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Application of viscometry and solubility parameters in miconazole patches development

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Abstract

Nine binary mixtures of seven different methacrylic copolymer systems (Plastoid® E 35 L (PLE) and Plastoid® L 50 (PLL); Eudragit® (Eu) NE, RL, RS, L, S) were tested as components of monolayer patches containing miconazole. Only three mixtures (PLE:EuNE, PLE:EuRL and PLE:EuRS) were suitable for the preparation of placebo matrices. Miconazole patches with good technological characteristics were obtained by using mixtures of PLE:EuNE and PLE:EuRL. The in vitro miconazole release rate from the two patches and from the patch prepared using only PLE were significantly different. The amounts of drug released in 24 h were quite satisfactory. A mathematical model based on capillary viscometry data was used for the evaluation of interactions between copolymers. This was useful to predict and understand the mechanisms related to the instability of the prepared mixture. The solubility parameters of the drug and of the matrix were also calculated. Miconazole release was faster when the difference between the solubility parameters of the matrix and of the drug was higher. A relationship between miconazole release rate and the difference of drug and matrix solubility parameters was found. Therefore, the solubility parameter could be applied in formulation studies of patches.

Keywords: Copolymer compatibility; Capillary viscometry; Solubility parameter; Patches formulation; Patches preformulation

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1. Introduction

In the design of monolayer self-adhesive patches it is often necessary to mix two different polymers to achieve the suitable properties of adhesion and drug release kinetic.

Nine formulations made of mixtures of two methacrylic copolymers were designed in order to obtain polymeric matrices suitable for the preparation of non-occlusive monolayer patches. Miconazole nitrate (MIC) was selected as model drug because its controlled delivery by dermal patches could be particularly useful in the treatment of tinea unguium (D'Arcy and Scott, 1978). On the basis of literature data (Pershing et al., 1994) and clinical indications, the MIC content was fixed in 500 μg/cm^2.

The designed matrices were constituted of binary mixtures of an adhesive copolymer and a non-adhesive copolymer, able to modify the drug release, in the ratio 70:30 w:w on the dried matrix.

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Plastoid® E 35 L and Plastoid® L 50 were used as adhesive polymeric systems. Both solutions contain a copolymer of methacrylic acid and excipients. The polymeric components were respectively Eudragit® E 100 for the Plastoid® E 35 L and Eudragit® L 100 for the Plastoid® L 50.

Eudragit® NE 40 D, Eudragit® RL 30 D, Eudragit® RS 30 D, Eudragit® L 30 D and Eudragit® S 30 D were used as non-adhesive copolymers.

Two types of backing layer were selected: an artificial silk and a polyurethane film; they are non-occlusive, have good compatibility with the coating process and satisfactory cohesion with the acrylic matrices (Minghetti et al., 1997a).

The study was organized in three steps: (1) evaluation of the compatibility of the copolymers in the mixtures; (2) preparation and characterization of placebo patches; (3) preparation and characterization of medicated patches.

In the preformulation studies a simple method to evaluate the stability of the mixture could be very useful. In this work, we used capillary viscometry, which estimates the compatibility of different pairs of polymers by using a mathematical model based on the Huggings constant (k') (Cragg and Bigelow, 1995). The theory is based on the fact that the viscosity of blends of two polymers is the sum of the values of the single components, by assuming the addition of this property. Repulsive interactions may cause shrinkage of the coils of macromolecules so that the viscosity reached by the mixture is below the expected value. On the other hand, attractive interactions may form associates of both kinds of macromolecules and expected values of viscosity are higher than the simple addition of the values of the two different polymers (Krigbaum and Wall, 1950).

The placebo patches were characterized by water vapor permeability (WVP) and adhesive properties. The performances of the medicated patches were evaluated also in term of dissolution profile.

In order to relate the release rate with a simple determinable parameter, we tried to see whether there is a correlation between the release rate and the solubility parameter. This correlation could be supposed as the release rate depends on the thermodynamic activity of the active principle in the matrix that is in turn related to the difference between the solubility parameters of the matrix and the drug (Martin, 1993).

