AAPS PharmSciTech, Vol. 9, No. 3, September 2008 (© 2008)
DOI: 10.1208/s12249-008-9102-4

Research Article

Design and Characterization of an Adhesive Matrix Based on a Poly(Ethyl Acrylate, Methyl Methacrylate)

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Received 19 December 2007; accepted 24 April 2008; published online 18 June 2008

Abstract. The main issue in the development of transdermal patches made of poly(ethyl acrylate, methyl methacrylate) (Eudragit® NE 40D, PMM) is the shrinkage phenomenon during the spreading of the latex onto the release liner. To solve this problem, the latex is usually freeze-dried and then re-dissolved in an organic solvent (method 1). To simplify the production process, we prepared an adhesive matrix by adding to the commercial PMM latex a plasticizer and an additive (anti-shrinkage agent) that avoids the shrinkage of the water dispersion spread onto the release liner (method 2). In some cases the active ingredient itself, such as potassium diclofenac (DK) and nicotine (NT), works as anti-shrinkage agent. In this work, the effects of the preparation method, types and concentrations of the plasticizer (triacetin and tributyl citrate) on the adhesive properties of the transdermal patches were investigated. The adhesive properties of the prepared patch were determined by texture analysis, peel adhesion test and shear adhesion. The PMM/plasticizer interactions were evaluated by ATR-FTIR spectroscopy. Furthermore, the *in vitro* skin permeation profiles of DK and NT released from the patch were determined by Franz cell method. Generally speaking, the variables that mainly modify the adhesive properties are the concentration and type of the plasticizer. The skin permeation profiles of DK and NT from the patch prepared by method 2 overlapped with those obtained with the commercial products. The results underline that the PMM latex can be used conveniently in the development of transdermal patches.

KEYWORDS: ATR-FTIR spectroscopy; poly(ethyl acrylate; methyl methacrylate); texture analysis; transdermal patches.

INTRODUCTION

The polymeric matrices used in transdermal patch formulations are mainly composed of "pressure sensitive adhesive" (PSA) which is defined as an adhesive material capable of bonding to surfaces by the application of a light pressure and being removed without leaving any visually noticeable residues.

Solvent-based PSAs have been traditionally used to manufacture transdermal patches, even if water-based PSAs are more beneficial as skin irritation, sensitization and environmental contamination risks are reduced. Most of the aqueous PSAs on the market are based on methacrylic copolymers, such as polyaminomethylmethacrylates, polymethylmethacrylates alone (1–3) or in combination with other polymers (4,5). The feasibility to formulate a PSA for transdermal matrices containing a copolymer of methyl and/or ethylesters of acrylic acid and methacrylic acid with an average molecular weight of 800,000 (Eudragit® NE, PMM) and esters of citric acid as plasticizers, is also reported in literature (6,7). PMM is commercially available as latex (Eudragit® NE 30D or Eudragit® NE 40D) and the polymeric systems, obtained by adding directly the plasticizer to the commercial latex, are unsuitable for patch preparation according to the current manufacturing practice. In fact, when the aqueous dispersions are coated onto the release liner, the mixtures shrink because of the low viscosity and the high surface tension. Therefore, the PSA was prepared dissolving the lyophilized latex in an organic solvent, i.e. methylene chloride (6) or acetone (7) even if this process presented some environmental risks associated with the use of organic solvents and high cost due to the freeze drying.

In a previous work, we simplified the production process of such PSA by adding directly to the PMM latex the plasticizer and an agent that avoids the shrinkage of the water dispersion spread onto the release liner (10) (anti-shrinkage agent). The anti-shrinkage agents are generally surfactants or in some cases active ingredients, such as potassium diclofenac and nicotine, which increase the viscosity of the latex and have a surface tension lowering effect.

Considering that the therapeutic performances of transdermal drug delivery systems are deeply affected by the quality of the contact between the patch and the skin (8,9) and few information are available on the adhesive properties of PSA based on PMM, the goal of the current study was to investigate the relevance of (1) the type and the concentration of the plasticizer (triacetin and tributyl citrate) and (2) the type of PSA dispersion (i.e. organic solution or commer-

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cial latex) on the adhesive properties of the transdermal patches. The safety and skin tolerability of the selected components have been well recognized in literature (11–13). The adhesive performances of the PSA were evaluated on film obtained on backing layer characterized by a high critical surface tension that permitted to spread the latex. Moreover, when the latex was used, the effect of two anti-shrinkage agents, namely potassium diclofenac and nicotine, was also evaluated.

