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ScienceDirect
Nanomedicine: Nanotechnology, Biology, and Medicine xx (2011) xxx–xxx
nanomedicine
www.nanomedjournal.com

Review Article

Computational approaches to the rational design of nanoemulsions, polymeric micelles, and dendrimers for drug delivery

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Received 10 February 2011; accepted 14 May 2011

Abstract

Nanoparticles are promising drug delivery systems whose selection and optimization can be gainfully conducted by theoretical methods. This review is targeted to experimentalists who are interested in enhancing their time and cost efficiency through the incorporation of theoretical approaches. This review thus begins with a brief overview of theoretical approaches available to the development of contemporary drug delivery systems. Approaches include solubility parameters, Flory-Huggins theory, analytical predictions of partition coefficients, and molecular simulations. These methods are then compared as they relate to the optimization of drug-material pairs using important performance-related parameters including the size of the delivery particles, their surface properties, and the compatibility of the materials with the drug to be sequestered. Next, this review explores contemporary efforts to optimize a selection of existing nanoparticle platforms, including nanoemulsions, linear and star-shaped block co-polymer micelles, and dendrimers. The review concludes with an outlook on the challenges remaining in the successful application of these theoretical methods to the development of new drug formulations.

Key words: Nanoparticle; Theoretical prediction; Molecular simulation; Drug-material compatibility; Drug formulations

Nanoparticles for drug delivery

It is estimated that 40% of the small molecules that are considered to be new drug candidates are hydrophobic in nature.[1] Full exploitation of the therapeutic potential of these drugs relies on their solubilization in nontoxic, biocompatible, and/or biodegradable formulations that protect the drugs during transportation and release them at the target tissue.[2]

The last few decades have produced an astounding number of nanoparticles; systems comprising particles with at least one dimension between 1 and 100 nm.[2-6] Nanoparticles share this size range with many biologically relevant molecules,[3] and biomedical applications abound.[5] Among these, nanoparticles composed of organic molecules are capable of modifying the apparent physicochemical properties of sequestered compounds. For example, drugs encapsulated by some nanoparticles exhibit enhanced aqueous solubility[7,8] and can be targeted to diseased tissue, improving the drug's therapeutic index.[9]

For a given application, the most appropriate nanoparticle delivery platform is rarely obvious.[10] Further, within each platform, nanoparticles must be optimized to achieve the desired properties.[11] Some of these properties are predictable by theoretical approaches, which can be employed to accelerate development efforts.[12] Important performance-related physicochemical parameters of drug delivery systems include the compatibility between the drug and the materials of the delivery system, and the surface properties and size of the particles.[13,14] Optimization of the compatibility between the drug and the

This study is supported by a grant from the Natural Sciences and Engineering Research Council of Canada to C. Allen as well as a University of Toronto Open Fellowship to L. Huynh. C. Neale is funded by the Research Training Center at the Hospital for Sick Children and by the University of Toronto. This work was funded in part by Canadian Institutes of Health Research Operating Grant MOP43998. R. Pomès is a Canada Research Chairs Program Chairholder.

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doi:10.1016/j.nano.2011.05.006

