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Research paper

Adhesion testing of transdermal matrix patches with a probe tack test – In vitro and in vivo evaluation

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ABSTRACT

It was the aim of the study to evaluate the suitability of the probe tack test as a method of predicting the long-term adhesion properties of transdermal patches to human skin. Twelve different types of polyacrylate pressure sensitive adhesives have been characterized using the probe tack test. For the analysis of the obtained data a novel procedure was developed that is based on two parameters: the deformation compliance κ and the critical return speed v_c. In addition to the in vitro characterization, the in vivo adhesive properties were investigated in a double-blinded and randomized wear study by eight volunteers for a period of 7 days of wear. The adherent area and the size of the dark ring were defined in a percentage of the patch area by analysing digital photographs. The in vitro data correlate mostly with the in vivo performance of the tested adhesives after 7 days. Accordingly, the probe tack test could be a helpful tool during the development of transdermal patches.

1. Introduction

The adhesion of Transdermal Drug Delivery Systems (TDDS) is one of the most critical parameters for product safety, efficiency and quality. Although several in vitro techniques have been proposed to monitor adhesive performance, e.g. peel adhesion, tack and shear strength, the in vivo human skin testing is still the most reliable method for the evaluation of TDDS [1]. The most established method of quality testing and comparative tests of various transdermal patch formulations is the 180° or 90° peel test from a stainless steel panel [2–5]. Several variations of panel material were investigated (artificial skin materials, HDPE, Teflon, neoprene) [6–13]. However, no correlation with the in vivo adhesive performance has been verified beyond doubt for any of these peel test modifications [1,6,7]. These measurements are focused mainly on initial adhesion for industrial application, rather than the long-term adhesion to human skin. The aim of this study was to investigate whether the probe tack test can help to estimate the long-term adhesion of TDDS to human skin to avoid adhesion problems in an early development stage of patch formulations.

Clinical TDDS studies are mainly focused on medical effectiveness and less on adhesive properties. The FDA provides a scoring system based on the percentaged adherent area of the patch [14]. Guidance for further data analysis and evaluation is not given. In many clinical studies the adherent area is estimated only visually by a specialized person or by the volunteers themselves [15–17]. In addition to the adhesive problems of patches, there is the phenomenon of the so-called dark ring on the skin. This ring is formed mostly by a mix of the adhesive with textile fibres and dust. Cold flow due to low cohesive strength is assumed to be the main reason for this [18]. The dark ring located predominantly under the patch is not only a cosmetic blemish. It decreases the contact area between the drug-loaded matrix and the skin. Therefore there is a connection between the size of the dark ring and the effectiveness of the patch for medical purposes. Unfortunately, this topic is still very rarely investigated.

To evaluate the suitability of the probe tack test as a method of predicting the long-term adhesive performance on human skin, different types of polyacrylate pressure sensitive adhesives have been analysed with both in vivo and in vitro methods. For the analysis of the in vitro data, a new method had to be found. The in vivo adhesive properties were examined in a volunteer study. The in vivo data were evaluated and correlated with the in vitro results.

2. Materials and methods

2.1. Materials

All pressure sensitive adhesives (PSA) used for investigations are polyacrylate adhesives, a kind donation from National Adhesives (Table 1). In this work the Duro-Tak types are named only with the last four numbers of product number (87-XXXX) to avoid redundancy. Duro-Tak 2051/2052 is a blend (1:1). For Placebo

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Table 1
Investigated Duro-Tak types.

Duro-Tak type 87-XXXX	Chemical composition	Functional group	Cross-linker added
900 A	Acrylate	–	Not applicable
9301	Acrylate	–	Not applicable
2353	Acrylate	–COOH	–
2852	Acrylate	–COOH	Cross-linked
4098	Acrylate–vinylacetate	–	Not applicable
2287	Acrylate–vinylacetate	–OH	–
2516	Acrylate–vinylacetate	–OH	Cross-linked
4287	Acrylate–vinylacetate	–OH	–
2051	Acrylate–vinylacetate	–COOH	–
2052	Acrylate–vinylacetate	–COOH	Cross-linked
2196	Acrylate–vinylacetate	–COOH	Cross-linked

patch preparation the Release Liner Scotchpak 9742 (3M, USA, St. Paul, Minnesota) and the backing liner Hostaphan MN med 15 (Mitsubishi Polyester Film Group, Germany, Wiesbaden) were used.

