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Research paper

Polymethacrylates as crystallization inhibitors in monolayer transdermal patches containing ibuprofen

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Abstract

The feasibility of a monolayer patch based on polydimethylsiloxane pressure sensitive adhesive containing ibuprofen (IB) in supersaturated condition was studied. The efficacy of three low molecular weight excipients (propylene glycol, PG, Cremophor EL and Cremophor RH) and of two copolymers of methacrylic acid (Eudragit® E, EuE, and Eudragit® RL, EuRL) as IB crystallization inhibitors was tested. The performances of the patches were evaluated in terms of drug release and human stratum corneum and epidermis (SCE) permeation profile. The interactions between IB and the other excipients were investigated by ATR–FT-IR spectroscopy. The stability of the patches, prepared without adding crystallization inhibitors, was unsatisfactory because crystals grew in less than 1 month. Among the low molecular weight molecules, only PG inhibited the IB crystallization up to 50 days without affecting the IB skin permeation profile. The addition of EuE or EuRL in the matrices prevented drug crystallization for more than 12 months. EuE significantly reduced the IB in vitro release rate and the IB permeated amount through the SCE compared to other formulations. These phenomena are attributed to a stronger association between IB and EuE than IB and EuRL.
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Keywords: Transdermal patches; Crystallization inhibitors; Ibuprofen; Eudragit®; Silicon PSA

1. Introduction

The transdermal administration of a drug is often compromised by its low bioavailability due to the skin barrier function. As a consequence, in the last decades many passive and active enhancement strategies were developed. Among the former, chemical enhancers are the most widely tested. In general, the chemical enhancers promote the drug flux across the skin by altering the stratum corneum barrier properties in a reversible way. A softer alternative method consists in the use of a system which, having chemical potentials greater than those of the corresponding saturated systems, promote the partition of the drug from the vehicle to the skin. The efficacy of such approach was widely proven by using either solutions [1,2], or monolayer transdermal patches [3]. Monolayer transdermal patches containing drugs in supersaturated conditions can be easily obtained by fast solvent evaporation or, in the case of hot-melt based system, by fast cooling of the matrix. Even if in both processes the drug supersaturation can be easily reached, the system often results unstable. As a matter of fact, the systems are thermodynamically unstable and the drugs frequently re-crystallize during the storage. The growth of drug crystals in the formulation lead to a reduction of drug thermodynamic activity and this consequently may reduce the drug flux through the stratum corneum [3,4]. Therefore, the inhibition of drug crystallization is imperative to maintain the efficiency and quality of transdermal systems and prolongs the shelf life of the product. Only in some cases, the drying condition or final thermal curing (e.g. temperature above the drug melting point) can prevent crystallization [5]. Thus, the basic approach for reducing the induction time for drug crystallization in patches is the addition of a crystallization inhibitor into the matrix that could retard the nucleation process. The proposed antinucleant agents are low molecular weight excipients, such as silicon dioxide [6],

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cholesterol, other steroidal molecules [7,8] and surfactants [3] or macromolecules. Among the last, the most widely used in the development of transdermal patches are water-soluble polyvinylpyrrolydones [3,9] or vinylpyrrolydone copolymers [6]. The efficacy of copolymers of methacrylic acid with different functionalities on the inhibition of estradiol and norethisterone crystallization in polyacrylic pressure sensitive adhesive matrices was also proven [10,11].

In this work, the feasibility of a stable monolayer patch based on polydimethylsyloxane pressure sensitive adhesives containing ibuprofen (IB) in supersaturated condition was studied. The efficacy of low molecular weight excipients such as surfactants (Cremophor® EL) and solubilizing agents (Cremophor® RH, propylene glycol) and of two copolymers of methacrylic acid (Eudragit® E and Eudragit® RL) as IB crystallization inhibitors was tested over a period of 1 year.

