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Journal of Controlled Release 48 (1997) 57–66

journal of controlled release

Computer simulation of molecular diffusion in amorphous polymers

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Received 28 September 1996; received in revised form 21 February 1997; accepted 6 March 1997

Abstract

Diffusion of small molecules in amorphous polymers has been examined by computer simulation. Diffusion coefficients of small molecules with molecular weights ranging from 16.04 (methane) to 452.50 (fluocinolone acetonide) Da in four amorphous polymers were calculated using the QUANTA, CHARMM and Cerius^2 programs. The four amorphous polymers used in our calculation were polyethylene (PE), poly(dimethyl siloxane) (PDMS), poly(methyl methacrylate-co-hydroxyethyl methacrylate) (P(MMA-co-HEMA)), and ethyl and benzyl esters of hyaluronic acid (HA-E, HA-B). The calculated diffusion coefficients (D_c) were compared with the experimentally obtained values (D_e) found in the literature. The ratio of D_c/D_e varied from 0.04 to 24 000. In general, the close values of D_c to D_e were obtained when the system dealt with hydrophobic molecules diffusing through hydrophobic polymers. The D_c/D_e ratio became either very high or very low when the experimental system included hydrophilic diffusants and/or a hydrophilic polymer. The simulation time and the size of molecular models also played key roles in determining the consistency of calculations and the correlation with experimental values. Our study suggests that the current computer simulation of molecular diffusion may be useful in obtaining relative values rather than absolute diffusion coefficient values. © 1997 Elsevier Science B.V.

Keywords: Diffusion coefficient; Molecular dynamics; Computer simulation; Amorphous polymers

1. Introduction

Recent advances in controlled drug delivery systems are largely based on the advances in polymer chemistry, e.g. the ability to fabricate different polymeric materials for controlling the diffusion of drug molecules. It is the polymeric membranes or materials that control the release of drug molecules at a certain desirable rate. Measurements of the diffusion coefficients of drug molecules through various polymeric matrices are important in developing controlled drug release systems. Since there are numerous polymeric materials that can be used in the development of controlled drug release systems, choosing a right polymer system for a certain drug may not be easy. While experimental measurements of diffusion coefficients can provide information necessary for choosing right polymers, it would be highly beneficial if we could predict the diffusion coefficients by computer simulations. If this is possible, not only the number of inconvenient and sometimes hazardous experiments can be reduced, but also some information about the diffusion mechanism can be obtained. Understanding the diffusional behavior of small molecules through polymers will allow us to establish the relationship among the

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PII S0168-3659(97)00033-3

chemical properties of drug molecules, physicochemical properties of polymers, and the diffusion coefficients. Such information, in turn, could help us evaluate various polymer systems more efficiently in designing delivery systems for specific drug molecules.

Computer simulation provides a new way of studying the diffusion process. The diffusional behavior of a permeant is dependent on the molecular structure of the polymeric system. Computer simulation has a potential to explain the diffusional behavior of permeants at the molecular level. Increased computing power of affordable computer systems has made it possible to simulate structural properties of polymers using molecular dynamics [1]. Molecular dynamics, which is based on the description of molecular motion by classical mechanics, allows calculation of thermodynamic properties of the molecular system with respect to time. Thus, it is suitable for studying the time-dependent properties such as diffusion [2]. Recently, a few investigators utilized molecular dynamics to study the diffusion processes of small molecules in amorphous polymers. Pant and Boyd have used molecular dynamics to calculate diffusion coefficients of methane in polyisobutylene and polyethylene [3–5]. Takeuchi et al. studied the effect of free volume distribution on the diffusion of O_2 in polyethylene using molecular dynamics simulations [6,7]. All these simulations were run for various time periods ranging from 50 picoseconds (ps) to 1000 ps. More recently, Tamai et al. carried out 5000-ps molecular dynamics simulations of methane, water, and ethanol in polyethylene and in poly(dimethyl siloxane) on a Cray Y-MP2E supercomputer [8]. The calculated diffusion coefficient of methane in polyethylene from the 5000-ps simulation, however, was not much different from the value obtained from a 200-ps simulation [4]. Apparently, in addition to the simulation time, other factors, such as force field, model expression (i.e. united or all atom expression), solvent and polymer density, affect the result of the computer simulation. In this paper, we present our preliminary study in the calculation of diffusion coefficients of various small molecules through amorphous polymers. Section 2 describes the procedure of calculating diffusion coefficients by molecular dynamics simulation.

