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Preparation, characterisation and photosensitivity studies of solid dispersions of diflunisal and Eudragit RS100® and RL100®

Rosario Pignatello [a,*], Marinella Ferro [a], Guido De Guidi [b], Gabriella Salemi [b], Maria Angela Vandelli [c], Salvatore Guccione [a], Marco Geppi [d], Claudia Forte [e], Giovanni Puglisi [a]

[a] *Dipartimento di Scienze Farmaceutiche, Università di Catania, Viale A. Doria, 6-I-95125 Catania, Italy*
[b] *Dipartimento di Scienze Chimiche, Università di Catania, viale A. Doria, 6-I-95125 Catania, Italy*
[c] *Dipartimento di Scienze Farmaceutiche, Università di Modena e Reggio Emitia, via Campi, 183-I-41100, Modena, Italy*
[d] *Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, I-56126 Pisa, Italy*
[e] *Istituto di Chimica Quantistica ed Energetica Molecolare del CNR, Area della Ricerca, Via Alfien 1, I-56010 Ghezzano (Pisa), Italy*

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Abstract

Solid dispersions of diflunisal (DIF) with Eudragit RS100 (RS) and RL100 (RL) with different drug-to-polymer ratios were prepared by a solvent method (coevaporates) and were characterised in the solid state in comparison with the corresponding physical mixtures. The work was aimed at characterising the interactions occurring between DIF and RS or RL polymers, along with their influence on the in-vitro drug-dissolution pattern. The findings suggest that the drug did not change its crystalline form within the polymer network. Drug dispersion in the polymer matrix strongly influences its dissolution rate, which appears slower and more gradual while increasing the polymer ratios. Moreover, DIF is known to be a photosensitive compound, and its photoproduct has been found to be a toxic agent. This can be evidenced by testing red blood cell membranes for their resistance to the osmotic shock induced by UVA irradiation in the presence of DIF. The presence of some DIF/RS coevaporates was shown to reduce significantly the drug photosensitization process towards cell membranes. This suggests the possibility of combining the design of a drug delivery system with a photoprotective strategy. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

In modern pharmaceutical technology, solid dispersion is a common strategy by which to

* Corresponding author. Tel.: +39-095-7307111.

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improve the dissolution rate and absorption of poorly water-soluble drugs using hydrophilic polymeric carriers as dispersing agents (Ford, 1986). Solid dispersions made using water-insoluble carriers loaded with hydrophilic drugs lead to delivery systems aimed at optimising pharmacokinetics and reducing drug side-effects [e.g. the gastric irritation due to non-steroidal anti-inflammatory drugs (NSAIDs)] (Karnachi et al., 1995; Vachon and Nairn, 1995).

Among these polymers, polymethacrylate resins, like Eudragit RS100 (RS) and RL100 (RL), have been used as film coatings or inert carriers to formulate oral controlled-release delivery systems of NSAIDs (Benita et al., 1985; Oth and Moës, 1989; Ho and Chiaw-Chi Hwang, 1992; Pignatello et al., 1997).

RS and RL are two copolymers synthesised from acrylic and metacrylic acid esters, containing a low level of quaternary ammonium groups. RS has a lower content of charged groups (4.5–6.8%), and it is considered less permeable to water with respect to the more readily permeable RL (8.8–12% ammonium groups). Both are insoluble at physiological pH values and capable of swelling (Eudragit Technical sheets, Röhm Pharma GmbH, Weiterstadt, Germany).

However, many papers describing polymer micro- and nanoparticulate systems very often lack a preliminary evaluation of the possible interactions between the drug molecule and the polymer structure. Being a simple surface physical absorption or a true chemical reaction, such interactions can affect the state of drug dispersion in the particles and its following release rate (Beten and Moës, 1994; Holgado et al., 1995; Vachon and Nairn, 1998).

Therefore, the purpose of the present investigation was to characterise the interactions occurring between diflunisal [2′, 4′-difluoro-4-hydroxy-(1,1′-biphenyl)-3-carboxylic acid] (DIF) and RS or RL polymers, and the evaluation of their influence on drug dissolution pattern. DIF is a NSAI agent belonging to the salicylate class; the pK_a of the acid group is 3.3 and the pK_a of the phenol group is 14 (Cotton and Hux, 1985). The presence of the carboxyl group allows chemical and/or physical interactions (zwitterionic adducts, ion pairs) to occur with the ammonium group of RS and RL polymers in the solid dispersions (Jequin et al., 1990; Kislalioglu et al., 1991; Pignatello et al., 1997; Heun et al., 1998).

DIF-loaded coevaporates of RS and RL have been prepared by co-dissolving the two components in ethanol and removing the solvent under vacuum.

Furthermore, since DIF is known to be a photosensitising compound (De Guidi et al., 1991) and it should be a cause of phototoxic side-effects (Condorelli et al., 1996), two sample DIF/RS coevaporates were subjected to specific photohemolysis assays using human erythrocytes as a membrane model. This phototoxicity text is directed to evaluate the cell-membrane resistance towards osmotic shock, which can be caused by transient species (free radicals, oxygen-activated species, etc.) or stable drug photo-products, as well as photo-modified bio-macromolecules generated by drug irradiation. This test is thus directed to verify the possible protective effect exerted by the polymer on drug phototoxicity.

2. Material and methods

2.1. Chemicals

DIF (Sigma) and Avicel PH-101 (Fluka) were purchased from Sigma-Aldrich Chimica Srl, Milan, Italy. Eudragit RS100 and RL100 were kindly donated by Rofarma (Gaggiano, Italy). Lactose and magnesium stearate were purchased from Carlo Erba (Milan, Italy). Solvents and buffers were of analytical grade.