The presence of IB crystals in the patches was investigated by polarized microscopy [7]. The possible interactions between IB and the other excipients were investigated by ATR–FT-IR spectroscopy. The effects of the addition of the selected crystallization inhibitors on the performances of the patches were evaluated in terms of in vitro drug release and ex vivo human skin permeation profile.

2. Materials and methods

2.1. Materials

Ibuprofen, IB (Francis, I); propylene glycol, PG (ACEF, I); Cremophor® EL, CrEL, and Cremophor® RH, CrRH (BASF, G); Eudragit® E100, EuE: poly[butyl methacrylate, (2-dimethylaminoethyl)methacrylate methyl methacrylate]; molar proportions of the monomer units: 1:2:1; molecular weight 150,000 Da and Eudragit® RL100, EuRL: poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyil methacrylate chloride); molar proportions of the monomer units: 1:2:0.2; molecular weight 150,000 Da (Rofarma, I); BIO-PSA® 7-4302, B43 (polydimethylsiloxane/silicate resin, molar proportion 45:55, capped with trimethylsiloxy group), and BIO-PSA® 7-4602, B46, (polydimethylsiloxane/silicate resin, molar proportion 45:55) (Dow Corning, US). Backing layer: Scotchpak® 1220 film, polyester film laminate (3M, US) with the following specifications: thickness 0.051 mm, elongation at break MD 100% and CD 100%, tensile strength MD 67.5 N/25 mm and CD 90 N/25 mm. Release liner: Scotchpak® 1022 film, polyester film (3M, US). Brufen crema® 10% m/m (Abbot spa, I).

All solvents unless specified were of analytical grade.

2.2. Patch preparation

The patches were prepared by using a laboratory-coating unit Mathis LTE-S(M) (Mathis, Switzerland) equipped with a blade coater. The mixture was spread on the release liner at the constant rate of 1 m/min. The coating thickness was fixed at 300 μm. The systems were dried at 50 °C for 20 min, covered with the backing layer and stored in an airtight container. The compositions of the dried patch matrices are reported in Table 1.

2.3. Drug content

A patch sample of 2.54 cm^2 was dissolved in 25 ml of ethyl acetate and diluted in 10 ml of methanol (HPLC grade). These solutions were filtered (Durapore® membrane, pore size 0.45 μm; Millex GV, Millipore Corporation, USA) and assayed by HPLC with the method reported in Section 2.6. Each value represented the average of three sample readings.

2.4. Ex vivo human skin permeation studies

Human abdomen skin, obtained with surgical operation, has been used within 24 h from removal. Human stratum corneum and epidermis (SCE) was prepared by immersion

Table 1
Composition of the matrices (%, m/m), drug content and crystallization induction time of the patches

Form *n*	Ingredients								IB content (μg/cm^2 ± sd)	Crystallization time (days)
	IB	B43	B46	CrEL	CrRH	PG	EuE	EuRL		
1	3	97	–	–	–	–	–	–	340 ± 26	5
2	3	–	97	–	–	–	–	–	353 ± 12	25
3	3	93	–	4	–	–	–	–	343 ± 23	3
4	3	–	93	4	–	–	–	–	377 ± 15	2
5	3	93	–	–	4	–	–	–	368 ± 15	3
6	3	–	93	–	4	–	–	–	323 ± 23	2
7	3	93	–	–	–	4	–	–	338 ± 10	5
8	3	–	93	–	–	4	–	–	368 ± 15	50
9	3	–	90	–	–	4	3	–	324 ± 3	> 365
10	3	–	90	–	–	4	–	3	345 ± 10	> 365

of the skin in distilled water at 60±1 °C for 1 min and peeling it from the derma. SCE membranes were dried in a desiccator at approximately 25% RH, wrapped in aluminium foil and stored at −18±1 °C until use. Dried SCE samples were rehydrated at room temperature by immersion in saline solution for about 16 h before use. Each membrane was carefully mounted on a modified Franz-type diffusion cell of approximately 5 ml receiver capacity and fastened with a rigid clamp. These cells had a diffusion area of 0.636 cm^2. Each cell was individually calibrated with respect to its receiver volume and diffusion area.

