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Intrinsic diffusion coefficients of drugs in pressure-sensitive adhesive polymer masses

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Summary

The determination of diffusion coefficients in pressure-sensitive adhesive polymers is a prerequisite to evaluate suitable adhesive polymers for transdermal patches. This paper reports on a membrane permeation technique through laminates composed of a pressure-sensitive adhesive layer and a microporous membrane for mechanical support, allowing easy handling of the adhesive without problems due to sticking. In order to determine intrinsic diffusion coefficents, the effects of the adjacent aqueous diffusion layers and of the microporous membrane were factored out by simultaneous data analysis of different adhesive layer thicknesses. To standardize the drug's thermodynamic activity, all experiments were carried out with saturated drug dispersions. The drugs investigated were three verapamil analogs, i.e. gallopamil, anipamil, and the verapamil carboxylic acid analog. To illustrate the method, experiments with different pressure-sensitive adhesives were carried out in which the effects of drug and polymer structure on diffusivity were clearly demonstrated. The effects of cross-linking, of polar and non-polar additives, and of initial drug loading were also studied, resulting in moderate or negligible effects on drug diffusivity. In agreement with theory, it was finally demonstrated that the contribution of the aqueous diffusion layers to the overall permeability of the laminates was significant when highly permeable adhesives were studied.

Introduction

The diffusion coefficient has become a common parameter for the evaluation of polymeric materials for drug delivery. Standard approaches to determine diffusion coefficients are membrane permeation and matrix release techniques. With pressure-sensitive adhesive polymers, however, simple membrane permeation experiments are technically unfeasible: Most pressure-sensitive adhesive polymers do not form self-supporting films, and due to their adherence to substrates such films would be difficult to handle as free membrane in a donor/receiver permeation experiment. Matrix release techniques, on the other hand, provide effective rather than intrinsic diffusion coefficients as the degree of saturation and interaction of the drug in the polymeric matrix is normally

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unknown. Approximative attempts to circumvent these problems arising with matrix experiments have been reported in the literature (Lee, 1980; Tojo et al., 1985), however, they involve the disadvantage of an intricate mathematical treatment.

This paper presents a simple technique to determine intrinsic diffusion coefficients in pressure-sensitive adhesive polymers using a laminate diffusion technique. The laminates investigated consisted of a microporous support film and the adhesive polymer. Thus, one side of the laminate was not adhesive and allowed easy handling of the adhesive without the unwanted problems caused by sticking.

Under steady-state conditions, the flux of drugs through a laminate is characterized by the additivity of the reciprocal permeabilities of the different lamina. In addition to the contributions of the two structural elements of the laminate, i.e. the adhesive and the support film, the overall permeability is influenced by another factor, namely the effect exerted by the two stagnant aqueous diffusion layers on both sides of the laminate on the kinetics of drug permeation. In the case of water-soluble polar compounds, this effect is normally negligible (Flynn et al., 1974), whereas the stagnant boundary layers may contribute significantly to the overall flux resistance of the system in the case of more lipophilic drugs.

The first objective of this study was to factor out the diffusivity of the adhesive polymer from the side effects of the support film and the two aqueous diffusions layers. Michaels et al. (1975) have previously reported on an approach to separate the intrinsic membrane diffusivity of polydimethylsiloxane polymers from the effects of the stagnant diffusion layers. The basic concept of this approach was that the simultaneous estimation of the individual effects of the polymer and the adjacent diffusion layers is possible when permeation is studied at more than one thickness of the polymer membrane. A related approach was also applied here. However, the linear regression method suggested by Michaels et al. (1975) turned out to be unsuitable for the evaluation of our data, presumably due to the grotesque effects of error propagation with reciprocal flux data. Instead, a non-linear regression approach was found to fit the data most smoothly and reasonably (Lichtenberger, 1988).

