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Modification of ketoprofen bead structure produced by the spherical crystallization technique with a two-solvent system

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Abstract

Poorly-compressible crystals of ketoprofen were agglomerated by the spherical crystallization technique with a two-solvent system (acetone/demineralized water). In order to study a possible modification of particle texture, spherical crystals were formulated with low concentrations of additives. The results showed that the procedure was possible with ethylcellulose, cross-linked PVP and cross-linked CMC, all at a concentration of 1%. However, no spherical beads could be obtained with the water-soluble compounds tested (PVP and Eudragit L100-55®), Eudragit RS100® and colloidal silica. These formulation trials have indicated two main factors with their possible influences: the polymer solubility and viscosity in the solvent/non-solvent system leading to two kinds of nucleation and changes in mass transfer and drug/polymer interactions leading to the formation of reversible complexes or irreversible complexes and possibility of drug release modifications. Moreover, formulations with the methacrylic acid derivatives were found to be incompatible with the operating conditions, in terms of temperatures changes, stirring or residence time. Furthermore, an optimization of the formulation with ethylcellulose yielded a controlled release form with 1% of the polymer, whereas the addition of very low concentrations increased the drug release. Copyright © 1996 Elsevier Science B.V.

Keywords: Ketoprofen; Particle structure; Polymers; Spherical crystallization; Texture

1. Introduction

The direct tableting technique has been successfully applied to numerous drugs on the industrial scale. However, when the mechanical properties

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of the drug particles are inadequate, this process requires formulations with large amounts of fillers (> 75%) (Cartensen and Toure, 1979).

When preliminary granulation is necessary, the spherical crystallization technique appears to be an efficient alternative for obtaining particles destined for direct tableting, since crystallization and agglomeration are carried out in a single step without any filler.

Two types of method have been described in the literature: the spherical agglomeration (SA) method and the quasi-emulsion solvent diffusion (QESD) method also known as the transient emulsion (TE) method (Fig. 1). They are essentially distinguished by the miscibility of the drug–solvent complex with the non-solvent.

The SA method has been studied more than the QESD method, because it was the first to be described for pharmaceutical drugs. Several applications can be found in the literature for numerous drugs: salicylic acid (Kawashima et al., 1982), naproxen (Gordon and Chowhan, 1990). On the other hand, other drugs, for example chlorpromazine hydrochloride (Niwa et al., 1994) and acebutolol hydrochloride (Kawashima et al., 1994) have been spherically crystallized by the QESD. The principal aim of all these studies was to improve mechanical properties of the solid drugs such as flowability, packability or comprimability. The different results have pointed out the importance of the particle texture, since a modification of the internal microstructure, crystal size or organization can change the mechanical properties.

In order to understand particles organization better, two different approaches can be used: the process approach and the formulation approach. The first has been developed in Espitalier's study, in which the main physicochemical parameters able to improve the crystallization process during the QESD method, were identified. It was shown that the shape and the internal and external structures were essentially dependent on the solvent/non-solvent ratio and the difference in temperature between the two solvents. These results were used as the basis for our study as far as the choice of drug (ketoprofen), solvent (acetone), non-solvent (water) and emulsifier (polyvinyl alcohol) was concerned.

The second approach is based on formulation trials. In previous works, numerous additives were studied with the aim of rendering crystallization possible rather than modifying it. They have mainly sought to stabilize the initial emulsion, which is an essential intermediate for forming spherical agglomerates: polyvinyl alcohol (Espitalier, 1994) or hydroxypropyl methylcellulose (Morishima and Kawashima, 1993).

On the other hand, some studies have described the main factors affecting solvent diffusion and also the mechanism of enhancement of solvent diffusion rate by additives. An example is given by the possibility of spherical crystallization of ketoprofen by enhancement of ethanol diffusion from the droplets to the aqueous phase, by the presence of a sugar ester (Kawashima et al., 1993), allowing the substitution of ethanol–Ketoprofen hydrogen bonds by sugar ester-Ketoprofen interaction. This displacement might reduce the

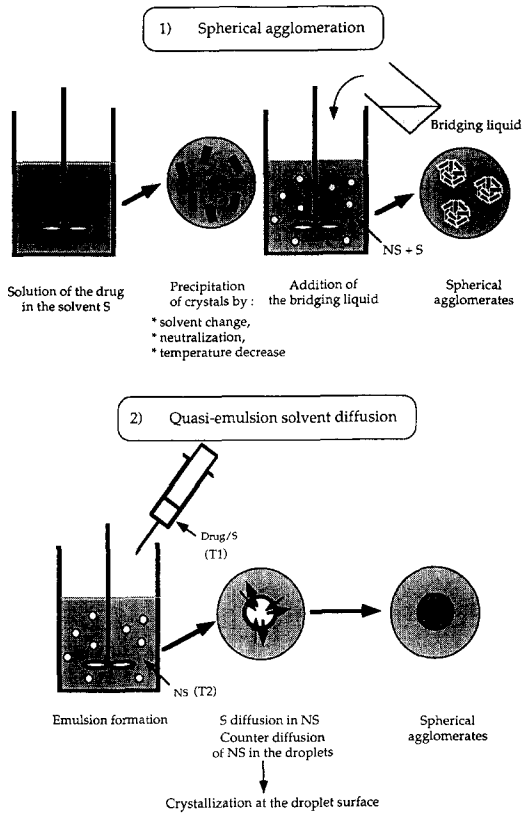

Fig. 1. Principle of spherical crystallization.

interaction between ethanol and ketoprofen and allow the solvent to diffuse more freely.

