The effects of monomer on the diffusion behavior of drug molecules in acrylic pressure-sensitive adhesive

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Abstract
Acrylic pressure-sensitive adhesive (PSA) is widely used in transdermal drug delivery systems (TDDS). In this study, PSAs with different monomer proportion were synthesized, the effects of soft monomer/hard monomer ratio on the diffusion of drug molecules were investigated by Fourier transform infrared attenuated total reflection (ATR-FTIR) measurement and molecular dynamics simulation. The accuracy of the diffusion coefficient was confirmed by the consistency of the results from the above two methods. Based on the characterization of diffusion behavior, the diffusion mechanism was revealed. Three dominant factors, which affect the diffusion behavior: the wriggling of the polymer chain, the free volume and the drug-PSA interaction, were discussed. The wriggling of the polymer chain and the free volume of PSA are positive to the diffusion process while drug-PSA interaction is negative. Through the synergy of the three factors, the diffusion rate of drug molecules in PSA can be controlled by adjusting the proportion of soft monomer and hard monomer.

Introduction
Transdermal drug delivery systems (TDDS) use skin as drug delivery channel. Compared with intravenous and oral drug delivery, TDDS can deliver drugs into systemic circulation constantly and control the blood concentration within a small fluctuation [1, 2]. Besides, it avoids the hepatic and gastrointestinal first-pass effects, improving the utilization of drugs while reducing the damage to liver and stomach [3–6]. Additionally, it is easy to use and is possible to terminate immediately after side effects, so it can improve patient compliance effectively. Pressure-sensitive adhesive (PSA) is the main material of TDDS, not only can it provide adhesion force for the patches, but also serves as a drug-loading reservoir and plays a significant role in controlling the release of the drug [6–10]. More than half of TDDS products take advantage of acrylic pressure sensitive adhesives approved by United States Food and Drug Administration (FDA) because of their physicochemical stability and acceptable miscibility with most transdermal drugs [11]. However, although acrylic PSAs have been used in TDDS for decades, the design of these adhesives is still largely based on the trial and error approach due, in part, to a lack of theoretical research. Hence, the investigation of PSA factors on drug diffusion and the diffusion mechanism is vital in the development of TDDS.

Diffusion coefficient is a key parameter to describe the diffusion process, it was mainly obtained by experimental measurements and model predictions [12]. The techniques that have been employed to measure diffusion of small molecules in polymers include gravimetry, NMR imaging, quartz crystal microbalance and various microscopic techniques [13, 14]. However, most of these techniques are not applicable to adhesives, they cannot monitor the diffusion process directly and/or constantly either. Besides, some of those techniques are hard to operate and expensive. As discussed in our previous work, Fourier transform infrared attenuated total reflection (FTIR-ATR) spectroscopy was used to measure diffusion coefficient [14]. It has been shown that the Time-resolved FTIR-ATR is a convenient and effective method to characterize the diffusion of small molecules.
in polymer film [15]. In addition, to a considerable extent, it can provide real-time molecular level contrast between diffusant and polymer [16].

Molecular dynamics (MD) simulation is another emerging and available way to obtain diffusion-related data of small molecules in polymers from molecular level. Using MD simulation in combination with FTIR experiment can help to verify the results. MD simulation is also capable of studying some parameters that cannot be measured experimentally to advance our understanding of diffusion. Wang *et al.* [17] calculated the diffusion coefficients of 13 small molecules in amorphous polyethylene terephthalate (PET) through MD simulation technique. By comparing with Piringer model and experimental prediction, the accuracy of the MD simulation for calculating the diffusion coefficient of migration in PET was verified. Bharadwaj and Boyd [18] and Hofmann *et al.* [19, 20] calculated small molecules diffusing in barrier based on MD simulation. Yang and Achenie [21] simulated the penetrant transport in the composite poly(4-methyl-2-pentyne) (PMP) and silica nanoparticle. Li *et al.* [22] studied the diffusion of small penetrants in rubbery-polymer-based hybrid membranes, and found that the diffusion coefficients were not only relevant to the fractional free volume (FFV) but also influenced by the interactions between calyx [4]-arene (CA) and the penetrants, and the MD simulation values were coincident with the experimental results. Many other works [23–28] have been published, they show the feasibility of MD simulation in diffusion study and provide valuable insights towards the diffusion process of small molecules in the polymers.

