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Measuring drug saturation solubility in thin polymer films: Use of a thin acceptor layer

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ABSTRACT

The saturation solubility of scopolamine base in two pressure sensitive adhesive DURO-TAKs has been determined using the 5-layer laminate technique. The acceptor layer had a thickness of less than 25 μm to promote a rapid partitioning equilibrium. With DURO-TAK 87-2510 the saturation solubility is 5.2 ± 0.6% w/w when measured after 7 days. With DURO-TAK 87-4098 the saturation solubility is slightly higher, 7.9 ± 0.7% w/w after 7 days. These values remained constant up to approximately 30 days' experimental time. In both cases the acceptor was free of crystalline material at the end of the experiment. This strongly suggests that that equilibrium had been reached between the saturated solution in the acceptor layer and the crystalline drug still present in the donor layer. The addition of light liquid paraffin to the acceptor produced a solubilizing effect with 87-4098 but not 87-2510. We recommend some experimental conditions that we consider to be necessary to achieve a reliable and accurate result with this technique. If performed correctly, it can give a feasible result.

1. Introduction

A-drug-loaded thin film made of a pressure sensitive adhesive polymer is the central element of any transdermal system of the drug-in-adhesive type (Tan and Pfister, 1999). The saturation solubility of the drug in this polymer, c_s^*, influences some essential properties of the transdermal system, most especially the release rate. It is therefore one of the system properties that needs to be known to allow judicious selection of a suitable polymer for a particular drug. There are numerous experimental methods available to determine the saturated solubility of a drug in a thin polymer film. They are all burdened by the necessity to avoid supersaturation of the polymer film with the drug and the resulting over-estimation of saturation solubility value (Latsch et al., 2003). The five-layer-laminate technique was originally developed by Liu et al. (1997) to avoid the likelihood of supersaturation. It uses a donor layer of polymer that contains an excess of crystalline drug and is laminated via a separating membrane to an initially drug-free acceptor layer of the same polymer. The two external surfaces of this central sandwich construction are both laminated with backing film or release liner to complete the five-layer-laminate. At the limit of equilibrium partitioning the acceptor layer will take up sufficient drug to reach its saturation solubility in the polymer and be in equilibrium with the drug crystals still present in the donor layer.

In our previous work we used the five-layer-laminate technique to determine drug solubility in various pressure sensitive adhesives (Reismann and Lee, 2012). The kinetics of drug uptake were measured and showed that >100 days were required to reach partitioning equilibrium at room temperature. In a further paper we solved the one-dimensional diffusion equation for this problem using numerical techniques (Bänsch et al., 2014). By simulating the kinetics of partitioning of the drug between the three central layers of the sandwich it was shown that a key factor determining the time necessary to reach equilibrium is the thickness of the acceptor layer. Our previous use of an acceptor layer of 100 μm thickness (Reismann and Lee, 2012) is the evident cause of the prolonged duration of the experiment.

The current paper presents new experimental results obtained using an acceptor layer thickness of <25 μm. This should reduce the time necessary to achieve partitioning equilibrium to <10 days, although this will depend on drug diffusivity, D (Bänsch et al., 2014). For this work we selected scopolamine base as a model drug because of its relevance for transdermal systems. Two different polyacrylate pressure sensitive adhesives of the DURO-TAK series (Henkel, 2014) were used that differ in their hydrophilicity. An attempt was made to alter the saturation solubility of scopolamine in these polymers by adding light liquid paraffin. The results of this work demonstrate the decisive benefit to be obtained by using an acceptor layer that is as thin as can

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feasibly be prepared. It also makes clear the difficulties in preventing oversaturation even with this technique, and underlines the importance of performing a kinetic experiment rather than just measuring at a single time-point.

2. Materials and methods

2.1. Materials

Scopolamine free base was commercially obtained and used as received. DURO-TAK 87-2510 (Henkel Ltd., Slough, UK) is a non-cross-linked polyacrylate adhesive with —OH groups supplied as a solution in ethyl acetate/hexane (91:9). DURO-TAK 87-4098 is a polyacrylate/vinyl acetate adhesive, non-cross-linked and with no functional groups. It was supplied as a solution in ethyl acetate (Henkel Ltd., Slough, UK). The release liner was Primeliner 75 μm (Loparex, Appeldoorn, NL) which is siliconized polyethylene terephthalate of thickness around 75 μm. Perthese silicone sheet (Aromando Medizintechnik, Düsseldorf, Germany) was selected for use as the separating membrane and has a stated thickness of 125 μm. It processes a low solubility for moderately lipophilic drugs and shows a rapid take-up of drug from an adjacent polymeric donor layer (Liu et al., 1997; Reismann and Lee, 2012). Additionally, it could be separated from the adhesive donor and acceptor layers in a ready fashion. The backing film was Hostaphan med 15 μm (Mitsubishi Polyester Film, Wiesbaden, Germany). Light liquid paraffin EuAB was obtained from Sigma Aldrich (Munich, Germany) and used as received.

2.2. Methods

2.2.1. Thin polymer film preparation (donor and acceptor layers)

As required, the scopolamine base and light liquid paraffin were first dissolved in the ethylene acetate solution of the particular DURO-TAK under investigation. This solution was then cast as a thin liquid film onto a sheet of release liner using a laboratory-scale film-casting rack (Casting Knife; BYK-Gardner, Geretsried, Germany). The wet film thickness was adjusted via the blade height. This bilaminate was dried in a forced convection oven at 45 °C for 30 min and the dried bilaminate then covered with backing film to prevent dust adhesion to its sticky surface. If it was intended for use as a donor layer, the dried bilaminate was left for 7 days at 45 °C to allow crystallization of the drug. The release liner was removed before use. The acceptor films were used immediately after their preparation.