At the start of the experiment a patch sample of 2.54 cm^2 was applied to the diffusion cell as donor phase. When the reference cream (Brufen® crema) was used, a sample of the semi-solid preparation was applied on the SCE surface in 1 mm-thick layers with the help of an excavated PTFE cylinder.

The receiver medium was constituted with phosphate buffer saline solution pH 7.4. The receiver medium was continuously stirred with a small magnetic bar and thermostated at 37±1 °C, so that the skin surface temperature was 32±1 °C. At predetermined times 0.2 ml samples were withdrawn from the receiver compartment and replaced with fresh receiver medium. Sink conditions were maintained throughout the experiments. Samples were analysed by HPLC, with the method described in Section 2.6. Each value represents the mean of three sample readings.

From the concentration of IB in the receiving solution the amount permeated through the membrane per unit area was calculated. The cumulative amount in μg cm^{-2} of IB permeated into the receptor compartment was plotted against time to obtain permeation profile. The steady-state flux (J in μg cm^{-2} h^{-1}) was estimated from the slope of the linear portion of the permeation profile [12]. The estimated parameters are presented as mean±standard deviation (SD). Tests for significant differences between means were performed by a one-way analysis of variance (one-way ANOVA). Differences were considered significant at the $P<0.05$ level. Statistical analysis has been conducted using SPSS 11.0 (SPSS Inc., Illinois, USA).

2.5. In vitro release studies

The dissolution test was performed using an apparatus SR8 PLUS Dissolution test station (Hanson Research, CA, USA) according to the Disk Method of the European Pharmacopoeia (Ph. Eur. IV Ed). A patch sample of 8.04 cm^2 was placed flat on the disk with the release surface facing up. The back of the patch was attached on the disk by using a cyanoacrylate adhesive. The experiment was performed by using 500 ml of phosphate buffer as dissolution medium maintained at 32±0.5 °C and stirred at 50 rpm. At fixed intervals, the dissolved amount of IB released from the patches was spectrophotometrically determined at 227 nm wavelength. The results were expressed as mean of three samples.

2.6. Drug assay

The concentrations of IB in the medium were determined by HPLC assay (HP 1100, Chemstations, Hewlett Packard, USA). A 20 μl sample was injected at room temperature on a C18 reverse-phase column (C18 Nova-Pak, 4.6× 150 mm—Waters-US). The wavelength was set at 264 nm. The composition of the eluent was acetonitrile:-water:acetic acid (50:46:4 v:v:v) and the flow rate was 1.5 ml/min. The drug concentrations were determined from IB standard curves (0.5–50 μg/ml).

2.7. Monitoring crystal formation

The transdermal patches were closed in airtight container and stored at 20±1 °C. Appearance of drug crystals was monitored visually and microscopically (Axioscope, Zeiss, G) throughout an area of 10 cm^2. The monitoring time intervals were daily for the first 2 weeks, bi-weekly for 3 months and then monthly for up to 12 months.

2.8. ATR–FT-IR spectroscopy

ATR–FT-IR spectra were recorded with a FT-IR spectrometer (Perkin–Elmer, USA) equipped with a diamond crystal. Sixty-four scans were collected for each sample at a resolution of 2 cm^{-1} over the wavenumber region 4000–650 cm^{-1}.

IB spectrum was obtained using the crystalline drug powder. The spectra of the patches were collected by applying a sample of the formulation directly on the ATR accessory. The spectra of Eudragits, as well as the binary mixture drug-polymer spectra, were obtained analysing a film prepared by extemporary solvent evaporation on the ATR accessory of the spectrophotometer. The primary solutions were: EuE (10% m/m in acetone); EuRL (10% m/m in acetone); IB:EuE 1:1 m:m (10% m/m in acetone); IB:EuRL 1:1 m:m (10% m/m in acetone). Physical mixture spectra were also collected using drug and polymer powders 1:1 (m/m) ratio.

