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Release of chemical permeation enhancers from drug-in-adhesive transdermal patches

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Abstract

There is only limited knowledge of how chemical permeation enhancers release from transdermal drug delivery systems of the drug-in-adhesive type. In this study, the release of eight commonly known enhancers from eight types of polymer adhesives was evaluated using Franz diffusion cells. It was shown that all the enhancers released completely from the adhesives and followed a square root of time kinetic (Higuchi law). Using a statistical analysis it was shown that the release rate was more dependent on the type of enhancer than on the type of polymers. The mean release rates were in the range from 2.2 to 11.1%/$\sqrt{t}$ for the slowest and fastest releasing enhancers, which correspond to a 50% release within 500 and 20 min, respectively. Furthermore, the release rates were inversely proportional to the cube root of the molal volumes of the enhancers and to their logarithmic partition coefficients between the polymer adhesive and the receptor fluid. It was found that the observed release rates were probably due to a high diffusion coefficient of the enhancers rather than due to an inhomogeneous embedment of the enhancers in the adhesives. The type of adhesive showed minor influence on the release rate, especially among the acrylic polymers no difference was seen. However, compared to the acrylic adhesives, the polyisobutylene adhesive showed slower release rates, while the silicone adhesive showed slightly faster release rates.

Keywords: Chemical permeation enhancers; Drug-in-adhesive; Transdermal drug delivery systems; Release; Diffusion

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1. Introduction

Transdermal drug delivery systems of the drug-in-adhesive type are patches consisting of a polymeric adhesive layer where the drug is directly embedded in a solubilised form. Placed in contact with the skin, the drug is released from the transdermal patch in a controlled rate and diffuses into the skin. However, in order to reach a therapeutically active concentration in the systemic circulation, it is often a prerequisite to add a chemical permeation enhancer to the formulation (Hadgraft, 1999). In transdermal patches where both a drug and an enhancer are incorporated, it is important that the enhancer is released at a rate that will result in an optimal effect upon drug permeation through the skin.

The release kinetic of enhancers from transdermal patches is only sparingly reported, and the aim of the present study is to evaluate the release kinetics for eight commonly known enhancers. The enhancers were selected from different chemical groups and represented different theoretical enhancing mechanisms (Barry, 1988). The adhesive component consisted of eight different commercial polymer adhesives, six acrylics, one polyisobutylene and one silicone. Using a statistical analysis the dependence of the release rate on the type of enhancer and the type of adhesive is evaluated. The release rates of the enhancers are related to their physicochemical characteristics such as their molal volumes and partition coefficients to the adhesives.

2. Materials and methods

2.1. Materials

Azone® was a gift from Durham Pharmaceuticals, (Durham, NC, USA). Carvone, lauric acid and PG were obtained from Merck (Darmstadt, Germany). Methyl laurate and NMP were from Fluka (Buchs, Switzerland). Oleic acid was from ICN (Costa Mesa, CA, USA) and ethyl oleate from Sigma (St. Louis, MO, USA). ^{14}C-Lauric acid and ^{3}H-oleic acid were from Amersham Pharmacia Biotech (Buckinghamshire, UK). The enhancers are shown in Fig. 1 and were of highest possible purity (> 99%) and shown to be chemi-

