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Research paper

The tape stripping procedure – evaluation of some critical parameters

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ABSTRACT

Tape stripping is a simple and efficient method for the assessment of quality and efficacy of cosmetical and dermatological formulations. After topical application and penetration of formulations, the cell layers of the stratum corneum are successively removed from the same skin area using adhesive films. The tape strips contain the amount of corneocytes and the corresponding amount of the penetrated formulation, which can be determined by classical analytical chemical methods. Different formulations can strongly influence the amount of stratum corneum removed with every tape strip. Therefore, it is essential for the comparison of the penetration of different formulations that the amount of formulation detected on the single tape strip is not related to the tape strip number as a relative measure of the penetration depths, but to their standardized real position in the stratum corneum. Therefore, different methods are reported for the determination of the amount of stratum corneum removed with every tape strip.

The tape stripping method in its standardized form is well-suited to determine the dermatopharmacokinetics of topically applied substances. Additionally, the method can be used to obtain information about the homogeneity and the distribution of formulations on the skin and in the stratum corneum. This is used, e.g., for the determination of the homogeneity of the distribution and the *ex vivo* determination of a universal sun protection factor (USPF) characterizing the efficacy of sunscreens.

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1. Introduction

The stratum corneum (SC) of the skin functions as the outermost barrier of the body avoiding or limiting, respectively, the entry of foreign substances into the body and the excretion of endogenous substances. Therefore, many dermatological studies are focused on the investigation of this skin layer. Tape stripping, the subsequent removal of the SC using adhesive tapes, has emerged as a useful technique in such studies [1–3]. This minimal invasive procedure can universally be used: both *in vivo* [4–6] and *in vitro* [7–9], and in humans [4–8] and animals, e.g., pigs [7,8,10], rats [11,12], guinea pigs [13,14] and mice [15]. It only failed to remove strongly coherent keratinocytes, e.g., from porcine snout [16]. Thus, tape stripping has become a basic method to study the penetration and the reservoir behaviour of topically applied or exogenous substances [17], the physiology of the SC [18,19], epidermal wound healing [20,21] and the excretion of endogenous substances [22].

The amount of SC removed by a single adhesive tape strip depends on several intrinsic and extrinsic factors. The size of the corneocytes is influenced by the anatomical site [4,23], the age [24] and the season [19]. In addition, the number of cell layers [25] and corneocytes [26], the thickness of the SC [27], the composition and amount of lipids [28] vary depending on the anatomical site. Skin parameters such as TEWL and pH value are affected by the season [19,26], the race [29] and the skin type [30] of the volunteer. Extrinsic factors that have been reported to affect the amount of SC removed by tape stripping or the type of adhesive tape [31], the force of removal from the skin [32,33], the duration of pressure onto the skin [30] and topically applied substances [34]. Even constant extrinsic factors following a strict standard protocol would not lead to a constant amount of SC an each tape strip, due to the various intrinsic parameters. However, the quantification of the amount of SC removed is pivotal for most of the mentioned studies, especially for the purpose of a cross-study data comparison.

In general, a uniform removal of the SC is necessary both in lateral and vertical direction. Prerequisites and steps of the procedure may affect this homogeneity of removal and are discussed herein. In addition, the main methods reported to quantify the removed SC amount are summarized. Finally, remarks on problems connected with the tape stripping are made.

2. Principles of tape stripping

The principal method of tape stripping more or less used in all protocols is described in Fig. 1. After topical application and

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penetration of the formulation, the tape stripping procedure starts. In the actual protocol the skin was not cleaned before tape stripping in order to have available the original amounts of the applied active substances. This is especially essential quantifying the protective efficacy of sunscreens based on absolute spectroscopic values, e.g., the remaining transmission after sunscreen application. Investigating other systems, the exact availability of the applied amount is the prerequisite to determine the percentage recovery.

Adhesive films are applied and removed successively from the same treated skin area. The adhesive tape should be pressed onto the skin using a roller to stretch the skin surface. This procedure will avoid the influence of furrows and wrinkles under the tape stripping procedure as will be described later.

The removed tape strips contain amounts of stratum corneum and amounts of topically applied substances. The typical distribution of the corneocytes on the tape strips removed from different depths of the stratum corneum is shown in Fig. 2.