2. Methods

Molecular dynamics is based on Newton's equation of motion:

$$F = ma \tag{1}$$

where F is the force applied to the object, m is the object's mass, and a is the acceleration. For an atom, it can be re-written as:

$$f_i = m_i \frac{d^2 r_i}{dt^2} \tag{2}$$

where f_i is the force applied to the atom, m_i is the atomic mass, and r_i is the position vector. Calculation of the forces of a given system allows prediction of the positions and velocities of all atoms at the next time step based on Eq. (2).

In molecular dynamics simulations, the interaction energies are calculated by molecular mechanics. Molecular mechanics is a method to calculate categorized empirical energy terms, such as van der Waals and electrostatic interaction energies. These energy terms, which are based on the parameters obtained from the known structures, are able to predict energies of the unknown structures. The definitions of these terms and the values of the parameters constitute a force field. The widely used force fields include CHARMM [9], AMBER [10], MM4 [11], and UFF [12]. Undoubtedly, the accuracy of a force field is the key to predict energies of an unknown structure. After the potential energy of the molecular system is calculated, the force on an atom can be obtained by taking the negative gradient of the energy.

Molecular mechanics makes it possible to simulate the realistic motion of a molecular system from a classical mechanics point of view. Exact molecular dynamics algorithm is very complicated. Simply speaking, however, molecular dynamics keeps track of energies, forces, velocities of a molecular system based on Newton's equation of motion at a specified temperature with respect to time. When a molecular dynamics simulation is completed, trajectory files of positions, velocities, energies are saved for further analysis. Although the theory is still based on the description of motion of classical mechanics instead

of quantum mechanics, molecular dynamics can provide detailed information about thermodynamic properties of large molecular systems which other simulation methods may have difficulties in providing.

Once the molecular dynamics simulation is done, diffusion behavior can be studied from the trajectory files. The displacement of penetrants can be plotted as a function of time and the diffusion coefficient can be calculated from the trajectory of atoms. The diffusion coefficient is defined as:

$$D = \frac{1}{6N} \lim_{t\to\infty} \frac{d}{dt} \left\langle \sum_i^N [r_i(t) - r_i(0)]^2 \right\rangle \quad (3)$$

where r_i is the position vector of penetrant i, N is the total number of penetrants, and the angular brackets represent mean-square displacement [2]. As a time correlation function, the mean-square displacement is defined by:

$$\left\langle \sum_i^N [r_i(t) - r_i(0)]^2 \right\rangle = \lim_{\tau\to\infty} \frac{1}{\tau} \int_0^\tau \left(\sum_i^N [r_i(t + t_0) - r_i(t_0)]^2\right) dt_0 \quad (4)$$

where τ is the difference between total simulation time and t [2]. The mean-square displacement represents an average squared distance accumulated over many different time origins. D is proportional to the slope of mean-square displacement. Eq. (3) and Eq. (4) indicate that the calculated diffusion coefficients become more accurate with longer molecular dynamics simulations.

In our simulations, we used QUANTA/CHARMM and Cerius^2 (Molecular Simulation Inc.) to carry out molecular dynamics. The platforms used were IBM RISC/6000 workstation, SiliconGraphics Personal Iris/30 workstation, and Cray C90 at the Pittsburgh Supercomputing Center. The procedures for running a simulation include polymer building, amorphous state building, molecular dynamics simulation, and data analysis. Normally, the simulation time of one calculation ranged from 10 ps to 50 ps due to the limited computing power available to us. The time step of 1 femtosecond (fs) was chosen for the simulation. After every 100 time steps (i.e. 100 fs or 0.1 ps), all the information on each atom, including atom's position, energy, and velocity, was saved. After the simulation, the snapshot information was used to form a trajectory file from which the diffusion coefficient was calculated. Simulations were run at the temperature of 300 K with constant volumes.

