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Research paper

Physical solid-state properties and dissolution of sustained-release matrices of polyvinylacetate

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Abstract

Solid-state compatibility and in vitro dissolution of direct-compressed sustained-release matrices of polyvinylacetate (PVAc) and polyvinylpyrrolidone (PVP) containing ibuprofen as a model drug were studied. Polyvinylalcohol (PVA) was used as an alternative water-soluble polymer to PVP. Differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD) were used for characterizing solid-state polymer–polymer and drug–polymer interactions. The mechanical treatment for preparing physical mixtures of polyvinyl polymers and the drug (i.e. simple blending or stressed cogrinding) was shown not to affect the physical state of the drug and the polymers. With the drug–polymer mixtures the endothermic effect due to drug melting was always evident, but a considerable modification of the melting point of the drug in physical binary mixtures (drug:PVP) was observed, suggesting some interaction between the two. On the other hand, the lack of a significant shift of the melting endothermic peak of the drug in physical tertiary drug–polymer mixtures revealed no evidence of solid-state interaction between the drug and the present polymers. Sustained-release dissolution profiles were achieved from the direct-compressed matrices made from powder mixtures of the drug and PVAc combined with PVP, and the proportion of PVAc in the mixture clearly altered the drug release profiles in vitro. The drug release from the present matrix systems is controlled by both diffusion of the drug through the hydrate matrix and the erosion of the matrix itself.

Keywords: Sustained-release matrix; Polyvinylacetate; Polyvinylpyrrolidone; Ibuprofen; Solid-state compatibility; Dissolution

1. Introduction

The successful formulation of an effective and stable pharmaceutical dosage form depends on the careful selection and characterization of excipients. It would be very important to have readily available knowledge of potential physical and chemical interactions between a drug and excipients, which might affect the chemical nature, stability, solubility, dissolution and in vivo absorption of the drug. Numerous polymers are used as excipients in the design of controlled-release pharmaceutical products. Physical and chemical interactions and incompatibilities have been found between many drugs and polymers as has been recently reviewed by Crowley and Martini [1].

Well-known examples of drugs that may readily undergo physical and/or chemical drug–excipient interaction are non-steroidal anti-inflammatory drugs (NSAIDs) [2–5]. Botha and Lötter [3] reported in a series of compatibility studies a number of interactions between ketoprofen and polyvinylpyrrolidone (PVP) and some other polymers. Pignatello et al. [4] studied the incorporation and release of diflunisal, flurbiprofen and

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piroxicam (NSAIDs) from Eudragit RS 100 and RL 100 polymers one of which was found highly dependent on the acid nature of these drugs which allow chemical and physical interactions. Compatibility studies between ibuproxan and pharmaceutical excipients have also been presented [5].

Vinyl polymers such as polyvinylacetate (PVAc), polyvinylalcohol (PVA) and PVP are widely used excipients in the development of oral controlled-release products [6]. PVAc is a homopolymer synthesized from vinyl acetate monomer via a free-radical polymerisation technique. Although water-insoluble, it is slightly hydrophilic and able to absorb water to a slight extent. PVAc has been reported to be effective in controlling the release of various chemical entities, including theophylline [7,8], nifedipine [9] and chlorpromazine hydrochloride [10]. PVA is a hydrophilic, semicrystalline copolymer of vinyl acetate and vinyl alcohol. The polymer's biocompatibility has made it an excellent material for use in medical applications as a drug delivery device [11]. PVP is a commonly used water-soluble and physiologically inert polyamide polymer that can be used as a co-polymer in controlled-release applications. PVP, however, has been reported to have physicochemical interactions with some other polymers including polyvinylacetate phthalate, PVAP [12] and polyacrylic acids (Carbopol) [13]. A physical mixture of PVAc and PVP, was recently introduced and commercially available (Kollidon RS), and it was demonstrated to effectively retard the release of some drugs [14,15].

The aim of the present study was to investigate the physical solid-state interactions between an acidic model drug (ibuprofen) and vinyl polymers (PVAc, PVA, and PVP, Fig. 1). Differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) were used for the assessment of the compatibility of ibuprofen with vinyl polymer excipients as well as between vinyl polymers. The influence of processing (simple blending or stressed cogrinding) on the physical stability of the drug was also evaluated. Finally, the release and influence of the polymer ratio on the release kinetics of the poorly water-soluble model drug (ibuprofen) from sustained-release matrices of PVAc were also investigated.

