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Dermal therapeutic systems permeable to water vapour

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Abstract

Dermal therapeutic systems (DTS) are self-adhesive patches that consist of a flexible backing layer and an adhesive controlled release matrix layer containing the drug. They are formulated to obtain a controlled release of drugs in order to treat topical skin pathologies. As permeability to water vapour is an important characteristic for DTS, the aim of this work was to develop systems with different predictable water vapour permeabilities (WVP), to be selected according to the therapeutic needs of the treated disease, and with good adhesive properties. In the present study, the WVP of 12 materials, usable as backing layers, were tested. In order to prepare DTS, the artificial silk was selected as a backing layer as it has good water vapour permeability, compatibility with the coating process and cohesion with the matrices. Two adhesive hydrophilic copolymers of dimethylaminoethyl methacrylate and neutral methacrylic esters (Plastoid® E 35 M–Plastoid® E 35 L) mixed with a non-adhesive hydrophobic copolymer of ethylacrylate and methylmethacrylate, supplied in suspension in two different concentrations (Eudragit® NE 30 D–Eudragit® NE 40 D), were used to prepare four series of DTS. Water vapour permeability and adhesion properties of the prepared DTS were evaluated. Adding 10–30% w/w of Eudragit® NE to Plastoid® E 35 permits the formulation of patches with higher water vapour permeability and good adhesive properties. © 1997 Elsevier Science B.V.

Keywords: Dermal therapeutic systems (DTS); Patches; Water vapor permeability

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1. Introduction

Dermal therapeutic systems (DTS) are self-adhesive patches formulated to obtain controlled release of drugs in order to treat topical skin pathologies. These systems have some theoretical advantages if compared with traditional topical pharmaceutical forms: they allow a precise dosage for a programmed period of time and a protection and isolation of the damaged area.

The simplest design of DTS consists of a flexible backing layer, an adhesive controlled release matrix layer containing the drug and a removable

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Table 1
Technical characteristics of the backing layers

Type	Thickness (μm)	Weight (g/m^2)	Elongation at break (%)	Tensile strength (MPa)
1	460	44	40	22
2	150	43	15	13.5
3	130	70	15	45
4	190	84	40	22
5	190	83	15	13.5
6	170	110	15	45
7	20	22.8	500	44
8	20	20.2	800	40
9	20	27.2	660	96
10	15	25.5	>500[a]	58[a]
11	15	27.9	>500[a]	32[a]
12	25	57	>450	>45

[a] Measured on a film of 25 μm in thickness.

protecting layer. The backing layer serves as a platform or carrier for the matrix and it is essential for the application and the removal of the system from the skin. Generally, the DTS should not be occlusive, because occlusion may result in a maceration of the skin due to water accumulation and may favor growth of pathogenic microorganisms (Hurkmans et al., 1985; Bucks et al., 1991).

The aim of this work was to test the water vapour permeabilities (WVP) of a number of materials to be used as backing layers and to develope DTS with different predictable WVP and with good adhesive properties, to be selected according to the therapeutic needs of the treated disease. WVP and adhesive properties of DTS are influenced by the backing layer and by the matrix composition. For the backing layer, 12 types of materials were considered. Acrylic polymers were chosen as constituents of the matrix because they are resistant to oxidation and have a high degree of stability during processing and storage (Satas, 1989).

Four series of mixtures, composed of a hydrophilic adhesive copolymer of dimethylaminoethyl methacrylate and neutral methacrylic esters (Plastoid® E 35) and a hydrophobic non-adhesive copolymer of ethylacrylate and methylmethacrylate (Eudragit® NE), were prepared.

Among the pressure sensitive adhesive polymers, Plastoid® E 35 L and Plastoid® E 35 M were selected because they are non-irritant to the skin and give films permeable to water vapour (Röhm Pharma Polymer, 1993c). Eudragit® NE 30 D or Eudragit® NE 40 D were added in different percentages to the Plastoid® E 35; they are both compatible with Plastoid® E 35, are well tolerated by the skin (Röhm Pharma Polymer, 1993a,b) and give films permeable to water vapour (Baert and Remon, 1993).

The adhesive properties of the two series of DTS, which were found to be more permeable to water vapour, were evaluated by the peel adhesion test and the thumb tack test. The first test provides a quantitative measure of the force required to peel away a strip of tape from a stainless-steel rigid surface. The second one is the simplest test that gives qualitative information about the skin adhesion of the system upon brief contact under light pressure (Hammond, 1989).

