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Preparation and study of the characteristics of dithranol:polyvinylpyrrolidone coevaporates

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Abstract

Dithranol:polyvinylpyrrolidone (Di:PVP) 1:2, 1:4, 1:9, 1:14, 1:25 and 1:40 coevaporates were prepared to increase the aqueous dispersibility of this hydrophobic and water insoluble drug, used for the topical treatment of psoriasis. The coevaporates contained small crystals of Di as well as nanoparticles of Di, embedded in the PVP matrix. This submicron fraction increased with increasing PVP, up to a Di:PVP ratio of 1:25. The coevaporates exhibited a hydrophilic character, allowing easy dispersion in water. This dispersion contained very small particles of submicron size (average diameter 0.1 μm) and an insoluble part consisting of small Di crystals. When the insoluble fraction was eliminated by filtration, an aqueous stable colloidal dispersion of Di was obtained. This extreme particle size reduction, combined with an enhanced hydrophilic character should provide Di with interesting characteristics for topical treatment of psoriasis.

Keywords: Polyvinylpyrrolidone; Dithranol; Coevaporate; Colloidal dispersion

1. Introduction

Dithranol (Di) is a potent drug which has been used for more than 75 years in the topical treatment of psoriasis (Ashton et al., 1983). The vehicle in which it is incorporated is often an anhydrous fatty substance because Di is readily oxidizable. The main decomposition products are 1,8-dihydroxyanthraquinone (danthron) and dithranol-dimer (Fig. 1) (Holder and Upadrashta, 1992). Aqueous environment, oxygen, light and high pH-values enhance this decomposition to inactive compounds (Ashton et al., 1983).

Irritation and staining of the skin caused by Di as well as the poor cosmetic acceptability of these fatty excipients are responsible for poor compliance with this treatment. In recent years, various aqueous vehicles have been proposed to reduce these disadvantages: o/w creams in which Di was

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shown to be stable (Seville et al., 1979; Wilson and Ive, 1980; Kudsi et al., 1991; Ros and Van der Meer, 1991; Ros et al., 1991), an aqueous dispersion of solid lipid crystals containing Di (Lindahl, 1992) and the inclusion of Di in liposomes (Van Hal et al., 1994; Gehring et al., 1995). However, clinical trials have shown that in spite of a better compliance, creams are generally less effective than corresponding ointments, due to a lack of occlusion and availability (Wilson and Ive, 1980; Whitefield, 1981; Kudsi et al., 1991).

Since Di is practically insoluble in water (0.1–0.2 $\mu g.ml^{-1}$) (Kneczke et al., 1989) and presents a hydrophobic character, it should be interesting to increase its solubility or its aqueous dispersibility in order to provide Di with a better bioavailability when applied from an aqueous vehicle. Moreover, this enhanced hydrophilic character would allow a better removal of the non absorbed Di upon washing, since the Di remaining on the skin surface is responsible for staining and perilesional irritation.

For this purpose, we investigated the preparation of coevaporates with PVP because this technique uses a non irritating, non toxic excipient and allows processing at low temperature.

The first studies on polyvinylpyrrolidone (PVP) coevaporates were reported by Tachibana and Nakamura (1965) and concerned an aqueous preparation of beta-carotene. Since then, this technique has been applied and studied by several workers to increase the aqueous solubility and the dissolution rate of poorly water-soluble drugs (Hajratwala and Ho, 1981; Oth and Moës, 1985; Ford, 1986) in order to increase their oral bioavailability. In the field of dermatological products, Morita and Hirota (1985) reported using hydrocortisone acetate-PVP and betamethasone dipropionate-PVP coevaporates. They showed a better cutaneous penetration when compared to the crystalline form of the drugs.