Another aspect of this paper concerns the evaluation of the effects exerted by different additives on the intrinsic diffusivity of film casts prepared from aqueous polymer dispersions. The additives studied, i.e. an ionic surfactant, a polymeric thickening agent and a lipophilic ester, represent major types of additives for pressure-sensitive film casts.

In the first place, this paper represents a practical contribution to the widespread interest in the use of pressure-sensitive adhesive polymers for manufacturing transdermal delivery patches (Musolf et al., 1987). Regarding this aspect, the intrinsic diffusivity of polymers per se is a basic parameter both for research and development and for quality control of pressure-sensitive adhesive polymers. On the other hand, the results presented here were the baseline for our research efforts to optimize the thermodynamic activity of drugs in pressure-sensitive polymeric carriers. Demonstrations of these results have been published (Lichtenberger et al., 1988, 1990).

Materials and Methods

Drugs and polymers

Three different verapamil analogs were investigated: anipamil base, gallopamil base and 2-methyl-3,9-bis(3,4-dimethoxyphenyl)-7-methyl-azanonan-3-carboxylic acid · HCl (verapamil-COOH). All drugs were gifts from Knoll AG (Ludwigshafen, F.R.G.). Whilst gallopamil and anipamil are liquids at room temperature, verapamil-COOH is a crystalline compound (F.: 146 °C).

The polymers used are listed in Table 1. All polymers are commercially available as aqueous dispersions and were supplied by BASF AG (Ludwigshafen).

Celgard 3401 (Celanese-Hoechst, Charlotte, NC, U.S.A.) was used as a mechanically stable support film of good aqueous wettability. The film is a microporous polypropylene membrane with a thickness of 25 μm and a porosity of 38%. A typical pore is elliptic and has dimensions of ap-

prox. 0.02×0.2 μm. The continous phase of the polymer is essentially impermeable to the diffusion of drugs.

Additives

As additives, Latecoll D® (BASF, Ludwigshafen, F.R.G.), sodium lauryl sulfate (NLS) (Fluka, Buchs, Switzerland) and isopropyl myristate (IPM) (Merck, Darmstadt, F.R.G.) were used. Latecoll D® is an aqueous dispersion containing 25% (w/w) of poly (acrylic acid); after neutralization with NaOH to pH > 7.5, Latecoll D® may be used as a thickening agent to improve the physical stability of aqueous polymer dispersions. Addition of NLS to aqueous polymer dispersions was carried out in order to improve incorporation of lipophilic additives and drugs. IPM may be used as a solvent for lipophilic drugs and to lower the polarity of the polymeric film carrier; incorporation of IPM into the polymer dispersions was by means of 4% (w/w) NLS and intense stirring.

Preparation of laminates

Film casting of the aqueous polymer dispersions on top of the support film was by means of a motor-driven blade device (Type 509/1, Erichsen, Hemer, F.R.G.) at room temperature. Depending on the desired thickness of the polymer cast, single or multiple casting runs were performed. Blades with fixed and variable widths were used (Erichsen Wasag model no. 335/288, 100 and 200 μm; Erichsen tilting blade, type 509/1). Between multiple casting runs, the intermediate films were dried for 45 min at room temperature. The final

TABLE 1

Polymer dispersions [a]

Code	Polymer	Particle size [b] (nm)	pH	Glas temperature (°C)
A-4 D [c,d]	Polybutylacrylate	250	6–7.5	−43
A-290 D	Butylacrylate-styrene copolymer (1 : 1)	200	7.5–9	22
A-80 D	Poly(2-ethyl-hexylacrylate)	300	4.5–5.5	−53
A-V 205	Poly(2-ethyl-hexylacrylate)	200	6–7	−53
A-500 D [c]	Butylacrylate-vinyl acetate copolymer	200	3.5–4.7	−13
B-430 D	Butadiene-styrene copolymer (1 : 1)	220	8–9.5	−10
P-800 D	Vinyl acetate-vinyl propionate graft copolymer	500	5–7	−2
A-DS 2117	Polyethylacrylate	–	2–3	−12

