Diffusion Behavior of Drug Molecules in Acrylic Pressure-Sensitive Adhesive

Xuexue Chen, Yaxin Wang, Zhipeng Cheng, Jie Wei, Yifeng Shi,* and Jun Qian*

ABSTRACT: Acrylic pressure-sensitive adhesive (PSA) is widely used in transdermal drug delivery systems, while the diffusion behavior of drug molecules in PSA is of great importance. In this paper, PSAs with different cross-link densities were prepared by adjusting the ratio of cross-linkers. The effects of cross-link density and temperature on the diffusion of drugs in PSA were investigated by Fourier transform infrared attenuated total reflectance and molecular dynamics simulation. The consistency between the experimental and simulation results demonstrated that molecular dynamics simulation could be used to predict the diffusion behavior of drugs in PSA. The results showed that free volume and the wriggling of polymer chains are positively related to the diffusion coefficient of drug molecules, while hydrogen bonds hinder drug diffusion.

INTRODUCTION

Compared to intravenous and oral drugs, transdermal drug delivery systems (TDDSs) have many excellent advantages: constant and controllable blood concentration, gentle blood concentration curve, gastrointestinal degradation, and liver first-pass effects.1−4 Pressure-sensitive adhesive (PSA) is a key material in TDDSs, which renders the drug delivery system closely adhere to the skin.5,6 It can also serve as a drug-loading reservoir or a viscous material to control the release rate of the drug.7−9 Acrylic PSAs are applied to more than half of the TDDS products approved by the US Food and Drug Administration (FDA)10 because of their physicochemical stability and acceptable miscibility with most transdermal drugs. Although they have been accepted in TDDS for decades, the selection and design of PSA are based on trial and error. Simultaneously, the drug release curve study is time-consuming, expensive, and often complicated to carry out.11,12 Therefore, the diffusion behavior and mechanism of drug molecules in polymers will be vital in the design of controlled release materials.

Drug diffusion in PSA is regarded as Fick diffusion, a material transport process. An important parameter describing the diffusion process is the diffusion coefficient. It is mainly derived from experimental measurements and model predictions.13 Marquardt et al.14 characterized the diffusion coefficient through weight variation after diffusion. Ordaz15 studied the effect of membrane thickness and polymer molecular weight on the diffusion coefficient of water in poly(methyl methacrylate) thin membranes supported on gold-coated surfaces by the quartz crystal microbalance method. Santos16 designed and developed an in situ pressure-contact Fourier transform infrared attenuated total reflectance (FTIR−ATR) spectroscopy apparatus for measuring liquid transport in free-standing polymer membranes. Even though these methods have been successfully applied to characterize the diffusion of small molecules in some polymers,17,18 they are rarely utilized in PSAs.

Molecular dynamics (MD) can make up for this deficiency.19−21 It is of significant value to obtain the diffusion and transport properties at the molecular level and they can be used in model prediction.22 Lin23 simulated the effects of molecular size, water, and temperature on the interdiffusion process through coarse-grained MD. Wang24 calculated the diffusion coefficients of 13 small molecules in amorphous polyethylene terephthalate (PET), based on MD simulation. The accuracy of the MD simulation technique for estimating the diffusion coefficient of migration in PET was evaluated by the Piringer model and experimental prediction. Through the MD simulation, Ling25 found that the diffusion simulation results of the diesel component model in polyvinyl alcohol were in great conformity with the experimental results, indicating that the dynamics simulation method could roughly predict the diffusion behavior of the diesel component in the
polymer membrane. Although MD could simulate various test situations to help people predict diffusion, because of its algorithms and the computer used, the simulation time and the simulation system are still limited. Therefore, not all simulation results could match well with the experimental results.

In this paper, the diffusion of drug molecules in acrylic adhesives was characterized by FTIR–ATR. Combined with the MD simulation, effects of cross-link density and temperature on the diffusion of drug molecules were investigated. In order to prove that the MD simulation results can match well with the experimental results, we compare and analyze the results of the experiment and MD. The similarities and differences between the experiment and MD are discussed. Based on the abovementioned data, the diffusion mechanism was revealed.

■ RESULTS AND DISCUSSION

Diffusion Characterized by ATR. The drug molecules diffuse from the PSA/drug layer into the pure PSA and reach the PSA/ATR interface. According to the Lambert Beer’s law, the change that happened in drug concentration of the PSA/ATR interface can be characterized by the change occurring in the absorbance of the characteristic peak. Based on Figure 1, peak area to A/A 1449 cm\(^{-1}\). After normalization, the effect of thickness can be ignored.