2.2. Probe tack test

The probe tack test has once been developed to replace the commonly used "thumb test" – touching the surface of a pressure sensitive adhesive with the thumb and feeling the force required to break the bond [19]. In the case of the probe tack test, a probe is pushed forward into contact with the adhesive surface and then retracted at a predefined speed (Fig. 1a). The force required to break the bond after a short period of contact is plotted in a force–time diagram.

The probe tack test was performed with the TAXT plus Texture Analyser (Stable Micro Systems, UK, Godalming, Surrey) with the following test parameters: test speed 0.04 mm/s, return speed 0.01–1.00 mm/s, applied force 0.5 N, contact time 1 s, temperature 32 °C, $n = 4$. The cylindrical probe consisted of stainless steel with a diameter of 2.00 mm and a cross-section area of 3.10 mm^2.

In preliminary tests patches consisting of backing liner and adhesive matrix were fixed by double-sided adhesive tape on the measuring table. The applied stress caused partial detachment of the specimen, so that the results were affected. To avoid this problem the PSA were laminated directly on glass using the Erichsen film applicator (Erichsen, Germany, Hemer) and dried 20 min at 80 °C in a drying oven LTU 60/60 (Vötsch Industrietechnik, Germany, Reiskirchen). The final film thickness of all dried adhesives was between 60 and 80 μm. In every case it was determined using the Minitest 600 (Elektro Physik, Germany, Köln), a thickness gauge working on the magnetic inductive principle with tolerance of ±(2% of reading + 2 μm). A ferromagnetic base material is needed for measurement. For this, the PSA were cast on a release liner, transferred to a metal plate after drying and gauged at 12 different points. In preliminary tests the thickness of the film cast on glass was determined by means of topography measurement. The results were comparable with the measurement by thickness gauge.

The results of the probe tack test are influenced by the film thickness. Therefore, the force–time curve was converted into a stress–strain curve with $\sigma = F/A$ (N/mm^2) for tensile stress and $\varepsilon = v \cdot t/d$ for strain. The distance d equates the film thickness of the adhesive and velocity v to the return speed of the probe. The contact area of the probe is assumed to be the cross-sectional area A [20].

The stress–strain curve of the probe tack test (Fig. 1b) is usually characterized by an initial peak and an extended tail, the latter being caused by the formation of fibrils [21]. The first part of the curve is the linear elastic domain [22]. The deformation then becomes non-linear, inhomogeneous and non-reversible [23]. The curve decreases slightly. Common parameters describing the probe tack curve are the initial stress peak σ_P, equated with the yield point, the stress level σ_S at the shoulder, the deformation at the break ε_B and the area under the curve [22,24]. In this study two new parameters are introduced: the deformation compliance κ (mm^2/N) and the critical return speed v_c (mm/s).

2.3. Deformation compliance κ

All Duro-Tak types were evaluated using the probe tack test. Stress–strain diagrams with a return speed of 1.00 mm/s were generated to determine the deformation compliance κ. The curve is divided into peak and tail areas by extrapolating the linear branches of the peak and the tail to a point of intersection (Fig. 1b). As a result, the deformation at the break ε_B can be divided into the parts of the peak and the tail lengths ε_T. The deformation at the break ε_B is determined as strain value at $\sigma = 0.01$ N/mm^2. The deformation compliance κ is now calculated as $\kappa = \varepsilon_T / \sigma_P$, with ε_T for the plastic portion of deformation, and σ_P for the initial stress peak.

2.4. Critical return speed v_c

Several combinations of test parameters for the tack test are described in literature as contact time, return speed and applied force. According to our investigations, the return speed appears to be the most relevant variable. Low speed causes low stress on polymer chains, visible as a smooth decline in the stress–strain diagram. The speed at which the probe can be retracted without a rapid breaking of the fibrils differs from one tested adhesive to another. This speed limit can be regarded as an additional value for characterizing PSA.

To evaluate critical return speed v_c the same adhesive is tested with return speeds in a range between 0.01 mm/s and 1.00 mm/s. The value of 0.01 mm/s is the minimum speed at which the probe can be retracted from the sticky surface by the Texture Analyser.