2. Theoretical considerations

2.1. Polymeric compatibility evaluation by capillary viscometry

Using the dynamic viscosity of the solution, η, and that of the pure solvent, η_0, the fractional increase in viscosity, due to the presence of the solute, defined as specific viscosity, η_{sp}, could be calculated:

$$\eta_{sp} = (\eta - \eta_0)/\eta_0 \tag{1}$$

Since the degree of viscosity enhancement is dependent on the amount of dissolved material as well as on the molecular size, a more fundamental parameter is the reduced viscosity, η_{red}:

$$\eta_{red} = \eta_{sp}/c \tag{2}$$

The limit of infinite dilution on the reduced viscosity (Eq. (2)) represents the intrinsic viscosity, $[\eta]$, that is the effective hydrodynamic volume in this situation and characterizes the fractional increase in viscosity due to each isolated molecule of solute:

$$[\eta] = \mathrm{Lim}_{c \to 0}(\eta_{sp}/c) \tag{3}$$

At higher concentrations, the reduced viscosity, η_{red}, increases because of mutual interference of solvent flow patterns around the solute, as expressed by the Huggins equation:

$$\eta_{red} = [\eta] + k'[\eta]^2 c \tag{4}$$

Eq. (4) can be illustrated as a linear plot where the intercept is the intrinsic viscosity and the Huggins constant (k') is a dimensionless parameter related to solvent–polymer interactions.

The constant k' describes the interaction resulting only from differences in the chemical structure of the polymer and/or the nature of the solvent.

The value of Huggins constant k' could be a source of information on the interactions in ternary polymer–polymer–solvent systems (Cragg and Bigelow, 1995).

The difference $\Delta k'_{\mathrm{m}}$ was defined as:

$$\Delta k'_{\mathrm{m}} = k'_{\mathrm{m,exp}} - k'_{\mathrm{m,cal}} \tag{5}$$

where $k'_{\mathrm{m,exp}}$ is the Huggins constant value obtained by experimental data from Eq. (4) and $k'_{\mathrm{m,cal}}$ is the theoretical value of the ternary system when there is no thermodynamic interaction between the molecules. It is defined by the following equation:

$$k'_{\mathrm{m,cal}} = (k'_1[\eta]_1^2 w_1^2 + k'_2[\eta]_2^2 w_2^2 + k'_1 k'_2 [\eta]_1 [\eta]_2 w_1 w_2) / ([\eta]_1 w_1 + [\eta]_2 w_2)^2 \tag{6}$$

where k'_1 and k'_2 are the Huggins constant, $[\eta]_1$ and $[\eta]_2$ the intrinsic viscosity, w_1 and w_2 are weight fractions respectively of the polymer 1 and the polymer 2.

If $\Delta k'_{\mathrm{m}} = 0$ it is possible to conclude that interactions other than hydrodynamic interactions are non-existent or at least negligible; instead, different values of $\Delta k'_{\mathrm{m}}$ indicate the existence of specific interaction forces, and might provide information about their nature. Negative values of $\Delta k'_{\mathrm{m}}$ are obtained when repulsion forces between molecules of the two different species of polymers are present; positive values may be attributed to attractive force between the two components.

2.2. Solubility parameter

The solubility parameter, δ, is defined as the square root of the cohesive energy density as described by the following equation:

$$\delta = (\Delta E_{\mathrm{V}} / V_{\mathrm{m}}) \tag{7}$$

where ΔE_{V} represents the energy of vaporization and V_{m} is the molar volume of the material.

Solubility parameters of the materials were calculated with the method proposed by Fedors (Fedors, 1974):

$$\delta = (\Sigma \Delta e_{\mathrm{i}} / \Sigma \Delta v_{\mathrm{i}})^{0,5} \tag{8}$$

where e_{i} and v_{i} are the additive atomic and group contributions for the energy of vaporization and the molar volume.

As the solubility parameter is an additive property its value for the placebo matrices was calculated on the basis of their composition according to:

$$\delta = \Sigma(\delta_{\mathrm{i}} \phi_{\mathrm{i}}) \tag{9}$$

where δ_{i} is the solubility parameter of the excipient *i* and ϕ_{i} is its volume fraction (Squillante et al., 1997).