Influence of Cross-Link Density on Diffusion. PSAs of different cross-link densities were prepared by adding different proportions of cross-linkers. The properties of the PSA are shown in Tables 1 and 2. From sample 1 to sample 6, the proportion of the cross-linker gradually increased. From sample 303 to 343, the diffusion temperature gradually increased. The diffusion coefficient of experiment (D-FTIR) and MD simulation (D-MD) was characterized under different conditions. D-polymer is the self-diffusion coefficient of the polymer in MD. Sample 1 was used as a master batch without cross-linking. It has high loop tack and peel strength and short hold time. Small changes in cross-link density have a strong effect on the mechanical properties because of chemical cross-linking. As the cross-link density increases, the interaction between the PSA and the polar groups on the surface of the test substrate decreases. It is difficult to form a dense adhesive layer at the interface, and eventually, the initial adhesion strength gradually decreases. The holding time of the PSA is affected by the cohesive strength. The cohesive force of the PSA is greatly enhanced after cross-linking, so samples 2–6 have excellent holding time. However, cross-linking will greatly reduce the deformability and fluidity of the PSA. Therefore, it is difficult to form a stable interface between the adhesive layer and the test substrate during the peel strength test. At the same time, stress concentration will occur in the adhesive layer, thereby reducing its peel strength. Despite the poor mechanical properties of high-cross-link-density PSAs, they are meaningful for diffusion research.

The cross-link density of the samples was characterized with \(^1\)H NMR transverse relaxation parameters. The higher the cross-link density of the polymer, the faster the proton transverse relaxation curve decayed. As shown in Figure 3, samples 1–6 showed the same regularity but sample 6 had the fastest recession rate, while noncross-linked sample 1 had the slowest recession rate. It was verified that the cross-link density of samples increased gradually from no. 1 to no. 6. As the proportion of the cross-linker became larger, the cross-link density of the PSA increased almost linearly.

![Figure 1. FTIR–ATR spectrum of PSA and PSA with the drug ketoprofen.](image)

![Figure 2. FTIR–ATR spectrum of the PSA/ATR interface at different diffusion times.](image)
It can be seen from Figure 4 that PSAs with different cross-linking densities have excellent thermal stability. The temperature at which the PSA has a weight loss of 5% and 50% is about 300 and \(385^\circ C\), respectively. Before 500 \(^\circ C\), the thermal weight loss curves of samples 1–6 are very similar. It is because at high temperatures, the weight loss of the PSA is mainly caused by the rupture of the carbon chain. Cross-linking does not contribute to it. After 500 \(^\circ C\), the remaining substances are cross-linkers, so from samples 1–6, the remaining weight gradually increased.

The change in the peak area of the drug molecules at the PSA/ATR interface with different cross-link densities is shown in Figure 5a, showing distinguished differences in the diffusion of drug molecules. The molecules spread fast in the PSA when the cross-link density was zero or low, while the molecule concentration in PSA/ATR became large within 10 h. When the cross-link density reached a certain extent, such as in sample 3–6, the diffusion rate suddenly became slow without significant variation in molecule concentration in 10 h. As the cross-link density increases, it took more time for the drug molecules to diffuse from the reservoir to PSA/ATR.

Therefore, the extracted drug contents (E-drug) from the reservoir gradually decreased (Table 3).
The diffusion coefficients shown in Table 2 and Figure 5b were based on eq 3. The diffusion coefficient $D$ decreased sharply against the cross-linker ratio first and then, the trend gradually became smaller. $D$ of drug molecules in noncross-linked PSA was $8.46 \times 10^{-8}$ cm$^2$/s. In the PSA with a cross-link density of $7.51 \times 10^{-4}$ mol/cm$^3$, $D$ came down to $3.17 \times 10^{-8}$ cm$^2$/s. In polymers, there is a large amount of physical cross-linking, but chemical cross-linking has a greater effect on diffusion. After chemical cross-linking, a three-dimensional network structure will be formed. The molecular chains become rigid, and the wriggling of the chains becomes worse. Compared with sample 1, sample 3 has more chemical cross-linking and has a stronger resistance to diffusion, so $D$ decreases rapidly.