Another use of additives is the addition of polymers, such as the mixed ethylcellulose/polyvinylacetate, in order to encapsulate the spherical agglomerates, for a better control of drug release by creating a diffusional barrier (Niwa et al., 1993).

All the above-mentioned additives can be defined as 'feasibility additives'.

Finally, Donbrow's work (Donbrow et al., 1990) has shown that it is possible to modulate the solvent diffusion across a coating polymer (Eudragit) by using a low concentration of an additive such as a non-walling polymer (polyisobutylene). Although Donbrow did not use the spherical crystallization technique, but rather the coacervation technique, his work and that of Kawashima with sugar esters have orientated us towards a strategy for a new study.

The aim of this work was to study the possible modification of particle texture with addition of low concentrations of additive directly into the organic phase of the droplets in order to act on the particle formation during the first steps of drug crystallization.

2. Materials and methods

2.1. Materials

Ketoprofen was a gift from Rhône-Poulenc Rorer, France. All the polymers used were USP or NF grade: Ethylcellulose (EC10®, Aqualon Hercules, η: 8 to 11 mPa·s, ethoxy content 47.5 to 49%), PVP (Kollidon 12 PF®, BASF, M_w: 2500 to 3000), cross-linked PVP (Kollidon CL M®, BASF, micronized powder), cross-linked CMC (Ac Di Sol®, Seppic), methacrylic and methyl methacrylate copolymer (Eudragit L100-55®, Röhm Pharma, water-soluble above pH 5.5), acrylic methacrylic acid ester copolymer with a low content of quaternary ammonium groups (Eudragit RS100®, Röhm Pharma, low permeability to water) and colloidal silica (Aerosil 200®, Degussa). Polyvinyl alcohol was supplied by Hoechst (Mowiol® 8/88). Acetone was purchased from Prolabo, France. All chemicals used were of analytical grade.

2.2. Preparation of particles

Ketoprofen (2.4 g) was dissolved in acetone (2 ml) at 50°C. The acetone solution was poured into demineralized water (50 ml) containing an emulsifier (10 mg of Mowiol® 8/88) under agitation (paddle method, 350 rpm) at room temperature. After 30 min of stirring, the solid particles were separated by filtration, washed with demineralized water (about 50 ml) and then oven-dried at 50°C under vacuum. In the case of particles formulated with additives, the polymer was added to the drug in the acetone solution.

2.3. Surface tension measurements

Measurements were carried out at room temperature, using the Wilhemy method, with a thin plate of platinum (length: 2 cm). A solution of ethylcellulose (2 μg/5 μl) in acetone was spread on a bidistilled water/air interface.

2.4. Particle shape

The external and internal structures of the particles were observed by scanning electronic microscopy (Digital Scanning Microscope, DSM 950, Zeitz) after spraying a thin layer of gold onto the particles.

2.5. Particle size

Particle mean diameters (Feret diameter) were determined by optical microscopy on sieved particles in the range of diameters from 250 to 1250 μm. The preliminary sieving was intended to eliminate the crystal dust and the large agglomerates which formed on the paddle.

2.6. Drug release test

Drug release tests were carried out using the paddle method. 100 mg of spherical crystals in the range of diameters from 500 to 1000 μm were dispersed in 1000 ml of phosphate buffer (pH 6).

