A Molecular Modeling Approach towards Engineering of Polymer Nanogels for Controlled Drug Delivery

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ABSTRACT

Traditionally, a drug is administered initially at a higher dosage so as to repeat the next dose after several hours or days. This, besides being un-economical, results in side effects. Recently, there has been an increased attention on the methods of continuous administration of drugs in a controlled fashion. One of the promising methods of accomplishing this is to incorporate a drug in the polymer matrix. Cross-linked polymeric gels like hydrogels are currently being evaluated as carriers in controlled delivery system. The cross-linking density is an important parameter to engineer a given hydrogel. Experimental estimation of cross-linking density is expensive and time consuming. Several theoretical models have also been developed to model the diffusion of molecules in hydrogels. However, application of these theoretical relations is limited. Molecular dynamics (MD) simulations offer a paradigm to explore various phenomena occurring at pico/nanosecond time scales. MD simulations also possess an inherent advantage over continuum modeling in addressing nano-scale interactions between drug and polymer networks which are crucial for designing customized gels. In this paper we report on the effect of cross-linking ratio on diffusivity of drug molecules in polymeric hydrogels as studied through MD simulations.

Keywords: hydrogels, controlled drug delivery, molecular dynamics, cross-linking density

1 INTRODUCTION

Hydrogels are cross-linked polymers with capability to hold large fraction of water within their structures. They find applications in various industries such as in controlled delivery system of bioactive molecules [1, 2], tissue engineering [3, 4], contact lenses [5], agricultural, cosmetic and food industry [6, 7, 8]. When designing a hydrogel based controlled drug release system, the drug release rate can be controlled by proper engineering of hydrogels [9]. The functionality of the hydrogel system depends on its structural and dynamic properties. These properties are affected by the conformation of polymer chains, nature of chemical junctions, grid/mesh size and the structuring/de-structuring of water molecules within the polymeric components. The cross-linking density is the most important parameter to characterize the molecular structure of hydrogels. It is a function of several parameters such as type and amount of cross-linking agent, temperature, method of cross-linking etc. It affects gel properties such as swelling, diffusion/release of molecules, stability and density. It is commonly used to tune key parameters like mesh size and molecular weight between cross- linkers in order to change macroscopic properties such as diffusion and Young's modulus of hydrogels.

Several experimental studies have been reported on hydrogels [10]. Many physical models have also been developed to model the diffusion of small solutes in hydrogels [11 - 18]. Molecular Dynamics (MD) simulations have been applied in recent times to study the polymer dynamics in melts and bulk networks. MD simulations possess an inherent advantage over continuum modeling in addressing nano-scale interactions between water and polymer networks which are crucial for designing customized gels. We report on the effect of cross-linking ratio and cross-linker molecule on diffusivity of drug molecules as studied through MD simulations.

2 METHODOLOGY

2.1 Model Development

A two step process is followed to develop the cross-linked polymer model. First a low density amorphous cell consisting of two polyvinyl alcohol (PVA) chains (M.W=7800, 187 monomers) and required number of cross-linker molecules is constructed using Amorphous Builder module of Material Studio [19] program. In the next step, polymers are allowed to cross-link as per the scheme presented in Fig. 1. The polymer network thus formed is equilibrated at high temperatures followed by minimization to arrive at the experimental density of the cross-linked PVA network. A cubic box consisting of water and drug molecules is then added to this cross-linked PVA system. The amount of water added to the system is computed as per the equilibrium swelling of PVA gels. The drug molecules are added according to their solubility in water. Three different cross-linker molecules [Glutaraldehyde (GA), Maleic acid (MA) and Hexamethylene disscocynate (HMDC)] are considered to study the effect of cross-linking

properties on drug diffusion. The drug molecules studied are Theophylline (D1), Buflomedil (D2) and Proxyphylline (D3).