The first tape strips contain almost a complete cell layer of corneocytes. With increasing the tape stripping number, the corneocytes and corneocyte aggregates become less and less.

The properties of the topically applied formulations have a strong influence on the amount of stratum corneum removed with every tape strip as demonstrated in Fig. 3. After application of an ethanolic solution the adhesion of the horny layer to the tape strips is enhanced while after application of an oily formulation to the other arm of the volunteer the adhesion to the tape strips is reduced. It needs more strips to remove a comparable amount of the stratum corneum.

As can be seen from Fig. 3, the amount of stratum corneum that is removed with five tape strips can differ by 100%. This can cause strong mistakes in the interpretation of the dermatopharmacokinetics of substances, if the tape stripping number is taken as a measure of the penetration depths of the topically applied substances.

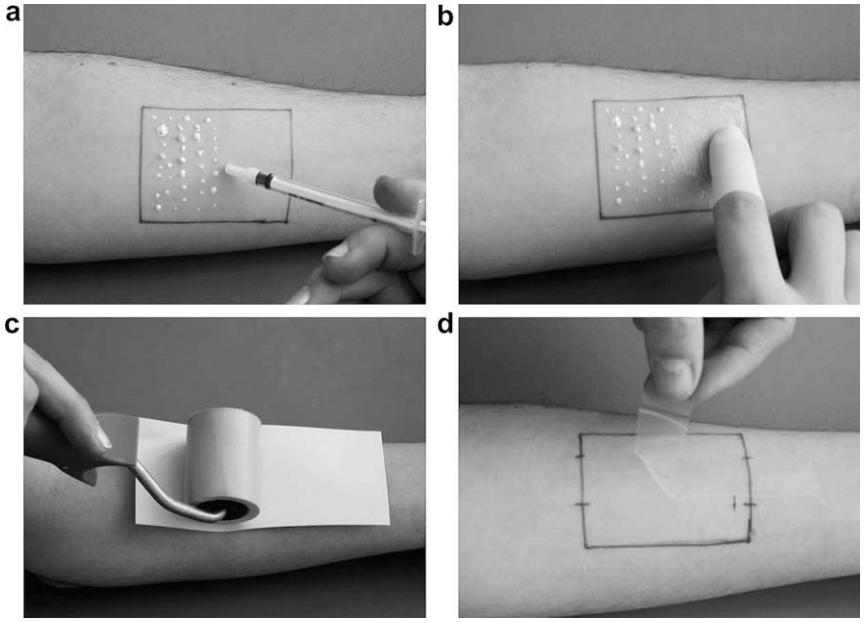

Fig. 1. Method of tape stripping (a) application of the formulation on a marked skin area; (b) homogeneous distribution; (c) the adhesive tape is pressed with a roller on the skin, an empty sheet of paper avoids the transfer of the formulation onto the back side of the tape; (d) removal of the tape.

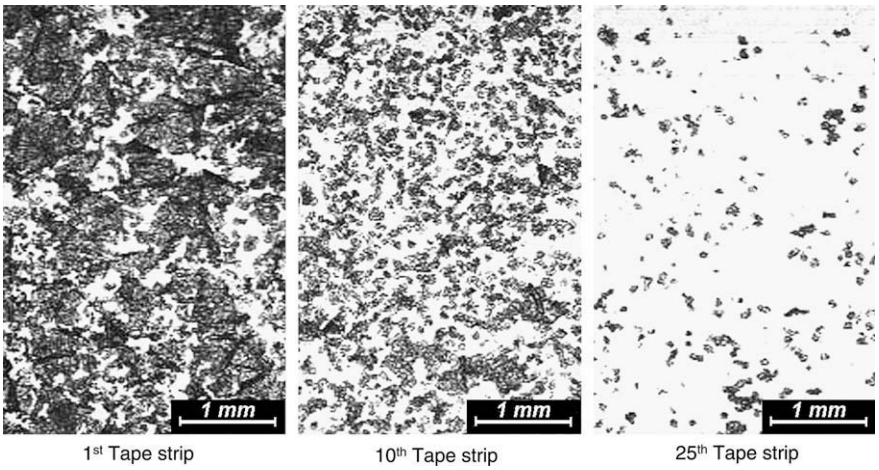

Fig. 2. Distribution of corneocytes on the removed tape strips.