**Influence of Temperature on Diffusion.** Five temperature levels of 303, 313, 323, 333, and 343 K were set in this experiment to investigate the effects of temperature on diffusion. The results are displayed in Figure 6. The increased temperatures accelerated the diffusion and promoted it to equilibrium. At low temperatures such as 303 or 313 K, diffusion continued slowly and the concentration of drug molecules in PSA/ATR had been accumulated during a limited observation period. With the temperature increasing, the diffusion time was sharply shortened, for example, from 6 h at 333 K to 4.5 h at 343 K. Because the thickness of the PSA/
drug layer was the same as that of pure PSA, the equilibrium concentration of drug molecules in pure PSA was one-half of that of the reservoir, as shown in Table 3. Based on the Arrhenius equation, the \( \ln D - \frac{1}{T} \) relationship curve is plotted in Figure 6f. The curve \( \ln D = -0.1364 - \frac{4926.35}{T} \) was obtained by data regression, so the activation energy \( E_a \) is 40.96 kJ/mol and the previous factor \( D_0 \) is 0.8725. The diffusion activation energy is determined by the diffusion molecules and the diffusion matrix. It is affected by the type and size of the diffusion molecules, \( T_g \) of the diffusion matrix, and the interaction between the diffusion molecules and the diffusion matrix. In the research of Rosca et al.,\(^{37}\) they also characterized the diffusion by ATR and the diffusion activation energy of DOP in nitrile butadiene rubber (\( T_g = -17 \degree C \)) is 40 kJ/mol. Iordanskii et al.\(^{38}\) found that the diffusion activation energy of water in poly-(3-hydroxybutyrate) films is 71 kJ/mol. By increasing the temperature, the dipole–dipole interactions are strongly reduced by the contribution of thermal energy and more free volume of holes is formed in the polymer matrix. These are conducive to diffusion.

The initial concentration of the drug in the reservoir can be calculated from the area of the characteristic peak, so \( E_{\text{drug}} \) from the reservoir can be expressed as the concentration of the drug at the PSA/ATR interface at 10 h divided by the initial concentration. \( E_{\text{drug}} \) in 10 h under different conditions is shown in Table 3. When diffusion reaches equilibrium at high temperatures such as 333 and 343 K, \( E_{\text{drug}} \) is 50%.

**Diffusion Characterized by MD.** Before calculating the diffusion coefficient, we optimized the simulation model in multiple steps. Figure 7a indicates that the spatial structure was gradually optimized after experiencing several relaxations at high temperatures. In the range of 0–300 ps, the system density tended to rise, while it fluctuated within the range of 1.015 ± 0.010 g/cm\(^3\) in the range of 400–1000 ps, as shown in Figure 7b. The fluctuation range indicating that the density had equilibrated was less than 1%. In Figure 7c, the kinetic energy, potential energy, nonbond energy, and total energy all
fluctuate within a certain range. The total energy was in the range of 12,150 ± 158 kcal/mol, and the fluctuation range was 1.30%, which illustrated that the system had reached equilibrium and the resulting trajectory could be used for the following analysis.

In MD simulation, we successfully simulated the diffusion of drug molecules in PSA with different cross-link densities, as shown in Figure 8a. In the first one or two hundred picoseconds, large slowing down is observed because of the subdiffusion, and mean square displacement (MSD) does not depend linearly on time but scales as $\Delta r^2 \approx t^\alpha$ with $\alpha < 1$.45 At the end of MSD curves, sample 1 and sample 2 exhibit plateau. It is because that low-cross-link density polymers have more homogeneous systems and the percolation threshold for polymer chains should be shifted to lower values.34 When near the percolation threshold, a large polymer content will limit the motion of small molecules and the trajectory will be smaller. Generally, only the middle section of the MSD curve is selected for calculation.32,33 Therefore, the MSD of the first and the last 200 ps was discarded in this work and the results were averaged from 200 to 600 ps.

In Figure 8a,b, the downward trend of MSD meant the decrease of the diffusion coefficient $D$, and the trend is the same as that in experiment. The influence of temperature in MD is shown in Figure 8c,d, revealing stronger effects on diffusion than cross-link density. The diffusion coefficient was maximized when the temperature was as high as 343 K, as shown in Table 2. According to the Arrhenius equation, the curve $\ln D = -0.5328 - 4690.15/T$ was obtained by data fitting and the activation energy $E_a$ is 39.00 kJ/mol and the previous factor $D_0$ is 0.5870.

No matter if it was the simulation of the cases of cross-link density or temperature, $D$ in MD simulation was larger than that in the experiment because of the negligence of hydrogen bonding between drug molecules and the polymer and the variation of concentration in MD. However, the activation energy is very similar in the experiment (40.96 kJ/mol) and MD (39.00 kJ/mol). At high temperatures, a large number of the hydrogen bonds are destroyed, so simulation will be close to the experiment.

**Diffusion Mechanism.** At present, many theoretical models have been proposed to explain the diffusion mechanism of small molecules in polymers. These models may be grouped into three classes. The first model is based on obstruction,39–41 where macromolecules are regarded as motionless obstacles, leading to a longer diffusion path. The second model is based on hydrodynamic theories,42,43 which takes into account hydrodynamic interactions such as friction. The third model is based on free volume theory, where the rearrangement of free volume creates holes being a transport channel for the diffusant.34–36 In this experiment, the size of polymer molecules has not been changed by cross-linking, and it is obviously unreasonable to regard polymer chains as motionless at high temperatures. Cross-linking and temperature will affect the mobility of polymer chains, cause rearrangement of free volume, and thus change the size and distribution of free volume. Hence, our results and discussion are based on the free volume model.