Here we will use a system consisting of ethanol in poly(dimethyl siloxane) (PDMS) as an example to show the common procedures we have used. First, four 100-monomer chains and two ethanol molecules were modeled individually and packed together, as illustrated in Fig. 1. The atoms' types and bonding information were saved for the next step. After setting up a model density (0.97 g/cm^3 in this particular case), a 3-dimensional amorphous polymer structure was generated using the rotational isomeric state (RIS) algorithm [13], as shown in Fig. 2. Then the amorphous polymer structure was allowed energy optimization and equilibrated at 300 K. Finally, simulation began and information on positions and velocities of all atoms at different time steps was collected to create a trajectory file. During the simulation, ethanol molecules underwent diffusive movements inside the PDMS network. Fig. 3 depicts

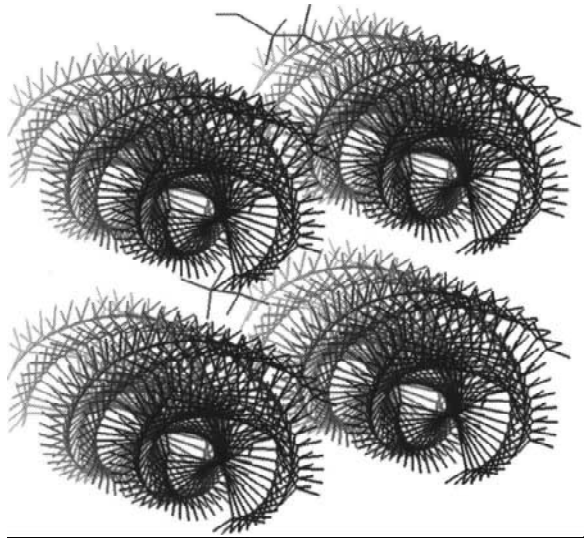

Fig. 1. Four 100-monomer chains of PDMS and two ethanol molecules from the polymer building step. The structural information, such as atoms' types and bonds, was used to generate the amorphous structure.

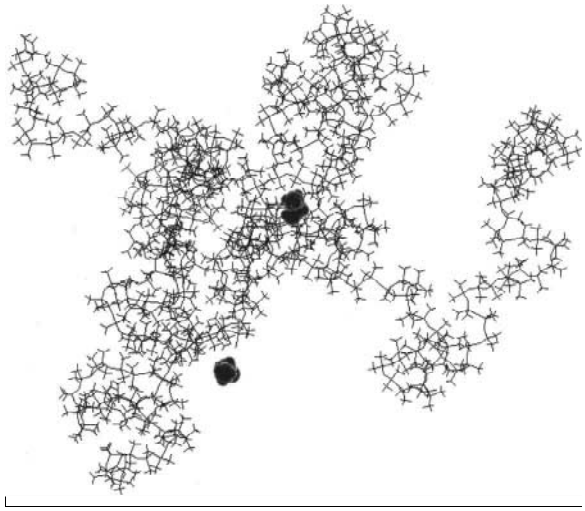

Fig. 2. The amorphous structure of four PDMS chains and two ethanol molecules generated by the amorphous building step. The rotational isomeric state (RIS) method was used to generate this structure from the structural information of the last step.

the displacement of an ethanol from its original position during a 40-ps molecular dynamics simulation. It shows that the diffusant jumped vigorously around the initial position. In the long run, such a vigorous jumping leads to the movement away from the initial position. The mean-square displacement was calculated using Eq. (3). The mean-square displacement is an average of squared distances summed up over all possible positions of the origin.

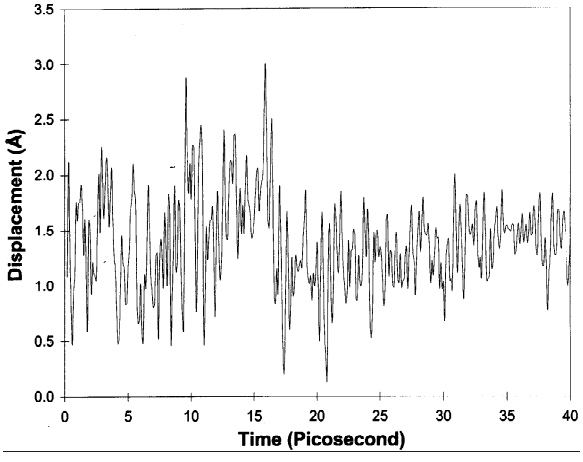

Fig. 3. Distance from the initial position of an ethanol molecule in PDMS during a 40-ps molecular dynamics simulation.