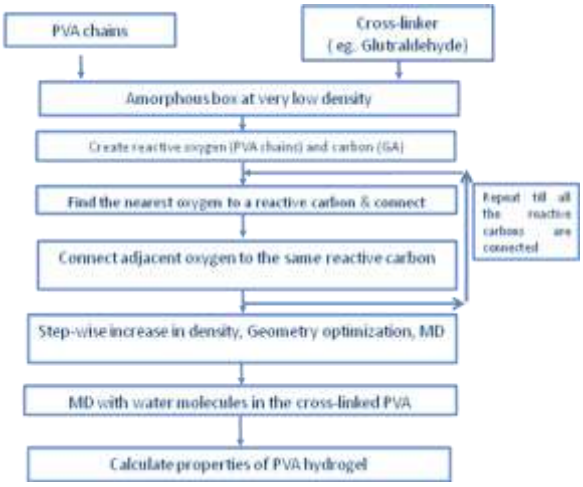

Figure 1: Schematic representation of cross-linking strategy of adapted in the present work.

2.2 Computational Details

The force field parameters and charges for modeling PVA chains are taken from Smith et al. [20]. DRIEDING force field [21] is used to model cross-linker and drug molecules. Water molecules are modeled using single point charge/extended (SPC/E) potential [22]. MD simulations are performed using LAMMPS MD simulator provided by Sandia National Laboratories [23]. Time integration is performed using the leapfrog algorithm with a time step of 1.0 fs. The short-range van der Wall interactions are computed using a cutoff distance of 1.0 nm. The long-range electrostatic interactions are computed by particle-particle particle-mesh (PPPM) method [24]. The system is fist equilibrated for 1 ns in an NPT (number of particles, pressure and temperature) followed by further equilibration for 1 ns with NVT (number of particles, volume and temperature) ensemble at 300 K. A production run of 2 ns is further applied for collecting sufficient statistics to compute various properties.

2.3 Mesh Size and Mesh Area

Mesh size is defined as average distance between two consecutive cross-links and mesh area is defined as the product of mesh size and average distance between two polymers at cross-linking locations as shown in Fig. 2.

2.4 Diffusion Coefficient

The water and drug diffusion coefficients (D) in cross-linked polymer system have been obtained from the long time slope of the mean square displacement:

$$D = \frac{1}{6} \lim_{t\to\infty} \frac{d}{dt} < |r(t) - r(0)|^2 > \quad (1)$$

Where r(t) and r(0) are the position vectors of the centre of the mass at time t and 0, respectively with an average performed over the simulation time and overall number of molecules.

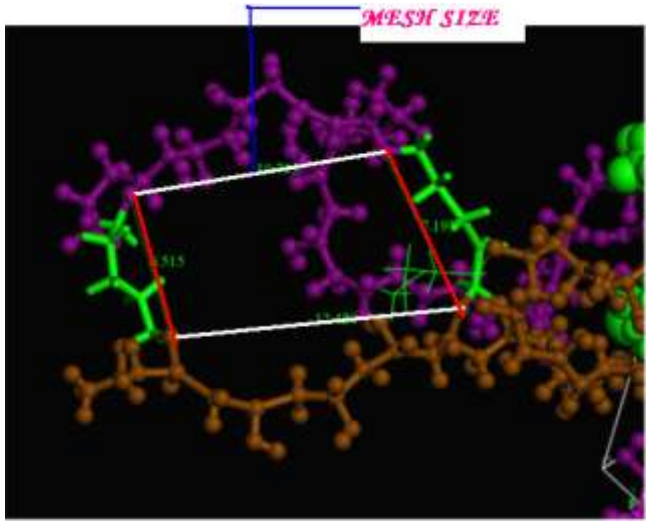

Figure 2: A schematic representation of mesh size and mesh area in the cross-linked PVA system.

3 RESULTS AND DISCUSSIONS

3.1 Model Validation

The potentials used in the modeling are validated by calculating diffusivity of drug molecules in water. As presented in the Table 1, the simulation results are in good agreement with the experimental results [25] as well as previous simulation results [26].