2. Materials and methods

2.1. Materials

Polyvinylacetate (PVAc, POVIAC), average MW 20,000–30,000 Da, was kindly supplied by the National Scientific Research Center, Cuba. PVP (MW 25,000 Da, Kollidon K-25, BASF Aktiengesellschaft, Germany) and PVA (MW 14,000 Da, BDH Chemical Ltd Poole, UK) were used as co-polymers. Ibuprofen USP was obtained from BASF Knoll Pharma Chemicals, UK.

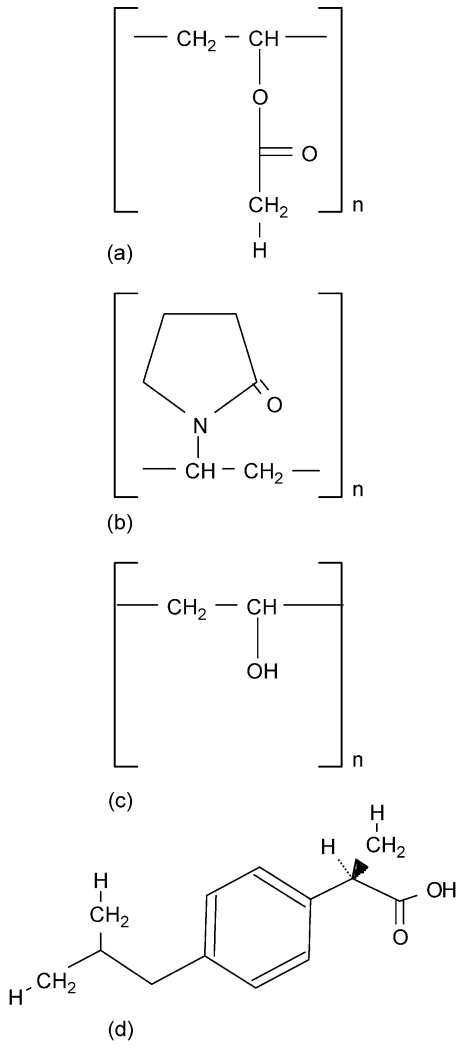

Fig. 1. Chemical structures of (a) polyvinylacetate (PVAc), (b) polyvinylpyrrolidone (PVP), (c) polyvinylalcohol (PVA), and (d) ibuprofen.

2.2. Preparation of physical mixtures and sustained-release matrices

Each material was sieved and the respective sieve fraction of 71–125 μm was selected. Physical mixtures (PM) of ibuprofen and polymers (Table 1) were prepared by gently blending in an agate mortar with a spatula at room temperature (22 ± 1 °C). Coground mixtures were obtained by grinding a portion of respective PMs with a pestle for approximately 10 min. These samples were applied to reproduce e.g. the physical changes that may happen during compression.

For compressing sustained-release matrices, quantities of each physical mixture were weighed out individually and poured into a die. The upper punch, the lower punch and the die were lubricated with 5% magnesium stearate acetone suspension. Matrix tablets were manually compressed using an instrumented Korsch EK-0 (Erweka Apparatebau GmbH, Germany) single-punch tablet machine. Flat-faced punches

Table 1
Composition of physical mixtures (PM) of ibuprofen and polymers

Material	Physical mixture (PM)									
	P1	P2	P3	P4	P5	D-P1	D-P2	D-P3	D-P4	D-P5
Ibuprofen	–	–	–	–	–	50%	50%	50%	50%	50%
PVAc	100%	80%	50%	20%	–	50%	40%	25%	10%	–
PVP or PVA	–	20%	50%	80%	100%	–	10%	25%	40%	50%

Percentages are expressed in terms of w/w.

9 mm in diameter were used. The breaking strength of the matrices ($n = 6$–8) was measured immediately after compression using a Schleuniger-2E tester (Schleuniger GmbH, Germany) and they were produced to a constant mechanical strength of 50–60 N.