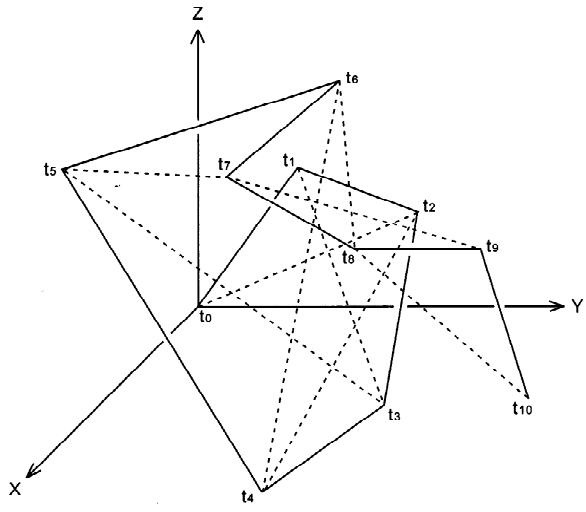

Fig. 4. A trajectory of 10 time steps from t_0 to t_{10} is shown by solid lines. The solid lines represent the distances of one time step, and dashed lines represent the distances of two time steps. In our simulations, each time step to calculate the mean-square displacement was 0.1 ps.

For example, Fig. 4 shows a trajectory with only the first 11 positions plotted for clarity. The consecutive positions are marked from t_0 to t_{10}. In our calculations, the time interval or step was 0.1 ps since we saved atoms' positions at every 0.1 ps. The mean-square displacement at the time equal to 1 time step is the average of distances from t_0 to t_1, from t_1 to t_2, ..., and from t_9 to t_{10} as indicated by the solid lines in Fig. 4. And the mean-square displacement at the time equal to 2 time steps is the average of distances from t_0 to t_2, from t_1 to t_3, ..., and from t_8 to t_{10} as indicated by the dashed lines in Fig. 4. After it was calculated, the mean-square displacement was plotted as a function of time and the diffusion coefficient was calculated from the slope of the mean-square displacement curve using Eq. (4) as shown in Fig. 5.

3. Results

We simulated four polymeric systems with various small molecules as diffusants. The four polymers were polyethylene (PE), poly(dimethyl siloxane) (PDMS), poly(methyl methacrylate-co-hydroxyethyl

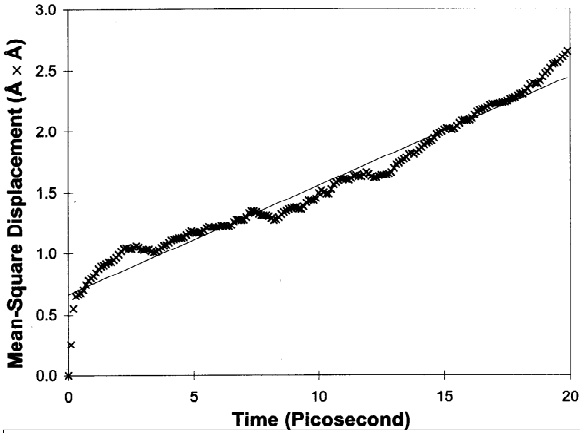

Fig. 5. Mean-square displacement calculated from a trajectory of an ethanol in PDMS from a 50-ps molecular dynamics simulation. The linear solid line indicates the best fit of all the data points.

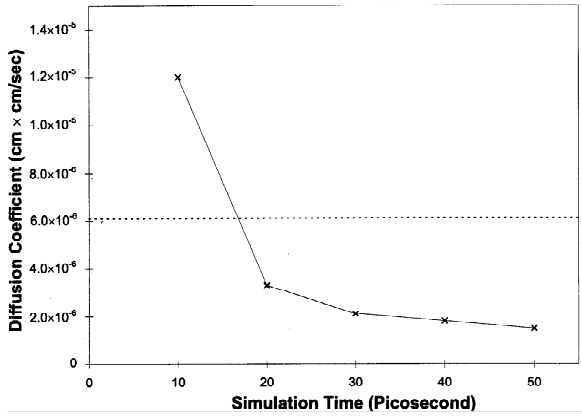

Fig. 6. Effect of simulation time on diffusion coefficient of ethanol in PDMS. The diffusion coefficient value of the dashed line represents the experimentally obtained diffusion coefficient of 6.1×10^{-6} cm^2/s [14].

methacrylate) (P(MMA-co-HEMA)), and ethyl and benzyl esters of hyaluronic acid (HA-E, HA-B). The selected small molecules included methane, methanol, ethanol, propanol, benzaldehyde, benzyl alcohol, acetophenone, benzoic acid, *p*-acetamido benzoic acid, progesterone, tetracycline, and fluocinolone acetonide.