[a] All polymers supplied as aqueous dispersions, 50 ± 1% (w/w) polymer content (gifts from BASF AG, Ludwigshafen, F.R.G.).
[b] Mean particle size measured according to DIN 53189, method C, data provided by manufacturer.
[c] Containing free carboxyl groups.
[d] Under addition of polyacrylate thickener (Latecoll D®, gift from BASF AG, Ludwigshafen, F.R.G.).
[f] Containing acrylnitrile groups, self-cross-linking in alkaline media; if necessary addition of 0.1 N sodium hydroxide to pH 10 for complete cross-linking within 10 days.

laminates were dried for 48 h at 50 °C. For the diffusion experiment square pieces of 80 cm^2 were used which were free of wrinkles and bubbles. The thickness of the polymer cast was calculated by means of the total weight of the laminate, its surface area, the density of the polymer and the given weight of the support film per surface area.

Diffusion experiments

The determination of the diffusion coefficients of drugs was based on steady-state diffusion experiments. Flow-through Stricker-type (Stricker, 1969) diffusion cells made of Persphex® were used throughout, consisting of two identical circular halves (donor and receiver compartments) each having a surface area for diffusion of 36.3 cm^2 and a void volume of 3.6 ml. Both cell halves were equipped with separate perfusion chambers for thermostatting the donor and receiver compartments (31 ± 0.2 °C). In addition, the jacketted reservoir beakers were also thermostatted. Throughout the studies, the support layer of the laminates was put on the donor side of the diffusion cell, and the polymer layer on the receiver side. Perfusion of both donor and receiver compartments was at 15 ± 0.5 ml min^{-1} using a tube pump (MV-CA 4, Ismatec, Zürich, Switzerland; Viton tubing, 2.00 mm i.d.). PTFE tubing (1.25 mm i.d.) was used throughout to avoid drug loss by absorption. For the same purpose, both cell halves were equipped with specially designed PTFE-coated, 7.35 cm diameter O-rings to keep the laminate in place.

Donor and receiver media are listed in Table 2. In order to establish maximum thermodynamic activity of the drugs and constant gradients for diffusion, the donor media were saturated with excess drug prior to the experiments. Perfect sink conditions were maintained throughout. In the donor media, the pH values were adjusted in order to ensure that at those values only unionized species could diffuse through the polymer laminate, except for the zwitterionic verapamil-COOH, where the isoelectric point pH 6.5 was chosen for both donor and receiver compartments. Where necessary, the receiver medium was periodically replaced. Intense stirring in the reservoir of the donor medium at approx. 250 min^{-1} was carried out in order to maintain saturation of the drug. With the solid compound verapamil-COOH, care was taken to avoid clogging of the donor cell compartment by means of a glass wool filter. No such precaution was necessary with the liquid compounds gallopamil and anipamil forming an emulsion in the donor medium. There was no measureable pH shift in the compartments even in the case of major pH gradients between them. For equilibration, the laminates were inserted into the

TABLE 2

Donor and receiver media

Drug	Donor [a]	Receiver [b]
Gallopamil	Isotonic glycine/NaOH buffer pH 11.0/methanol, 3 : 1	0.05 N HCl/methanol, 3 : 1
Anipamil	Isotonic phosphate buffer pH 6.0/ 2-propanol, 3 : 1	0.05 N HCl/2-propanol, 3 : 1
Verapamil-COOH	Isotonic phosphate buffer pH 6.5	Isotonic phosphate buffer pH 6.5

[a] Donor media were saturated with excess drug. Saturation of donor media was at at 31 °C and 36 h prior to the diffusion experiment. Buffers were 0.05 N. Isotonicity was by means of NaCl addition. Donor volume was 50 ml for gallopamil and anipamil, but 7.0 ml for verapamil-COOH.

[b] Study under sink conditions. Receiver volume was 100 ml throughout.

diffusion cell 60 min previous to the experiment. During this period, perfusion was restricted to the receiver compartment. This treatment was also used to check the integrity of the laminate.