2.3. Differential scanning calorimetry (DSC)

DSC measurements were performed using a DuPont differential scanning calorimeter (Model 910S, TA Instruments, New Castle, DE, USA) coupled with a computer data station (Thermal analyst 2000, TA Instruments, New Castle, DE, USA). The temperature axis and the cell constant of the DSC cell were calibrated with indium (10 mg, 99.999% pure, peak maximum at 156.6 °C and heat of fusion = 28.4 J/g). Weighed samples of 5–15 mg were placed in aluminum pans and the samples were scanned from 30 to 300 °C using a heating rate of 10 °C/min in crimped pans under static air. Peak transition temperature was determined by the integration of the heat flow versus temperature peak data with DSC standard Data Analysis System Software V4.0.

2.4. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction data were collected using a theta–theta diffractometer (D8 Advance, Bruker axs GmbH, Germany). The XRD experiments were performed in a symmetrical reflection mode using CuKα radiation (1.54 Å) at 40 mA and 40 kV using Göbel Mirror bent gradient multilayer optics. The scattered intensities were measured with a scintillation counter. The angular range was from 3 to 40° with steps of 0.05°, and the measuring time was 1 s/step.

2.5. Dissolution test

The in vitro release tests of the matrices were performed using a USP dissolution apparatus I (basket method). The dissolution medium was 900 ml of phosphate buffer solution (pH 7.2) maintained at 37 ± 0.5 °C as described in the USP 24. The basket rotation speed was set at 100 rpm. The samples were filtered through a filter of 0.45 μm pore size and assayed by UV spectrophotometry (Perkin-Elmer, Perkin-Elmer GmbH, Germany) at 221 nm for ibuprofen. Six parallel tests were performed for each matrix systems. To visually characterize the residues of sustained-release matrices after the dissolution test, stereomicrographs were taken using a Leica MZ6 stereomicroscope (Leica Imaging Systems Ltd, UK).

2.6. Modeling the drug release kinetics

The drug release kinetics was analysed versus time and the data was fitted to the following exponential model proposed by Korsmeyer et al. [16] for the first 60% of the total amount of drug released

$$M_t/M_\infty = kt^n \quad (1)$$

where M_t/M_∞ is the fractional drug release into the dissolution medium, k is a constant related to the properties of the drug delivery system, and n is the diffusional exponent, which characterizes the drug release mechanism. For matrix tablets, when $n \sim 0.5$, the drug diffuses through and is released from the polymeric matrix by quasi-Fickian drug diffusion. When $0.5 < n < 1.0$, an anomalous, non-Fickian solute diffusion mechanism occurs and, when $n = 1.0$, can be interpreted as zero-order drug release kinetics [17].

3. Results and discussion

3.1. Solid-state polymer–polymer and drug–polymer interactions

3.1.1. Differential scanning calorimetry

The DSC thermal parameters for the polyvinyl polymers and the physical binary mixtures of these (P1-5) were analyzed (data not demonstrated in the figures). Pure polymer components showed the characteristic thermal parameters in each case. A small endothermic peak was observed for PVAc corresponding to glass transition (Tg onset at 33.8 °C) in agreement with earlier reports on this polymer [8]. PVAc is amorphous due to the presence of an acetate ester side chain in the backbone structure (Fig. 1), and the glass transition is relatively low due to its highly flexible backbone structure. PVP exhibited a shallow broad endothermic effect in the 60–120 °C range due to the polymer dehydration.

On the other hand, PVA showed a typical behavior with two endotherms. The first one was present at 70.6 ± 3.2 °C (onset temperature), corresponding to the glass transition temperature of the amorphous region. The second endotherm exhibited at 212.1 ± 0.3 °C (onset temperature), corresponding to the crystalline region melt. The thermal parameters of each pure component could be observed in all physical binary mixtures even when a slight shift of thermal parameters was evident, but these changes may be ascribed to the mixing of the components which is in agreement with earlier reports [5]. For all binary mixtures of PVAc and PVA tested, as the proportion of semicrystalline PVA component decreased in binary mixtures the melting point for the PVA shifted toward a melting point lower than that for pure polymer. These results suggest that PVAc and PVA or PVP are not miscible over the whole composition range and the conditions of the present study.

