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SATURATION SOLUBILITY OF SCOPOLAMINE IN THIN FILMS OF POLYACRYLATE PRESSURE SENSITIVE ADHESIVES IS TEMPERATURE DEPENDENT

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ABSTRACT: The method of drug uptake from solid solution has been used to measure the saturation solubility of scopolamine base in various pressure sensitive adhesive DURO-TAKs at elevated temperature. The saturation solubility was strongly temperature dependent, being 50 – 100 % larger at 45°C than at 25°C. The higher temperature also caused much more rapid approach to equilibrium distribution of the drug between donor, separating membrane, and acceptor layers. With a cross-linked DURO-TAK 87-2677 the saturation solubility is 10.7 ± 0.30 % (n=4) at 25 °C, rising to 16.5 ± 0.54 % at 45 °C (n=4). The non-cross-linked DURO-TAK 87-4098 gives lower values of 6.3 ± 0.27% w/w(n=4) at 25 °C, rising to 13.2 ± 1.14 % at 45 °C. The hydrophobic DURO-TAK 87-2510gives the lowest values of 4.2 ± 0.17 % w/w (n=4) at 25 °C and 8.7 ± 0.45 % (n=4) at 45°C. The thermodynamic activity of the drug in the thin polymer film will therefore decrease as temperature increases.

INTRODUCTION: The saturation solubility of a drug in the thin film of pressure sensitive adhesive of a drug-in-adhesive type of transdermal system influences its release rate from the film. There are various experimental methods available to determine the saturated solubility, including detecting of crystalline drug in the polymer film using light microscopy, differential scanning calorimetry, wide-angle X-ray diffraction, infra-red or Raman spectroscopy, measurement of drug release rate, crystal seeding, and drug uptake from a liquid solution or a solid solution [1]. Most of these techniques encompass the danger of super-saturation of the polymer film with the drug and a resulting over-estimation of saturation solubility value [2].

The two techniques that appear best to minimize this danger are crystal seeding and drug uptake from a solid solution. The published work citing results using these techniques gives values determined at a single temperature, i.e. room temperature or 25°C [3]. We could find no published literature that examines experimentally the effects of temperature on the saturation solubility of a drug in such thin polymer films made from pressure sensitive adhesives. We have measured saturation solubilities only at 25°C [3-5] and have never considered if the technique od drug uptake from solid solution could be done at elevated temperature.

In this short paper we present some results to measure the saturation solubility of the drug scopolamine base in thin films of polyacrylates at 25 °C and 45 °C. This elevated temperature was chosen to improve the likelihood of finding a clearly measurable effect of temperature on solubility, if such exists. We selected the technique of drug uptake from a solid solution developed by

Liu et al [1] and extensively further investigated by us [3 - 5]. 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.

A diffusion-driven equilibrium partitioning of the drug between the three layers will start as soon as the laminate is prepared. The acceptor layer will take up sufficient drug to reach its saturation solubility in the polymer. The results of this work demonstrate that this technique works also at elevated temperature and that the saturation solubility is indeed strongly temperature dependent.

MATERIALS AND METHODS:
Materials:
Scopolamine free base was commercially obtained and used as received. DURO-TAK 87-2677 (Henkel Ltd., Slough, UK) is a self-curing polyacrylate adhesive containing-COOH groups. It is supplied as a solution in ethyl acetate/isopropanol/heptane/toluene (37:37:21:5). DURO-TAK 87-2510 (Henkel Ltd., Slough, UK) is a non-cross-linked polyacrylate adhesive with -OH groups. It is supplied as a solution in ethyl acetate/hexane (91:9). DURO-TAK 87-4098 (Henkel Ltd., Slough, UK) 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 used as the separating membrane and has stated a thickness of 125 µm. The backing film was Hostaphan med 15 µm (Mitsubishi Polyester Film, Wiesbaden, Germany).

Methods:
Thin polymer film preparation (donor and acceptor layers)
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(for acceptor) or backing film (for donor) using a laboratory-scale film-casting rack (Casting Knife;

BYK-Gardner, Geretsried, Germany). The wet film thickness was adjusted via the blade height. This was dried in a forced convection oven at 45 °C for 30 min. If intended as a donor layer, it was left for 7 days at 45 °C to allow crystallization of the drug. If intended as an acceptor layer, it was used immediately after preparation.

