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Molecular dynamics simulation of drug uptake by polymer

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Abstract Drug uptake by polymer was modeled using a molecular dynamics (MD) simulation technique. Three drugs—doxorubicin (water soluble), silymarin (sparingly water soluble) and gliclazide (water insoluble)—and six polymers with varied functional groups—alginic acid, sodium alginate, chitosan, Gantrez AN119 (methyl-vinyl–ether-co-malic acid based), Eudragit L100 and Eudragit RSPO (both acrylic acid based)—were selected for the study. The structures were modeled and minimized using molecular mechanics force field (MM+). MD simulation (Gromacs-forcefield, 300 ps, 300 K) of the drug in the vicinity of the polymer molecule in the presence of water molecules was performed, and the interaction energy (IE) between them was calculated. This energy was evaluated with respect to electric-dipole, van der Waals and hydrogen bond forces. A good linear correlation was observed between IE and our own previous data on drug uptake* [R^2=0.65, $R^2_{adj} = 0.65, R^2_{pre} = 0.56$, and a F ratio of 30.25, P<0.001; Devarajan et al. (2005) J Biomed Nanotechnol 1:1–9]. Maximum drug uptake by the polymeric nanoparticles (NP) was achieved in water as the solvent environment. Hydrophilic interaction between NP and water was inversely correlated with drug uptake. The MD simulation method provides a reasonable approximation of drug uptake that will be useful in developing polymer-based drug delivery systems.

Keywords Drugs polymer interaction · Molecular dynamics simulation · Interaction energy · Hydrophobic interaction

Abbreviations

MD	Molecular dynamics
MM	Molecular mechanics
IE	Interaction energy
TE	Total energy
Doxo	Doxorubicin
Glic	Gliclazide
Sily	Silymarin
NaA	Sodium alginate
Alg	Alginic acid
Gant	Gantrez
Chit	Chitosan
EL100	Eudragit L100
ERSPO	Eudragit RSPO
DDS	Drug delivery system
NP	Nanoparticles
GIT	Gastro intestinal tract
EM	Energy minimization
RMSD	Root mean square deviation

Introduction

The development of synthetic polymers as drug carriers and in therapeutics is now one of the most active areas of biomedical research, both in academic laboratories and in the pharmaceutical industry. Non-covalently linked poly-

* Data obtained from our previous work [16]

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mer or biopolymer complexes are, in principle, simpler as no chemical conjugation steps are needed to connect the polymer to the therapeutic agent [1]. Polymeric nanoparticles (NP) have received attention as targeted delivery systems of antitumor drugs because they were found to be able to concentrate efficiently at tumor sites. Doxorubicin, a potent anticancer agent, loaded onto oligomeric polyalkylcyanoacrylate NP, was found to cure hepatic metastases much more efficiently than the free drug [2]. Core–shell drug-delivery systems are especially useful as they enable the drug to be encapsulated inside a core. Such a structure allows hydrophobic drugs to be contained in the core, whilst the shell separates the drug from the hydrophilic external environment [3]. The delivery system can also be designed to transport drugs from the blood, across the hematoencephalic barrier, and into the central nervous system [4, 5]. The ability to maintain drug stability is closely related to the physicochemical properties of the microenvironment in the delivery system, and to the interactions between the drug and the polymer [6].

Polysaccharides such as alginate, and chitosan are regarded as biocompatible, non-toxic, non-immunogenic and biodegradable polymers [6, 7]. Chitosan is an abundant and natural polysaccharide with the ability to interact with different substances (e.g., both hydrophilic and hydrophobic drugs). These characteristics are extremely important for medical and pharmaceutical applications, namely for the development of controlled drug release devices. It has also been recognized that, for ocular applications, chitosan-based formulations allow a prolonged precorneal residence time, an ability to increase solution viscosity and excellent mucoadhesive properties [8, 9]. Gantrez AN119 was examined as immunoadjuvant and its protective effect on ovalbumin was studied in sensitized mice [10]. Eudragit®L is insoluble in saliva and gastric juice but starts to be soluble in the duodenum (pH around 6) [11]. NP-based drug carriers allow the properties of the drug being carried to be hidden, and protect the drug against chemical and biological degradation, thereby permitting controlled and targeted drug release based on the physiochemical properties of the NP [12–15].

