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Research paper

A few aspects of transonychial water loss (TOWL): Inter-individual, and intra-individual inter-finger, inter-hand and inter-day variabilities, and the influence of nail plate hydration, filing and varnish

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ABSTRACT

The aim of the study was to measure transonychial water loss (TOWL) in order to identify the extent of inter-individual, intra-individual inter-finger, inter-hand, and inter-day variabilities, and the influence of nail wetting, filing and varnishing on TOWL, with a view to determine parameters for the measurement of TOWL and its possible applications. Fingernail and toenail TOWL was measured using the condenser-chamber AquaFlux (Biox) and a specially designed Nail Adaptor supplied by Biox. A wide range of TOWL values (28–75 g/m^2 h for fingernails and 26–48 g/m^2 h for toenails) were found, with significant inter-individual variability. Intra-individual variability was lower; however, in the same individual, inter-finger, inter-hand/foot and inter-day variabilities were found, as well as a strong correlation between nail plate thickness and TOWL. Wetting the nails, even briefly, resulted in a significant rise in TOWL, which subsequently took much longer to return to control values. Filing the nail plate surface with a pharmaceutical file caused large increases in TOWL, whose profile (with number of filing strokes) was fairly different among individuals. As expected, nail varnish application reduced TOWL; the different extent of TOWL reduction by different varnishes suggests a potential use of TOWL measurements for product comparisons.

1. Introduction

Transepidermal water loss (TEWL) – insensible water loss from the body through the skin to the outside environment – is a widely employed parameter to characterize the barrier function of human skin. Thus, TEWL is used in the pharmaceutical and cosmetic industries to determine the (negative or positive) influence of chemicals and formulations on skin, as well as a diagnostic tool in skin disorders, such as dermatitis.

Transonychial Water Loss (TOWL) – water loss from the body through the nail plate to the outside environment – has also been measured, but to a much more limited extent [1–7], presumably due to the less extensive research in nail diseases and their treatment. The nail plate – a hard, yet slightly elastic, translucent, convex structure, consisting mainly of the fibrous proteins, keratins – is obviously very different from the skin and TOWL can be expected to be different to TEWL. In general, TOWL values have been found to be higher than TEWL values. Spruit reported mean TOWL values of 24 g/m^2 h, found TOWL (in one individual) to be higher for the thinner nail plates, to decrease upon the application of nail varnish, and to increase upon application of various solvents such as acetone [1,2]. In contrast to Spruit [1], who measured TOWL in one individual, Jemec et al. reported a lack of influence of nail plate (thumb in 21 healthy individuals) thickness on TOWL [3]. Gender has been reported to have no effect on TOWL [3], but age and disease did – TOWL being lower in older people [3] and in diseased nails in patients with atopic eczema, psoriasis and onychomycosis [4]. TOWL has also been used in a very small number of instances to evaluate the nail quality [5,6].

A wide range of values for TOWL through healthy nails have been reported in the literature: mean of 24 g/m^2 h (range 18.5–30.7 g/m^2 h, 10 fingernails of 1 individual [1]), median of 19.4 g/m^2 h (range 11.7–33.5 g/m^2 h, thumbnails of 21 individuals [3]), mean 38.0 ± SD 11.6 g/m^2 h (left index fingernail in 8 individuals [7]) and mean 12.9 g/m^2 h (4 fingernails in each individual, 10 individuals [4]). The wide range and large standard deviations could be due to a number of factors, such as the different nails tested and averaged, and the different measuring devices and techniques. TOWL was measured with the apparatus used for TEWL measurements, sometimes with fairly basic adaptation to take account of the very different nail structures. Jemec et al. [3], Kronauer et al. [4] and Kruger et al. [5] used an open-chamber evaporimeter while Nuutinen et al. [7] used a closed-chamber VapoMeter. To

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ensure contact between the probe and the rigid nail plate (compared to the skin), Kronauer et al. used Plasticine around the aperture of the protection cover [4], Nuutinen et al. used an elastic adapter [7], while Jemec et al. [3], Kruger et al. [5] and Zaun [6] reported no special measures. Zaun [6] raised the problems of ensuring contact between the probe and the rigid nail plate and questioned the accuracy of TOWL measurements, given that the probe used was designed to measure water loss from the elastic skin.

