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Modified TEWL in vitro measurements on transdermal patches with different additives with regard to water vapour permeability kinetics

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ABSTRACT

Water vapour permeability (WVP) and water absorption capacity (WAC) influence physicochemical properties and wearability of transdermal patches considerably. For determination of WVP, a modified transepidermal water loss (TEWL) measurement was developed. These measurements continuously measure WVP of transdermal patches in vitro along with time required to reach steady state, and its magnitude according to the type of polymer used. Additionally, WAC of the patches was examined and related to WVP. According to literature in the field of WVP determination, usually selected points are taken from the evaporation time curve and averaged over a given time span without knowing whether steady state has already been reached or not. The latter causes errors upon averaging. The advantage of the in vitro TEWL measurement presented includes reproducibly adjustable conditions for every time span desired, thus providing information on the kinetics of the experiment and avoiding biased results from averaging. Knowing the shape of the evaporation time curve and thus the kinetics of the experiment allows for focusing on the relevant part of the measurement, i.e. the determination of the steady state level and the time to reach it.

Four different polymers (P1–P4) based on sugar-modified polyacrylates were investigated with regard to WVP and WAC of the matrices prepared thereof along with the influence of drug loading and the incorporation of a variety of additives commonly used for transdermal patches. A clear correlation between WVP and the hydrophilicity in terms of the number of free hydroxyl groups of the polymer was elaborated. Additives of higher hydrophilicity compared to that of the polymer itself led to higher WVPs and vice versa. The combination of the model drug lidocaine in its free base form together with the additive succinic acid (Suc) resulted in ionization of the drug and thus in substantially increased WVPs. Addition of α-tocopherol acetate (Toc) into P3 and P4 and Suc into the drug-free matrix of P3 decreased WVP probably by affecting the structure of the polymer network. The same effects were found for WAC upon incorporation of succinic acid into drug-loaded matrices of P3 and P4 (drug-loaded patches of P1 and P2 were not tested) but not for additives which were likely to modify the polymer network structure.

1. Introduction

Transdermal patches are made of different layers mainly consisting of polymers. They are comprised of at least a backing membrane and an adhesive layer containing the active product ingredient (drug-in-adhesive type). These layers may be affected by water vapour permeation and especially by water absorption, influencing physicochemical properties and wearability of transdermal patches considerably. Furthermore, evaporation of water from the skin is hampered, potentially leading to occlusion and strong hydration of the skin along with an increase in skin permeability.

The main function of the stratum corneum (SC) as the outermost layer of the skin is to protect the organism against harmful substances from the environment and to prevent evaporation of water from the underlying viable tissue. The combination of the intercellular lamellar lipids along with the highly keratinized intracellular environment in the dead and flattened corneocytes make the stratum corneum a very effective barrier in this context. Normal healthy skin of the lower arm shows a water loss of approximately 5–10 g/m^2 per hour in dependence of the site (Pinnagoda et al., 1990; Casiraghi et al., 2002).

Under occlusive conditions the outermost layer of the skin, the SC, swells leading to an enhanced permeability for many drugs or other additives (Treffel et al., 1992; Qiao et al., 1993; Hotchkiss et al., 1992). Thus, the permeation behaviour of the active ingredient might be influenced. Besides this, the water vapour permeability

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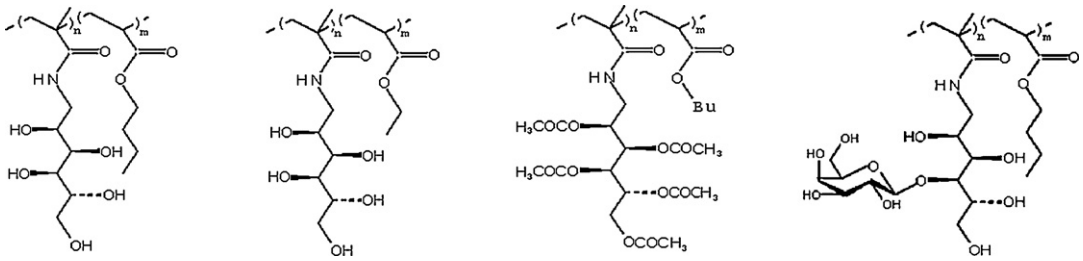

Fig. 1. Structural formulas of P1–P4 (from left to right).

of transdermal patches is crucial for their tolerability on the skin, especially when continuously applied for several days on the same site. Occlusive properties can break up the interlocking of the corneocytes and loosen the highly ordered structure of the SC (Neubert and Wepf, 2007) leading to skin irritation, maceration and thus a higher risk for bacterial infections (Bucks et al., 1991). Sometimes the regeneration takes longer than the patch-free interval allows. This leads to a poor patient compliance (Zhai and Maibach, 2001). Although literature describes the correlation between transepidermal water loss and percutaneous absorption or skin integrity (Lotte et al., 1987; Bucks and Maibach, 1999; Heylings et al., 2001; Levin and Maibach, 2005), only few data is available concerning the water vapour permeability (WVP) kinetics of transdermal patches in vitro (Fauth, 2003) and the changes brought about by different additives. Actually no data or explanation is given for the change in WVP kinetics determined on pure matrices without backing membranes.