DSC thermograms of the physical mixtures of ibuprofen and the present polyvinyl polymers are shown in Fig. 2. In order to evaluate the effects of mechanical treatment on the physical state of the drug and polymers, two different techniques were used to prepare the physical binary mixtures: simple blending and stressed cogrinding. The DSC profiles of both physical binary and tertiary mixtures between drug and vinyl polymers were not influenced by the sample treatment, and the same thermal behavior was observed for the two series of samples.

The DSC curve for pure ibuprofen exhibited a single melting endothermic at 77.3 °C (enthalpy of melting 111.4 J g^{-1}), which is in agreement with the values reported in the literature [2,18]. The thermal profile corresponding to the physical binary mixture between ibuprofen and PVAc showed combined thermal characteristics of drug and polymer, indicating that the drug remains in the crystalline state after cogrinding with PVAc.

In the case of the physical binary mixtures of IBU:PVP and IBU:PVA, a typical melting peak for ibuprofen was observed. As seen in Fig. 2, a considerable shift of the endothermic peak temperature (from 77.25 to 72.11 °C) of the mixture of ibuprofen and PVP was observed, indicating a greater aptitude of this polymer for interaction with the drug. A similar result has been reported between ibuproxan (NSAID) and PVP in a physical mixture with a noticeable shift of peak temperature by more than 5 °C [5]. In addition, a concomitant reduction in peak size and enthalpy per unit mass of ibuprofen was evident (ΔH of ibuprofen decreased from 111.7 to 41.81 J g^{-1}). It may be attributed to some solid–solid interaction, although it does not necessarily indicate any incompatibility [2].

The DSC thermograms of the physical binary mixtures of IBU:PVA showed that ibuprofen and vinyl polymer share some characteristics features (Fig. 2). The first endothermic effect was due to the melting peak of the drug at 74.65 °C ($\Delta H = 57.29$ J/g), indicating that ibuprofen remains in its original state (drug in the mixture 50% w/w). The second endothermic signal was due to the crystalline region melt corresponding to PVA. These results suggest

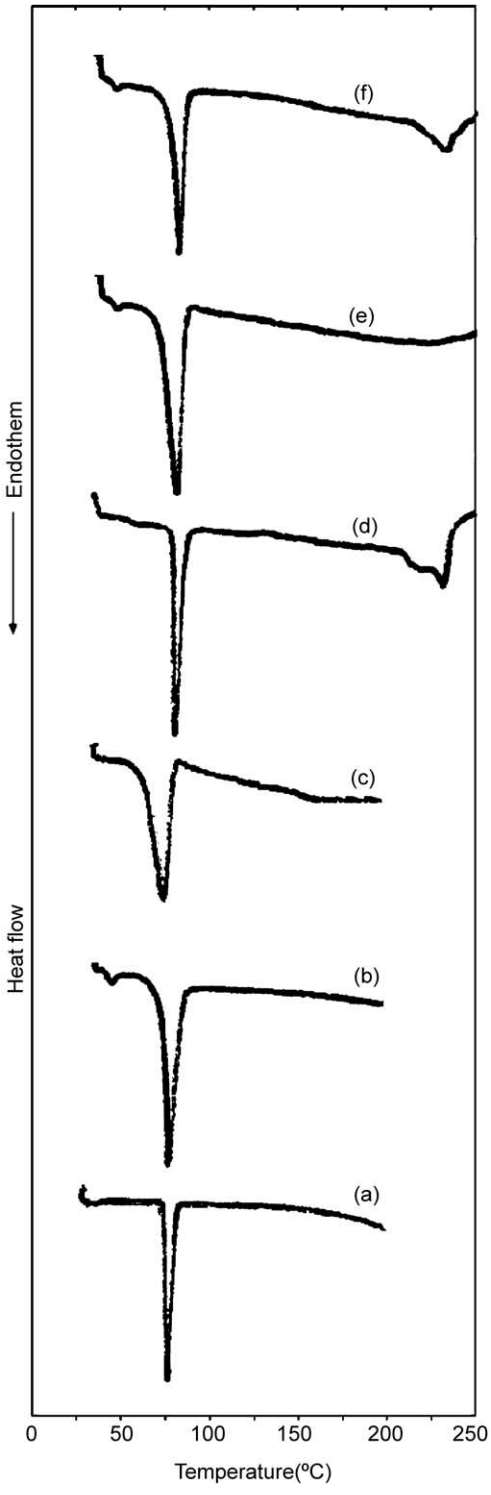

Fig. 2. DSC thermograms of the physical binary and tertiary mixtures of ibuprofen and polyvinyl polymers. The drug–polymer ratio is 1:1 (w/w). Key: (a) pure IBU, (b) IBU:PVAc, (c) IBU:PVP, (d) IBU:PVA, (e) IBU:(PVAc:PVP) (50:50), (f) IBU:(PVAc:PVA) (50:50).

that no interaction between drug and polymer has occurred.