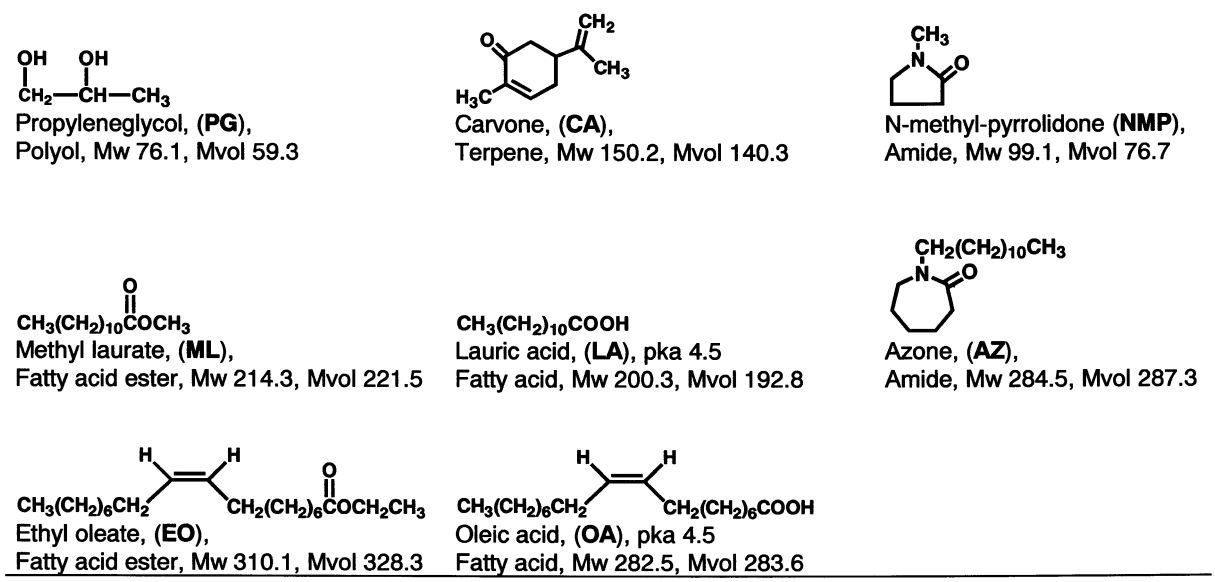

Fig. 1. The selected enhancers and the abbreviations used in this study, their structure, chemical group, molecular weight (M_w in g/mol), molal volume (M_{vol} in cm^3/mol, calculated from Flynn et al., 1974) and pK_a values.

Table 1
List of polymers adhesives used in this study

Adhesive type	Product code	Abb. [a]	Functional group	XL [b]
Acrylic	Durotak 87-2287	A87	OH	–
	Durotak 87-2516	A16	OH	+
	Durotak 87-2051	A51	COOH	–
	Durotak 87-2052	A52	COOH	+
	Durotak 87-2676	A76	OH/COOH	+
	Durotak 87-4098	A98	–	–
Pib [c]	Durotak 10711-58	P58	–	–
Silicone	DC MD7-4602	S46	–	–

[a] Abb. = Abbreviations.
[b] XL = Crosslinker.
[c] Pib = Polyisobutylene.

cally stable during the study period. Both ^{14}C-methyl laurate and ^{3}H-ethyl oleate were synthesised, using the respective acids, and methanol (Merck) or ethanol (Merck), respectively, with concentrated sulphuric acid (Merck). Methods of syntheses (refluxing with excessive alcohol) shown in literature to be high efficient were used (Vairamani and Rao, 1985; Christie, 1993; Choo et al., 1996) and validated using thin layer chromatography (TLC), ^{1}H-NMR and ^{13}C-NMR techniques. All other chemicals were of analytical grade or better and used as supplied from commercial sources.

For the transdermal patches the eight commercial adhesive products in Table 1 were used, and they all consisted of polymers suspended or dissolved in various organic solvents. The Duro-tak® acrylics and the polyisobutylene polymers were gifts from National Starch and Chemical (NSC) (Zutphen, The Netherlands). The silicone adhesive (MD7-4602) was obtained from Dow Corning (Coventry, UK). Scotch Pak® release liner 1022 and Scotch Pak® backing membrane 1109 were obtained from 3M Medica (Borken, Germany) and Rexam® release liner was from Rexam Release (Chicago, IL, USA).

2.2. Methods

2.2.1. Preparation of laminates

Laminates were produced with a content of 7.5% (w/w), and a coat weight of 100 g per square meter. Preliminary results had shown that these parameters were optimal in order to secure that the matrix was homogenous, the adhesive properties were not changed unacceptably and that both low (e.g. 1%) and high (e.g. 100%) amounts of released enhancer could be measured using the analytical methods. Enhancers were mixed with the adhesives using a Rotamix RK 20-VS (Heto-Holten A/S, Allerød, Denmark) at 10 rpm in 2 h. The blend was cast onto a release liner using a modified Laboratory Drawdown Coater LC 100 from ChemInstruments (Mentor, OH, USA). For all the acrylics and the polyisobutylene adhesives, the Rexam release liner was used (silicopolymer coated). For the silicone adhesive, the Scotch Pak 1022 release liner was used (fluoropolymer coated). The solvent from the adhesive was allowed to evaporate for 10 min, at 40 °C in an oven with air flow (LUT 6050 from Heraeus Instruments in Newtown, CT, USA). The backing film was added using a Benchtop Laboratory Laminator from ChemInstruments with an air pressure of 20 psi. The laminates were visually inspected for homogeneity with a MZM1 light microscope (Askania-Werke Rathenow, Germany). As the enhancers NMP and PG were known to evaporate to some extent during drying, the laminates with these enhancers were produced with a surplus of 21 and 27%, respectively. After production the content was determined using an extraction process followed by quantitative analysis. Laminates that did not have a content of 7.5% ($\pm$0.5%) were discarded and re-manufactured.