Generally, soft and hard monomer are defined by the glass transition temperature (Tg). In this paper, PSAs with different ratio of soft monomer and hard monomer were prepared and the effects of monomer proportion of polymer on the diffusion of drug molecules were investigated. The diffusion of drug molecules in acrylic pressure sensitive adhesive was characterized by FTIR-ATR and MD simulation and the results agreed well with each other. Then, based on further simulation and solubility experiment, the affecting factors of diffusion behavior of drug molecules in PSA were resolved and the diffusion mechanism was revealed. Most previous studies were limited to separate chemical experiments or computer simulations, lacking cross-reference and support. In this paper, through the combination of MD simulation and experiment, the accuracy of the results was well proved, meanwhile the diffusion mechanism was decomposed and discussed in depth. Exploring the concrete effects of monomer on the diffusion behavior of drug molecules in PSA can help to design and prepare TDDS products quickly and easily. Instead of the trial and error approach, we can use the results of this study to quickly design a PSA with a desired drug diffusion rate for the specific applications. It helps to save time and money for TDDS products development. Besides, diffusion of molecules in polymers exists in many fields, such as textile dyeing, functional polymer film and plasticizer addition. Therefore, the study of the diffusion mechanism is meaningful not only for TDDS research but also for other polymer preparation and application which are related to molecular diffusion.

**Experimental**

**Chemicals**

Monomers used in this paper, 2-ethylhexyl acrylate (2-EHA), vinyl acetate (VAC) and 2,2-Azobis (AIBN), were purchased from Shanghai Titan Technology Co. Ltd The drug Ketoprofen was from Hangzhou Rongfang Pressure Sensitive New Material Co. The molecular dynamics simulation was constructed in Materials Studio 6.1 (Accelrys Inc., San Diego, CA, USA).

**Synthesis and characterization of PSA**

The acrylic PSA was synthesized by 2-EHA and VAC with AIBN, a free radical initiator. 2-EHA was a soft monomer (with low Tg) and VAC was a hard monomer (with high Tg). The monomers and AIBN were mixed in a certain proportion and polymerized for 8 h at 77 °C. The reaction was carried out via starved-feed semi-batch copolymerization [29, 30], 70% of the total VAC, 8% of the total 2-EHA, and AIBN were prepared as the initial
mixture to load in the reactor. When the polymerization started, a large amount of the 2-EHA (92% of the total) mixed with the remaining 30% VAC and AIBN were fed over a certain feeding time at a fixed low rate. Since 2-EHA is more prone to self-polymerization, most of the 2-EHA was fed under monomer-starved condition, enabling the homogeneous random copolymer to be prepared [31, 32]. In this way, a series of PSAs with different monomer ratio were synthesized by controlling the weight ratio of 2-EHA and VAC to 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2. The structure of monomers and the prepared random copolymerized PSA is shown in figure 1. According to the recipe of the PSAs, the theoretical solid content of the adhesive solution is 40%, which is the same as the actual test results. Besides, according to the following FTIR spectrum of PSA, no peaks can be found between 1700 cm$^{-1}$ and 1610 cm$^{-1}$ (–C=–C– stretching vibration). These mean that we can view the polymerization as fully proceeding, so the monomer ratio of the polymerization system was consistent with our initial design. Then the PSA was coated as a film with a thickness of 50 μm with the applicator and dried at a temperature of 120 °C for 5 min. Finally, the film was covered with release paper and the PSA film sample was made.

Figure 2. The Experimental Model and Diffusion Process of Drug Molecules.

Figure 3. FTIR-ATR spectrum of PSA and PSA with drug Ketoprofen.
Diffusion characterized by FTIR-ATR

Measurement principle

The diffusion of drug molecules in PSA was measured by FTIR-ATR (Thermo Scientific Nicolet iS10). The ATR crystal is a diamond with a refractive index of 2.4. The penetration depth is 2.03 μm (at 1000 cm$^{-1}$). The experimental model and diffusion process are depicted in figure 2. A double-layer diffusion model was devised, the upper layer was PSA mixed drug and the lower layer was identical PSA without drug. The lower layer was in direct contact with the ATR element. The diffusion process started when two layers bonded. As drug molecules gradually diffused from upper layer reservoir to the lower layer receiver, the increase in drug concentration in the lower layer would be detected by ATR.