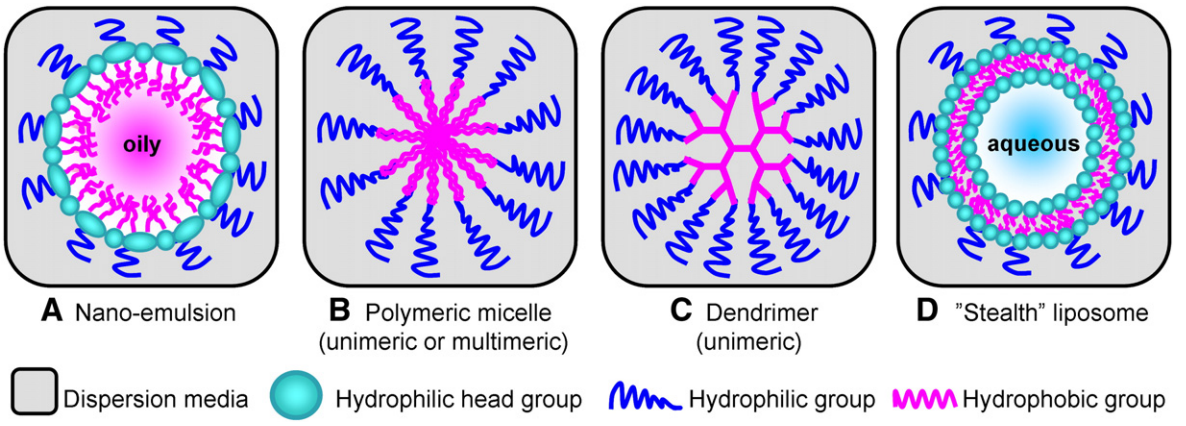


Figure 1. Nanoparticle platforms that have been investigated using molecular simulations. **(A)** Nanoemulsions with an oily hydrophobic core and hydrophilic surfactant corona. **(B)** Linear or star-shaped block co-polymer micelles composed of hydrophobic and hydrophilic blocks. The ends of the hydrophobic blocks are covalently bonded for the star-shaped block co-polymer micelles. **(C)** Dendrimers with a hydrophobic core and hydrophilic peripheries. **(D)** Liposomes (not covered in this review) have a lipid bilayer that forms a hydrophobic domain for solubilizing hydrophobic drugs, and an inner aqueous volume for solubilizing hydrophilic drugs. Stealth liposomes are further coated with PEG. In the above platforms **(A-D)** the hydrophobic environment (*pink*) serves as cargo space for lipophilic solutes, and the hydrophilic components (*blue*), often composed of PEG, protect the core from the external environment.

solubilizing media can significantly improve drug loading, drug retention, and thereby the chemical stability of the fomulation.[7,8] Additionally, the surface properties of the delivery system influence its stability during storage and following in vivo administration.[15]

This review focuses predominantly on theoretical approaches for predicting the physicochemical properties of a small group of nanoparticles including nanoemulsions, polymeric micelles, and dendrimers (Figure 1). In many cases, the techniques that we review are equally applicable to other nanoparticle platforms. We also briefly highlight the relationships between the physicochemical properties of nanoparticles and their biological performance.

Theoretical approaches to developing nanoparticles

Theory has been used to complement experiment in the development of effector molecules such as drugs.[12,16,17] Although it remains viable to experimentally prepare and separately evaluate a variety of drug formulations, this is costly and time-consuming.[10] Further, material optimization involves significantly more possibilities, and the number of full factorial combinations quickly becomes unfeasibly large for experimental methods.[18] More fundamentally, experimental studies of novel drug formulations do not disclose the molecular basis for their performance (e.g., the reason why the drug precipitates), and hence do not indicate possible avenues by which they may be improved. In contrast, theoretical methods are capable of identifying the molecular basis of drug formulation inadequacies,[16,19] and systematic theoretical studies may suggest fruitful avenues for material modification.[12,16,20]

A variety of computational methods exist to predict physicochemical properties including the solubility and lipophilicity of small molecules[21,22] and structural properties of formulation materials.[20,23-25] These theoretical approaches can be broadly divided into two categories: analytical models and molecular simulations.

Analytical models represent presumptive relationships in a convenient mathematical form and are parameterized to reproduce experimental data.[26-28] There are, for example, a variety of theories that apply a group contribution method to sum structure-based molecular descriptors over predefined fragments of a complex molecule. These methods are widely used because they predict relevant physicochemical properties, such as lipophilicity[22] and solubility parameters (SPs)[21,29,30] very quickly (overnight for thousands of compounds using computerized automation). Applications include predicting which drug-material pairs will perform optimally as a formulation based on the theoretical cohesive energy of the compounds,[21] or predicting the loading and/or retention of drug in the formulation.[22]

