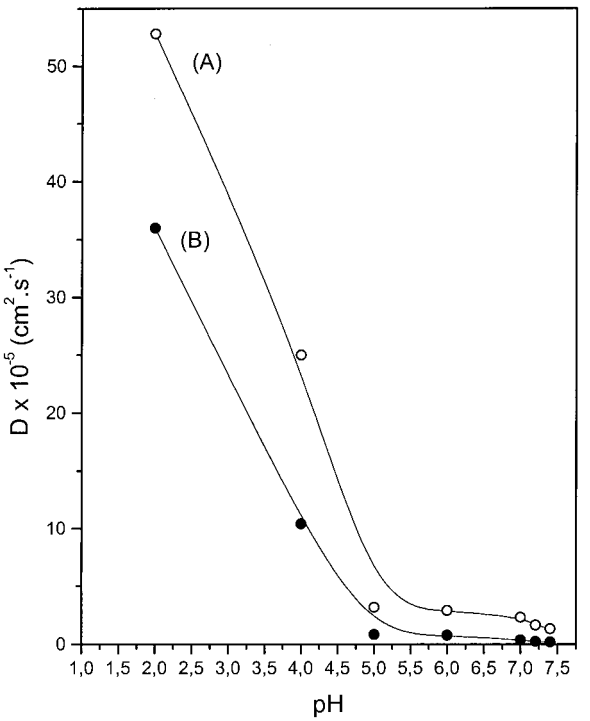

Figure 9 Variation of the diffusion of 2′,4′-difluoro-4-hydroxy-(1,1′-biphenyl)-3-carboxylic acid (DIF) with pH for DIF : VP-co-DMAm. coevaporated (A) and cofused systems. Each point is the average of three individual determinations. In all cases the standard deviation was less than 2.5%, $p < 0.0045$.

is associated with a decrease in the diffusion coefficient, indicating that the diffusivity of the dissociated DIF is less that of the undissociated forms.

Thermodynamic parameters for the process of DIF dissolution in VP-co-DMAm aqueous solutions were determined from the variation of drug solubility at each VP concentration in the copolymer as a function of temperature.

It is well known that the Gibbs free energy, G, governs the dissolution processes. From the first and second thermodynamic laws, the Gibbs free energy change may be related in an isothermal process to the enthalpy and entropy change by:[44]

$$\Delta G = \Delta H - T\Delta S \tag{6}$$

where ΔH and ΔS are the enthalpy and entropy change, respectively. Thus, for the attainment of a homogeneous solution, a decrease in Gibbs free energy ($\Delta G < 0$) has been observed.

If all components behave ideally, the free energy may be written as:

$$\Delta G = -RT\ln K_{eq} \tag{7}$$

and eq. (6) may be written as:

$$K_{eq} = e^{-\frac{\Delta H}{RT}} e^{\frac{\Delta S}{R}} \tag{7}$$

or

$$\ln K_{eq} = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} \tag{8}$$

where K_{eq} is the equilibrium constant.

The values of ln K_{eq} (where $K_{eq} = N/N_o$, N, and N_o represent the mole fraction of solubility of DIF in aqueous solution, with and without VP-co-DMAm present) were plotted against the inverse of the absolute temperature. The enthalpy values were calculated from the slopes of these plots and the free energy variation and the change in entropy associated with the dissolution process were evaluated.

The representative results of the thermodynamic parameters at 37°C are listed in Table I. As is evident from the results summarized by Table I, the binding process is exothermic; furthermore, it is invariably accompanied by a positive entropy change. The ΔH values found suggested an involvement of hydrogen bonds in the DIF–polymer interaction in solution. Also increased binding affinities, in going from 0 to 100% VP content (w/w), are associated with large changes in ΔS rather than with small changes in ΔH. The most obvious explanation for this trend is in terms of increased van der Waals forces that accompany increased molecular size.