Furthermore, laminates without enhancer were produced in a process similar to above. However, instead of a backing film, a second release liner was attached.

2.2.2. Analytical methods

Quantitative analysis of Azone and PG was done using gas chromatography (GC) with flame ionisation detector (HP Series 6890 with HP GC CHEMSTATION Version A.06.01 software, Agilent Technologies, Palo Alto, CA, USA). For Azone the injection port was fitted with a H&P liner, part no. 19251-60540 and the purge flow was 33.1 ml/min with a purge time of 1.00 min. The overhead pressure was constant at 7.00 psi. Azone in the samples was extracted to heptane prior to injection. The column was a J&W 5012-2222 DB-5 (J&W Scientific, Folsom, CA, USA) and the temperature of the oven started a 215 °C and then raised to 235 °C with a rate of 4 °C/min. For PG the column was a HP-17 from Agilent. The injection port was fitted with a HP liner, 18740-80190. The oven temperature was 70 °C and the overhead pressure was constant at 3.00 psi.

For carvone and NMP, high performance liquid chromatography was used. The apparatus consisted of a Pharmacia LKB 2248 constant flow pump, a Pharmacia LKB Uvicord 2251 detector, a Marathon XT Auto Sampler and a computer with the Ezchrom Chromatography Data System, Version 6.6 (Amersham Pharmacia Biotech AB). The column used was a Nucleosil 5 C18 100A from Phenomenex (Torrance, CA, USA). For carvone, the mobile fluid was methanol–purified water (72:28, v/v) with a flow rate of 1.3 ml/min and the UV absorbance was measured at 220 nm. For NMP, the mobile fluid was methanol–purified water (15:85, v/v) with a flow rate of 1.0 ml/min and the UV absorbance was measured at 200 nm.

For methyl laurate, lauric acid, ethyl oleate and oleic acid, liquid scintillation counting (LSC) was done using LSC-vials, Ultima Gold® scintillation liquid and a Packard Tri-Carb 2100TR Scintillation Counter (Packard Instrument Company, Inc. Meriden, CT, USA). The radioactive purity was controlled by TLC, using hexane–ethyl ether–acetic acid (90:10:1, v/v/v) as a mobile fluid. For ^{14}C-methyl laurate and ^{14}C-lauric acid, a DC Fertigplatten Kieselgel 60 TLC plate (Merck Art. 5626) and bromocresol green (Merck) as developing agent were used. For ^{3}H-ethyl oleate and ^{3}H-oleic acid, a DC Fertigplatten Kieselgel 60 Silanisiert TLC plate (Merck Art. 5746) and phosphomolybdaic acid (Sigma) as a developing agent were used. Furthermore, total recovery of the radioactivity was performed on randomly chosen diffusion cells.

2.2.3. Solubility of enhancers in the receptor fluid

The solubility of the enhancers in a 0.05 M phosphate buffer, pH 7.4 was measured in triplicate at 32 °C. Furthermore, for Azone®, lauric acid, oleic acid, methyl laurate and ethyl oleate the solubility was also measured in a 0.05 M phosphate buffer, pH 7.4 containing 4% (w/w) polysorbate 80.

2.2.4. Miscibility of the enhancers with the adhesives

To measure if the enhancers were miscible with the polymers, two methods were used depending on whether the enhancers were crystalline or liquid. For lauric acid, the only crystalline enhancer, a three-phasic system was set up. Patches of 10 cm^2 were placed in test tubes containing 10.0 ml of the receptor fluid and lauric acid was then added. After equilibration on a Rotamixer (Heto-Holten A/S), lauric acid was extracted from the patches and quantitatively determined.

For the other enhancers the miscibility was measured by applying the enhancer onto patches of non-loaded adhesive in a ratio of 1:1 in a closed test tube. After 24 h it was visually evaluated whether the enhancer was dissolved homogenously with the adhesive.

2.2.5. Partition coefficients of enhancers between the receptor fluid and the adhesives

Patches of 10 cm^2 from the non-loaded laminates were transferred to test tubes after removal of the release liners. Receptor fluid containing a non-saturated amount of enhancer was added and the system was allowed to equilibrate for at least 72 h at 32 °C before sampling.

2.2.6. Release of enhancers from loaded adhesives

Modified Franz diffusion cells from Permegear (delivered by Vangard, NJ, USA) with a diffusion area of 1.77 cm^2 and a receptor volume of 12.1 ml were used. Circular patches of 2.11 cm^2 were punched out and attached to adhesive tape, (Blenderm®, 3M). The release liner was removed and the tape was mounted between the receptor and donor cells and receptor fluid was added. Samples were withdrawn at predetermined time intervals in a period of up to 168 h depending on the enhancers release rates. The receptor fluid consisted of a 0.05 M phosphate buffer, pH 7.4 and was maintained at 32 °C using a water bath. To obtain sink condition during the study, it was necessary to add polysorbate 80 (4% w/w) as a solubilising agent for some of the enhancers (Section 3.1).