Coevaporation with PVP can give rise to a high energy solid state (Simonelli et al., 1970) or inhibit the crystallisation of the drug, thus leading to an amorphous solid state (Sekikawa et al., 1978; Kearney et al., 1994). The formation of high-energy complexes (Simonelli et al., 1969, 1976), the presence of amorphous drug and the interaction between PVP and drugs such as hydrogen bonding (Shefter and Cheng, 1980; Doherty and York, 1987; Tantishaiyakul et al., 1996) can explain the solubility enhancement. Sekikawa et al. (1979) noticed that coacervate formation is responsible for the enhanced dissolution of sulfamethizole.

In the present work, we prepared different Di:PVP coevaporates and studied their physicochemical characteristics.

2. Materials and methods

2.1. Materials

Coevaporates were prepared with dithranol (Ph. Helv. VII, Federa, Belgium), polyvinylpyrrolidone (Kollidon®25, BASF, Germany) and methylene chloride (DAB/NF, Merck, Germany). Dithranol BP CRS, Danthron DAB 8 and Dithranol Dimer BP CRS were used as analytical reference standards.

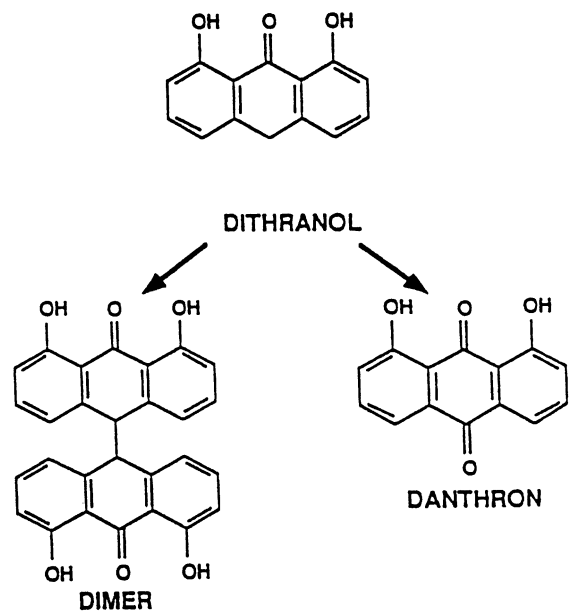

Fig. 1. Structure of dithranol, danthron and dithranol-dimer.

Fig. 2. HPLC chromatogram. Retention times: Di, 5.3 min; danthron, 8.9 min; ortho-nitroaniline, 25.4 min; dimer, 31.9 min.

2.2. Methods

2.2.1. Preparation of the Di:PVP coevaporates

Six coevaporates with different Di:PVP ratios, namely 1:2, 1:4, 1:9, 1:14, 1:25 and 1:40 (w/w) were prepared by dissolving Di and PVP in methylene chloride (15 ml per gram of PVP). The solution was evaporated under vacuum at 40°C in a rotary evaporator. The residue was ground,