The aim of the work described in this paper was to conduct a systematic investigation of TOWL, using a specially designed measurement cap for the nail plate, to identify the variables which affect TOWL and to identify possible uses of TOWL measurements. In the last decade or so, the high incidence of nail diseases, such as fungal infections, their physical and psychological impact on sufferers, the problems of existing therapies such as adverse events and drug interactions, and the size of the pharmaceutical market have been recognised. Consequently, research into the topical treatment of nail diseases is on the increase [8], and it is expected that TOWL measurements will be an additional tool in the ungual diagnostic and drug delivery fields. In this manuscript, we present inter-day, inter-finger and inter-hand/foot variabilities in the same individual, as well as inter-individual differences, and the influence, on TOWL, of nail plate thickness, hydration/dehydration and filing, and of nail varnish application and removal. The possibility of using TOWL to compare cosmetic and pharmaceutical nail varnishes is also explored.

2. Materials and methods

2.1. Materials

The condenser-chamber AquaFlux (Biox, UK) was used to measure TOWL. The coupling between the nail plate and the measurement chamber used a Nail Adaptor supplied by Biox. It consists of a short stainless steel tube fitted with a rubber O-ring for sealing against the nail plate. The tube internal diameter was 3.8 mm and the instrumental flux density calibration was adjusted in the software via a Biox-supplied correction factor of 0.542.

The cosmetic nail varnish formulations, Snowdrop No. 17 Lasting Fix and Teflon® Tuff™, were obtained from Boots Chemists, UK, and from Superdrug stores plc, UK, respectively. The pharmaceutical nail varnish formulations, Curanail® (5% amorolfine nail lacquer), and Nailon™ (8% ciclopirox nail lacquer), were purchased from community pharmacies in the UK and India, respectively. Penlac® (the original 8% ciclopirox nail lacquer by Aventis Pharma Deutschland GmnH) was a gift from York Pharma (UK). An acetone-based nail varnish remover called Nail Polish Remover was purchased from Marks and Spencer, UK, while the cosmetic nail file used was part of a nail kit from Searenity, purchased from Debenhams, UK.

2.2. Methods

2.2.1. TOWL measurement

TOWL of healthy finger and toenails of 3 individuals were measured. The volunteer study was approved by the Pharmaceutics Departmental Ethics Committee of the School of Pharmacy, University of London, 30 October 2006, via the standard ethics review procedure of the school. Each measurement was made over a period of 120 s and was repeated 3–10 times, with an interval of 160 s between measurements. Prior to TOWL measurements, individuals rested for at least 40 min in the laboratory, and avoided contact with water. All measurements were conducted in the same laboratory, where the ambient air humidity and temperature fluctuated between 26–47% and 18–25 °C, respectively. According to the manufacturer, measurements are said to be unaffected by ambient air movements, room temperature and humidity, as the closed chamber of the AquaFlux provides its own measurement microclimate [9], and therefore an outer box was not used. Special handling precautions were also unnecessary as its measurements are not affected by heat from the operator's hand [9]. The finger or toe was placed on a flat surface for support and the probe was applied to the center of the nail plate, using medium pressure (subjectively judged) to ensure a good seal. The pressure applied was found to be important: application of low, medium and heavy pressure gave rise to statistically different readings, which were, respectively, means ± SD 38.4 ± 0.8, 36.1 ± 0.3, and 32.9 ± 0.8 g/m^2 h. Medium pressure was selected for all measurements as it had the lowest standard deviation and was felt, by the operators, to be the easiest pressure to maintain consistently for the duration of the measurement. In Figs. 1–7 (except for Fig 5), means ± SD of 3–10 TOWL measurements are shown. In Fig. 5, one TOWL measurement at a specific time is shown, as changes in TOWL with time was determined.

2.2.2. Influence of nail plate thickness on TOWL

To determine the influence of nail plate thickness on TOWL, the latter for all fingernails was measured on the same day and the thickness of freshly cut nail clippings was measured using an electronic micrometer. The clipping thickness was taken as an indication of the (whole) nail plate thickness. Ideally, the thickness of the middle portion of the nail plate (where TOWL was measured) would be determined in vivo. However, a practical, absolute method to measure the thickness of nail plates overlying the nail bed in vivo is lacking, though ultrasonography and optical coherence tomography are being researched [10,11].