2. Materials and methods

2.1. Backing layers

Twelve types of backing layers, whose technical data are reported in Table 1, were tested:

1. Woven/non woven (W.N.W.) net form based on polyester fibers (Bouty, Milan, Italy).

2. W.N.W. compact form based on cellulose and polyester fibers compacted with a binding agent (Bouty, Milan, Italy).
3. Artificial silk based on fibers of rayon acetate (Bouty, Milan, Italy).
4. W.N.W. net form based on polyester fibers coated with an adhesive matrix made by an acrylic polymer based on ethylesylacrylate (Bouty, Milan, Italy).
5. W.N.W. compact form based on polyester fibers coated with an adhesive matrix made by an acrylic polymer based on ethylesylacrylate (Bouty, Milan, Italy).
6. Artificial silk based on fibers of rayon acetate coated with an adhesive matrix made by an acrylic polymer based on ethylesylacrylate (Bouty, Milan, Italy).
7. Faitex® 01 polyurethane film (FAIT, Brescia, Italy).
8. Faitex® 011 polyurethane film (FAIT, Brescia, Italy).
9. Faitex® 015 film based on polyester (FAIT, Brescia, Italy).
10. Pebax® MV 1041 polyether blocked with polyamide (PEBA) (Elf Atochem, Milan, Italy).
11. Pebax® MV 3000 polyether blocked with polyamide (PEBA) (Elf Atochem, Milan, Italy).
12. Platilon® U 073 polyetherurethane (Elf Atochem, Bonn, Germany).

2.2. Polymers

Plastoid® E 35 L (PL L) and Plastoid® E 35 M (PL M) are aqueous solutions of copolymers of dimethylaminoethyl methacrylate and neutral methacrylic esters neutralised by fatty acids which have, respectively, a dry weight of 34% w/w and 30% w/w.

Eudragit® NE (EU NE) is a neutral copolymer of ethylacrylate and methylmethacrylate. It is supplied as an aqueous dispersion at 30% w/w (EU NE 30 D) and 40% w/w (EU NE 40 D). The composition of the suspending medium was not given by the producer.

All the polymers were kindly donated by Rofarma-Röhm, Milan, Italy.

2.3. Preparation of polymeric matrices

The compositions of the four series of mixtures used for the preparation of the DTS matrices and the percentages of EU NE on the total weight of the dried matrix, made by a mixture of Eudragit® and Plastoid®, are shown in Table 2.

Two DTS were also prepared with 100% of PL M and PL L (Table 2; no. 20 and 21).

Weighed amounts of Plastoid® and Eudragit® were mixed using a mechanic stirrer (IKA RW20DZM). The mixtures were stirred at 50 rpm for 1 h and used after 24 h of rest.

2.4. Preparation of DTS

The DTS were prepared using a laboratory coating unit (Mathis LTE-S(M), Switzerland). The polymeric mixure was spread on the backing layer at the constant rate of 2.2 m/min and at the thickness of 500 μm. The systems were dried at 60°C for 12 min and covered with a protective release liner.

The weights of the dried matrices, evaluated for formulation no. 1 and no. 15 (see Table 2), the smallest and largest weight of the dry matrices, respectively, were 7.56 ± 0.11 mg/cm^2 and 9.86 ± 0.47 mg/cm^2. For the other tested formulations the weights were mantained between these two values.

For the preparation of thicker DTS, two or more additional coatings were performed on the first one, by the method described above.

2.5. Water-vapour permeability (WVP) evaluation

The WVP of the backing layer, hence the DTS, was determined with the foam dressing method (British Pharmacopoeia 1993, Appendix XXJ). The apparatus consists of a cylindrical glass chamber with a separate lid, completely closed except for a circular opening (40 mm diameter) which is covered with the material being examined. About 20 ml of water were poured into the chamber and the sample was mounted in the center of the top surface of the cell. The chambers were placed into a natural air circulating oven and maintained for 24 h at 37 ± 1 C°. The chambers

Table 2
Composition of the mixtures used for the preparation of DTS matrices

	Formulation no.	Adhesive polymers (% w/w)		Non-adhesive polymers (%w/w)		EU NE[a] (% w/w)
		PL M	PL L	EU NE 40D	EU NE 30D	
Series 1	1	60	—	—	40	40
	2	70	—	—	30	30
	3	80	—	—	20	20
	4	90	—	—	10	10
Series 2	5	50	—	50	—	57
	6	60	—	40	—	47
	7	70	—	30	—	36
	8	80	—	20	—	25
	9	90	—	10	—	13
Series 3	10	—	50	—	50	47
	11	—	60	—	40	37
	12	—	70	—	30	27
	13	—	80	—	20	18
	14	—	90	—	10	9
Series 4	15	—	50	50	—	54
	16	—	60	40	—	44
	17	—	70	30	—	34
	18	—	80	20	—	23
	19	—	90	10	—	12
	20	100	—	—	—	0
	21	—	100	—	—	0