2.2. Preparation of solid dispersions (solvent method)

Weighed amounts of DIF (0.5 g) and RS or RL (0.5–2.5 g) were dissolved in 50 ml of absolute ethanol at different drug-to-polymer ratios (1:1, 1:2 and 1:5). The solution was stirred at room temperature for 4–6 h, and the solvent was then removed under vacuum in a rotary evaporator, at a maximum temperature of 40°C. Solid residue was dried in a desiccator for 24 h at room temper-

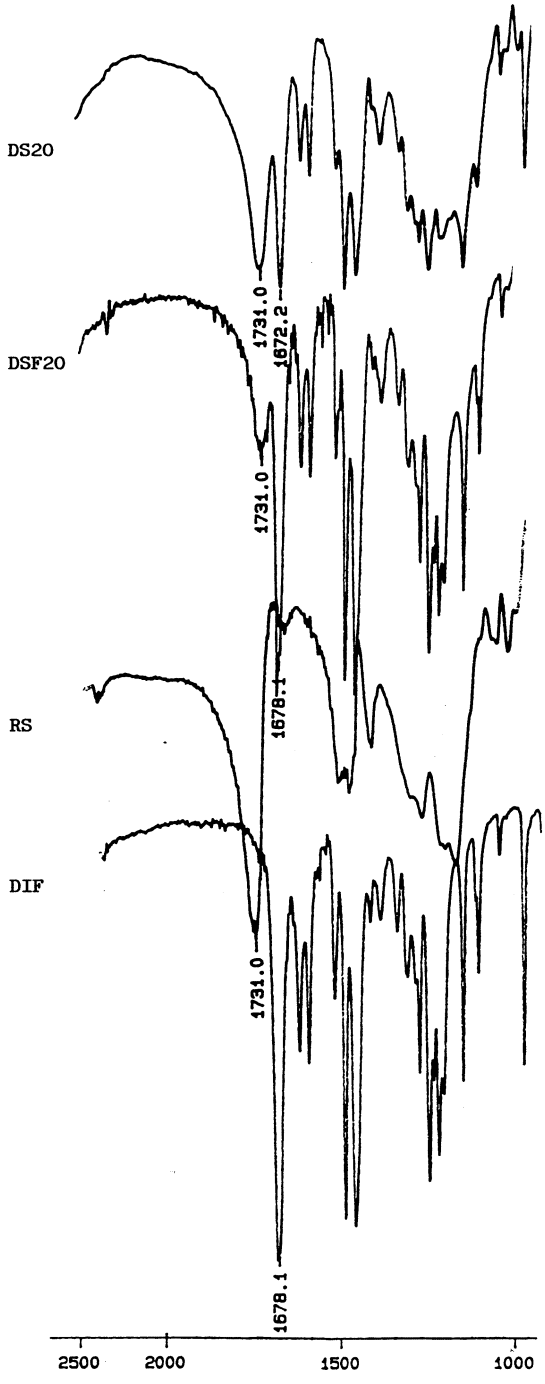

Fig. 1. IR spectra of DIF, RS, and their coevaporates (DS) and physical mixtures (DSF).

ature, pulverised and sieved. Powder samples below 420 μm (40 mesh) were stored in closed containers away from the light and humidity until use.

When using the higher polymer:drug ratios, a rubbery residue was obtained after ethanol evaporation, which was solidified by triturating with light petroleum ether.

2.3. Determination of drug content

Several hundred micrograms of each solid dispersion were dissolved in 5 ml of UV-grade methanol. DIF was determined spectrophotometrically (Shimadzu UV-1601) at 254 μm. The mean of at least three determinations was calculated. The polymers did not interfere ($< 3\%$) with the absorbance of the drug.

Drug content was expressed both as the percentage incorporation (actual amount of drug in the coevaporates vs. the initially added amount) and as the drug content (mg incorporated DIF in 100 mg of coevaporate) (Table 1).

2.4. Preparation of the physical mixtures

Samples with the same actual composition of the solid dispersions were prepared by simply triturating the powdered drug and RS or RL in a porcelain mortar. The mixtures were then sieved, and the fractions below 420 μm were collected and stored in capped amber-glass containers until use.

2.5. FT-IR spectrophotometer

IR spectra of coevaporates, physical mixtures, DIF and pure polymers were obtained with a Perkin-Elmer 1600 spectrophotometer, using the KBr disk technique (about 10 mg of sample for 100 mg of dry KBr) (Fig. 1).

2.6. Differential scanning calorimeter (DSC)

Thermal analysis was performed on the drug, coevaporates, physical mixtures and Eudragit us-

Table 1
Properties of diflunisal/Eudragit RS100 and RL100 coevaporates prepared by the solvent method

Formulation	Type of polymer	Drug/polymer ratio (w/w)	Loading efficiency		Percentage incorporation (% w/w)	Production yield
			Theoretical drug content (%w/w)	Actual drug content (%w/w)		
DS10	RS	1:1	50	43	87 ± 2	90 ± 5
DS20	RS	1:2	33	27	76 ± 1	93 ± 1
DS50	RS	1:5	16	14	85 ± 4	88 ± 1
DL20	RL	1:2	33	28	83 ± 3	86 ± 4
DL50	RL	1:5	16	14	78 ± 6	41 ± 2

ing a Mettler DSC 12E differential scanning calorimeter equipped with a Haake D8-G thermocryostat, a detection system (Mettler Pt 100 sensor) and a computer.

Samples (10–15 mg) were weighed into 40 μl aluminium pans and sealed. DSC runs were performed over a temperature range of 25–240°C, at 5°C/min. An indium standard was used to calibrate the instrument. Typical DSC scans are shown in Figs. 2–4.

2.7. X-ray powder diffraction

Diffraction patterns were recorded with a Philips diffractometer Pw 1050/25 for powders (Fig. 5). A voltage of 40 kV and a current of 30 mA for the generator were used, with Cu as the tube anode material. The samples were exposed to CuKα radiation ($\alpha_1 = 1.54060$ Å and $\alpha_2 = 1.54439$ Å, with an α_1/α_2 ratio of 0.5), over a range of 2θ angles from 3 to 30°, at an angular speed of 1° (2°) per minute, using divergence and receiving slits of 0.50 or 10 and 0.20, respectively.

2.8. Solid-state ^{13}C-NMR spectrometry

^{13}C CP-MAS spectra (Pines et al., 1972) were recorded on a Bruker AMX300 WB spectrometer equipped for solid samples and a CP-MAS 4 mm probe, which worked at 75.47 MHz for ^{13}C. The 90° pulse was 3.6 μs. The contact time and relaxation delay were experimentally optimised for each sample: the contact time was 1 ms for the polymer, 10 ms for the drug and 5 ms for the mixtures; the relaxation delay was 4 s for the polymer and 240 s for the drug, and ranged between 10 and 30 s for the mixtures. The spectra were acquired after 800 or 1600 scans.

