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RESEARCH PAPER

Adhesive Backing Foil Interactions Affecting the Elasticity, Adhesion Strength of Laminates, and How to Interpret These Properties of Branded Transdermal Patches

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ABSTRACT

Standard tensile strength and peel adhesion tests were carried out to investigate interactions of pressure-sensitive adhesives (PSAs) with several backing foils used for transdermal patches. Seven branded transdermal patches (Alora®, Cutanum®, Estraderm MX® 50, Estraderm TTS® 50, Fem7®-50 μg, Menorest®, Oesclim®) were included in the investigation. Their skin adhesion measured in several clinical trials was compared with the results of the laboratory measurements according to PSTC-1 (Peel Adhesion for Single Coated Tapes 180° Angle, Pressure Sensitive Tape Council, Illinois, 1996), such as Young's modulus at 3% elongation and peel adhesion to stainless steel. Data obtained for the PSA-coated backings (laminates) show increasing elasticity with increasing PSA thickness. Interactions of PSAs with backing foil became evident in significant changes in Young's modulus by low PSA thickness, as seen for the silicone adhesive. The Young's moduli of the laminates were found to be influenced not only by the elasticity of the backing foil but also by the chemical structure of the PSA. There was no correlation between the elasticity and peel adhesion of both the laminates and the branded patches. Likewise, for the branded patches the peel

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adhesion to stainless steel does not correlate with skin adhesion values obtained from clinical trials.

The Young's modulus of the branded patches was between 4 N/mm² (Oesclim®) and 501 N/mm² (Fem7®). For the branded transdermal patches no correlation was found between Young's modulus and both the peel force on stainless steel and the skin adhesion reported in studies.

Key Words: *Transdermal; Pressure sensitive adhesive; Backing foil; Young's modulus; Tensile strength; Peel test; Skin irritation*

INTRODUCTION

The adhesion of a transdermal patch is a crucial factor for any successful hormone replacement therapy (HRT) using patches because, if the full surface area of the patch does not stay in contact with the skin throughout the application period,[1] this can affect the drug delivery to the skin. The elasticity of the backing material has a profound effect on the ability of the transdermal patch to adhere to the skin. In addition, elastic patches cause less irritation, since the skin is free to move in a natural way.[2] Therefore we applied Young's modulus as a tool to compare different systems regarding their elastic behavior. Skin movement within the ideal elastic behavior of the patches is required for these considerations. Recoverable elongation for Fem7®-50 µg, the stiffest of the investigated patches, is 4%. We suppose that skin under the patches does not move more than 4%, so the Young's modulus seems to be valid as a comparing value for stiffness.

The properties of the pressure-sensitive adhesive (PSA) layer in a transdermal patch depend on the incorporated drug, the components of the transdermal patch (e.g., backing foil, BF), the excipients (e.g., penetration enhancers, solubilizers), and the chemical composition of the PSA.[3] For a particular drug, the mechanical properties of the transdermal patch depend on the type and concentration of enhancer, the type of PSA, and the coating thickness.

The coating thickness, the concentration of the enhancer, and the type of the adhesive affecting the adhesion were found to be statistically significant.[3]

For three different types of PSAs commonly used for the manufacture of transdermal patches[4,5]—silicones (S), polyisobutylenes (PIB), and polyacrylates (PA)—the penetration enhancer isopropyl myristate (IPM) was shown to influence adhesion and skin irritation.[6] As the excipient level was increased, the skin adhesion values increased due to the plasticizing effect of IPM. For PAs, drug–polymer interactions have been reported to affect the adhesion strength and release kinetics of films.[7]

However, so far as we are aware, no experimental data are available showing the relationship between adhesion caused by PSA and the elasticity of the BF used as second component of a laminate designated as a patch for HRT.

The adhesion strength of a patch should be in the range of about 0.4 to 2 N/cm, sufficient to stay in adhesion, but not so aggressive as to damage the stratum corneum.[2] In fact, no data have been reported on elasticity. However, recent studies have revealed a value for the Young's modulus of skin between 0.1 and 0.3 MPa.[8] That of the patch should be of the same order to allow skin to move in a physiological way.