Drug	Solubility (g/l)	Dsim (x 10^{-7} cm^2/s)	Dexpt (x 10^{-7} cm^2/s)
Theophylline	8.3	119.4	117.6
Proxyphylline	1000	75.2	74.9
Buflomedil	650	49.4	51.7

Table 1: Diffusivity of drug molecules in water.

3.2 Cross-linking Properties and Their Effect on Drug Diffusion

Three types of cross-linker molecules are considered to study to variation in cross linking of PVA chains. The mesh size in the system is varied by changing the cross-linker molecule and keeping the cross-linking ratio constant. The average mesh size in glutaraldehyde cross-linked PVA

hydrogel is found to be 26.6Å, whereas for maleic anhydride and hexamethylene disscocynate corsslinkerd PVA hydorgel, it is 25.9 and 21.9Å, respectively (Table 2).

Cross-linker	Mesh Size (A^0)	Mesh Area $(A^0)^2$	Diffusivity (x 10^{-7} cm^2/s)			
			Water	D1	D2	D3
GA	26.6	178.22	17.4	0.33 (0.31)	0.21 (0.21)	0.18 (0.16)
MA	25.9	246.05	17.8	0.62	0.34	0.29
HMDC	21.9	267.08	18.0	0.66	0.49	0.36

Table 2: Effect of cross-linker molecules on mesh size, mesh area and diffusivity of drugs (The values indicated in the brackets represent experimental values taken form ref. 27)

The effect of type of cross-linker molecule on diffusivity of drug molecules is presented in Fig. 3. It is expected that as mesh size increases diffusivity increases as there will be an increase in void space leading to easy movements of molecules within the polymer network. However, a reverse trend is observed, that is, as the mesh size increases the diffusivity of drug molecules decreases. This can be explained in terms of mesh area. Since the change in cross-linker molecules does not affect the mesh size but does alter the void area available for drug molecule as each cross-linker is of different chain length, it is expected that as the mesh area increases, the diffusivity of drug molecule should increase (Fig. 4). These findings reveal that mesh area is more appropriate parameter for fine tuning the drug diffusivity in cross-liked hydrogels.

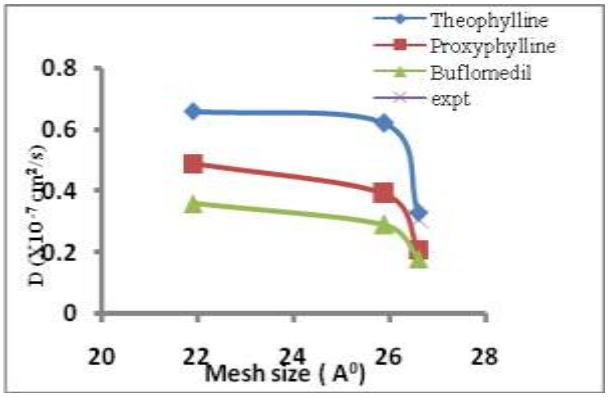

Figure 3: Effect of mesh size on diffusivity of drug molecules.

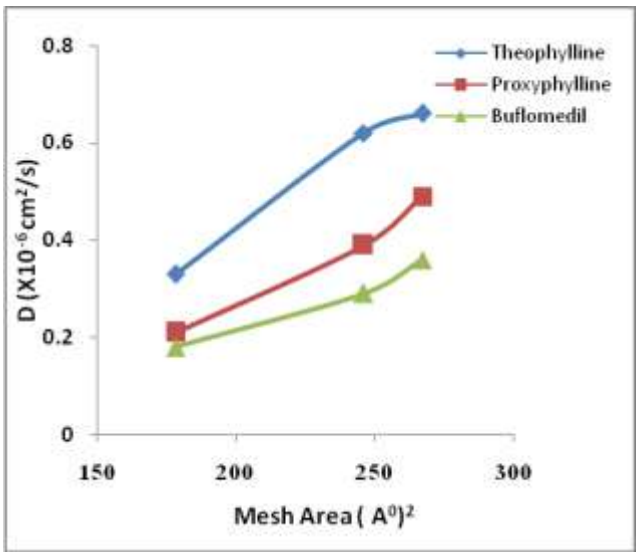

Figure 4: Effect of mesh area on diffusivity of drug molecules.

