Expert Opinion

Adhesive properties: a critical issue in transdermal patch development

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Introduction: Transdermal patches and medicated plasters (patch) represent well-established prolonged release dosage forms. Even if satisfactory adhesion to the skin is strictly linked to the efficacy and safety of the therapeutic treatment, nowadays numerous reports of *in vivo* 'adhesion lacking' are still addressed to regulatory agencies. The adhesive properties of a patch should be characterized considering i) the ability to form a bond with the surface of another material on brief contact and under light pressure (tack); ii) the resistance of the adhesive to flow (shear adhesion); and iii) the force required to peel away a patch from a surface (peel adhesion).

Areas covered: In this manuscript, the most widely used methods to measure adhesive properties during development studies are described, along with the quality control of patches. The influence of formulative variables on patch adhesive properties, and their possible relationship with the *in vivo* adhesion performances, is also discussed.

Expert opinion: The Pharmacopoeias should consider the opportunity of introducing compendial testing to assay the quality of adhesive patch properties, and regulatory agencies should issue proper guidelines to evaluate these features during development.

Keywords: adhesive properties, medicated plaster, peel adhesion, shear adhesion, tack, transdermal patch

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1. Introduction

Drugs are normally applied on the skin either for the treatment of systemic pathologies or localized diseases in an attempt to limit blood levels of the active ingredient. In the last decades, bioadhesive dosage forms, the patches, have been gaining an increasing interest as an alternative to semisolid dosage forms due to the possibility of prolonging the drug release over a period of time up to 7 days and predetermining the administered dose and the area of application. As differences exist in therapeutic goals pursued administering a drug onto the skin, three different monographs are reported in the European Pharmacopoeia (Ph. Eur.). The 'Transdermal patches' monograph [1] refers to drug delivery systems intended to be applied to the unbroken skin in order to deliver the active substance(s) to the systemic circulation after passing through the skin barrier. In the other two monographs, patches are reported to maintain the active substance(s) in close contact with the skin such that these may be absorbed slowly, in order to guarantee a regional effect, or act as protective or keratolytic agents (medicated plasters) or to administer a drug to skin such that it may act locally (cutaneous patches) [2].

The Japanese Pharmacopoeia (JP) distinguishes between plasters intended to locally release the active ingredient [3] and transdermal systems assuring a systemic effect [4].

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Article highlights.

- Transdermal drug delivery systems in the form of patches have been available on the market for four decades, but concerns about their adhesion to skin and, therefore, the efficacy and safety of the therapeutic treatment still persist.
- The fulfilled *in vitro* evaluation of a patch adhesiveness requires the technological determination of three different properties: tack, shear adhesion or holding power and peel adhesion.
- The addition of additives (e.g., active ingredients, skin penetration enhancers, stabilizers) to the adhesive matrix determines unpredictable variation on the patch adhesive properties.
- Technological assays intended to establish relationships between the *in vivo* patch adhesive performances and the *in vitro* quantitative determinations should be developed.
- Pharmacopoeias should introduce at least one technological assay to test the patch adhesive properties as well as regulatory agencies should consider these features in issuing guidelines.

This box summarizes key points contained in the article.

According to the United States Pharmacopeia (USP), 'transdermal systems' [5] are designed to deliver the drug(s) through the skin to the systemic circulation. However, in the note it is also specified that patches intended to localize the effect of drugs are defined traditionally as 'plasters' or 'tapes.'

Even if the adhesion of the patch to the skin is critical to assure the efficacy of the therapeutic treatment and JP and Ph. Eur. monographs clearly state that a patch has to adhere to the skin, no compendial assays aimed to verify the adhesive properties quality of a patch is described.

Generally speaking, adhesion is guaranteed by a specialized class of materials called 'pressure-sensitive adhesives' (PSAs) that are defined as adhesives capable of bonding to surfaces with the application of light pressure and, when removed, do not leave any visually noticeable residues. A PSA can be used as main constituent of the formulation (i.e., it serves as a carrier for the active ingredient, assures the control of drug release and, at the same time, confers adhesion properties to the dosage form) or merely added to assure the intimate contact between the dosage form and the skin. Patches can be classified as matrix (drug-in-adhesive) systems, or reservoir, or membrane-controlled systems [6].

According to the performance characteristics of the PSAs, patches can be classified into matrix (drug-in-adhesive), or reservoir, or membrane-controlled systems [6]. Since the first configuration is currently likely to be favored in the patch design, PSAs should satisfy peculiar requirements. Indeed, besides being biocompatible, a PSA should be also physically and chemically compatible with drugs and other excipients and/or additives and assure sufficient cohesive properties at the required thickness.

In this paper, the adhesive properties of patches and the PSAs used in their development are briefly described. Of particular interest are considered the methods commonly used to measure patch adhesive properties during product development and quality control, attempting to evidence possible relations to the *in vivo* adhesion performances. The impact of the main formulative variables on the patch adhesive properties is also discussed.

2. Patch adhesive properties and assays

The fundamental features of patch adhesion are described by the following terms. 'Tack' relates the ability of an adhesive to form the initial bond with an unlike substrate on brief contact and under light pressure. 'Shear adhesion' or 'holding power' defines the resistance of the matrix to flow. 'Peel adhesion' is referred to the force required to peel away the patch from an adherend.