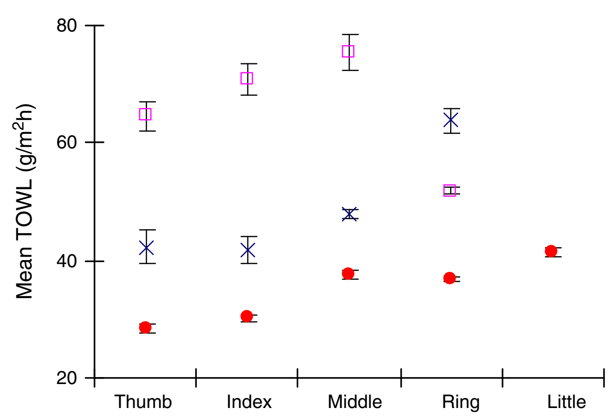

Fig. 1. Left fingernail TOWL in 3 individuals: Individual 1 (×); Individual 2 (□); Individual 3 (•). For each individual, all TOWL values were measured on the same day. However, TOWL for the 3 individuals was measured on 3 different days due to time constraints.

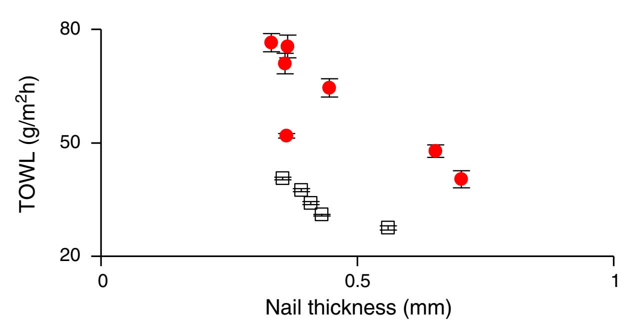

Fig. 2. The influence of nail (finger and toe) plate thickness on TOWL in 2 individuals, Individual 1 (•); Individual 2 (□).

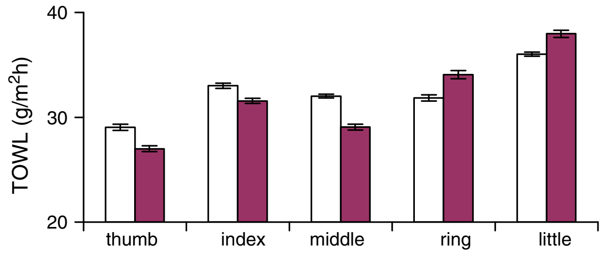

Fig. 3. Fingernail TOWL of left (■) and right (□) hands in one individual, measured on the same day. Right fingernail plate thicknesses were 0.555, 0.541, 0.462, 0.412 and 0.393 for thumb, index, middle, ring and little finger, while left fingernail thicknesses were 0.567, 0.494, 0.452, 0.407 and 0.378 mm, respectively.

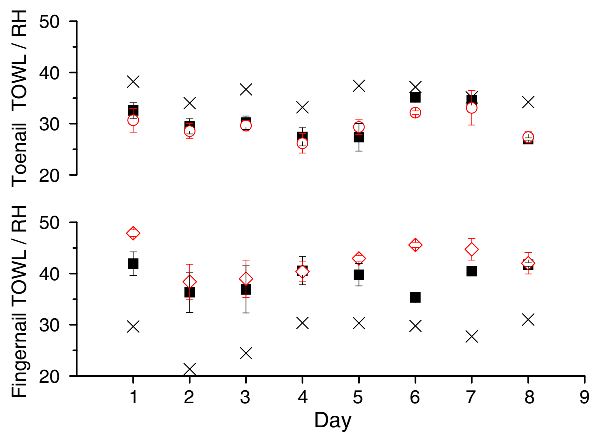

Fig. 4. Relative humidity and finger/toe nail TOWL measured for the same nails on 8 days. Humidity (×); toenail (left ■; right ○); left fingernail (middle ◇; index ■).