Conversely, physics-based models generate predictions from first principles, or approximations thereof.[26-28,31] The simplest of these are closed-form approximations that have analytical solutions. These are, however, unavailable for molecules of interest to pharmaceutical formulation because of the complex nature of their conformational and chemical properties. In their place, one may use *molecular simulations*[32,33] to solve *n*-body problems based on the application of statistical mechanics to quantum- or molecular-mechanics force fields. Molecular simulations may be conducted via Monte Carlo (MC) or molecular dynamics (MD) approaches. MC simulations employ a stochastic algorithm to accept or reject arbitrary configurational moves by evaluating the change in potential energy, whereas MD simulations numerically integrate the differential equations of motion to generate a time trajectory.[32,33] These simulations can provide quantitative measurements at the atomistic level that are difficult to obtain experimentally.[20,23,34] This review discusses studies that apply MC[35-37] and MD[20,23,38-40] simulations to characterize the structural and dynamic properties of nanoparticles and their cargo. For example, simulations can estimate the loading by predicting the compatibility between the

drug and delivery materials.[20,21,35,41,42] Simulations can be applied to correlate drug release[19,38,43,44] with kinetic properties such as diffusion,[19,43] and thermodynamic properties such as composition,[20] orientational preferences, and free volumes.[37,39,45]

Overall, the utility of analytical models and molecular simulation will be discussed throughout this review. In general, analytical models are excellent tools to rapidly eliminate material combinations that are unlikely to be miscible and thus enrich the probability of compatibility within the remaining materials (library enrichment). These methods are often quantitatively wrong, however, and are most useful as preliminary tools to reduce the number of evaluations to be conducted with experimental or more time-consuming theoretical approaches, such as molecular simulations.

Identifying optimal drug-material pairs

During formulation development, promising drug-material pairs can be rapidly identified by predicting the strength of drug-material interactions through the estimation of physicochemical parameters such as solubility, lipophilicity, and chemical compatibility.

Solubility and solubility parameters

The aqueous solubility of a drug strongly influences its biological activity and can be predicted using various computational models.[46] Solubility is a measure of the maximum amount of solute that forms a homogeneous solution with a specified solvent under equilibrium conditions.[47] In contrast, an SP[31,48] is a scalar value that gives an *indication* of the predicted miscibility of two components. Materials with similar SPs are indicated to be miscible. SPs are useful for rapidly ranking materials based on their predicted relative abilities to solubilize a drug.

Hildebrand[31] and Hansen[49] approaches have been used to calculate SPs, as shown in Eqs 1a and 1b, respectively, in Table 1, and reviewed elsewhere.[50] The Hildebrand SP is related to molecular self-interaction energies and is defined as the square root of the energy of vaporization of a compound per unit volume in the amorphous state (i.e., in the absence of crystallization) (Eq 1a).[31,48] The Hansen SP is based on partial energies of cohesion, dissected into a sum of dispersion, dipolar, and hydrogen-bonding components (Eq 1b).[49]

Two compounds with similar patterns of polar and hydrogen-bonding interactions are predicted to be compatible when the difference in Hildebrand SPs is <1.8 $cal^{1/2}\cdot cm^{-3/2}$ (or 3.7 MPa).[49] However, for compounds with dissimilar patterns of polar and hydrogen-bonding interactions, the difference in Hildebrand SPs below which two compounds are predicted to be compatible can be 1.5- or 2-fold larger,[21,50,51] especially in solid dispersions.[52] Although the Hildebrand SP is useful for predicting the miscibility of nonpolar materials and materials with sufficiently similar coulombic interactions,[31] it often performs poorly as an indicator of miscibility for compounds capable of forming hydrogen bonds or salt bridges because these orientation-dependent interactions are not necessarily conserved in different solvents.[53] In these cases, one can apply the Hansen SP, which, although it requires more data and is thus harder to determine than the Hildebrand SP,[49] is useful for predicting the miscibility of polar materials with the potential to engage in hydrogen-bonding interactions.[49] Compounds are predicted to be compatible when the difference in Hansen SPs is less than or equal to the Hansen SP sphere radius (Eq 1c, Table 1).[49]