Usually the patch is carefully applied onto the skin and, therefore, low-tack PSAs are required. The shear adhesion property has to guarantee that the PSA will remain attached to the skin for a specific period of time despite tangential stresses caused by both body movements and cloth frictions. Finally, the peeling-off procedure should be ease and painless, without leaving patch residues and causing skin damages.

These features depend on both the critical surface energy and the viscoelastic properties of PSAs. By separating PSA adhesion in bonding and debonding steps, two mechanisms are involved: the former is due to the viscous flow proceeding by biased diffusion via free volume and the latter is caused by the elastic distortion, which stores free energy [7].

2.1 Rheological properties

PSAs are viscoelastic materials and, therefore, their adhesive properties are strictly related to the solid- and liquid-like behaviors that are dependent on frequency of the applied stress at a given temperature. Dynamic mechanical analysis (DMA) is considered the technique of choice to characterize the rheological properties of this family of materials, and the measurements are usually carried out on circular specimen obtained by solvent evaporation or melting.

The output of stress–strain measurements is commonly made in regard to the modulus of the material, which is found by dividing the stress by the strain. The result gives the complex modulus (G*) of the material:

$$G^* = G' \cdot \sin(\omega t) + G'' \cdot \cos(\omega t),$$

where G′ is the elastic or storage modulus and G″ is the viscous or loss modulus. The values of these two moduli can be used to discuss the behavior of PSA under stress. If G′ > G″, then the material is more solid than liquid. The converse is also true. The ratio between the loss and storage moduli (G″/G′) gives the useful quantity known as the loss tangent (tan δ), which is a measure of the amount of

deformational energy that is dissipated as heat during each cycle. The tan δ values allow the full characterization of the PSA rheology as this output is closely related to its glass transition temperature.

Frequency-dependent data at different temperatures can be superimposed to yield the desired master curve over an extended frequency window and at a reference temperature range. In this way, it is possible to describe the dependence of these moduli as a function of the oscillation frequency, which is related to the initial bonding or tack, shear adhesion and peel adhesion [8].

Initial bonding typically occurs at low frequencies and the PSA liquid-like nature predominates since it must wet the substrate; therefore, low values of G′ and tan δ peak are desirable [8]. According to the Dahlquist's criterion of tack, PSAs require a G′ value determined at 1 Hz, lower than 0.1 MPa, in order to bond properly to an adherend surface [9].

Conversely to tack, shear adhesion occurs at slightly higher frequencies and requires high values of G′. Moreover, it was demonstrated that shear strength of the adhesive is related to the plateau modulus of the master curve: the longer the rubbery plateau modulus, the higher the shear resistance.

Debonding process occurs at high frequencies and requires high cohesive strength, in other words a solid-like behavior. Therefore, the viscous modulus and the elastic modulus should predominate at low frequencies (G″ > G′) and at high frequencies (G″ < G′), respectively. As an example, the rubber-like PSA tack occurs at low frequencies in the range from 0.005 to 0.05 rad/sec. Shear resistance is a slightly high-rate process ranging from 0.05 to 0.5 rad/sec. Peel adhesion, which is a typical high-rate process, takes place in a range between 100 and 1000 rad/sec [7].

Even if the rheological characterization is very useful in the PSA development, a true relationship between the quantitative determination of the adhesive properties of final patch and viscoelastic measurements has not yet found, since tack, shear adhesion and peel adhesion properties are strongly influenced by surface properties and backing layer mechanical properties. As a matter of fact, the peeling performances of a patch can be related to the rheological pattern of the PSA when the former is applied on a rigid adherend and the latter has a well-defined structure. In the presence of a flexible adherend with a low surface energy, such as the human skin, the debonding mechanism becomes so complex to make difficult the elaboration of theoretical models. Consequently, contrasting opinions on the power of the rheological analysis in providing provisional information on patch adhesion have been reported [8,10,11].

2.2 Tack

The initial bonding of a PSA onto an adherend typically occurs in a very short time, usually fraction of seconds [12], and is determined not only by rheological properties at low frequencies, but also by molecular interactions at the adhesive/adherend interface. In particular, when the surface energy of the PSA is much lower than that of the adherend, the PSA performance is primarily governed by the viscoelastic properties of the adhesive material (the rate of wetting), while for low-energy surfaces the wetting of the substrate depends on the PSA critical surface tension, which usually is in the 28 – 32 dyne/cm range. The lower the critical surface value of the adherend, the worst the wetting and the lower the tack. The skin surface energy is related to its hydrolipidic balance and the values reported in literature ranged from about 25 dyne/cm for dry skin to 56 dyne/cm increasing the relative humidity and temperature of the skin [10,13,14]. Therefore, PSA tack performances are strongly influenced by gender and age as well as physiopathological conditions.

However, a patch requires low tack values as it is applied on the skin with accuracy.

Since the time required for obtaining the optimum adhesion is difficult to evaluate, the tack methods measure the force of debonding after a short contact time and applying a light pressure. Standard tack test methods fall in the following categories [15]. The rolling ball tack tests combine the bond making and breaking processes. In this test, the motion of a stainless steel ball rolling down on an incline is arrested by coming into contact with a horizontal upward-facing patch at the bottom of the track. The distance taken for the adhesive layer to halt the ball (with a specified initial momentum, controlled by the height and angle of the incline) is measured as tack. Short stopping distances are equated with high tack, even if there is no proportion to the ratio of distance.