2.2.7. Release through non-loaded adhesive layers

The release liner was removed from the loaded laminates and a non-loaded layer of the same adhesive polymer was applied, resulting in a non-loaded adhesive membrane on the release side of the laminate. Release through the non-loaded adhesive was measured (Section 2.2.6).

2.2.8. Evaluation of release data

Theories of the release of drugs from topical products have previously been discussed in details by Higuchi (1960) and Higuchi (1962). For drug release from an ointment in which the drug is initially uniformly dissolved, the following equation was derived using Fick's laws of diffusion:

$$Q = hC_0\left[1 - \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}\exp\left(\frac{-D(2m+1)^2\pi^2 t}{4h^2}\right)\right] \quad (1)$$

where Q is the cumulative amount of drug released, t is the time, h is the thickness of the adhesive layer, C_0 is the initial drug concentration in the matrix and D is the diffusion coefficient. A simplified form of this equation may be used, if per cent released is not too large ($< 60\%$) (Higuchi, 1962):

$$R = 200\left(\frac{Dt}{\pi h^2}\right)^{1/2} \approx k\sqrt{t} \quad (2)$$

where R is per cent released and k is a release rate constant. When R, per cent released is plotted versus the square root of time, $\sqrt{t}$ a straight line is obtained with the slope of k.

2.2.9. Statistical analysis

The effect on type of enhancer and adhesive on the release rate and partition coefficient was analysed statistically by using the software MODDE 5.0 from Umetri AB (Umeå, Sweden). A multiple linear regression model with two factors (enhancer and adhesive) was used with a confidence level of 0.95:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + e \quad (3)$$

where Y is the response parameter of interest, X_1–X_3 are independent variables, β_0 is a constant (arithmetic mean), β_1–β_3 are scaled and centred coefficients and e is the residual error. $\beta_X X_X$ represents a first-order effect (e.g. a general effect of an enhancer in all the adhesives) while $\beta_{XY} X_X X_Y$ represents a second-order effect (e.g. a specific enhancer in a specific adhesive).

3. Results and discussion

3.1. Solubility of enhancers in the receptor fluid

To secure that sink condition in the receptor fluid was maintained during the release studies the solubility of the enhancers had to be at least 1.3 mg/ml. For NMP, PG and carvone, a 0.05 M phosphate buffer, pH 7.4 was adequate, as NMP and PG are completely miscible and carvone had a solubility of 151.1 mg/ml. However, for the other enhancers, a solubilising agent was needed. Polysorbate 80 (4%, w/w) showed to be a potent solubiliser for these compounds as the following solubilities were obtained: Azone® 2.0 mg/ml, ethyl oleate 2.2 mg/ml, lauric acid 11.5 mg/ml, methyl laurate 3.5 mg/ml and oleic acid 6.7 mg/ml. Furthermore, preliminary studies indicated that polysorbate 80 had an insignificant diffusion

Table 2
Logarithmic partition coefficients (log P) for the enhancers between the adhesives and the receptor fluid

	Acrylics						Pib [a]	Silicone
	A16	A51	A52	A76	A87	A98	P58	S46
NMP	<-1.0	<-1.0	<-1.0	<-1.0	<-1.0	<-1.0	-1.0	0.1
PG	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.5	<0.5
CA	1.9	2.0	1.9	1.8	1.9	1.8	2.0	2.0
LA	0.5	0.6	0.6	0.4	0.4	0.5	0.6	0.3
OA	0.7	0.8	0.8	0.8	0.7	0.8	1.0	0.5
ML	1.0	1.0	1.0	1.0	0.9	1.0	1.0	1.0
AZ	1.3	1.4	1.4	1.4	1.4	1.3	1.4	1.3
EO	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4

Relative standard deviations ($n = 3$) are not shown, but were in the range of 0.3–13.0% (mean was 2.0%).
[a] Pib = polyisobutylene.

into the polymer adhesives and did not interfere with the analytical techniques for the enhancers.

3.2. Miscibility of the enhancers with the adhesives

All enhancers except lauric acid were shown to be miscible with the adhesives at a ratio of at least 1:1 (50% w/w). The solubility of lauric acid in eight different adhesives was at least 100 mg/g ($>10\%$ w/w). All enhancers were therefore soluble in the polymer adhesives in a concentration of at least 7.5% (w/w). This means that the laminates could be produced with this concentration of the enhancers without getting overloaded. An overload of enhancer would influence the release kinetic, as this would consist of both dissolution and diffusion mechanisms.