The aim of this study was therefore to investigate the elasticity and adhesion strength of laminates consisting of S, PIB, or PA as adhesive, and three branded BFs as second component. The objective of the investigation was to show potential interactions between the adhesive and the backing foil with regard to adhesion and elasticity of the laminate. Ethyl oleate (EO), the well-known enhancer for patches, was included in this part of the investigation.

In addition, we investigated the adhesion and elasticity of branded HRT patches. As there are very few studies that correlate wear properties of patches with measured physical attributes,[5] an attempt was made to correlate the results of investigations of adhesion and elasticity with clinical data published for these patches.

MATERIALS AND METHODS

Materials

The materials used were the PSAs Bio-PSA® HX13014 (S, Dow Corning, Midland, USA),

Table 1

Selection of Branded Transdermal HRT Patches and Their Skin Adhesion Expressed as a Percentage of Patches Remaining Attached After the Treatment Period Calculated from Observations of Several Clinical Studies

Brand	Patch Area (cm^2)	Treatment Period× Number of Patients	Patches Completely (c) or Partially (p) Detached (%)	Skin Adhesion %	Skin Adhesion Ref.
Alora®	18	3.5 days×96 subjects	10 high achievers, 30 moderate achievers, 65 low achievers (35)	65	9
Cutanum®	12.5	7 days×99 subjects	1.4 (p)+0.3 (c)=1.7 (1.7)	98	10
Estraderm® MX 50	22	3.5 days×34 subjects	(c+p)=8.8 (8.8)	91	11
Estraderm® TTS 50	10	3.5 days×140 subjects	1.9 (c)+8.4 (p)=10.3	80	10
		3.5 days×99 subjects	8.9 (c)+11.1 (p)=20[b]		11
		3.5 days×34 subjects	10 (c)+14.2 (p)=24.2[a] (c+p)=27.5 (20.5)		12
Fem7®-50 µg	15	7 days×186 subjects	(c+p) 9.2[II] resp. 6.6[III] (7.9)	92	13
Menorest® 50	14.5	4 days×24 subjects	8.3 (c)+29.2 (p)[c]=38	76	12
(Vivelle® 0.05)			13.1 (c)+6.9 (p)=20[b] 7.2 (c)+4.1 (p)=13.3[a] (23.8)		14
Oesclim® 50	22	4 days×24 subjects	4.2 (c)+8.3 (p)[c]=12.5 (12.5)	87	14

[a]Abdominal skin.
[b]Buttocks.
[II]Phase II.
[III]Phase III.
[c]Discrepancy between report and discussion.

MA-24A® (PIB, Adhesives Research, Limerick, Ireland), and Duro-Tak® 387-2052 (PA, National Starch, Bridgewater, NJ), the backing foils CoTran® 9726, 9737 (3M, St. Paul, MN) and Hostaphan® MN med 15 (Mitsubishi, Wiesbaden, Germany), and the penetration enhancer ethyl oleate (EO, Fluka, Neu-Ulm, Germany). The PSAs contained as solvents ethyl acetate (S), heptane (PIB), ethanol (22%), isopropanol (26%), ethyl acetate (39%), heptane (12%) (PA). The investigation also included a selection of seven branded transdermal patches designated for HRT (Table 1).

Methods

Preparation of Laminates (Solvent Cast Method)

The PSA solution as delivered by the supplier and in the solvent described above was cast onto transfer foil Scotchpak 9742 using a suitable device (Erichson, Hemer, Germany or Mathis AG, Niederhasli, Zurich, Switzerland, respectively). The laminates were dried using air (80°C) for 20 min and re-laminated with one of the BFs. The samples were stored at room temperature (20°C) and protected from moisture. The thickness of the laminates was measured at five points, avoiding the edges, using a DELTASCOPE® MP30 (Helmut Fischer GmbH & Co., Sindelfingen, Germany). Laminates showing large variations in thickness and inhomogeneous structure were rejected.