In physical tertiary drug–polymer mixtures, an endothermic effect due to drug melting was always evident (Fig. 2), and the lack of a significant shift of the melting endothermic peak of the drug revealed no evidence of solid-state interaction between ibuprofen and polyvinyl polymers after either simple blending or cogrinding. These results suggest the absence of strong interaction between the drug and physical binary mixtures of polyvinyl polymers over the composition range and experimental conditions studied. Furthermore, no thermal signals due to the decomposition products were found in the physical binary and tertiary mixtures of ibuprofen and PVAc, PVP, or PVA, suggesting chemical stability of the drug in these systems.

3.1.2. Powder X-ray diffraction

The XRD patterns of PVAc, PVP and PVA, and the physical binary mixtures of these are shown in Fig. 3. The amorphous PVAc and PVP showed two slight diffuse halos over the 8° 2θ–30° 2θ angular range with the maximums at 13° 2θ and 22° 2θ (for PVAc) and at 12° 2θ and 20° 2θ (for PVP). PVA displayed one broad peak at 19° 2θ (d-spacing 4.54 Å), reflecting its semicrystalline nature. The XRD patterns for the physical binary mixtures of the PVAc and PVP were similar to those obtained with respective individual polymers, suggesting that the mixtures are amorphous. The physical binary mixtures of PVAc and PVA displayed one broad peak at 19° 2θ predominant to PVA.

The XRD patterns of the physical binary or tertiary mixtures of ibuprofen and the polyvinyl polymers prepared by cogrinding, are shown in Fig. 4. The diffractogram of ibuprofen had a numerous distinct peaks, indicating a crystalline nature of the drug. Characteristic peaks of ibuprofen appeared at a diffraction angle of 2θ at 6.09°, 16.69°, 20.19°, and 22.42°, being comparable to that reported in the powder diffraction files of the International Center for Diffraction Data (ICDD). Interestingly, the diffraction peaks of crystalline ibuprofen appeared at the same positions in both the binary and the tertiary drug–polymer physical mixtures over the composition range studied (Fig. 4), indicating that mechanical treatment had no influence on the physical state of the drug in the polymer matrices. On the other hand, a slight increase of the intensity of the ibuprofen peaks was observed with the physical mixtures of IBU:(PVAc:PVA) compared to those observed with the physical mixtures of IBU:(PVAc:PVP). This may be due to the fact that ibuprofen peaks are overlapped by the broad signal due to the crystalline region of the PVA. The results confirmed that ibuprofen remained in crystalline state over the composition range of the physical mixtures and experimental conditions studied.

3.2. Dissolution and release kinetics of sustained-release matrices

Mathematical models have been used to describe the drug release behavior for which the swelling property of the system is responsible and where the diffusion is not the only