TABLE I
Thermodynamic Parameters for the Dissolution of 2′,4′-Difluoro-4-hydroxy-(1,1′-biphenyl)-3-carboxylic (DIF) in VP-co-DMAm Aqueous Solution in McIlvain Buffer (pH 7.0, 37°C)

%VP (w/w)	ΔG_{coev}[a] (kcal/mol^{-1})	ΔH_{coev} (kcal/mol^{-1})	ΔS_{coev} (cal/molK)	ΔG_{cofus} (kcal/mol^{-1})	ΔH_{cofus} (kcal/mol^{-1})	ΔS_{cofus} (cal/molK)
0	−5.93 ± 0.10	−4.1 ± 0.13	5.9 ± 0.17	−5.26 ± 0.22	−3.8 ± 0.19	4.7 ± 0.27
29.3	−6.27 ± 0.12	−2.7 ± 0.09	11.5 ± 0.16	−4.94 ± 0.11	−1.9 ± 0.12	9.8 ± 0.37
62.7	−6.56 ± 0.17	−1.1 ± 0.08	17.6 ± 0.21	−4.87 ± 0.18	−0.9 ± 0.03	12.8 ± 0.57
100	−6.42 ± 0.11	−1.8 ± 0.15	14.9 ± 0.32	−5.19 ± 0.23	−1.5 ± 0.16	11.9 ± 0.11

[a] Subscripts coev and cofus indicate the DIF : VP-co-DMAm systems obtained by the coevaporation and cofusion techniques, respectively.