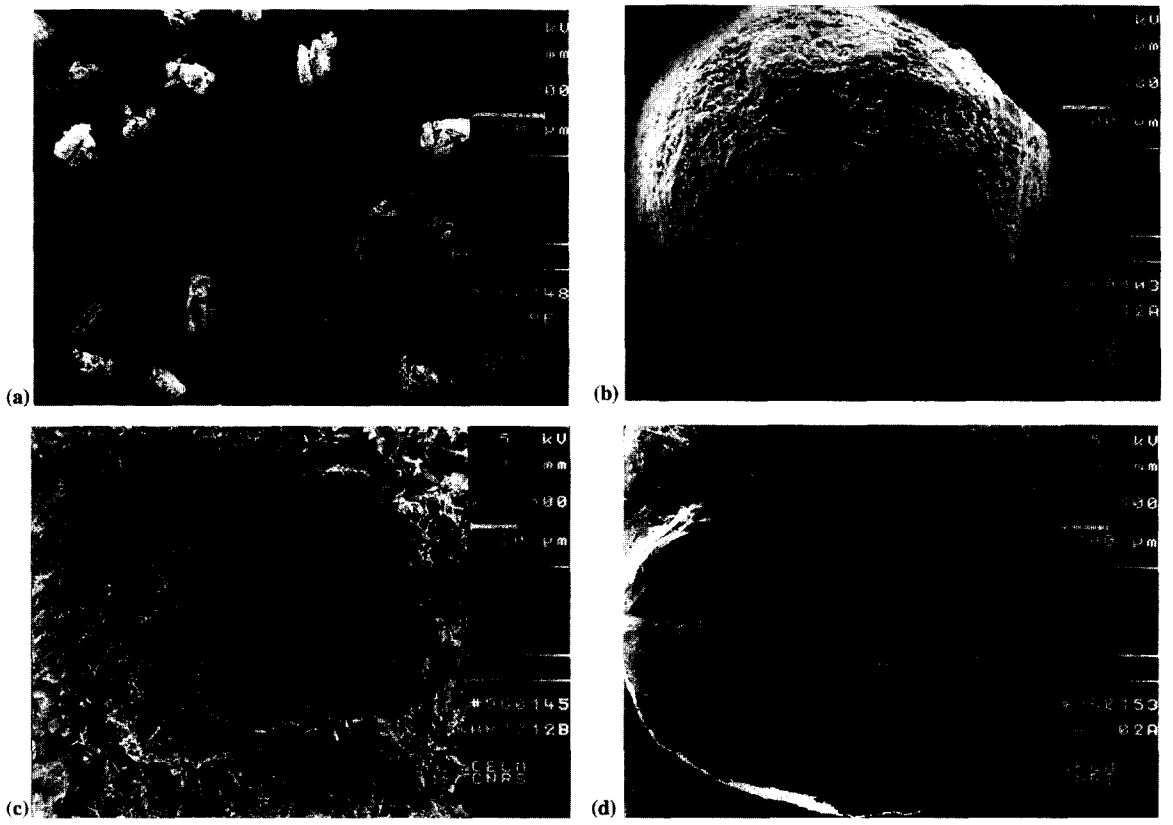

Fig. 2. Scanning electronic micrographs of control spherical crystals: (a) ketoprofen powder, (b) spherical crystals, (c) external structure, (d) internal structure.

The dissolution medium was stirred at 120 rpm. The amount of drug dissolved was determined spectrophotometrically at 260 nm. To compare dissolution profiles, release profiles were fitted according to a first order law.

2.7. Thermal analysis

In order to observe a possible modification of crystallinity, melting point and melting enthalpy measurements on ketoprofen were carried out with a differential scanning calorimeter (DSC 7, Perkin Elmer) using sealed 40 μl aluminium pans without holes, at a scanning rate of 5°C/min. The thermal analysis required about 5 mg of material.

3. Results

3.1. Process feasibility without additive

The ternary system evaluated was composed of ketoprofen (the drug), acetone (the solvent) and water (the non-solvent). For this system, according to Espitalier's results, there is a critical ratio *Ra* (acetone/water; w/w) which determines the shape and the texture of the particles ($Ra = 0.05$). Our experiments were carried out under conditions which allowed us to obtain spherical beads ($Ra = 0.0316$). The scanning electronic microscopy observations have confirmed the particle sphericity, in accord with the *Ra* value (Fig. 2). Moreover, on the sectioned particles, a cavity was

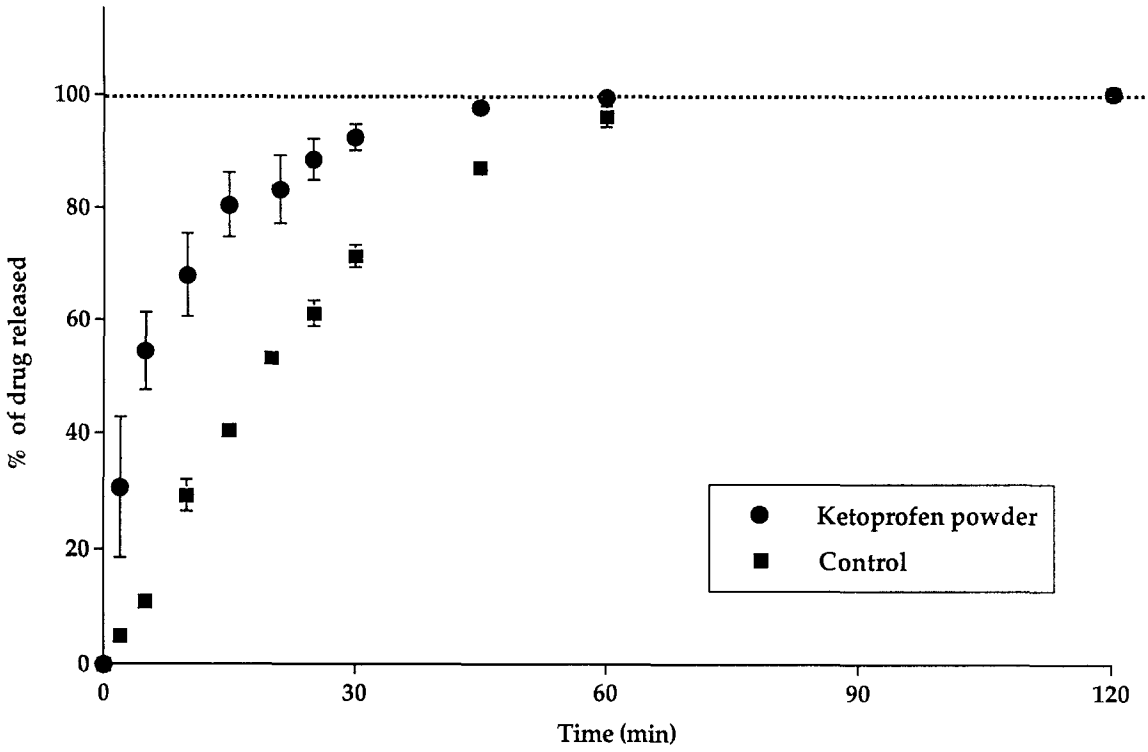

Fig. 3. Dissolution kinetics of control spherical crystals compared with the native powder.

observed surrounded by a crust. On the edge of the agglomerates, the longest faces of the crystals are perpendicular to the particle radius, forming the first compact layer. From this first layer, other crystals have grown radially towards the cavity center. On the other hand, the external structure exhibits several crystal habits (sheets and needles). The same diversity of crystal habits has been observed on the ketoprofen powder.

The size distribution gives a particle mean diameter close to 770 μm with a standard deviation of 210 μm.