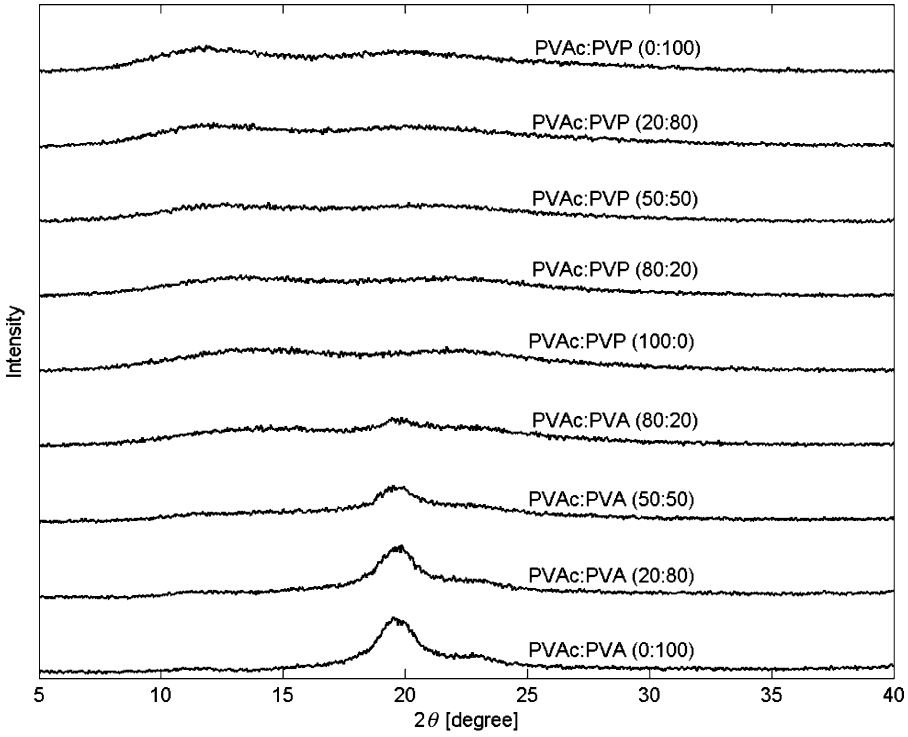

Fig. 3. X-ray powder diffraction patterns of PVAc, PVP and PVA, and physical binary mixtures of these. Physical mixtures were prepared by gently blending in an agate mortar with a spatula at room temperature (22 ± 1 °C).

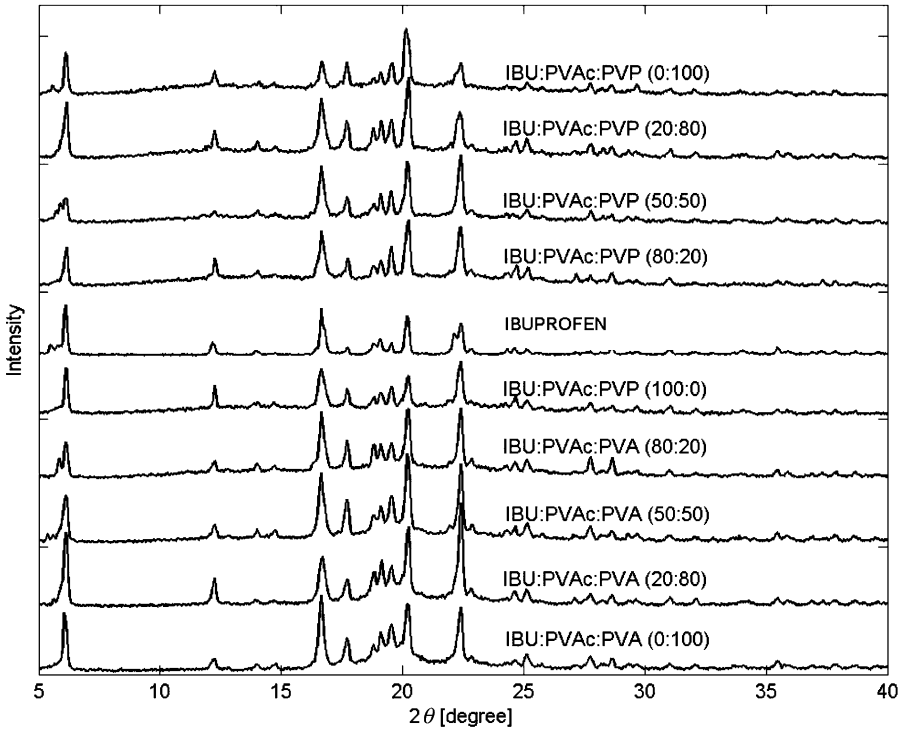

Fig. 4. X-ray powder diffraction patterns of physical binary or tertiary mixtures of ibuprofen and polyvinyl polymers (PVAc, PVP and PVA) prepared by cogrinding. The drug–polymer ratio is 1:1 (w/w). The ratio of polymers is shown in parenthesis.

mechanism by which solutes are released. The erosion and dissolution of the matrix itself following hydration of polymers will contribute to the overall release. To account for these dual release mechanisms, a simple empirical equation (Eq. (1)) was used. Ritger and Peppas claimed that Eq. (1) could adequately describe the release of solutes from different geometric release devices. A first estimate of applicability of this equation in a swellable system [19] is that the system does not swell more than 25% of its original volume (equilibrium swelling ratio is not higher than 1.33). This equation has usually been applied to study the in vitro release of a highly water-soluble model compound from heterogeneous PVAc matrix tablets with Kollidon® SR (physical mixture between PVAc and PVP) as retarding polymers [15].