Tensile Strength Test

The tensile strength of the foils and laminates was determined on a force–distance tester (ZW 2.5/TN 1S, Zwick, Ulm, Germany) modified from PSTC-1.[15] The tester was equipped with a 100-N tension loading cell. The cross-head speed was controlled at 40 mm/min. Four strips (10 mm × 40 mm) of each foil or laminate were examined for their tensile strength at an elongation of 3%, and the mean±SD calculated.

The Young's modulus was calculated as follows:

$$E = \frac{TS}{ws}\frac{L_0}{\Delta L} = TS \times \frac{100}{\varepsilon} \quad (1)$$

Table 2

Parameters and Settings of 180° Peel Test

Parameter	Settings	
	As selected	According to Ref. 15
Width of the strip (mm)	10	12.7–25.4
Length of the strip (mm)	30–50	~305
Substrate	stainless steel	stainless steel
Rubber roller, weight (g)	2250	2250
Time (min)	10	≤1
Peel velocity (mm/min)	300	~305
Peel distance (mm)	40	50.8
Temperature (°C)	20±2	23±2
Relative humidity (%)	50±2	50±2
No. of samples	4	—
Unit F_S	N/cm	oz/in.

where:

E = Young's modulus (N/mm^2)
TS = tensile strength (N) at 3% elongation
w = width of the strip (mm)
s = thickness of the strip (mm)
L_0 = original length of the strip (mm)
ΔL = change in length because of the elongation (mm)
ε = stretching rate of the strip [%]

The statistical analysis of the data was carried out as usual (mean, standard deviation).

Peel Adhesion Test

The peel adhesion test was performed according to No. 1 method of the PSTC test[15] in a slightly modified manner (Table 2).

We performed our investigations according to a standard procedure of the Pressure Sensitive Tape Council No. 1[15] with a few manipulations. Table 2 shows the chosen settings. Because of the fixed patch sizes we had to adjust the *length* and *width* of the samples, and the *peel distance* to suitable sizes. To find a suitable contact time we compared the adhesion strengths of patches after contact times between 1 min and 180 min. For patches 1 min contact time is too short to reach their full adhesion strength (Fig. 1). Therefore measurements were performed after a *contact time* of 10 min.

It is a well-known fact that the time of the beginning of the plateau is much influenced by the surface roughness of substrates and the viscoelastic properties of the PSA.[16] For our purposes a contact time of 10 min seems to be optimal for investigating the adhesion strength of patches. To compare adhesion strengths with values determined by other companies we have to know first, which contact time they used. Small variations in *peel velocity* result from the conversion of the units. Measurements were carried out in a room with a *temperature* of 20±2°C. Measurements are influenced by many factors. That is why we did *four measurements* for each patch according to the Japanese Pharmacopeia.[17]

The adhesive properties of the patches were evaluated using the force–distance tester (ZW 2.5/TN 1S, Zwick, Ulm, Germany) and by applying the

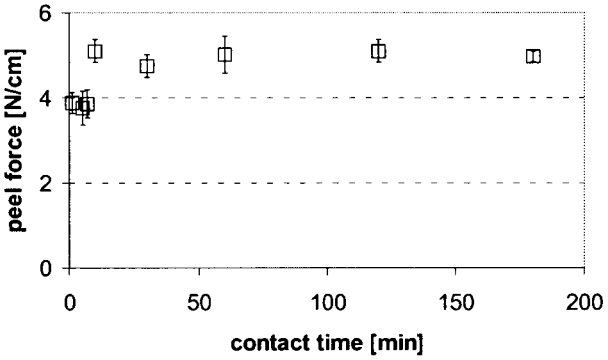

Figure 1. Relationship between the contact time and the peel force of a laminate (adhesive: Duro-Tak® 387-2052, backing foil: CoTran® 9720).