The probe tack tests are intended to measure the force required to separate the probe from the adhesive surface after applying a light pressure. Hence, tack is expressed as the maximum value of the force required to break the bond after a short time of contact.

The loop tack tests define tack as the force required to separate, at a specified speed, a loop made by clamping the ends of a patch strip that has been brought in contact with a specified area of a defined surface.

2.3 Shear adhesion or holding power

Shear adhesion reveals the resistance of a PSA to tangential stresses and, therefore, the cohesion of the matrix [16].

The shear adhesion methods measure the force required to pull a standard area of a patch from a standard flat surface (adherend plate) in a direction parallel to the surface to which it has been affixed. These static tests indirectly quantify the force required to skid the patch on the adherend plate by determining the time necessary to remove a standard area of the patch from the adherend plate under a standard load [15]. In the holding power tests, the adhesive should fail cohesively, leaving an adhesive layer on either the adherend

plate or the backing layer. Only if this mode of failure occurs, the results can be considered a true measure of the internal strength of the adhesive. The higher the adhesive thickness, the higher the number of shearing layers and, therefore, the lower the matrix cohesion. So the holding power is related to matrix thickness of patches by an exponential relationship [17,18]

2.4 Peel adhesion

Among the key attributes of patches, the peeling-off plays a crucial role as the higher the peel adhesion, the more painful the removal. Peel resistance should not be assumed as an expression of the strength of the adhesive bond because this parameter does not necessarily relate to the intrinsic adhesiveness. The detachment is a complex process that involves the extension and the bending of the patch matrix and the backing layer prior to the separation. Hence, the overall force required to peel a patch off from the adherend is decades higher than that necessary to hold it in place [19].

The different modes of failure of patches from a rigid surface can be considered as an index of the cohesion of the matrix and the adhesion to the backing layer (**Figure 1**). Generally speaking, when the patch is peeled away, it is expected to strip cleanly from the adherend (**Figure 1**, case I), leaving no noticeable residues [15,20].

The method to assess adhesion is selected on the basis of the type of the stress applied in the specific exercise. A comprehensive description of the methods proposed by the adhesive tape associations had been previously reported [15]. Briefly, the standardized testing procedures require the application of a patch strip to a rigid standard test plate (adherend plate), generally made of stainless steel, applying a definite pressure to assure the contact; after a prefixed time, the strip is removed from the plate at a specified angle (i.e., 180° or 90°) and speed (i.e., 300 mm/min).

During the detachment process, the stress is transmitted through the adhesive matrix to the backing layer. Thus, the formulation composition, which affects flexibility and elongation, and the thickness of the backing layer, can cause differences in behavior during the detachment. Indeed, as the backing layer thickness and/or rigidity increases, the energy required to deform the backing layer itself increases. At the same time, the strip used in the peel test forms a larger moment arm determining a lower peel force and counteracting the energy dissipated in the backing layer deformation. The influence of the backing layer characteristics is less pronounced in a 90° peel adhesion test with respect to a 180° peel test, since a lower energy is required to deform the backing layer. Moreover, tests carried out at two peeling angles provide different information, since the 180° peel is a combination of tensile and shear processes, while the 90° peel depends only on tensile events; therefore, the standard deviations of data obtained by measuring the peel force at 90° is lower than that at 180° [21]. It is also to be noted that while both the 90° and 180° peel tests are being pulled at the same rate, the peel front of the 90° test is moving at twice the rate of 180°. So the adhesion results of the two peeling angles are not truly comparable. As an example, in the case of patches prepared using a neoprene rubber PSA, the 90° test allowed to discriminate the influence of the PSA thickness and the peel strength resulted about an order of magnitude higher than the experiments performed at 180° [22].

As in the case of holding power, the matrix thickness influences the peel adhesion of patches, but in a different way. The thicker the adhesive matrix, the higher the peel strength [23-25] leveling off at some thickness [17,22]. This feature can be explained considering the double effect of thickness on the peel force. Indeed, thicker PSAs increase the volume of matrix undergoing deformation and, therefore, increasing the peel force. But in patches at elevated thickness, because of an increase in the angle and the moment arm, the peel force decreases causing a reduction in the detachment work. At certain critical value of the matrix thickness, the PSA deformation in the crack area is large enough to make a further increase in thickness no longer noticeable.

3. PSAs used in pharmaceutical field

The roots of PSA reside in the half of '800 when adhesive dressings based on the use of sticky natural rubbers were proposed in medical field [25]. The development of synthetic tackifyng resins permitted to improve the quality of the adhesive. In particular, the first uses of synthetic PSAs, namely oxidation-resistant acrylic copolymers, were possible only when their purity was enough to guarantee biocompatibility with the skin. Indeed, the features that make a PSA suitable for patch development are the following: i) to adhere to the skin; ii) not to lead to itching or irritation of any kind; iii) to be comfortable to wear; iv) to allow the removal without excessive trauma; v) to leave no residues on skin on removal; and vi) to be chemically and physically compatible with a wide range of drugs and excipients.

