Interaction Between Drugs and Pressure-Sensitive Adhesives in Transdermal Therapeutic Systems

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Release experiments with four drugs using representative pressure-sensitive adhesive (PSA) matrices were performed at 37°C, and drug–PSA polymer interaction was determined by the Williams, Landel, and Ferry (WLF) equation. Two acrylic-type [2-ethylhexylacrylate and acrylic acid copolymer (2EHA/AA) or acrylamide copolymer (2EHA/AAm)], one rubber-type (a mixture of high and low molecular weight polyisobutylene), and one silicone-type PSA were used, and dipropylphthalate (PP), aminopyrine (AMP), ketoprofen (KP), and lidocaine (LC) were selected as model drugs because of their molecular size and functional groups. PSA containing acrylic acid (2EHA/AA) strongly interacted with the amide LC, with the tertiary amine AMP, and with the carboxylic acid KP; PSA-containing acrylamide (2EHA/AAm), however, did not interact with LC or AMP, although it markedly interacted with KP. The rubber-type and silicone-type PSAs, composed of no or only a few polar functional groups, did not interact with any of the drugs used in this experiment. Therefore, the diffusion coefficient of the drugs through PSA was influenced by the drug–PSA polymer interaction, and the extent of this interaction can be estimated by the relationship between the drug concentrations in the PSA and their diffusion coefficients.

KEY WORDS: transdermal therapeutic system; pressure-sensitive adhesive; interaction; diffusion coefficient; Williams, Landel, and Ferry (WLF) equation.

INTRODUCTION

Most transdermal therapeutic systems have pressure-sensitive adhesive (PSA) to maintain intimate contact between the system and the skin surface. Common PSA is based on rubber, acrylate, and silicone polymers. The properties of adhesion to the skin surface, skin irritation, solubility, and diffusivity of a drug in the PSA are key factors in the selection of a PSA polymer (1). From previous studies, we offered information on drug diffusion in PSA, by calculating the diffusion coefficient in the PSA (2), by analyzing the relationship between the obtained drug diffusion coefficient and the physical property of PSA (3), and by estimating the influence of the interaction between a drug and PSA on drug diffusion (4). These studies did not, however, clarify all the details of drug diffusion behavior.

In the present study, we evaluated the effect of interaction between four drugs and PSAs using the modified WLF equation proposed by Williams, Landel, and Ferry (5) on diffusion of drugs in various PSAs. Four model PSAs were used: two kinds of acrylic PSAs with different functional groups [2-ethylhexylacrylate (2EHA) and acrylic acid (AA) copolymer and 2EHA and acrylamide (AAm) copolymer (78/22 each)]; one rubber-type PSA [a mixture of low and high molecular weight (100/75) polyisobutylene (PIB)]; and one silicone-type PSA (Dow Corning 2920; lower interaction with drugs than Dow Corning 355). Four drugs with different functional groups, dipropylphthalate (PP), aminopyrine (AMP), ketoprofen (KP), and lidocaine (LC) (Fig. 1), were selected to investigate the interaction between the functional group of a PSA component and that of a drug. A release experiment was performed on the four drugs from the four PSAs, which contained the drugs at three concentrations. The interaction was evaluated from the relationship between the diffusion coefficient of drug and the drug concentration in the PSA and between the extent of interaction and the structure of the drug and PSA polymer.

THEORY

The diffusion coefficient of a drug through a PSA matrix, D, can be calculated from the release profile of the drug using the following equations (6,7).

Case I: when a drug is dissolved in a PSA matrix ($C_o \leqq C_s$),

$$Q = LC_0 \left[1 - \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)} \exp\left(- \frac{D\pi^2}{4L^2} (2n+1)^2 t \right) \right] \tag{1}$$

Case II: when a drug is suspended in a PSA matrix ($C_o > C_s$),

$$Q = [DC_s (2C_o - C_s)\, t]^{1/2} \tag{2}$$

where Q, L, C_o, and C_s are the cumulative amount of drug released at time t per unit area of system, thickness of the adhesive layer, initial concentration of drug in the matrix, and drug solubility in the matrix, respectively. The integer n goes from 0 to ∞.