Fig. 3 presents the percentage of released drug from spherical crystals as a function of time. The ketoprofen dissolution rate from control beads appeared lower than that of the native powder, with a first-order rate constant, k_r, equal to $(4.65 \pm 0.17) \times 10^{-2}$ min^{-1} and $(7.5 \pm 0.5) \times 10^{-2}$ min^{-1}, respectively. However, although the release of the drug was slowed down, probably due to a decrease of the specific area, the dissolution rate of the spherical crystals remained acceptable; all the drug was released in less than one hour.

3.2. First formulation screening

3.2.1. Process feasibility with additive

In order to modify drug release from beads, additives were selected according to different strategies. Firstly, additives able to create an internal hydrophilic network within the particles, were considered: a water-soluble PVP with a low molecular weight (M_w: 2500 to 3000) and a methacrylic acid derivative (water-soluble above pH 5.5). Secondly, another strategy was to introduce into the particles a compound known to be a swelling disintegrating agent (cross-linked PVP and cross-linked CMC) or a non-water-soluble additive able to induce the same effect such as colloidal silica or acrylate methacrylate copolymer. The third strategy was aimed at modifying nucleation and crystal growth mechanisms and thus to creating lattice imperfections (Chiou and

Table 1
Process feasability for the first formulation screening

Additive	Amount (w/w; additive/drug)	Process feasibility	Spherical particles	Ovoid particles	Observations
PVP *Kollidon 12 PF®*	10%	—			Majority of powder Few spherical crystals
Methacrylic and methyl methacrylate copolymer *Eudragit L100-5.5®*	10%	—			Rubbery compound
Cross-linked PVP	10%	+	+	++	Rough surface
Kollidon CL M®	1%	++	++		
Cross-linked CMC	5%	++	++		
	2%	++	++		
Ac Di Sol®	1%	++	++		Rough surface
Acrylate methacrylate copolymer *Eudragit RS 100®*	10%	—			Rubbery compound
Colloidal silica *Aerosil 200®*	5%	—			
Ethylcellulose *EC10®*	1%	++	++		

Kyle, 1979; Burt and Mitchell, 1981). According to previous studies (Berkovitch-Yellin et al., 1985; Klein et al., 1993) additives with a chemical structure close to that of the crystallizing solute, referred to as 'tailor-made additives', offer a means of selectively modifying the crystal habit through adsorption onto the growing-crystal surfaces. Ethylcellulose was chosen because of its good solubility in acetone, like that of the drug. Although ethylcellulose cannot be considered a tailor-made additive for ketoprofen, this polymer exhibits some properties similar to the drug (in terms of hydrophobicity, solvent solubilities, etc.). Moreover, cellulose derivatives have already been shown to modify the crystallization kinetics of other drugs (Ring, 1991).

The amounts of polymers to be used were chosen, in a first step, according to their usual pharmaceutical applications in the range of 1% to 10% w/w; polymer/drug concentration. Table 1 shows that spherical crystallization of ketoprofen could be achieved with three additives: both disintegrating agents (the cross-linked PVP and the cross-linked CMC) and ethylcellulose. On the contrary, preparation of spherical crystals was not possible with the water-soluble compounds chosen. The result was that a majority of powder and only a few spherical crystals were obtained. On the other hand, colloidal silica and acrylate methacrylate copolymer, both non-water soluble compounds, did not allow spherical particles to be formed. In these cases, the respective results were a rubbery compound and a majority of powder.

3.2.2. Drug release from particles formulated with 1% of polymer

For a better comparison between additives, size distribution experiments and dissolution tests were carried out for a fixed amount of each additive equal to 1% (w/w; polymer/drug). As shown in Table 2, the formulated mean particle diameters were all close to the control preparation (700–800 μm). As shown in Table 2 and Fig. 4, the dissolution profiles were identical for the

Table 2
Comparison between the drug release rate constants, k_r, of beads formulated with 1% of ethylcellulose, cross-linked CMC or cross-linked PVP

	Amount polymer/drug	k_r (min^{-1}) ± S.D.	Mean diameter (μm) ± S.D.
Control	—	4.65 ± 0.17	770 ± 210
EC10	1%	2.60 ± 0.46	710 ± 180
Cross-linked CMC	1%	4.74 ± 0.63	730 ± 200
Cross-linked PVP	1%	4.47 ± 0.09	740 ± 250

preparations with disintegrating agents (cross-linked CMC and cross-linked PVP) and the control with a first-order rate constant, k_r, close to 4.6×10^{-2} min^{-1}. In contrast, the formulation with 1% of ethylcellulose exhibited a lower drug release. These results suggest that there are no interactions between the disintegrating agents and ketoprofen, while ethylcellulose seems to modify ketoprofen release, because of the creation of a diffusional barrier between the drug and the dissolution medium.

3.3. Optimization of the formulation with ethylcellulose

To complete the study, spherical crystals were formulated with an amount of ethylcellulose which could not saturate the acetone droplet/water interface, in order to avoid the diffusional barrier. Therefore, we first determined the critical amount of ethylcellulose which could lead to the formation of a continuous monomolecular layer at the particle surface.

3.3.1. Determination of the molecular area of ethylcellulose

Fig. 5 shows surface tension values as a function of the amount of ethylcellulose spread on a bidistilled water/air interface (area 34.2 cm^2). When the acetone solution of ethylcellulose was spread on this interface, a significant decrease of surface tension to reach a steady state (37 mN/m) was noted with an amount of polymer equal to 12.6 μg. As a control, a similar volume of pure acetone was spread on the bidistilled water/air interface without any effect on the surface tension value.