Measurement of saturation solubility: [8]
This was performed as described in detail before [3, 5]. In brief, amulti-layer laminate was assembled by placing the Perthese separating membrane onto the free side of the donor film. The free side of the acceptor film was then placed on the remaining free side of the separating membrane.

The result was a central 3-layer laminate of donor/membrane/acceptor covered on its top and bottom sides by release liner or backing film, respectively. Cylindrical pieces of this laminate of diameter 1.6 cm were then cut-out with a punch and stored at either 25 °C ± 0.2 °C or 45 °C ± 0.2 °C for the duration of the experiment.

At each measurement time 3 patches were analysed to determine the drug concentration in the each layer of the central 3-layer laminate, as fully described before [5]. The HPLC method used to determine the extracted scopolamine has also been described before [5].

RESULTS AND DISCUSSION:
Fig. 1A &B show a comparison of the distribution kinetics of the scopolamine for the DURO-TAK 2677 thin polymer films at T = 25 °C and T = 45°C, respectively. These data are presented as two figures for the sake of clarity. The three profiles in each figure show the scopolamine concentrations within the donor layer, $c_d(t)$, in the separating membrane, $c_{sm}(t)$, and in the acceptor layer, $c_a(t)$. Each co-ordinate pair is given as the average ± standard deviation of n = 3 replicate laminates. In both experimental series the donor layer contained initially approximately 30 % w/w scopolamine base and was extensively crystallized.

The acceptor layer was pre-loaded with approximately 1 % w/w of the drug and was isotropic.
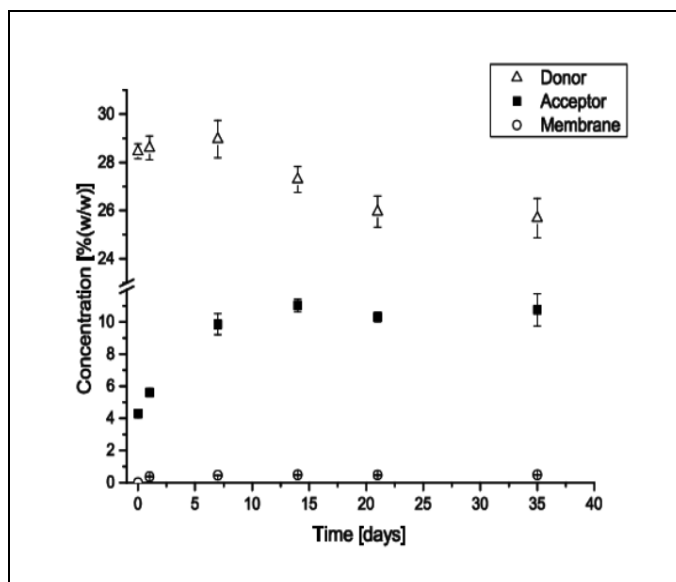
(A)
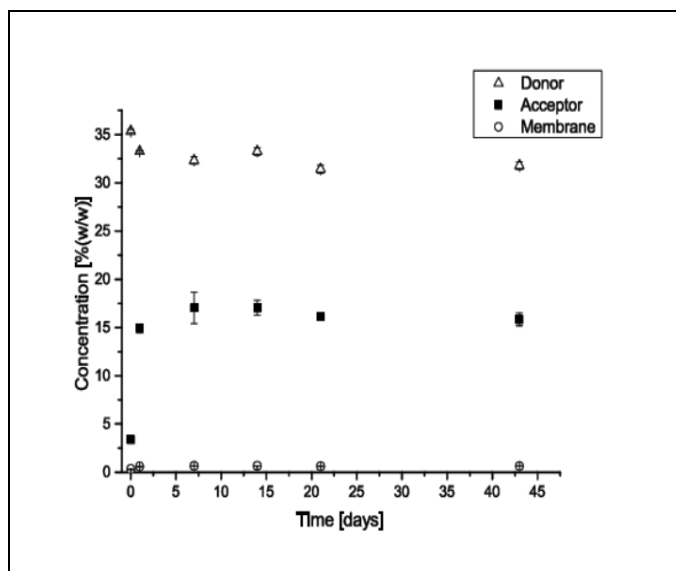
(B)

FIG. 1: DURO-TAK2677AT A) 25 ° C and B) 45° C. A) $c_d(0) = 34$ % w/w; $c_a(0) = 1$ % w/w;B) $c_d(0) = 25.7$ % w/w; $c_a(0) = 0.9$ % w/w.