All the experiments were run at room temperature using ^{1}H-high power decoupling and spining at the magic angle with a MAS rate of 6 kHz. Chemical shifts were referenced to external adamantane.

^{1}H relaxation measurements were performed at 20 MHz on a Varian XLlOO spectrometer interfaced with a Stelar DS-NMR acquisition system, working at a low resolution. The 90° pulse was

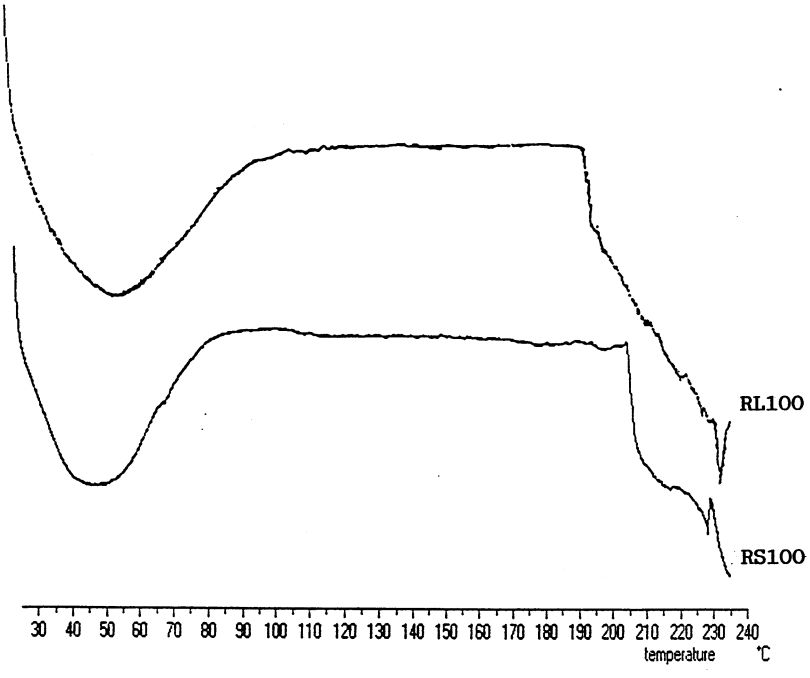

Fig. 2. DSC runs of Eudragit RL100 and RS100.

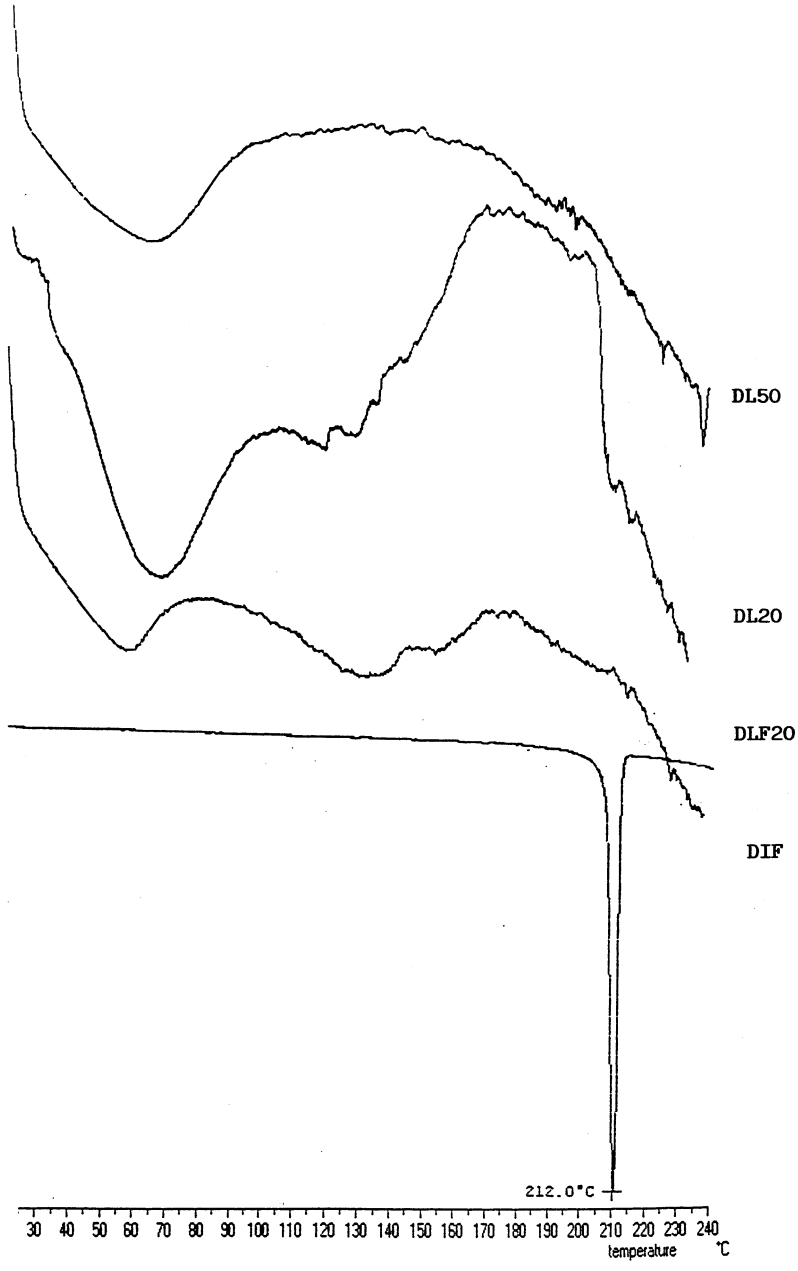

Fig. 3. Comparison among DSC curves of pure DIF, DIF–RL100 coevaporates (DL) and physical mixtures (DLF).

2.1 μs. The FIDs were recorded using an inversion recovery pulse sequence followed by a solid echo (Kenwright and Say, 1993) with an echo delay of 12 μs. All measurements were made at room temperature.

2.9. In-vitro drug dissolution studies

Drug dissolution tests from coevaporates were performed according to the F.U.I. X Ed. rotating basket method, at 37°C and 100 rpm. The dissolu-

tion medium consisted of 900 ml of pH 7.4 phosphate buffer.