In the beginning we examined the effect of simulation time on the calculated values of diffusion coefficients. Eq. (3) and Eq. (4) indicate that as the simulation time becomes longer, the calculated diffusion coefficient value becomes closer to the value obtained at the infinite simulation time. For a short simulation time, the mean-square displacements show a non-linearity as a function of time and this tends to overestimate the diffusion coefficient [8]. The effect of simulation time on the values of diffusion coefficient of ethanol in PDMS is shown in Fig. 6. It is seen that the diffusion coefficient value decreases as the simulation time increases. Simulation time longer than 20 ps did not change the diffusion coefficient value very much. The dashed line in Fig. 6 is the experimentally obtained diffusion coefficient value [14]. The experimental value was between the values calculated with 10 ps and 20 ps simulations. In this particular case, the longer simulation time did not necessarily result in a value which was close to the experimental value as shown in Fig. 6. Obviously, this observation may not apply to other systems. In this study, however, we limited our simulation time to 10 ps or 20 ps in most cases mainly due to the limited computer resources.

Fig. 7 shows the calculated diffusion coefficient values as a function of the polymer density of four systems, i.e. progesterone in PDMS, benzyl alcohol, benzaldehyde, and benzoic acid in polyethylene. Since the void volume of the polymer network provides the diffusional pathway for the diffusants, diffusants are expected to move faster in a looser network of the same polymer. As shown in Fig. 7, all the four diffusants have lower diffusion coefficients at higher polymer densities. The data indicated that

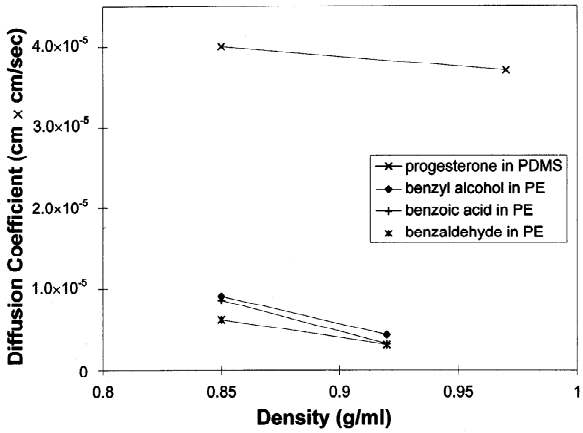

Fig. 7. Effect of polymer density on diffusion coefficient.

Table 1
Calculated diffusion coefficients (cm^2/s) of selected small molecules in amorphous polymers and comparison with corresponding experimental values