Table 3

Young's Moduli [Y (N/mm^2)] and Thickness Values [s (μm)] of the Backing Foils and Their Laminates with Several PSAs

	Backing Foil Unlaminated		S Laminate		PIB Laminate		PA Laminate		PA+EO Laminate	
Backing Foil	Y	s	Y (%)	s	Y (%)	s	Y (%)	s	Y (%)	s
CoTran® 9726	102	52.8	49	119.2	66	83.4	58	96.8	44	97.6
CoTran® 9737	77	72.9	64	141	79	108.4	72	119.6	56	121.4
Hostaphan®	2128	16.3	22	87	40	47.8	33	59	—	—

Table 4

Young's Modulus (Y) and Thickness (s) of the Branded Transdermal Patches

Brand	Y (N/mm^2)	s (μm)	Brand	Y (N/mm^2)	s (μm)
Alora®	78	106.7	Fem7®-50 µg	501	107.6
Cutanum®	43	159.4	Menorest® 50	190	186.4
Estraderm MX® 50	466	96.2	Oesclim® 50	4	507.0
Estraderm TTS® 50	337	112.2			

180° dynamic adhesive strength peel test. The objective of the 180° peel test was to determine the peel force (N/cm) needed to remove the laminate from a standard stainless steel surface, using a 180° peel angle with a constant peel rate of 30.0 cm/min at constant temperature and relative humidity.

Statistical data analysis was performed as mentioned above.

Skin Adhesion Evaluation

The skin adhesion data were derived from several clinical studies (Table 1). Reported data include percentages of partially and completely detached patches. To compare the patches percentages of partially and completely detached patches were added for each study. If more than one study was included, the mean of these data was calculated ($\overline{N_d}$). The skin adhesion value (A_s) was calculated as follows:

$$A_s = 100 - \overline{N_d} \quad (2)$$

where

A_s = skin adhesion (%)
$\overline{N_d}$ = number of patches (mean) completely and partially detached in relation to the total number of applied patches (%)

RESULTS AND DISCUSSION

Elasticity

The Young's moduli (Y) of the BFs investigated were between 77 N/mm^2 for the very elastic CoTran® 9737 and 2128 N/mm^2 for the rigid Hostaphan® MN med 15. The elasticity of the BFs was found to increase as a result of PSA coating (Table 3). The influence of the PSA coating on the Young's modulus proved higher for the rigid foil and lower for the elastic foil. The influence of the PSA coating on laminate elasticity depends on its chemical nature and/or the solvent. The influence of PSA is increasing in the order PIB < PA < S. The addition of the enhancer EO resulted in a further increase in the influence of the PSA on elasticity.

The Young's moduli of branded transdermal patches were between 4 N/mm^2 and 501 N/mm^2 (Table 4).

We can calculate that, relative to the skin elasticity of 0.3 N/mm^2, there is one patch whose elasticity is 10 times lower (Oesclim®) and there are two patches whose elasticity is about 100 times lower (Cutanum® and Alora®) as well as four patches whose elasticity is about 1000 times lower (Menorest®, Estraderm® TTS, Estraderm MX®, and Fem7®).

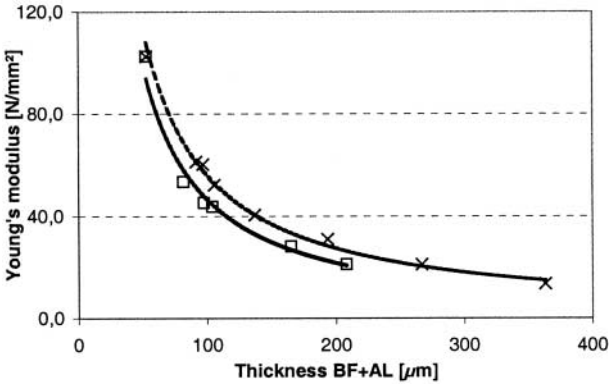

Figure 2. Dependence of Young's modulus on the thickness summarized for BF (CoTran® 9726) and AL consisting of PA (×) and PA+EO (□), respectively.