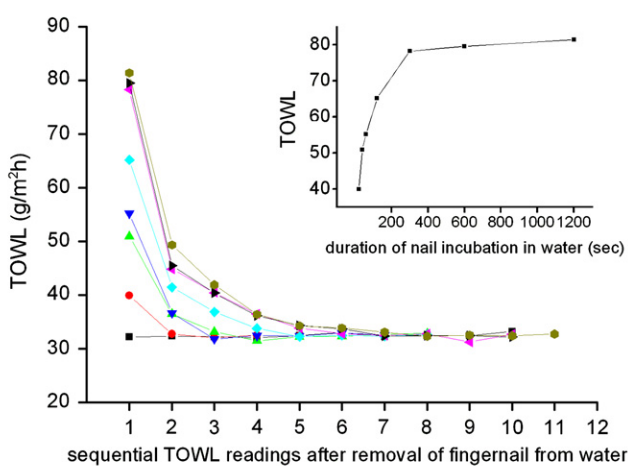

Fig. 5. Sequential TOWL readings after removal of fingernail from waterbath. Topmost to bottom curves are for water incubation times of 1200, 600, 300, 120, 60, 40, 20 and 0 s. Inset of this figure shows TOWL following fingernail incubation in water for defined durations (0–1200 s).

2.2.3. Nail plate hydration and dehydration, and the influence on TOWL

To determine the rate of nail plate hydration and dehydration and the influence on TOWL, the left index finger of one individual was used and all measurements were conducted on the same day. Ten control (dry fingernail) readings were taken to get a mean value, after which the finger was immersed in distilled water in a glass beaker for different periods of time: 20 s, 40 s, 60 s, 2 min, 5 min, 10 min and 20 min. Immediately after removal of the finger

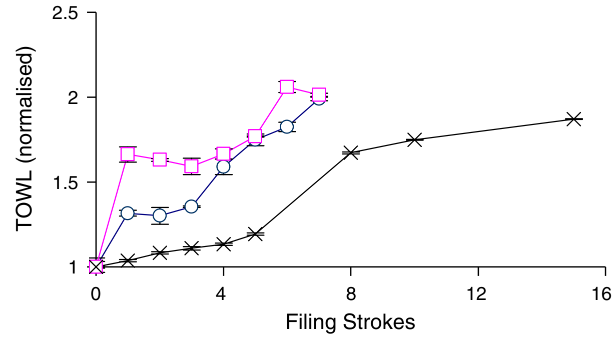

Fig. 6. Change in TOWL upon filing the nail plate surface; Individual 2 fingernail (○); Individual 2 toenail (□); Individual 1 fingernail (×).

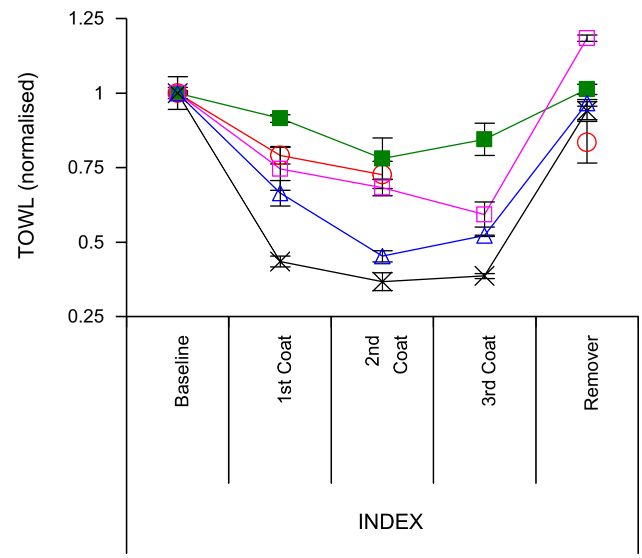

Fig. 7. Changes in TOWL following the application of nail varnish and its removal; Nailon (■); Curanail (○); Teflon Tuff (□); Penlac (Δ); Cosmetic varnish (×). The data show means ± SD of 3 measurements on the left index fingernail. Similar profiles were obtained for the left middle finger, right index, and left and right middle fingers and toenails (data not shown).

from water, the finger was wiped dry with paper towels and TOWL measurements (of 120 s duration at 160 s intervals) were taken until the control value was re-established.

2.2.4. Influence of cosmetic and pharmaceutical filing of nail plate surface on TOWL

To determine the influence of filing on TOWL, the nail plate surface was filed using cosmetic or pharmaceutical files. For cosmetic filing, the file provided for dorsal surface nail filing in a cosmetic nail kit (Searenity) was used, and the dorsal nail surface was filed with a forward and backward movement, as per product guide, for 15 s, which equated to approximately 30 filing strokes. For pharmaceutical nail filing, the files provided in packs of Curanail were used. To quantify filing, a stroke was defined as filing the nail plate using the whole length of the file (~10 cm) in one direction. TOWL was measured after each stroke. Due to the different TOWL values for finger and toenails in different individuals, TOWL values were normalized to enable comparisons.