[a] EU NE (%w/w) represents the percentage of EU NE on the total weight of the dried matrix.

were weighed 1 h before the test and again 1 h after removal from the oven. The WVP is given by the following equation:

$$WVP = W/A$$

where WVP is expressed in $g/m^2 \times 24$ h, W is the amount of vapour permeated through the patch expressed in g/24 h and A is the effective area of the exposed samples expressed in m^2.

Each WVP value represents the average of five sample readings.

2.6. Adhesive properties evaluation

2.6.1. Peel adhesion 180° test (PSTC-1; Pr EN AFERA 4001, 1994)

Adhesive patches were cut in strips, 2.5 cm in width, and conditioned for 24 h at 23 ± 2°C and 50 ± 5% U.R. The tests were performed in the same enviromental conditions with an Instron Corporation Series IX Automated Material Testing System 1.26. The samples were applied to a stainless steel plate, smoothed with a 4.5 lb roller, and pulled from the stainless steel at a 180° angle at a rate of 300 mm/min. The force was expressed in cN/cm width of adhesive tape under test. Peel adhesion values represent the mean of three samples.

2.6.2. Thumb tack test (Hammond, 1989)

The thumb was pressed lightly on a sample for a short time and then quickly withdrawn. By varying the pressure and time of contact and noting the difficulty of pulling the thumb from the adhesive, it is possible to perceive how easily, quickly, and strongly the adhesive can form a bond with the skin. Some major drawbacks of the thumb tack test are its subjectivity and the fact that the data are difficult to quantify. However, it is the simplest and most straightforward test for the evaluation of the adhesive–skin bond. All the tests were simultaneously performed and blind. The adhesive properties of the DTS were expressed by the following value range: good adhesion (**), poor adhesion (*) and no adhesion (○).

3. Results and discussion

3.1. Selection of backing layer

The WVP values measured for the different materials are shown in Table 3. WVP values obtained for all backing layers were higher than 500 g/m^2 × 24 h, and therefore they can be considered permeable to water vapour according to the British Pharmacopoeia.

The permeability was reduced, relative to the open chamber, to $\approx 65\%$ for the types 1, 2 and 3, to $\approx 35–50\%$ for the types 7, 8, 9, 10, and 11 and to $\approx 20\%$ for the self-adhesive material 4, 5, 6 and for the type 12.

Preliminary coating experiments were performed to verify the factibility of the process and the cohesion between all the selected backing layers and the polymeric mixtures. Types 1 and 2 (Table 3) were incompatible with the coating process because of the high water content in the mixtures. All the other materials, even those without adhesive properties, showed satisfactory cohesion properties with the four polymeric mixtures.

Table 3
WVP values of backing layers

Type	Backing layers	WVP[a] (g/m^2 × 24 h)
1	W.N.W. net form	2841 ± 165
2	W.N.W. compact form	2800 ± 117
3	Artificial silk	2777 ± 129
4	W.N.W. self-adhesive net form	853 ± 21
5	W.N.W. self-adhesive compact form	870 ± 32
6	Self-adhesive artificial silk	728 ± 40
7	Polyurethane (Faitex 01)	1535 ± 72
8	Polyurethane (Faitex 011)	1982 ± 82
9	Polyester (Faitex 015)	2229 ± 106
10	Polyether/polyamide (Pebax® MV 1041)	1678 ± 84
11	Polyether/polyamide (Pebax® MV 3000)	1740 ± 70
12	Polyetherurethane (Platilon® U 073)	685 ± 41
	Open chamber	4367 ± 278

[a] Mean ± S.D. of five samples.

The artificial silk (type 3) was chosen as backing layer for the further development of DTS for its good WVP, compatibility with the coating process and cohesion with the matrices.

3.2. Water-vapour permeability of DTS

In Fig. 1 the WVP values of the four series of DTS are reported and related to the percentages of Eudragit® NE in the dried matrices. The WVP of the artificial silk was reduced to about one third by the matrices made by the adhesive polymer only (Table 2, no. 20 and 21). The WVP values increased, even in a very significant way, when Eudragit® NE was added to the matrix (Table 2, no. 3, 8, 9, 12–14, 17–19); the maximum was reached when the w/w percentage of Eudragit® NE was 10% in the case of Plastoid® E 35 L and 20–30% w/w of Eudragit® NE when the Plastoid® E 35 M was used. The WVP of the DTS was reduced to values lower than those obtained with 100% Plastoid® when Eudragit® NE was 50% w/w.