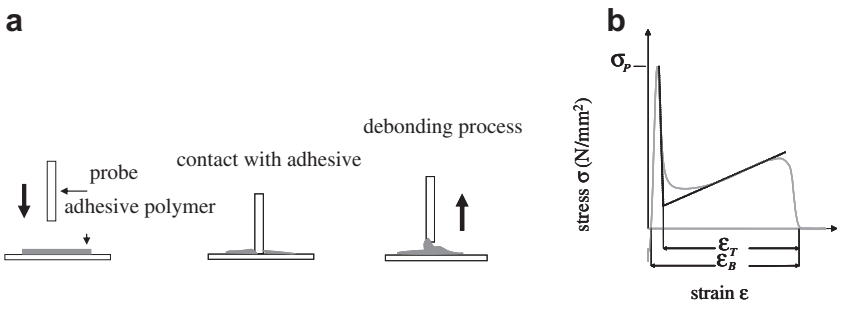

Fig. 1. (a) Technical performance of the probe tack test and (b) stress–strain diagram of the debonding process divided into peak and tail areas by extrapolating the linear branches to a point of intersection with ε_B for the deformation at break, ε_T for the tail fraction of the strain and σ_P for the initial stress peak.

Critical return speed is shown in a curve with a transition from a clear breaking point to a smooth decline in the logarithmic plotting of the stress–strain diagram.

2.5. In vivo human study

The PSA were cast on the release liner using an Erichsen film applicator (Erichsen, Germany, Hemer). After drying for 20 min at 80 °C in a drying oven LTU 60/60 (Vötsch Industrietechnik, Germany, Reiskirchen), the adhesive side was laminated with the backing layer. Placebo patches with an area of 5 cm^2 were punched out. The final thickness of the PSA layer was approximately 70 μm.

The adhesive properties of the 12 Duro-Tak types were investigated in a double-blinded and randomized wear study. Each Placebo patch formulation was tested by eight volunteers. Two equal patches were applied to each upper arm ($n = 16$). Every volunteer tested four different formulations simultaneously. Volunteers were allowed to maintain their normal activity. Digital photographs of both upper arms were taken after the first, the third and the seventh day.

2.6. In vivo data analysis

The adherent area and the size of the dark ring were defined in a percentage of the patch area. To obtain this data, the digital photographs were analysed with the Axiovision (Carl Zeiss Microimaging, Germany, Jena) software. The adherent area was rated with a scoring system, provided by FDA [14]. 0: area ⩾ 90% (essentially no lift off the skin); 1: area 75% to <90% (only some edges lifting off of the skin); 2: area 50% to <75% (less than half of the system lifting off of the skin); 3: area <50% (more than half of the system lifting off the skin without falling off) and 4: patch completely detached off the skin.

The size of the dark ring as a percentage of the entire patch area is scored as follows: 0: area <10% (small dark ring); 1: area 10% to <15% (moderate dark ring); 2: area 15% to <20% (large dark ring) and 3: area ⩾ 20% (unacceptable dark ring).

3. Results

3.1. In vivo characterization of the long-term adhesion

To interpret the adhesion data, the percentage of the amount of patches evaluated with scores of 0 and 1 are summarized, meaning an adherent area of at least 75% is defined as good adhesion. The number of patches with good adhesion is plotted in a diagram against the number of patches with a small dark ring (Fig. 2). The in vivo properties are classified into four groups. In group I more than 50% of all investigated patches have a good adhesion and a small dark ring. This represents the most favorable in vivo result of patch formulations. In group II the adhesion behaviour is still as good as in group I, but the dark ring is more pronounced. In group III adhesion had deteriorated and the dark ring had increased. Group IV characterizes poor adhesion combined with a slightly developed dark ring.

The main focus of this study was the long-term adhesion of TDDS, defined as 7 days of wear. To monitor the adhesion performance, additional photographs of the patches were taken after 1 and 3 days of wearing and analysed by the scoring systems (Fig. 2, days 1 and 3). After the first day in all cases the dark ring is predominantly small. Most adhesives are in group I with the exception of Duro-Tak 4098, 2353, 2196 and 2852 (group IV). On the third day two additional Duro-Tak types (2052 and 9301) changed from group I to group IV, because of decrease in adhesion performance. Duro-Tak 2051 and 900 A changed from group I to group II, which indicates an increase in the dark ring.

After 7 days the adhesives of group I and II showed an increase in the dark ring and a decrease in the adhesion performance (Fig. 2, day 7). Duro-Tak 2051 and 2287 changed to group III. Duro-Tak 2051/2052, 2516 and 4287 remained in group I and Duro-Tak 900 A in group II. The patches with Duro-Tak 2196, 2353 and 2852 completely detached off the skin after 7 days, the dark ring could not be evaluated for these samples. In the diagram the data of the third day were used. Duro-Tak 2052 and 4098 showed the lowest adhesive performance, but the best outcome for the dark ring. In Tables 2 and 3 the scores obtained for the adhesion and the dark ring after 7 days of wear are displayed.