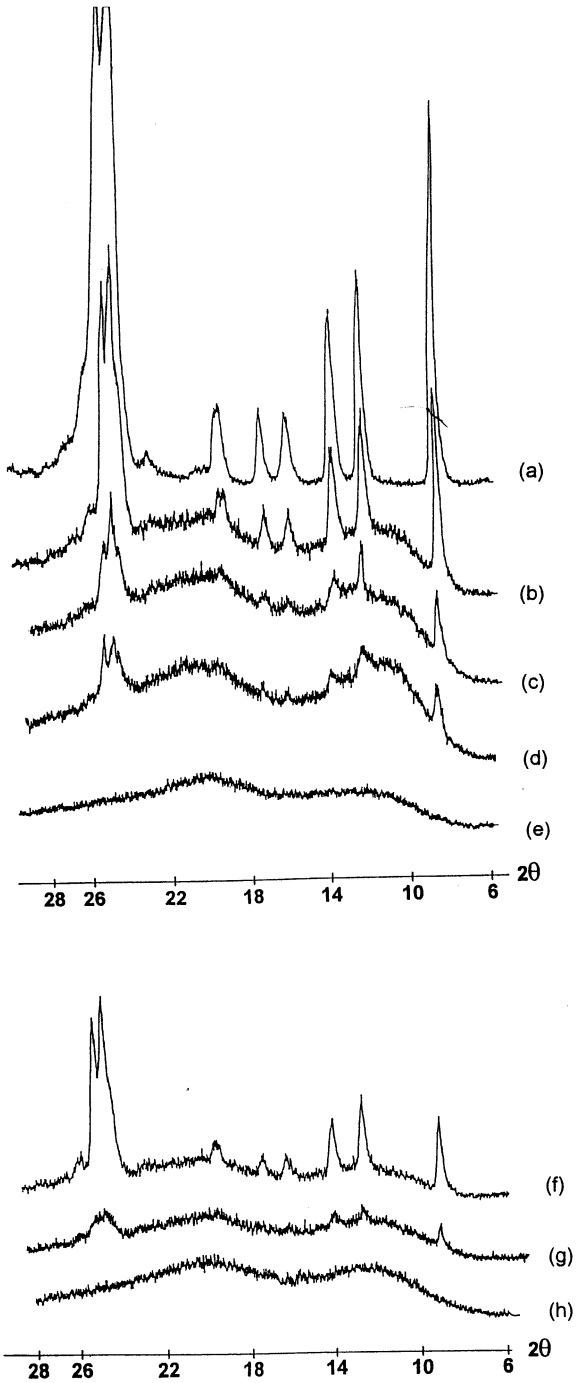

Fig. 3. X-Ray diffraction spectra: (a) Di; (b) Di:PVP 1:2 physical mixture; (c) Di:PVP 1:9 physical mixture; (d) Di:PVP 1:14 physical mixture; (e) PVP; (f) Di:PVP 1:2 coevaporate; (g) Di:PVP 1:9 coevaporate; (h) Di:PVP 1:14 coevaporate.

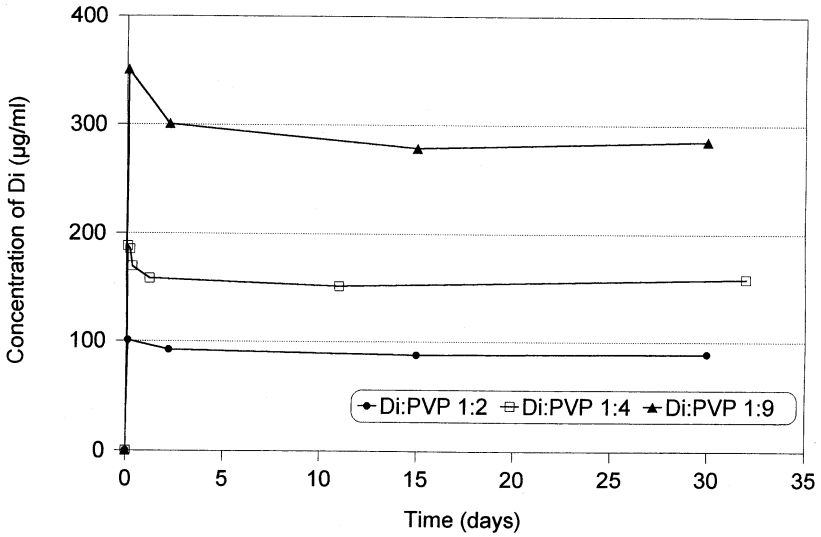

Fig. 4. Concentration of Di ($\mu g.ml^{-1}$) in the filtrates of aqueous suspensions of Di:PVP 1:2, 1:4 and 1:9 coevaporates, between 15 min and 30 days ($n = 3$).

dried in a vacuum oven at 40°C for 48 h and finally stored under nitrogen in light-resistant flasks containing a desiccant.

2.2.2. X-Ray analysis

Powder X-ray diffractometry was carried out with a Philips PW 1130/00 diffractometer using Cu Kα radiation (40 kV, 20 mA).

2.2.3. Light polarised microscopy

The coevaporates were examined under a light polarised microscope (Leitz Wetzlar, Germany).