A major limitation of NP as a drug delivery system (DDS) is drug loss during processing. Unless optimized, a major proportion of the drug may remain unentrapped (free) and is thereby wasted or would require specialized recovery methods, thus making the DDS unaffordable and impractical for high-cost drug molecules. Standard methods of optimization would entail a number of experimental runs, which would require adequate quantities of the drug, and could therefore be a serious limitation for high-cost drugs, or for drugs available only in limited quantities, during high throughput screening [16]. Molecular modeling and dynamics thus has the potential to play a significant role in achieving better design and administration of controlled release systems and in designing patient-specific treatment regimens. Drug release from polymer-coated oral delayed-release systems includes a number of mass transfer processes involving multiple species as the capsule transits through the gastro-intestinal tract (GIT). Molecular dynamics (MD) allows the study of structure and key properties like stability, diffusion, binding between molecules, behavior and vibration. It is widely used in drug design [17] to study the three-dimensional properties and interaction energies of molecules, and can be used in simulation studies, etc. [16]. Therefore, predictive computational models can be used to accelerate the selection process of lead compounds to deliver drugs from large polymer libraries prior to synthesis and biological characterization. MD simulations have been used to predict the macro-scale transport properties of the drug and the biologic fluid [18].

A similar investigation was performed to determine the interaction between drugs and oligomeric Eudragit® RL or Eudragit® RS resins under physiological conditions (310 K). The MD of this system was performed for 50 ps surrounded by water molecules [19, 20].

The software package GROMACS was developed for the purpose of simulating bio(macro)molecules in solution. Classical MD simulations of molecular systems involve the solution of Newton's equations of motion in small time steps, based on Cartesian coordinates of the particles and using a conservative force field. To avoid adverse boundary effects, periodic boundary conditions are employed [21].

The aim of the present work was to study and understand the interaction between various drugs and polymeric NP using MD techniques, and to correlate the experimentally observed drug uptake values [16] with interaction energy (IE). From the IE studies, it is possible to derive the optimum drug delivery system. The current study included three drugs of different water solubility in combination with six polymers of different solubility and with different functional groups.

Experimental and simulation details

The experimental procedures and results are given in more detail elsewhere [16]. The NP of various polymers, viz. alginic acid (Alg), sodium alginate (NaA), Eudragit L100, chitosan (Chit), Gantrez AN119 (Gant), Eudragit RSPO, with the three drugs, viz doxorubicin, silymarin and gliclazide (water soluble, sparingly soluble and water insoluble, respectively) were prepared by a controlled precipitation method. The drug to polymer ratio was kept constant (50 mg drug: 100 mg polymer) in all cases and no other excipients were added. All other processing parameters, including stirring speed (3,000 rpm) and stirring time

(60 min) were kept constant. Doxorubicin was solubilized in 10 ml water while the other two drugs were solubilized in 10 ml methanol. The NP suspensions were subjected to centrifugation at 20,000 rpm for 40 min, and the supernatant was then analyzed for the unentrapped drug using a fluorimeter. The sediments were washed three times and freeze dried to obtain the drug-loaded polymeric NP.

The amount of drug entrapped within the NP was determined by measuring the amount of non-entrapped drug in the supernatant recovered after centrifugation and washing of the NP. The percentage encapsulation efficiency (%uptake) was determined from these values [16]. The measurements were performed with an accuracy of 0.1%.

%Encapsulation effiency

= Mass of drug added during NP preparation

− Mass of free drug in supernatant

× 100/Mass of drug during NP preparation

The structures of the drugs and polymer molecules were built with HYPERCHEM® software (Hypercube, Gainesville, FL) and their minimum energy conformations were determined using MM+ force field in vacuum. Force field is the functional form to describe the potential energy of the system of particles. This is calculated as [22]:

$$\Sigma \text{ potential energy} = \Sigma \text{ bond} + \Sigma \text{ angle} + \Sigma \text{ diherdral} + \Sigma \text{ electrostatics} + \Sigma \text{ vanderwaals}$$

The sum of all these forces is called the force field of the molecule. The drug-loaded NP molecules were modeled by placing each drug adjacent to each polymeric molecule separately, thereby giving 18 merged (combined) systems of drug and polymer. Decamers (E L100 and E RSPO) and hexamers (Alg, NaA, Chit, Gant) of the polymers were used for the study.