As an alternative to the direct evaluation of SPs using cutoffs, as outlined above, both Hansen and Hildebrand SPs have been used to predict enthalpies of mixing by accounting for the volume fractions of components within a mixture.[29,53,54] Hansen SPs and Hansen SP-based enthalpies of mixing have been used to estimate the compatibility of materials for polymer-lipid hybrid nanoparticles. Specifically, enthalpies were predicted for mixing a drug-polymer complex (verapamil HCl in dextran-sulfate-sodium) with 15 different lipids including fatty acids, triglycerides, glycerol esters, and mixtures of glycerol esters.[51] Based on these calculations, dodecanoic acid and monoglyceryl behenate were identified as the most suitable components to solubilize the drug-polymer complex.[51] Nine lipids were selected for experimental evaluation, and of these, the apparent partition coefficient of the drug-polymer complex between lipidlike substrates and the aqueous phase was greatest for dodecanoic acid. However, the drug-polymer complex had poor relative affinity for Compritol ATO 888 (Gattefossé Corp.), which is a mixture of glycerol esters with 15% of monoglyceryl behenate. Of the materials evaluated experimentally, the top three predictions were reproduced in rank order, although several of the materials predicted to be more suitable (e.g., pure monoglyceryl behenate) were not evaluated.[51] Unfortunately, the relative utilities of SPs and theoretical enthalpies of mixing for rank-ordering materials remain unclear. Determination of the optimal theoretical treatment requires that these methods be systematically compared over a wide range of compounds.

In comparison to molecular simulation or experimental approaches, calculations of Hildebrand and Hansen SPs using group contribution methods[53] are fast, because they avoid evaluation of different materials as a mixture (e.g., drug A in oil B), as would be necessary in a direct evaluation of solubilities. They are therefore well suited to rapidly eliminate materials that are likely to be incompatible, thereby enriching the library of materials under consideration in the early stages of formulation development before application of more computationally and/or experimentally expensive methods.[22,29] SPs are, however, based on the assumptions of regular solution theory for liquids and do not take into account the effects of entropy and the free volume of amorphous solids.[50] Further, SPs do not account for any dependencies on concentration, conformation, or unique interactions between molecules that may be present in binary mixtures. SPs are therefore sometimes inaccurate. Indeed, studies have shown that SPs calculated based on group contribution methods only provide accurate predictions when comparing materials that have similar chemical structures.[21] Similarly, Lipinski postulated that prediction of the aqueous solubility of druglike compounds is more successful with neutral compounds and within a series of compounds with similar chemical structures.[1]

Flory-Huggins interaction parameter

The Flory-Huggins (FH) theory[55-57] was established with the intent to describe the thermodynamic behavior of nonidealized polymer-solvent solutions. The FH interaction parameter, χ_{FH}, is a dimensionless quantity that represents the interactions that contribute to the enthalpy of mixing of a polymer and a solvent. Compounds are predicted to be miscible when χ_{FH} is <0.5 (or phase separated when χ_{FH} >0.5).[55] Experimentally, χ_{FH} can be determined from the enthalpy change associated with creation of a binary mixture as shown in Eq 2a (Table 1).[55] Theoretically, χ_{FH} can be obtained from MC[58] and MD[59] simulation, as outlined in Eq 2b (Table 1), or using group contribution implementations of Hildebrand and Hansen SPs, as outlined in Eq 2c (Table 1),[31,49,55] although the inaccuracies of these concentration (and possibly conformation and hetero-interaction)-independent SPs are, in this case, propagated to χ_{FH}.[60] These inaccuracies are important because many studies have shown that the χ_{FH} varies as a function of the volume fraction of the solute and solvent components in the mixtures.[21,55,61] Importantly, the FH theory has recently been extended to predict the miscibility of drugs and carrier materials.[21,30,62]

Recently, Dwan'Isa et al calculated χ_{FH} values from Hansen SPs for drug-polymer pairs. This was a systematic study of 19 drugs and segments of two polymers: hydrophilic monomethoxy PEG (MePEG), and a hydrophobic co-polymer of equimolar randomly distributed poly(ε-caprolactone) and trimethylene carbonate (PCL-*co*-TMC).[30] The linear diblock co-polymer MePEG-*b*-(PCL-*co*-TMC) can form micelles with an inner hydrophobic PCL-*co*-TMC core and an outer hydrophilic MePEG shell. To predict drug loading in these micelles, χ_{FH} was separately evaluated for the drug with the hydrophobic PCL-*co*-TMC and the hydrophilic MePEG. Rank order was then determined based on the root-sum-squared value of these two χ_{FH} values. Drug loading was evaluated experimentally for eight hydrophobic drugs in MePEG-*b*-(PCL-*co*-TMC) micelles. The aqueous solubilities of these drugs ranged from 0.01 mg/mL to 1 mg/mL. Rank-order agreement between theoretical predictions and experimental results was obtained for the top three predictions of drug-loading capacity (3.7, 10.5, and 19.6 mg/mL for indomethacin, cimetidine, and ketoprofen, respectively). These three drugs were not the most hydrophobic drugs, indicating that the χ_{FH} predictions were more useful than a simple hydrophobicity scale. Incorrect rank-ordering of the other five drugs can be attributed to several factors including the ad hoc combined theoretical score, conditions of the experimental study, and limitations of the theory related to both drug rigidity and the interfacial tension between molecules.[30] Nevertheless, this method appears to be a good initial step for library design and material acquisition.