The molecular weight of the grade 10 ethylcellulose is given as about $M_w = 70\,000$. So, the molecular area calculated at the discontinuous point (Fig. 5) was about 3000 $Å^2$.

For the application of this determination to spherical crystallization, the mean particle diameter of 750 μm was assumed. Therefore, the total surface area of beads was 300 cm^2 for the initial acetone solution of ketoprofen. In these conditions, only 110 μg of ethylcellulose is enough to saturate the acetone droplet/water interface (corresponding to 45 ppm).

For the following experiments, polymer amounts below and above this critical value were used; i.e., 10, 40 and 500 μg of ethylcellulose corresponding to 4, 16 and 200 ppm (w/w; polymer/drug).

3.3.2. Study of particles formulated with 4, 16 and 200 ppm of ethylcellulose

In the good accordance with the spherical crystals formulated with 1%, spherical beads were also obtained with very low concentrations of ethylcellulose. In terms of size distribution, Table 3 shows a constant mean diameter for all the formulations, close to 750 μm. In comparison with the control bead size, no significant difference was observed.

The dissolution profiles of the different formulations are presented in Fig. 6. To emphasize the differences in the profiles, the graph only presents the first hour of dissolution. The results show that the drug release rate was increased by the addition of very low concentrations of ethylcellulose. The release rate constants, k_r, were equal to 7.4 ± 0.5, 6.1 ± 0.3 and $(5.4 \pm 0.2) \times 10^{-2}$ min^{-1} for the beads containing 4, 16 and 200 ppm of polymer, respectively. The comparison between the different release rate constants, k_r, pointed out that the

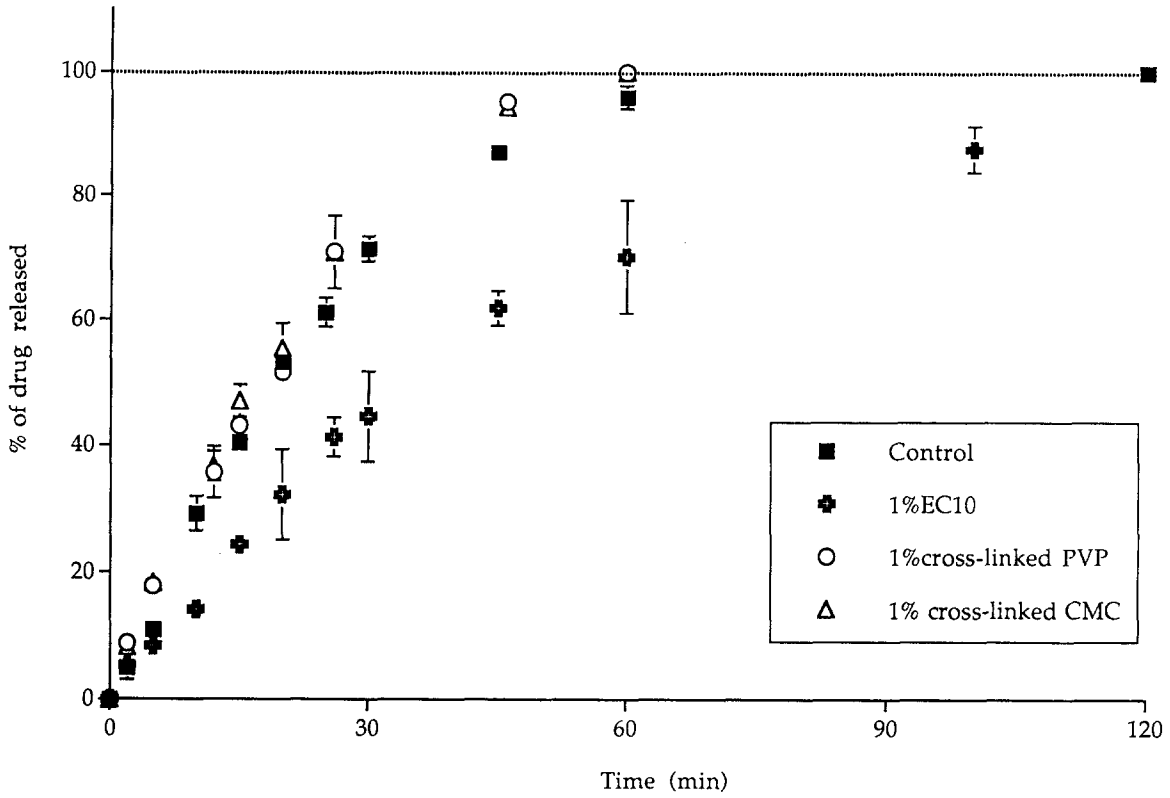

Fig. 4. Comparison of the dissolution kinetics of spherical crystals formulated with the same amount of polymer.

increase in the drug release was more significant with the lowest amount of polymer (i.e., 4 ppm of ethylcellulose).

3.3.3. Storage of particles

Each batch of beads was stored in a closed box, protected from light, at room temperature. Dissolution tests were performed after different storage times (Fig. 7). It seems that the initial increase in drug release was transient, since the k_r values obtained after a few days of storage exhibited a downward trend to reach the control k_r values (about 4.5×10^{-2} min^{-1}). The same tendency was found for all the formulations. It was observed that all the dissolution kinetics became similar to the control one, after only one week.

4. Discussion

4.1. First formulation screening

To explain the feasibility of the procedure in the presence of additives, several hypotheses can be put forward the influence of additive solubility in the acetone/water system, structural compatibility and/or compatibility with the operating conditions. It should be mentioned that all the formulation trials were carried out under operating conditions which allowed spherical crystals to be prepared without any additive.