There are two main approaches to drug molecules diffusing in the polymer. First, the free volume of the polymer creates holes, being a transport channel for the diffusant, and small molecules can achieve transition through holes. Second, the wriggling of polymer chains drives the small molecules to diffuse far (Figure 9). Based on free volume theory, the free volume in the polymer provides places for the small molecules to diffuse, and the wriggling of the polymer chains creates a motion path for small molecules. The effect of the polymer chains can be regarded as a driving force, pushing small molecules to a low-concentration area from a high-concentration one. This process, like a pump, also accelerates the frequency of small molecule movements to promote the diffusion, so the wriggling of polymer chains is positive for diffusion.

**Movement of Polymer Chains and Free Volume.** It was not suitable to evaluate the wriggling of the chains from the MSD of the center-of-mass. The wriggling of the polymer chains was measured from the MSD of chains.28 Symmetrical
moving of the chains might cause little change in the center of mass, leading to smaller MSD. Hence, the MSD of atomic groups of the polymer main chain was utilized to describe the wriggling of the polymer chains and the results were averaged over all atomic groups.

The MSD of the polymers with different cross-link densities is shown in Figure 10a, which demonstrated the difference in the movement ability between different polymer chains. The MSD curves of the polymer became more smooth with the increase in the proportion of the cross-linker, resulting in the decline of the polymer self-diffusion coefficient (Figure 10b). The relationship between the self-diffusion coefficient of the polymer \( (D_p) \) and the ratio of the cross-linker was particularly similar to the diffusion coefficient of the drug molecules \( (D_s) \) and cross-linker, and there was a positive correlation between \( D_p \) and \( D_s \) (Figure 10c). The polymer established a three-dimensional network structure when cross-linked. It weakened the wriggling of molecular chains and caused the reduction of the movement of small molecules.

For free volume (Figure 10d), few differences were discovered between PSA of different cross-link densities. It increased from 15.28 to 16.82% and then decreased to 16.10%. The molecular chains of the noncross-linked polymer would be naturally distorted and intertwined with each other. With a certain degree of cross-linking, a spatial network structure was formed between the molecular chains. The three-dimensional network structure limited the wriggling of chains and the accumulation of molecules, so the free volume increased first. Then, with the cross-link density continuously rising, the network became more and more compact and the intermolecular forces gradually increased. Hence, the free volume will slowly decrease.

Radial distribution functions (RDFs) are computed from the equilibrium MD simulations to measure the mean distance between cross-links, as shown in Figure 11. The position of the first peak represents the mean distance between cross-links. As the cross-link density increases, the mean distance gradually decreases, from 5.3 to 4.3 Å. This result indicates that the three-dimensional network is much denser in polymers with a high cross-link density. The distribution of free volume is affected by the three-dimensional network. Hence, we propose a mechanism conjecture for the influence of the free volume on diffusion. Although the size of the free volume has little effect on the diffusion, its distribution plays an important role in the
diffusion path of drug molecules. As shown in Figure 12, the free volume is distributed densely in the polymer with longer distance between the cross-links. The migration path of drug molecules in the free volume is shorter, so that it could move to the destination quickly. Conversely, in the polymer with high cross-link density, the shorter distance between cross-links leads the free volume to be distributed scattered. Multiple and time-consuming migrations are needed for drug molecules to achieve the same effect as that in the polymer of low cross-link density.

According to the theory of free volume, free volume is not the only factor affecting diffusion, for the maximum values of free volume and diffusion coefficient are unable to match each other at the same cross-link density, but $D_p$ is positively correlated with $D_c$. Therefore, the mobility of the polymer chains is essential to the diffusion of drug molecules.

It can be seen from Figure 13a,b that as the temperature got higher, the MSD curve of the polymer rose faster and the self-diffusion coefficient of the polymer increased exponentially, ranging from $6.72 \times 10^{-8}$ to $4.51 \times 10^{-7}$ cm$^2$/s (Table 2). This meant the dramatic enhancement of the wriggling of polymer chains. Figure 13c demonstrates the linear relationship between $D_p$ and $D_c$ at the same time, the free volume fraction also increased almost linearly from 16.64 to 20.5% (Figure 13d). The high temperature provided more energy for the molecular chains and the drug molecules to move. The molecular chains stretched and expanded, causing the increase of free volume. The improvement of free volume and wriggling of the polymer provided the diffusion with more place, ways, and impetus. Hence, there were more obvious diffusion changes by adjusting the temperature than the cross-link density of the polymer. We are able to make a conclusion that the diffusion of drug molecules in the polymer is not only affected by the polymer chain wriggling but also by the free volume of the polymer.