Therefore, a continuous in vitro-method under reproducibly adjustable conditions should be developed to measure WVP of pure matrices of transdermal patches along with the effects of different additives. The patches were prepared from four different polymers made of polyacrylates functionalized with sugar moieties from growing raw materials (P1–P4).

Furthermore, WAC was determined because the level of hydration affects patch adhesion (Kenney et al., 1992). Adhesion of a patch to the skin is a crucial factor for transdermal patch administration (Minghetti et al., 2004; Wokovich et al., 2006). For good adhesive properties, two main aspects have to be met: viscoelasticity including both sufficient adhesive and cohesive properties, as well as good wetting of the skin by the patch matrix (Martin-Martinez, 2005). The latter implies an equal or lower surface tension of the patch compared to that of the skin itself.

The incorporated amount of water does not only affect viscoelasticity and surface tension but also solubility of incorporated substances, particularly solubility of the active product ingredient (API). Changes in solubility lead to changes in thermodynamic activity of a drug molecule, thus influencing its flux through the skin (Hadgraft, 2004).

2. Materials and methods

2.1. Materials

The polymers P1–P4 (molecular formulas and names see Fig. 1 and Table 1, respectively) were synthesized according to Kundratek (2007). Lidocaine (L), which has a log *P* value of 2.26 (Strichartz et al., 1990) was supplied by cfm Oskar Tropitzsch (Marktrewitz, Germany), α-tocopherol acetate (Toc) and glycerol (Gly) were purchased from Caesar & Loretz GmbH (Hilden, Germany), tributyl acetyl citrate (Tbac), succinic acid (Suc) and propylene glycol (Pg) were supplied by Sigma Aldrich (Steinheim, Germany). A Spectra/Por membrane (MWCO: 12–14.000, Spectrum Laboratories, Inc., Rancho Dominiguez, Canada) was used for mechanical support of the matrices during the experiments. Transtec® Placebo was supplied by Grünenthal GmbH (Aachen, Germany) and Testoderm®-TTS Placebo was supplied by Ferring Arzneimittel (Wien, Austria).

2.2. Patch preparation

Different amounts of drug, dry polymer and additives (total amount 700 mg) were weighed into vials and shaken until dissolved in 2.0 ml methanol. This mixture was cast on circular disks of siliconised PET foil (diameter 5.65 cm, resulting in patches with 27.9 mg/cm^2) and was let to dry for seven days at 23 ± 3 °C and 30–90% relative humidity.

The patches were labelled as follows: the type of polymer first, followed by the additives if applicable. L stands for 20% (w/w) lidocaine base. The content (w/w) of all the other additives is given in percentage as numbers placed in front of the abbreviations.

2.3. WVP measurement

For WVP, a TEWAMETER® Multiprobe Adapter 5 (Courage and Khazaka, Köln, Germany) was used, designed for measuring the transepidermal water loss (TEWL) in vivo with or without the application of dermatological or cosmetic products. The principle of measurement is based on Fick's first law (Eq. (1)), describing the diffusion flux *J* (amount of water per unit area per unit time). This flow of water molecules has its specific diffusion coefficient *D* and is proportional to the water vapour gradient between skin and surrounding atmosphere $\partial\phi/\partial x$ with concentration ϕ and position *x*.

$$J = -D\frac{\partial \phi}{\partial x} \quad (1)$$

Fick's first law only applies to a homogeneous diffusion zone which the probe of the TEWAMETER® allows for. The detector head of the probe is a hollow cylinder (10 mm inner diameter and 20 mm clear height), avoiding turbulent flow. Water evaporates from the skin and flows through the detector head. The resulting water vapour gradient between skin and surrounding atmosphere is measured by a pair of built-in sensors and transformed by a microprocessor. This measuring principle, based on the measurement of diffusing water, was first described by Nilsson (1977).

For the measurements circular samples with a diameter of 17 mm were punched out from the prepared patches and covered with same-sized SpectraPor membranes. The PET foil was removed and the samples were mounted with the SpectraPor membrane on the bottom side on a 5 ml tablet vial containing distilled water up to a marked position of about 3 mm beneath the sample. The rim of the vial was modestly lubricated with silicone paste to achieve a tight sealing between patch and rim of the glass. The SpectraPor membrane was necessary for mechanical support to prevent sagging of the patches due to softening of some patches during the experiments. This would have caused an uncontrolled larger diffusion area and thus false WVP data. In preliminary experiments, it was shown that the SpectraPor membrane had no impact on the