2.2.2. The 5-layer laminate technique (Liu et al., 1997)

This was performed as described in detail before (Reismann and Lee, 2012). Briefly, the 5-layer laminate was assembled by placing the Perthese separating membrane of thickness 125 μm onto the free side of the donor film bilaminate. The donor film had a thickness of 60–80 μm, its thickness being known to have only a very weak influence on the kinetics of drug uptake into the acceptor (Bänsch et al., 2014). The free side of the acceptor bilaminate was then placed on the remaining free side of the separating membrane to produce the complete 5-layer laminate. Cylindrical pieces of this laminate of diameter 1.6 cm were then cut-out with a punch and stored at room temperature for the duration of the experiment.

At each measurement-time 3 patches were analyzed to determine the drug concentration in the three central layers of the laminate. Each patch was first separated into its component layers for analysis. The donor bilaminate was first removed from the other layers. The Perthese separating membrane could then be removed from the underlying acceptor bilaminate. The drug contents of the donor and acceptor layers were determined after dissolving fully the polymer layer in acetone followed by precipitation of the polymer by adding sodium lauryl sulfate solution. The drug content of the separating membrane was determined by multiple extractions into acetone. In each case the dissolved scopolamine was determined using the HPLC method described below. The result is presented as % w/w of the drug in the

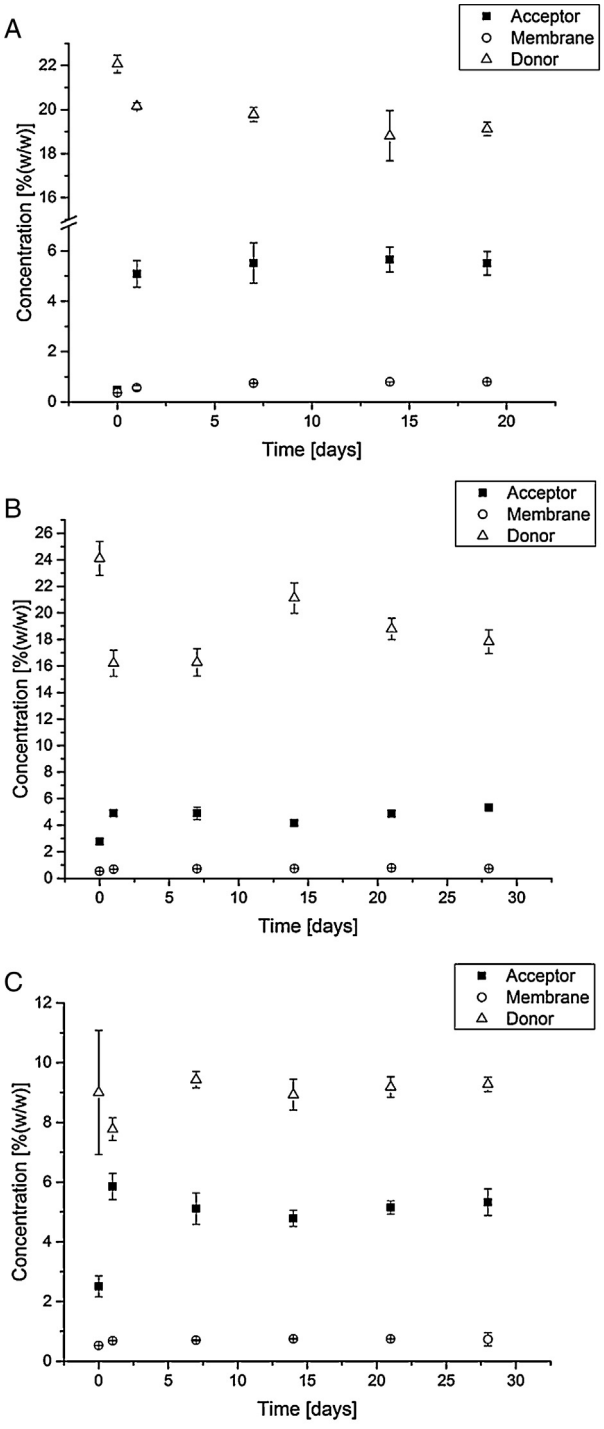

Fig. 1. 5-layer laminate experiment with scopolamine base in DURO-TAK 2510 under different pre-loading conditions. (a) $c_d(0) = 22\%$ w/w; $c_a(0) = 0.48\%$ w/w; acceptor layer thickness = 23.4 ± 10.3 μm. (b) $c_d(0) = 24\%$ w/w; $c_a(0) = 2.8\%$ w/w; acceptor layer thickness = 16.3 ± 2.4 μm. (c) $c_d(0) = 9\%$ w/w; $c_a(0) = 2.5\%$ w/w; acceptor layer thickness = 15.7 ± 1.2 μm. The three plots show the kinetic development of drug concentration in the donor layer, $c_d(t)$, drug concentration in the separating membrane, $c_{sm}(t)$, and drug concentration in the acceptor layer, $c_a(t)$.