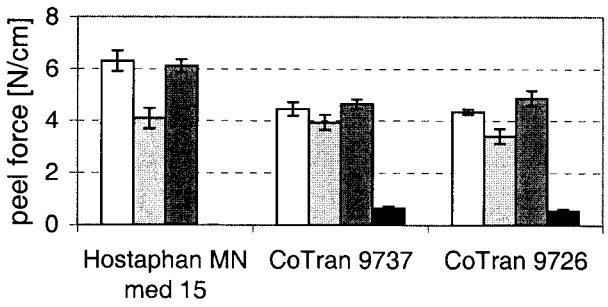

Figure 3. Peel force (N/cm) of laminates with PIB (□), PA(■), S (■), and PA+EO (■) in dependence on the backing foil.

The Young's moduli of the PA laminates without enhancer and those containing the enhancer EO proved dependent on thickness summarized for BF and the adhesive layer (AL) (Fig. 2). For the PA laminates without EO and containing EO, there was an exponential relationship between the Young's moduli (Y) and thickness values (s) as follows:

$$Y = a \times s^b \tag{3}$$

The following results were obtained:

$a = 6355$ (PA), 7235 (PA+EO);
$b = 1.028$ (PA), 1.096 (PA+EO); and
$R = 0.9924$ (PA), 0.9855 (PA+EO).

Adhesion to Stainless Steel

The adhesion to stainless steel expressed as peel force of the laminates was different depending on the backing foil (Fig. 3). It was between 0.55 N/cm [CoTran® 9726+(PA+EO)] and 6.3 N/cm [Hostaphan® MN med 15+(PIB)]. The highest peel force was found for the laminates with Hostaphan® MN med 15. There was no significant difference between the peel forces of the CoTran® foils coated with PIB, PA, or S. In general, the lowest peel force was found for the CoTran® laminates coated with PA+EO.

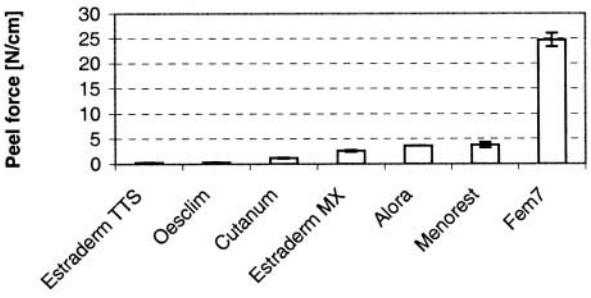

Figure 4. Peel force on stainless steel for seven branded patches.

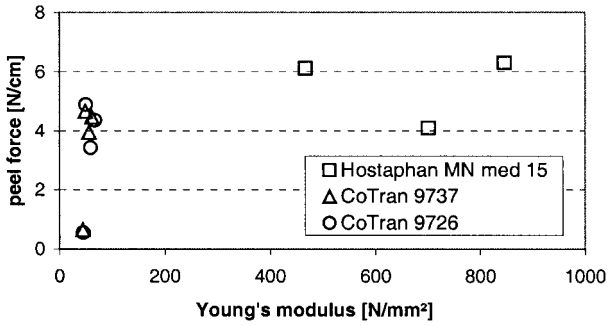

Figure 5. Relationship between Young's modulus and peel force on stainless steel for laminates.

The peel force found for branded patches (Fig. 4) was between 0.25 N/cm (Estraderm TTS® 50) and 24.72 N/cm (Fem7®).

The requirement of an adhesion strength ranging between about 0.4 and 2 N/cm[2] was only fulfilled by Cutanum®. The adhesion values found for Estraderm® TTS 50 and Oesclim® were below this range (peel force < 0.5 N/cm). For Estraderm® MX 50, Alora®, and Menorest® 50 we found a moderate adhesion between 2.6 N/cm (Alora®) and 3.76 N/cm (Menorest®). An extremely high adhesion to stainless steel was found for Fem7® (peel force ~ 25 N/cm).