2.2.4. Dissolution and solubility characteristics

The solubility was evaluated in purified water containing ascorbic acid 0.1% (w/v) and EDTA 0.05% (w/v) as antioxidants. Known amounts of coevaporates or physical mixtures were introduced in flasks containing 50 ml of dissolution medium. The quantities were respectively 150, 250, 500, 750, 1300 and 2050 mg for the 1:2, 1:4, 1:9, 1:14, 1:25 and 1:40 Di:PVP coevaporates. They corresponded to a total Di concentration of 0.1% (50 mg) in the dissolution medium and to coevaporate concentrations of 0.3%, 0.5%, 1%, 1.5%, 2.6% and 4.1% for respectively the 1:2, 1:4, 1:9, 1:14, 1:25 and 1:40 coevaporates. Further experiments were performed with higher Di concentrations. The amount introduced in the dissolution medium was thus calculated as a function of the Di:PVP ratio. The flasks, protected from light, were purged with nitrogen before being stoppered and submitted to gentle mechanical shaking in a water bath at 25°C. At fixed intervals (between 15 min and 30 days), samples were withdrawn, filtered through a 0.22-μm membrane (mixed cellulose esters, Millipore, USA), immediately diluted with 96% acetic acid and assayed for Di content by UV spectrophotometry at 354 nm.

2.2.5. Stability of the aqueous suspensions of the Di:PVP coevaporates

Suspensions containing 0.1% of Di were prepared with Di:PVP 1:9 and 1:14 coevaporates. Respectively 150 and 225 mg were dispersed in purified water (15 ml) containing ascorbic acid 0.1% (w/v) and sodium edetate 0.05% (w/v). The flasks, protected from light, were purged with nitrogen and submitted to gentle mechanical shaking at 25°C. At fixed intervals (between 14 and 64 days), the stability of Di was evaluated in three separate flasks: the suspensions were filtered through a 0.22-μm membrane and 2 ml of the filtrate were extracted for 10 min by 4 ml of a methylene chloride/acetic acid (95/5 v/v) mixture containing 450 $\mu g.ml^{-1}$ ortho-nitroaniline as the

Table 1
Concentration of Di (μg.ml^{-1}, mean $\pm$ S.D.) in the filtrates of aqueous suspensions of Di, of Di:PVP 1:9 and 1:40 physical mixtures (PM) and of 1:2, 1:4, 1:9, 1:14, 1:25, and 1:40 coevaporates

Di:PVP ratios							
1:0	1:9 and 1:40 PM	1:2	1:4	1:9	1:14	1:25	1:40
<0.2	<0.2	94 ± 9	152 ± 17	292 ± 16	457 ± 60	610 ± 38	620 ± 65

The suspensions were filtered and assayed after a shaking time of 14 days. The results are the means of triplicate determinations performed on three different batches of each coevaporate.

Table 2
Influence of the addition of PVP to the dissolution medium. The dissolved amount of Di (μg.ml^{-1}) was measured for a Di:PVP 1:4 coevaporate

Coev. 1:4 (% w/v)	Added PVP (% w/v)	Total PVP (% w/v)	Dissolved Di (μg.ml^{-1})
0.5	0	0.4	141
0.5	0.5	0.9	140
0.5	1.0	1.4	142
0.5	2.1	2.5	143

internal standard; 0.5 g anhydrous sodium sulphate was then added as a flocculating agent for the PVP and extraction was carried out for 5 min. After centrifugation, the water layer was discarded and an aliquot of the methylene chloride solution was diluted ten times with a n-hexane/acetic acid (91/3 v/v) mixture prior to injection into the HPLC system. The filtrates were assayed for Di and danthron content. Other impurities were expressed as a percentage of the Di peak area.

The HPLC technique described in the European Pharmacopoeia (1997) for related substances of Di was used for the assays. The HPLC system consisted of a L-6000 pump, a L-4000 UV-detector and a D-2500 chromato-integrator (Merck-Hitachi, Darmstadt, Germany; Tokyo, Japan); 20 μl samples were injected onto a 5-μm Lichrospher Si 60 (125×4 mm) column (Merck, Darmstadt, Germany) maintained at 25°C. The mobile phase was a mixture of n-hexane/methylene chloride/acetic acid 82:5:1 (v/v/v). The flow rate was 2.0 ml.min^{-1} and UV detection was carried out at 260 nm. All standard and sample solutions were freshly prepared and protected from light.