The adhesive properties of the patches were characterized considering (a) the features that enable an adhesive to form a bond with the surface of another material upon brief contact and under light pressure (*Tack*); (b) the resistance of the matrix to flow that could be considered as an expression of the cohesiveness of the matrix itself (*Creep resistance*); (c) the force required to peel away a patch from a surface (*Peel adhesion*). Furthermore, the biopharmaceutical performances of the patches loaded with the two active ingredients were also investigated by determining the *in vitro* permeation profile through human skin.

MATERIALS AND METHODS

Materials

Poly(ethyl acrylate, methyl methacrylate); molar proportions of the monomer units 1:1; molecular weight 800,000 Da (PMM). This material is supplied as 40% w/w copolymer latex under the trade name of Eudragit® NE40D (Rohm, G). To obtain the PMM organic solution, the latex was freeze dried and then dissolved in acetone at 20% w/w concentration. The freeze dried material and water evaporated PMM, which was obtained as described in the patch preparation section, are mentioned in the text as fdPMM and wePMM, respectively. Tributyl citrate (Citroflex 4, TBC) was supplied by Morflex (USA). Potassium diclofenac (DK) and nicotine (NT) and triacetin (TAc) were obtained from Sigma (USA). The release liner and the backing layer used for the patch preparation were a siliconized PET film (FL2000 PET 75 μm S1, Loparex, I) and a polyester film with a thickness of 36 μm (Polifibra, I). Nicotinell® (Novartis, CH). Dicloreum Tissugel® (Alfa Wasserman, I). All solvents were of analytical grade, unless specified.

Patch Preparation

The PSA dispersions were prepared by adding a plasticizer to the PMM organic solution (series A and B, fdPMM, Table I) or the PMM latex (series C and D, wePMM, Table I). The amount of the plasticizer in the dried film was ranging from 25% to 125% by weight based on the dry copolymer weight. When an active ingredient (DK or NT) was added to the latex as the anti-shrinkage agent, it was contained in 3% *w/w* calculated on the PSA film. The final compositions of the designed PSA are reported in Table I.

The polymeric dispersions/solutions were mixed with a magnetic stirrer for 1 h and used after 16 h of rest. The PSA films were prepared by using a laboratory-coating unit Mathis LTE-S(M) (Mathis, CH) equipped with a blade coater. The mixture was spread on the backing layer at the constant rate of 1 m/min. The coating thickness was set in order to obtain a dry film of about 50 μm thickness. The systems were dried at 50 °C for 20 min, covered with the release liner and stored in an airtight container at 25±0.1 °C until use (1 week). The drying conditions were set up in order to obtain dry matrices with a loss on drying less than 0.05% *w/w*. The loss in drying

Table I. Compositions (% *w/w*) of PSA

		Composition (%, *w/w*)					
Series	Form.	fdPMM	wePMM	TAc	TBC	DK	NT
A	1	80.00	–	20.00	–	–	–
	2	66.67	–	33.33	–	–	–
	3	57.14	–	42.86	–	–	–
	4	50.00	–	50.00	–	–	–
	5	44.44	–	55.56	–	–	–
B	6	80.00	–	–	20.00	–	–
	7	66.67	–	–	33.33	–	–
	8	57.14	–	–	42.86	–	–
	9	50.00	–	–	50.00	–	–
	10	44.44	–	–	55.56	–	–
C	11	–	80.00	20.00	–	–	–
	12	–	66.67	33.33	–	–	–
	13	–	57.14	42.86	–	–	–
	14	–	50.00	50.00	–	–	–
	15	–	44.44	55.56	–	–	–
D	16	–	80.00	–	20.00	–	–
	17	–	66.67	–	33.33	–	–
	18	–	57.14	–	42.86	–	–
	19	–	50.00	–	50.00	–	–
	20	–	44.44	–	55.56	–	–
	21	–	48.50	–	48.50	3.00	–
	22	–	48.50	–	48.50	–	3.00

was determined by thermogravimetry at 120 °C (Mettler LP15, G).