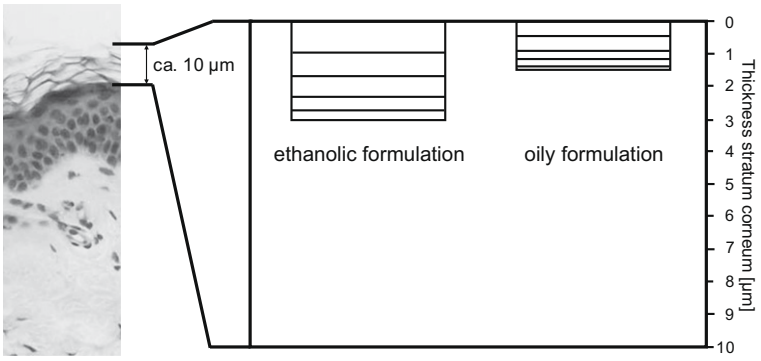

Fig. 3. Influence of the formulation on the amount of stratum corneum removed with every tape strip.

3. Prerequisites and steps of tape stripping

3.1. Site of application

Tape stripping to remove the SC should be applied in a uniform manner. For this procedure, the site of application must be free of both terminal and vellus hairs and uneven areas, e.g., caused by scars and underlying muscles. In the case of studying hairy sites, the hairs should be carefully removed by using scissors or a special hair cutter. Shaving the skin should be avoided, because it can be expected that the superficial layers of the SC will also be removed.

3.2. Type of tape

Several types of adhesive tapes have been used for the stripping of the SC including both commercial [30,34] and self-made [35] products. In any case, a uniform composition and distribution of the adhesive layer on the tape strip should be guaranteed. In some studies, tapes with a defined size (i.e., constant area) were applied. In other investigations, the tape strips were directly used from the spool showing a constant width and a variable length. In general, the properties, e.g., transparence and flexibility, of the adhesive tape are determined by the subject of the study and the method to quantify the amount of SC, respectively. The compatibility to the skin should be proven beforehand, in order to prevent adverse effects.

3.3. Application of the tape strip

The strips or discs of adhesive tape are carefully adhered to the marked skin site of interest avoiding folds. This procedure becomes difficult, if the tape strip has the same size as the area under investigation. In the case of a larger skin area, the position of the tape should be marked on the skin surface. In some studies, a thin stencil was fixed onto the skin and the tape stripping was applied over the opening [36]. If the area of interest is smaller than that of the tape strip, the mark on the skin must be renewed after removal of several strips.

3.4. Application pressure

As well as the type of tape, the uniform pressure is a basic factor influencing the amount of SC removed [37]. However, this parameter, in many studies, has not been described in detail. A constant weight [38], a spatula [39] and a roller [34] were used to press the tape onto the skin surface. In comparison to a constant weight, the roller can also press a thin and flexible tape strip into the furrows of the skin avoiding a disturbing effect, as in *in vivo* studies, on the penetration of topically applied substances [41]. Especially for physiological studies, the optimal way seems to be the combination of a constant weight and a roller as realized by Surber and co-workers [36]. The weight of the roller itself was used to press the tape 10 times onto the skin surface [42] reaching presumably the optimal adhesive bond of the tape with the SC [37].

3.5. Velocity of removal

Up to now, the velocity of stripping the tape, another important factor influencing the amount of removed SC [37], is not standardized. This means that the bias of the applicator determines this amount. A constant velocity should always be applied. A slowing down or stopping of the procedure could lead to an increase in the SC amount adhered on the tape strip, whereas, an increase in speed could result in a decreased amount of corneocytes [37]. A higher extension of the skin by the slow removal causing stress for the connecting corneodesmosomes is discussed as a reason for a more efficient SC disruption.