The values of the kinetic parameters obtained from the data fitting to the Eq. (1) are listed in Table 2. The plots of this equation obtained in each case are shown in Fig. 5, which shows great differences between the dissolution profiles of the five matrices studied. With formulation D-P5, the drug was rapidly released and reached 100% within 4 h, in contrast to the formulation D-P1 from which only approximately 20% of the drug was released within the same time. The profiles of behavior obtained for each formulation illustrate the degree of control of drug release that can be achieved by addition of different percentages of PVAc in the matrix tablets. As seen in Fig. 5, the drug release was significantly increased when the proportion of a water-soluble polymer (PVP) was increased in the formulation, resulting in a shorter time of release. When the dissolution medium penetrates into swellable matrices, the particles of the polymer swell, modifying the matrix volume and the behavior according to the solubility of the loaded drug and the characteristics of the excipients. Based on the percolation theory, water-soluble excipients could facilitate the drug release process by increasing the formation of an infinite cluster, which spans the whole tablet and makes all the drug particles accessible to the surrounding dissolution medium [20].

The slower drug release from the D-P1 matrices was attributed to the higher PVAc content, which had a major

Table 2
Diffusion exponent and mechanism of diffusional release from the sustained-release matrix tablets of ibuprofen containing PVAc and PVP

Code	Percentage of PVAc (w/w%)	$M_t/M_\infty = kt^n$		Release kinetics
		n	r^2	
D-P1	50	0.380	0.996	Fickian diffusion
D-P2	40	0.417	0.995	Fickian diffusion
D-P3	25	0.592	0.982	Anomalous diffusion
D-P4	10	0.782	0.997	Anomalous diffusion
D-P5	0	0.937	0.995	Zero-order

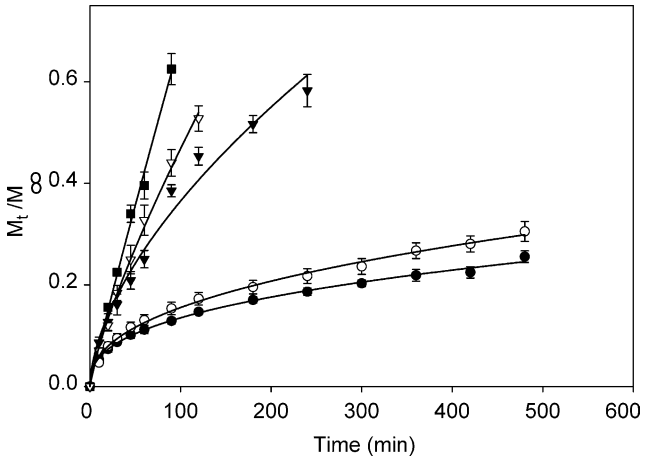

Fig. 5. Release profiles of ibuprofen from sustained-release matrices of ibuprofen and polymers ($n=6$) as fitted Eq. (1). The drug–polymer ratio is 1:1 (w/w). Key: (●) IBU:PVAc $r^2=0.996$, (○) IBU:(PVAc:PVP) (80:20) $r^2=0.995$, (▼) IBU:(PVAc:PVP) (50:50) $r^2=0.982$, (▽) IBU:(PVAc:PVP) (20:80), $r^2=0.994$, (■) IBU:PVP $r^2=0.995$.

decreasing influence on the drug release rate. This polymer effect on drug release is similar to that obtained with encapsulated bases comprising ibuprofen, polyethylene glycol (PEG), and various concentrations of PVAc [21]. PVAc is in a rubbery state during the dissolution test since the glass transition temperature of the polymer is very close to the temperature of the dissolution medium.