Diffusional flux of the drug from the donor into the receiver compartment was continously monitored by flow-through UV spectroscopy of the receiver compartment (anipamil, 272 nm; gallopamil, 277 nm; verapamil-COOH, 278 nm; Beckman, model DB-GT, München, F.R.G.). Only the linear portions of the resulting concentration vs time profiles were further evaluated.

Treatment of diffusion data

Non-linear regression analysis was used to evaluate the diffusion data. As variables, the experimentally obtained total flux, $J_{t,ij}$, through the laminate and the corresponding thickness of the polymer layer, l_{ij}, were used. The function applied was

$$J_{t,ij} = J_b \frac{T_{m,i}}{J_b l_{ij} + T_{m,i}} \quad (1)$$

Eqn 1 includes the transference of the individual polymer, $T_{m,i}$, and the flux contribution of the combined barrier, J_b, of the supporting film and the stagnant diffusion layers on both sides of the laminate. $T_{m,i}$ represents a constant for each individual polymer, whereas J_b is a constant independent of the polymers used; l_{ij} denotes the thickness of the polymer layer of the laminate. The subscripts i and j indicate the different polymers (i) and the different thicknesses (j) for the i-th polymer, respectively. The derivation of Eqn 1 is set out in detail in Appendix A.

Non-linear regression analysis of the data was carried out by means of a Simplex algorithm (Nelder and Mead, 1965) using a routine written by Süverkrüp (1985). All drugs were separately evaluated, but within each drug the data of all polymers and thicknesses were pooled.

Intrinsic diffusion coefficients, D_{in}, were calculated from the transference T_m according to

$$T_m = J_m l = K D_{in} C_{s,d} \quad (2)$$

where K is the partition coefficient between the polymer and the donor medium and $C_{s,d}$ is the solubility of the drug in the donor medium. Both parameters were independently determined (Lichtenberger, 1988) for all three drugs, using the same media as for the diffusion experiments (Table 2).

Results and Discussion

Drug and polymer effects

The results for the three drugs are indicated in Table 3, containing the transferences and the intrinsic diffusion coefficients in the different polymers.

The results (Table 3) for gallopamil and anipamil show that within the same drug the

TABLE 3

Transferences, partition coefficients and intrinsic diffusion coefficients of the drugs in different polymers

Polymer	n [a]	Transference [b] ($T_m \times 10^{10}$) (g cm^{-1} s^{-1})	K [c]	Intrinsic diffusion coefficient [d] ($D_{in} \times 10^9$) cm^2 s^{-1})
Gallopamil				
B-430 D	6	0.671	141.6	0.862
A-80 D	3	1.465	183.4	1.149
A-290 D	2	0.367	535.3	0.350
A-4 D	6	2.431	292.3	1.197
A-DS 2178	2	2.06	330.0	0.9
P-800 D	5	1.841	267.1	0.992
A-500 D	3	1.613	194.7	1.192
Anipamil				
B-430 D	3	1.262	618.9	1.702
A-80 D	3	6.374	801.1	6.640
AV 205	3	6.086	801.1 [e]	6.340
A-290 D	3	1.558	083.7	1.551
A-4 D	7	6.512	835.2	6.499
P-800 D	4	5.070	782.9	5.364
Verapamil-COOH				
A-4 D	2	0.256	0.82	1.17

[a] Number of experiments per polymer.
[b] Transference $T_m = J_m l$ observed with saturated donor solution, $C_{s,d} = 6.97 \times 10^{-4}$ (gallopamil), 1.1×10^{-4} (anipamil), 2.8×10^{-2} (verapamil-COOH) g cm^{-3}; solubility data from Lichtenberger (1988).
[c] Partition coefficient (data from Lichtenberger, 1988).
[d] Intrinsic diffusion coefficient, calculated from $T_m = D_{in} K C_{s,d}$.
[e] Taken from A-80 D.

transferences and intrinsic diffusion coefficients remain reasonably constant, except for two polymers, i.e. A-290 D and B-430 D, where the coefficients attain only about one-fifth to one-half of the other values. This appears to be due to the styrene component of the respective polymers, resulting in greater rigidity of the polymeric structure and hence lower diffusivity.