The coordinates and input topology files for the modeled structures of individual and merged molecules were extracted from the PRODRG online server (a tool used for conversion of coordinate files for small molecules) [22]. The individual drug and polymer molecules and the combined molecules were then subjected to MD simulation in aqueous environment, with GROMACS© 3.3 (Groningen Machine for Chemical Simulations) software (Department of Biophysical Chemistry, University of Groningen, The Netherlands). The above processes were carried out on a Vega cluster workstation using message passing interface (MPI) implementation. The cluster uses a standard method to minimize edge effects in a finite system that can be applied to periodic boundary conditions. In this method, each molecule is placed inside a cubic triclinic box and solvated with explicit single point charge (SPC) water molecules [11, 19]. The system is solvated with equal number of water molecules (11,300) since all the experiments were carried out with same volume of aqueous solution. The molecules were then subjected to energy minimization (EM) using the steepest-descent algorithm to obtain the lowest energy conformation of the structures, which will eliminate close contacts and unrealistic initial atomic positions. The time step was set to 2 fs (0.002 ps). The molecules were soaked in water by restraining the molecules for 20 ps, since the relaxation time for water is 10 ps. This is followed by simulation. All the MD simulations were executed for 300 ps at a temperature of 300 K using Gromacs forcefield (ffgmx) [23]. The trajectory frequency was set to 500 and the output is obtained for every picosecond. Equilibration of the drug, polymer and the combination with the solvent occurs only after 30 ps. This force field is part of the GROMACS package, and includes bonded and non-bonded parameters [22].

$$\Sigma_{\text{bonds}}\, k_b\,(b-b_0)^2 + \Sigma_{\text{angles}}\, k_\theta\,(\theta-\theta_0)^2 + \Sigma_{\text{dihedrals}}\, k_\varphi\,[1+\cos(n\varphi-\delta)] + \Sigma_{\text{impropers}}\, k_\omega\,(\omega-\omega_0)^2 + \Sigma_{\text{Urey-Bradley}}\, k_u\,(u-u_0)^2 + \Sigma_{\text{nonbonded}}\, \epsilon\,[(Rij/r_{ij})^2-(R_{ij}/r_{ij})^6]+q_iq_j/\varepsilon r_{ij}$$

A twin-range cutoff was used for both Lennard–Jones and Coulombic calculations with a cutoff radius of 1.0 nm to distinguish between short-range and the long-range forces. The LINCS algorithm was used to constraint the bonds [24], and MD simulation was performed using the leap-frog algorithm [2]. The trajectory files that comprise of the motion of the molecules were viewed with VMD 1.8.6 (Visual Molecular Dynamics, Theoretical and Computational Biophysics Group, University of Illinois and Beckman Institute, Urbana, IL) software [25] and also with ngmx (the Gromacs trajectory viewer). Root mean square deviation (RMSD) values were estimated using the software Xmgrace, Version 2, (Free Software Foundation, Boston, MA).

The IE is calculated from the total energy (TE) of the individual and the merged molecules. It is the difference between the TE of the drug-loaded NP and the sum of the energies of the individual drug and the polymer. IE is correlated linearly with the percentage uptake obtained from experimental studies. Statistics such as R^2, R^2_{adj}, R^2_{pre} F ratio and *P* value are also estimated for the fit and reported here.

Results and discussion

The uptake of the drug by the polymers was studied using molecular modeling and dynamic simulation techniques. The drugs considered were doxorubicin, gliclazide and silymarin, and the polymers were sodium alginate, alginic acid, chitosan, Gantrez AN 119, Eudragit L100 and Eudragit RSPO. The results of MD simulations for various drug-polymer combinations are listed in Table 1. They include RMSD values, number of hydrogen bonds between the encapsulated drug and the polymer and the interaction energies. Table 1 also lists experimentally determined drug uptake.

The minimum energy conformation of the polymer molecules revealed a helical structure, brought about by the non-bonded interactions (van der Waals, electric-dipole), with the side chains pointing out radially. This is favorable for the uptake of drug molecules. This kind of helical conformation of polymer was also reported in the case of polyalkylcyanoacrylate NP [2], with the structure enabling higher entrapment of the drug. The modeled low energy conformers of the molecules were very well equilibrated after undergoing MD simulations at a constant temperature of 300 K for 300 ps simulation. The changes in RMSD (in nm) of the drug–polymer–water system as a function of simulation time indicated that it reached a steady value at around 300 ps. Hence all the MD simulations were carried up to this time.