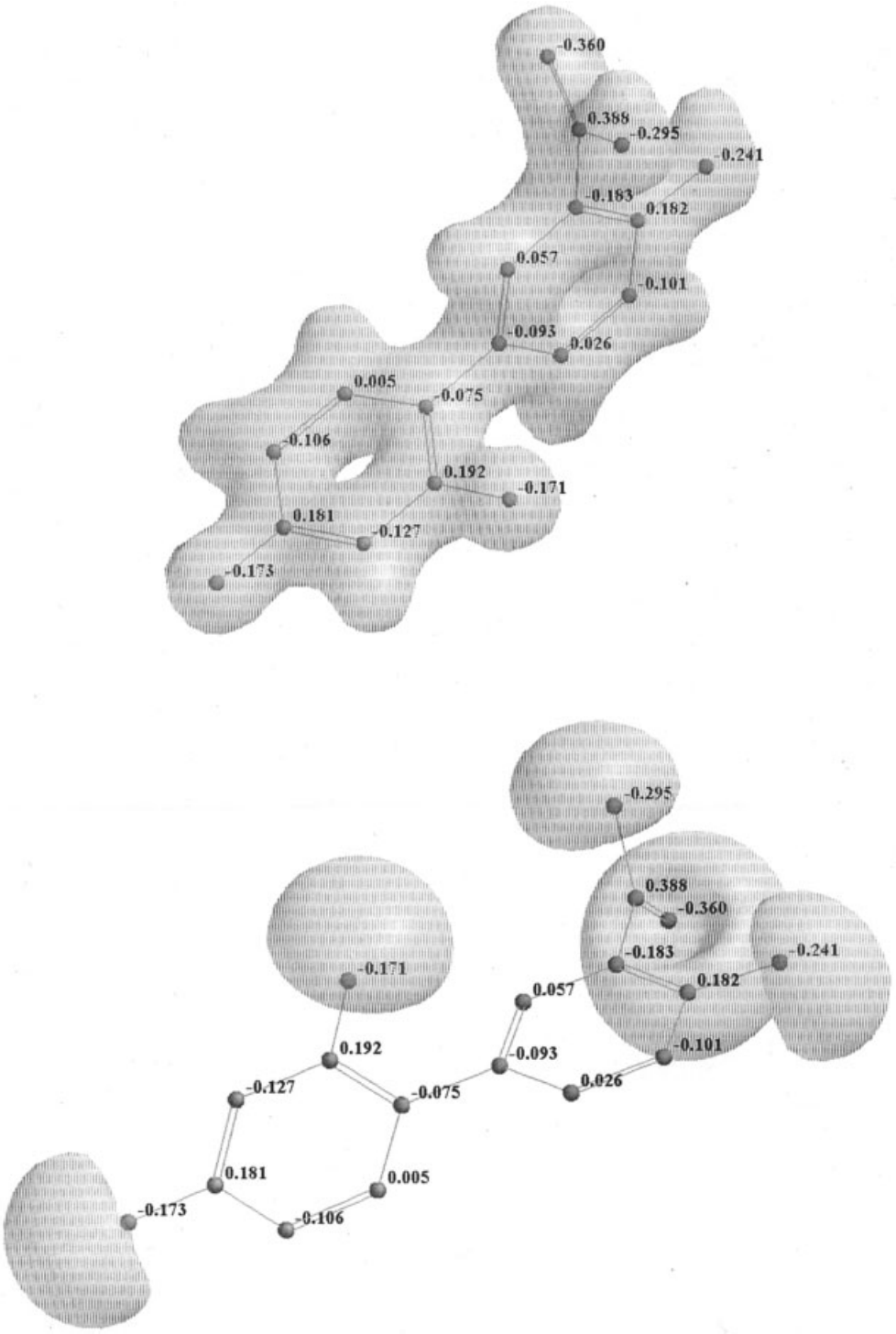

Figure 10 Isopotencial surfaces for 2′,4′-difluoro-4-hydroxy-(1,1′-biphenyl)-3-carboxylic acid (DIF) showing the reactive sites of the molecule. The negative charges represent the distribution of the Mülliken charges.

Another possible explanation for the interaction of DIF with high VP content copolymers may be the charge-transfer complex formation due to the interaction of the aromatic ring of DIF with the VP structure of VP-co-DMAm copolymers. Furthermore, it can be seen in Table I that the coevaporated systems are thermodynamically more stable than the cofused systems.

Computer modeling with energy minimization calculations are a powerful means for evaluating and understand the molecular interactions in computer-aided drug design pharmaceutical research.[45,46]

The complex formation between DIF and VP-co-DMAm could be studied by quantum chemical calculations. Assuming that a charge-transfer interaction