3. Materials and methods

Micronized miconazole nitrate (Industrie Chimiche Italiane, Milan, Italy).

Eudragit® E 100 (EuE): poly(butyl methacrylate, (2-dimethylaminoethyl) methacrilate methyl methacrylate); molar proportions of the monomer units 1:2:1; molecular weight 150,000 daltons (Röhm, Darmstadt, Germany);

Eudragit® RL 100 (EuRL): poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl metacrylate chloride); molar proportions of the monomer units 1:2:0.2; molecular weight 150,000 daltons (Röhm, Darmstadt, Germany);

Eudragit® RS 100 (EuRS): poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl metacrylate chloride); molar proportions of the monomer units 1:2:0.1; molecular weight 150,000 daltons (Röhm, Darmstadt, Germany);

Eudragit® S 100 (EuS): poly(methacrylic acid, methyl methacrylate); molar proportions of the monomer units 1:2; molecular weight 135,000 daltons (Röhm, Darmstadt, Germany); Eudragit® L 100 (EuL): poly(methacrylic acid, methyl methacrylate); molar proportions of the monomer units 1:1; molecular weight 135,000 daltons (Röhm, Darmstadt, Germany);

Eudragit® NE 40 D (EuNE) poly(ethyl acrilate, methyl methacrylate); molar proportions of the monomer units 1:1; molecular weight 800,000 daltons (Röhm, Darmstadt, Germany). This material is supplied as aqueous dispersion containing 40% w/w of the copolymer.

Plastoid® E 35 L (PLE) aqueous polymeric system based on Eudragit® E 100 (35% w/w) and containing as excipients glycerin 2.6% w/w, adipic acid 1.7% w/w and lauric acid 8.4% w/w (Röhm, Darmstadt, Germany).

Plastoid® L 50 (PLL) aqueous polymeric system based on Eudragit® L 100 (50% w/w) and containing as excipients glycerin 9.8% w/w and PEG 400 22.5% w/w (Röhm, Darmstadt, Germany).

Polyethylene glycol 400 (ACEF, Piacenza, Italy). Propylene glycol, adipic acid and glycerol (Carlo Erba, Milan, Italy). Lauric acid and succinic acid (Fluka, Buchs, Switzerland).

Artificial silk based on rayon acetate fibers: thickness 130 μm, weight 70 g/m^2, elongation at break 15%, tensile strength 45 MPa (Bouty, Milan, Italy). The WVP was 2777 ± 129 $g/m^2 \times 24$ h, $n = 5$, mean $\pm$S.D (Minghetti et al., 1997a);

Faitex® 01 polyurethane film: thickness 20 μm, weight 22.8 g/m^2, elongation at break 500%, tensile strength 44 MPa (FAIT, Brescia, Italy). The WVP was 1535 ± 72 $g/m^2 \times 24$ h, $n = 5$, mean $\pm$S.D. (Minghetti et al., 1997a).

3.1. Preparation of the polymeric mixtures

The composition of the nine mixtures is shown in Table 1. The ingredients were mixed using an under vacuum paddle stirrer and stirred at 50 rpm for 1 h. For the preparation of medicated patches, MIC was added to the other ingredients before mixing.

3.2. Stability of the polymer mixtures

3.2.1. Visual observation

The stability of the nine mixtures was evaluated by visual observation after 2 h at rest. The mixtures that appeared homogeneous and without aggregates were considered suitable for the preparation of patches.

3.2.2. Evaluation of compatibility by capillary viscometry

The viscosity of the binary blends of the pure copolymers was measured with an Ubbelhode viscometer 200 s (Permax, Milan, Italy). The fixed w/w ratio and the solvents used for the different blends are shown in Table 2. Acetone and tetrahydrofurane were selected because a previous work had showed that they are good solvents (Cilurzo et al., 1999). The measurements were carried out of 25 ± 0.1°C in a thermostated water bath (Haake F6, Karlsruhe, Germany).