In another study, Mahmud et al calculated χ_{FH} values from Hansen SPs for the anticancer drug cucurbitacin I and various hydrophobic core-forming polymers including PCL, poly(α-benzylcarboxylate-ε-caprolactone) (PBCL), and poly(α-cholesteryl carboxylate-ε-caprolactone) (PChCL).[62] Based on the calculated χ_{FH} values, PChCL and PCL were identified as the most and least suitable core-forming polymers, respectively. This finding agreed well with the experimental molar loading ratios of drug to core-forming repeat unit in the micelles, which were 3%, 8%, and 15% in MePEO-*b*-PCL, MePEO-*b*-PBCL, and MePEO-*b*-PChCL micelles, respectively.[62] Nevertheless, MePEO-*b*-PBCL exhibited the best controlled release of cucurbitacin I.[62] Mahmud et al interpreted this in light of the fact that more negative χ_{FH} values represent stronger interactions and better compatibility between the drug and material.[62] Nevertheless, the release rate is a kinetic quantity, and there is no a priori reason to assume that the release rate is related to χ_{FH}, a thermodynamic indicator. Importantly, rates of drug uptake and release can be rigorously derived from molecular simulations.[63]

Although the FH model is useful, it is founded on some assumptions that may lead to discrepancies between experimental data and theoretical predictions of drug-material interaction based on χ_{FH}.[55] Specifically, FH theory assumes that there is a *random distribution* of polymer segments and that the attraction between polymer and solvent is negligible, and thus the volume of mixing will be unchanged upon mixing of polymer and solvent.[55] Further, FH theory does not account for the molecular weight (MW) of polymers.[55] There is thus a need to improve and extend FH theory so as to more accurately predict drug-material interactions.

Lipophilicity

Lipophilicity represents the affinity of a molecule for a lipidic environment.[64] Lipophilicity can be determined by measuring the partition coefficient, *P*, which is the ratio of solute concentrations in binary phases of organic and aqueous solvents, such as octanol and water, under equilibrium conditions.[28] Because the value *P* ranges widely, the lipophilicity of compounds is represented as the logarithm of *P*, log*P*. In addition to the aforementioned experimental evaluation, log*P* can be predicted using a theoretical group contribution approach first introduced by Rekker and Mannhold,[28,65,66] which they termed the fragmental method (Eq 3, Table 1). Detailed methods for theoretical calculation of log*P* can be found in review articles by Leo[67] and Lipinski et al.[26] Successful applications of Rekker and Mannhold's equation for the theoretical calculation of log*P* have been reported for various drugs[65] and other small molecules.[68] Alternatively, log*P* can be predicted by summing the single-atom contributions.[69] Calculation of log*P* using an atom contribution method is demonstrated in Table 2.

The value of log*P* is also related to hydrophobicity, a phenomenon that drives the association of nonpolar groups or molecules in an aqueous environment. The tendency of water to exclude nonpolar molecules[64] arises because nonpolar groups cannot take part in hydrogen bonding with water. Although most hydrophobic compounds are also lipophilic, there are compounds such as fluorocarbons that are both hydrophobic (for the aforementioned reasons) and lipophobic, because they cannot take part in the strong dispersion forces among hydrocarbons.[70] The weak dispersion forces associated with fluorocarbons are attributed to the high electronegativity of fluorine, which reduces the polarizability of the atom.[70] Nevertheless, major components of hydrophobicity and lipophilicity remain intertwined, and the terms are often used interchangeably.