At predetermined times, 2 ml samples were withdrawn and replaced with the same volume of pre-warmed dissolution medium. The drug concentration was determined spectrophotometrically at 252 nm vs. a calibration curve made up in a pH 7.4 phosphate buffer (Fig. 8). Three to five repetitions of each run were carried out.

2.10. Photobiology tests

2.10.1. Materials

Phosphate-buffered saline (PBS) (pH 7.4) consisted of a 10 mM phosphate buffer solution added with 0.135 M NaCl solution.

Red blood cells (RBCs) were prepared from samples of out-of-date (no more than 15 days from the date stated) packed human erythrocytes,

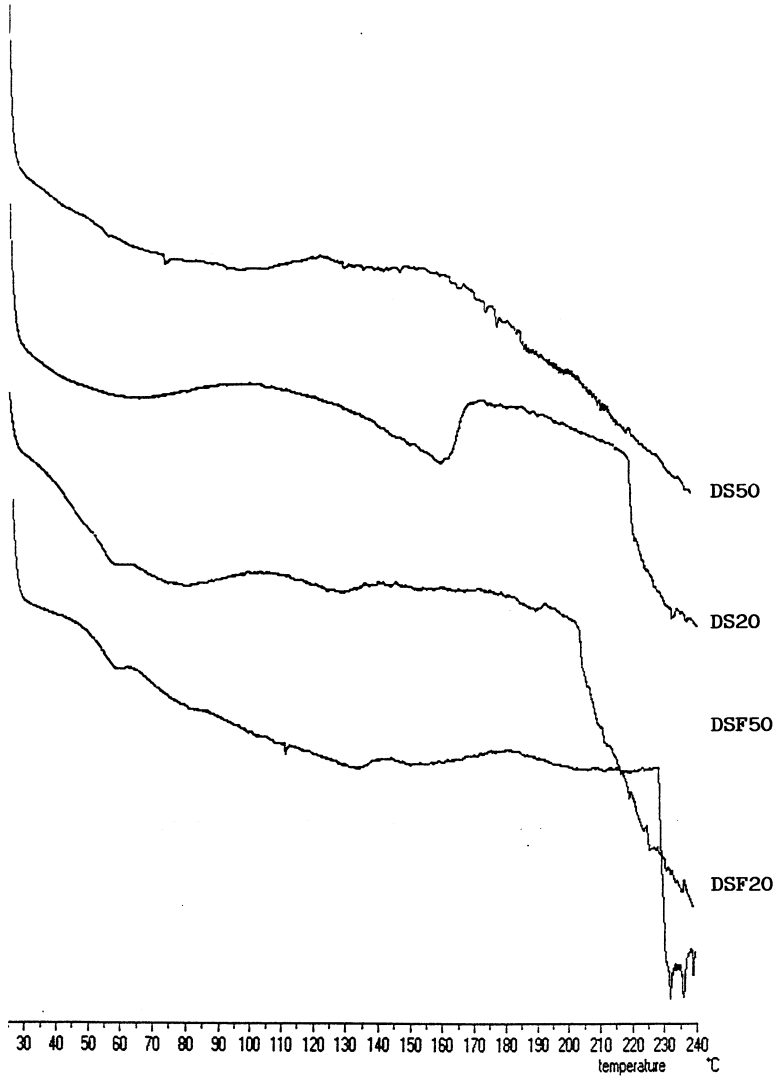

Fig. 4. Comparison between DSC curves of DIF–RS100 coevaporates (DS) and physical mixtures (DSF).

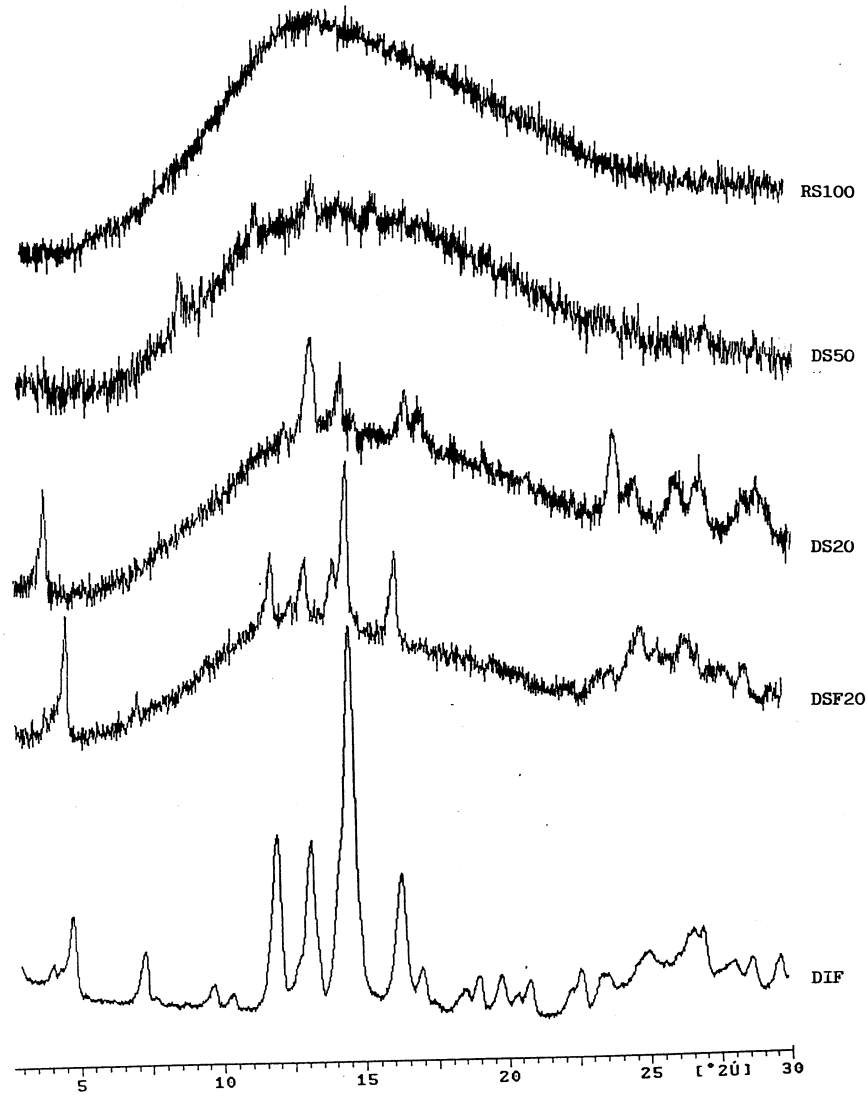

Fig. 5. X-ray diffraction patterns of DIF, RS and DIF–RS physical mixture (DSF) and coevaporates (DS).

supplied by the local blood bank, by washing them four times with a 10-fold volume of PBS and centrifuging the cells at 2500 × *g* for 15 min. The supernatant was carefully removed. Erythrocytes from the out-of-date packed cells gave reproducible results over many days (Wang and Kagan, 1989). Proof of reproducibility is provided by results shown in Figs. 9 and 10, where a 5% S.D. value is obtained also by using different blood samples.