PSAs are classified according to their chemical structure [26] or the physical form in which they are supplied. In the latter case, PSAs fall into three broad product categories: solvent based, water based and hot-melt. Solvent-based PSAs are traditionally used in patch production, even if water-based and hot-melt PSAs are more beneficial with regard to skin irritation, sensitization and environmental contamination risks. Nowadays, acrylics- and silicone-based PSAs have been largely replaced by polyisobutylenes (PIBs) due to the reduced allergenicity. Other materials frequently used in patch formulation include hydrocolloids [26], that is, PSAs containing large amount of water [27-29] and matrices that acquire adhesive properties as a result of their moisture content [30].

3.1 PIB-based adhesives

PIB-based adhesives (PIB-PSAs) were used in the earliest traded transdermal patches delivering scopolamine [31]. PIB-

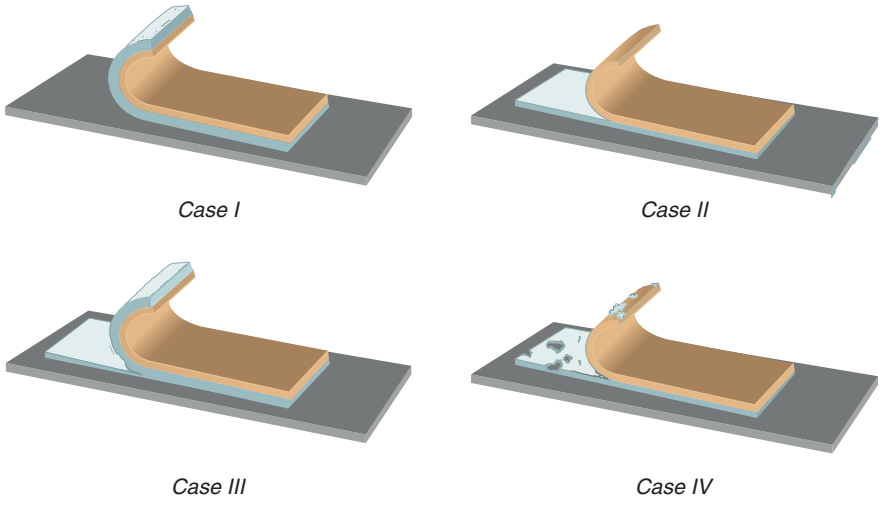

Figure 1. Patch modes of failure. When a patch is peeled away from an adherend, four types of failure can occur. Case I (adhesive failure) is the only acceptable form of patches. When the pressure-sensitive adhesive does not strictly adhere to the backing layer, it may transfer to the adherend, leaving no matrix on the backing layer (case II). Case III refers to what happens when the matrix has good adhesive strength but poor cohesive strength. Case IV is a combination of adhesive and cohesive failure at the same time. The shift from one to another type of failure is affected not only by additives but also by peel rate [20].

PSA suitable for the production of patches can be compounded by blending high- and medium-molecular-weight PIBs, or adding low-molecular-weight polybutylene to this blend [26]. The former formulation is characterized by low peel adhesion values, which decrease as the percentage of the medium-molecular-weight PIB increases. In the latter, the use of low-molecular-weight polybutylene permits to expand the formulation range of the PIB blends conferring to the matrix adhesive properties in terms of tack and peel adhesion [32].

The main disadvantages in using PIBs are related to their easy oxidation and low air and water vapor permeability [32]. The latter feature can be favorably exploited to enhance the drug flux through the skin; on the other hand, the skin maceration can occur, especially when the patch remains in the same position for prolonged period of time [33,34].

3.2 Acrylic-based adhesive

Acrylic-based PSAs are obtained by combining 'hard' and 'soft' monomers [26] at different ratios in order to tune up the final characteristics of the polymer. A third monomer can also be added to improve cohesive properties of the matrix. The large variety of substituted monomers (**Table 1**) allows the incorporation of specific functional groups into the acrylic-based adhesives as well as the synthesis of polymers having versatility in physicochemical properties. Due to the presence of saturated functional groups, the acrylic-based PSAs are more resistant to oxidation with respect to PIB-PSAs; moreover, they are colorless, transparent and do not turn yellow on exposure to sunlight [35].

3.3 Silicon-based PSA

Silicon-based PSAs are made up of a long chain polymer (polydimethyl siloxane) and a silicate resin [36]. The resin has a high glass transition, while the polymer has a notably low glass transition. The raw material is provided as a mixture of these components and the adhesive properties of the final product depend on their ratio. Since the silanols of such PSAs are susceptible to react with amines, several products have been trimethylsilylated to improve the chemical compatibility and, therefore, patch stability in the presence of cationic drugs and excipients [37]. The silicon-based PSAs excel in drug diffusivity [38,39], but at the same time a pronounced tendency to drug crystallization was reported [40].

3.4 Other PSA

The main families of PSAs present several drawbacks related to their chemical structures. As a matter of fact, PIB-PSAs are provided as dispersions in aromatic solvents due to the apolar nature and the requirement of mineral oil as plasticizer, and their use is limited only to low polar drugs. The selection of suitable monomers in acrylic-based PSAs allows the synthesis of copolymers tailored on the basis of drug solubility and adhesive properties, but at the same time the safety of the novel excipient has to be assessed in *in vivo* studies. The disadvantages of silicon-based adhesives are related to drug physical stability [38,40,41] and high cost.