Index	System	Molecular weight of diffusant	Configuration (# of chains, # of monomers per chain, # of diffusants and total # of atoms)	Simulation density (g/cm^3)	Simulation time (ps)	Calculated diffusion coefficient D_c (cm^2/s)	Experimental diffusion coefficient D_e (cm^2/s)	D_c/D_e	Reference for experimental value
1	Methane in PE	16.04	9, 40, 4 and 1118.	0.85	40	7.4×10^{-7}	4.5×10^{-7}	1.6	[3]
2	Benzyl alcohol in PE	108.14	10, 80, 4 and 2484.	0.85	20	9.1×10^{-6}	1.2×10^{-9}	7600	[18]
				0.92		4.3×10^{-6}			
3	Benzaldehyde in PE	106.12	10, 80, 4 and 2476.	0.85	20	6.2×10^{-6}	5.4×10^{-8}	110	[18]
				0.92		3.1×10^{-6}			
4	Benzoic acid in PE	122.12	10, 80, 4 and 2480.	0.85	20	8.6×10^{-6}	1.5×10^{-9}	5700	[18]
				0.92		3.2×10^{-6}			
5	Acetophenone in PE	120.15	10, 80, 4 and 2488.	0.85	20	5.8×10^{-6}	5.9×10^{-8}	98	[18]
6	Fluocinolone acetonide in PE	452.50	2, 400, 2 and 2528.	0.85	40	2.3×10^{-7}	1.1×10^{-8}	21	[21]
7	Methanol in PDMS	32.04	3, 100, 6 and 3042.	0.97	10	5.5×10^{-6}	1.0×10^{-5}	0.55	[14]
8	Ethanol in PDMS	46.07	4, 100, 2 and 4030.	0.97	50	1.5×10^{-6}	6.1×10^{-6}	0.25	[14]
9	Propanol in PDMS	60.10	4, 100, 4 and 4060.	0.97	30	2.2×10^{-7}	5.4×10^{-6}	0.04	[14]
10	Progesterone in PDMS	314.47	6, 50, 4 and 3224.	0.85	20	4.0×10^{-5}	2.2×10^{-8}	1800	[22]
				0.97		3.7×10^{-5}			
11	Tetracycline in P(MMA-co-HEMA)	444.43	2, 100, 2 and 3132.	1.0	40	3.2×10^{-6}	8.0×10^{-9}	400	[20]
12	P-acetamido benzoic acid in ethyl ester of hyaluronic acid (HA)	179.18	1, 70, 2 and 3756.	1.3	10	4.3×10^{-5}	2.8×10^{-7}	150	[19]
13	P-acetamido benzoic acid in benzyl ester of HA	179.18	1, 70, 2 and 4036.	1.1	10	9.6×10^{-5}	4.0×10^{-9}	24 000	[19]
14	Benzyl alcohol in ethyl ester of HA	108.14	1, 80, 2 and 4272.	1.3	10	2.7×10^{-5}	5.0×10^{-7}	54	[19]
15	Benzyl alcohol in benzyl ester of HA	108.14	1, 80, 2 and 4594.	1.1	10	5.0×10^{-5}	1.3×10^{-7}	380	[19]

the results of our simulations were in the right direction. This, however, requires further study, especially in comparing the results with the free volume theory [15,16].

Table 1 lists all the information on the simulation conditions, such as simulation time, polymer configuration, and polymer density, for all systems used in our study. The calculated diffusion coefficient values and their comparisons with the experimental values are also shown in Table 1. The ratio of the calculated and experimental diffusion coefficients (D_c/D_e) varies from as small as 0.04 to as large as 24 000. Considering the fact that the computer simulation does not reflect the experimental system and condition exactly, one can easily understand the differences between D_c and D_e values to a certain extent. If the difference is less than 2 orders of magnitude, for example, one may consider the calculated value reasonable. The difference shown in Table 1, however, is sometimes as large as 24 000-fold. It should be pointed out here that different programs were used to carry out computer simulations. In Table 1, systems #1, #6 and #11 were simulated by QUANTA. Systems #2–#5, #7, #10, and #12–#15 were simulated by Cerius[2]. On the other hand, systems #8 and #9 were simulated by CHARMM [9]. QUANTA and CHARMM use the CHARMM force field while Cerius[2] uses UFF [12]. Consistency could be observed among the systems which use the same force field, e.g. systems #2–#5, and #12–#15. Using different force fields may be one of the reasons causing inconsistencies observed among the results of the same system, e.g. methane in PE (system #1 in Table 1) as compared to other molecules in PE (systems #2–#5 in Table 1). The same observation could be made for PDMS (between systems #10 and #8–#9). Table 1 also showed that some values of relatively large molecules (systems #10 and #11) and complex systems (systems #12–#15) seem unreasonably large. This clearly indicates that in some cases, the molecular modeling and simulation still need much more refinements to reflect the real system.

To examine whether the molecular size of diffusant is a significant factor in causing discrepancies between calculated and experimental values, we plotted the D_c/D_e ratios as a function of the molecular weight of the diffusants in Fig. 8. The calculated diffusion coefficients of the four smallest diffusants (methane, methanol, ethanol, and propanol) were very close to their corresponding experimental values. However, for three large diffusants (*p*-acet-