3.3. Partition coefficients of enhancers between the receptor fluid and the adhesives

Average and logarithmic values for the triple determinations of the enhancers partition coefficients between the adhesive and the receptor fluids ($\log P_{A/R}$) are shown in Table 2. A statistical analysis showed that there was a significant difference in partition coefficient between the enhancers ($P \leq 0.05$). In general, the measured partition coefficients are consistent with the observed solubilities of the enhancers in the receptor fluid.

3.4. Release from transdermal patches

The fraction released, R, versus the square root of time, $\sqrt{t}$, was plotted for all 64 combinations of enhancers and adhesives. Examples of releases of three enhancers from an acrylic adhesive are shown in Fig. 2 for up to 19 $\text{min}^{1/2}$ (360 min). However, all enhancers were released from the drug-in-adhesive patch in the examined time period of up to 168 h. The profiles showed a straight line, which passed through origin except for Azone® and ethyl oleate where lag times of approximately 2–5 $\text{min}^{1/2}$ were observed. From the slope of the straight line, the mean release rate constant, k and RSDs were calculated (Table 3).

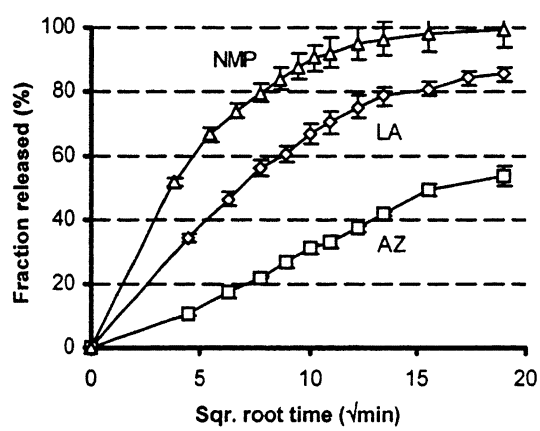

Fig. 2. Mean diffusion profiles ($n = 3$) for NMP, LA and AZ from the acrylic adhesive, A16.

Table 3
Data from the release assay direct from the patches

	Acrylics												Pib [a]		Silicone	
	A16		A51		A52		A76		A87		A98		P58		S46	
	k	RSD	k	RSD	k	RSD	k	RSD	k	RSD	k	RSD	k	RSD	k	RSD
NMP	12.2	3.3	11.1	7.3	12.5	5.1	9.1	4.3	11.6	5.8	8.9	6.3	8.5	9.2	15.5	5.5
PG	5.9	5.2	7.1	5.2	7.2	4.1	5.9	0.6	5.9	4.1	6.7	3.8	20.7 [b]	7.1	7.0	0.5
CA	10.7	4.4	13.0	2.4	9.6	9.7	8.8	12.9	8.0	3.8	7.7	1.9	7.2	5.9	9.3	6.2
LA	7.3	3.9	7.9	1.8	8.3	4.7	8.2	6.8	7.9	5.6	7.6	4.2	3.2	5.6	6.9	0.2
OA	5.2	8.7	4.9	5.5	4.6	1.9	4.9	1.9	5.0	0.8	4.6	2.0	2.7	6.2	5.3	0.8
ML	5.0	1.3	5.7	1.8	5.6	3.1	4.8	2.5	5.2	1.3	5.5	1.7	3.5	1.8	5.5	1.5
AZ	3.1	1.4	2.4	3.0	2.5	2.8	3.5	3.8	2.1	4.5	1.8	17.1	0.7	4.5	3.2	7.2
EO	2.2	2.8	2.6	3.4	2.0	1.3	2.2	1.8	2.2	1.4	2.0	2.1	1.9	3.6	3.0	5.0

Average release rate constants, k (%/$\sqrt{t}$) and relative standard deviations, RSD (%) calculated from the straight slopes in the square root release profiles ($n = 3$).

[a] Pib = polyisobutylene.

[b] The results for PG in Pib were identified as statistical outliers.

The mean RSD was 4.1%, whereas some individual combinations showed somewhat higher values. As the profiles from these data had the same appearance as the other combinations, they were regarded as a result of a random statistical variation. The statistical test was conducted and the results are shown in Fig. 3 for the first-order results (enhancers and adhesives). The statistical analysis showed that the type of enhancer (A) generally had larger influence than the type of adhesive (B) on the release rate as the statistical coefficients were generally larger. The values for PG in the P58 adhesive (large second-order effect) were excluded from the statistical analysis as they were identified as statistic outliers in the normal probability plot.