Matrix Thickness

A sample of 2.5×2.5 cm of the patch (matrix and backing layer) was placed between the jaws of the MI 1000 micrometer (ChemInstrument, USA). The accuracy of the instrument was 2.5 μm±0.5%. Firstly, the whole thickness (T_w) was measured. After solubilising the adhesive in 25 ml acetone, the backing layer was washed with 20 ml of fresh acetone, dried then and the thickness of the treated backing layer (T_b) was also measured.

The thickness of PSA films was calculated as $T_w - T_b$. The results are expressed as the mean of five determinations.

Uniformity of Content

The drug content was determined according to the Ph. Eur. monograph 2.9.6. Uniformity of content of single-dose preparations. A patch sample of 2.54 cm^2 containing DK or NT was dissolved in 25 ml of methanol. The solution was filtered (Durapore® membrane, pore size 0.45 μm; Millex GV, Millipore Corporation, USA) and assayed by HPLC according to the method reported below.

Monitoring DK Crystal Formation

The appearance of DK crystals was monitored visually and microscopically (Axioscope, Zeiss, G) throughout an area of 10 cm^2 after preparation and before testing.

Evaluation of Adhesive Properties

Texture Analysis

The patch was placed on a flat surface adhesive uppermost. A 2.04 kg cylinder with an 8 mm diameter hole was placed on the top of the sample, ensuring to centre the patch with the cylinder hole. The cylinder plus sample was then clamped in the testing position of a software controlled dynamometer (AG/MC, Acquati, I) equipped with a 5 Da N cell. The stainless steel probe (diameter: 6 mm) was then lowered into the cylinder and a constant force of 0.05 N was applied onto the sample for 5 seconds and, finally, the probe was removed with a constant rate. The debonding velocity (V_d) in this set of experiments was 5 mm/s. The absence of PSA residues from the stainless steel surface of the probe (adhesive failure) was visually determined.

The stress/strain curves were analyzed in order to clarify the mechanisms involved in detachment of the PSA during the texture experiments. Depending on the viscoelastic characteristic of the adhesive and the probe rate during debonding, five subsequent events can be detected in the curves. According to the adhesion theory, they are attributed to: (a) homogeneous deformation of the adhesive before maximum detachment force, (b) cavitation around the maximum detachment force, (c) rapid growth of cavities during the step where the detachment force decreases; (d) slow growth of these cavities represented graphically by a plateau; (e) elongation of the walls in-between (fibrillation) and complete debonding (14).

The detachment force and the elongation at break were measured and expressed in Newton (N) and millimetres, respectively. The area under the curve recorded by the instrument software was assumed as the work of separation (W). The stress (σ) and the strain (ε) values for each experiment were calculated according to the following equations:

$$\varepsilon = \frac{(h(t) - h_0)}{h_0} \quad (1)$$

$$\sigma = \frac{F}{A} \quad (2)$$

where $h(t)$ is the PSA elongation at time t, h_0 is the PSA initial thickness, F is the force registered during the detachment and A is the probe surface area.

The results are expressed as the mean±standard deviation (n=6).

Shear Adhesion Test

The test was performed with an apparatus designed according to PSTC-107 specifications (Ichemico, I). Each value is the mean of five determinations. The adhesive patches were cut into strips and the specimen was applied at tab end, in contact to an adherent stainless steel plate. The specimen, reinforced with an adhesive tape on the backing layer, was laid parallel to the length of the test surface and smoothed with a 2.04 kg roller for three times. The sample was placed in the shear adhesion rack to hold plates at 2° inclined from vertical so that the back of the plate formed an angle of 178° with the extended piece of sample. A weight of 500 g was secured to the free end of the patch. The shear adhesion value is the time required to separate the sample from the plate. The registered values were considered the real measure of the internal strength of the adhesive only if at the end of the experiment the adhesive left an adhesive layer visually detectable on either the stainless steel plate or the backing layer (cohesive failure).

Peel Adhesion 180° Test

The test was performed using an apparatus designed according to PSTC-101 Test method A specifications. Adhesive patches were cut into strips and applied onto a stainless steel adherent plate, smoothed with a 2.04 kg roller for five times, maintained at 20 °C for 10 min and pulled from the plate at a 180° angle at a rate of 300 mm/min. To avoid deformations that could affect the results, the backing layer of the patches were reinforced by an adhesive tape. The test was performed by a software-controlled dynamometer (AG/MC Acquati, I). The force was expressed in cN per centimetre width of adhesive patch under test. Peel adhesion values are expressed as the mean of three determinations.