3.2. In vitro characterization and correlation with in vivo results

The stress–strain diagrams of Duro-Tak 2051, 2052 and 2051/2052 with return speed 0.01–1.00 mm/s exemplify the determination of the critical return speed v_c (Fig. 3). Here the critical return speed v_c is 0.90 mm/s for Duro-Tak 2051 and 0.20 mm/s for Duro-Tak 2051/2052. In case of Duro-Tak 2052 no critical return speed can be determined, v_c is <0.01 mm/s.

The deformation compliance κ and the critical return speed v_c were examined for all 12 Duro-Tak types (Table 4). The investigated adhesive types were sorted into groups in accordance with the analysis of their in vivo behaviour.

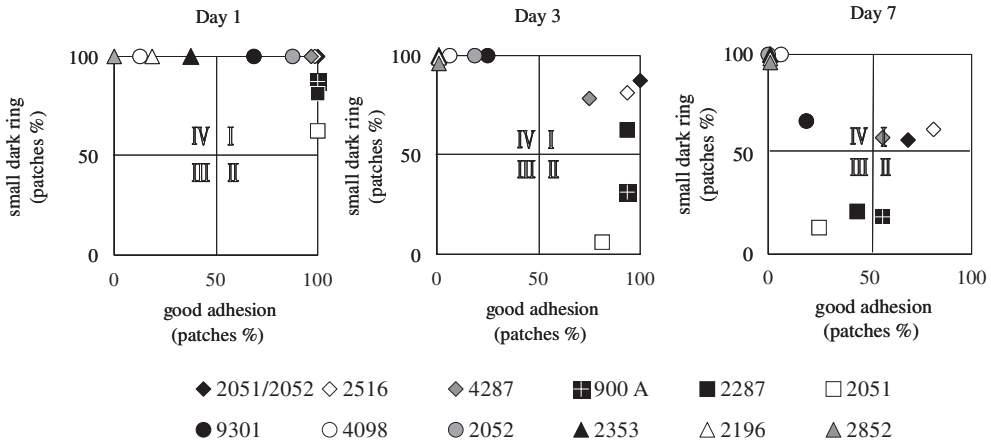

Fig. 2. The number of patches with good adhesion (scores 0 and 1) is plotted against the number of patches with a small dark ring (score 0) for a period of 1, 3 or 7 days of wear.

Table 2
Evaluation of the adherent area of transdermal patches with different Duro-Tak types during in vivo study for a period of 7 days of wear by score system (score 0: ⩾90%, score 1: 75% to <90%, score 2: 50% to <75%, score 3: <50%, score 4: patch completely detached off the skin), $n = 16$.

Duro-Tak	900 A	2051	2052	2051/2052	2196	2287	2353	2516	2852	4098	4287	9301
Score 0	-	-	-	1	-	-	-	-	-	-	1	-
Score 1	9	4	-	10	-	7	-	12	-	1	8	3
Score 2	7	9	4	3	-	6	-	4	-	2	1	2
Score 3	-	2	1	-	-	1	-	-	-	2	2	1
Score 4	-	1	11	2	16	2	16	-	16	11	4	10

Table 3
Evaluation of the size of the dark ring of transdermal patches with different Duro-Tak types during in vivo study for a period of 7 days of wear by score system (score 0: <10%, score 1: 10% to <15%, score 2: 15% to <20%, score 3: ⩾20%), $n = 16$.

Duro-Tak	900 A	2051	2052	2051/2052	2196	2287	2353	2516	2852	4098	4287	9301
remaining patches after 7 days												
	16	15	5	14	0	14	0	16	0	5	12	3
Score 0	3	2	5	8	-	3	-	10	-	5	7	2
Score 1	4	1	-	4	-	3	-	6	-	-	3	1
Score 2	5	-	-	2	-	3	-	-	-	-	2	-
Score 3	4	12	-	-	-	5	-	-	-	-	-	-

A similarity in Duro-Tak types belonging to the same group can be observed in both parameters. A high value for the deformation compliance κ is characteristic for group III, an intermediate value for group I and a low value for groups II and IV. The adhesives in group IV had to be stressed with a very low velocity, maximal 0.10 mm/s. At this speed a clear breaking of the stretched fibrils could be avoided. The adhesives of group III have much more resistance to tensile forces. Duro-Tak 2287 shows a critical return speed of 0.70 mm/s and 2051 one of 0.90 mm/s. Those found in group I and II v_c are mostly in an intermediate range of 0.20–0.40 mm/s with the exception of Duro-Tak 2516. Here the critical return speed is slower than 0.01 mm/s.