2.2.5. Influence of nail varnish application and removal on TOWL, and comparison between nail products

To determine the influence of nail varnish application on TOWL, different cosmetic and pharmaceutical nail varnishes (Snowdrop

No. 17 Lasting Fix, Teflon® Tuff™, Curanail®, Nailon™ and Penlac®) were applied using the implement provided – a brush for the cosmetic formulations, Penlac® and Nailon™, and a plastic applicator for Curanail®. Three coats of nail varnish were applied, then removed using a cosmetic nail varnish remover. TOWL was measured after each coat of nail varnish had dried on the nail plate and 5 min after removal of the varnish film with the varnish remover. The varnish coats were applied as one would apply them in practice, i.e. the brush/plastic applicator was dipped in the varnish and the amount of varnish on the brush/applicator was evenly applied over the nail. While this would not necessarily result in the same amount of varnish applied on the nail for all formulations, it closely mimics the situation in practice. The experiment was conducted using both index and middle fingernails, and big toenails in one individual. Some of the measurements were repeated in another individual and similar results were found.

3. Results and discussion

3.1. Inter-individual variability in TOWL

A broad range of TOWL values were recorded; 28–75 g/m^2 h for fingernails and 26–48 g/m^2 h for toenails and significant differences in TOWL among individuals were observed (Fig. 1 and Table 1). This was expected, given the obvious inter-individual variabilities in the nail plate properties, such as nail plate thickness. The chemical composition of nail plates, such as water and lipid content, is also likely to differ among individuals, which would influence TOWL values. Inter-individual variability in TOWL was found to be much greater than intra-individual variability for both finger and toenails (Fig. 1 and Table 1). The lower intra-individual variability suggests that when comparisons are made, for example, when the influence of disease on TOWL is investigated, the TOWL of diseased nails should be compared against TOWL of healthy nails in the same individual, rather than comparing the mean healthy and mean diseased TOWL from all the subjects of the study.

3.2. Influence of nail plate thickness on TOWL

From Fig. 1, it can be seen that the different fingernails of the same hand of the same individual, measured on the same day have fairly different TOWL values. The differences in TOWL can be partially assigned to the different thicknesses of the nail plates, as shown in Fig. 2, where a relatively good correlation between thickness and TOWL was found (Pearson correlations were found to be −0.83 and −0.92 for Individuals 1 and 2). When TOWL vs nail plate thickness for the 2 individuals was grouped, the Pearson correlation was much lower (−0.42), suggesting that the nail plate thickness was not the only reason for the different TOWL values in the 2 subjects. Individual 2 had consistently lower TOWL values than Individual 1 for similar nail plate thicknesses. This implies that other factors such as the composition of the nail plate, e.g. lipid content, also influences TOWL. Although TOWL in a limited number of individuals was measured, this study explains the discrepancy in the literature, where Spruit showed an influence of the nail plate thickness on TOWL when he measured TOWL in one individual [1], while Jemec et al. concluded a lack of influence when they measured thumbnail TOWL in 21 individuals [3]. It is likely that in Jemec's study, large inter-individual variability masked the influence of nail plate thickness.

Table 1
Toenail TOWL in 2 individuals

Subject	Mean TOWL (g/m^2 h)± SD ; (n = 3–8)	
	Left big toe	Right big toe
1	47.8 ± 1.7	40.4 ± 2.2
2	30.5 ± 1.2	29.6 ± 1.6

TOWL could only be measured for the big toes where the nail plate had an area that was sufficient for probe application. For each individual, the TOWL values were measured on the same day.

3.3. Inter-hand/foot variability in TOWL

TOWL values for the same digits of the opposite hands of the same individual were found to be different, though the difference was not very large (Fig. 3). The small differences in TOWL values were not related to the different thicknesses of the opposite fingernails (listed in the legend of Fig. 3) as shown by different left and right hand thickness-normalized TOWL values (not shown). Such small differences in TOWL were also recorded between the right and left, index and middle fingernails in another individual (data not shown). Toenail TOWL of the opposite feet was also found to be different in one, but not a second individual (Table 1). Different TOWL values in opposite finger and toenails were not unexpected, as the nails cannot be expected to have exactly the same thickness and/or composition. This shows that the opposite digits should not be used as controls for one another.