Therefore, aiming to solve these issues and overcome the intellectual property barriers, novel families of PSAs have been developed. Besides the synthesis of new polymers [42], another strategy is based on the exploitation of the peculiarities of pharmaceutical

Table 1. Monomers in common use for the preparation of acrylic pressure-sensitive adhesive copolymers and their glass transition (T_g) values.

Soft monomers	T_g (°C)	Hard monomers	T_g (°C)
Butyl acrylate	-54	Methyl methacrylate	105
Isobutyl acrylate	-40	Vinyl acetate	29
2-Ethyl hexyl acrylate	-85	Styrene	100
Ethyl acrylate	-22	Acrylonitrile	100

excipients used with different purposes. Among them, polyvinylpyrrolidone (PVP) [43], poly(methyl methacrylate)s [44-46] or mixtures thereof [30,33,47] are commonly used because of their well-recognized biocompatibility and safety, even if additives [42,44,48] and/or chemical cross-linking agents [49] are required to provide them appropriate adhesive properties.

More recently, PSAs containing a large amount of water are gaining interest in transcutaneous vaccination or administration of proteins by mean of iontophoretic patches. The application as wound dressing and electrically conductive pads was also reported [50]. These types of hydrophilic PSAs consisting of swollen polymers require a chemical or photo cross-linking to increase their very low creep resistance [51,52]. Very few investigations deal with alternative strategies in order to avoid a final curing, which could determine a physical or chemical instability of the loaded drugs. As an example, Zhang and coauthors proposed a hydrophilic PSA containing about 25% w/w water suitable to deliver ibuprofen and salicylic acid by blending PVP and lactide oligomers [27,28]. A poly(sodium methacrylate, methylmethacrylate) PSA containing a larger amount of water (up 40% w/w) was also proposed [29] to administer proteins or hydrophilic drugs.

4. Prediction of patch *in vivo* adhesive performances

During clinical studies, the *in vivo* adhesive performances of a patch are usually evaluated calculating the percentage of dosage form remained attached to the skin over the entire period of application, namely the so-called patch survival rate [53]. More appropriately, it has been proposed a scoring system based on the observations regarding the permanence of the patch, the behavior during detachment and other subjective considerations of the users/patients [38]. The FDA suggests an arbitrary adhesion scoring system in which the volunteer/patient selects one of the following scores:

- Score 0: 90% adhered (essentially no lifting off of the skin);
- Score 1: 75 to 90% adhered (some edges only lifting off of the skin);
- Score 2: 50 to 75% adhered (less than 50% of the system lifting off of the skin);
- Score 3: < 50% adhered but not detached (more than 50% of the system lifting off of the skin without falling off); and
- Score 4: patch completely off the skin. [54].

The feasibility to elaborate an *in vivo* quantitative measurement of the patch adhesion to the skin was also studied adapting assays that generally are carried out to determine the peeling force [55,56], or the tackiness by quick stick test [57], or modified probe tack tests [58]. In the last case, the stress–strain curves that are generated on the patch removal are registered by means of a dynamometer connected to the patch sample applied on the forearm, or the dorsal side of the hand, of volunteers. Raynaud and coworkers reported a deeper insight on the *in vivo* adhesive performances of a testosterone transdermal patch [59]. The adhesion was qualitatively and quantitatively determined by a peel test performed at the standard peel rate of 300 mm/min and an inclination of 135°. The quantitative analyses evidenced a strong dependence of the peel strength on the application site according to the following rank order: thigh > lower back > arm, other than the experimental setup [59].

The *in vivo* evaluations of the adhesiveness present ethical issue due to the possible safety risks related to the drug adsorption and, therefore, these tests should be performed only using the optimized formulation and preferably during clinical study, even if this approach can give bias problems.

To reduce the *in vivo* studies, several efforts were made to propose *in vitro* assays drawing relationship between the *in vivo* performances and the *in vitro* quantitative determinations.

The experimental parameters, such as removal speed and/or the adherend material, were varying in order to improve the significance of the *in vitro* tests. It was demonstrated that besides the 300 mm/min proposed by standardized tests of the adhesive tape associations [15], the peeling-off at slower rate (i.e., 100 mm/min) better represents the patch removal rate from the skin [20]. Furthermore, if the detachment of the patch occurred cohesively (**Figure 1**, case I), the use of a peel rate lower than 300 mm/min generally leads to a decrease in the peel strength [60]

The peel adhesion values determined *in vitro* by using a stainless steel plate could not be correlated to the *in vivo* performances of patch [61], because of the great difference in the interface condition between the patch and the adherends, namely the skin (28 – 29 dyne/cm) [13] and the stainless steel plate (40 dyne/cm) [62]. Some authors suggested the use of poly(tetrafluoroethylene) (PTFE) [10,63] or polyethylene (PE) [62] plates. The former material permitted to establish a good relationship between the *in vitro* and *in vivo* data by peel adhesion test on silicon-based PSA [10]. The latter provided contrasting results depending on the PE density. The *in vitro* peel force required to remove a medical tape from human skin from cadaver resulted generally closer to that registered using high-density PE plate than that determined using stainless steel [64]. Low-density PE seemed to better

discriminate different methacrylic patches with respect to stainless steel [62]. On the contrary, the stainless steel had a greater discrimination for transdermal patches than high-density PE [65].