Table 1
Theoretical methods used for the calculation of physicochemical properties of compounds

Theoretical relations	Component symbols	Refs
Solubility parameter	δ_{HIL}, Hildebrand solubility parameter E_{coh}, cohesive energy V, total volume CED, cohesive energy density	31,48
$^{\delta}HIL = \sqrt{\frac{E_{coh}}{V}} = \sqrt{CED}$ (1a)		
$^{\delta}HAN = \sqrt{\left(\delta_d^2 + \delta_p^2 + \delta_h^2\right)}$ (1b)	δ_{HAN}, Hansen solubility parameter δ_d, partial dispersion component δ_p, partial dipole-dipole component δ_h, partial hydrogen-bonding component R_o, radius of interaction sphere in Hansen space 1 or 2 – (subscript) indicates compound 1 or 2, respectively	49
$4(\delta_{d1}-\delta_{d2})^2 + (\delta_{p1}-\delta_{p2})^2 + (\delta_{h1}-\delta_{h2})^2 \le R_o^2$ (1c)		
$\delta = \sqrt{\frac{E_{coh}}{V}} = \sqrt{\frac{(E_{vac} - E_{bulk})C}{V}} = \sqrt{CED}$ (1d)	δ, solubility parameter E_{coh}, cohesive energy E_{vac}, energy of molecule in vacuum state E_{bulk}, energy of molecule in amorphous state V, total volume C, unit conversion factor CED, cohesive energy density	31
Flory-Huggins interaction parameter	χ_{FH}, Flory-Huggins interaction parameter ΔH_{mix}, enthalpy change upon creation of a binary mixture k, Boltzmann constant. T, absolute temperature N_1, number of molecules of solvent ϕ_2, volume fraction of polymer	55
$\chi_{FH} = \frac{\Delta H_{mix}}{kTN_1\phi_2}$ (2a)		
$\chi_{FH} = \frac{V_{ref}(\phi_1 CED_1 + \phi_2 CED_2 - CED_{12})}{RT}$ (2b)	χ_{FH} – Flory-Huggins interaction parameter V_{ref} – molar volume of the smaller molecule in the binary mixture ϕ_i – volume fraction of compound i in the binary mixture CED – cohesive energy density 1 or 2 – (subscript) indicates compound 1 or 2, respectively	58,59
$\chi_{FH} \approx \frac{VA_{12}}{RT} + \beta$ (2c) $A_{12} = (\delta_1 - \delta_2)^2$ or $A_{12} = (\delta_{d1} - \delta_{d2})^2 + 0.25(\delta_{p1} - \delta_{p2})^2 + 0.25(\delta_{h1} - \delta_{h2})^2$ $\beta = 0$ or 0.34 when Hansen and Hildebrand solubility parameters are used, respectively	χ_{FH} – Flory-Huggins interaction parameter V – the molar volume of the solute R – gas constant T – absolute temperature δ_i – Hildebrand solubility parameter of compound i δ_d – partial dispersion component (Hansen) δ_p – partial dipole-dipole component (Hansen) δ_h – partial hydrogen-bonding component (Hansen) β – correction to the Flory combinatorial entropy 1 or 2 – (subscript) indicates compound 1 or 2, respectively	31,49, 55
Enthalpy	ΔH_{mix}, enthalpy change upon creation of a binary mixture χ_{FH}, Flory-Huggins interaction parameter R, gas constant T, absolute temperature ϕ_1, volume fraction of component i n_1, mole fraction of component i H_1, enthalpy of component i at pure-state H_{12}, enthalpy of mixture of component 1 and 2 1 or 2 – (subscript) indicates compound 1 or 2, respectively	53, 55-57
$\Delta H_{mix} = \chi_{FH} RT\phi_1\phi_2$ $\Delta H_{mix} = H_{12} - n_1H_1 - n_2H_2$ (2d)		
Lipophilicity	P, partition coefficient n, functional groups of the molecule f_i, hydrophobic fragmental constant a_i, incidence of functional group Cm, the Correction factor (CM = 0.219) K_i, the frequency of Cm	28,65,66
$\log P = \sum_{i=1}^{n} a_i \cdot f_i + \sum_{i=1}^{M} k_i \cdot C_m$ (3)		
Radius Flory's theory:	R_g, radius of gyration of linear polymer R, end-to-end distance a, bond length of monomer N, degree of polymerization of polymer α, swelling exponent	55,79
$R_g = \frac{R}{\sqrt{6}}$, $where: R \approx aN^{\alpha}$ (4)		