As far as additive solubility in the acetone/water system is concerned, three different types of behaviour can be distinguished: the acetone/water-

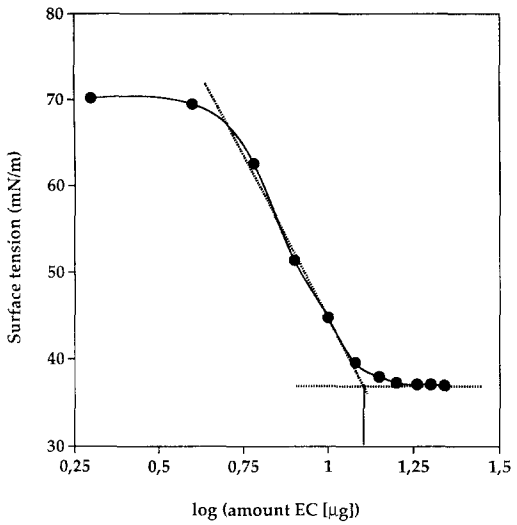

Fig. 5. Surface tension values versus amount of ethylcellulose spread on the bidistilled water/air interface.

soluble compounds, the acetone-soluble/non-water-soluble compounds and the non-acetone/non-water-soluble compounds.

The acetone/water-soluble compounds, uncross-linked PVP and Eudragit L100-55®, are precipitated with ketoprofen. In this case, it seems that crystal formation results from primary homogeneous nucleation without any external support. We can assume that in the acetone solution, strong molecular interactions between the drug - the polymer and the solvent can be formed, inducing close mixing. However, no spherical crystals could be obtained with either of these polymers. For PVP, its low molecular weight (about 2500) and its high water solubility allow the polymer escape into the aqueous phase. The spherical structure could be destroyed leading to a classical crystallization by solvent change. The result is a majority of ketoprofen powder with a few spherical particles. This mixture of products can be explained by competition between polymer escape and ketoprofen precipitation at the droplet surface, the latter occurring in less than one minute. On the other hand, formulation with Eudragit L100-55® did not lead to spherical ketoprofen precipitation, but rather to a non-solidified rubbery compound. In contrast to PVP, which had a viscosity similar to that of water, the high molecular weight of Eudragit L100-55®, close to 135 000, gives this polymer solution a significant viscosity. When the viscous acetone solution is poured into the aqueous phase, larger droplets are formed with a tendency to coagulate. The significant droplet viscosity and the preferential polymer flow towards the aqueous phase (pH above 5.5) delayed first the solvent diffusion and then ketoprofen precipitation. Thus, over the time period used (30 min), ketoprofen does not solidify.

Table 3
Mean diameters and drug release rate constants, k_r, of spherical crystals formulated with 4, 16 and 200 ppm of ethylcellulose

	Mean diameter (μm) ± S.D.	k_r (min^{-1}) ± S.D.
Control	770 ± 210	4.7 ± 0.2
Crystals with 4 ppm of EC10	740 ± 190	7.4 ± 0.5
Crystals with 16 ppm of EC10	760 ± 220	6.1 ± 0.3
Crystals with 200 ppm of EC10	810 ± 170	5.4 ± 0.2

As far as the acetone-soluble/non-water-soluble compounds was concerned, spherical crystals could be prepared with ethylcellulose, whereas no good result could be obtained with Eudragit RS100®. When the polymer mass was considered, there was a significant difference between polymers, with molecular weights of about 70 000 and 150 000 respectively, leading to an increase in the viscosity of the acetone droplets for Eudragit RS100®. As the previous case, this can retard and reduce solvent/non-solvent diffusion. Moreover, it seems that there is no chemical incompatibility between ketoprofen and Eudragit RS100® since, in a previous study, Eudragit RS100® microcapsules containing 20 to 40% of ketoprofen were obtained by acetone evaporation in a liquid paraffin phase (Goto et al., 1986). However, it should be noted that the operating conditions included a gradual temperature increase from 10 to 35°C. According to the specifications, Eudragit® may be unstable at high temperature, when the temperature is changed rapidly and during the spherical crystallization process, the acetone solution was heated at 50°C and then poured quickly in the aqueous phase at a lower temperature (20°C). Therefore, although no che-