2.10.2. Irradiation conditions

Photohemolysis tests were performed using a Rayonet photochemical reactor equipped with eight "black light" phosphor lamps with emission in the 310–390 μm range with a maximum at 350 μm. The incident photon flux on 3 ml of solution in quartz cuvettes (optical length, 1 cm) was 6×10^{15} quanta/s, which is of the same order of solar fluence incidence on skin, as measured on a sunny June day at Southern Italy latitude. A 'merry-go-

round' (carousel) irradiation apparatus placed in the centre of the photo-reactor was used to ensure that all the samples received equal radiation.

Light intensity was measured by a digital radiometer (Spectroline Mod. DRC-100 ×) equipped with a sensor DIX-365, with a spectral range of 320–380 um.

2.11. Photohemolysis assay

In all experiments, an amount of DIF–RS coevaporates was used in a such way to obtain a drug concentration of 0.3 mM, which corresponds to the value used in previous photosensitization experiments (De Guidi et al., 1991). This concentration is very close to that reached in blood serum levels after DIF oral adrumistration (Moffat, 1986). In order to assess the influence of the drug-to-polymer ratio on the photo-protective activity of RS, we tested two samples of DIF–RS coevaporates showing different drug loading (DS10 and DS20).

DIF–RS samples for hemolysis tests were prepared by suspending the coevaporates in PBS and keeping them at room temperature under continuous stirring for different times (incubation times), during which drug release from the polymer matrix occurred, before the addition of RBCs.

Other samples containing pure DIF or polymer were prepared as controls to check the photosensitising activity of both the drug and polymer network alone. After addition of RBCs (3×10^6 cells ml^{-1}), samples were irradiated under the irradiation conditions reported above.

For both photohemolysis and dark hemolysis experiments, RBCs were diluted in PBS containing the DIF alone or included in Eudragit so that the resultant suspension had an optical density of 0.4–0.8 at 650 nm. An absorbance of 0.5 corresponded to 3.3×10^6 cells/ml.

Each series of tests was performed in triplicate with aliquots from the same sample of blood. Results were expressed as a percentage of total hemolysis by comparison with a sample in which cells had been completely hemolised by brief sonication (Figs. 9 and 10).

Photohemolysis experiments were carried out in PBS by measuring the decrease in absorbance at 650 nm as a function of the time measured from the beginning of the irradiation (delayed hemolysis time), since the optical density is linearly proportional to the number of intact RBCs (Valenzeno and Trank, 1985). Further details regarding preparation and handling of erythrocytes can be found in a previous paper (Giammona et al., 1996).

3. Results and discussion

3.1. Physicochemical characterisation of DIF–RS/RL solid dispersions

The physical state of DIF within the RS and RL matrices (solid dispersions and physical mixtures) was studied by classical spectroscopic techniques (FT-IR, X-ray diffraction, DSC, solid-state ^{13}C-NMR).

All the analytical investigations agree in suggesting that the drug maintained its crystalline form within the polymer network. The preparation conditions for the solid dispersions did not induce polymorphism or amorphisation of the drug, since their spectroscopic profiles are quite similar to the mere physical mixtures of the two components. The progressive disappearance of drug IR, X-ray and DSC signals in the spectra of coevaporates is rather related to the increasing amount of the polymer, which exerts a ''diluting'' effect (the so-called ''matricial effect'').

The IR spectra of both physical mixtures and coevaporates show the presence of the characteristic DIF and Eudragit peaks (Fig. 1). In particular, in the physical mixtures, while both the signal of drug and polymer carboxyl groups are visible (at 1680 and 1735 cm^{-1}, respectively), in the corresponding coevaporates, the former peak is shifted around 1690 cm^{-1}, and another sharp peak around 1720–1725 cm^{-1} appeared. A somewhat weak electrostatic interaction between the drug and polymers seems then to occur at the level of DIF Carboxyl group during the co-dissolution and solvent evaporation, not resulting from the simple blend of the ingredients. The comparison between the ratio of the peak heights at about 1210 and 1225 cm^{-1} (Cotton and Hux, 1985) in

the pure drug and coevaporates, however, allows to settle that no polymorphic change occurred to drug crystals after inclusion in the polymer matrix.

In the DSC analysis, the pure drug exhibits a sharp endothermic peak around 212.0°C (melting point) (Fig. 3). A blend of the drug with polymers resulted in the disappearance of such a fusion peak, replaced by broad endothermic signals exhibiting a reduced melting endotherm and a lowering of the peak temperatures (130–150°C) (Figs. 3 and 4). Physical mixtures showed a similar behaviour, and the effect was more evident with increasing the polymer-to-drug weight ratio (2:1 vs. 5:1). As already shown for other drugs (Vachon and Nairn, 1995), these findings suggest that DIF is able to dissolve in the polymer to a certain degree to form a solid solution. The presence of endothermic signals at the 2:1 polymer:drug ratio confirmed that DIF crystals still exist in solid dispersions.

Polymer X-ray diffraction patterns show the typical profile of amorphous materials (Fig. 5). DIF-loaded solid dispersions still show an interference due to the pure drug peaks in the DS20 system (DIF/IRS 1:2), as well as in the corresponding 1:2 physical mixture. Conversely, the drug signals totally disappeared in the system with a higher polymer ratio (DS50; DIF/RS 1:5) (Fig. 5). The drug then appears to undergo microcrystallization within the RS matrix when the drug concentration overcomes the drug solubility in the polymer, despite their blending conditions, i.e. co-solution (coevaporates) or dry grinding (physical mixtures).