4. Methods to quantify the amount of SC removed

The decisive way to avoid the influences of the discussed disturbances is the determination of the SC amount removed with each individual tape strip. Therefore, several methods have been proposed to quantify the amount of horny layer removed by tape stripping. Most methods, including differential weighing [13,19,34], spectroscopic [34,43–45] and microscopic [49] measurements, were available to determine the amount of SC, adhered to each tape strip. In contrast, the measurement of the transepidermal water loss (TEWL) can be used to determine the remaining SC [14,27] but problems arise quantifying the exact amount of the corneocyte density on the first tape strips, which is often the most decisive one.

In general, the homogeneity of distribution of the corneocytes on the tape strips should be checked visually before quantification.

4.1. Weighing

The difference in the weight of a tape strip, weighed prior to the application onto the skin and after the removal, was often used to determine the mass of the SC removed as a value for its amount [34,39,43]. This very tedious and time-consuming approach [39] is based on the assumption that the parts of the SC are exclusively removed. Sebum and topically applied substances might increase the weight difference for the initial tape strips. Interstitial fluid derived after removal of several tape strips may also increase the weight difference for the strips removed from deeper parts of the skin [34,43]. Volatile components of the adhesive layer would re-

sult in a time-dependent decrease in weight and should be avoided by testing the tape before application.

4.2. Protein content

Several approaches to quantify the amount of removed SC are based on the determination of the proteins in the corneocytes as the major component of the SC. These proteins show an absorption at 278 nm [46] that can be measured directly on the tape strips using a UV-spectrometer [39,45]. This signal was successfully compared with the pseudo-absorption of the corneocytes ($R^2 = 0.92$) [45]. The weakness of this absorption and a possible superposition with stronger absorption bands of other substances (e.g., from the adhesive layer, topically applied substances [34]) in the same spectral range might limit the application of this method.

Therefore, attempts were developed to increase the absorption of proteins and shift it to the visible range (with fewer possibilities of superpositions). In the most convenient manner, the cells were stained whilst they adhered on the tape strips. Martin et al. [39], stained the SC proteins with Brilliant Blue R 250. The comparison with the weight of the corneocytes resulted in a low correlation coefficient $R^2 = 0.71$ presumably due to the background colour of the tape after staining. In another study, Trypan blue was used as a reagent to stain the SC particles selectively [45]. The measured absorption at 652 nm correlated well with the pseudo-absorption of the corneocytes before staining ($R^2 = 0.95$).

In a more time-consuming manner, Dreher et al. [44] extracted the proteins from the tape strips followed by staining and colorimetric determination of the stained proteins. The impact of endogenous components on the mass of corneocytes was overcome by using SC cells isolated from excised skin, which had been treated with trypsin. The calibration curve obtained by correlating the stained SC proteins with the corneocyte mass was used to calculate the mass of corneocytes removed by tape stripping. Recently, this method was extended to use 96-well microplates [50]. However, high variations in the amount of corneocytes detected for four sub-areas (with a diameter of 5 mm) were obtained due to the microscopical inhomogeneous distribution of the cells. In addition, a higher SC mass was generally determined using the colorimetric method as compared to weighing. The determination of SC proteins was used in physiological studies on the SC [47].

4.3. Optical spectroscopy

The pseudo-absorption of the corneocytes was used as a value for the amount of SC removed [34]. Therefore, a tape strip removed from the skin was measured using a UV/vis spectrometer. The corneocyte aggregates decrease the transmission of light by reflection, diffraction and scattering resulting in a linearly increasing absorption with a decreasing wavelength (so called pseudo-absorption) [39]. This method was confirmed by comparison of the pseudo-absorption to the data of weighing [34] and the number of removed SC cell layers [48]. In addition, a good correlation of the pseudo-absorption with the protein content [45] and the relative covering density of the cells on a tape strip [49] was reported. A relatively large measuring area of 1×1 cm is a basic prerequisite for this method in order to overcome the microscopical inhomogeneous distribution of the corneocytes on the tape strip [50]. The fast and simple determination of the removed corneocytes *via* optical spectroscopy can be universally used in studies on both the behaviour of topically applied substances and SC physiology, as described in the literature [43,51]. Recently, a reliable system was introduced to quantify the proteins on the D-Squames semi-quantitatively by a spectroscopic absorption method [52].