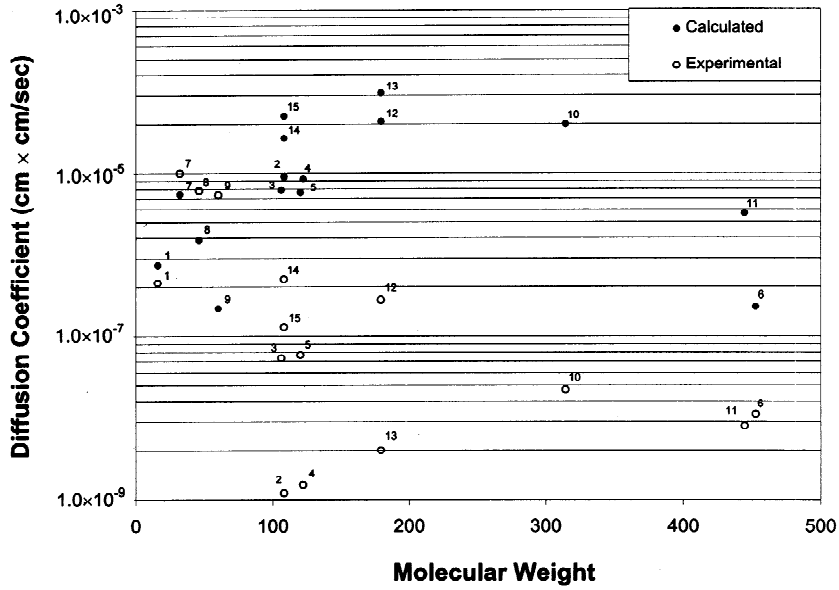

Fig. 8. Comparison between calculated and experimental values of diffusion coefficients as a function of molecular weight. The number next to each circle is the system index shown in Table 1.

amido benzoic acid, progesterone, tetracycline), calculated diffusion coefficients were dramatically different from experimental values. The largest molecule used in our simulation, fluocinolone acetonide (#6 in Fig. 8), however, showed the D_c/D_e of 21. In general, the molecular weight of the diffusant was not the prime factor which caused the differences between the calculated and experimental values.

Another interesting point in Fig. 8 is that the calculated diffusion coefficient values of benzyl alcohol, benzaldehyde, benzoic acid, and acetophenone in polyethylene are very close to each other (see #2, #3, #4 and #5 in Fig. 8). Due to their similar molecular structures and similar molecular weights (108 for benzyl alcohol, 106 for benzaldehyde, 122 for benzoic acid, and 120 for acetophenone), it is understandable that their calculated diffusion coefficients in amorphous polyethylene are close to each other. However, their experimental values are far below our calculated values. Another big difference between the calculated and experimental values was observed with *p*-acetamido benzoic acid and benzyl alcohol in esters of hyaluronic acid, with tetracycline in P(MMA-co-HEMA), and with progesterone in PDMS.

4. Discussion

In computer simulation, the system size is very important for obtaining the results close to the real values. We chose systems with the size of a few thousand atoms, as other scientists in the literature do. Without doubt, the larger the system, the better the results. In addition to the system size, the duration of simulation, or simulation time, is also important. Since diffusion is a time-dependent phenomenon, it is necessary to run the molecular dynamics simulation as long as possible. The impact of simulation time on the result of computation is larger than the system size provided that a system has a proper size. There is yet another concern when building polymer systems. It has been shown that the number of monomers per chain affects the free volume and its distribution [17]. Since shorter chains have higher mobility than longer chains, redistribution of free cavities becomes much easier for shorter chains. As a result, the diffusion coefficient increases in the polymeric system consisting of shorter chains. Our choices of chain length and number of monomers per chain were made based on the systems widely used by other investigators in the literature and the computer resources available to us.