**Hydrogen Bond.** Another important factor hindering the diffusion is the hydrogen bond between the drug molecules and the polymer. Figure 14 shows the FTIR spectrum of the ketone carbonyl group in adhesives after diffusion for 10 h. As the cross-link density enhanced, the characteristic peak position of the ketone carbonyl group moved to a lower wavenumber. It appeared at 1661 cm$^{-1}$ in the noncross-linked PSA (sample 1), while it appeared at 1658 cm$^{-1}$ in the one with highest cross-link density (sample 6). The magnitude of movement of the peak position also indicated that the hydrogen bond became stronger as the cross-link density increased.

![Figure 12. Sketch of the diffusion path of drug molecules in free volume (green parts: polymer).](image)

![Figure 13. Diffusion in different temperatures. (a): MSD of PSA; (b): relationship between the self-diffusion coefficient of PSA and temperature; (c): influence of the self-diffusion coefficient of PSA on the diffusion coefficient of the drug; and (d): free volume fraction of PSA in different temperatures.](image)
The carboxyl group is a strong hydrogen bond donor and acceptor, while the ester group is a weak hydrogen bond acceptor. In the PSA synthesized in this experiment, the ester group is the main factor because the proportion of the ester group is much larger than that of the carboxyl group. When the drug enters into the pure PSA, it will react with the ester group to form a hydrogen bond, which hinders the diffusion of other small molecules. However, the hydrogen bond is weak and can be easily damaged by temperature or other force such as the wriggling of polymer chains. The more the cross-link density increases, the less the hydrogen bond will be destroyed, resulting from the freezing of the molecular chains. Moreover, the hydrogen bond will be surrounded by the network in the PSA and be more stable, which further hinders the diffusion of other drug molecules.

**CONCLUSIONS**

In this paper, the diffusion behavior of the drug molecules in the PSA with different cross-link densities and different temperatures was investigated by FTIR−ATR and MD. The change tendency of D was similar, and the activation energy ($E_a = 40.96$ kJ/mol) in FTIR was close to that in MD ($E_a = 39.00$ kJ/mol). This demonstrated that MD could help predict the diffusion behavior for further research. Combining the diffusion behavior in FTIR−ATR and MD, the diffusion mechanism was proposed. The free volume and the wriggling of molecular chains are positively related to the diffusion coefficient of drug molecules, while the distribution of free volume will change the path length of the drug molecule. Hydrogen bonds are detrimental to diffusion.

As the cross-link density increases, the wriggling of the molecular chains was impaired, so the diffusion driving force is reduced. The dispersion of the free volume lengthens the diffusion path of the drug molecules. At the same time, although the number of groups to form hydrogen bonds is gradually reduced, freezing of the molecular chains makes the hydrogen bonds more stable. It further hinders the diffusion of drug molecules.

As the temperature rises, both the wriggling of molecular chains and the free volume will increase but the hydrogen bonds will be destroyed. On account of the enhancement of the motion place, the driving force, the energy, and the reduction of hindrance, the drug molecules get into a state where the diffusion becomes more rapid.

**EXPERIMENT AND THEORETICAL METHODS**

**Materials.** Monomers used in this paper are isooctyl acrylate, methyl acrylate, acrylic acid, and AIBN, and the cross-linker aluminum acetylacetonate and acetylacetonate were purchased at Shanghai Titan Technology Co., Ltd. The drug sample Ketoprofen was supplied by Hangzhou Rongfang Pressure Sensitive New Material Co., Ltd. The MD simulation was constructed in Materials Studio 6.1 (Accelrys Inc., San Diego, CA, U.S.A.).

**Synthesis and Characterization of PSAs with Different Cross-Link Densities.** The acrylic PSA is formed by solution polymerization of three monomers of isooctyl acrylate, methyl acrylate, and acrylic acid (the weight ratio is 0.7:0.2:0.1) at 75 °C. AIBN is used as the initiator. The structure of the random copolymerized PSA is shown in Figure 15. The cross-link density is controlled with the level of the cross-linker aluminum acetylacetonate, which is 0, 1.43, 2.86, 5.72, and 11.45 wt %. $T_g$ of PSAs is $-10.50$ °C. The cross-linker was added into the polymer solution and stirred well before coating. We designed a film with a thickness of 50 μm, adjusted with the solid content of the adhesive solution and the proportion of the ester group is much larger than that of the carboxyl group. When the drug enters into the pure PSA, it will react with the ester group to form a hydrogen bond, which hinders the diffusion of other small molecules. However, the hydrogen bond is weak and can be easily damaged by temperature or other force such as the wriggling of polymer chains. The more the cross-link density increases, the less the hydrogen bond will be destroyed, resulting from the freezing of the molecular chains. Moreover, the hydrogen bond will be surrounded by the network in the PSA and be more stable, which further hinders the diffusion of other drug molecules.