The mean release rate were 2.2%/$\sqrt{t}$ for the slowest releasing enhancer ethyl oleate, which correspond to a 50% release within 500 min. The fastest release rates were found for NMP, which had a mean release rate of 11.1%/$\sqrt{t}$, meaning that 50% was released within 20 min. The mean release rates of the other enhancers were within the range of these two values. Thus the relative order of the release rates for the enhancers were NMP > carvone > PG > lauric acid > oleic acid > methyl laurate > Azone® > ethyl oleate. In Fig. 4, it is shown that the release rates of the enhancers were inversely proportional to both the cube root of the molal volumes (A) and the logarithmic partition coefficients between adhesives and receptor fluids (B). This is fully in agreement with the physicochemical theories regarding diffusion of molecules as presented by Flynn et al. (1974) and Mauger (2000) where the diffusion coefficient, D is related to molal volume and partition coefficient by the following equations:

$$d = \frac{kT}{6\pi\eta}\left(\frac{(4\pi N)^{1/3}}{(3v)^{1/3}}\right) \Rightarrow D \propto \frac{1}{(v)^{1/3}}, \quad (4)$$

where k is the Boltzmann constant, T is the absolute temperature, N is the Avogadro number, η is the solvent viscosity and v is the molar volume of the diffusant, and:

$$Q = \left(\frac{K_{m/r}D}{h_m}\right)C_t \Rightarrow D \propto \frac{1}{K_{m/r}} \quad (5)$$

where $K_{m/r}$ is the partition coefficient between membrane and receptor fluid.

Regarding the influence of the types of adhesives on release rates, the statistical test showed that it was generally lower than the type of enhancers, as the calculated statistical coefficients for the adhesives were smaller than those calculated for the enhancers. Furthermore, no differ-

ences between the acrylics were seen, despite they had different physical characteristics, e.g. functional groups and cross-linkers. Reports of other studies have shown that different functional groups in acrylic adhesives could result in different release rates (Guyot and Fawaz, 2000). However, no clear effect of such characteristics is seen in the present study. A possible explanation could be that the enhancers in this study had considerably higher release rates than the reported drug compounds (Hadgraft et al., 1991; Guyot and Fawaz, 2000). The polyisobutylene adhesive, P58, resulted in significantly slower release rates than the acrylics, whereas the silicone, S46, showed faster but statistically non-significant release rates. Previously, relatively low release rates of fentanyl from polyisobutylenes compared to acrylic adhesives have been reported (Roy et al., 1996).

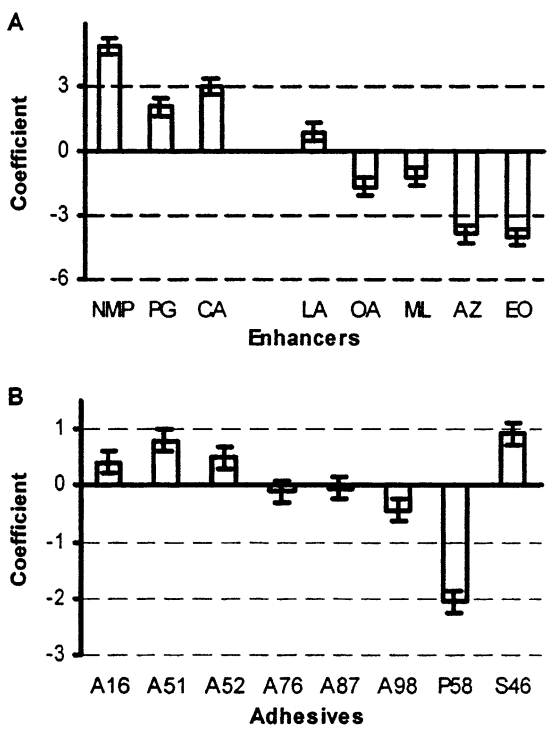

Fig. 3. First-order results of the statistical analysis of the enhancers release rate constants from the adhesives with standard deviations and a confidence level of 0.95. (A) The influence of enhancers and (B) the influence of adhesive. The statistical coefficients are scaled and centred, meaning that the average release rate of all formulations is set to '0' and that a positive or negative bar denotes that the factor causes higher or lower release rate, respectively.

Generally, the release rates of some of the enhancers from the adhesives were somewhat higher than expected and therefore the following study was done to exclude inhomogeneity in the transdermal system as a reason for the high release rates.