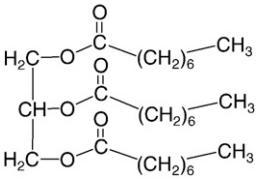
Table 2
(A) Hildebrand and Hansen solubility parameters[53] of tricaprylin and **(B)** log*P* calculation for tricaprylin with an atom contribution method[69]

(A) Calculation of Hildebrand and Hansen solubility parameters

$^{\delta}HIL = \sqrt{\frac{\sum E_{coh}}{V}}$

$^{\delta}HAN = \sqrt{\left(\delta_d^2 + \delta_p^2 + \delta_h^2\right)}$

where $\delta_d = \frac{\sum F_d^2}{V}, \delta_p = \sqrt{\frac{\sum F_{pi}^2}{V}}, \delta_h = \sqrt{\frac{\sum E_h}{V}}$



Fragments	Frequency	V (cm^3 mol^{-1})	Hansen solubility parameter[53]			Hildebrand solubility parameter[53]
			F_d ($J^{1/2}$ $cm^{3/2}$ mol^{-1})	F_{pi} ($J^{1/2}$ $cm^{3/2}$ mol^{-1})	E_h (J mol^{-1})	E_{coh} (J mol^{-1})
CH_3	3	100.5	1260	0	0	14,130
CH_2	20	322	5400	0	0	98,800
CH	1	−1.0	80	0	0	3430
COO	3	54.0	1170	720,300	21,000	54,000
			δ_p = 16.6351	δ_p = 1.78487	δ_h = 6.646	δ_{HIL} = 18.928 ($J^{1/2}$ $cm^{3/2}$ mol^{-1})
				δ_{HAN} = 18.002 ($J^{1/2}$ $cm^{3/2}$ mol^{-1})		

(B) Calculation of log*P* using atom contribution method

$log\ P = \sum_i^n n_i a_n$ Where n_i is number of atoms of type *i*, and a_i is contribution of an atom of type *i*.

Type	Description*	Frequency	Hydrophobic contribution†
1	C in CH_3-R	3	−1.8111
2	C in CH_2-R_2	18	−7.731
40	C in COO (R-C(= X)-X	3	0.0834
6	C in R-CH_2-X	2	−1.6376
8	C in R_2-CH-X	1	−0.5995
46	H attached to C_{sp3}^0, having no × attached to next C‡	39	16.5126
47	H attached to C_{sp3}^1	5	1.805
51	H attached to α-C‖	6	1.1214
58	O in = O	3	−0.7419
60	O in Al-O-Ar, Ar_2O, R…O…R, R-O-C = X	3	0.5814
			log*P* = 7.5827

* R represents any group linked through carbon; X represents any heteroatom (O, N, S, P, Se, and halogens); Al and Ar represent aliphatic and aromatic groups, respectively; = represents double bond; represents triple bond; … represents aromatic single bonds.
† Atomic hydrophobicity in the unit of $\log P_{o/w}$.
‡ Subscripts represent hybridization, and superscripts represent formal oxidation numbers. The formal oxidation number of a carbon atom = sum of formal bond orders with electronegative atoms.
‖ An α-C can be defined as a C attached through a single bond with -C = X.

Theoretical calculations of log*P* are valuable for rapid prediction of lipophilicity. The fragmental[65,66] or atom contribution[69] approaches, however, may produce inaccurate log*P* values, because they do not consider the conformation of the compound.[67] Further, the polarity of a compound is not additive.[67] Nevertheless, theoretical calculations of log*P* may be used for rapid screening before time-consuming and expensive experimental studies. Lipophilicity and hydrophobicity can also be used to predict drug retention in a formulation[22] or drug permeability through a membrane.[26]

Architectural and conformational contributions to drug-material compatibility

The efficient and stable encapsulation of hydrophobic compounds into nanoparticles is governed not only by the solubilities of drugs and materials[22,38,42] but also by other physical properties. These properties include rigidity, conformation, and the MW of the drug and the materials.[34] As an alternative to analytical methods, molecular simulations provide ensemble representations of biomaterials from which one can extract properties such as size, conformation,[20] and the interfacial structure of drug-material or material-material pairs.[45,71] Molecular simulation can reveal the fundamental interactions governing drug-polymer assembly, elucidating the physical and chemical features that can be modified to influence drug loading or release.[35,38,43]