![Figure 14. FTIR−ATR spectrum of PSA with different cross-link densities.](image-url)

![Figure 15. Structure of PSA.](image-url)
layer is PSA with different cross-link densities; when the upper layer stuck with the lower layer, the time was recorded as zero time. The PSA side of the device was placed on the ATR crystal to test the infrared absorption spectrum as a function of time, characterizing the diffusion process of drug molecules. With further diffusion, the drug molecules gradually diffused from the reservoir of the upper layer into the PSA of the lower layer, reaching the interface between the PSA and the ATR, thus being detected by ATR, as shown in Figure 16.

**Figure 16.** Diffusion process of drug molecules in PSA.

**Diffusion Coefficient and Diffusion Activation Energy.** The diffusion of drug molecules in PSA is consistent with Fick diffusion. The following eq 1 is the Fick diffusion formula

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial z^2}$$  \hspace{1cm} (1)

At present, a large number of papers have reported different calculation formulas of diffusion coefficients, based on different diffusion structure devices. Comyn\textsuperscript{29} proposed a symmetrical three-layer composite model, as shown in Figure 17. In this model, both the top layer and bottom layer are pure polymer membranes and the middle layer is a polymer membrane doped with drugs, with the initial concentration determined.

The thickness of the doped layer and the undoped layer is 2h and L − h, respectively. The coordinate origin is in the midpoint of the intermediate layer. The concentration formula of the polymer membrane on both sides is as follows (eq 2)

$$C = \frac{1}{2} C_0 \sum_{n=-\infty}^{n=+\infty} \left( \text{erf} \left( \frac{h + 2nl - x}{2\sqrt{Dt}} \right) + \text{erf} \left( \frac{h - 2nl + x}{2\sqrt{Dt}} \right) \right)$$  \hspace{1cm} (2)

The diffusion structure designed in this experiment can be regarded as half of the three-layer symmetric composite model, with the PSA/drug surface as the coordinate origin. Hence, the coordinates of the PSA/ATR surface are −L\textsubscript{1} − L\textsubscript{2}, and the surface concentration formula is changed into the following

$$C(z = -L_1 - L_2) = \frac{1}{2} C_0 \sum_{n=-\infty}^{n=+\infty} \left( \text{erf} \left( \frac{L_2 + 2n(L_1 + L_2) + 2L_1}{2\sqrt{Dt}} \right) \right. \left. + \text{erf} \left( \frac{-2n(L_1 + L_2) - L_2}{2\sqrt{Dt}} \right) \right)$$  \hspace{1cm} (3)

where C is the concentration at the interface between the polymer membrane and ATR, C\textsubscript{0} is the initial concentration of the drug in the PSA, L\textsubscript{1} is the thickness of the polymer membrane doped with drugs, L\textsubscript{2} is the thickness of the pure polymer membrane, t is the diffusion time, and D is the diffusion coefficient. When n is −4 to 4, the error is less than 0.01%. Calculations were done in Microsoft Excel.

$$\text{erf}(x) = \frac{2}{\sqrt{\pi}} \sum_{n=0}^{\infty} \frac{1}{n!} \frac{x^{2n+1}}{(2n+1)} (-1)^n$$  \hspace{1cm} (4)

The diffusion coefficient at different temperatures is obtained by changing the temperature of diffusion, and the activation energy (E\textsubscript{a}) of the diffusion can be analyzed using the Arrhenius formula (eq 5).

$$\ln D = \ln D_0 - \frac{E_a}{RT}$$  \hspace{1cm} (5)

**Molecular Dynamics simulation (MD).** The diffusion model was constructed using an Amorphous Cell module in Materials Studio. The model contained 10 drug molecules and 10 polymer chains with a polymerization degree of 30 in a periodic cubic simulation cell (with a length of approximately 42.5 Å). We randomly generated ten groups of polymer chains with the same weight ratio as that in the experiment and selected the group with the lowest energy after optimization. For the cross-linking process, it did not simulate the actual reaction. The carboxyl groups were set as cross-links, and MD calculations were performed on 10 molecular chains to determine the distance constantly between the cross-links. When the distance is shorter than the cutoff one, the cross-links will be chemically bonded. Once the ratio of carboxyl groups to be reacted (10) configurations were generated and three of them were selected for equilibration by following subsequent procedures, as shown in Figure 18: (1) 5000 steps energy minimization; (2) 500 ps export. (The noncross-linked polymer can be washed away by toluene by the extraction method, and the degree of the cross-linking reaction can be calculated from the remaining polymer, that is, the ratio of carboxyl groups to be reacted.)