According to Lambert Beer’s law, the time-dependent change of concentration of the diffusant could be characterized by the absorbance signal intensity of characteristic peak. Compared FTIR-ATR spectrum of pure PSA and PSA mixed drug in figure 3, the peaks of C=O ketone carbonyl at 1660 cm$^{-1}$ and C-H out-of-plane bending vibration on benzene ring at 720 cm$^{-1}$, 700 cm$^{-1}$ can be found in PSA with drug but not in pure PSA, so they can be used as characteristic peaks. CH$_3$ bending vibration peak at 1373 cm$^{-1}$, which is coincident in both spectrums, can be an internal standard peak.

Diffusion coefficient measured by FTIR-ATR

According to Fick diffusion formula and the three-layer composite model proposed by Comyn [33], the diffusion structure devised in this paper can be regarded as half of the three-layer symmetric composite model and the diffusion coefficient of drug molecules in the model can be calculated by equation (1):

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

where $C$ is the concentration at the interface between PSA and ATR, $C_0$ is the initial concentration of the drug in PSA, $L_1$ is the thickness of the upper-layer PSA doped by drugs, $L_2$ is the thickness of the lower-layer pure PSA, $t$ is the diffusion time, $D$ is the diffusion coefficient. When $n$ is $-4$ to $4$, the error is less than 0.01%. Calculations were performed with Microsoft Excel. erf$(x)$ is as follows (equation (2)):

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

Molecular dynamics simulation

Simulation details

Molecular models were designed according to the structures of synthesized PSA and relevant calculations were done by Materials Studio. The structures of the 2-EHA and VAC monomer units and Ketoprofen after a 5000-step energy minimization are shown in figure 4.

The simulation procedure started by building a cubic simulation cell with proper polymer chains and drug molecules. The simulation cell (with a length of approximately 45.3 Å) contained 6 Ketoprofen molecules and 10 polymer chains with a polymerization degree of 40. The choice of polymerization degree depended on a pre-experiment. Due to this study focused on the diffusion of drug molecules, the effects of the polymerization degree on the diffusion coefficient were explored in the pre-experiment, and it proved that the diffusion was hardly affected above 40 degree of polymerization. Considering the more atoms in the simulation system, the closer to reality, but the longer simulation time as well. Hence, this study selected as many chains as possible in an acceptable simulation time.
Energy minimization and anneal were performed to relax the structure of the cell. The MD simulation was performed with NPT (constant number of molecules, pressure and temperature) and NVT (constant number of molecules, volume and temperature) at 298K, which was similar to room temperature. The pressure was kept at 1.01 × 10^5 Pa for the NPT ensemble.

Ten configurations were generated and three of them were selected for equilibration by following subsequent procedures in figure 5: (1) 5000-step energy minimization; (2) 500 ps thermal anneal (from 300 to 500 K with 5 annealing cycles); (3) 1000ps NPT-MD simulation (1.01 × 10^5 Pa, 298 K); (4) 1000ps NVT-MD simulation (298 K); (5) 2000 ps NVT-MD simulation (298 K).

Properly, in all our MD simulation, 3D periodic boundary conditions were imposed. The COMPASS force field which had confirmed a high accuracy in predicting the properties of polymer materials was applied in the dynamics simulation process [34]. Electrostatic interaction force was summated with Ewald method [35] while van der Waals force with Atom-based method [36] for cutoff distance of 12.5Å (the spline width was 1Å and the buffer width was 0.5Å). The Smart method was utilized for energy minimization. Temperature and pressure were controlled by the Andersen [37] and Berendsen [38] method, respectively.

**Diffusion coefficient calculated by MD simulation**

The diffusion coefficients of the drug molecules in PSA were calculated from the slope of the penetrant mean square displacement (MSD) as equation (3) [39]:

$$\lim_{t \to \infty} \langle |r(t + \Delta t) - r(t)|^2 \rangle = 6D\Delta t$$

(3)

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

Similarly, the self-diffusion coefficient of the polymer chains, which can characterize the wriggling of the polymer chains, can be computed.