2.9. Peel adhesion 180° test

Two weeks after preparation, a sample of the testing formulation was cut into strips 2.5 cm wide, applied to an adherent plate, smoothed three times with a 4.5 kg roller, maintained for 10 min at 20 °C and pulled from the plate at 180° angle and at the speed rate of 300 mm/min. The 300 mm/min rate was selected being the rate recommended by the standard procedure PSTC101 [13]. The peel adhesion test was performed by using Teflono plate instead of a stainless steel plate, recommended by the standard method [13], as the adhesion strength on the stainless steel plate was

higher than the elongation of the backing layer at break. The test was performed with a tensile testing machine Acquati mod. AG/MC 1 (Acquati, Italy). The force was expressed in cN/cm width of the patch under test. Peel adhesion values were obtained as average of three replicates.

3. Results and discussion

The final matrix weight of the different formulations was in the range from 100 to 130 g/m^2. The drug content of IB in each patch (Table 1) was in the range 75–125% of the mean value and consequently the drug content can be considered equivalent in all patches [14].

The patches containing 3% m/m of IB without crystallization inhibitors permitted of obtaining fluxes (Form 1: $J = 7.2 \pm 0.6$ μg/cm^2/h; Form 2: $J = 6.1 \pm 0.7$ μg/cm^2/h) comparable to that determined with Brufen crema® ($J = 7.1 \pm 0.8$ μg/cm^2/h) containing 10% m/m of IB. Nevertheless, in both patches the drug crystals grew in few days (Table 1). The IB crystallization indicated that, in these matrices, the active ingredient was in supersaturated condition. In the case of Form 2, the skin permeation profile was determined also after 2 months of storage when the crystallization of the IB in the matrix occurred, and, as expected, a reduction of the flux was observed ($J = 4.0 \pm 0.3$ μg/cm^2/h). The addition of the low molecular weight molecules to both matrices had different effects on the stability of the patch depending on the used PSA (Table 1). In particular, when B43 was used the addition of CrEL, CrRH and PG (Forms 2, 5 and 7) did not significantly modify the crystallization induction time probably because these excipients were not completely mixable with B43. As an example in Fig. 1(A) the microphotography of Form 7 is shown.

When CrEL and CrRH were added to B46 (Forms 4 and 6) the crystallization induction time dramatically decreased with respect to the control formulation (Form 2) indicating that these materials accelerated the IB nucleation process. This behaviour was previously described also in the case of norethindrone acetate loaded in acrylic matrices [9] and ketoprofen loaded in polyisobutylene matrices [3]. Only the addition of PG to the B46 (Form 8) permitted of inhibiting the crystallization up to 50 days (Table 1). As far as the microstructure of the matrix is concerned, the PG added to B46 is homogeneously mixed. The microphotography of Form 8 after 3 months of storage is shown in Fig. 1(B). The effect of PG on IB crystallization could be due to either a nucleation inhibition process or a solubilizing effect. Considering that the skin permeation profile of IB obtained using the Form 8 overlapped with that obtained with the Form 2 (Fig. 2), it is possible to suppose that PG did not significantly reduce the supersaturation level of the drug in the polydimethylsyloxane matrix; consequently, the reduction of the crystallization induction time could principally be due to a nucleation inhibition process.