It is evident that the equilibrium distribution between the 3 layers is more rapidly reached at the higher than at the lower temperature. Furthermore, the equilibrium saturation solubility in the acceptor layer, c_s^*, is substantially larger at the higher temperature. The more rapid attainment of equilibrium can be explained by higher diffusivity, D [cm^2/s], of the scopolamine within the polymer layers of DURO-TAK 87-2677. This has been demonstrated by simulations using a numerical solution to this 3-layer diffusional problem [4]. The values for c_s^* read-off from the individual plots of $c_a(t)$ are 10.7 ± 0.30 % and 16.5 ± 0.54 % at T = 25

°C and T = 45 °C, respectively (**Table 1**). The saturation solubility is therefore increased by more than half at the higher temperature. Because this is only a two-point measurement, the type of relationship between c_s^* and T cannot be ascertained, for example linear or a Arrhenius-type. It is, however, possible to say that the dissolution of the drug in the polymer film is an endothermic process[6].Note that the equilibrium solubility of the scopolamine in the Perthese separating membrane is not measurably increased by temperature in the range examined but remains at the low level of < 0.5 %.

TABLE 1:SATURATION SOLUBILITIES, c_s*, OF SCOPOLAMINE BASE IN VARIOUS DURO-TAKs. MEAN ± SD (n = 3)

| DUROTAK Conditions	T = 25 °C			T = 45 °C		
	$c_d(0)$ [% w/w]	$c_a(0)$ [% w/w]	c_s* [% w/w]	$c_d(0)$ [% w/w]	$c_a(0)$ [% w/w]	c_s* [% w/w]
87-4098	34.0	1.0	6.3 ± 0.27	25.7	0.9	13.2± 1.14
87-2510	24.0	2.8	4.2 ± 0.17	27.2	0.97	8.7 ± 0.45
87-2677	28.5	4.3	10.7 ± 0.30	35.4	3.4	16.5± 0.54

Change to the non-cross-linked DURO-TAK 87-2510 reaches equilibrium after a shorter time, and to a lower value of saturation solubility of the scopolamine at both 25 °C (**Fig. 2 a)** and 45 °C (**Fig. 2 b**). The rate of uptake of scopolamine into the acceptor at times up to 2 days is, however, the same with both polymers. With DURO-TAK 2510 this uptake is completed after 2 days, but with DURO-TAK2677 the uptake continues until equilibrium is reached at day 15. This indicates that the diffusivity of the scopolamine is similar in both polymers. The observed shorter time to reach equilibrium in DURO-TAK 2519 is just a result of the higher value of c_s* that has to be reached.

Again, the equilibrium distribution between the 3 layers is more rapidly reached at the higher temperature.

The equilibrium saturation solubility in the acceptor layer, c_s*, isalso larger at the higher temperature. The values for c_s* are 4.2 ± 0.17 % and 8.7 ± 0.45 % at T = 25 °C and T = 45 °C, respectively (Table 1). Note that the saturation solubility of scopolamine in DURO-TAK 87-2510 is therefore more than doubled at the higher temperature. This means that the effect of temperature on c_s* is stronger than that seen with the DURO-TAK 87-2677.
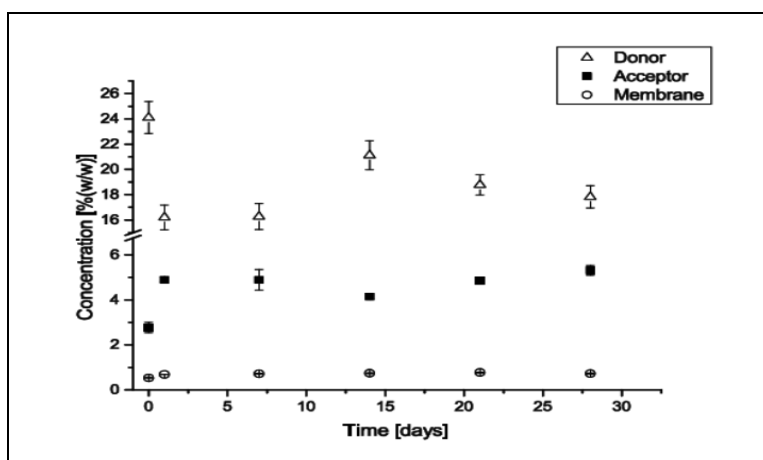