**Free volume**

The polymer matrix consists of two phases: the occupied volume and the free volume. According to the free volume theory [40, 41], the free volume can be expressed in the unoccupied volume in the polymer system. The Connolly simulation was employed to perform the free volume. The Connolly radius was set to 1 Å. The fraction free volume, which represents the proportion of the free volume to the total volume, was acquired as follows (equation (4)):

$$FFV = \frac{V_f}{(V_f + V_o)}$$

(4)

where FFV is the fraction free volume, V_f is the occupied volume of polymers and drug molecules, and V_o is the free volume which is the total volume of the polymers and drug molecules except the occupied volume.

**Drug-PSA interaction energy**

According to the thermodynamic theory, the interaction energy between drug molecules and polymers can be measured as follows [42]:

$$\Delta E = (E_{drug} + E_{polymer}) - E_{total}$$

(5)

where \(\Delta E\) is interaction energy between drug molecules and polymers, \(E_{total}\) is the energy of the entire MD simulation system, the \(E_{drug}\) and \(E_{polymer}\) are the energy of the isolated drug molecules and polymers respectively.
DREIDING [43] force field was used to calculate energy, because it was a pure diagonal force field which was suitable to calculate the bonding energy of various polymers and organics.

Drug solubility in PSA
Drug solubility in PSA experiment is another way to characterize Drug-PSA interaction strength, higher drug solubility indicates stronger interaction strength, so that it can collate with the values from MD simulation.

On the one hand, drug solubility in PSA can be measured directly by experiments. In this study, Optical microscopy and x-ray diffraction (XRD) were combined for the measurement of drug solubility in PSA. Samples of different Ketoprofen concentration (20%-35%, three samples per 1%) were prepared and settled at room temperature for 1 week to ensure that the crystal separated out from PSA [44]. Compared with figure 6(a) that no crystallization existed, when the drug concentration reached a certain level where crystallization started to be observed as figure 6(b), this concentration could be regarded as the maximum drug loading in PSA basically.
Then, samples with smaller drug concentration differences around this rough maximum drug loading were prepared (at a concentration gradient of 0.1%), and the value of drug solubility in PSA was further determined precisely by XRD. As shown in figures 7, (a) and (b) are XRD spectrums of pure PSA and pure drug respectively, 7(c) and 7(d) are XRD spectrums of PSA mixed with different concentration of drug. Compared with 7(a) and 7(b), 7(c) is similar to 7(a), there are no peaks of drug, which means the drug concentration is below the solubility. However, 7(d) can be seen as a superposition of 7(a) and 7(b). In figure 7(a), there is an obvious broad peak between 9.9 and 30 with the apex at $2\theta = 19.2$. Similarly, as shown in figure 7(d), a convex can be observed in the same range and a peak appears at $2\theta = 19.2$. Besides, due to the excess of drug solubility, the crystallization peaks appear at $2\theta = 6.5, 13.3, 17.4, 22.8$ and 23.2 in figure 7(d), which is the same position as the sharp peaks in figure 7(b). Therefore, the drug solubility in PSA is determined by the maximum drug concentration without crystallization peaks in XRD spectrum.

Taking PSA with 50% 2-EHA as an example, drug crystal couldn’t be observed under the microscope when the drug concentration was 28%, 29% and 30%. But when the drug concentration reached 31%, crystallization appeared. Thus, the maximum drug loading was between 30% and 31%. Then further measurements were made with XRD. There were no crystallization peaks in the spectrums when the drug concentration was 30.0%, 30.1%, 30.2%, 30.3%, 30.4% and 30.5%. But when the drug concentration was 30.6%, 30.7%, 30.8% and 30.9%, the crystallization peaks appeared. Thus, the conclusion could be made that the drug solubility was 30.5%.

Besides, the solubility parameter of the drug ($\delta_1$) and PSAs with different soft monomer/hard monomer ratio ($\delta_2$) can be calculated by MD simulation. According to solubility parameter parameter theory and Flory equation [45], the relative value of drug solubility in different PSAs can be reflected by the deviation between $\delta_1$ and $\delta_2$. The less the deviation is, the larger the drug solubility is [46].

## Results and discussion

### Drug diffusion in PSAs with different monomer ratio

In this study, PSAs with different monomer ratio were prepared and their Tg was shown in table 1.