A typical HPLC chromatogram is given in Fig. 2 and shows a good separation of Di (RT = 5.3 min) from its main degradation products: danthron (RT = 8.9 min) and dimer (RT = 31.9 min) as well as from the internal standard (RT = 25.4 min).

2.2.6. Particle size analysis

An aqueous dispersion of a Di:PVP 1:9 coevaporate containing 0.1% Di was filtered through a 0.22-μm membrane and the filtrate was analysed for particle size by laser light scattering with a Malvern Mastersizer (Malvern Instruments, UK). A control measurement was performed with a PVP solution.

2.2.7. Characterisation of the undissolved fraction

The residues obtained after the dissolution of the 1:4, 1:9 and 1:14 coevaporates were collected, washed three times with distilled water and dried for 24 h in a desiccator. An aliquot was dissolved in methylene chloride and diluted 10 times with n-hexane/acetic acid 91:3 (v/v) prior to injection into the HPLC system. The residues were also analysed by X-ray diffractometry.

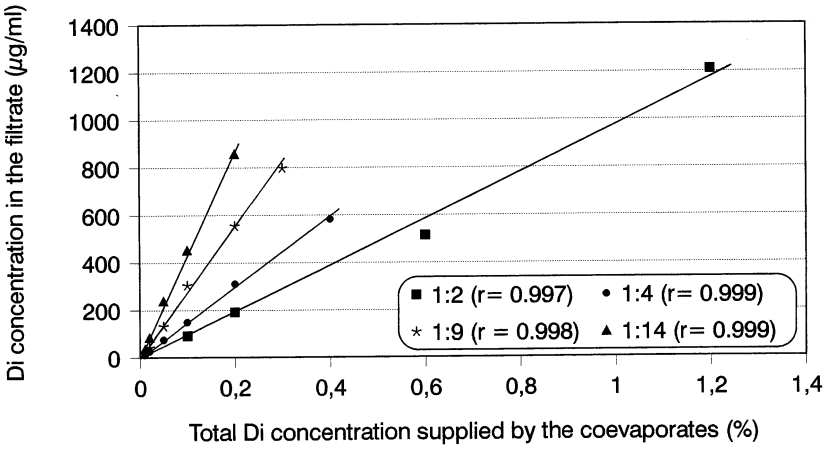

Fig. 5. Concentration of Di in the filtrate ($\mu g.ml^{-1}$) as a function of the total Di concentration (% w/v) introduced into the dissolution medium by the 1:2, 1:4, 1:9 and 1:14 coevaporates.

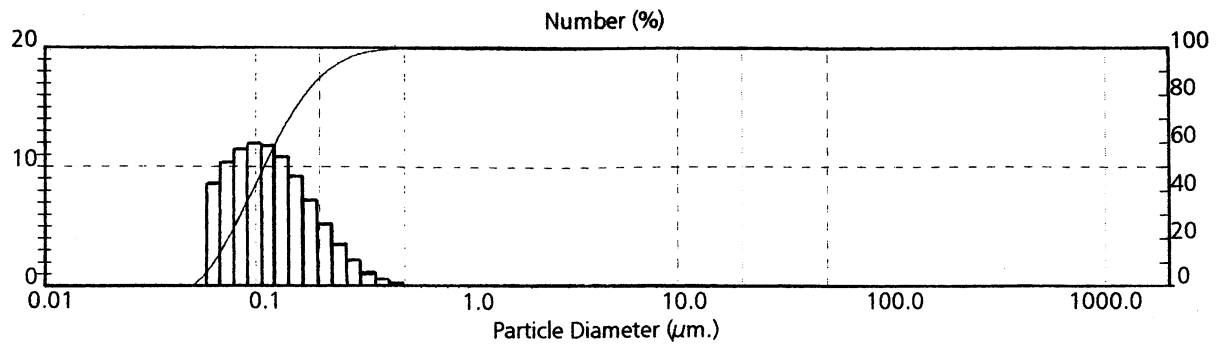

Fig. 6. Particle size distribution in the filtrate (0.22-μm membrane) of an aqueous suspension of a Di:PVP 1:9 coevaporate.