The general consideration that can be withdrawn is that the use of materials with energy surface lower than stainless steel can allow obtaining data closer to those of the human skin. Nevertheless, a true relationship was not found since other variables play a key role in the determination of patch adhesion on and detachment from the skin. For instance, it is difficult to individuate an artificial material that is able to properly simulate the continuous variations of skin humidity, which reflects on the critical surface tension, surface roughness and peculiar mechanical properties with particular emphasis on its deformability.

The effects of relative adherend humidity on peel adhesion performances can be studied by using collagen-coated plate [50].

Skin deformability is probably the most critical issue to consider in the development of *in vitro* tests reliable to predict the *in vivo* performances, because it is a high-compliant substrate. When a patch is peeled off, not only the detachment angle and the tensile strength of the patch, but also the tensile deformation, bending stiffness and substrate deformation have to be considered.

The stress distribution on skin deformation was measured *in vivo* by tension, torsion, suction and indentation tests [66-69]. These data were recently used to elaborate skin models for adhesion test, which kept into account the skin deformability [22,70-72] and rugosity [73,74].

Deformable materials were studied as skin surrogates for peel adhesion or probe tack tests [22,60,70,75]. The work expended in the patch detachment includes the adherend deformation, other than the surfaces separation, adhesive layer deformation, and patch stretching and bending. The force required to achieve the maximum extension, which is generally quite low (1.7 N), depends on the peel contact angle [76]. The production of a substrate with a Young's modulus (about 7 – 10 kPa) [77] close to that of human skin would better discriminate patch performances including the adhesive/cohesive shift as a function of peel rate and application time [70].

The so-called dark ring on the skin is a less frequently studied issue related to the prolonged application of patches onto the skin [78] and due to the low resistance of a PSA to the tangential stresses caused by the body movement. In this case, the patch can ooze or leave adhesive residues on its outside edges after skin application [20]. Beside of being un-esthetical, as these adhesive residues can collect dirt and textile fibers, this phenomenon causes an alteration of the patch/skin contact area and, consequently, can determine an alteration of the drug absorption especially for long-term applications. The possible correlation among the *in vitro* adhesion properties and the *in vivo* performances of patches over a 7-day period of application can be established by the probe tack test. Gutschke *et al.* drew a good relationship between the 'dark ring on the skin' and the deformation compliance extrapolated from the stress–strain curves [78].

5. Adhesive properties and formulation studies

The formulative studies aim to obtain stable patches able to assure the maximum flux of drug through the human skin and a suitable patch/skin adhesion. High fluxes are required to administer drugs by means of a patch with discrete dimension: the higher the flux, the lower the patch surface, the higher the patient compliance.

Among the most critical formulative variables influencing the patch adhesive properties, there are worthy of carefully selection: i) the type and concentration of additives, ii) the matrix thickness, which is correlated to the active ingredient dose [17] and, eventually, the drug penetration enhancement [57] and iii) the backing layer [61,62].

The addition of drugs or other excipients, such as penetration enhancers, drug crystallization inhibitors, antioxidant and/or preservatives, can determine a modification of the rheological characteristics of the PSA itself and, therefore, can cause an alteration of the adhesive properties (**Table 2**).

Generally speaking, when a substance is added to a PSA, an unpredictable alteration of the adhesive properties can occur due to its plasticizer/antiplasticizer effect. As an example, the loading of piroxicam in a poly(amino methylmethacrylate) (PAMA)-based PSA decreased the peel adhesion strength because the drug probably caused an increase in the glass transition temperature of the polymer. To counterbalance this effect, the amount of plasticizer loaded in the PAMA matrix was increased [44]. Meanwhile the peel adhesion of analogous patch matrices was not significantly affected after loading coumarin [20]. The addition of captopril ethyl esters to acrylic-based PSA modified the adhesive properties as a function of the drug/PSA ratio: the adhesion work measured by the probe tack test increased increasing the drug content until a maximum value; afterward further addition caused a decrement [79]. The loading of miconazole nitrate in a methacrylic-based PSA significantly decreased both peel adhesion [80] and shear adhesion values [17]. When benzotropine was introduced in acrylate-based PSA, a progressive increase in the peel force was concomitant to the reduction in both tack and shear strength [81].

In general, these effects can be attributed to variation on the entanglement among polymer chains in presence of a drug acting as plasticizer. To counterbalance the unpredictable effects caused by active ingredients, the possibility to modify adhesiveness by changing ratios among polymeric components as well as between plasticizer and tackifier was also investigated [44,48,82,83]. The effects of triacetin on adhesion strength of PAMA-based PSA were investigated [84]. Triacetin or citric acid ester resulted suitable to modulate the properties of a poly(methylmethacrylate ethylacrylate)-based PSA, which

Table 2. Effect of pressure-sensitive adhesive (PSA) additives on adhesive properties of patches.