**Figure 17.** Symmetrical three-layer composite model proposed by Comyn.
thermodynamic anneal; (3) 1000 ps NPT MD (T, 1.01 × 10^5 Pa); and (4) 1000 ps NVT MD (1.01 × 10^5 Pa).

The dynamics simulation process uses the COMPASS force field; the SMART method is used for energy minimization calculation. The Ewald method and the atom-based method are utilized respectively in the electrostatic interaction force calculation and the van der Waals force, setting the cutoff distance to 12.5 Å. For the simulation of diffusion in PSAs with different cross-link densities, the NPT ensemble simulation conditions are temperature 298 K with an Andersen thermostat and pressure 1.01 × 10^5 Pa with a Berendsen barostat. The NVT ensemble simulation conditions are temperature 298 K with an Andersen thermostat and the time step is 1 fs. For the simulation of diffusion at different temperatures, the pressure stays the same, while the temperature is changed according to the experimental setting. The RDF is calculated for the carbon atoms of the carboxyl groups. The free volume is calculated by the Connolly surface method. The proportion of the free volume to the total volume is called the free volume fraction (\(\phi_{\text{FFV}}\)).

\[
\phi_{\text{FFV}} = \frac{V_f}{V_o + V_f}
\]

where \(\phi_{\text{FFV}}\) is the free volume fraction, \(V_o\) is the occupied volume of polymers and small molecules, and \(V_f\) is the free volume. Free volume is the total volume of the polymers and small molecules excluding the occupied volume.

In the MD simulation, the diffusion coefficients of drug molecules in the polymer were calculated from the slope of the drug MSD as follows:

\[
\lim_{t \to \infty} (r(t + \Delta t) - r(t))^2 = 6D\Delta t
\]

where \(D\) is the self-diffusion coefficient, \(t\) is the time, and \(r(t)\) is the position vector of the center-of-mass of the drug molecule at time \(t\).

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### Notes

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## REFERENCES

1. Kumar, S. V.; Tarun, P.; Kumar, T. A. Transdermal drug delivery system for non-steroidal antiinflammatory drugs. *Indo Am. J. Pharm. Res.* 2013, 3, 3588–3605.

2. Shubhangi, C.; Push, S.; Ajay, A.; Shiv, G. K. Transdermal patches review on novel approach for drug delivery. *Indo Am. J. Pharm. Res.* 2015, 5, 531–548.

3. Lee, E.-Y.; Choi, S.-H.; Chun, M.-K.; Choi, H.-K. Development of transdermal drug delivery system of selegiline. *J. Pharm. Invest.* 2015, 46, 147–152.

4. Marwah, H.; Garg, T.; Goyal, A. K.; Rath, G. Permeation enhancer strategies in transdermal drug delivery. *Drug delivery 2016*, 23, 564–578.

5. Czech, Z.; Kurzawa, R. Acrylic pressure-sensitive adhesive for transdermal drug delivery systems. *J. Appl. Polym. Sci.* 2007, 106, 2398–2404.

6. Imani, M.; Lahooti-Fard, F.; Taghizadeh, S. M.; Takrousta, M. Effect of adhesive layer thickness and drug loading on estradiol crystallization in transdermal drug delivery system. *AAPS PharmSciTech* 2010, 11, 1268–1275.

7. Banerjee, S.; Chattopadhyay, P.; Ghosh, A.; Datta, P.; Veer, V. Aspect of adhesives in transdermal drug delivery systems. *Int. J. Adhes. Adhes.* 2014, 50, 70–84.

8. Lobo, S.; Sachdeva, S.; Goswami, T. Role of pressure-sensitive adhesives in transdermal drug delivery systems. *Ther. Delivery* 2016, 7, 33–48.