4.4. Microscopy

Microscopic techniques were used to determine the relative covering density of the corneocytes adhered to a tape strip [49]. Images were taken from 10 sub-areas of 3.68 cm^2 on a tape strip using microscopy. The relative area, covered by the corneocytes, was automatically calculated as an average value of the covering rates of all sub-areas. The advantage of this time-consuming method is the usage of widely available microscopic equipment. It was confirmed by comparison of the data with the pseudo-absorption of the corneocytes. In a similar way, the ratio between the total area of stripped corneocytes and the adhesive surface was detected by an optical microscope after staining using a solution of gentian violet and brilliant green [29].

4.5. Transepidermal water loss

The decrease in the SC thickness caused by tape stripping was measured by an increase in TEWL [27,53]. Usually, the TEWL was measured prior and after removal of several tape strips. A linear correlation between 1/TEWL and the cumulative mass of removed SC is based on the application of Fick's law considering the SC as an homogeneous membrane [27]. This relationship confirmed in several studies [53] can be used to determine the remaining amount of SC on the skin. However, it is not suited to measure this amount per single tape strip [54]. The remaining SC can be calculated as relative amount [42] and less accurately as total thickness or mass using an additional method to quantify the removed SC (e.g., weighing [29]) in combination with a mean density of 1 g/cm^3 and a controversially discussed partition coefficient K [27]. In addition, the sensitive measurement of TEWL is influenced by several environmental parameters [55] and it is expected to be effected by topically applied substances and interstitial fluid.

5. Influencing parameter

5.1. Effect of furrows

The skin surface topography is characterized by an elastic network of furrows [56]. It might cause the removal of SC parts from different cell layers with one tape strip, as discussed as a disadvantage of the tape stripping [57] limiting studies on penetration and permeation of topically applied substances. *In vivo*, such effects were avoided by using an adhesive tape with high flexibility that was pressed onto the skin surface using a roller [41]. The stretching of the living, i.e., elastic skin during this protocol was discussed as the reason for this observation. In addition, a swelling of the tissue during the procedure of complete SC removal was observed resulting in a smoothing of the skin. This biological reaction was also limited to *in vivo* studies.

On the other hand, *in vitro* tissue shows other properties compared to living skin depending on the conditions of source, removal, storage and experiment [58]. This might affect the amount of removed SC. In the case of an inhomogeneous removal, tape stripping can only be used to remove the SC completely and to study all tape strips in summary. In some cases, the SC could not be completely removed by tape stripping as observed in *in vitro* studies on human skin [41,57]. Parts of the SC remained in the furrows. Therefore, the homogeneity of the SC adhered to the single tape strips and the remaining tissue after

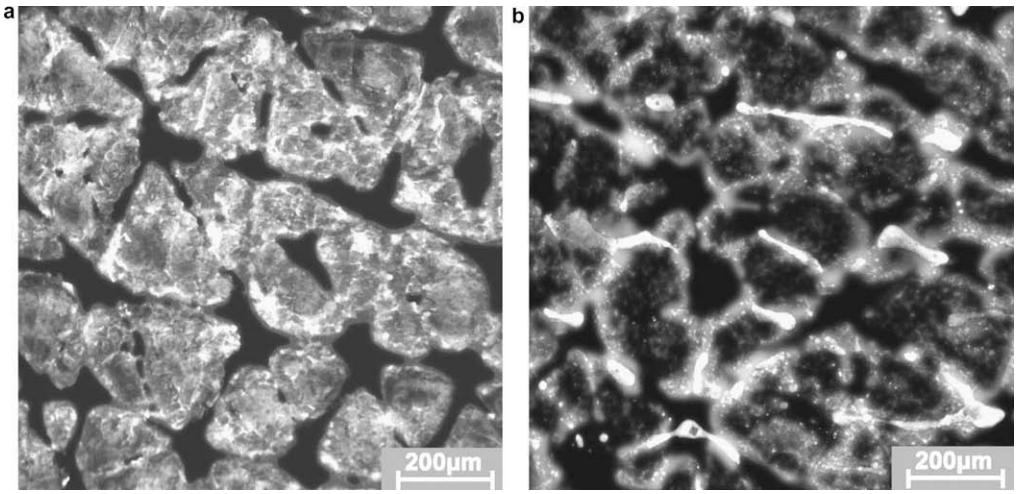

Fig. 4. Distribution of a fluorescent dye on the first tape strips removed from skin areas treated with two different formulations (a) oily formulation; (b) ethanol formulation.

stripping should be investigated prior to the experiment in *in vitro* studies.