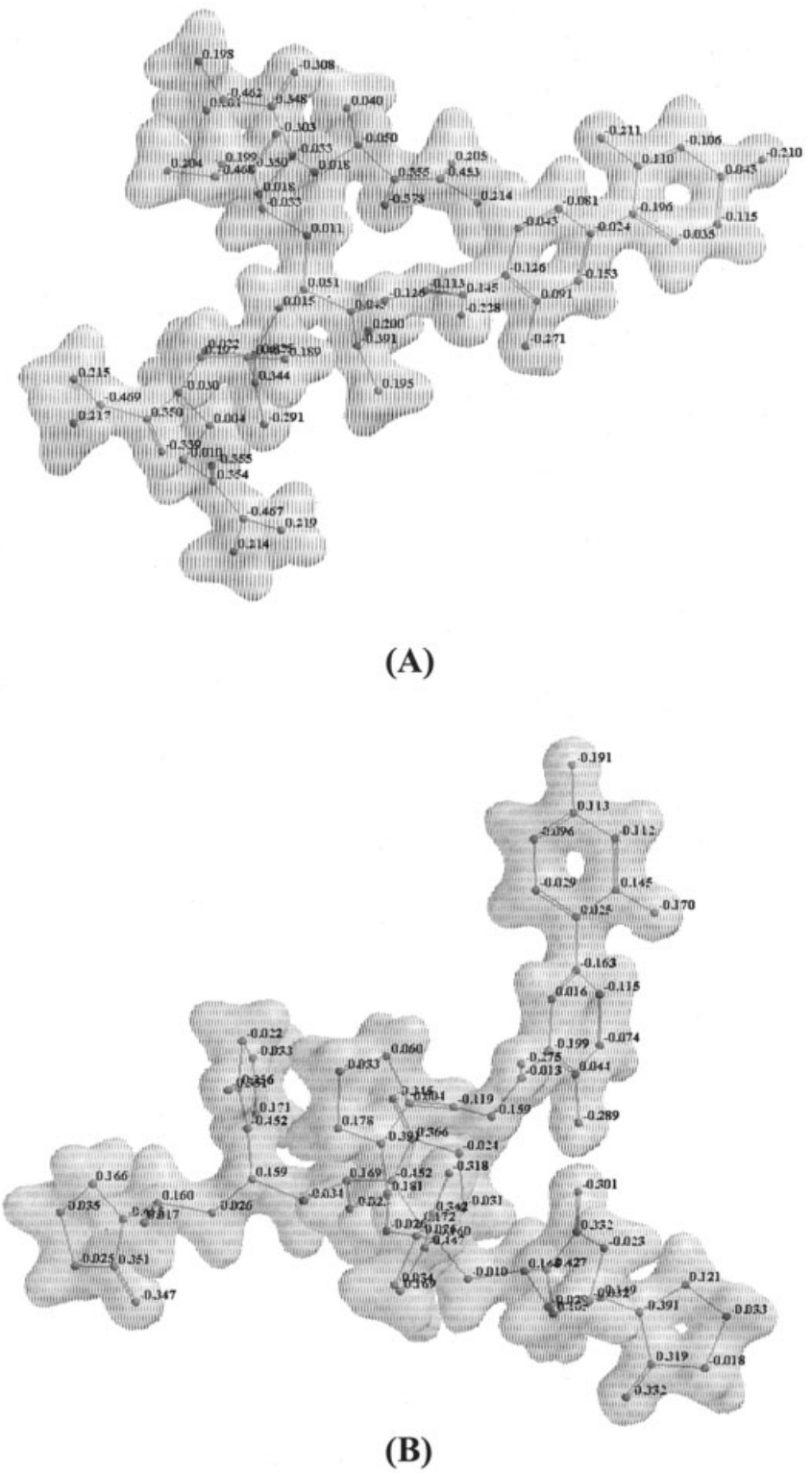

Figure 11 Interaction of 2′,4′-difluoro-4hydroxy-(1,1′-biphenyl)-3-carboxylic acid (DIF) with VP (A) and DMAm (B) oligomeric structures. ΔH_f(VP), −366.73kcal/mol; ΔH_f(DMAm), −219.66 kcal/mol. The numbers represent the Mülliken charges.

may be responsible by the complex formation between VP or DMAm monomeric units and DIF, the possible bonding sites are the carbonyl and the nitrogen alone pair of the monomeric structures present in the macromolecule.

Figures 10 and 11 show the semiempirical quantum chemical calculation using MNDO-d (TITAN) on a model system. The isopotencial DIF surfaces (Fig. 10) indicate that the carboxyl groups and the fluorine atoms in the molecule are highly reactive species as

can be seen by the distribution of the Mülliken charges (reactive atom or groups present negative Mülliken charges).

The isopotencial surfaces of the DIF: VP or DIF: DMAm charge-transfer complexes are shown in Figure 11. As pointed out by the Mülliken charges distribution, the interaction between the drug and the oligomeric structures preferentially occurs with the carboxyl groups. The heat formation of the charge-transfer complexes DIF : VP and DIF : DMAm are -366.73 and -219.66 kcal/mol^{-1}, respectively.

Thus, the higher VP units content in the VP-co-DMAm copolymers may contribute to the formation of more stable drug–polymer complexes.

CONCLUSION

In the present work, the incorporation of DIF, an NSAID drug, was performed in solid dispersions (coevaporates and cofused systems) made from random copolymers of VP-co-DMAm, with selected monomer ratios. The dispersed drug did not change its crystalline status, however, reaching microcrystalline form in the matrixes, as suggested by FT-IR, XRD, and DSC analyses. In aqueous phase studies, the coevaporated DIF/VP-co-DMAm systems exhibited faster drug dissolution rates than cofused DIF/VP-co-DMAm systems, possibly due to an increase in the wettability of the drug particles and a local solubilization effect by the carrier at the DIF layer caused by a major interaction between the drug and the macromolecule. Thermodynamically, the interaction between DIF and VP-co-DMAm appears to be more intense in the copolymers with higher VP content in the copolymer.

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