Drug diffusion in PSAs with different monomer ratio was characterized by FTIR-ATR experiment and MD simulation. Figure 8(a) shows the drug characteristic peak area increased with time, which means drug molecules migrated to lower-layer pure PSA gradually. Figure 8(b) shows the change in the ratio of drug characteristic peak area to internal standard peak area ($A_{dp}/A_{ap}$) in PSAs with different monomer ratio (error bar $< 0.01$). Obviously, as soft monomer (2-EHA) increased, the concentration of drug molecules on PSA/ATR side at the same diffusion time went up, inferring a faster diffusion rate. The drug molecules spread fast in the PSA with 80% 2-EHA. As the proportion of 2-EHA decreased from 80% to 50%, the diffusion slowed down.

### Table 1. The Tg of PSAs with Different Monomer Ratio.

| Proportion of 2-EHA (%) | 20  | 30  | 40  | 50  | 60  | 70  | 80  |
|------------------------|-----|-----|-----|-----|-----|-----|-----|
| Tg (°C)                | 29.19 | 20.69 | 3.20 | $-10.81$ | $-17.29$ | $-24.79$ | $-30.96$ |

![Figure 8. The Change of Drug Characteristic Peak with (a) Time; (b) Proportion of 2-EHA.](image)
Figure 9. (a) System Density in NPT MD; (b) System Energy in NVT MD.

Figure 10. MSD of Drug in PSAs with Different Proportion of 2-EHA.

Figure 11. Diffusion Coefficient of Drug Molecule in PSAs with Different Proportion of 2-EHA.
As 2-EHA continued to decrease, the drug molecules diffused very slowly and there was only slight variation on the PSA-ATR side drug concentration in 7 h in the PSA with 30% and 20% 2-EHA. To achieve accurate MD simulation results, a series of optimization steps were implemented. In MD simulation, the criteria for judging whether the system has reached equilibrium are temperature equilibrium and energy equilibrium. Figure 9(a) shows the system density eventually stabilized within the range of $0.972 \pm 0.010 \text{ g cm}^{-3}$ and the fluctuation was less than 1%. Figure 9(b) shows that the kinetic energy, potential energy, non-bond energy and total energy were almost constant. Therefore, it indicated that the system had reached equilibrium and could be used for subsequent calculations.

Figure 10 shows the MSD of drug in PSAs with different proportions of soft monomer which were calculated by MD simulation. When applying the Einstein equation to the diffusion trajectory, the impact of the anomalous diffusion should be considered, so that the random walk regime could be isolated. In general, anomalous diffusion due to the transient motion of the atoms occurs at the beginning of the MD simulation, when the MSD curve with time is not linear [42, 47]. Therefore, the MSD of the first 100 ps was discarded and the results were averaged by linear portions [48, 49] from 100 ps to 1500 ps. It can be easily found that the slope of the MSD curves gradually becomes steeper as the proportion of 2-EHA increased, meaning an acceleration of diffusion.

Diffusion coefficient of drug molecules (D-drug) in PSA measured by FTIR experiment and MD simulation were shown in figure 11. It indicates that the diffusion of drug molecules was promoted as the proportion of soft monomer in PSA scaled up. Besides, the results got from experiments were highly consistent with the values received from MD simulation, which proved the accuracy of the conclusion. In the previous work, Pairatwachapun [50] measured D of ASA in CAR hydrogels to be $7.68 \times 10^{-7} \text{ cm}^2 \text{ s}^{-1}$. Lambert [51] reported that D of several penetrants in three different polymer matrix was from $3.5 \times 10^{-9} \text{ cm}^2 \text{ s}^{-1}$ to $7.5 \times 10^{-7} \text{ cm}^2 \text{ s}^{-1}$. Paradee [52] measured D of BA in Alginate hydrogel to be $2.01 \times 10^{-7} \text{ cm}^2 \text{ s}^{-1}$. Many other works [53–55] have been reported that the diffusion coefficients of different molecules in different polymers are between $1 \times 10^{-9} \text{ cm}^2 \text{ s}^{-1}$ and $1 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$. The results in this paper are within this range.