3. Results

3.1. X-Ray diffraction spectra

The spectra of the Di and the PVP treated by the same solvent evaporation method as the coevaporates are shown in Fig. 3a,e. PVP is amorphous and shows no diffraction peak whereas the structure of Di is crystalline. The spectra of the coevaporates and of the Di:PVP physical mixtures of the same ratio are shown in Fig. 3b–d,f–h. The coevaporation of Di and PVP induces a loss of crystallinity, when compared to the physical mixtures of the same Di:PVP ratios. The Di:PVP 1:14 coevaporate shows no diffraction peaks and could be considered as amorphous.

3.2. Light polarised microscopy

This technique showed that the 1:14, 1:25 and 1:40 coevaporates still contain a few Di crystals. These apparent discrepancies between X-ray diffractometry and light polarised microscopy can be attributed to the high dilution of the drug in the PVP matrix for PVP:Di ratios higher than 14.

3.3. Dissolution and solubility characteristics

The concentration of Di in the filtrate of the 1:2, 1:4 and 1:9 coevaporate suspensions was evaluated between 0 and 30 days. This concentration, corresponding to the apparent solubility of Di, is expressed in terms of dissolved amount in the

Table 3
Concentration ($\mu g.ml^{-1}$) and stability (HPLC determination) of Di in the filtrates of aqueous coevaporate suspensions between 2 h and 64 days

Time	Di:PVP 1:9			Di:PVP 1:14		
	Di ($\mu g.ml^{-1}$)	Da (%)	Imp (%)	Di ($\mu g.ml^{-1}$)	Da (%)	Imp (%)
2 h	335 ± 17	1.4	2.8	537 ± 40	1.6	1.9
14 days	272 ± 9	3.3	1.9	448 ± 20	2.8	1.6
28 days	268 ± 15	3.5	2.8	446 ± 13	2.9	1.7
64 days	265 ± 11	3.8	2.6	386 ± 5	3.7	4.2

The concentration of Di is expressed as the mean $\pm$ S.D. ($n = 3$), Da is danthron and Imp are the other detected impurities expressed as % area of the Di peak.

following discussion. In this first set of experiments, the amount of coevaporate introduced in the dissolution medium was calculated to give a total concentration of 0.1% Di. Fig. 4 shows that during the first hours, supersaturation is observed. After a 30-day period, the dissolved amount was approximately the same as that measured after 10–14 days. We can then consider that an equilibrium between the solid phase and the dissolved fraction is reached at that time. Consequently, the following dissolution determinations were performed after 14 days.

In order to check the batch-to-batch variability, the concentration of Di in the filtrate was evaluated in triplicate after 14 days for three batches of each coevaporate, as well as for Di drug substance and Di:PVP 1:9 and 1:40 physical mixtures (Table 1). Here again, the total Di concentration was 0.1%. No difference was noticed between pure Di and the physical mixtures. On the other hand, a gradual increase of the dissolved amount of Di can be noticed from the 1:2 coevaporate to the 1:25 coevaporate and a linear relationship ($r = 0.983$) is obtained when this amount is plotted against the PVP:Di ratio. However, the 1:40 coevaporates gave values similar to those of the 1:25 coevaporates.