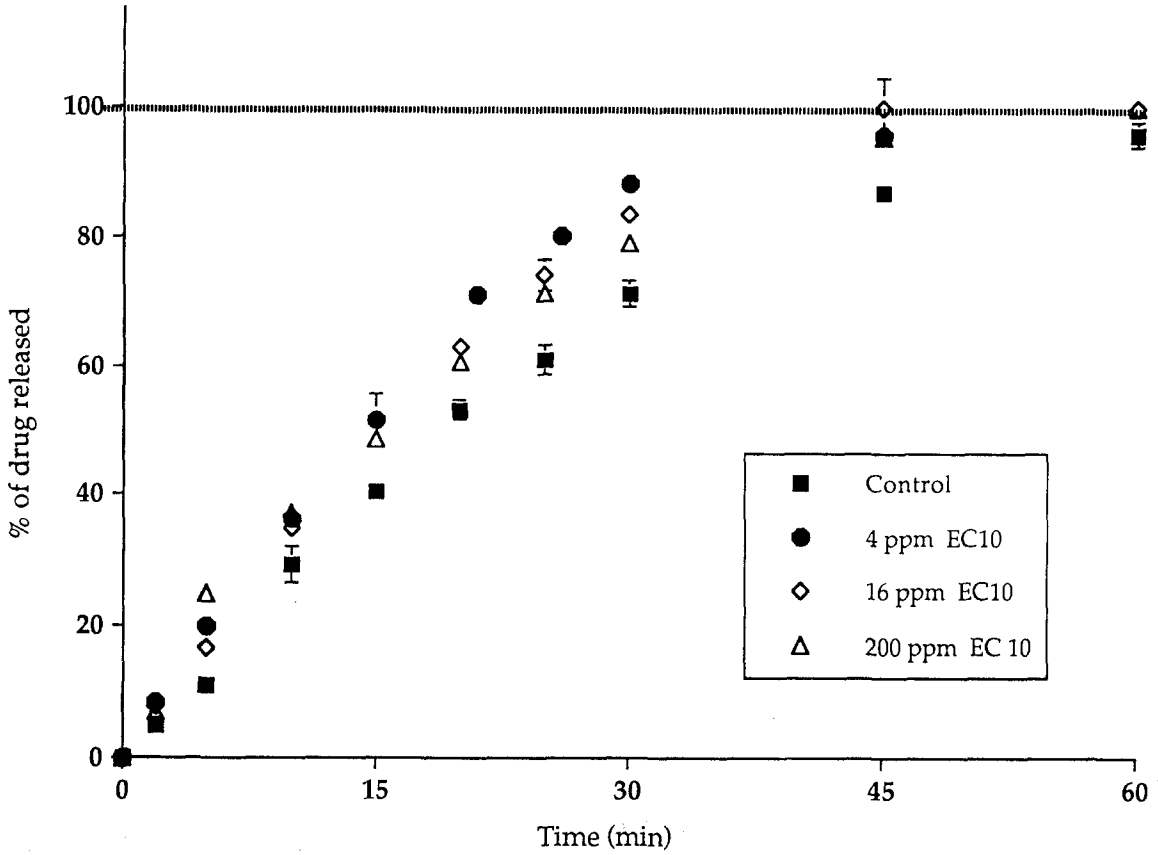

Fig. 6. Dissolution kinetics of spherical crystals formulated with 4, 16 and 200 ppm of ethylcellulose.

mical degradation is expected, it seems that Eudragit® may be unstable under the temperatures conditions of our preparation procedure.

Finally, the third kind of additive is represented by cross-linked PVP, cross-linked CMC and colloidal silica. All these compounds are non-acetone/non-water-soluble. During the process, it can be supposed that the crystal formation results from heterogeneous nucleation. The suspended additive particles could provide sites at which ketoprofen could crystallize because of reduced energy requirements. The results indicate that the procedure is feasible with both polymers, while the use of colloidal silica prevented the formation of spherical crystals. Previous studies have used differential scanning calorimetry as a screening technique to assess the compatibility of ketoprofen with some additives, including colloidal silica (Mura et al., 1995). According to the results, no incompatibility between ketoprofen and the colloidal silica (at 1:1 weight ratio) was observed, after several different procedures: blending, co-grinding with a pestle, compression (30 kN for 2 min), and kneading (paste obtained after slurrying the physical mixture with ethanol and then dried to produce solid compound). So, it can be concluded that ketoprofen crystallization cannot occur on the surface of colloidal silica which does not present suitable sites for crystallization, maybe because of (i) the smooth particle surface and (ii) the presence of silanols groups on the particle surface. Taking into account these observations, it seems that the surface properties of the individual particles are more important than the total specific area, since the adsorption of drug molecules onto the additive particles is necessary