4. Discussion

4.1. In vivo data

The adhesive performance underwent a definite change with the wearing period on human skin. All PSA showed very strong initial adhesive properties. A daily application seems to be non-critical for most adhesives. But for long-term therapy, a weekly application would be reasonable. That places high demands on the in vivo behaviour of a patch. A twice weekly application would seem to be a compromise, considering the observed increase in dark ring formation and the deterioration of the adherent area. The patch's intended clinical application period must be taken into account, not only for final in vivo study design, but also for testing, during the development process.

The in vivo study has shown that a given patch formulation has a certain variance in its long-term adhesive performance (Tables 2 and 3). This could be caused by many factors, for example varying skin types and different levels of activity of the volunteers during the study.

The in vivo data show a relation between the adhesive performance and the appearance of a dark ring (Fig. 2). Predominantly, only patches with low adhesion have a small dark ring. It can be concluded that in the cases of the tested adhesives, a patch with good adhesion is always associated with the appearance of a dark ring. Accordingly, during the development of a patch formulation, a balance between the dark ring and the adhesion properties must be found.

The different adhesive properties of the tested Duro-Tak types after 7 days is supposed to be caused by the variance of the viscoelasticity of the polymers. The adhesive film between the skin and

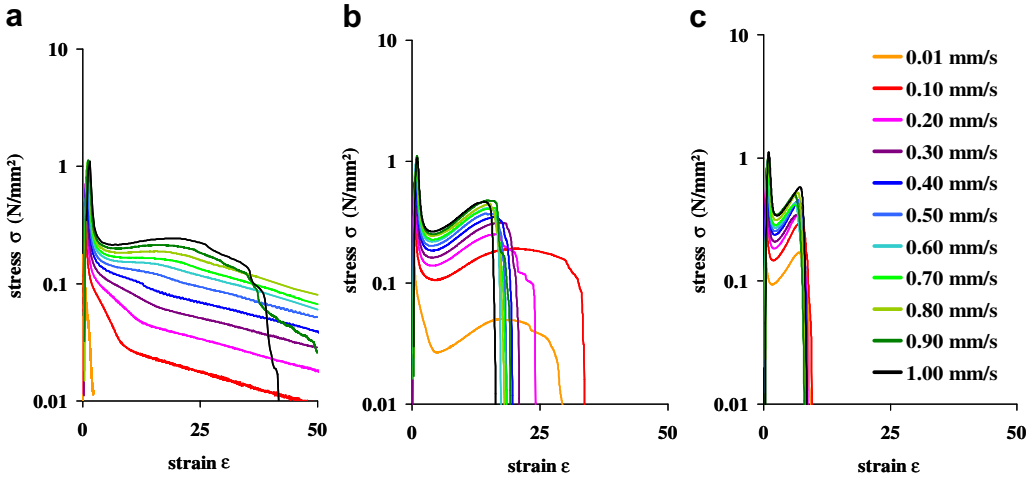

Fig. 3. Stress–strain diagrams in logarithmic plotting with return speed 0.01–1.00 mm/s, (a) Duro-Tak 2051 with critical return speed v_c 0.90 mm/s, (b) Duro-Tak 2051/2052 with critical return speed v_c 0.20 mm/s, (c) Duro-Tak 2052 with critical return speed $v_c < 0.01$ mm/s, $n = 4$.

Table 4
Deformation compliance κ (mean value ± SD) and critical return speed v_c of different Duro-Tak types, sorted in accordance with the in vivo classes, $n = 4$.

Group	I			II	III		IV					
Duro-Tak	2051/2052	2516	4287	900 A	2287	2051	9301	4098	2353	2353	2196	2852
κ (mm²/N) ± SD	16.3	14	12.1	4.3	28.9	31.3	3.4	1.8	6.0	7.1	4.1	2.3
	1.1	1.7	3.0	0.2	2.8	7.1	1.2	0.1	2.0	0.7	0.7	0.3
v_c (mm/s)	0.20	<0.01	0.40	0.30	0.70	0.90	0.01–0.10	0.01–0.10	0.01–0.10	<0.01	<0.01	<0.01

the backing layer of the patch is sheared by skin movement. The matrix must dissipate the stored energy caused by elastic strain to avoid breaking the adhesive bonds [25]. This is represented by the viscose aspect of a viscoelastic system. On the other hand, the elastic aspect is necessary for matrix cohesion.