Effects of the polymer chain wriggling
Since the Ketoprofen drug is mixed into PSA to construct the diffusion system, PSA can be regarded as the carrier for drug molecules. Therefore, the wriggling of the polymer chain would be an important influencing factor of drug diffusion, it can drive the drug molecules from a high concentration to a low concentration zone like a peristaltic pump. Besides, the addition of soft monomer would improve the flexibility of the polymer chain, so it can be speculated that the increase in 2-EHA will enhance the wriggling of the polymer chain.

In this study, the polymer chain wriggling was denoted by the polymer self-diffusion coefficient (D-polymer). D-polymer could be calculated by the slope of the MSD curve. Figure 12 shows that the MSD curve was steeper and the D-polymer was higher as the proportion of soft monomer rose. It indicates that the more 2-EHA, the stronger polymer chain wriggling. Compared figure 12(b) and figure 11, it could be found that the D-polymer had a similar but not identical change trend with the D-drug, meaning that the polymer chain wriggling played an important role in drug diffusion but was not the only influencing factor.

![Figure 12](image-url)
Effects of free volume

The free volume provides space for the migration of drug molecules, hence that the free volume would make an impact on drug diffusion could be inferred. In order to study the change of the free volume with monomer ratio, the fraction free volume (FFV) of the PSAs with different proportion of 2-EHA was calculated. The results are shown in figure 13. It illustrates that the free volume increased along with the growing number of 2-EHA.

If we regard the polymer backbone as a linear chain and the side chains of the polymer as its branches, then it is easy to see that the branches from 2-EHA are longer than that from VAC. As shown in figure 14, compared with short branches, long branches can tangle with each other and support a larger hole, which means the increasing number of 2-EHA can create bigger cavities and larger free volume in polymer system. When the cavities are bigger, the drug molecules will have more space for movement and more spacious migration channels, which are conducive to diffusion. Therefore, the increase of 2-EHA is able to facilitate the diffusion of drug molecules in PSA.

Effects of drug-PSA interaction

Another important factor affecting drug diffusion is the strength of the interaction between drug molecule and PSA. A strong drug-PSA interaction demonstrates a higher energy barrier at the contact interface of drug-PSA and can restrain the movement of drug molecule, so as to hinder the drug diffusion [56]. In order to evaluate

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**Figure 13.** FFV of the PSAs with Different Proportion of 2-EHA.

**Figure 14** Effect of Branch Length on Free Volume.
drug-PSA interaction strength exactly, two methods were used in this study: MD simulation and drug solubility experiment.

The drug-PSA interaction strength is capable of being characterized by the interaction energy between drug molecule and PSA \( E \) from MD simulation. Table 2 lists the energy of drug \( E_{\text{drug}} \), PSAs with different monomer ratio \( E_{\text{polymer}} \) and overall system \( E_{\text{total}} \), \( E \) is the interaction energy from equation (5). As shown in table 1, the values of \( E \) decrease with the growth of the 2-EHA proportion. It indicates that when 2-EHA increases, the interaction between drug molecule and PSA becomes weaker, and the diffusion of drug molecules will be easier.

Besides, drug-PSA interaction can be denoted by drug solubility. On the one hand, according to the solubility parameters of PSAs with different monomer ratio \( E_{\text{polymer}} \) and drug \( E_{\text{drug}} \), PSAs with different monomer ratio \( E_{\text{polymer}} \) and overall system \( E_{\text{total}} \), \( \Delta E \) is the interaction energy from equation (5). As shown in table 1, the values of \( \Delta E \) decrease with the growth of the 2-EHA proportion. It indicates that when 2-EHA increases, the interaction between drug molecule and PSA becomes weaker, and the diffusion of drug molecules will be easier.

![Figure 15. Drug Solubility in the PSAs with Different Proportion of 2-EHA.](image)

**Table 2. Values of \( E_{\text{drug}}, \ E_{\text{polymer}}, \ E_{\text{total}} \) and \( \Delta E \).**

| Proportion of 2-EHA (%) | \( E_{\text{drug}} \) (kcal mol\(^{-1}\)) | \( E_{\text{polymer}} \) (kcal mol\(^{-1}\)) | \( E_{\text{total}} \) (kcal mol\(^{-1}\)) | \( \Delta E \) (kcal mol\(^{-1}\)) |
|------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 20                     | 750.76                          | 9331.65                         | 9902.91                         | 179.49                          |
| 30                     | 697.98                          | 4748.68                         | 5271.52                         | 175.14                          |
| 40                     | 713.96                          | 7031.96                         | 7573.10                         | 173.82                          |
| 50                     | 768.62                          | 17495.74                        | 18094.48                        | 169.87                          |
| 60                     | 714.26                          | 9491.29                         | 10047.32                        | 158.22                          |
| 70                     | 706.34                          | 7132.67                         | 7692.46                         | 146.55                          |
| 80                     | 745.82                          | 1912.11                         | 2528.02                         | 129.91                          |