The series containing Eudragit® NE 40 D (Table 2, series 2 and 4) showed a higher permeability than the series with Eudragit® NE 30 D (Table 2, series 1 and 3). This behaviour could be due to the different percentages of suspending agents in the two types of polymeric suspensions (EU NE 30 D and EU NE 40 D).

The maximum WVP values were obtained in series 4 when Eudragit® NE 40 D was 12% w/w of the dried matrix (WVP = 1471 g/m^2 × 24 h) and in series 2 when Eudragit® NE 40 D was 25% w/w of the dried matrix (WVP = 1490 g/m^2 × 24 h).

The effect of the thickness of the system (expressed in mg/cm^2) was evaluated, performing one or more coatings over the first one. In Fig. 2, the WVP values plotted versus the thickness of the matrices related to formulations no. 7 and 17 (Table 2) are shown. These formulations were chosen because of their good permeability to water vapour. In the evaluated range of thickness (10–40 mg/cm^2) the DTS had a good permeability to water vapour and the reduction of the WVP values was linear and predictable ($r^2 = 0.9755$ for no. 7 and $r^2 = 0.9933$ for no. 17).

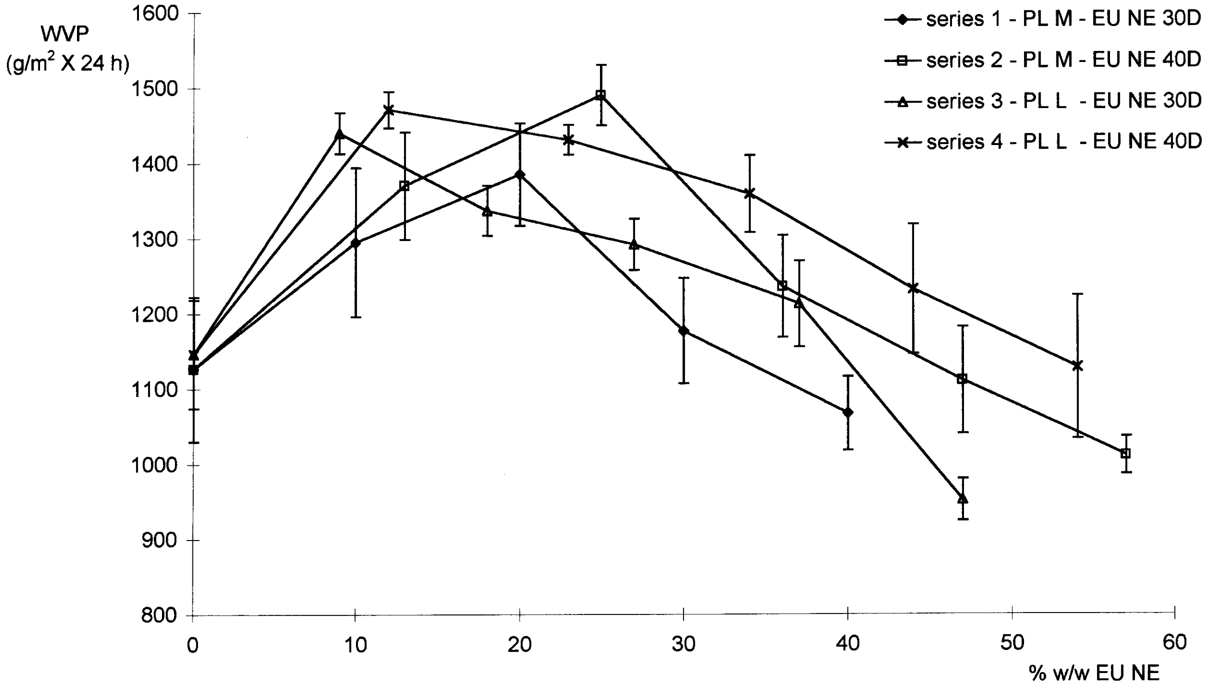

Fig. 1. Effect of the percentage of Eudragit® NE in the dried matrix on the WVP of the four series of DTS.

3.3. Adhesion properties

The adhesion properties were measured for series 2 and 4 (Table 2) which showed the best WVP properties. In Table 4 the results of the thumb tack and the peel adhesion tests are reported.