The ^{13}C cross-polarisation magic-angle spinning (CP-MAS) NMR spectra of DIF and Eudragit are reported in Fig. 6. The two compounds give quite separated spectra; in fact, the polymer shows resonances between 10 and 70 ppm and a peak around 175 ppm, the latter due to the ester carbons, whereas the drug shows peaks in the 100–180 ppm region, the only overlap with the polymer spectrum being the carboxylic carbon at 175 ppm.

Fig. 7 shows the ^{13}C CP-MAS spectra of DS20, DS50 and the 1:2 and 1:5 DIF–RS physical mixtures. The spectra of the physical mixtures are clearly a superposition of those of pure DIF and RS, confirming the absence of significant chemical interactions between drug and polymer after their simple mixing in the solid state. In the spectra of the coevaporates, a variation in signal shape and intensity is observed in the 100–130 ppm region, i.e. in the region of the drug resonances, indicating an interaction of DIF with the polymer.

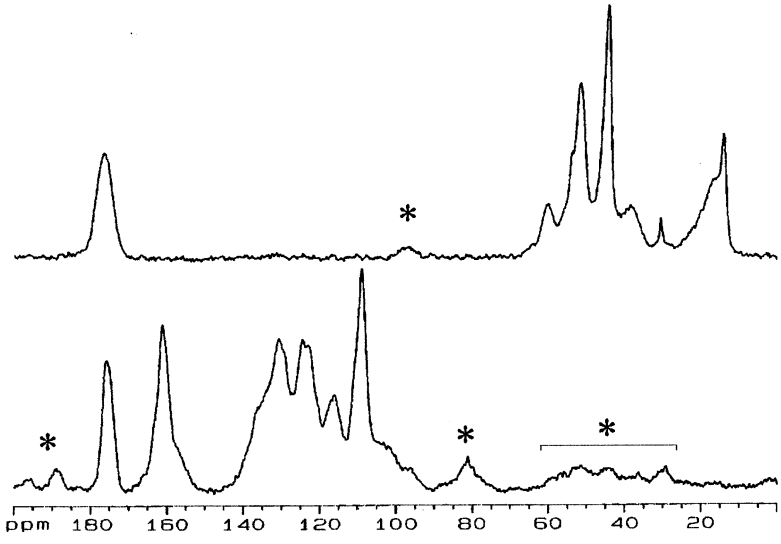

Fig. 6. ^{13}C CP-MAS spectra of RS (top) and DIF (bottom). Asterisks indicate spinning sidebands.

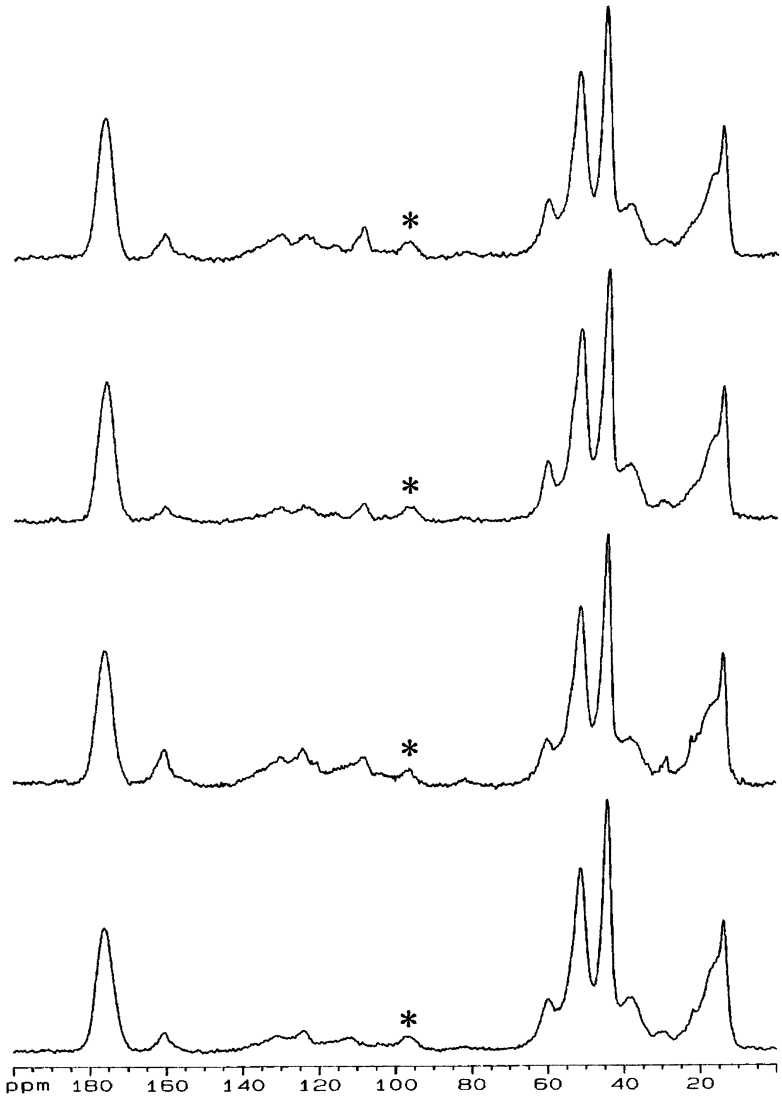

Fig. 7. ^{13}C CP-MAS spectra of (from top to bottom): DS20, DS50 and of the 1:2 and 1:5 DIF–RS physical mixtures. Asterisks indicate spinning sidebands.

^{1}H spin lattice relaxation times (T_1) were measured in order to obtain information on the level of mixing of the two components in the different mixtures. In fact ^{1}H T_1 values in heterogeneous systems are strongly influenced by the spin diffusion process (McBrierty and Packer, 1993), which tends to average them to a single value. Therefore, the measurement of ^{1}H T_1 can be used to estimate domain dimensions on the 100 Å scale. The two pure compounds show remarkably different relaxation times: while the value observed for the polymer is of the order of 100 ms, the value measured for DIF is significantly higher, i.e. 35 s. A single average T_1 value, slightly higher than that observed in the pure polymer, is determined in the coevaporates; this is an indication of an intimate degree of mixing between DIF and RS100. On the contrary, in the mechanical mix-

tures, two different relaxation times, one of the order of 100 ms and the other of 10 s, are measured, indicative of the presence of domains of DIF much larger than 100 Å, and hence of a lower degree of mixing.