3.5. Release profiles through non-loaded layer of adhesive

Release profiles through a non-loaded layer of adhesive are shown in Fig. 5 for three enhancers from an acrylic adhesive. A lag time could be observed for majority of the enhancers and the release rates were lower compared to the study where the enhancers were released directly from the adhesive. All combinations of enhancers and adhesives showed profiles with straight lines in the R versus $\sqrt{t}$ transformation. From the slopes, k and RSDs were calculated and are shown in Table 4. The results of the statistical analysis are shown in Fig. 6 for enhancers (A) and adhesives (B). The release rates for the enhancers generally followed the same pattern found in the study where direct releases from the adhesives were measured. This indicates that the enhancers release from the adhesives most likely is due to a high diffusion coefficient and not an inhomogeneity in the distribution of the enhancers in the adhesives.

The acrylics show no difference in release rates, while the polyisobutylene and the silicone showed lower and higher release rates, respectively. Thus, the same pattern as in the release study directly from the adhesives was seen.

Interestingly for PG, no second-order effect was observed in the statistical test on the release rates from the polyisobutylene adhesive when a non-loaded adhesive layer was applied. This was in contrast to the direct release study and one could speculate that this is due to an inhomogeneity in this specific combination.

In designing of a transdermal system more than one enhancer could be incorporated. These enhancers could represent different enhancing mechanisms and release kinetics, and a synergistic effect in enhancing the permeation of a drug substance might be obtained. One approach could

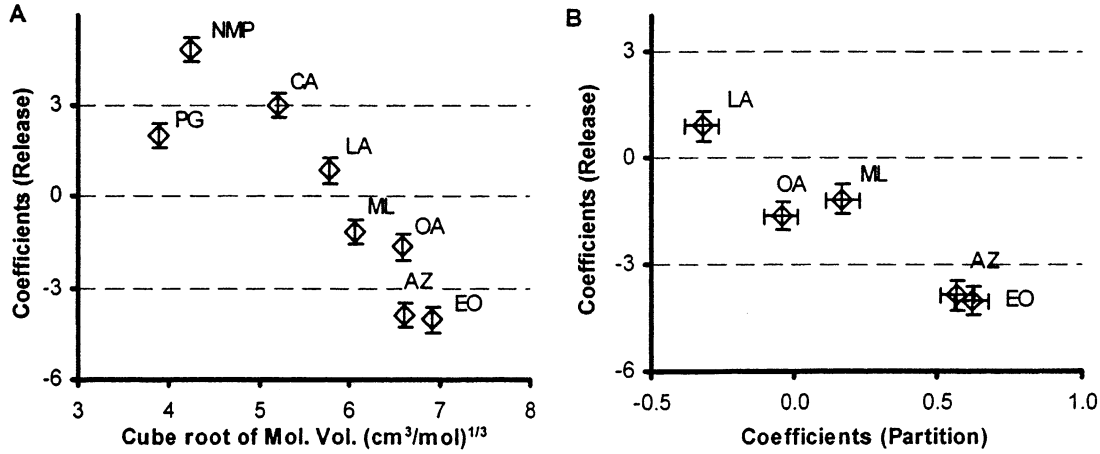

Fig. 4. Statistical coefficients of the release rate of the enhancers compared to their molal volumes (A) and the statistical coefficients of log P (B), respectively. The length of the bar marks the standard deviation. In B the results for the enhancers where the partition study was performed with P80 added to the receptor fluid are only shown.

be a fast releasing enhancer (e.g. NMP) acting as a solubiliser for the drug substance in stratum corneum (thereby favour the partition coefficient to the skin) and a slower releasing enhancer (e.g. Azone®) acting by disruption of the lipid lamellas between the cells of stratum corneum. However, further studies are needed to evaluate this approach.

The type of adhesive had less influence on the release rate than the type of enhancers. Furthermore, there was generally no difference between the acrylic adhesives despite their different functional groups. The adhesives of polyisobutylene and silicone gave a slower and slightly faster release rate, respectively, compared to the acrylic adhesives.

4. Conclusions

The release experiments showed that the eight enhancers were released from the adhesives in a controlled manner, following a square root kinetics as described by Higuchi. The mean release rates were in the range from 2.2 to 11.1%/$\sqrt{t}$ for the slowest and fastest releasing enhancers, respectively. The release rates were inversely proportional to both the cube root of the molal volumes and the measured logarithmic partition coefficients between the polymer adhesives and the receptor fluids. The release rates for the enhancers were somewhat higher than that previously reported for drug compounds. It was found that this probably was not due to an incorrect embedment of the enhancer in the adhesive, but rather that the enhancer molecules have higher diffusion coefficients than typical drug substances.