DTS no. 5 and no. 15 did not exhibit any adhesion properties and DTS no. 6 and no. 16 exhibited poor adhesion properties as confirmed by both tests.

The minimal polymeric adhesive amount in the dried matrix required to obtain DTS with good adhesion properties when artificial silk is used as backing layer is about 65% w/w.

4. Conclusion

Among the tested materials the artificial silk exibited the best WVP value combined with mechanical characteristics suitable for the coating process and was therefore selected as a backing layer. Patches made with 100% of one of the two adhesive polymers showed significantly reduced WVP values. By mixing each of the two adhesive polymers (Plastoid® E 35 M and Plastoid® E 35 L) with one of the two Eudragit® NE suspensions it is possible to obtain patches with WVP values as high as about 1500 mg/cm^2 × 24 h. This value is significantly higher than that obtained by each adhesive polymer, which is lower than 1150 mg/cm^2 × 24 h in both cases.

This increase in WVP could be related to a different organization of the three-dimensional network formed by the hydrophilic chains of the adhesive polymer due to the presence of the hydrophobic polymer.

The patches mantained good adhesion properties when percentages up to 30% w/w of both types of Eudragit® NE were added in the polymeric mixture. With these polymers it is possible to prepare monolayer DTS with good WVP values and also good adhesive properties using a wide range of different percentages. This flexibil-

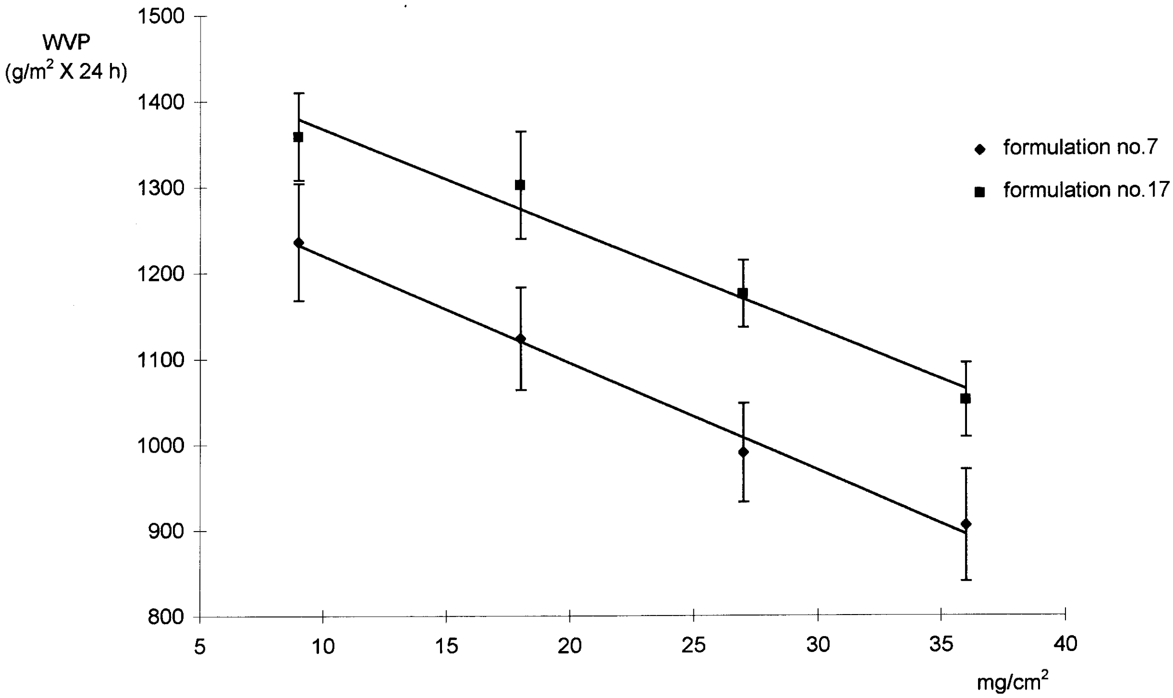

Fig. 2. Effect of the number of coatings on the WVP of DTS obtained with formulations no. 7 and no. 17.

ity in the formulation allows the possibility of the incorporation of drugs with different physicochemical properties, although further studies are necessary to evaluate the influence of the presence of the active principle on these properties.

Table 4
Peel adhesion test values and thumb tack test evaluation

Formulation no.	Adhesion (cN/cm)[a]	Tack evaluation
5	7	○
6	75	*
7	432	**
8	507	**
15	6	○
16	16	*
17	379	**
18	417	**

**, Good adhesion; *, poor adhesion; ○, no adhesion.
[a] S.D. was <15%

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