Between the drugs, there is a remarkable differences between gallopamil and verapamil-COOH on one side, and anipamil on the other. This reflects the effect of the more flexible *n*-dodecyl side chain of anipamil vs the de facto more voluminous and inflexible isopropyl side chain of gallopamil. Moreover, gallopamil contains five methoxy substituents as compared to two with anipamil. Therefore, the difference in intrinsic diffusivities appears to be reasonable (Perrin, 1980). The spatial configuration of verapamil-COOH is very similar to that of gallopamil. This dominating influence on the effective volume of the molecules serves as an explanation for its similar intrinsic diffusivity (Peterlin, 1975). The observation of high transferences of gallopamil vs the lower value of verapamil is readily explained by the higher degree of drug/polymer interactions with the more lipophilic gallopamil as compared to the less lipophilic verapamil-COOH, as reflected by the marked differences with respect to the partition coefficients (Table 3).

Combined effect of boundary layers and support film

Typical examples of the effect observed when the thickness of the adhesive polymer in the laminate is varied are given in Fig. 1. This graph exemplifies the quality of the fits using Eqn 1. It is remarkable that for the three drugs investigated, the independent estimation of the combined contributions of the microporous support film and the two aqueous diffusion layers results in a practically constant J_b between 1.31×10^{-7} (anipamil) and 1.41×10^{-7} g cm^{-2} s^{-1} (gallopamil and verapamil-COOH), showing that — as predicted — the hydrodynamics of the diffusion cells are essentially independent of the respective polymer/drug combination.

The effect of the significance of J_b is further demonstrated in Figs 2 and 3. In each figure two

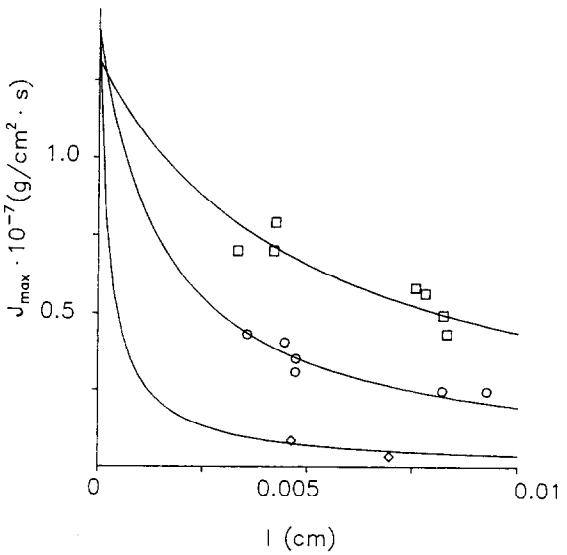

Fig. 1. total flux J_t of anipamil (□), gallopamil (○) and verapamil (◇) through polybutylacrylate laminate (A-4 D) vs thickness of polymer cast. Solid line: best fit of Eqn 1. The intercepts on the J_t axis indicate practically constant J_b for all drugs.

different fits are presented: one with and one without considering the contribution of J_b. It is clearly evident that in the case of the example with anipamil (Fig. 2), the contribution of J_b is most