It was shown (3) that the relationship between the obtained diffusion coefficient of a drug and the physical property of the PSA polymer can be expressed by the WLF equation. It showed that the temperature dependence of the polymer viscosity can be expressed as follows:

$$\eta/\eta_g = \exp \frac{-40.0\,(T - T_g)}{51.6 + (T - T_g)} \tag{3}$$

where T and T_g are the temperature and glass transition temperature of the PSA polymer, respectively, and η and η_g are the viscosity at T and T_g. This equation can be rewritten using the Stokes–Einstein equation ($D = K/\eta$; K is a constant) as

$$\log D - A = - \frac{896.2}{51.6 + (T - T_g)} \tag{4}$$

where A is a constant. This equation suggests that the D

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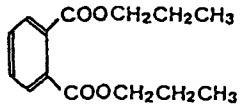
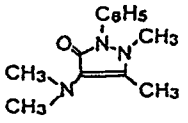
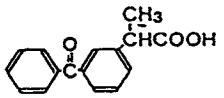


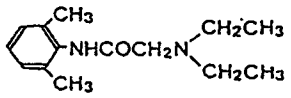
Dipropylphthalate (PP)
Mv = 219.8



Aminopyrine (AMP)
Mv = 194.2



Ketoprofen (KP)
Mv = 195.6



Lidocaine (LC)
Mv = 216.2

Fig. 1. Chemical structure of drugs used in this study. The molar volume (M_v) of a drug was calculated using the group contribution method proposed by Fedors (11).

value is determined by the T_g of the polymer, assuming that there is no effect of molecular size of drug on the diffusion.

We showed, however, that the D value of different drugs of almost the same molar volume was not necessarily consistent (4); the reason may lie in the drug–PSA polymer interaction. Actually, the extent of the interaction can be expressed as a parameter, β, by evaluating the relationship between the drug concentration in the PSA matrix and its T_g value using the following equation (8,10):

$$T_g = T_g^\circ - (\beta/\alpha_2)\, C \qquad (5)$$

where T_g° is the T_g of the pure polymer (without drug), and C is the thermal expansion coefficient and the drug concentration in the PSA matrix, respectively.

From Eqs. (4) and (5), the following equation can be obtained:

$$\log D - A = \frac{-896.2}{51.6 + [T - T_g^\circ + (\beta/\alpha_2)\, C]} \qquad (6)$$

This equation indicates that the drug–polymer interaction can be estimated by the diffusion coefficient of the drug in the PSA polymer.

MATERIALS AND METHODS

Materials and PSA Matrices

PP was purchased from Tokyo Kasei Kogyo Co. (Tokyo), and AMP, KP, and LC from Wako Pure Chemical Industries (Osaka, Japan). 2EHA (Mitsubishi Petrochemical Co., Tokyo), AA, and AAm (Wako Pure Chemical) were source materials of acrylic-type PSA. 2EHA/AA and 2EHA/AAm copolymers were synthesized by a free radical-initiated solution polymerization as follows: 2EHA, AA (or AAm), and ethyl acetate–acetone mixing solvent were placed in a 3-L three-necked round-bottomed flask equipped with a mechanical stirrer, a dropping funnel fitted to a drying tube, and a reflux condenser. Under a continuous purge of dry nitrogen gas and refluxing at 87°C, the synthesis was initiated by the dropwise addition of dilauroyl peroxide solution. After reaction for 16.5 hr, the reaction mixture was cooled to room temperature and used as acrylic-type PSAs. Rubber-type PSA was prepared by PIB mixing of high and low molecular weights (Vistanex LM-80, LMMH, Exxon Chemical Co., TX) in toluene. Silicone-type PSA was a gift from Dow Corning Co. (MI). All other chemicals and solvents were of reagent grade and obtained commercially. The resulting PSAs were used without purification. PSA matrices containing the drugs were prepared by casting PSA solution onto polyethylene terephthalate film; the resulting matrices were kept at 120°C for 3 min to remove solvent. The thickness of the obtained PSA matrices was 40 ± 1 μm. Residual solvent in the PSA matrices was measured by gas chromatography and confirmed to be less than a few parts per million.

Release Experiments

Drug release from the PSAs was determined in single diffusion cells having a volume of 2.5 mL and an effective diffusion area of 0.95 cm^2 as described previously (3). The PSA matrix was in contact with water or 40% polyethylene