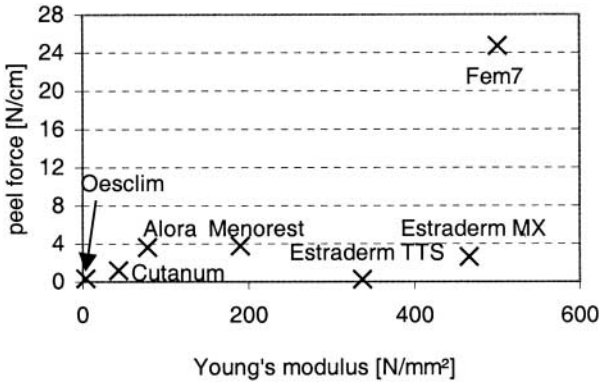

Figure 6. Relationship between Young's modulus and peel force on stainless steel for branded patches.

We evaluated the relationship between the Young's modulus and the peel force. There was no correlation in both cases for laminates (Fig. 5) and branded transdermal patches (Fig. 6).

No correlation was found between Young's moduli and peel force values of laminates. Most of the laminates had a Young's modulus between 44 N/mm^2 (CoTran® 9737 with PA+EO) and 67 N/mm^2 (CoTran® 9726 with PIB). The values for Hostaphan® foils with three of the adhesives (PIB, S, PA) had a Young's modulus higher than 400 N/mm^2.

No correlation was found between Young's moduli and peel force values of branded transdermal patches. The Young's moduli varied over a broad range from 4 N/mm^2 (Oesclim®) to 501 N/mm^2 (Fem7®), but peel forces on stainless steel were nearly in the same range, between 0.25 N/cm (Estraderm TTS® 50) and 3.76 N/cm (Menorest®), with the exception of Fem7®.

Skin Adhesion

Data on adhesion to skin were available for the branded patches only. The data on skin adhesion (%) as derived from the clinical trials (Table 1) ranged between 65% (Alora®) and 98% (Cutanum®) (Fig. 7).

Two 7-day patches are included in this investigation, Cutanum® and Fem7®-50 μg. These patches ranked on top of the clinical performance. Two of the 3-day patches (Estraderm MX® 50 and Oesclim®) have a skin adhesion of nearly the same order. For the

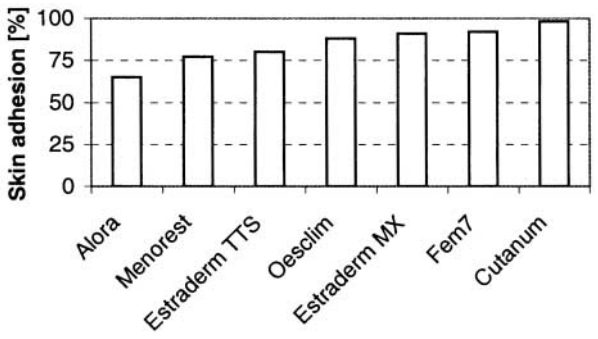

Figure 7. Skin adhesion (%) as derived from the clinical trial (Table 1) for seven branded transdermal patches.

remaining three patches—Alora®, Menorest®, and Estraderm® TTS 50—the skin adhesion was ≤80%.

These data calculated from several clinical trials do not agree with adhesion data performed with the 180° peel test on stainless steel (Fig. 4).

The claim in Ref. 2 that the skin adhesion depends on the Young's modulus has not proved true in our investigations. The value of A_s did not increase with decreasing Young's moduli of the patches. Skin adhesion appeared to increase with increasing Young's moduli (Fig. 8). This could be due to non-illustrated adhesion properties. To verify this, attempts to combine peel data on stainless steel and Young's moduli were made to predict the skin adhesion. We assumed that A_s increased with increasing peel force but decreased with increasing Young's modulus. We used different possible equations, but none proved to correlate with the skin adhesion data. Furthermore, for branded patches, no correlation was found between skin adhesion and peel force on stainless steel. The peel force varied over a broad range (Fig. 9). Patches with the highest peel force (Menorest® and Alora®) showed the lowest skin adhesion.