5.2. Discarding of the first tape strip

In studies on the behaviour of topically applied substances, the first tape strip is often discarded because it represents unabsorbed drug on the skin surface [14]. However, this amount is necessary to calculate the concentration of substance recovered within the SC in the case of applying a definite dosage. Recently, a standardized method of preparing the surface was proposed [59]. Secondly, different amounts of SC can be removed with the first tape strips in studies comparing different vehicles [35] or penetration times [59]. This effect might be caused by differences in the cohesion of the corneocytes and the adhesion of the tape to these cells, respectively. At least, the reservoir for the topically applied substances in the furrows of the skin surface might be a subject of interest, especially in kinetic studies of the SC reservoir [60]. Therefore, the amount of SC and substance topically applied beforehand should be determined and considered in the study.

6. Applications of tape stripping

6.1. Determination of the distribution of topically applied substances

The removed tape strips contain not only information about the amount of corneocytes and the penetrated substances but also about the distribution of the substances in the different depths of the stratum corneum. In Fig. 4, the distribution of a fluorescent dye on the first tape strips removed from skin areas treated with two different formulations is demonstrated. In the first case of an oily formulation (left picture) the fluorescent dye is distributed homogeneously on the corneocytes while in the case of an ethanol formulation (right picture) the dye is almost located in the furrows and wrinkles. Using *in vivo* laser scanning microscopy, it was shown that the distribution of the dye on the tape strips corresponds exactly to the distribution in the human skin under *in vivo* condition [61].

The influence of the skin profile on the variation of the sunscreen efficacy is discussed in detail in [62]. This effect can be taken as the basis for the determination of a homogeneity factor characterizing the distribution of a formulation on the skin. It is based on the relation of the dye absorption determined on the removed tape strips and in the extract obtained from the same tape strip. The absorption values of the dye on the removed tape strips described its *in vivo* distribution in the skin, reflecting the degree of non-homogeneity of the distribution. In the solution, the same amount of dye is distributed homogeneously.

This homogeneity factor as the relation between these two absorption values is of special interest for the optimization of sunscreen formulation, whose protection efficacy is determined not only by the absorption properties and the concentration of the UV filter substances but also by the homogeneity of their distribution on the skin.

6.2. Ex vivo determination of the protection efficacy of sunscreens by tape stripping

Recently, the effect that the concentration and distribution of sunscreens in the stratum corneum under *in vivo* conditions can be transferred to tape strips was used for the determination of a universal sun protection factor of sunscreens [63]. During this procedure, cell layers of the stratum corneum are removed by tape stripping after application and penetration of sunscreens. The tape strips were measured in a special UV–vis spectrometer with a measuring area of 1 cm^2 [40].

Because sunscreens are usually located only on the skin surface and in the upper layers of the stratum corneum, usually only 5–10 tape strips have to be taken to remove the sunscreen completely from the skin. After measuring the single tape strips, the sun transmission was determined in the whole UV spectral range. A typical example of this procedure is presented in Fig. 5. The spectra describe the sum transmission curves calculated for each tape strip taking into account all proceeding spectra until the changes become negligible. The area under the bold curve corresponds to the relative amount of UV photons passing the skin barrier protected by the sunscreen and reaching the living epidermis.

If this value is determined in the UVB spectral range, it corresponds to the classical sun protection factor (SPF) [64] determined by the minimal erythema dose under *in vivo* conditions. Should this value be determined in the whole UV range (UVB + UVA), it corresponds to a universal sun protection factor also taking into consideration the protection efficacy in the UVA part of the spectrum.