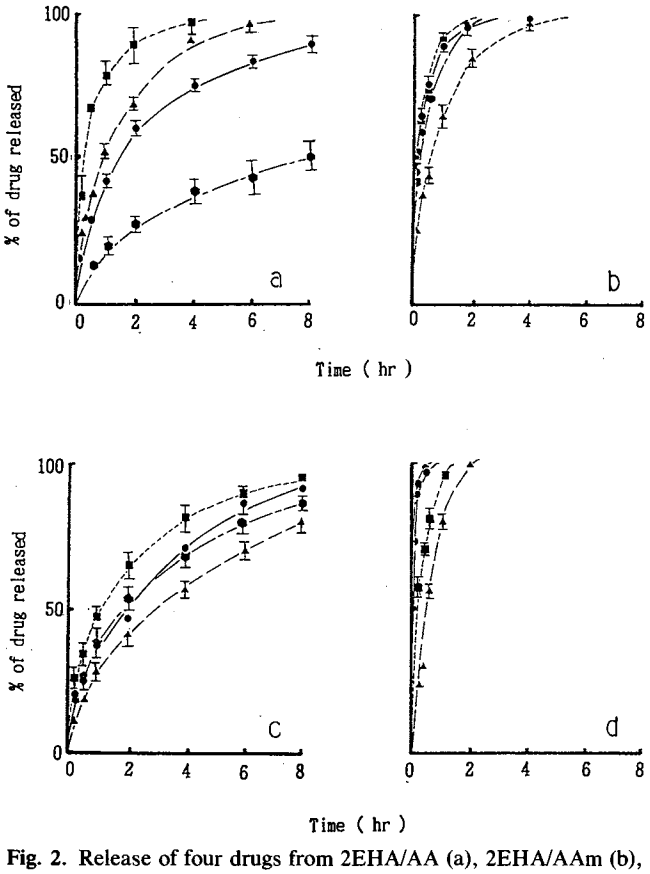


Fig. 2. Release of four drugs from 2EHA/AA (a), 2EHA/AAm (b), PIB (c), and silicone (d) PSA. (●) PP; (■) AMP; (▲) KP; (◆) LC. Each value represents the mean ± SD of three experiments.

Table I. Solubility and Diffusion Coefficients of Four Drugs in the PSA Matrices and the β Value Obtained from the log$D$ − C Profile

Matrix	PP	AMP	KP	LC
	(a) Solubility (mg/cm^3)[a]			
2EHA/AA	223.7 (3.3)	95.1 (3.2)	61.3 (3.3)	438.6 (49.3)
2EHA/AAm	216.2 (16.1)	14.1 (1.6)	95.9 (5.1)	199.7 (12.3)
PIB	62.7 (2.7)	48.3 (0.3)	0.8 (0.2)	62.4 (2.8)
Silicone	12.9 (1.8)	39.6 (4.0)	4.2 (0.6)	81.0 (1.7)
	(b) Logarithm of diffusion coefficient (cm^2/s)[a]			
2EHA/AA	−8.57 (0.07)	−9.13 (0.02)	−8.74 (0.01)	−10.25 (0.03)
2EHA/AAm	−8.10 (0.03)	−8.25 (0.04)	−8.84 (0.02)	−8.31 (0.03)
PIB	−9.30 (0.07)	−9.42 (0.08)	−9.60 (0.02)	−9.34 (0.04)
Silicone	−8.01 (0.13)	−7.35 (0.01)	−8.34 (0.06)	−7.38 (0.02)
	(c) β value[b]			
2EHA/AA	0.0002	6.15	3.66	25.1
2EHA/AAm	0.845	0.0001	6.54	0.187
PIB	1.75	0.509	−0.0005	−0.0001
Silicone	—	−0.0004	−0.0004	−0.0035

[a] Each value represents the mean ± SD of three experiments.
[b] Each value was calculated by curve fitting the mean log$D$ − C profiles to Eq. (6).

glycol. The receiver solution (500 μL) was withdrawn and the same volume of fresh solvent was added to maintain a constant volume. The amount of drug released was determined by HPLC. The experiment was performed in triplicate.

Measurement of Drug Solubility in the PSA Matrix

The solubility of a drug in the PSA was determined by partition coefficient defined as an equilibrium ratio of the drug concentration in the PSA to that in the solution (3). Since the amount of drug migrating into the PSA was almost the same for each drug at 8 and 24 hr, the solubility was calculated from the partition coefficient obtained at 24 hr.

Measurement of the Glass Transition Temperature of PSA

The T_g of the PSAs was evaluated after vacuum-drying for a day prior to measurement by differential scanning calorimetry (DSC) from −150 to 0°C (Shimadzu DSC-50, Kyoto, Japan).

Thermal Expansion Coefficients of PSA Polymers

The thermal expansion value, α_2, for various polymers was approximately 4.8×10^{-4} deg^{-1} with the exception of unusual polymers such as silicone (9,10). For the present analyses, therefore, α_2 was set as 12.0 and 4.8×10^{-4} deg^{-1} for silicone-type and other PSA polymers.

Calculation of Unknown Parameters

D value was calculated by curve-fitting the release data to Eq. (1) or (2). The interaction parameter, β, was also calculated by curve fitting for the relationship between the D value and the drug concentration in the PSAs based on Eq. (6).

RESULTS AND DISCUSSION

Figure 2 shows the release profiles of the four drugs (at a single concentration) from the four PSAs. All drugs were rapidly released from silicone-type PSA with low T_g and large expansion values, whereas the release rate from the acrylic-type PSA, especially the 2EHA/AA type, was markedly changed depending on the kind of drug. This may be governed by the interaction between the drug and the PSA. The release of all drugs from the rubber-type PSA (PIB type) was similar, because this type of PSA has no functional groups among its polymer components.