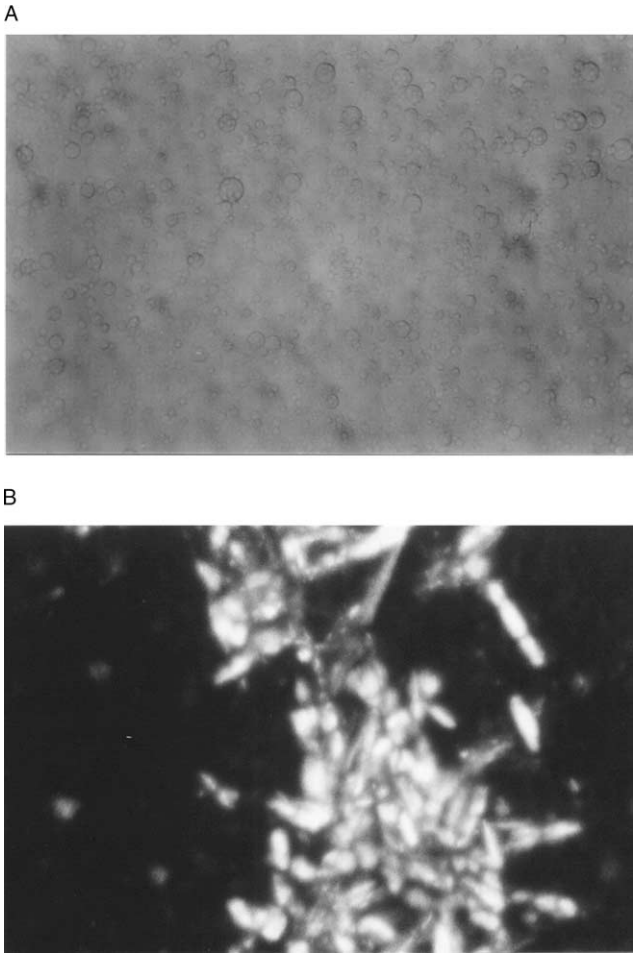

Fig. 1. Microphotographies of Form 7 (A) immediately after preparation, Form 8 (B) after 3 months of storage.

Moreover, PG caused a very significant reduction of the peel adhesion values (Form 2: 350 ± 30 cN/cm; Form 8: 180 ± 28 cN/cm). The effect of PG on the peel force can be considered advantageous because the transdermal patches should be removed easily and painlessly.

The addition of EuE or EuRL to B46 matrix containing PG (Form 9 and 10) effectively prevented the IB crystallization. In fact, no drug crystals were observed in patches

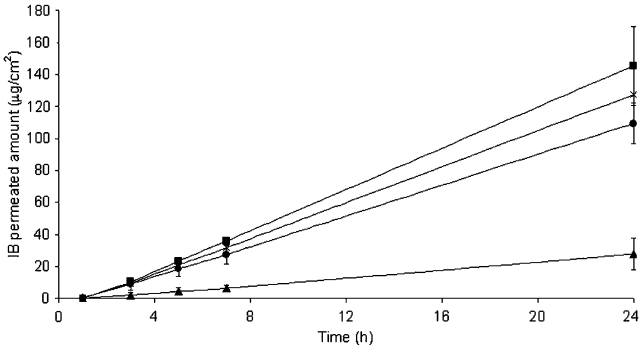

Fig. 2. IB skin permeation profiles of Form 2 (×), Form 8 (●), Form 9 (▲) and Form 10 (■); error bars represent the standard deviation ($n = 3$).