4.2. In vitro characterization and correlation with in vivo results

In the probe tack test, adhesive types belonging to the same in vivo group show similar in vitro results (Fig. 4). This can be used for a prediction of the long-term adhesion on skin.

Low values for the deformation compliance κ (1.8–6.0 mm²/N), as in group IV, indicate an inadequate adhesion. In contrast to those in group III, the deformation compliance is much higher (28.9–31.3 mm²/N). Here the adhesive performance is also low. A high κ value represents a low cohesive material. This kind of patch produces a large dark ring that minimizes the adhesive area. Group I shows optimal adhesion and an optimal dark ring size. This in vivo behaviour is combined with intermediate values for the deformation compliance κ (12.1–16.3 mm²/N). Duro-Tak 900 A has an intermediate state. The long-term adhesion is very favorable, as in group I, but the dark ring phenomenon is similar to that of group III. The value for κ of 4.3 mm²/N is not intermediate between group I and III, as would be expected. Duro-Tak 900 A can be regarded as an outlier of the in vivo–in vitro correlation. The reason for this is currently unclear and needs to be determined in further investigations.

It turns out that stress–strain diagrams of probe tack test bear some resemblance to stress–strain diagrams obtained from mechanical tensile tests of viscoelastic materials [26]. The debonding process of the probe runs in separate stages and is characterized by extensive cavitation between the probe surface and the film. Polymers with a pronounced plateau in the stress–strain diagram show fibril formation during the separation process [27]. If a polymer is not cross-linked, the adhesive can be stretched without resistance [22]. This is represented by a smooth decline in the stress–strain diagram. In cross-linked polymers, the force for stretching the polymer chains can exceed the interfacial bonding strength between the adhesive and the probe surface or inside the adhesive itself. Consequently the curves have the tendency to form a short plateau followed by a short and clearcut breaking point.

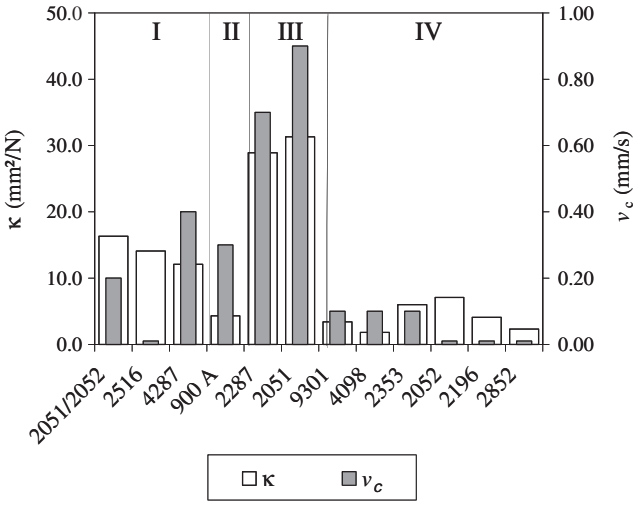

Fig. 4. Graphical comparison of the in vitro and the in vivo adhesion data of different Duro-Tak types: deformation compliance κ and critical return speed v_c, sorted in accordance with the in vivo classes.

From our investigations the probe tack test proved to be a simple and rapid test method to characterize the viscoelastic behaviour of pressure sensitive adhesives. The deformation compliance κ represents the ratio between viscous and elastic behaviour. Adhesives with more viscous properties have a long plateau in the stress–strain diagram meaning high κ values. The adhesive film between the skin and the backing layer is easily sheared by the skin movement. This is visible as a slight displacement of the patch (Duro-Tak 2287 and 2051) after 7 days. Adhesives that form a rigid layer between the skin and the backing foil have a more semisolid character. The shear stress causes a breaking of the adhesive connection, the patch becomes detached. The plateau in the stress–strain diagram is very short, meaning low κ values. The optimal balance between viscous and elastic ratios, generate an ideal adhesive behaviour on skin represented by group I. The Duro-Tak types of this in vivo group could be a basic selection for the development of TDDS for long-term wearing. Of course the influence of the drug and the additives must be explored (amount and chemical composition). To evaluate an unknown PSA by probe tack test, a deformation compliance κ between 12.1 mm²/N and 16.3 mm²/N (group I) is a first indication for long-term adhesion.