It should be noticed that for a 0.1% Di concentration in the dissolution medium, the corresponding concentration of PVP will depend on the type of coevaporate: coevaporates with a higher PVP:Di ratio will lead to a higher PVP concentration in the dissolution medium. Therefore, we investigated the influence of the addition of PVP to the dissolution medium with a Di:PVP 1:4 coevaporate. The results of this study are given in Table 2. In the last three rows of this table, PVP was added to the dissolution medium in such quantities that the total amount of PVP was equivalent to that supplied by the 1:9, 1:14 and 1:25 coevaporates. The results indicate that this additional PVP did not increase the amount of dissolved Di. Since no modification of the dissolved quantities was observed for the physical mixture (Table 1) and for the coevaporate with an external admixture of PVP, it could be assumed that no interaction occurs in water between Di and external PVP and that only the coevaporation process is responsible for the modified dissolution characteristics.

Further experiments were performed with 1:2, 1:4, 1:9 and 1:14 coevaporates using higher Di concentrations (ranging from 0.2 to 1.2%), in order to achieve complete saturation. However, concentrations higher than 0.2% (1:14 coevaporate), 0.3% (1:9 coevaporate) or 0.4% (1:4 coevaporate) could not be tested because filtration was impossible. For the same reason, concentrations higher than 0.1% could not be tested for the 1:25 and 1:40 coevaporates. Experiments with lower Di concentrations (namely 0.01, 0.02 and 0.05%) were also performed. We observed (Fig. 5) that the Di concentration in the filtrate was proportional to the amount of coevaporate introduced to the dissolution medium. The linear relationship, obtained when the amount of Di present in the filtrate is plotted against the percentage of coevaporate in the dissolution medium, indicates that, over this range of concentrations, a constant fraction of the Di present in the coevaporate is

found in the filtrate. These average Di fractions in the filtrate are respectively $9.32 \pm 0.6\%$, $14.4 \pm 1.1\%$, $25.4 \pm 4\%$ and $43.2 \pm 3.8\%$ for the 1:2, 1:4, 1:9 and 1:14 coevaporates.

The proportionality between the Di concentration in the filtrate and the amount of coevaporate introduced in the dissolution medium cannot be explained in terms of solubility since a solubility value should be constant and independent of the excess of drug. These results can be explained by the release of a submicron Di fraction embedded in the PVP matrix. These particles lead to a colloidal dispersion of Di in water, comparable to that obtained by Tachibana and Nakamura (1965) with β-carotene:PVP coevaporates or by Thakkar et al. (1977) with nabilone:PVP coevaporates.

3.4. Particle size analysis

The colloidal nature of Di was proven by performing a particle size analysis on the filtrate of an aqueous dispersion of a Di:PVP 1:9 coevaporate. Fig. 6 shows the particle size distribution. The average diameter is 0.1 μm. The control performed with a PVP solution gave no signal. So, in the dissolution experiments, the concentrations of Di measured in the filtrates corresponded to the colloidal fraction of Di that was able to cross the 0.22-μm membrane.

3.5. Stability of the dissolved fraction

We studied the stability of aqueous suspensions of Di:PVP 1:9 and 1:14 coevaporates over a 2-month period. The assays were only performed on the filtrates because the withdrawal of a homogeneous aliquot of aqueous suspensions was impossible. Moreover, the fraction present in the filtrate should be the less stable one. The results reported in Table 3 confirm the dissolution values obtained by UV (slight supersaturation during the first few days) as well as the good chemical stability of Di, at least for the 1:9 coevaporate since the 1:14 coevaporate seems to be less stable after 64 days. These results indicate that it is possible to stabilise the water dispersed fraction of Di when care is taken to avoid contact with oxygen.

3.6. Study of the undissolved fraction

The undissolved fractions of 1:4, 1:9 and 1:14 coevaporates were assayed by HPLC and examined by X-ray diffractometry. We can conclude that these insoluble particles are pure crystalline Di: their Di content was $100 \pm 1.2\%$ and they showed the typical diffraction pattern of crystalline Di.

4. Discussion

PVP is a polymer known to give glassy solid dispersions upon coevaporation (Chiou and Riegelman, 1971). This process has the advantage of reducing the particle size of the drug and of increasing its wettability (Duchêne, 1985; Ford, 1986). An important physico-chemical characteristic of the coevaporates is the decrease or even the loss of drug crystallinity (Simonelli et al., 1970; Sekikawa et al., 1978).