The mean of six determinations was calculated. The single experiment was accepted when the CV was less than 1%. These data were used to calculate the $\Delta k'$ values as described in Section 2.

3.2.3. pH measurement

The pH of the commercial dispersions and of the mixtures was measured with a digital pH meter (388 AMEL, Milan, Italy). The stability of the solutions/dispersions was evaluated in the range of pH 1–14; the pH of the solutions/dispersions varied when solutions of NaOH or HCl 10% w/w were added.

3.3. Preparation of patches

The patches were prepared by using a laboratory coating unit Mathis LTE-S(M), (Mathis, Zurich, Switzerland). The mixture was spread on the backing layer at the constant rate of 1 m/min

Table 1
Composition (% w/w) and pH of the polymeric mixtures that constituted the matrices

Formulation No.	Adhesive copolymers		Non-adhesive copolymers					pH
	PLE	PLL	EuNE	EuRL	EuRS	EuL	EuS	
1	72	–	28	–	–	–	–	5.4
2	66	–	–	34	–	–	–	5.4
3	66	–	–	–	34	–	–	5.4
4	66	–	–	–	–	34	–	5.5
5	66	–	–	–	–	–	34	5.5
6	–	64	36	–	–	–	–	6.4
7	–	57	–	43	–	–	–	6.6
8	–	57	–	–	43	–	–	6.6
9	–	57	–	–	–	–	43	6.6

Table 2
Values of $\Delta k'_m$ of the blends made of the pure polymers, which constituted the formulations shown in Table 1 that proved to be stable

Formulation No.	Composition of the blends		Solvent	$\Delta k'_m$
	Polymers	Weight ratio		
1	EuE/EuNE	0.3/0.7	acetone	−0.285
		0.5/0.5		−0.282
		0.7/0.3		−0.115
2	EuE/EuRL	0.3/0.7	acetone	0.121
		0.5/0.5		0.163
		0.7/0.3		0.179
3	EuE/EuRS	0.3/0.7	acetone	0.072
		0.5/0.5		0.120
		0.7/0.3		0.119
6	EuL/EuNE	0.3/0.7	tetrahidrofurane	−0.340
		0.5/0.5		−0.330
		0.7/0.3		−0.130
9	EuL/EuS	0.3/0.7	tetrahidrofurane	−0.043
		0.5/0.5		−0.038
		0.7/0.3		−0.188

and with a constant thickness of 500 μm. The systems were dried at 60°C for 15 min, covered with the protecting layer and stored in an airtight container until used.

3.4. Drug content

A sample of 4.9 cm^2 of patches was solubilized with 50 ml methanol. The solution was filtered through filter Durapore® with pore size 0.45 μm (Millex® GV, Millipore Corporation, Bedford, MA, USA) and assayed by the HPLC method described below. Each value represents the average of three different samples.

3.5. Dissolution test

A modified Cell Method (Ph. Eur., ed. 1997, 2.9.4.2) was used. The support was modified: the cavity intended to hold the reservoir patch was eliminated and the inferior part was designed to minimize the dead volume between the cell and the bottom of the vessel.

The patch was cut into a 4.9 cm^2 sample and put flat on the cell with the release surface uppermost with a Cuprophan® membrane on it. A distance of 25 ± 2 mm was maintained between the paddle blade and the surface of the patch. The temperature was kept at 32 ± 0.5°C, the paddle speed was 50 rpm, and 900 ml of acetate buffer pH 4.5 was used as dissolution medium. At specified times, samples were withdrawn from the vessels, filtered and assayed by the HPLC method (see below). Each value represents the average of six sample determinations.

Treatment of the data involved the use of impair two-tailed Student's *t*-test. The α value was set at 0.05 and the null hypothesis assumed the variances between different release profiles to be equal.