3.2. Dissolution studies

The DIF dissolution profiles at pH 7.4, as a pure drug powder and from selected coevaporates (DS10, DS20 and DS50, Table 1), are compared in Fig. 8.

The powdered drug displayed a very fast and complete dissolution, due to its rapid dissociation in the alkaline medium. The dispersion of the drug in the polymer matrix strongly influences its dissolution rate, which appears slower while increasing the polymer ratios (e.g. DS50 vs. DS10). The presence of the polymer also reduces the phenomenon of the massive initial drug dissolution, despite 50% of the drug still going into solution within 15 min from the coevaporates obtained with lower polymer amounts. The dispersion containing the higher RS ratio (DS50) exhibited a slower and almost linear drug release from 0 to 28 h.

At this time, none of the coevaporates apparently allowed the complete release of DIF into the dissolution medium, releasing the 55–90% of the initial drug amount in the dispersions (Fig. 8). Such behaviour, already observed for similar systems (Pignatello et al., 1997; Khalil and Sallam, 1999) can be justified by a re-adsorption of the dissolved drug from the medium back onto the polymer particles, due to the presence of opposite electrical charges. In this case, too, the observed effect was proportional to the amount of polymer present. The precipitation of the drug in the dissolution medium over a certain concentration can be excluded (i.e. a steady state was maintained in the test), since the tablet prepared by diluting the free drug with lactose showed a complete release of DIF.

3.3. Protective activity of RS from DIF phototoxicity

It is known that DIF is quite phototoxic in vivo, as tested in the mouse-tail assay in sub-lethal doses (Ljunggren and Lundberg, 1985). Moreover, when DIF is irradiated together with RBCs in the range of concentrations attained in blood serum after therapeutic administration, it causes a

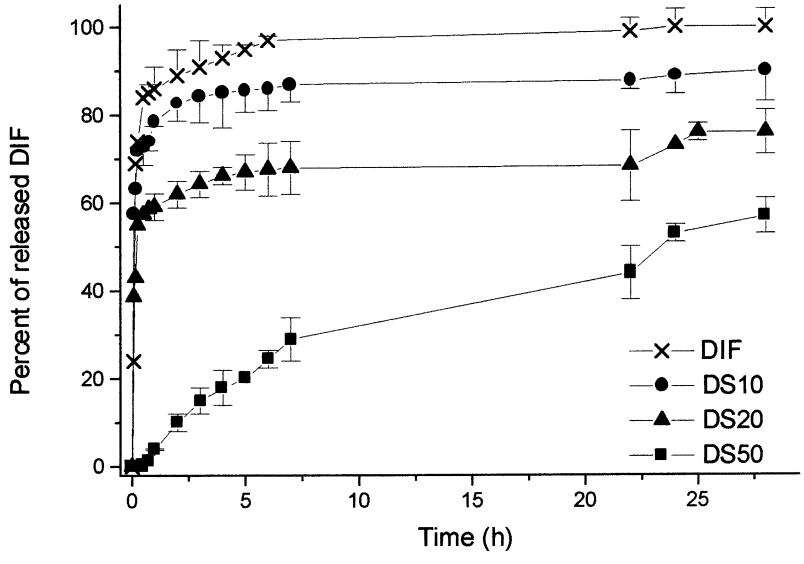

Fig. 8. In vitro dissolution pattern of DIF from the solid dispersions at pH 7.4. Mean ± S.D. of three to five experiments.

certain degree of hemolysis (De Guidi et al., 1991).

As regards DIF photochemistry, defluorination was found to be the primary photochemical act, leading to the photosensitization process; the noxious species involved were the consequently formed free radicals, superoxide anion, singlet oxygen and, mostly, the main photoproduct, the 2′-(2‴, 4‴-difluoro-3″-carboxy-[1″, 1‴-biphenyl]-4″-oxy)-4′-fluoro-4-hydroxy-[1,1′-biphenyl]-3-carboxylic acid. The photoreactivity of this drug is quite unusual for fluorinated derivatives. Indeed, defluorination occurs through a reaction involving electrons yielded by DIF photoionization caused by a DIF molecule in the ground state. Electron production leads to two radicals, and their combination is responsible for the stable photoproduct formation (Sortino et al., 1999). The latter has been found to be the main phototoxic agent by disrupting activity in the dark towards membranes (De Guidi et al., 1991).

Photohemolysis experiments have been then performed to study the ability of RS in modifying DIF phototoxicity against cell membranes. Photohemolysis experiments were carried out with RBC suspensions in the presence of DIF–RS coevaporates with two different drug percentages: DS10 and DS20, containing 43 and 27% drug, respectively (Table 1). The photohemolysis data were expressed in terms of semi-hemolysis time (T_{50}) as a function of the incubation time. T_{50} represents the time needed to reach 50% delayed hemolysis after irradiation, whereas the incubation time is the time during which the suspensions of DIF–RS coevaporates are left in PBS at room temperature under continuous stirring before addition of RBCs and before irradiation. The higher value is T_{50}, and the longer value is the resistance of membrane cell to the photosensitizing damage. All the photohemolysis values were obtained by analysis of a sigmoidal Boltzman fit. For the pure drug, irradiation started immediately after drug dissolution in PBS.

The RS polymer matrix is able to reduce DIF photosensitization. In fact, in the presence of RBCs, DIF alone shows a lower T_{50} than its RS coevaporates. We have compared the hemolysis test results of DIF-loaded coevaporates at different loading percentages (DS20 and DS10), using an irradiation time of 30 min for DS20 and 15 min for DS10, respectively. The latter irradiation time was lowered because of the short T_{50}, probably due to the high release rate of DIF from such a system.

Photohemolysis test results showed that the lower the drug-loading extent, the stronger is the protection against photosensitised damage; this could be partially explained by the different release rates. In fact, release tests showed that DIF dissolved more slowly from DS20 than from DS10 (Fig. 8).

RBC-DIF suspensions irradiated in the absence of polymer for 30 min showed a T_{50} value of 45 min, whereas the DS20 displayed a T_{50} in the range 190–55 min for incubation times ranging between 0.5 and 24 h (Fig. 9). Conversely, RBC-DIF suspensions irradiated for 15 min gave a T_{50} value of 60 min. DS10 showed T_{50} values in the range 150–65 min for incubation times between 5 and 120 min (Fig. 10).