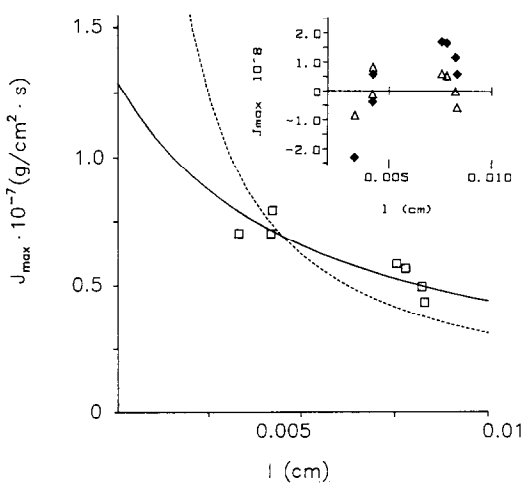

Fig. 2. Effect of consideration of J_b on the quality of fit of total flux data, J_t, of anipamil through polybutylacrylate (A-4 D) vs thickness of polymer cast. Dashed line: fit without J_b, i.e. when $J_t = T_m/l = J_m$. Solid line: fit using J_b and Eqn 1. Inset indicates residuals without (◆) and with J_b(△).

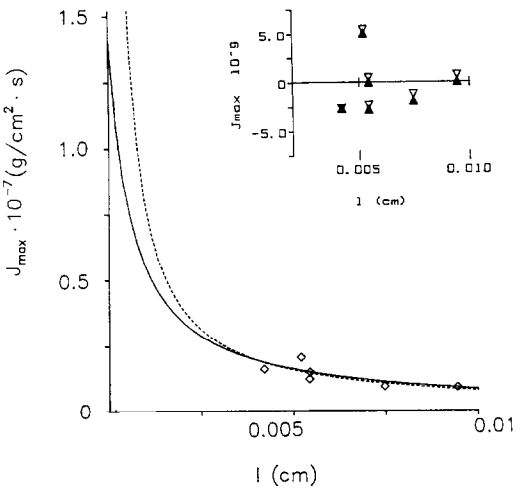

Fig. 3. Effect of consideration of J_b on the quality of fit of total flux data, J_t, of gallopamil through butadiene-styrene copolymer (B-430 D) vs thickness of polymer cast. Dashed line: fit without J_b, i.e. when $J_t = T_m/l = J_m$. Solid line: fit using J_b and Eqn 1. Inset indicates residuals without (▲) and with J_b (▽).

relevant, whereas it is negligible in the case of the gallopamil example. Since J_b is basically a function of the porosity of the support film and of the hydrodynamics in the diffusion cell, its absolute value is essentially independent of the polymer used. However, the relative significance of J_b as compared to the flux contribution of the polymer itself, J_m, may vary, depending on the absolute value of J_m. Therefore, this is consistent with the theory that for the much higher total flux level in the anipamil example (Fig. 2), the effect of J_b becomes significant, whilst it turns out to be negligible with the much lower total flux level in the gallopamil example (Fig. 3), using a butadiene-styrene adhesive of rather low intrinsic diffusivity.

Cross-linking effect

Cross-linking effects were investigated in poly(1-ethylhexylacrylate) (A-80 D) as the polymer and anipamil as the permeant. The polymer of this dispersion can be cross-linked by lowering the pH via the addition of aqueous NaOH solution.

As expected, cross-linking leads to a significant lowering of the permeability of anipamil with diffusion coefficients from $D = 6.64 \times 10^{-9}$ cm^{2}s^{-1} for the non-crosslinked A-80 D polymer ($n = 3$) to $D = 4.56 \times 10^{-9}$ cm^2 s^{-1} for the completely cross-linked A-80 DV ($n = 4$). This effect may be attributed to a combined effect of both (i) lowering of the free volume for diffusion, and (ii) reduction of the free volume for drug/polymer interactions which can lead to a decrease in solubility of the drug in the polymer.

Effects of polar and non-polar additives

The effects of polar and non-polar additives on polymer film permeability were studied as regards the aspect that such agents may be used to facilitate the incorporation of drugs into aqueous polymer dispersions for transdermal patch preparation. The purpose of the study was to determine whether such agents have a modifying effect on the permeability of drug-free films cast from aqueous dispersions.