3.6. Drug assay

MIC concentrations in the dissolution medium were assayed by HPLC assay (HP 1100, Chemstations, Hewlett Packard, USA). The HPLC system was a Waters (Milford, MA, USA) LC Module 1. The column was a C 18 (Spherisorb ODS2 5 μm, 15 cm-Shandon HPLC-UK). The wavelength was set at 232 nm. The composition of the mobile phase was methanol:ammonium carbonate 0.1 N:tetrahydrofurane (78:20:2 v:v:v). The drug concentration was determined from MIC standards curves (1–50 μg/ml). The theoretical quantitative detection limit was about 0.5 μg/ml. The standard curves had coefficients of correlation of $0.9997 \pm 2.05 \times 10^{-4}$ ($n = 5$; mean $\pm$SD). The interday coefficient of variation ($n = 10$) was 3.35% for a 5 μg/ml standard solution.

3.7. Adhesion properties

3.7.1. Peel adhesion 180° test

Immediately after preparation adhesive patches were cut into strips 2.5 cm wide and applied to a polyethylene plate (Minghetti et al., 1999), smoothed with a 4.5 pound roller for five times, and pulled from the plate at an angle of 180° and at a rate of 300 mm/min. The force was expressed in centiNewton (cN) per cm width of adhesive tape under test. The tests were performed with a tensile testing machine Acquati A 10 I (Acquati, Milan, Italy). Peel adhesion values represent the mean of three samples.

3.7.2. Thumb tack test

The thumb was pressed lightly on a sample for a short time and then quickly withdrawn (Hammond, 1989). By varying the pressure and time of contact and having considered the difficulty of pulling the thumb from the adhesive, it is possible to set a scoring as to how easily, quickly, and strongly the adhesive can form a bond with the skin. All the tests were simultaneously performed and blind.

The adhesive properties of the patches were expressed by the following value range: very good adhesion; good adhesion; poor or null adhesion.

3.8. Water vapour permeability (WVP) evaluation

WVP was determined with foam dressing method (BP 1993 ed. Appendix XX J). The air-forced oven was replaced by a natural air circulation oven. The WVP is given by the following equation: $\mathrm{WVP} = W/A$, where WVP is expressed in g/m^2 per 24 h, W is the amount of vapor permeated through the patch expressed in g/24 h and A is the effective area of the exposed samples expressed in m^2. For non-occlusive dressing WVP has to be higher than 500 g/m^2 per 24 h. Each value represents the average of five determinations.

4. Result and discussion

4.1. Evaluation of the stability of the mixtures

Only the aqueous mixtures made of PLE and EuNE or EuRL or EuRS (formulations nos. 1, 2 and 3, Table 1) were homogeneous and did not show aggregates.

The cationic copolymers mixed with the anionic copolymers (formulation Nos. 4, 5, 7 and 8, Table 1) formed visible aggregates also when dissolved in organic solvents. It is known that when mixed in various ratios in a common solvent acid and basic methacrylic copolymers form primary association complexes that are so stable that they do not dissociate upon dilution (Cragg and Bigelow, 1995).

The viscosity was determined for the blends of the pure polymers that constituted the formulation Nos.1, 2, 3, 6 and 9 (Table 1) in which phenomena of aggregation were not noticeable in organic solvents. On the basis of the calculated $\Delta k'_{\mathrm{m}}$ values, the cationic EuE resulted compatible with the cationic EuRL and EuRS. The neutral EuNE was incompatible with both the anionic EuL and the cationic EuE (Table 2). The anionic copolymers EuL and EuS were incompatible.

The repulsive forces between EuE and EuNE shown by the viscometric analysis seem to be responsible for the absence of aggregates in the aqueous mixture even after weeks of storage. The compatibility of pure EuE with EuRL and EuRS was shown to cause the formation of aggregates also in the mixtures. The aggregates were not visible during the period of 2 h set for the evaluation of the stability because they appeared only after 24 h.

The $\Delta k'$ evaluation of the blends of pure polymers EuL and EuS and of EuL and EuNE respectively, did not explain the formation of aggregates in their aqueous polymeric systems.

Table 3
pH of the commercial polymeric aqueous systems and their pH range of stability

Aqueous polymeric system	pH	pH range of stability
PLE	5.3	3.5–6.5
PLL	7.0	5.5–8.5
EuNE	7.8	1.0–14.0
EuRL	5.0	1.0–14.0
EuRS	4.7	1.0–14.0
EuL	2.6	1.3–5.0
EuS	2.3	1.7–5.3

The nucleation process exhibited by formulation 9 could be related to its pH value.