Solubilities of the drugs in PSAs are shown in Table Ia. These data were used to confirm whether a drug was dissolved or suspended in the PSA. The calculated D values are summarized in Table Ib. On the whole, these values were larger in the silicone-type than in other PSAs. The D value in the acryllic-type PSA was markedly changed by the kind of drug. T_g values were determined from the change in heat capacity shown on the DSC chart and were almost the same (2EHA/AA, −63.82°C; 2EHA/AAm, −72.86°C; PIB, −71.19°C), except for silicone-type PSA (−127.83°C).

Figure 3 shows the relationship between log$D$ and the initial concentration of the drugs in the PSAs. β values calculated are shown in Table Ic. A larger β value indicates a stronger drug–polymer interaction. LC, with a NH–CO group, markedly interacted with 2EHA/AA (β = 25.1), as did AMP, with a tertiary amino group, and KP, with a carboxyl group (AMP, 6.15; KP, 3.66). But PP, with an ester group, interacted little (0.0002) due to its low polarity. In contrast, KP interacted with 2EHA/AAm (6.54), whereas there was little interaction by LC, AMP, or PP (0.0001–0.845). These results suggested that the extent of the drug–polymer interaction was greatly influenced by the polar functional groups, of the drug and the PSA polymer. The resulting change in the extent of the interaction induced a change in

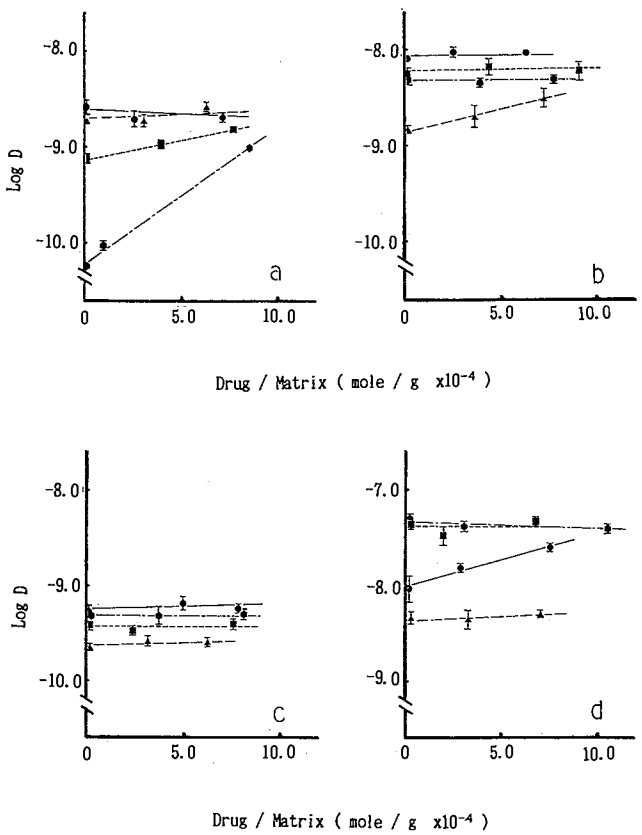


Fig. 3. Effect of drug concentrations in 2EHA/AA (a), 2EHA/AAm (b), PIB (c), and silicone (d) PSA on their diffusion. Symbols are the same as in Fig. 2. Each value represents the mean ± SD of three experiments.

the D value from 1×10^{-11} to 1×10^{-9} cm²/sec. The D value of the four drugs was almost the same in rubber-type PSA, independent of the initial concentration of the drug; β values for all four drugs were very low (−0.0005–1.75). This may be due to PIB having no polar functional group in the polymer. The β value was minimal except for PP for silicone-type PSA (−0.0035 to −0.0004) because of the small polar functional group in the polymer. The large change in the D value of PP observed in the log D − C profile may be the result of PP having been poorly solvent and condensing the silicone polymer. The small D value of KP in silicone PSA was because of its low solubility (0.4%); thus the release of KP from this PSA may be governed by the dissolution process of KP particles into the PSA matrix. The D value of LC and AMP in silicone-type PSA ($\simeq 10^{-8}$ cm²/sec) was 10–100 times higher than those in other PSAs. This difference was due to the markedly different T_g and expansion values among the PSAs.

The β value can be used as an indicator of the interaction as mentioned above. However, the rank order of the β value using different drugs and PSAs did not necessarily parallel that of their interaction. Use of drugs with the same functional group (4) showed a much clearer relationship. Nor can the β value be used to evaluate the interaction at the molecular level. It should also be noted that the D values of drug obtained in the several PSAs obtained in this study were for only part of the drug, within a narrow range of molar volumes, M_v (194–220). The influence of drug size on diffusion was described previously (4).

The interaction of a drug and PSA affects the D value of the drug in the PSA and causes a change in release rate. This change in D value also affects the skin permeation rate of drug after application of the PSA to the skin. However, the skin permeation rate cannot be determined except by other factors such as the thickness of the PSA layer and the D value of the drug in the skin (12,13).

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