As additives the polar agents sodium lauryl sulfate (NLS) and Latecoll D®, and the non-polar isopropyl myristate (IPM) were investigated. The results are listed in Table 4. NLS is a stabilizing agent for aqueous polymer dispersions and facilitates the incorporation of lipophilic liquids, either additives or drugs. An increase in NLS concentration from 0 to 4% leads to a significant increase, approx. 50% in the intrinsic diffusivity within the polymer film. Possibly a somewhat less dense polymeric matrix (Vanderhoff, 1973) is created as a consequence of the coherent hydrophilic surfactant network within the polymer which leads to enhanced swelling of the membrane due to the uptake of water from the circulating donor and receiver media.

Latecoll D® as a hydrophilic polymer may be used as a thickening agent to improve the physical stability of drug-loaded dispersions and, therefore, the uniformity in content of the resulting polymer film casts. Its effect on drug diffusivity in the films was negligible. This result is in marked contrast to the data of Pflegel et al. (1981, 1982), demonstrating pronounced effects of hydrophilic polymer additives by a factor of 10 on the diffusivity of poly(acrylate) membranes. Nevertheless, it is reasonable from our data, that the addition of small amounts of additives (< 2%) does not result

TABLE 4

Transferences and intrinsic diffusion coefficients of gallopamil in poly(butylacrylate) films (A-4D); effects of polar and non-polar additives

Additives	n [a]	Transference [b] ($T_m \times 10^{10}$) (g cm^{-1} s^{-1})	Intrinsic diffusion coefficient [c] ($D_{in} \times 10^9$) (cm^2 s^{-1})
Sodium lauryl sulfate (w/w)			
0%	6	2.431	1.34
2%	2	2.587	1.38
4%	2	4.643	2.13
Latecoll D® thickener (w/w) [d]			
1.5%	4	4.497	2.0 [e]
Isopropyl myristate (w/w) [d]			
15%	2	4.980	2.2 [e]

[a] Number of experiments per polymer.
[b] Transference $T_m = J_m l$ observed with gallopamil saturated donor solution, $C_{s,d} = 6.97 \times 10^{-4}$ g ml^{-1}, solubility data from Lichtenberger (1988).
[c] Intrinsic diffusion coefficient, calculated from $T_m = D_i K C_{s,d}$; partition coefficients, from Lichtenberger (1988).
[d] Polymer dispersion containing 4% sodium lauryl sulfate.
[e] Partition coefficients for calculation taken from additive-free polymer preparation.

in a marked change in the overall drug permeability.

Addition of IPM may be performed concerning two aspects: (i) it may play a role as a suitable solvent for lipophilic drugs which otherwise may be difficult to incorporate into an aqueous polymer dispersion; and (ii) to modify the overall polarity of the film cast and thereby optimize drug/polymer interactions within the polymeric matrix for maximum drug release. The effect of IPM on gallopamil diffusivity can be equally neglected. Its addition does not significantly change the transference and diffusivity of the films for this particular drug.

The results show that the polymer dispersion used tolerates the addition of several auxiliary compounds without dramatic effects on the diffusivity and transference of its film casts. This is a crucial prerequisite for the practical use of aqueous polymer dispersions for transdermal patch manufacturing. Nevertheless, their addition to certain polymeric matrix systems can markedly enhance the overall release rate of a drug, then due to diminished drug/polymer interactions. Such preparations have been suggested elsewhere (Lichtenberger et al., 1990).