Our computer simulation on the diffusion of small molecules through polymeric systems resulted in diffusion coefficient values which are either close to or vastly different from experimental values found in the literature. In general, the big disagreement between calculated and experimental values was observed when the polymeric system was hydrophilic and experiment was done in aqueous solution. In experiments for obtaining diffusion coefficient values of benzyl alcohol, benzaldehyde, benzoic acid, and acetophenone in polyethylene, a diffusion cell was used and two chambers containing aqueous solution were separated by a polyethylene film [18]. As pointed out in the paper, both benzoic acid and benzyl alcohol were able to form dimers by hydrogen bonding and hydrophobic interaction. The dimeric diffusants have slower diffusional movements. Moreover, water molecules that diffuse into the polymer film could affect the diffusion process of these four small molecules. Not only could water molecules interact with the diffusants, but also occupy the free space inside the polymer network. In the measurements of *p*-acetamido benzoic acid and benzyl alcohol in esters of hyaluronic acid, experiments were carried out in 0.1 M phosphate buffer at pH 7.4 [19]. It was reported that the weight of hydrated benzyl esters was increased about 34% and more than 200% for hydrated ethyl esters. The absorption of water molecules into the polymeric system was most apparent with the esters of hyaluronic acid. It was also reported that P(MMA-co-HEMA) membranes were about 7% hydrated in the diffusion cell when the experiments to measure diffusion coefficients of tetracycline were carried out in water solution [20]. On the other hand, the experiments to measure methanol, ethanol, and propanol in PDMS were carried out in vacuum and no solution was involved at all [14]. A PDMS slab was suspended in the vacuumed gas cell as the diffusion membrane and it was exposed to an alcohol vapor of a very low pressure. The diffusion coefficients were obtained from the measurement of the decrease in

the amount of free diffusants in the gas cell by IR. This experimental polymer membrane is very closely represented by our computer model in terms of the structural constitution. As shown in Table 1, our simulation results of methanol, ethanol, and propanol were very close to the values measured by these experiments. For methane in polyethylene, the experimental value shown in Table 1 was derived from the measured data of methane in semicrystalline PE [3]. By considering the volume fraction of amorphous and crystalline phases in the semicrystalline PE, the value of diffusion coefficient in amorphous PE can be corrected from the experimental data. Our calculated value of methane in PE was the closest to the experimental value. Consequently, the results from our simulations, which only considered amorphous polymer models without water molecules, were close to those experimental values which were measured in the absence of any bulk solution. The simulation results, however, were far different from those measurements carried out in aqueous solutions.

For relatively large molecules (e.g. progesterone and tetracycline), the values of the simulation results seem unreasonably large. Since the diffusive behavior of large molecules takes a longer time to show up than small molecules, simulations for very short periods of time (e.g. less than 50 ps) may count self-rotation and self-vibration of large penetrants as their diffusive movements. It has been shown by other investigators that the calculated diffusion coefficient value decreases as the simulation time increases [8]. Our simulations of 40 ps may be less than enough to isolate the diffusion from other movements of large penetrants. Furthermore, complex polymeric systems, such as P(MMA-co-HEMA) and HA in our study, may also have the same problem. Movements of atoms along the backbone of a more complicated system could be slower than those of simple systems, and thus these slow movements affect the flexibility of polymer chains [23]. The long simulation time could equilibrate the system better and reduce the artifacts arising from the short time simulation. Another limitation is the number of computations of each configuration. The simulation value would be closer to the experimental value, if several simulations are run and their average value is used. This is because the amorphous structure generated for the molecular dynamics simulation is one of huge number of conformations that one system has at a certain temperature. In practice, however, only one simulation was made for each configuration due to the limited computer resources.

While obtaining reasonable diffusion coefficient values from computer simulation depends on many factors, the most critical factor is how closely the computer model describes a real system where the experimental values are obtained. It should be pointed out, however, that the experiments normally yield mutual-diffusion coefficients instead of the self-diffusion coefficients. This is due to the presence of a gradient driving force (e.g. concentration gradient) during the measurements [24]. Other important factors which also affect the calculated diffusion coefficient values are temperature, chain mobility, void volume, and the distribution of void space [6,7]. Although considering all these factors surely improve the quality of the calculated values, the limited power of current computer resources prohibits a full investigation on these effects. Due to such a limitation, not only the simulation time has to be short but also the powerful modeling and simulation methods become impractical. To fully study the diffusion behavior, more powerful and easily affordable computer platforms are needed to provide plenty of computing time and to support large and complex computer models. In addition, current molecular modeling and simulation methods have to be improved, especially the parameters for hydrophobic interaction have to be added and improved.

Computer simulation is a potentially powerful tool for the study of the diffusion. Computational methods could provide much useful information which otherwise may be difficult to obtain. Such information can help understand the diffusion mechanism at the molecular level. Furthermore, the understanding of the diffusion phenomenon could lead to the design of new polymeric systems and/or optimization of the existing polymeric systems for controlled release devices with desired release properties.

Acknowledgments

This study was supported by Purdue Research Foundation and in part by a grant from the Pittsburgh Supercomputing Center.

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