Type of additive	Additive name	PSA type	Investigated adhesive property	Effect on the adhesive properties	Ref.
Active ingredient	Piroxicam	Acrylates	Peel adhesion	Reduction	[44]
	Coumarin	Acrylates	Peel adhesion	none	[20]
	Captopril ethyl esters	Acrylates	Tack	Increase up 13.3%, then decrease	[79]
	Miconazole	Acrylates	Peel adhesion	Reduction	[80]
	Miconazole	Acrylates	Shear adhesion	Reduction	[17]
	Benztropine	Acrylates	Peel adhesion	Increase	[81]
		Acrylates	Tack	Reduction	
		Acrylates	Shear adhesion	Reduction	
	Nicotine	Acrylates	Peel adhesion	Increase	[48]
			Shear adhesion	Reduction	
	Diclofenac	Acrylates	Peel adhesion	Reduction	[48]
			Shear adhesion	Reduction	
Plasticizer	PEG 200	Acrylates	Peel adhesion	Increase	[82]
	Propylene glycol	Acrylates	Peel adhesion	Increase	[82]
	Diethyl phthalate	Acrylates	Peel adhesion	Increase	[82]
	Triacetin	Acrylates	Peel adhesion	Increase	[84]
	Triacetin	Acrylates	Tack	Increase	[48]
			Shear adhesion	Increase	
	Tributhylcitrate	Acrylates	Tack	Increase	[48]
			Shear adhesion	Increase	
	Propylene glycol	Acrylates	Peel adhesion	None	[87]
	Glycerin and/or PEG	Acrylate/water	Tack	Increase	[29]
	Sorbitol	Acrylate/water	Tack	None	[29]
		Acrylate/water	Shear adhesion	Increase	[29]
	PEG	Acrylate/water	Shear adhesion	Decrease	[29]
	Glycerin	Acrylate/water	Shear adhesion	None	[29]
	Glycerin	Gelatine/acrylate	Peel adhesion	None	[83]
	Propylene glycol	Gelatine/acrylate	Peel adhesion	Increase	[83]
Skin penetration Enhancer	Isopropyl myristate	Silicon	Peel adhesion	Increase	[85]
			Shear adhesion	Decrease	
	Isopropyl myristate	Acrylate	Shear adhesion	Decrease	[82]
	Isopropyl myristate	Acrylate	Peel adhesion	Decrease	[85]
	Oleic acid	Acrylate	Peel adhesion	Increase	[44]
	Oleic acid	Acrylate	Peel adhesion	Decrease	[86,87]
	Azone®	acrylate/PVA	Peel adhesion	Decrease	[57]
	Sodium lauryl sulfate	Polyisobutylenes	Peel adhesion	Decrease	[88]
	DMSO	Polyisobutylenes	Peel adhesion	Decrease	[88]
	Methyl laurate	Acrylate	Peel adhesion	Decrease	[23]
	Arlacel 80®	Acrylate	Peel adhesion	Decrease	[24]
	Transcutol®	Acrylate	Peel adhesion	Increase	[24]
	Lauric acid	Acrylate	Tack	Increase up 6% then decrease	[94]
Crystallization inhibitors	PAMA	Silicon	Peel adhesion	Decrease	[41,89]
	PAMA	Acrylate	Peel adhesion	None	[55]
	PVP	Acrylate	*In vivo*	Decrease	[93]
	PVP	Acrylate	Peel adhesion	Increase	[94]
	PVP	Acrylate	Tack	Increase up 15% then decrease	[94]
	PVP	Polyisobutylenes	*In vivo*	None	[93]

DMSO: Dimethylsulfoxide; PAMA: Poly(amino methylmethacrylate); PVP: Polyvinylpyrrolidone.

were altered by active ingredients, such as nicotine or diclofenac [48]. It was also reported that plasticizers with limited differences in the chemical structure acted in very different ways. In gelatine-based PSA, glycerin did not significantly affect the peel strength, while increasing the amount of propylene glycol in the same matrix, the initial peak stress was significantly increased [83].

When isopropyl myristate was introduced into a silicon-based PSA to enhance the drug permeation, the matrix flew easily favoring the rapid wetting of skin, which increased the

initial peel strength and reduced the cohesion strength [85]. On the other hand, the addition of the same substance to a PAMA-based matrix introduced a decrease in the peel adhesion strength [82].

Also in the case of oleic acid, contrasting results were obtained: this skin permeation enhancer caused a decrease in peel adhesion of acrylic-based PSA [86,87] and the opposite pattern was observed on PAMA-based PSA [44] probably because of its migration on the adhesive surface in the first case and a plasticizing effect in the latter.

Azone® decreased the *in vivo* peel strength of a hydrated PSA made of a plasticized mixture of PAMA and poly(vinyl alcohol) [57]. Adding sodium lauryl sulfate or dimethyl sulfoxide to PIB-PSA, both the glass transition temperature and the peel strength decreased indicating a trade-off between the enhancer activity and adhesive properties [88]. The same modification was described when methyl laurate [23] or Arlacel® 80 [24] were added to acrylic matrices, but the addition of Transcutol® caused opposite effects [24]. These contrasting data did not permit to accurately predict the effects of skin permeation enhancers on the adhesive properties, unless in very limited cases. For instance, it was possible to relate the decrease in adhesion strength of PAMA-based PSA to the low-solubility parameter of small molecules added in the matrix [44,82].