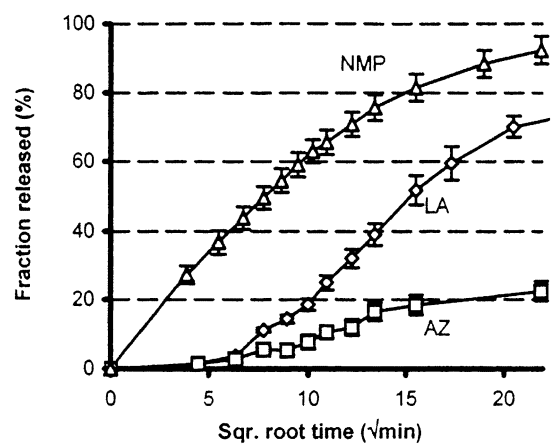

Fig. 5. Mean diffusion profiles ($n = 3$) through unloaded layers of adhesives for NMP, LA and AZ from the acrylic adhesive, A16.

Table 4
Data from the release assay through an unloaded layer of adhesive

	Acrylics												Pib [a]		Silicone	
	A16		A51		A52		A76		A87		A98		P58		S46	
	k	RSD	*k*	RSD	*k*	RSD	*k*	RSD	*k*	RSD	*k*	RSD	*k*	RSD	*k*	RSD
NMP	6.2	5.4	6.4	9.4	7.7	7.1	5.1	4.3	5.8	2.8	5.4	2.6	4.2	2.2	6.5	8.2
PG	1.8	10.5	2.1	7.2	2.4	14.3	1.8	8.6	1.9	13.3	1.4	10.8	3.7	11.5	4.9	7.8
CA	7.6	8.3	7.2	9.1	6.8	6.0	7.4	10.8	6.1	1.3	7.6	2.1	4.5	2.1	10.7	10.8
LA	4.6	4.2	5.0	4.3	4.7	4.1	5.2	4.2	5.4	4.1	4.6	4.1	3.2	5.5	5.7	4.3
OA	3.7	4.4	4.2	8.0	3.9	3.2	4.1	2.6	4.2	3.6	3.9	2.7	2.6	2.2	4.6	3.4
ML	3.5	7.7	3.5	3.4	3.5	9.6	3.5	11.2	3.3	6.6	3.2	6.7	2.2	9.3	3.9	5.1
AZ	2.0	10.1	1.5	8.0	2.0	3.5	1.3	1.3	1.5	3.1	0.9	6.5	0.2	13.3	0.8	5.7
EO	0.3	3.9	0.2	7.2	0.2	6.2	0.2	12.7	0.2	13.1	0.2	6.2	0.2	4.0	0.3	101

Average release rate constants, k (%/$\sqrt{t}$) and relative standard deviations, RSD (%) calculated from the straight slopes in the square root release profiles ($n = 3$).

[a] Pib = polyisobutylene.

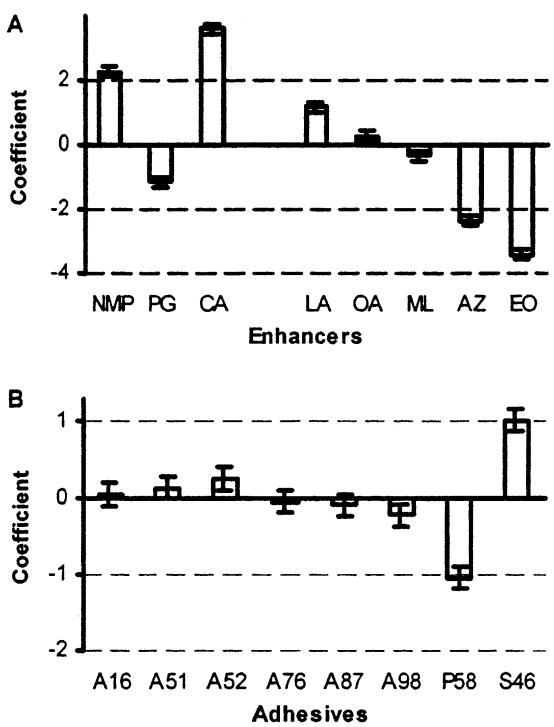

Fig. 6. First-order results of the statistical analysis of the enhancers release rate constants through an unloaded layer of adhesive with standard deviations and a confidence level of 0.95. (A) The influence of enhancers and (B) the influence of adhesive. The statistical coefficients are scaled and centred, meaning that the average release rate of all formulations is set to '0' and that a positive or negative bar denotes that the factor causes higher or lower release rate, respectively.

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