From Table 1 it can be seen that, maximum doxorubicin is taken up by the polymer Gantrez AN119, followed by Eudragit RSPO, sodium alginate, alginic acid, chitosan and Eudragit L100. In the case of gliclazide, maximum drug is taken up by Gantrez AN119, followed by chitosan, Eudragit L100, Eudragit RSPO, alginic acid and finally by sodium alginate. Maximum uptake of silymarin is observed with Gantrez AN119, followed by Eudragit RSPO, chitosan, Eudragit L100, alginic acid, and by sodium alginate. Hydrophobicity is one of the most important properties affecting drug-uptake by the polymer. It acts as a stabilizing factor for the aggregation of molecules [2], which in turn is responsible for the conformational changes in the polymers. Higher IE is brought about by hydrophobic (van der Waals) and electrostatic interactions, which also result in the higher uptake of drug by the polymer. Similar IE calculations have also been reported by others [9].

The formation of hydrogen bonds denotes the hydrophilic nature of the drug–polymer combination. The IE between drug and NP, and the number of hydrogen bonds are negatively correlated (-0.64, $P<0.01$). Relatively higher IE values were observed in drug-loaded NP with fewer hydrogen bonds compared to those with more hydrogen bonds (Table 1). This high hydrophobicity will

Table 1 Results of molecular dynamics (MD) simulation for 300 ps and experimental % drug uptake. *Alg* Alginic acid, *NaA* sodium alginate, *EL100* Eudragit L100, *Chit* chitosan, *Gant* Gantrez AN119, *ERSPO* Eudragit RSPO, *RMSD* root mean square deviation, *IE* interaction energy

Drug	Polymer	RMSD (nm)	No. of H-bonds	IE (kJmol^{-1}) (SD)	Drug uptake [%(SD)][1]
Doxorubicin	NaA	0.580	4	386,353 (450.964)	74.8 (7.2)
	Alg	0.914	6	385,451 (560.175)	45 (4.5)
	Chit	0.495	3	385,430 (463.253)	20 (4.2)
	EL100	0.410	2	385,166 (441.432)	51.5 (5.2)
	ERSPO	0.201	1	386,934 (461.963)	74.8 (7.1)
	Gant	0.349	2	387,395 (416.817)	82.6 (7.5)
Gliclazide	NaA	0.423	3	385,887 (420.229)	38.05 (2.6)
	Alg	0.508	1	386,669 (498.421)	36.7 (4.5)
	Chit	0.980	4	387,306 (631.308)	86.6 (8.6)
	EL100	0.244	0	386,967 (472.143)	80.99 (8.2)
	ERSPO	0.166	0	386,875 (409.374)	42 (5.6)
	Gant	0.259	0	387,784 (422.214)	83.9 (6.5)
Silymarin	NaA	0.378	3	387,039 (457.561)	96.44 (9.2)
	Alg	0.458	1	387,351 (445.237)	97.4 (9.4)
	Chit	0.759	1	387,751 (446.546)	99.9 (7.6)
	EL100	0.315	0	387,714 (461.184)	99.5 (9.3)
	ERSPO	0.356	0	388,038 (432.111)	96.44 (10.2)
	Gant	0.276	0	388,778 (391.973)	99 (8.9)

[1] From [16]

ensure passage of drug–polymer conjugates through biological membranes [4, 5]. The polymers Gantrez AN119, EL100, ERSPO show higher interaction with drug molecules due to their hydrophobicity, and form fewer hydrogen bonds. The polymers chitosan, alginic acid and sodium alginate show a higher interaction with the drug molecules by forming a relatively greater number of hydrogen bonds. However, comparatively hydrophobic polymers interact with drugs better than hydrophilic polymers.

It was observed that the strongest hydrophobic interaction was obtained for the Gantrez AN119 loaded drugs and they formed the least number of H-bonds, in some cases none, with the three drugs. This was followed by Eudragit ESPO and Chitosan loaded drugs, which also formed low numbers of H-bonds. Sodium alginate and alginic acid formed more H-bonds than the other polymers, leading to the least hydrophobic interaction between the drug and the polymer. It was predicted that the anhydride groups of Gantrez molecules and the non-polar groups of the Eudragit resins accounted for the hydrophobic property of the respective polymers. Although chitosan contains polar side chain groups, it is less hydrophilic than sodium alginate and alginic acid molecules, favoring higher interaction with the drugs.