6.3. Determination of the penetration profiles

The discussed possibilities using tape stripping and spectroscopy clearly show that the pseudo-absorption correlates to the

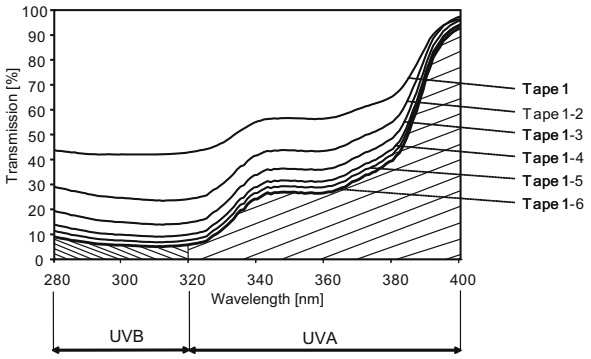

Fig. 5. Determination of the sun transmission spectra of a sunscreen by tape stripping.

amount of removed stratum corneum [34]. The horny layer profile was calculated by adding the single amounts of the stratum corneum removed during the tape stripping procedure. The penetration profile was determined correlating the amount of topically applied UV filter removed with the single tape strips to the horny layer thickness.

In Fig. 6, the penetration profiles of sunscreen and a steroid are presented. In both experiments tape stripping starts 1 h after application. The distances between the horizontal lines correspond to the amounts of removed stratum corneum. As can be seen, these amounts are reduced with increasing tape stripping numbers. The upper line of the profiles corresponds to the skin surface and the lowest line to the boundary of the living cells.

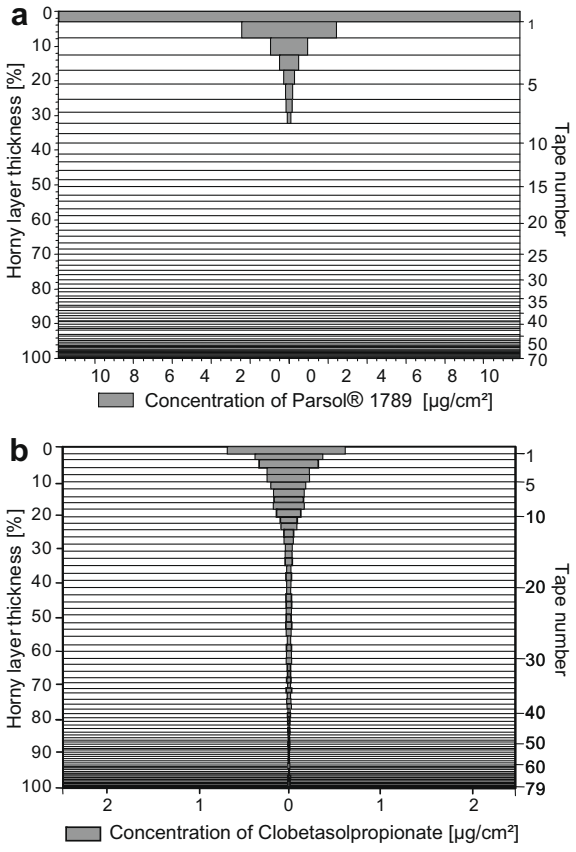

Fig. 6. Penetration profiles of topically applied substances (a) sunscreen; (b) steroid.

The sunscreen formulation was optimized to stay in the upper part of the stratum corneum. The penetration profile in Fig. 6a demonstrates that, indeed, the UV filter substances are located only in the upper 30% of the horny layer. In contrast, the steroid should pass the barrier to reach the living cells. From the penetration profile of the steroid in Fig. 6b, it is seen that the substance could be detected in all depths of the stratum corneum up to the boundary of the living cells.

7. Conclusion

Tape stripping seems to be a robust and simple method to perform studies related to the SC. However, several parameters summarized and discussed herein should be taken into consideration before and during the application of this procedure in order to remove the SC homogeneously. In addition, the amount of removed SC should be determined for all tape strips. Under these conditions; the method of tape stripping has a further increasing future potential in dermatological and pharmacological research. An extent in its application can be expected, e.g., from the combination with the technique of skin surface biopsies to distinguish between the transepidermal and the follicular routes of absorption for topically applied substances.

Additionally, the method of tape stripping can be used for the determination of a homogeneity factor, which characterizes the distribution of topically applied formulations under *in vivo* conditions on the skin.

The tape stripping technique, in combination with optical spectroscopy, is of high importance taking into account the actual discussion concerning the UVA protection ability of sunscreens. The proposed universal sun protection factor quantifies the efficacy of sunscreens in the UVB and UVA spectral range objectively.

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