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Release and Skin Permeation of Scopolamine From Thin Polymer Films in Relation to Thermodynamic Activity

Anders Kunst, Geoffrey Lee*

Division of Pharmaceutics, Friedrich-Alexander University, Erlangen, Germany

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ABSTRACT

The object was to demonstrate if the diffusional flux of the drug out of a drug-in-adhesive–type matrix and its subsequent permeation through an excised skin membrane is a linear function of the drug's thermodynamic activity in the thin polymer film. The thermodynamic activity, a_p^*, is defined here as the degree of saturation of the drug in the polymer. Both release and release/permeation of scopolamine base from 3 different poylacrylate pressure-sensitive adhesives (PSAs) were measured. The values for a_p^* were calculated using previous published saturation solubilities, w_p^s, of the drug in the PSAs. Different rates of release and release/permeation were determined between the 3 PSAs. These differences could be accounted for quantitatively by correlating with a_p^* rather than the concentration of the drug in the polymer films. At similar values for a_p^* the same release or release/permeation rates from the different polymers were measured. The differences could not be related to cross-linking or presence of ionizable groups of the polymers that should influence diffusivity.

Introduction

T. Higuchi[1] recognized that the flux of a drug permeating through a skin membrane under steady-state conditions, J [mol/m^{2}s], can be expressed in terms of the thermodynamic activity of the drug in its vehicle, a_p [mole/L]:

$$J = \frac{D \cdot a_p}{\gamma_m \cdot h} \tag{1}$$

where D [m^2/s] is the effective diffusivity of the drug and γ_m the activity coefficient of the drug in the skin membrane of thickness h [m]. Activity is related to mol fraction, x, in the usual way via the activity coefficient, γ:

$$a = \gamma \cdot x \tag{2}$$

The use of activity rather than concentration avoids a partitioning discontinuity at the polymer/skin membrane surface and hence use of a partition coefficient. If we define the activity as the degree of saturation of the drug in the vehicle (p), DS, then:

$$a_p = DS = \frac{x_p}{x_p^s} \tag{3}$$

where, x_p^s is the drug's saturation solubility [mole fraction] in the vehicle. Equation 1 now becomes:

$$J = \frac{D \cdot a_p \cdot x_m^s}{h} \tag{4}$$

Equation 4 predicts that J is a linear function of DS as long as the drug present in the vehicle is in molecular disperse solution and neither drug nor vehicle alters the barrier function of the skin membrane.[2] Because it is readily possible to prepare a metastable, supersaturated solution of many drugs in vehicles, this relation should also hold for values of DS >1.0. Indeed, a number of studies have demonstrated a linear relation between both the amount of drug permeation through or uptake into a membrane and the DS of the drug in the vehicle.[3-7] A current issue is to find ways of maintaining the metastable, supersaturated state of the drug over a sufficiently long period to allow its exploitation for percutaneous enhancement in practice.[8]

Equation 4 should also hold independent of the vehicle's composition. This means that at any particular value of DS the flux should be the same in different vehicles, although the drug concentrations, x_p, in the vehicles are different because of differing

* *Correspondence to:* Geoffrey Lee (Telephone: 49 9131 8529551; Fax: 49 9131 8529545).
E-mail address: geoff.lee@fau.de (G. Lee).

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saturation solubilities.[9] To demonstrate this requires showing that the flux depends linearly on *DS* and, hence, a_p^* but is independent of x_p, that is, the drug concentration between the different vehicles. This has indeed been shown for permeation data from saturated and supersaturated drug solutions in liquid and semisolid formulations.[9]

This article contains the results of our efforts to show this effect using thin polymer films that are suitable for use as drug-in-adhesive–type transdermal systems. We selected 3 different polyacrylate pressure-sensitive adhesives (PSAs) from the DURO-TAK product range. The saturation solubilities as weight fraction, w_p^s [wt/wt], of the model drug scopolamine base in thin films made of these PSAs have been determined using the 5-layer laminate technique[10,11] and published in a previous article.[12] We have measured the drug flux out of the thin films and through membranes of hairless mouse skin. Because the scopolamine shows different saturation solubilities in the 3 PSAs, the flux could be measured at a number of fixed drug concentrations in the thin films, w_p^0, that are equivalent to different *DS*s and a_p^* in the various polymers. The results should demonstrate if the different fluxes between the 3 PSAs each loaded at the same w_p^0 can be correlated to the differing w_p^s and hence also differing *DS* between the PSAs.