We compared our peel force data with the suggested peel forces for transdermal patches of at least 0.4 N/cm.[2] Only Oesclim® and Estraderm® TTS achieved peel forces less than this value. Considering this, we expected poor performance for these two patches. Obviously, this is the case with Estraderm® TTS (80% skin adhesion) but not with Oesclim® that has a relatively high skin adhesion (87%). For most of the other patches we obtained peel forces higher than 2 N/cm, so the skin adhesion data were expected to be relatively high. But this was not the case for Alora® and Menorest®. In spite of peel

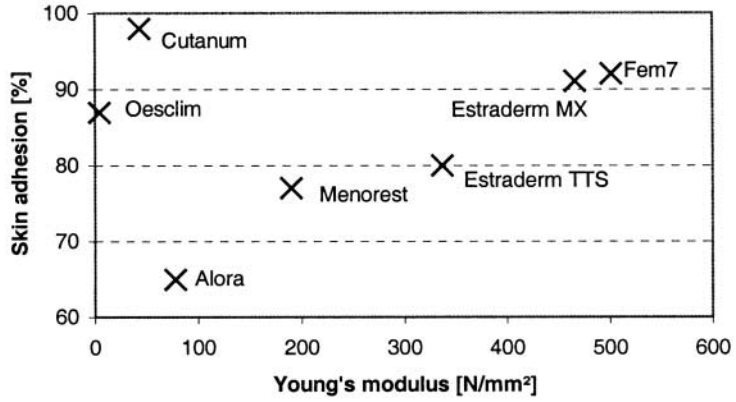

Figure 8. Relationship between skin adhesion and Young's modulus for branded patches.

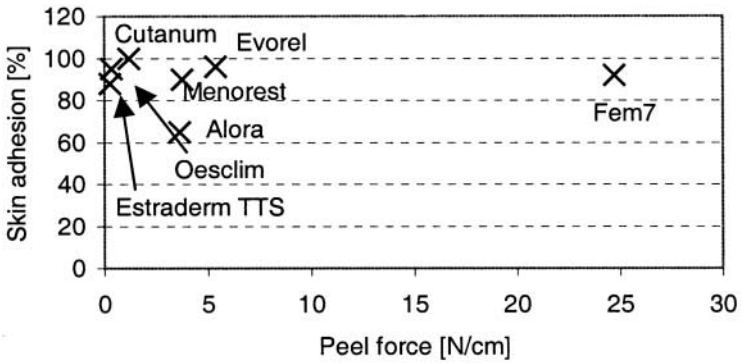

Figure 9. Relationship between skin adhesion and peel force on stainless steel for branded patches.

forces >2 N/cm (3.6 and 3.8 N/cm, respectively), these two patches showed the worst skin adhesion (65% and 77%, respectively).

Obviously, the peel data do not correlate with skin adhesion data. That might be due to several facts. Firstly, skin adhesion data resulted from different studies and were evaluated using different adhesion scores. Secondly, adhesion to skin seems to be a more complex process than adhesion to stainless steel. However, validity as a quality control tool to screen incoming adhesives and monitor batch-to-batch variations may remain.

CONCLUSION

The Young's moduli of the transdermal patches investigated were much higher (10, 100, 1000 times) than those of skin, reported between 0.1 and 0.3 Mpa.[8] Surprisingly, the Young's moduli do not influence the adhesion of the patches, whether to stainless steel or to skin. The adhesion strength on stainless steel does not correlate with that on skin. Consequently, we questioned the use of the peel adhesion test on stainless steel as a reasonable quality control test for the skin adhesion of transdermal patches. Therefore, key parameters should be characterized in the future. Regarding the influence of elasticity on skin adhesion as discussed in Ref. 2, the mentioned profound effect of elasticity on the ability of the transdermal patch to adhere to the skin has not been confirmed. This may be due to the unreliable skin adhesion data obtained from different clinical studies with different evaluation techniques for adhesion.

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