ATR-FTIR Spectroscopy

Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were recorded with an ATR-FTIR spectrometer (Perkin Elmer, USA) equipped with a diamond crystal. For each sample 64 scans were collected at a resolution of 2 cm^{-1} over the wavenumber region 4,000–650 cm^{-1}.

In Vitro Permeation Profile

Skin Preparation

The skin used in the transdermal permeation studies was obtained from the abdominal skin of a single donor (Eurasian female), who underwent cosmetic surgery. The full-thickness skin was sealed in evacuated plastic bags and frozen at −20 °C within 24 h after removal. Prior to preparation, the skin was de-frozen to room temperature, and the excess fat was carefully removed. The skin sections were cut into squares and, after immersing the skin in water at 60 °C for 1 min, the epidermis was gently separated from the remaining tissue with forceps. The epidermis was carefully inspected visually for any defects, before mounting onto the Franz diffusion cells.

Permeation Experiment

A patch sample (2.5 cm^2) was applied with slight pressure to the human epidermis. The epidermal skin layer was mounted carefully on the lower half of the Franz cell with the epidermis facing upwards and the stratum corneum side in contact with the patch. The upper and lower parts of the Franz cell were sealed with Parafilm® and fastened together by means of a clamp, with the epidermis acting as a seal between the donor and receptor compartments.

These vertical cells have a wider column than the original Franz-type diffusion cell, and the bowl shape was removed. They have a diffusion area of 0.636 cm^2 and a 5 ml (approx.) receptor compartment. The receiver volume of each cell was individually calibrated. The receiver compartments were filled with freshly prepared degassed medium. Ultrapure water or pH 5 phosphate buffer was used for DK and NT, respectively.

Special care was taken that there were no air bubbles between the medium and the epidermis in the receptor compartment. The Franz cells containing the medium were kept at 37±1 °C with a circulating water bath, throughout the experiment, so that the skin surface temperature was 32±1 °C. Only the receptor compartment was in contact with the circulating water at 37 °C and each Franz cell was equipped with a stirring magnet. At predetermined times 0.2 ml samples were withdrawn from the receiver compartment and immediately replaced with fresh receiver medium. Sink conditions were maintained throughout the experiment. The withdrawn samples were assayed directly by HPLC to determine concentrations of DK or NT permeated through the epidermis. The permeation data were plotted as the cumulative amount of drug permeated through the skin as a function of time. The results of each permeation experiments are expressed as the mean of three replicates.

HPLC Analyses

Potassium Diclofenac

The concentrations of DK 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 (C_{18} Nova-Pak, 4.6×150 mm, Waters, USA). The composition of the eluent was acetonitrile/water/acetic acid (50:46:4, % *v*/*v*/*v*). The flow rate was 1.5 ml/min. The wavelength was set at 254 nm. The drug concentration was determined from sodium diclofenac standard curves (0.5–20 μg/ml).

Nicotine

The concentrations of NT in the medium were determined by HPLC assay (HP 1100, Chemstations, Hewlett Packard, USA). A 25 μl sample was injected at room temperature on a C18 reverse-phase column (Lichrospher, 100 RP-18E, Agilent, G). The composition of the eluent was 2.31 g/l sodium dodecyl sulphate in acetonitrile/ a 13.6 g/l potassium dihydrogen phosphate solution (25:75, % *v*/*v*). The flow rate was 1.5 ml/min. The wavelength was set at 254 nm. The drug concentration was determined from NT standard curves (1–100 μg/ml).

RESULTS AND DISCUSSION

Adhesive Properties

The addition of the two plasticizers to the PMM latex in a percentage lower than 42.86% *w*/*w* calculated with respect to the dry copolymer (formulations nos. 11, 12, 16 and 17) did not permitted to obtain a continuous film as the obtained mixtures did not wet the backing layer. The other PSAs of the series C and D (formulations nos. 13–15, 18–20) permitted to obtain continuous films even if the shrinkage of the latex cast on the backing layer slightly occurred during the drying process; however, in the homogeneous portion the PSA films appeared homogeneous and transparent.

The thickness of the films was in the 48–54 μm range. Considering the accuracy of the instrument, the PSA film thickness can be considered similar.