We also studied the effect of cross-linking ratio on the diffusivity of drug molecules. We constructed three systems at different cross-linking ratios 0.01, 0.1 and 0.25, respectively. As presented in Fig. 5. the mesh size/mesh area decreases with increasing cross-linking ratio. The effect of cross-linking ratio on diffusivity of drug molecules is plotted in Fig. 6. It is interesting to note that with increase in cross-linking ratio diffusivity of drug molecule decreases, which is due to the reduced mesh size/mesh area.

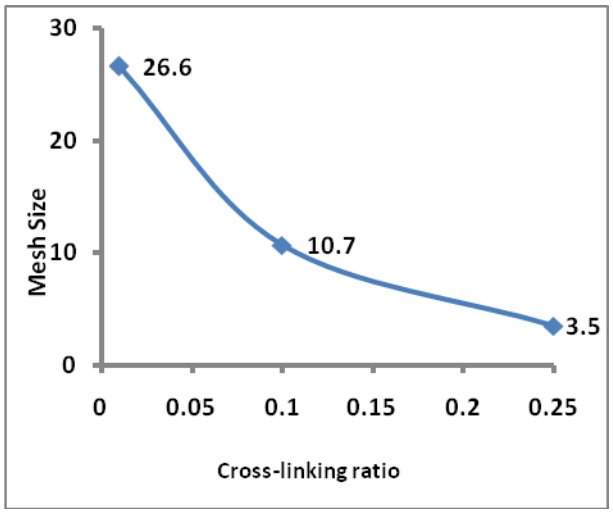

Figure 5: Effect of cross-linking ratio on mesh size.

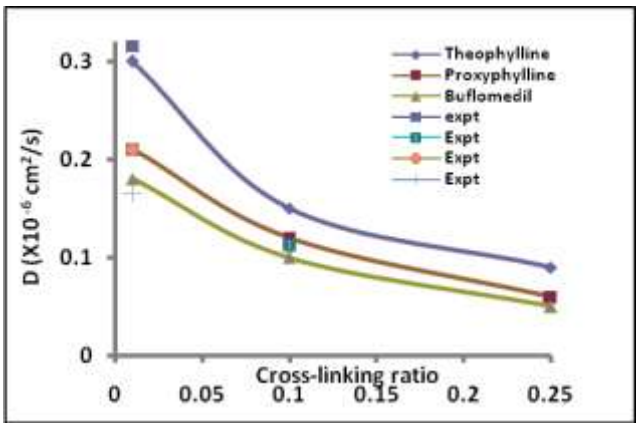

Figure 6: Effect of cross-linking ratio on diffusivity of drug molecules.

4 CONCLUSIONS

We have developed an atomistic level molecular dynamics simulation method to model cross-linked polymer hydrogels. We have further explored swelling properties of hydrogels and diffusivity of drug molecules in cross-linked polymer systems. The role of cross-linker molecule on diffusivity of drug molecules is studied. We have shown that mesh area varies with the type of cross-linker molecule which in turn affects the diffusion properties of drugs. The drug diffusivity also decreases if cross linking ratio increases.

The developed systematic approach shall be useful in the screening of different cross-linker molecules for a given hydrogel-drug system so as to arrive at the desired diffusion properties. The computed diffusivities are in line with the experimental values.

5 ACKNOELEDGEMENTS

Authors are thankful to Mr. K Ananth Krishnan, Vice President and Chief Technology Officer, and Dr. Pradip, Vice President and Chief Scientist, Tata Consultancy Services Ltd. for their support and encouragements extended throughout the course of this work. We also acknowledge Computational Research Laboratories, Pune, India for providing computational facilities.

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