The adhesive properties of a PSA can also be modified by blending it with another polymeric material added with different purpose, such as the inhibition of drug crystallization [38,41,55,89-93]. As an example, when PAMA was used as a crystallization inhibitor of ibuprofen in silicon-based PSA, a reduction of the patch adhesion properties was evident [41,89]. On the contrary, the same copolymer resulted not influencing the adhesive properties of an acrylic-based PSA [55].

Since additives and backing layer can cause opposite effects and mutual interferences on at least one of the adhesive properties, multiple analyses have to be carried out to clarify these features. Moreover, statistical approaches, namely factorial designs, result in useful tools to evidence the contribution of each variable on the patch performances [29,47,94]. As an example, a central composite design using a polynomial model including interactions and quadratic terms permitted to discriminate the contribution of several formulative variables on the skin penetration of fentanyl and patch adhesiveness, that is, tackiness and peel strength, allowing the selection of the optimal formulation [94].

6. Expert opinion

Since drug absorption is governed by its partition between the patch matrix and the skin, variations of their contact area due to dislodging or detaching would cause unpredictable bioavailability and failure of the therapeutic treatment. The critical role played by the adhesion to determine the safety and the efficacy of a transdermal patch is clearly underlined by several reports received in FDA's Drug Quality Reporting System [95]. As an example, lack of adhesion can involve environmental condition use failure due to heat, cold, sweating, showering, swimming as well as lack of quality occurs when the release liner cannot be removed properly thus making the patch unusable, or when the patches result not sticking after 24 h, or edges result curling up [95].

In light of these considerations, it appears essential to develop methods to evaluate the adhesive performances with a view to recommend robust and standardized compendial assays. As a matter of fact, the number of papers and reviewers dealing with critical aspects of adhesiveness in the medical and pharmaceutical fields has increased about fourfold in the last decade. Considering that the methods normally used to check the adhesive quality of an adhesive tape are not always applicable due to the peculiarities of the skin, most of these works aimed to develop adhesive tests to monitor the patch performances in the development phase. This scenario is mainly addressed to evaluate the effects of the addition of active ingredient/s and/or additives on the structure of PSA in an attempt to predict the *in vivo* adhesive properties by mean of suitable *in vitro* methods.

DMA provides a deep inside on the PSA structure as well as the viscoelastic properties of the adhesive contained in a patch. Since special *ad hoc* prepared samples are analyzed usually varying the running temperature, these measurements are related to the properties of the adhesive in bulk, without exhibiting the true nature of the final patch formulation, which is usually prepared by a different method. Conversely, the texture analysis experiments are performed at room temperature on samples prepared as the final patch. Nevertheless, the information is limited to the debonding process, which could be related to the rheological behavior of the adhesive only to some extent.

The evaluation of the adhesive physical properties by these methods does not provide a true indication on how the patch performs in its intended use because the influence of the backing layer is not evaluated and the patch is attached to a substrate, namely the skin, which is a compliant and exhibits a relative high elasticity. Therefore, an analysis of the *in vitro* adhesive properties by the holding power and peel adhesion tests should be recommended by guidelines on the development of patches issued by the regulatory agencies, other than the evaluation of the percentage of patch lifted and/or detached off during pharmacokinetic and clinical studies.

The *in vivo* patch adhesion behavior can be estimated by means of *in vitro* testing, even if one of the major concerns is the use of human skin, which, independently of the source (cadaver or surgical reduction), poses ethical issues, restricted availability and technical limitation. Therefore, the research of alternative materials exhibiting critical surface tension, flexibility and, if possible, roughness close to the skin, is worthy of great interest to shorten the product development and optimization process.

If the definition of methods suitable to correlate *in vitro* adhesiveness and *in vivo* performance appears very complex,

simple and highly discriminating assays allowing the quality control of produced batches are of utmost importance and substantial efforts and resources go in to their development. In the last years, several papers have been focused on the selection of the adherend plate to be used in the peel test for quality control purposes [64,65]. The authors concurred that the higher the critical surface tension of the material, the greater the discrimination of the performance of transdermal patches. This statement is also in agreement with the thermodynamic model of adhesion based on the wetting criteria [96].

Among materials constituting the adherend plate, the guidelines issued by the adhesive tape industrial associations [15] and the past edition of several Pharmacopoeia [97,98] require the use of stainless steel plates also because the surface roughness is easily standardized. Nevertheless, several examples reported in literature underline how the suitability of this model is strictly dependent on the physicochemical properties of the components constituting the patch matrix and the overall formulation. As an example, when the adhesion strength of the matrix to the adherend plate is higher than the tensile strength of the backing layer, the peel adhesion and shear adhesion values cannot be determined since the patch can warp or break during the experiment [62].

Even if the criticism of evaluating the quality of adhesion of patch is well discussed in literature, manufacturers have no official indications on how critically choose the methods to determine the shear and/or peel adhesion in the batch quality control. In light of the considerations reported in this paper, the opportunity of reintroducing assays to test the patch adhesive properties in the Pharmacopoeias should be considered.

Declaration of interest

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