In the selected experimental conditions, the formulations nos. 1 and 6 resulted not-sticky. In all other cases, the texture analysis allowed us to characterize the debonding process due to the initial adhesion, or tack.

The stress–strain curves showed that the detachment force rapidly dropped to zero after their maximum values indicating that no fibrillar structure occurred upon the debonding of the PSA from the stainless steel probe. The formulations nos. 2 and 7 showed a slight different stress–strain curve patterns that were attributed to the growth of cavities at the interface during the detachment process (11). The features of the two types of the stress–strain curves are exemplified in Fig. 1. At the end of each experiment, no residues of the adhesive were visually observed on the probe surface indicating that the PSA failed adhesively.

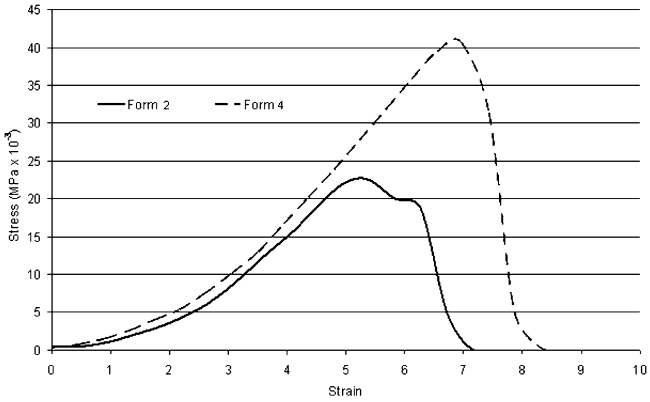

Fig. 1. Texture profiles of formulations nos. 2 and 4 (Series B). Formulation no. 4: the detachment force dropped rapidly to zero after their maximum value. Formulation no. 2: the plateau registered after the maximum was attributed to the growth of cavities at the interface during the detachment process[11]

The quantitative parameters used to describe the process, namely the maximum nominal stress, σ_{max}, the maximum nominal strain, ε_{max}, and the work of separation, W, are reported in Table II.

In general, when the σ_{max} value is low, the initial adhesion onto the surface occurs slowly. In transdermal field, this behaviour is desirable as patches are generally applied on the skin slowly and with accuracy. The increase of the percentage of the two plasticizers in the PSAs caused an increase of σ_{max} and, consequently, W. According to the theory, in regime of adhesive failure, W is mainly controlled by σ_{max} (11). The increase of σ_{max} can be due to a softening effect exerted by both plasticizers.

The PSAs of series A showed significantly higher values of σ, ε_{max}, and W with respect to the corresponding PSA of the series C ($p<0.032$). These different performances can be ascribed to the different spatial organization of the polymer chains in the PSA films obtained by drying the organic solution and the latex.

When TBC was used, no significant modifications of tack values were found underlining that in this case the three-dimensional organization of the PSA was not affected by the use of the latex instead of the organic solution.

The data obtained with the standard creep resistance test can be considered the true measure of the internal strength of the PSAs as all films failed cohesively (Table II). The use of the commercial latex or acetone solution did not determine significant differences in the shear resistance values. When TBC was added to wePMM or fdPMM the creep resistance values resulted two-fold higher than those measured in presence of the same concentration of TAc. As expected, higher concentrations of plasticizers determined an increase of the PSA creep compliance. This pattern was more evident when TAc was added to PMM (Table II). The low creep resistance registered (<10 min) at highest percentages of plasticizers resulted in the same order of magnitude of nitroglycerin transdermal patches available on the market (15).

The different effect on creep resistance values obtained with the two plasticizers was ascribed to a different effect of the two low molecular-weight molecules on the number of PMM interpolymeric entanglements. Such hypothesis is supported by the analysis of the ATR-FTIR spectra. The analyses of the ATR-FTIR spectra of the PSA films showed some modifications in the wavenumber and morphology of the main bands of the copolymer and both the plasticizers. The main bands detectable in the ATR-FTIR spectra were the bending and the stretching bands of ester groups –COOR and $-CH_x$. The wavenumbers of these bands registered in the series prepared using the latex are reported in Table III. In the case of the PSA films containing TBC, the bending ester band at 1,179 cm^{-1} of the plasticizer significantly shifted toward lower wavenumbers; while the wePMM bending ester band at 1,155 cm^{-1} shifted toward higher wavenumbers