(A)
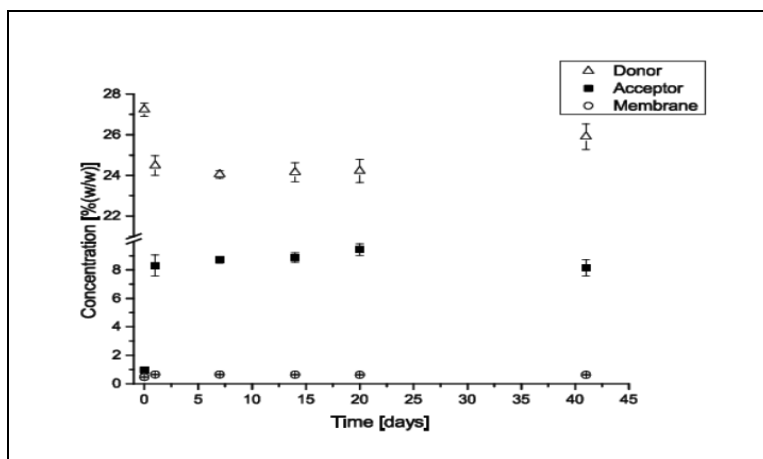
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FIG.2:DURO-TAK 2510AT A) 25 ° C and B) 45° C. A) $c_d(0)$ = 24 % w/w; $c_a(0)$ = 2.8 % w/w;B)$c_d(0)$ = 27.2 % w/w; $c_a(0)$ = 0.97 % w/w.

The third polyacrylate examined here, DURO-TAK 87-4098, is a further non-cross-linked polymer. The equilibrium distribution between the 3 layers at 25 ° C (**Fig.3A**) takes, however, much longer, 15 days, than the 2 days with DURO-TAK 87-2510 (cf. **Fig.2A**) despite the saturation solubility being lower. This means that the rate of uptake is slower into DURO-TAK 87-4098 than DURO-TAK 87-2510. This suggests a lower diffusivity of the

scopolamine in the DURO-TAK 87-4098 than in the other 2 polymers. We find therefore no correlation between rate of uptake and cross-linking of the polymers. The rate of uptake is lowest with the non-cross-linked DURO-TAK 87-4098. Furthermore, it does not differ between the non-cross linked DURO-TAK 87-2510 and the cross-linked DURO-TAK 87-2677.
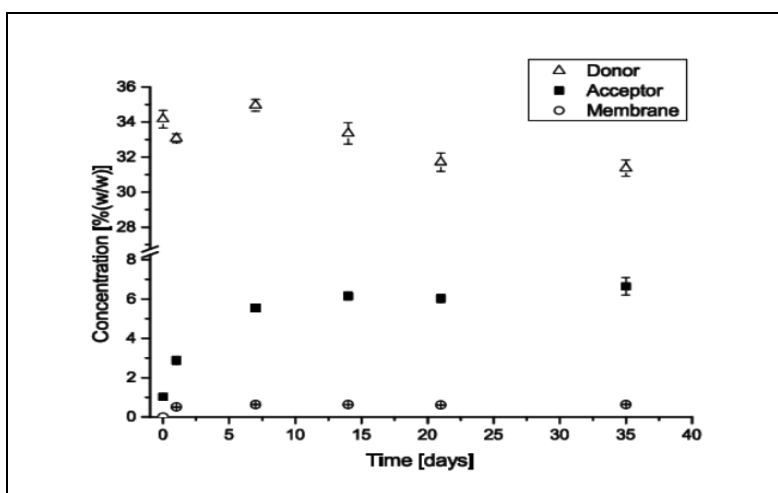
(A)
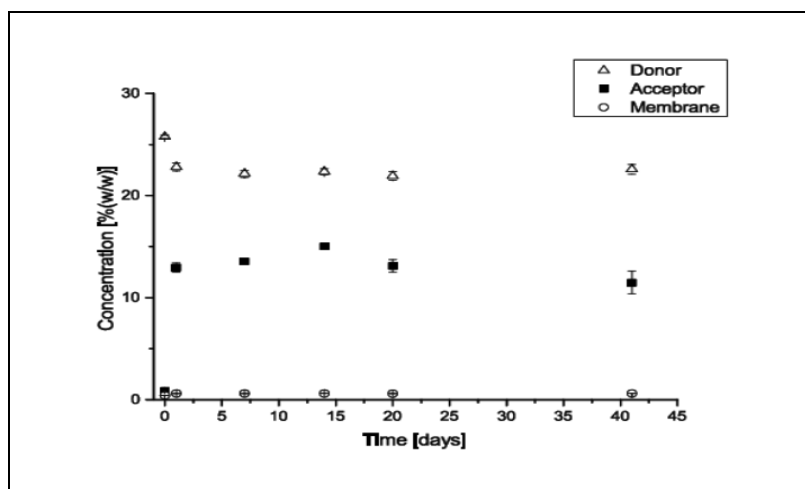
B)