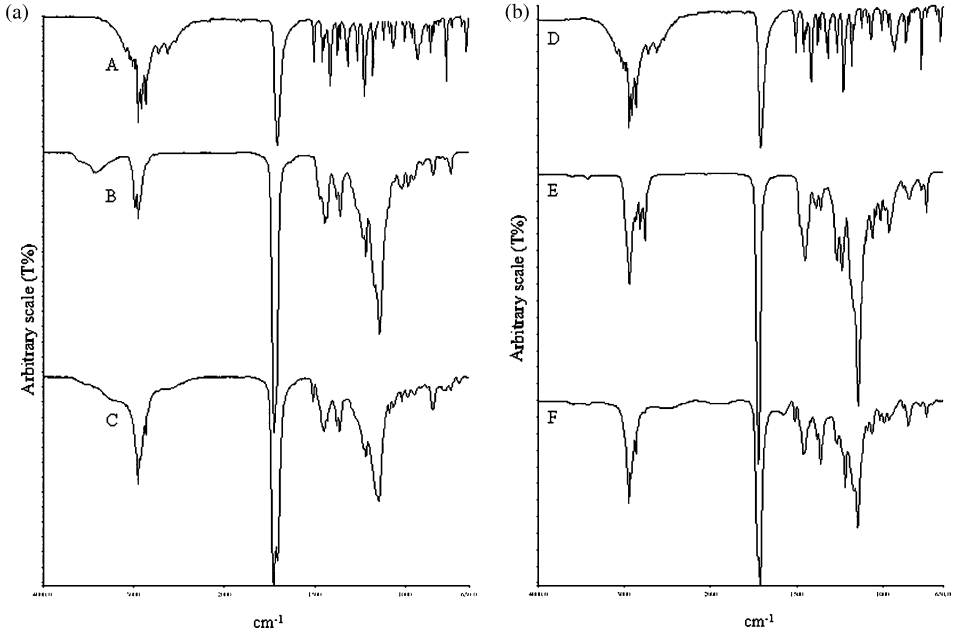

Fig. 3. FT-IR spectra of (a) IB (A), EuRL film (B) and IB/EuRL film (C) and of (b) IB (D), EuE film (E) and IB/EuE film (F).

containing 3% m/m of EuE or EuRL up to 12 months of storage. The peel adhesion values of these two formulations were not different in a significant way from that of the Form 8 (data not reported).

As the polydimethylsyloxane bands hid all the peaks of the other patch components, the ATR–FT-IR analysis was performed by using binary mixtures of IB and the Eudragit® polymers. The Fig. 3(a) and (b) show the infrared spectra of IB/EuRL and IB/EuE films, of each copolymer and of the solid crystalline IB. The most interesting bands of ATR–FT-IR spectra are in the C=O stretching vibrations region. In both films, the C=O band of crystalline IB (at 1710 cm^{-1}) shifted to the high-wave number region and precisely at 1729 cm^{-1}. Similar shift of IB C=O band was also found in IB-polyvynilpyrrolidone film and in IB-polyethylene glycol solid dispersion. It was attributed to the breakage of the IB–IB interactions that are characteristic of the solid form of this drug once the IB was finely dispersed into the polymer [15,16].

The shift of the IB carbonyl band is simultaneous to the shift of the C=O band of the EuE and EuRL carbonyl peaks (1723 and 1725 cm^{-1}, respectively) to the low-wave number region (IB/EuE film: 1714 cm^{-1}; IB/EuRL film: 1710 cm^{-1}) indicating that IB determined a disruption of the typical intermolecular interactions between the chains of each of the two copolymers. These results suggested that when the IB/EuRL and IB/EuE films were formed, a new H-bond between the –OH of IB and the C=O of the copolymer was created. This hypothesis is also supported by the morphological changing of the OH bands of IB in the region of about 3000 cm^{-1} where the typical broad band of the crystalline IB, attributed to the associated OH, was less evident in both IB/copolymer films. In the ATR–FT-IR spectra other minor modifications were detected in the region of 1400–1550 cm^{-1}.