The pH of the polymeric aqueous blends, the pH range at which they did not form visible aggregates in the set time, and the pH values of the polymeric mixtures that constituted the matrices were measured and shown in Tables 1 and 3, respectively.

The two anionic copolymers (EuS and EuL) maintained their physical stability only in the range $1 < pH < 5$. These copolymers are insoluble below pH 5, and dissolve in a neutral or alkaline medium with consequent salt formation. The pH of formulation 9 was higher than that of formulation 5 and, therefore, out of the range of stability of the EuS. In this case the formation of aggregates could be related to the partial solubilization of the EuS and to the partial precipitation of EuL, the polymeric compound of PLL.

The aggregates formed in formulation 6 were not justifiable neither by compatibility evaluation nor by pH measurements. In order to clarify this fact, EuNE was mixed with each one of the plasticizers contained in PLL. The formation of aggregates was related to the plasticizer effect of PEG 400 that makes EuNE latex unstable.

Table 4
Composition of the placebo patches

Patches	PL/Eu 70/30 (% w/w[a])	Backing layer
Is	E/NE	Artificial silk
Ip	E/NE	Polyurethane
IIs	E/RL	Artificial silk
IIp	E/RL	Polyurethane
IIIs	E/RS	Artificial silk
IIIp	E/RS	Polyurethane

[a] Calculated on the dried matrix.

4.2. Characterization of the placebo patches

Formulations 1, 2 and 3 (Table 1), that showed no aggregates, were used to prepare six types of placebo patches with two different backing layers (Table 4); their adhesive properties and WVP were evaluated (Table 5). The peel force significantly varied by changing the non-adhesive copolymer in the preparation of the matrix: the patches made of EuNE (Is and Ip, Table 4) showed very good adhesive properties, the patches made of EuRL (IIs and IIp, Table 4) had sufficient adhesive properties, while the patches made of EuRS (IIIs and IIIp, Table 4) did not show any adhesive properties.

The characteristics of the backing layer influence the geometry in the failure area, the energy lost to deform the backing layer and the moment

Table 5
Adhesion and water vapor permeability (WVP) of the placebo patches[a]

Patches	Peel Force (cN/cm ± S.D.)	Thumb tack test[b]	WVP (g/m^2 per 24 h ± S.D.)
Is	282 ± 11	***	1394 ± 63
Ip	419 ± 29	***	1445 ± 76
Iis	46 ± 22	**	1280 ± 78
Iip	30 ± 13	**	1285 ± 74
IIIs	0	*	–
IIIp	0	*	–

[a] 0, not detectable; –, not determined;

[b] Very good adhesion (***); good adhesion (**); poor or null adhesion (*).

Table 6
Composition of the patches containing miconazole nitrate

Patches	PLE (% w/w)[a]	EuNE (% w/w)[a]	EuRL (% w/w)[a]	MIC (% w/w)[a]	Backing layer
1s	67.2	28.8	–	4.0	Artificial silk
1p	67.2	28.8	–	4.0	Polyurethane
2s	67.2	–	28.8	4.0	Artificial silk
2p	67.2	–	28.8	4.0	Polyurethane
3p	96.0	–	–	4.0	Polyurethane

[a] calculated on the dried matrices.

arm. The combined effects of the backing layer on the peel force are quite complex and not easily predictable. In any case, the peel force is directly proportional to the energy required to deform the backing layer (Satas, 1989). The different physicochemical characteristics of the two materials and the lowest thickness of the polyurethane film resulted in an easy deformability of the polyurethane film in respect to the artificial silk, as shown by the relative values of elongation at break. This could explain the higher peel force showed by the patch having polyurethane film as backing layer when the matrix contained EuNE. When EuRL was used, a significant difference of peel force was not determined (IIs and IIp, Table 5) probably because EuRL increased the hardness of the matrix and the energy required to deform the matrix was higher than that necessary to deform the backing layers.