The RMSD values of the drug-loaded NP increase as the number of hydrogen bonds increases (Table 1). Hydrogen bond formation between the drug and polymer decreases the uptake of the former by the latter, and so, in such cases, hydrophobic and charge-dipole stabilization factors are essential for increasing uptake. Our study also indicated that no H-bonds formed within (intra molecular) the individual molecules and that H-bonds were formed only between the drug and polymer (inter molecular) systems.

Regression model

Table 1 also shows the %drug uptake by the polymer obtained from our previous experimental studies [16]. Figure 1 shows the fit between IE and %drug uptake with 95% prediction bands. All the data is within this prediction range. There is a very strong correlation (correlation coefficient =0.8, $P<0.001$) between IE and % rug uptake. A linear regression relation as shown below relates these two variables. $R^2=0.65$, $R^2_{adj} = 0.65, R^2_{pre} = 0.56$, and F ratio of 30.25 ($P<0.001$), indicates that the regression fit is reasonably good.

$$\%\text{Drug uptake} = 0.0218\text{IE} - 8366.9$$

Figure 2 shows a few typical interactions between different drugs and polymers. The Gantrez AN119 polymer shows the strongest interaction with all three drugs. Chitosan, Eudragit RSPO and Eudragit L100 resins account for the next highest drug uptake. Alginate and sodium alginate show the lowest drug uptake and also lowest IE with the drugs silymarin and gliclazide. Chitosan shows the smallest IE, as well as lowest uptake of the drug doxorubicin.

Hydrophobic polymers are less soluble in water. Solubility issues are not a concern in silico since here the polymers are used as single chain [26]. In our MD simulation study, we used explicit water solvents (individ-

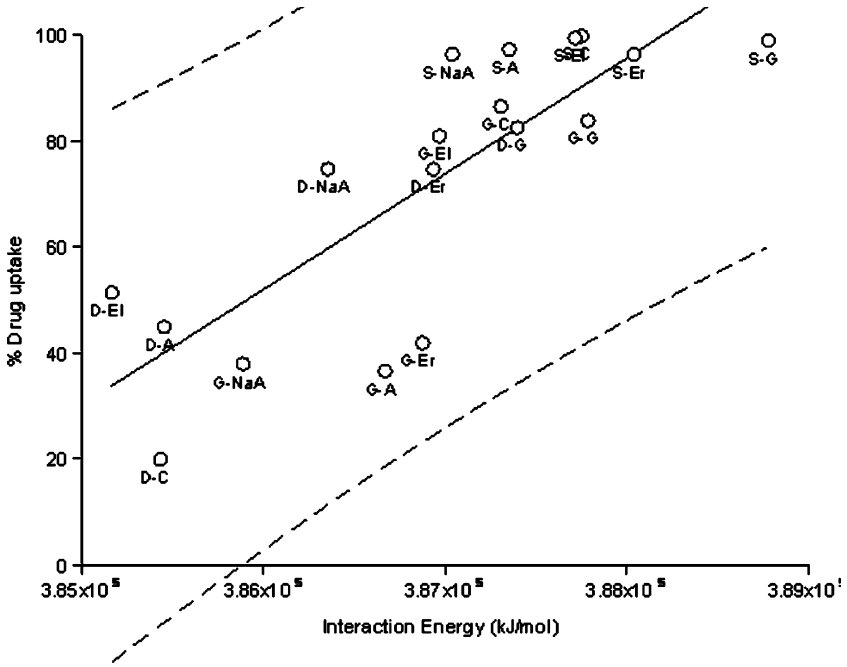

Fig. 1 Plot of interaction energy (IE) and the drug uptake efficiency. *Dotted lines* 95% prediction band