The strong association between the drug and each copolymer could be responsible of the inhibition of the IB crystal growth in the Forms 9 and 10. The addition of EuRL to the Form 8 (Form 10) affected neither the in vitro IB release profile (Fig. 4) nor the IB permeation through SCE (Fig. 2). On the contrary, the addition of EuE (Form 9) significantly reduced the in vitro IB release (Fig. 4) and consequently the IB permeated amount through the SCE (Fig. 2). This different pattern could be attributed to the stronger interaction between the EuE and IB than between the EuRL and IB. This hypothesis is supported by the higher decrease in the electron density of the oxygen of the esteric group of EuE than of EuRL in the region of 1150–1260 cm^{-1} evidenced by ATR–FT-IR analysis and by the comparison of the solubility parameters of the considered materials. As a matter of fact the solubility parameter is

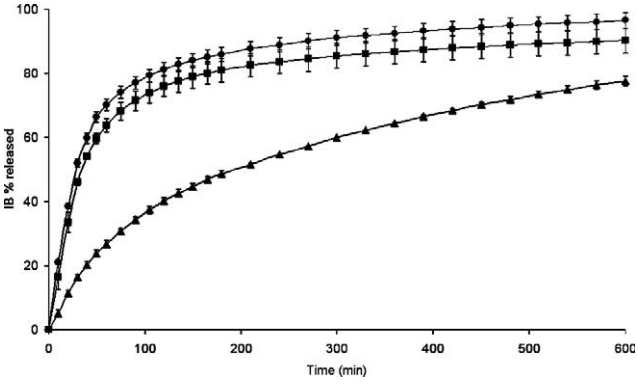

Fig. 4. In vitro IB release profile of Form 8 (●), Form 9 (▲) and Form 10 (■);error bars represent the standard deviation ($n=3$).

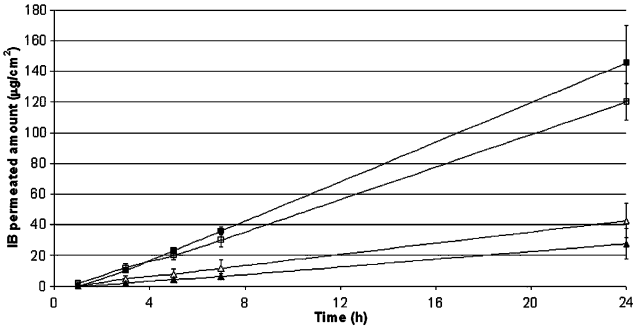

Fig. 5. Effect of storage time on IB skin permeation profile (▲) Form 9 after 15 days of storage; (△) Form 9 after 1 year of storage; (■) Form 10 after 15 days of storage; (□) Form 10 after 1 year of storage; error bars represent the standard deviation ($n=3$).

directly related to the cohesive energy density of a molecule. Generally, small differences in the solubility parameter of two materials indicate high miscibility. The solubility parameter of IB calculated according to Fedors method [17] was 19.0 $(J/cm^3)^{1/2}$ while the solubility parameters of EuRL and EuE are 21.6 and 19.2 $(J/cm^3)^{1/2}$, respectively, indicating a higher affinity of IB for the last copolymer.

The performances of the Forms 9 and 10 in term of drug skin permeation profile were also evaluated after 1 year of storage. No significative variation in IB permeation profiles was evidenced (Fig. 5) confirming the physical stability of the systems.

The aim of preventing active ingredient crystallization in transdermal patches by adding antinucleant agents can be reached when interactions between the active ingredient and the agent occur. These interactions can effectively prevent the collision of drug molecules and subsequent formation of nuclei. However, they can reduce the active ingredient diffusibility in the matrix, which could determine a reduction of drug release and thus a decrease of the drug amount permeated through the skin. This is the case of the addition of EuE to the silicon matrix containing IB. As reported by Kim and co-workers [3], a decrease of the flux is still acceptable if the new formulation permits to stabilize the drug kinetic for the shelf life period, but this negative effect can be counterweight only by increasing the release surface which leads to a lower compliance. The ideal situation is when the crystallization inhibitor increases the flux, as in the case described by Kotiyan and Vavia [11], or at least it does not reduce the flux, as in our work when EuRL was added to the matrix.

The types of interactions formed between the drug and the antinucleant agent should be always carefully evaluated as they are relevant in determining crystallization inhibition but they can also negatively act on the performance of the patch reducing the skin flux.

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