FIG.3: DURO-TAK 4098AT A) 25 ° C and B) 45° C. A) $c_d(0) = 28.5$ % w/w; $c_a(0) = 4.3$ % w/w; B) $c_d(0) = 35.4$ % w/w; $c_a(0) = 3.4$ % w/w.

In DURO-TAK 87-4098 the equilibrium saturation solubility in the acceptor layer, c_s^*, is again larger at 45 °C (**Fig. 3 B**) than at 25 °C (**Fig. 3 A**). The values for c_s^* are 6.3 ± 0.27 % and 13.2 ± 1.14 % at T = 25 °C and T = 45 °C, respectively (**Table 1**). The saturation solubility is therefore again more than doubled at the higher temperature. This is the same effect of temperature on c_s^* than seen with DURO-TAK 87-2510 above.

The % recovery, R, of the scopolamine from the three polymer layers is calculated from:

$$R[\%] = \frac{m_a(t) + m_{sm}(t) + m_d(t)}{m_a(0) + m_{sm}(0) + m_d(0)} * 100$$

This is a mass balance equation would should account for all of the drug present in the laminate at any time point. The results for recovery are given in **Table 2** for the different polymers at the two

different temperatures. The time point selected for calculation was at onset of equilibrium distribution at = 1 day for DURO-TAK 87-4098 and 2510 at T = 45°C, and t = 7 days for all DURO-TAKs at T = 25°C and the DURO-TAK 2677 at both temperatures.

In almost all experiments the recoveries deviate only marginally from 100 % (**Table 2**). The exception is DURO-TAK 2510 at T = 25 °C where only some 80 % recovery is found. The reason for this deviation is evident from the kinetic profiles of this experiment in **Fig. 2 a**. There is substantial erratic variation in the measured values for $c_d(t)$which will give a large variation in $m_a(t)$ a correspondingly large variation in the calculated recovery [12].

TABLE 2: CALCULATED RECOVERY, R, OF SCOPOLAMINE. MEAN ± SD (n = 3).t = 1 DAY (87-4098 AND 87-2510 @ 45 °C) or t = 7 DAYS (ALL @ 25 °C AND 87-2677 @ 45 °C)

DURO-TAK	R at T = 25 °C	R at T = 45 °C
87-4098	102 ± 0.5	104 ± 0.5
87-2510	82.1 ± 1.8	102 ± 1.7
87-2677	107 ± 1.4	98.7 ± 0.43

One further issue to note is that crystalline material was not observed visually within any of the acceptor layers at the end of these experiments with the three different DURO-TAKS. This means that the drug's saturation solubility in the acceptor has not been exceeded during drug uptake. Super-saturation of the acceptor is also unlikely to have occurred, otherwise the set of three profiles in each of the Figures would not so clearly have reached equilibrium.

CONCLUSION: The results of this work allow the following conclusions to be drawn:

1. The method of drug-uptake from solid solution can be used to determine the saturation solubility of a drug in a thin polymer film at temperatures above the ambient.

2. The saturated solubility of scopolamine in the three DURO-TAKs examined is strongly temperature dependent, being 50 – 100 % higher at 45 °C than at 25 °C.

3. In the cross linked DURO-TAK 2677 the saturation solubility is highest. It is lowest in the non cross-linked hydrophilic DURO-TAK 2510.

4. The strong temperature dependence of the saturation solubility means that the thermodynamic activity of the drug in the thin polymer film [7] will decrease at higher temperature. This could alter the rate of drug release [8].

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