The second investigated parameter of the in vitro characterization is the critical return speed v_c. The speed, with which the probe can be retracted without a clear breaking of the adhesive fibrils, appears to be a function of the cohesiveness of the PSA. Like the deformation compliance κ the critical return speed v_c is associated with the viscoelastic behaviour. The correlation with the in vivo results is very similar to the deformation compliance κ. Values below 0.10 mm/s indicate an inadequate long-term adhesion property (group IV). High values (0.70–0.90 mm/s) are typical for adhesives with low cohesion and a large dark ring (group III). A critical return speed of medium range (0.20–0.40 mm/s) is characteristic for the optimal long-term adhesion of patches (group I). Duro-Tak 2516 has an unusual behaviour to this in vivo–in vitro interrelationship, v_c is lower than 0.01 mm/s but the long-term in vivo adhesion is very good. The intermediate position of group II between the favorable long-term adhesion of group I and the pronounced dark ring phenomenon of group III is reflected in the v_c value.

The evaluation of the parameter critical return speed v_c needs several tests with variable film thickness and is less precise than the evaluation of deformation compliance κ. But this parameter can support the in vitro predictability of the probe tack test. The deformation compliance κ as well as the critical return speed v_c each show an outlier, which is dissimilar in both cases. We suggest that both parameters during the development of a matrix patch would be determined, since they are obviously complementary.

The model adhesives used for this research work were polyacrylate polymers belonging to a kit of adhesives being used for the

development of transdermal patches. It must be evaluated in further investigations, whether the method is also applicable to other PSA materials (silicone, polyisobutylene). Another important evaluation would be not only to use other PSA materials but also to use adhesive polymers in the presence of drugs and other additives. Beside the adhesive properties, the pain during removal of the patch is an important parameter influencing patients compliance.

5. Conclusion

The probe tack test with its newly introduced parameters, deformation compliance and critical return speed, can help to determine the cohesiveness of the matrix formulation. The in vitro results correlate mostly with the in vivo performance of the tested PSA after 7 days. Accordingly, the probe tack test can support to estimate the long-term adhesive performance. Of course the predictability of any in vitro adhesion testing method is limited. But the probe tack test is simple, reproducible and independent of skin material. The method could be used not only in quality control and stability testing of TDDS, but also during the development process of transdermal patches.