**Table 3. The Solubility Parameters of PSAs with Different Monomer Ratio.**

| Proportion of 2-EHA (%) | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
|------------------------|----|----|----|----|----|----|----|
| \( \delta_2 \) (\( \text{J cm}^{-3} \text{m}^{-1/2} \)) | 16.797 | 16.595 | 15.956 | 15.269 | 15.211 | 14.691 | 14.158 |
| \( \delta_1 \) (\( \text{J cm}^{-3} \text{m}^{-3/2} \)) | 6.999 | 7.201 | 7.840 | 8.527 | 8.585 | 9.105 | 9.638 |
Diffusion mechanism
The diffusion process of drug molecules in the polymer can be split into three parts. Firstly, cavities in polymer matrix provide motion space and migration channels for drug molecules. The size of the cavities is determined by the free volume [57–60]. Secondly, the wriggling of polymer chains can be considered as a driving force of drug molecules from one cavity to another [61–63]. Thirdly, the interaction between drug and polymer might inhibit the diffusion [64, 65]. Therefore, we can divide the diffusion coefficient of drug (D) into three parts: the diffusion coefficient triggered by the polymer chain wriggling (Dw), free volume (Df) and drug-polymer interaction (Di). As discussed above, D can be defined by the following equation (equation (6)):

\[
D = D_w + D_f - D_i
\]  

Figure 16 shows the relationships between D and Dw, Df, Di. Respectively, Dw is indicated by polymer self-diffusion coefficient (figure 16(a)), Df is indicated by FFV (figure 16(b)), and Di is indicated by \(\Delta E\) (figure 16(c)). The linear correlation between D and those three factors confirms the rationality of the above mechanism conjecture formula, revealing that drug diffusion in polymer is determined by the wriggling of polymer chains, free volume and drug-polymer interaction. Also, soft monomer in polymer can enhance drug diffusion by improving Dw and Df meanwhile suppressing Di. With the combination of the three factors, D boosts with the increase of the proportion of 2-EHA as shown in figure 16(d).

Conclusions
In this paper, the diffusion behavior of the drug molecules in PSAs with different monomer proportion was investigated by FTIR-ATR and MD simulation, and the diffusion coefficients measured by the two methods were very close. Most previous studies used only experimental methods or MD to characterize the diffusion, and they are rarely utilized in PSAs due to the particularity of adhesives and limitations of test conditions. The combination of the two methods can fill the gap in the single approach and expand a new way of thinking for studying diffusion behavior. Based on the limitation of computational modeling, the structure of polymer chain constructed by MD simulation is very similar to reality but may not be exactly identical, and there may be errors.
in the calculation results. So it is important to combine the experiment and MD simulation to support each other and verify the correctness of the results. In this study, the high matching of the two results indicated the accuracy of the conclusion.

The diffusion is accelerated and the diffusion coefficient of drug molecules increases along with the increasing of the ratio of soft monomer. Within the limits of this investigation, through the combination of experiment and MD simulation, the dominant factors that affected the diffusion process were analyzed and the diffusion mechanism was proposed. The diffusion behavior of drug molecules in PSAs is determined by three key factors: the wriggling of polymer chain, the free volume and the interaction between drug molecules and PSA. On the one hand, the wriggling of polymer chain endows the diffusion with driving force, the free volume provides diffusion path, both are positive to the diffusion process of drug molecules. On the other hand, the interaction between drug molecules and PSA restrains the migration of drug molecules and is negative to the diffusion. In order to clarify the diffusion mechanism, D is split into Dw, Df and Di. As the proportion of soft monomer increases, both Dw and Df enhance but Di reduces, this synergy prompts the drug molecules to get into a faster state of diffusion. These results can help to predict diffusion behavior, which is instructive for further research, such as developing a PSA with specified drug diffusion rate.

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Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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