3.4. Inter-day variability in TOWL

When TOWL for the same finger/toenail (in the same individual) was measured on different days, TOWL was found to vary to a small extent. The % coefficient of variation in TOWL values measured on 8 different days for the left index fingernail and left and right toenails in one individual was found to be between 7% and 11%. Some of the inter-day variability in TOWL for the same nail could be assigned to slightly different relative humidities on different days. When the relative humidity and TOWL over the 8 days were plotted together (Fig. 4), the relative humidity profile reflected the TOWL profiles to a certain extent, and Pearson correlation values of 0.5–0.6 were found. Similar results, but with slightly lower Pearson correlation values (0.3–0.5) were found when all the left hand fingernails TOWL was measured on 3 days for a different individual.

Increase in relative humidity of the environment is expected to increase water content of the nail plate (especially of the upper nail layers), as more water is absorbed by the nail plate from the atmosphere and/or as less water is lost from the nail plate to the atmosphere. A direct relationship between relative humidity and nail water content has been reported in vitro and to a much smaller extent, in vivo [12–15]. Gunt and Kasting measured the water content of nail (g water/g dry nail tissue) to increase by approximately 24% or 31% (when water content was measured by desorption or uptake, respectively) when the relative humidity was increased from 30% to 44% [15]. Increased nail water content could result in higher TOWL, as more water was available in the nail for diffusion into the TOWL measurement chamber. In addition, it has been shown that water diffusivity in nail plates increases greatly with nail plate hydration [16]. Such increased water diffusivity would also contribute to increased TOWL. The variability in TOWL values on different days shows the importance of taking TOWL measurements in a room with controlled humidity, and of resting the subjects in that room prior to measurements in order to increase the accuracy of measurements.

3.5. Influence of nail plate hydration and dehydration on TOWL

It is easily observed that nail plates rapidly absorb water when exposed to the latter, for example, during handwashing, and that they also subsequently lose the absorbed water. In this study, we attempted to measure the speed of water absorption and desorption using TOWL measurements. Following various periods of fingernail immersion in distilled water, the nail was blotted dry and TOWL was measured immediately. TOWL increased rapidly as the water absorbed by the nail plate during immersion was released during TOWL measurement (inset of Fig. 5). The longer the duration of fingernail immersion in water, the greater amount of water was absorbed by the nail plate and subsequently released, i.e. the greater the TOWL, until a saturation point was reached after a 5-min immersion in water. This reflects the everyday observation of rapid water absorption by the nail plates when exposed to water. The plateau observed after a 5-min immersion in water (inset of Fig. 5) also reflects saturation in weight gain within 10 min when nail clippings were incubated in water and weighed at time intervals (data not shown).

Sequential (at 5-min intervals) TOWL measurements after water exposure show the rate of water desorption from the hydrated fingernails (Fig. 5). Most of the absorbed water was lost from the nail plate within 5 min of removal from the water bath. After the first 5 min, however, smaller changes in TOWL were observed, showing a much slower rate of water desorption from the nail plate until control (dry) TOWL values were reached. As expected, the longest times to return to control values were found for nail plates that had absorbed the greatest amount of water, i.e. those with the longest incubation times in water ($\geqslant$5 min). The large difference between the speed of water absorption (maximal within 5 min) and that of desorption (up to 35 min) was, however, quite surprising. Fig. 5 shows the importance of avoiding contact with water prior to TOWL measurements, and if nails have been wetted, of waiting for a sufficient time period (in that individual, 35 min) before taking TOWL readings. Nail plate variability between individuals means that a 35-min wait for desorption of any absorbed water may not necessarily be applicable for all individuals.

3.6. Influence of pharmaceutical and cosmetic filing of nail plate surface on TOWL

The nail plate is said to be composed of 3 layers; dorsal (topmost), intermediate and ventral (next to nail bed). Kobayashi et al. calculated the thickness ratio of each layer to be 3:5:2 for dorsal: intermediate: ventral [17]. In clinical trials, filing the nail plate surface prior to drug application/re-application was found to be essential for the success of topical treatment [18,19], and patient information leaftlets of the pharmaceutical lacquers, Curanail, Loceryl®, Penlac® and Nailon™ advise patients to file the infected parts of the nail plate before applying the lacquer. Kobayashi et al. [17] found that filing the dorsal nail greatly increased drug flux in vitro and suggested that the dorsal nail surface is the main barrier to drug penetration into the nail plate.