Effect of initial drug loading

Similar to the effect of an additive, the incorporation of drug itself may vary the diffusivity and transference of pressure-sensitive polymer, depending on its concentration in the film. For evaluation, film casts were prepared using poly(butylacrylate) (A-4 D) dispersion containing 9% (w/w) gallopamil and 4% (w/w) NLS as surfactant. Prior to the diffusion experiments, the drug was completely washed out of the films. The transference and diffusivity of the casts ($n = 4$) were $T_m = 6.431 \times 10^{-10}$ g cm^{-1} s^{-1} and $D_{in} = 3.12 \times 10^{-9}$ cm^2 s^{-1}, respectively. This corresponds to an increase by about one-third as compared to the values in the case of the film cast prepared without drug (see Table 4). This effect is significant but not dramatic. It may be caused by the interaction of the polymer and the drug having similar solubility parameters ($\delta = 9.0$ cal$^{0.5}$ cm$^{-1.5}$ for the polymer vs 9.27 cal$^{0.5}$ cm$^{-1.5}$ for the drug; data from Lichtenberger, 1988). This also explains why IPM did not exhibit any significant effect on transference and diffusivity of the cast polymer. As indicated by its solubility parameter $\delta = 8.0$ cal$^{0.5}$ cm$^{-1.5}$ (Vaugham, 1985), IPM shows no detectable interaction with the polymer.

Appendix

Under perfect sink and steady-state conditions, the flux J_t across a laminate is constant and is expressed as

$$J_t = P_t C_{s,d} \qquad \text{(A1)}$$

where P_t denotes the total permeability coefficient and $C_{s,d}$ the solubility of the drug in the donor compartment. The resulting concentration change

dC_r/dt in the receiver compartment is proportional to the constant flux J_t across the laminate:

$$dC_r/dt = \frac{A}{V_r} J_t \quad \text{(A2)}$$

or by combination with Eqn A1

$$dC_r/dt = k_{d/r} C_{s,d}$$

and

$$C_r = k_{d,r} C_{s,d} t \quad \text{(A3)}$$

where $k_{d/r}$ is an experimental transport coefficient (s^{-1}) across the laminate, including the area available for diffusion A and the receiver volume V_r. $C_{s,d}$ is the saturation concentration of the drug in the donor medium. $k_{d/r}$ can be obtained from a linear plot of C_r vs time t considering the saturation concentration. The total flux J_t is then determined from Eqn A2.

The relationship (Michaels et al., 1975) between the total flux, J_t, the theoretical contributions of (i) the flux through the barrier of the polymer layer alone, J_m, and (ii) the flux through the adjacent combined barrier of the stagnant diffusion layers on both sides of the laminate and the microporous film supporting the polymer membrane, J_b, is given by

$$\frac{1}{J_t} = \frac{1}{J_m} + \frac{1}{J_b} \quad \text{(A4)}$$

Division by the thickness of the membrane barrier yields

$$\frac{1}{J_t l} = \frac{1}{J_m l} + \frac{1}{J_b l} \quad \text{(A5)}$$

The product $J_m l$ is the transference of the membrane, T_m, a parameter which characterizes the diffusional properties of the membrane and is independent of its thickness l (Michaels et al., 1975; Theeuwes et al., 1976). By introducing T_m into Eqn A5, one obtains:

$$\frac{1}{J_t l} = \frac{1}{T_m} + \frac{1}{J_b} \frac{1}{l} \quad \text{(A6)}$$

Based on linear regression analysis, Eqn. A6 has been applied by Michaels et al. (1975) to make simultaneous estimations of the transference of polymer films, T_m, as a characteristic parameter, and J_b as the flux contribution of the adjacent aqueous diffusion layer. The two constant parameters are the reciprocal values of the intercept and of the slope, respectively, when $1/(J_t l)$ and $1/l$ are the variables.

In our study, J_b contains the contributions of both (i) the aqueous diffusion layers on both sides of the laminate and (ii) the supporting film. It is reasonable to assume that — for the hydrodynamics given — this contribution is constant and independent of the polymer investigated. After rearranging Eqn A6, non-linear regression analysis can be applied using

$$J_{t,ij} = J_b \frac{T_{m,i}}{J_b l_{ij} + T_{m,i}} \quad \text{(A7)}$$

with the subscripts indicating different polymer materials (i), and different thicknesses (j) of the i-th polymer. The constant parameters are the desired transferences for each individual polymer, $T_{m,i}$, and J_b as the constant flux contribution of the combined effects of the support film and the stagnant diffusion layers. The variables are $J_{t,ij}$ and l_{ij}.

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