References

[1] A.M. Wokovich, S. Prodduturi, W.H. Doub, A.S. Hussain, L.F. Buhse, Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute, Eur. J. Pharm. Biopharm. 64 (2006) 1–8.
[2] R. Toddywala, K. Ulman, P. Walters, Y. Chien, Effect of physicochemical properties of adhesive on the release skin permeation and adhesiveness of adhesive-type transdermal drug delivery systems (a-TDD) containing silicone-based pressure-sensitive adhesives, Int. J. Pharm. 76 (1991) 77–89.
[3] D. Dimas, P. Dallas, D. Rekkas, N. Choulis, Effect of several factors on the mechanical properties of pressure-sensitive adhesives used in transdermal therapeutic systems, AAPS PharmSciTech 1 (2000) 16.
[4] J. Fang, S. Chen, Y. Huang, P. Wu, Y. Tsai, In vitro study of transdermal nicotine delivery: influence of rate-controlling membranes and adhesives, Drug Dev. Ind. Pharm. 25 (1999) 789–794.
[5] A. Chiche, W. Zhang, C.M. Stafford, A. Karim, A new design for high-throughput peel tests: statistical analysis and example, Meas. Sci. Technol. 16 (2005) 183–190.
[6] A.M. Wokovich, S.A. Brown, M. Shen, W.H. Doub, B. Cai, N. Sadrieh, M.L. Chen, S. Machado, L.F. Buhse, Evaluation of substrates for 90° peel adhesion – a collaborative study. II. Transdermal drug delivery systems, J. Biomed. Mater. Res. 88B (2009) 61–65.
[7] C. Fauth, S. Wiedersberg, R. Neubert, M. Dittgen, Adhesive backing foil interactions affecting the elasticity adhesion strength of laminates and how to interpret these properties of branded transdermal patches, Drug Dev. Ind. Pharm. 28 (10) (2002) 1251–1259.
[8] J. Renvoise, D. Burlot, G. Marin, C. Derail, Adherence performances of pressure sensitive adhesives on a model viscoelastic synthetic film: a tool for the understanding of adhesion on the human skin, Int. J. Pharm. 368 (2009) 83–88.
[9] P. Minghetti, F. Cilurzo, L. Montanari, Evaluation of adhesive properties of patches based on acrylic matrices, Drug Dev. Ind. Pharm. 25 (1) (1999) 1–6.
[10] P. Minghetti, F. Cilurzo, L. Tosi, A. Casiraghi, L. Montanari, Design of a new water-soluble pressure-sensitive adhesive for patch preparation, AAPS PharmSciTech 4 (2003) 8.
[11] D. Maillard-Salin, P. Becourt, G. Couarraze, A study of the adhesive-skin interface: correlation between adhesion and passage of a drug, Int. J. Pharm. 200 (1) (2000) 121–126.
[12] F. Cilurzo, P. Minghetti, A. Casiraghi, L. Tosi, S. Pagani, L. Montanari, Polymethacrylates as crystallization inhibitors in monolayer transdermal patches containing ibuprofen, Eur. J. Pharm. Biopharm. 60 (2005) 61–66.
[13] A.J. Steven-Fountain, A.G. Atkins, G. Jeronimidis, J.F.V. Vincent, D.F. Farrar, R.A. Chivers, The effect of flexible substrates on pressure-sensitive adhesive performance, Int. J. Adhes. Adhes. 22 (2002) 423–430.
[14] FDA, Center for Drug Evaluation and Research, Skin irritation and sensitization testing of generic transdermal drug products, Guidance for Industry, 1999.
[15] P. Minghetti, F. Cilurzo, S. Pagani, A. Casiraghi, Formulation study of oxybutynin patches, Pharm. Dev. Technol. 12 (2007) 239–246.
[16] P.N. Kotiyan, P.R. Vavia, Eudragits: role as crystallization inhibitors in drug-in-adhesive transdermal systems of estradiol, Eur. J. Pharm. Biopharm. 52 (2001) 173–180.
[17] J. Toole, S. Silagy, A. Maric, B. Fath, E. Quebe-Fehling, P. Ibarra de Palacios, L. Laurin, M. Giguere, Evaluation of irritation and sensitisation of two 50 μg/day oestrogen patches, Maturitas 43 (2002) 257–263.
[18] M. Horstmann, W. Müller, B. Asmussen, Principles of skin adhesion and methods for measuring adhesion of transdermal systems, in: E. Mathiowitz, D.E. Chickering, C.-M. Lehr (Eds.), Bioadhesive Drug Delivery Systems – Fundamentals, Novel Approaches and Development, Marcel Dekker Inc., New York Basel, 1999, pp. 175–195.
[19] D. Satas, Tack, in: D. Satas (Ed.), Handbook of Pressure Sensitive Adhesive Technology, Satas & Associates, Warwick, Rhode Island, 2002, pp. 36–61.
[20] A. Zosel, Adhesive failure and deformation behaviour of polymers, J. Adhes. 30 (1989) 135–149.
[21] D. Dimitrova, D. Johannsmann, N. Willenbacher, A. Pfau, Mesoscopic fibrillation properties of pressure sensitive adhesives based on latex films, Langmuir 19 (2003) 5748–5755.
[22] H.K. Chuang, C. Chiu, R. Paniagua, Avery adhesive test yields more performance data than traditional probe, Adhes. Age (1997) 18–23.
[23] W. Bergmann, Polymerwerkstoffe, in: W. Bergmann (Ed.), Werkstofftechnik, Carl Hanser Verlag, Munich, 2000, pp. 289–383.
[24] A.E. O'Connor, N. Willenbacher, The effect of molecular weight and temperature on tack properties of model polyisobutylenes, Int. J. Adhes. Adhes. 24 (2004) 335–346.
[25] P. Minghetti, F. Cilurzo, A. Casiraghi, Measuring adhesive performance in transdermal delivery systems, Am. J. Drug Deliv. 2 (2004) 193–206.
[26] A. Zosel, The effect of fibrilation on the tack of pressure sensitive adhesives, Int. J. Adhes. Adhes. 18 (1998) 265–271.
[27] B. Lestriez, H. Lakrout, A. Chiche, A. Roos, C. Creton, Probe tack tests as a characterization tool in pressure-sensitive-adhesives, in: Proceedings of the PSTC Technical Seminar TECH XXIV, Orlando, USA, 2001.