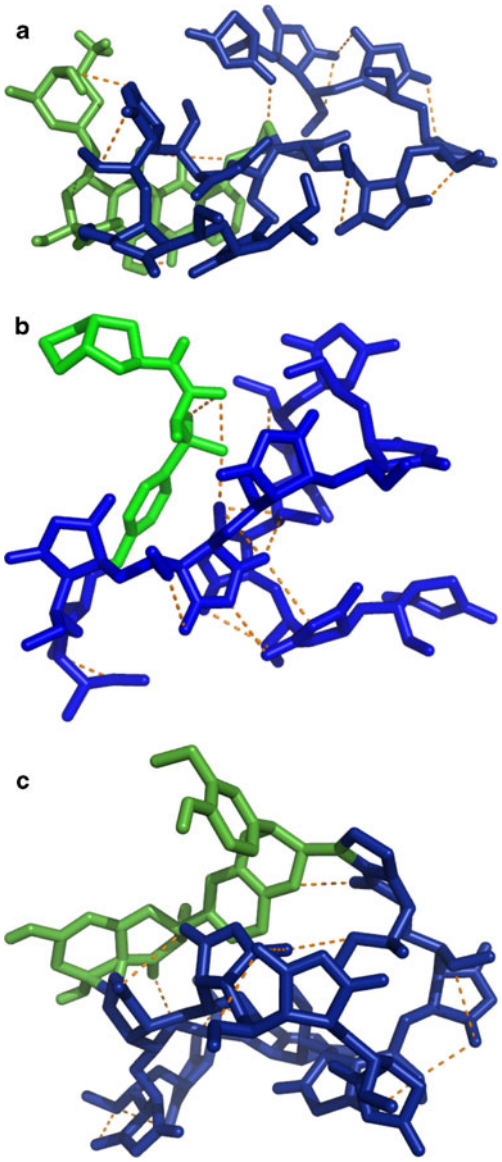

Fig. 2a–c Structural representation of interaction (*orange dashes* non-hydrogen bond) between drugs and polymers. Interaction of (**a**) doxorubicin with Gantrez AN119, (**b**) gliclazide with Gantrez AN119, (**c**) silymarin with Gantrez AN119. *Green* Drug, *blue* polymer

ual solvent). Most such simulations are carried out in explicit solvents, except in cases of biomolecule folding and structure prediction, where implicit solvents (continuum solvent) are used. Implicit solvents are used to study solute–solvent interactions [27], where hydrogen bonds are formed in higher numbers due to polarization effects. Only when the shell particles (virtual particles) are added to the molecules, do they show this polarization effect. Since we use explicit solvent, no significant interaction is exerted between the polymer and the water. A similar simulation study on Eudragit resins was reported, where the authors did not calculate the polymer–water interactions [19]. The explicit solvent shows a hydrophobic effect and the model used here is a SPC water model [22]. Therefore, in our study, the hydrophobic polymers Gantrez, ERSPO and EL100 show a hydrophobic effect, and the other polymers, namely chitosan, sodium alginate and alginic acid, show hydrophilic interactions due to polarization effects.

As reported by others, avoidance of metabolism or degradation of these biopolymers during transit of the drug is important [24]. Also, biopolymers are sensitive to environmental factors such as variations in temperature, pH and ionic strength during formulation and transport. As a consequence, usage of biopolymers for real patient benefit will require the development of sophisticated chemistries in the polymer carrier systems to ensure drug stability, transport and release [28].

An increase in the temperature of the system can alter interaction between drug and polymer. The pH level and ionic strength of the physiological system can also affect drug delivery by polymers. This study of interaction and uptake of drugs by highly biocompatible and biodegradable polymer NP will help our further understanding of drug uptake systems.

Conclusions

Polymers are a novel carrier for the delivery of drugs to their target region, and the present study was undertaken to examine the proficiency of polymer drug uptake. In this study, the molecules were constructed through computer-aided molecular modeling methods followed by MD simulation in aqueous medium. This is a reliable and predictive method to explore the way in which polymers interact with drug molecules. A good correlation was observed between the experimental data and the simulation, which revealed that the controlled uptake of a drug by a polymeric NP can be achieved effectively with water as the solvent environment. Hydrophobic interactions play an important role in the uptake of the drug by the polymer.[1] Such an approach can save considerable time during the selection of the best polymer for a particular drug. The simulations can be easily extended to incorporate solvent mixtures. Future investigation of the drug-delivery system should also include experimental and modeling studies to investigate drug release from nanoparticles.

[1] The modeling study reported here is novel and such techniques have not been exploited fully. The polymers built are also reasonably large (6–10 mers)

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