During the coevaporation process, the crystallisation of Di was inhibited by the viscosity induced by PVP. This viscous medium partially inhibited the diffusion of the molecules of Di, the nucleation and the crystal growth. This was observed from the 1:2 to the 1:14 Di:PVP coevaporates (X-ray diffraction spectra), the last one showing no diffraction peaks. However, a reduction of crystallite size to an extremely fine crystalline dispersion (less than 0.2 μm) may also attenuate the height of diffraction peaks (Chiou and Riegelman, 1971). Moreover, the high dilution of the drug in PVP does not allow us to draw any conclusion about the total absence of crystallinity of Di in this coevaporate. This was confirmed by light polarised microscopy: crystalline particles were observed in each coevaporate but their number markedly decreased from the 1:2 to the 1:40 coevaporate. We can thus consider that the coevaporates are dispersions of Di crystals and nanoparticles in a PVP matrix. When the amount of PVP increases, the inhibition of crystal growth during the coevaporation process becomes more important. Thus, a greater amount of extremely small particles is formed and fewer crystals are observed. This extreme dispersion of Di in the

PVP matrix explains the apparent loss of crystallinity observed by X-ray diffractometry.

In water, the PVP of the coevaporates is solubilised and releases particles of Di. The largest particles settle, whereas the submicron particles form a stable colloidal suspension, as evidenced by the constant solubility value measured over a 30- to 60-day test period. It is thus logical for the amount found in the filtrate to be proportional to the quantity of coevaporate introduced in the dissolution medium, since the submicron fraction of Di present in the coevaporate will form the colloidal dispersion. However, this effect seems to reach a plateau. In fact, the 1:40 coevaporates gave results similar to those for the 1:25 coevaporates. This colloidal state was confirmed by the particle size distribution measured by laser light diffraction. Whereas a PVP solution gave no signal, the filtrate of the coevaporate suspension was shown to contain particles with an average diameter of 0.10 μm.

The results obtained after 30 and 64 days (Fig. 4, Table 3) indicate the good physical stability of the suspensions: no crystallisation of the submicron particles on the largest particles was observed since the quantity of Di particles crossing a 0.22-μm membrane remained constant. In fact, in aqueous suspensions, the inhibition of crystal growth by PVP is a well-known phenomenon (Simonelli et al., 1970; Sekikawa et al., 1978; Rodriguez-Hornedo, 1990). The supersaturation observed during the first days indicates that PVP releases Di in an unstable (microdispersed) state, leading to a slight supersaturation phenomenon prior to achieving a stable colloidal dispersion.

The influence of the addition of external PVP in the dissolution medium was studied because hydrophilisation by PVP or molecular interactions between PVP and the drug can enhance the aqueous solubility (Corrigan and Timoney, 1975; Oth and Moës, 1985; Tantishaiyakul et al., 1996), although generally to a lesser extent than the coevaporation process. In our case, external PVP did not increase the solubility. This confirmed the fact that no physico-chemical interaction occurred between Di and PVP in water and that the reduction of particle size upon coevaporation caused the modifications of the dissolution characteristics, owing to the formation of an aqueous colloidal dispersion. On the other hand, partial complexation or amorphous phase formation cannot be totally excluded as an additional or parallel phenomenon to colloidal dispersion.

The HPLC assays were very useful to confirm the solubility values obtained by UV spectrophotometry and also to determine the stability of the Di dispersed in water since related substances eventually produced upon degradation could not be determined by the UV spectrophotometric assay. The results indicate a good stability of the colloidal Di for at least 2 months for the Di:PVP 1:9 coevaporate.

These promising results demonstrate the ability of formulating homogeneous aqueous colloidal dispersions of Di (up to 650 $\mu g.ml^{-1}$) with a good stability. This reduction in particle size and the hydrophilic character of the coevaporates will allow further investigations in order to develop a topical form containing water dispersible dithranol and to investigate its performances in vivo.

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