Table II. Adhesive properties of the placebo patches

Series	Form.	ε_{max}	σ_{max} (MPa×10^{-3})	W (MPa×10^{-3})	Shear adhesion (min)	Peel adhesion (cN/cm)
A	1	–[a]	–[a]	–[a]	–[b]	142±24
	2	6.14±0.36	22.47±3.12	0.125±0.029	1067±102	179±56
	3	7.17±0.17	28.45±0.64	0.187±0.011	87±6	–[c]
	4	8.73±0.24	32.65±1.62	0.217±0.012	13±1	–[c]
	5	18.34±4.18	52.55±9.38	0.536±0.111	4±0	–[c]
B	6	–[a]	–[a]	–[a]	–[b]	48±9
	7	8.35±0.34	32.41±2.13	0.207±0.017	2041±448	61±3
	8	8.09±0.12	28.66±0.61	0.189±0.018	227±5	67±11
	9	10.31±1.11	39.01±2.98	0.289±0.015	21±1	75±5
	10	20.11±3.17	53.96±7.16	0.580±0.145	4±0	109±8
C	13	7.47±0.21	21.23±2.50	0.136±0.006	104±17	47±6
	14	8.07±0.16	28.93±1.46	0.178±0.005	12±1	–[c]
	15	8.14±0.34	29.10±3.41	0.180±0.014	2±0	–[c]
D	18	7.06±0.22	30.70±4.65	0.162±0.018	239±22	59±8
	19	9.34±0.21	45.12±3.47	0.262±0.027	22±1	66±2
	20	10.38±0.35	49.89±1.64	0.368±0.016	4±1	62±4

[a] Not detectable
[b] >10 days
[c] Cohesive failure

Table III. Main ATR FTIR bands registered on pure constituents and the PSA films of the series C and D

	Pure constituent			Formulation no.					
Vibration bands	wePMM	TAc	TBC	13	14	15	18	19	20
Stretching ν–(CH_x)	2,981.82			2,982.19	2,982.08	2,982.39			
		2,970.5	2,960.34				2,959.77	2,960.08	2,959.97
	2,952.27			2,952.43	2,951.08	2,954.15			
			2,875.16	2,890.5	2,890.35	2,891.12	2,876.35	2,875.92	2,876.05
Stretching ν–(C = O)	1,725.02								
				1,729.37	1,732.99	1,733.3	1,728.76	1,729.09	1,729.51
		1,737	1,733.64						
Bending ν–(C = O)			1,179.11					1,174.46	1,174.84
	1,154.87			1,157.02	1,158.81	1,158.75	1,158.62	1,160.58	1,158.75
				1,113.27	1,112.87	1,113.3			
		1,100.1							
	1,021.46		1,020.23	1,047.85	1,047.99	1,047.83	1,020.79	1,020.80	1,020.82
		1,015.3		1,017.74	1,017.27	1,017.08			

(1,159–1,160 cm^{-1}). In the wePMM/TAc PSA, the ester bending bands of the copolymer and plasticizer shifted towards higher wavenumbers (Table III). Moreover, a significant modification of the CH_x stretching bands of TAc and wePMM in the 2,900–3,000 cm^{-1} region was detected. Indeed, the presence of bands at higher wavelength can be interpreted as a fluidization of the PMM structures. These different features between TBC and TAc, that were recognizable also in the corresponding series prepared with the organic solution (series A and C) suggested that TAc interacted more strictly with PMM than TBC.

During the peel adhesion tests, the formulations nos. 3–5, 14, 15 left matrix residues onto the stainless steel plate due to the PSA poor cohesive strength and/or low adhesion to the backing layer (cohesive failure). When the other patches were peeled away from the stainless steel surface, they cleanly stripped, without leaving visually noticeable residues (adhesive failure).