All these findings agree with those obtained by the above drug-release experiments. The RS polymer network provides a significant reduction of the DIF photosensitising activity, by considering that for all the systems, the lower T_{50} value is reached with incubation times during which the drug release is estimated to be complete. Only after this time the hemolysis rate is comparable to the T_{50} value of the pure drug.

By contrast, no photosensitising action was displayed by empty coevaporates (pure RS), and no lysis was observed when cells were irradiated in the absence of DIF or incubated with DIF in the dark.

These results suggest that the key photochemical step in drug photo-degradation, which involves an electron-trapping reaction, could be strongly influenced by the presence of an efficient electrostatic interaction between the drug and the polymer network. This could be accompanied also by a scavenging action of the host organic functional groups towards the radicals generated by drug irradiation. Indeed, it has been shown that other delivery polymeric systems loaded with NSAIDs, like Suprofen or Tolmetin, show a pho-

toprotective activity towards the same kind of biological target (Giammona et al., 1998; Condorelli et al., 2000). A similar behaviour was also observed in the photochemistry of DIF in the presence of cyclodextrins as a host–guest system (unpublished results). This hypothesis may well account for a scavenging (photo-protective) effect developed by the polymer towards the photodamage produced by DIF irradiation.

Further experiments are in progress to assess if the observed photo-protective action can be attributed not only to DIF release from Eudragit matrices, but also to a change in DIF photochemistry in the presence of the polymer.

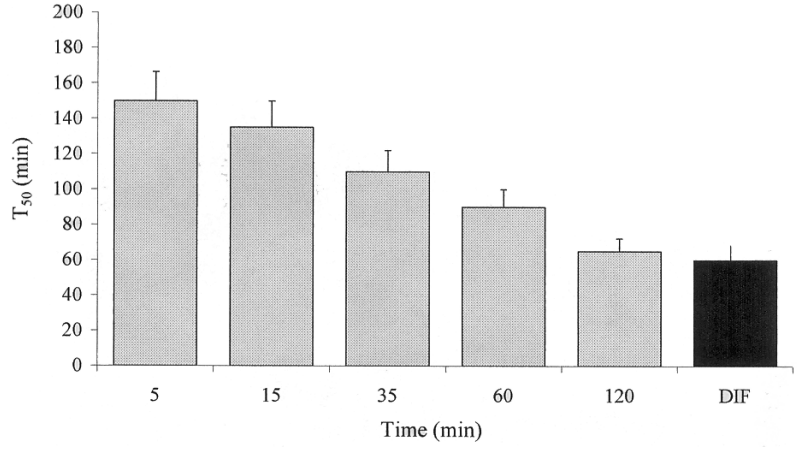

Fig. 9. Semi-hemolysis time versus incubation time for DS10. Irradiation time: 30 min. [DIF] = 0.3 μM. Each point represents the mean of three experiments (S.D. = 5%).

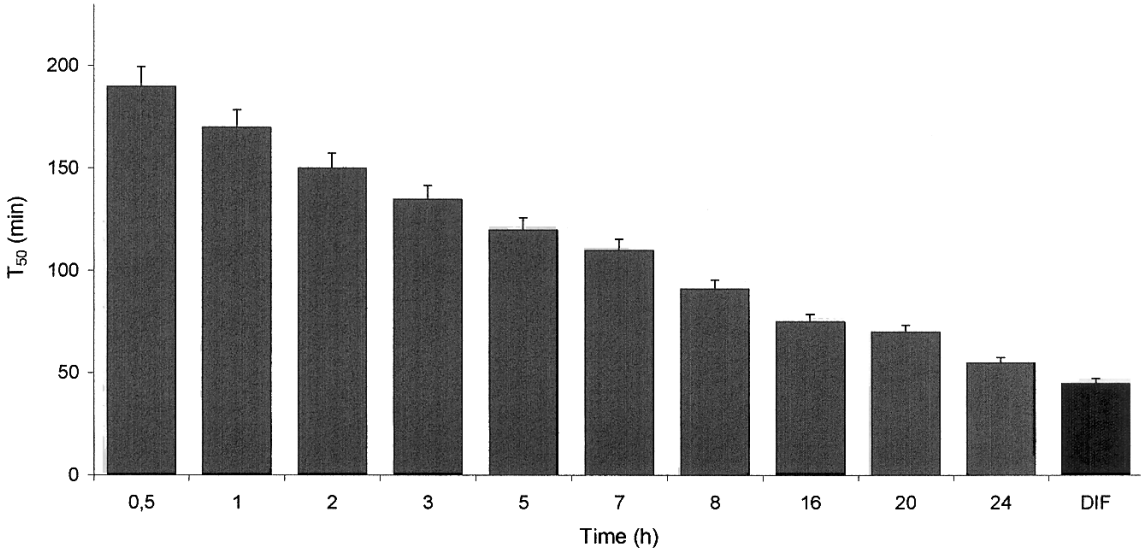

Fig. 10. Semi-hemolysis time versus incubation time for DS20. Irradiation time: 15 min. [DIF] = 0.3 μM. Each point represents the mean of three experiments (S.D. = 5%).

4. Conclusions

The incorporation of drugs into polymer matrixes, leading to coprecipitates, solid dispersions or micro- and nanoparticulate systems, is considered a valid tool in order to optimise insufficient features of the drug molecule, like solubility, stability or toxic effects.

In the present paper, the incorporation of DIF, an NSAID agent was performed in solid dispersions (coevaporates) made from inert and pH-unsensible water-insoluble polymers (RS and RL). The dispersed drug did not change its crystalline status, however, reaching a molecular or microcrystalline form in the matrixes, as different analytical techniques suggested. Such studies can also become important for the optimisation of DIF-loaded polymeric microparticle systems.

The dispersion of the drug in the polymer network altered its dissolution profile at pH 7.4, thus making it possible to obtain a gradual and prolonged release, and to modulate the release pattern as a function of the ratio between the two components.

Moreover, in-vitro tests indicated that the presence of the polymeric system changed significantly the susceptibility of the drug photosensitization process towards the cell membrane, probably due to a change in DIF photochemistry in the presence of the polymer. This suggests the possibility of combining the design of a drug-delivery system with a photo-protective strategy.

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