Materials and Methods

Materials

Scopolamine-free base was obtained commercially and used as received. The DURO-TAK PSAs were all obtained from Henkel Ltd. (Slough, United Kingdom); 87-2510 is a non–cross-linked polyacrylate with -OH groups supplied as a solution in ethyl acetate/hexane (91:9); 87-4098 is a non–cross-linked polyacrylate/vinyl acetate that carries no functional groups. It was supplied as a solution in ethyl acetate; 87-2677 is a self-curing polyacrylate with -COOH groups and supplied as a solution in ethyl acetate/isopropanol/heptane/toluene (37:37:21:5). Primeliner 75 μm (Loparex, Appeldoorn, The Netherlands) was used as a release liner and is siliconized polyethylene terephthalate of thickness around 75 μm. Hostaphan med 15 μm (Mitsubishi Polyester Film, Wiesbaden, Germany) was used as the backing film.

Cellulose acetate membrane filters of pore diameter 0.2 μm (Sartorius Stedim Biotech, Göttingen, Germany) and excised hairless mouse whole-skin membranes (athymic nude Foxn1nu; Harlan Labs, Venra, Holland) were used. The mouse whole-skin membranes were received as 8 × 8-cm sheets stretched on a polystyrere grid and were stored as such at −20°C until used.

Preparation of Thin Polymer Films

The scopolamine base was dissolved in the organic 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 to 150 μm via the blade height. This was dried in a forced convection oven at 45°C for 30 min and then covered with backing film. Circular laminates were cut out individually with a diameter of 2 cm and a dry adhesive-layer thickness of 50 μm.

Measurement of Drug Release Rate

The release liner was removed from a transdermal therapeutic system, which was then placed and adhered over the circular orifice (area = 1.05 cm^2) of a vertical-type diffusion cell,[13] which was already covered by a prewetted membrane filter. The acceptor chamber was filled with 15 mL of 0.05 M (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) buffer at pH 7.2 containing 0.05% wt/vol sodium azide as a preservative. The filled diffusion cell was placed in the custom-made heating/stirring block at 32°C and stirred at 200 rpm. Samples of 5 mL were drawn from the acceptor solution at various times and replaced with blank buffer. These were then assayed for their scopolamine content using the HPLC described fully before.[12]

Measurement of Drug Permeation Rate

This was performed as described previously for drug release rate but using a mouse skin membrane in place of the membrane filter. This was cut to a circular shape of 2 cm^2 that fitted over the circular orifice of the diffusion cell.

Results and Discussion

Figure 1a gives the release profiles for scopolamine out of the thin films of 87-4098 through the membrane filter. The latter is of the foam-type and has a high porosity but a low tortuosity of close to unity. The plots of amount released, $m_{rel}(t)$, versus root time, $\sqrt{t}$, show a short lag-phase because of the presence of the membrane filter followed by an approximately linear section. We take the slope of this section, $\Delta m_{rel}(t)/\Delta\sqrt{t}$, which has units of $\mu g/cm^2 min^{1/2}$, as a quantitative measure of the release profile and release rate. In Figure 1b, we see the permeation profiles of amount permeated, $m_{per}(t)$, versus t out of these same thin films through the mouse skin membrane. The lag-phase is much longer because of the higher diffusional resistance of the skin, followed by a linear steady-state phase lasting until at least 33 h. We characterize the permeation profile by its slope, $\Delta m_{per}(t)/\Delta t$. Note that the corresponding release and permeation profiles from the thin films of 87-2510 and 87-2677 PSAs are not shown here, for brevity, but differ from those in Figures 1a and 1b only in their slopes.

The plots of $\Delta m_{rel}(t)/\Delta\sqrt{t}$ versus initial scopolamine content, w_p^0, are shown in Figure 2a for the release experiments with the different DURO-TAK types examined. All 3 plots show an approximately linear relation between release rate and w_p^0. It is evident that the release rate out of the thin films at any particular w_p^0 depends on the polymer and increases in the sequence: 87-2677 < 87-4098 < 87-2510. The plots for the skin permeation experiments in Figure 2b of $\Delta m_{per}(t)/\Delta t$ versus initial scopolamine content, w_p^0, are also linear up to the highest w_p^0 examined here. The permeation rate through the skin membrane at any particular w_p^0 increases in the same sequence as for release, that is, 87-2677 < 87-4098 < 87-2510.

The combined release/permeation problem appears therefore to be determined by the release rate out of the polymeric thin film. The 3 different polymers produce different permeation profiles. The applicable expression for release from a slab of thickness h into a well-stirred donor during early times is[14]:

$$m_{rel}(t) = 4m_p^0\left(\frac{Dt}{\pi h^2}\right)^{1/2} \quad (5)$$

where m_p^0 is the initial drug mass and *D* the diffusivity of the drug in the slab. According to Equation 4, the different slopes of the plots in Figure 2a might be caused by different diffusivity of the scopolamine molecules in the different polymer thin films. There is, however, no clear correlation between diffusion-relevant properties of the 3 polymers and the sequence of release rates. For example, 87-2677 is the only self-curing polymer of the 3 DURO-TAKS examined here and indeed has the lowest release rate. Cross-linking has been shown to reduce the rate of drug release