The permeability to water vapor was measured only for the placebo patches that exhibited good adhesive properties (Is, Ip, IIs and IIp, Table 4). Each placebo patch showed good permeability; obtained values were always higher than the BP limit for non-occlusive patches (Table 4). The highest values were found for the patches made of EuNE. No significant differences were detected when changing the backing layers, as their permeabilities, measured with the same method, were higher than those of the corresponding patches.

4.3. Selection of the final formulations

The formulations of patches Is, Ip, IIs and IIp (Table 4) were chosen on the basis of their good adhesiveness and WVP in order to prepare the corresponding medicated patches. Their composition, expressed as per cent w/w on the dried matrix, are shown in Table 6. The polymeric mixtures was spread in order to obtain patches loaded with 500 μg/cm^2 of MIC. A patch made only of PLE was also prepared (3p, Table 6) in order to evaluate the ability of the non-adhesive polymers to modify the drug release.

4.4. Characterization of the patches containing MIC

The peel adhesion values (Table 7) of the medicated patches confirmed the data obtained with the placebo patches. The patches of EuNE (1s and 1p, Table 6) showed higher adhesive proper-

Table 7
Peel adhesion values and water vapor permeability (WVP) of patches containing miconazole nitrate

Patches	Peel force (cN/cm ± S.D.)	Thumb tack test[a]	WVP (g/m^2 per 24 h ± S.D.)
1s	208 ± 3	***	1333 ± 58
1p	332 ± 56	***	1459 ± 79
2s	23 ± 4	**	1306 ± 28
2p	16 ± 1	**	1294 ± 43

[a] Very good adhesion (***); good adhesion (**); poor or null adhesion (*).

ties than those prepared with EuRL (2s and 2p, Table 6). The presence of MIC influenced the adhesive properties of the patch; when EuNE was used, the peel adhesion values were 20% lower than those of the placebo patches.

All the patches were stripped cleanly from the plate, leaving no visually notable residue; as a result, the anchorage of the matrices to the backing layer and the cohesion of the matrix were good.

The 'thumb-tack test' proved the good adhesion of the patches to the skin.

The addition of MIC to the placebo formulations did not influence the WVP of the patches (Table 7).

Our previous tests (Minghetti et al., 1997b) showed that, in this case, the type of backing layer has no influence on the 'in vitro' release profile of the drug from the matrices. Therefore, the dissolution tests were performed only with the patches having a polyurethane film as a backing layer (1p, 2p, and 3p, Table 6). The release profiles obtained are shown in Fig. 1. The amounts of MIC released from the three formulations after 24 h were significantly different ($P < 0.05$).

The release rate is related to the thermodynamic activity of the drug as when thermodynamic activity increases the interfacial transport from the matrix to the dissolution medium is promoted. The thermodynamic activity is at its highest level when the drug concentration reaches maximum solubility. When the difference between the solubility parameter of the matrix and the drug is at the highest point the thermodynamic activity increases and, consequently, the highest release rate could be expected.

The solubility parameters calculated according to Fedors method for the MIC, the excipients and the matrices of the placebo patches are reported in Table 8.

The release was faster when the absolute difference between the solubility parameter of the matrix and the drug ($\Delta\delta^2$) was highest (Fig. 2).

5. Conclusion

Among the nine polymeric mixtures examined, only the three mixtures made of PLE and EuNE or EuRL or EuRS were suitable for the preparation of patches.

All prepared patches showed good water vapor permeability.