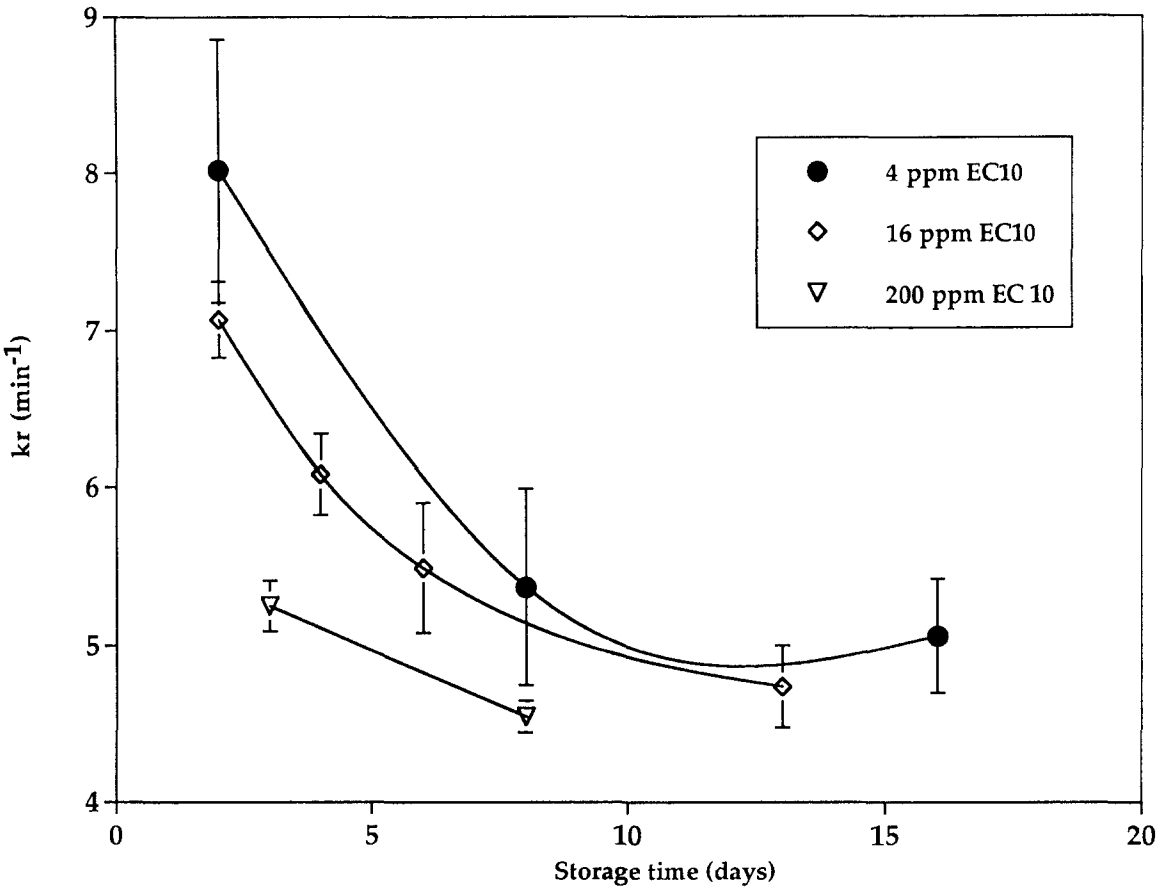

Fig. 7. Relationship between the drug release rate constants, k_r, and the storage time.

to create a nucleus, an essential step for the formation of crystals. Furthermore, in the case of the formulation with cross-linked PVP, the DSC thermograms showed a decrease in the melting enthalpy of ketoprofen (Table 4). This results points out some interactions between ketoprofen and the polymer. Nevertheless, it seems that these interactions have no effect on drug release (Fig. 6). These observations are in a good accordance with numerous previous studies which have demonstrated that PVP and cross-linked PVP can form reversible complexes with several drugs (Fassihi and Persicaner, 1987).

In conclusion, the first formulation screening did not reveal a typical polymer allowing spherical crystals to be obtained under fixed operating conditions but these trials have indicated two main factors with their possible influence. These are the polymer solubility and viscosity in the solvent/non-solvent system, leading to two kinds of nucleation and changes in mass transfers and the drug/polymer interactions which lead to the formation of reversible complexes or hinder the control of drug release. Moreover, formulations with the methacrylic acid derivatives were found to be incompatible with the operating conditions, in terms of temperatures changes, stirring or the duration of the procedure.

4.2. Optimization of the formulation with ethylcellulose

The surface tension experiments, described above, show that ethylcellulose can behave as a

Table 4
Effects of additives and storage time on thermal behaviour of ketoprofen

	Storage	Onset temp. (°C) ±S.D.	Peak temp. (°C) ±S.D.	Melting enthalpy (J/g) ±S.D.
Powder		94.2 ± 1.1	95.5 ± 1.1	116 ± 12
Control		95.5 ± 0.0	97.5 ± 0.2	106 ± 1
Particles with 1% cross-linked PVP		93.7 ± 0.6	95.9 ± 0.3	99 ± 1
Particles with 1% cross-linked CMC		94.4 ± 0.3	96.7 ± 0.2	105 ± 1
Particles with 1% ECIO		93.4 ± 0.9	95.0 ± 0.2	98 ± 4
Particles with 4 ppm EC 10	After 2 days	95.2 ± 0.0	97.4 ± 0.1	100 ± 1
	After 10 days	93.6 ± 0.5	95.4 ± 0.2	99 ± 4
	After 2 months	94.6 ± 1.4	96.5 ± 1.3	104 ± 2
Particles with 16 ppm EC 10	After 2 days	95.2 ± 0.1	97.3 ± 0.1	100 ± 1
	After 10 days	94.4 ± 0.3	96.5 ± 0.2	100 ± 1
	After 2 months	94.2 ± 1.4	96.7 ± 1.4	105 ± 1

surfactant, decreasing the surface tension of water. This property suggests that the polymer might be preferentially localized at the acetone droplet surface. Since ethylcellulose is dominantly hydrophobic, the polymeric chains are extended at the acetone/water interface, with only the hydroxyl groups orientated towards the aqueous phase. The addition of 25 ppm of ethylcellulose is enough to form a monomolecular layer and the superposition of a sufficient number of layers induces the formation of a physical barrier with the possibility of the sustained drug release. The diffusional barrier becomes efficient with the addition of several hundred molecular layers, such as 1% of polymer corresponding to about 500 layers; the calculation of the layer number assuming that all the polymer takes place onto the particle surface. With only 10 layers, there is no decrease in drug release. Probably, the thickness of the barrier is an important parameter for the control of drug release. In contrast, the addition of very low concentrations of ethylcellulose, below the critical value (25 ppm) enhances drug release. We could suppose that this enhancement of drug release results from a wettability increase induced by the ethylcellulose molecules adsorbed on the particle surface. After storage, the similarity of the release profiles between the formulated crystals and the control could be the effect of a migration of the polymer into the particle core, due to an activation by residual solvent. Therefore, we can observe a modification of the external structure to become as identical as the control one.

On the other hand, in order to explain the drug dissolution enhancement, another hypothesis could be the creation of crystal defects allowing a faster release of ketoprofen from the beads.

In summary, ethylcellulose acts as a surface agent, modifying the surface properties of the beads and so, improving the wettability of the drug. Nevertheless, at large concentrations, this effect is masked by the creation of a diffusional barrier.

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