These preliminary data proved that the series D was worth further investigations since the preparation method is simplified and TBC guaranties a lower creep compliance of the PSA. Within this series, the formulation no. 19 was selected to evaluate the effect of the two active ingredients on the spreading characteristics of the latex because the PMM/TBC ratio at the centre of the series presented suitable features in terms of adhesive properties

As far as the anti-shrinkage agents is concerned, the addition to the formulation no. 19 of the active ingredient, DK or NT, permitted to avoid the shrinkage of the polymeric dispersion after spreading onto both the backing layer and release liner and obtain homogeneous matrices in which drug crystals were not detectable. Nevertheless, their presence affected the adhesive performances of the PSA films. Both drugs caused a reduction of the creep adhesion that fell down from 22 to 2 min. The drugs had an opposite effect on the peel adhesion that resulted higher in the case of NT (100± 10 cN/cm) and lower in the case of DK (49±8 cN/cm) with respect to formulation no. 19 underlining that the addition of an anti-shrinkage agent can cause unpredictable effects on the PSA adhesive properties.

In Vitro Permeation Profiles

Human epidermis permeation profiles obtained by using the formulations nos. 21 and 22 were compared to those obtained by using Nicotinell® and Dicloreum Tissugel®.

The drug content of the formulations nos. 21 and 22 were 0.32±0.01 and 0.34±0.01 mg/cm^2, respectively.

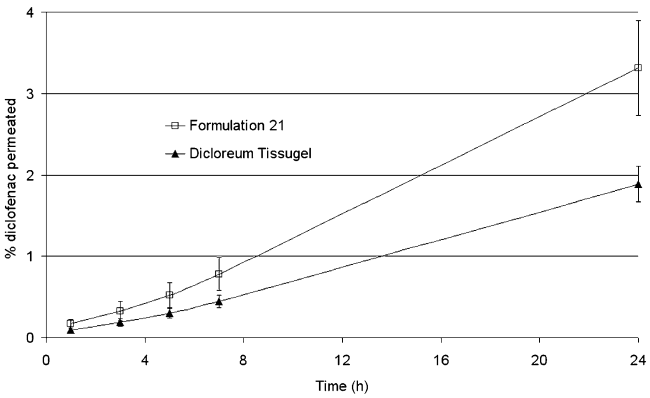

Fig. 2. Skin permeation profile of DK from formulation no. 21 and Dicloreum Tissugel®

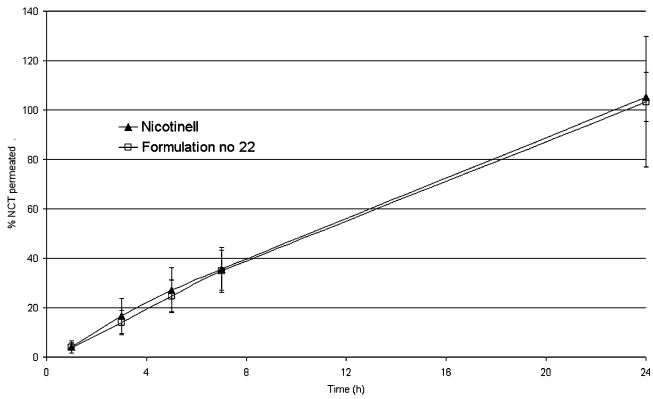

Fig. 3. Skin permeation profiles of NT from formulation no. 22 and Nicotinell®

Since the drug loadings in the patch of the present study were lower than those of both the reference products (Dicloreum Tissugel® = 1 mg/cm^2; Nicotinell® = 1.7 mg/cm^2), the drug amounts permeated through human epidermis were expressed as percentage. The results of the parallel experiments are reported in Figs. 2 and 3.

In the case of nicotine patches, the drug permeated amounts per square centimetre after 24 h were slightly higher than the drug amount loaded per square centimetre. This pattern is due to the edge effect that led to an overestimation of the cumulative amounts of NT that permeated through skin (16).

CONCLUSION

Considering that the PSA has to guarantee the contact between the transdermal patch, or the plaster, and the skin, the following adhesive requirements should be taken into account in the selection of the optimal formulation. The PSA must stick securely to the skin (tackiness), the matrix must exhibit a resistance to the tangential stresses due to the skin movements and, at the end of the application, it is essential that the patch is removed easily without causing pain or discomfort. On the basis of the obtained data, it is possible to conclude that the PSA prepared directly by using the commercial latex of the PMM can be used for the development of transdermal patches, or plaster. The results underline also that the addition of TBC permitted to obtain patches with lower creep compliance and peel adhesion than TAc.

The *in vitro* permeation results evidenced also that PMM based matrices be taken into consideration to administrate drugs with different chemical structures, such as DK and NT.

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