9. McDonnell, M. T.; Greeley, D. A.; Kit, K. M.; Keffler, D. J. Molecular dynamics simulations of hydration effects on solvation, heat transfers, and softening in pressure-sensitive adhesives. *J. Appl. Polym. Sci.* 2016, 133, 48121.
diffusivity, and permeability in chitosan/chitin films. J. Phys. Chem. B 2016, 120, 8997−9010.
(10) Tan, H. S.; Pfister, W. R. Pressure-sensitive adhesives for transdermal drug delivery systems. Res. Focus. 1999, 2, 60−69.
(11) Vasiliev, A. E.; Krasnyuk, I. I.; Ravikumar, S.; Tokhmakhchi, V. N. Transdermal therapeutic systems for controlled drug release(a review). Pharm. Chem. J. 2001, 35, 613−626.
(12) Uhlich, J.; Czarniara, S. M.; Langer, R. S.; Shakesheff, K. M. Polymeric systems for controlled drug release. Chem. Rev. 1999, 99, 3181−3198.
(13) Frisch, H. L.; Stern, S. A. Diffusion of small molecules in polymers. Crit. Rev. Solid State Mater. Sci. 2006, 11, 123−187.
(14) Marquardt, A.; Mogharebi, S.; Neuking, K.; Varnik, F.; Eggeler, G. Diffusion of small molecules in a shape memory polymer. J. Mater. Sci. 2016, 51, 9792−9804.
(15) Ordaz, I.; Singh, L.; Ludovice, P. J.; et al. Small molecule diffusion in polymer ultra-thin films. MRS Online Proc. Libr. 2005, 899, 0899-N05-05.
(16) Santos, M. C.; Bendiksen, B.; Elabd, Y. A. Diffusion of liquid water in free-standing polymer films using pressure-contact time-resolved Fourier transform infrared attenuated total reflectance spectroscopy. Ind. Eng. Chem. Res. 2017, 56, 3464−3476.
(17) Soniát, M.; Houle, F. A. Swelling and diffusion during methanol sorption into hydrated nafion. J. Phys. Chem. B 2018, 122, 8255−8268.
(18) McAuley, W. J.; Mader, K. T.; Tetteh, J.; Lane, M. E.; Hadgraft, J. Simultaneous monitoring of drug and solvent diffusion across a model membrane using ATR-FTIR spectroscopy. Eur. J. Pharm. Sci. 2009, 38, 378−383.
(19) Rocco, P.; Cilurzo, F.; Minghetti, P.; Vistoli, G.; Pedretti, A. Molecular dynamics as a tool for in silico screening of skin permeability. Eur. J. Pharm. Sci. 2017, 106, 328−335.
(20) Mejer, A.; Vardenega, D.; Tangour, B.; Gharbi, T.; Picaud, F. Encapsulation into carbon nanotubes and release of anticancer cisplatin drug molecule. J. Phys. Chem. B 2015, 119, 604−611.
(21) Casalini, T.; Salvaglivo, M.; Perale, G.; Massi, M.; Cavallotti, C. Diffusion and aggregation of sodium fluorescein in aqueous solutions. J. Phys. Chem. B 2011, 115, 12896−12904.
(22) Kiesling, E.; Günther, M.; Stummer, C.; Wakolbinger, L. M. Agent-based simulation of infection diffusion: a review. Cent. Eur. J. Oper. Res. 2011, 20, 183−230.
(23) Lin, E.; You, X.; Kriegel, R. M.; Moffitt, R. D.; Batra, R. C. Interdiffusion of small molecules into a glassy polymer film via coarse-grained molecular dynamics simulations. Polymer 2017, 115, 273−284.
(24) Wang, Z.-W.; Wang, P.-L.; Hu, C.-Y. Molecular dynamics simulation on diffusion of 13 kinds of small molecules in polyethylene terephthalate. Packag. Technol. Sci. 2010, 23, 457−469.
(25) Ling, C.; Liang, X.; Fan, F.; Yang, Z. Diffusion behavior of the model diesel components in different polymer membranes by molecular dynamics simulation. Chem. Eng. Sci. 2012, 84, 292−302.
(26) Wang, X.-Y.; Raharjo, R. D.; Lee, H. J.; Lu, Y.; Freeman, B. D.; Sanchez, I. C. Molecular simulation and experimental study of substituted polycatenylenes: fractional free volume, cavity size distributions and diffusion coefficients. J. Phys. Chem. B 2006, 110, 12666−12672.
(27) Wang, C.; Jagirdar, P.; Nasirifar, S.; Sahimi, M. Molecular simulation study of gas solubility and diffusion in a polymer-boron nitride nanotube composite. J. Phys. Chem. B 2016, 120, 1273−1284.
(28) Zhao, Z.-J.; Wang, Q.; Zhang, L.; Liu, Y.-C. A Different Diffusion Mechanism for Drug Molecules in Amorphous Polymers. J. Phys. Chem. B 2007, 111, 4411−4416.
(29) Comyn, J. Introduction to polymer permeability and the mathematics of diffusion. Polymer Permeability; Springer, 1985; pp 1−10.
(30) Sun, H. COMPASS: An ab Initio Force-Field Optimized for Condensed-Phase Applications Overview with Details on Alkanes and Benzene Compounds. J. Phys. Chem. B 1998, 102, 7338−7364.