In this study, we attempted to measure filing-induced changes in nail plate barrier properties by measuring TOWL after each filing stroke (Fig. 6). As expected, TOWL increased as filing removed sequential layers of the nail plate. TOWL did not, however, increase proportionally with the number of filing strokes or to the same extent in the 2 individuals or for finger and toenail in the same individual. In Individual 1, more than 5 filing strokes were needed before a substantial rise in TOWL was observed, whereas in Individual 2, the first filing stroke caused considerable increase in TOWL, i.e. considerable reduction in the barrier properties of the nail plates. In the same Individual 2, toenail TOWL increased to a greater extent compared to fingernail TOWL, at least initially.

The observed differences could be due to a number of factors, for example, a harder nail plate in Individual 1 such that less nail plate was removed at every filing stroke, a thinner dorsal layer in Individual 2 such that a large proportion of the dorsal nail layer (the main barrier) was removed after the first filing stroke, and different permeabilities of the dorsal nail layer in the 2 individuals. While these factors were not investigated in detail, the TOWL profiles in Fig. 6 show that nail plate filing is likely to increase nail plate permeability, though to different extents in different individuals.

The surface of healthy nail plates is also often filed for cosmetic purposes, for example, to increase shine. Like pharmaceutical filing, cosmetic filing increased TOWL as some of the topmost nail surface was removed. However, the surface of the cosmetic file being much smoother than the pharmaceutical one, the increase in TOWL was much smaller: 120–125% of the original value compared to around 200% with the pharmaceutical file.

3.7. TOWL measurements to evaluate and compare nail varnish formulations

Spruit reported a significant decrease in a fingernail TOWL, from 16 to 4 g/m^2 h upon the application of nail varnish, and hypothesized that the reduced water loss from the nail surface to the atmosphere could result in nail hyperhydration, especially of the upper nail layers [2]. Marty suggested that such hyperhydration by nail lacquers could assist drug diffusion into the nail [20]. Subsequently, Gunt and Kasting showed (by incubating nail plates at different relative humidities) that in vitro nail hydration did indeed increase diffusivity of water and of the anti-fungal ketoconazole in the nail [16,21]. While the hydration state of varnished nail plates has not been reported to our knowledge, one could hypothesize that nail varnish formulations which cause the greatest reduction in TOWL could cause the greatest increase in nail plate hydration and thereby the greatest enhancement of drug permeation into the nail. Before such a hypothesis is tested, we measured changes in TOWL upon nail varnish application and removal, in an attempt to determine whether TOWL could be used to evaluate and compare different nail varnish formulations (Fig. 7).

It can be seen that application of one coat of nail varnish formulations decreased TOWL (as water loss from the nail surface was impeded by the nail varnish film), and that its subsequent removal resulted in TOWL returning to baseline values. Slightly different profiles were obtained with the varnish formulations, which reflected the different polymeric films formed on the nail plate following application of the nail varnish, and their different permeabilities to water vapor. The latter is known to depend, to a large extent, on the nature of the polymer which was nitrocellulose, poly(tetrafluoroethene), Eudragit RL100, butylmonoester of poly(methylvinyl ether/maleic acid) in the cosmetic nail varnish, Teflon Tuff™, Curanail and Penlac®, respectively. So far, we have not been able to determine the nature of the polymer in Nailon™.

The profiles in Fig. 7 show that TOWL measurements could be used to compare nail varnish preparations for their ability to reduce TOWL, and thereby compare their ability to increase nail plate hydration and drug permeation, at least in initial studies, if the hypothesis above is proven.

4. Conclusions

A wide range of TOWL values were found, which correlated to a certain extent with the literature. The significant inter-individual variability observed indicates the difficulties when TOWL values are averaged for comparison purposes. The lower intra-individual variability observed suggests that using an individual's own nails as controls, e.g. when investigating the influence of disease, might be more appropriate. However, intra-individual variability among fingers of the same hand and opposite (left/right) fingers/toes was found, which showed that, whenever possible, a nail should serve as its own control. The inter-day variability in TOWL suggests a possible influence of the environment's humidity on nail water content, though this needs further in vivo investigation. The rapid response in TOWL upon nail wetting warns that the subject should avoid nail wetting for a suitable period before TOWL measurements. As expected, filing increased TOWL considerably while varnish application reduced TOWL. The variable extent of TOWL reduction by different nail varnish products suggests a potential use of TOWL measurements in product comparisons.

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