The values for the exponential diffusional coefficient (n) vary from approximately 1.0–0.4, suggesting that the release pattern approaches the Fickian diffusion model as the PVAc content was increased in the present matrices (i.e. with D-P1 and D-P2), implying a diffusive-controlled mechanism with n values lower than 0.5. Values for $n>0.5$ were obtained with the matrix systems of D-P3 and D-P4 as a result of the combination of PVAc and PVP. This model can identify the different contribution of the relaxation or mechanism erosion and of the diffusive mechanism. In these cases, both diffusion of the drug through the hydrate matrix and the erosion of the matrix itself after the relaxation of polymer chain control the release of ibuprofen from these formulations.

The central element of the release mechanism in swellable systems is the gel-layer formation around the matrix in response to water penetration. Phenomena that govern the gel-layer formation and, consequently, the drug release rate are water penetration, polymer swelling, drug dissolution and diffusion, and matrix erosion. Additionally, the viscosity of a polymer has a great influence on the erosion rate that can be adjusted also by using different viscosity grades of polymers or by combining different kinds of polymers.

The matrix system D-P5 showed an n value very close to 1.0 (zero-order kinetics) and a decrease in the total period of drug release was observed. This result is in agreement with the behavior of a water-soluble polymer or of a low molecular weight polymer, and suggests erosion-controlled drug release mechanism from the present matrix tablets.

Stereomicrographs on the residues of sustained-release matrices following the dissolution test are shown in Fig. 6. The matrices composed of PVAc 25% (w/w) or more did not disintegrate and they remained virtually intact after the 8-h treatment in phosphate buffer solution (pH 7.2). The matrices composed of ibuprofen and PVP (D-P5) were totally dissolved after the exposure of 4 h to the present dissolution medium.

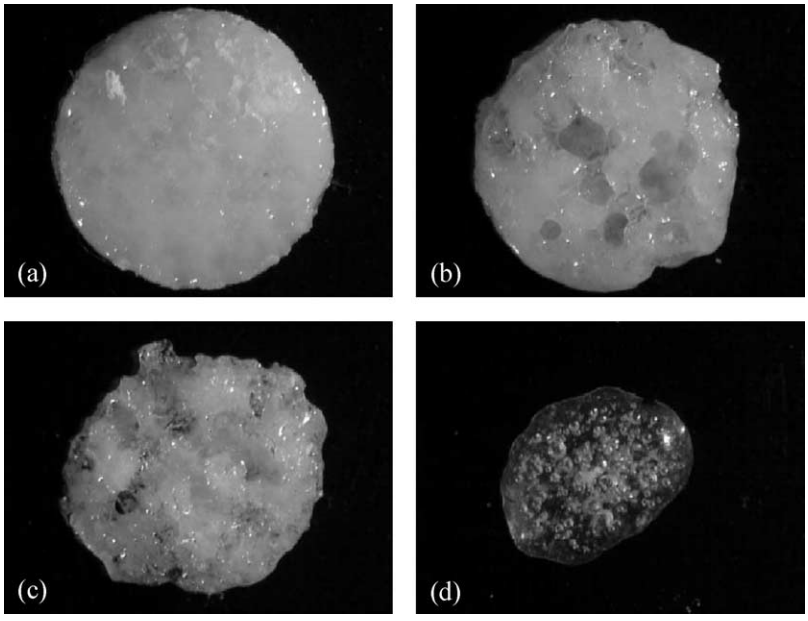

Fig. 6. Stereomicroscopic photographs on the residues of sustained-release matrices after the dissolution test. Key: (a) IBU:PVAc, (b) IBU:(PVAc:PVP) (80:20), (c) IBU:(PVAc:PVP) (50:50), (d) IBU:(PVAc:PVP) (20:80). Magnification ×20.

4. Conclusions

No significant solid-state incompatibilities are expected in physical binary or tertiary mixtures of PVAc, PVP and PVA, and in respective direct-compressed solid matrices. Solid-state compatibility of ibuprofen with the present polyvinyl polymers is also indicated. Sustained-release dissolution profiles can be achieved with the direct-compressed matrix systems made from powder mixtures of the drug (ibuprofen) and PVAc combined with PVP, and the proportion of PVAc in the mixtures clearly alters the drug release profiles in vitro. The release pattern approaches the Fickian model as the PVAc content increased in the present matrices.

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