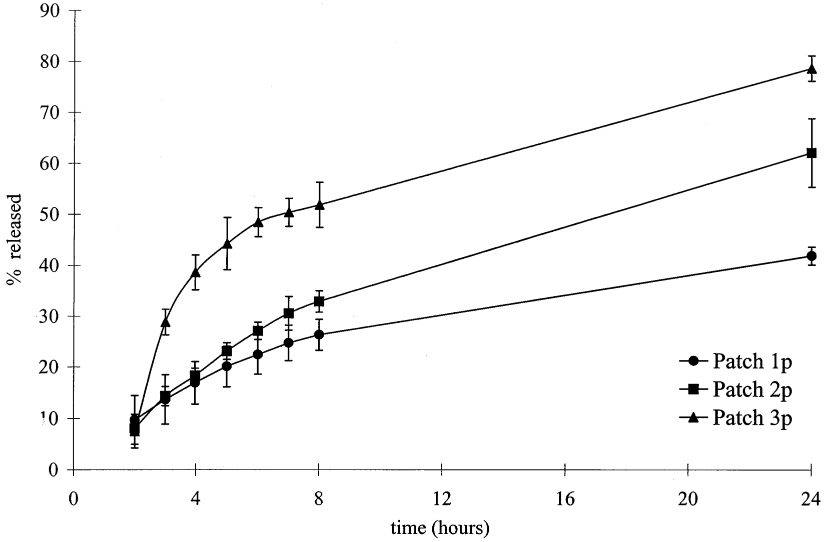

Fig. 1. MIC release profile of the tested patches.

Table 8
Solubility parameters of components of the matrices and matrices of the placebo patches

	δ (MPa$^{1/2}$)
Materials	
MIC	23.20
EuRS	20.60
EuRL	21.24
EuNE	20.07
EuE	19.24
Adipic acid	24.79
Lauric acid	19.11
Glycerol	33.47
Matrices of patches	
I	23.14
II	23.50
III	24.60

The adhesive properties of the placebo patches made of PLE and EuRS were not satisfactory and, therefore, only the other two formulations were used to prepare the medicated patches. The type of backing layer influenced the peel adhesion that was highest when the polyurethane film was used instead of the artificial silk.

MIC patches with good technological characteristics were obtained with matrices of EuNE or EuRL, that were selected as final formulations.

The amounts of drug released in vitro in 24 h from the medicated patches were higher than the dose normally applied when using ointments (Pershing et al., 1994); consequently, they will be used for clinical trials.

The suitability of the capillary viscometry approach for the evaluation of the compatibility between the considered methacrylic copolymers was confirmed. Compatibility is one of the several factors that can cause the instability of polymeric mixtures. The identification of the types of interactions between the polymeric compounds could be useful to better understand the mechanisms related to the instability phenomena.

The differences obtained in the release rate had a good linear correlation with the $\Delta\delta^2$ values. Therefore, if this correlation is confirmed for other active substances and matrices, the solubility parameter could be useful in the formulation studies of patches as this parameter is predictive of the thermodynamic activity of the drug in the matrix.

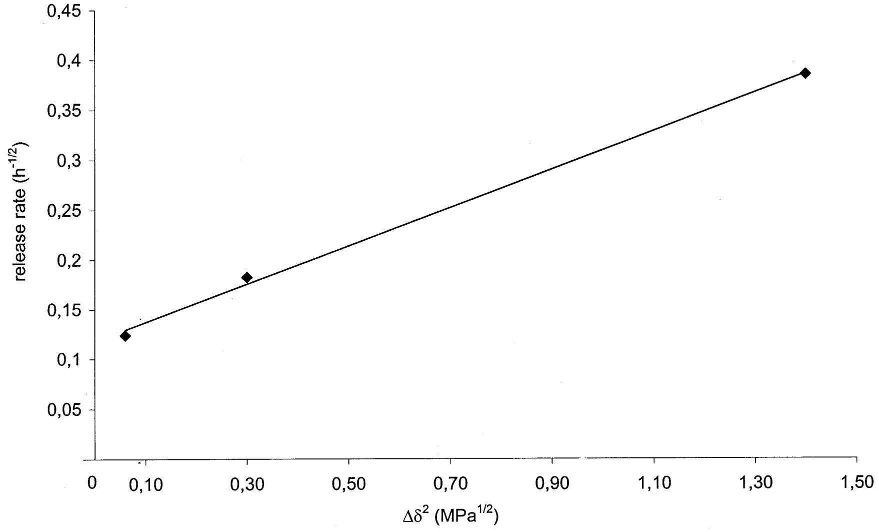

Fig. 2. Relationship between the $\Delta\delta^2$ and the MIC release rate.

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