Interestingly, Hildebrand SPs can be evaluated from simulation (Eq 1d, Table 1).[21,25,31] To our knowledge, the Hansen SP has not been calculated from molecular simulations. A unique aspect of molecular simulation is that it can explicitly evaluate the conformations of the components, both individually and as

a binary mixture. It is, then, not surprising that SPs based on simulations have been more accurate than those obtained analytically.[21] A simulation study has shown that the relative solubilities predicted from MD simulations of docetaxel, an anticancer drug, in various excipients (triglycerides, vitamin E, and β-caryophyllene) were in good agreement with experimentally determined values.[21] In that study, the intermolecular interactions between drug and excipient were taken into account explicitly for the calculation of χ_{FH} based on the energy of mixing obtained from simulation as shown in Eq 2c (Table 1). The deviations of the predicted and experimental solubilities of docetaxel in good excipients (various triglycerides and vitamin E) were between 2% and 15%. Although the simulation method was unable to accurately predict the solubility of docetaxel in the poor excipient β-caryophyllene, where the prediction was quantitatively incorrect, the rank order of all solubility predictions was correct. The inaccuracy of the predicted solubility of docetaxel in β-caryophyllene in this study is probably due to the assumption that the mixing ratio of the drug and excipient at $\chi_{FH} = 0.5$ can be converted to the maximum solubility for the solute.[21] Nevertheless, the ability to rank-order candidate materials is sufficient for library enrichment. Interestingly, the disparity between the SP values obtained from simulation and group contribution methods increases with MW, indicating that the dependence of solubility on conformation and molecular orientation increases with size.[21]

Recently, Pajula et al used MC simulations to predict the χ_{FH} values for binary mixtures of 34 small drug molecules.[72] Temperature-dependent χ_{FH} values were generated based on potential energies calculated from many configurations of interacting drug pairs. Drug pairs were predicted to be miscible and immiscible for negative and positive χ_{FH} values, respectively. Predictions for 27 drug pairs were validated by hot-stage polarized light microscopy, assuming that a binary mixture is thermodynamically miscible when it does not crystallize following heat-cool treatment.[72] The immiscible predictions were correct for all 16 selected pairs where 13 of these pairs are strongly predicted to be immiscible ($4.5 < \chi_{FH} < 26.6$) and 3 pairs are weakly predicted to be immiscible (χ_{FH} of 0.1 and 0.6). The predictions of miscibility were correct in only 8 of 11 selected pairs, where the 8 experimentally miscible drug pairs have a predicted $-6.5 < \chi_{FH} < -0.4$ and the 3 experimentally immiscible drug pairs incorrectly predicted as miscible had χ_{FH} values of −0.2, −0.4, and −2.2. Therefore, although this method is imperfect, it remains an excellent method to accelerate material development.

Generally, a realistic representation of drug delivery systems based on polymer micelles is composed of millions of atoms, including explicit solvent, and atomistic simulations may not be feasible because of a lack of computer resources.

To overcome computational limitations, molecular simulations have been applied to single-chain block co-polymers or low-MW oligomeric unimers for the prediction of drug-polymer compatibility. To this end, Patel et al reported an in silico method for predicting the compatibility of poorly water-soluble drugs and poly(ethylene oxide)-*b*-PCL (PEO-*b*-PCL) by means of the χ_{FH} parameters of drug-polymer pairs.[25] Patel et al calculated concentration-dependent χ_{FH} values from enthalpies of mixing derived from MD simulations using Eq 2d (Table 1).[53,55-57] To circumvent limitations on the achievable simulation time scales, the authors reduced computational expense by using, in place of PEO-*b*-PCL micelles, a simulation system containing a drug and a single unimer of PEO-*b*-PCL that was allowed to interact with itself over periodic boundary conditions. These studies revealed the interactions of binary mixtures of a unimeric diblock co-polymer chain of PEO-*b*-PCL with various concentrations of cucurbitacin B and I, which are hydrophobic drugs with multiple hydrogen acceptor and donor groups.[25] At low drug concentration (≤40% wt/wt drug/polymer), the simulation results agreed well with the experimental solubilities of cucurbitacin in diblock co-polymer PEO-*b*-PCL micelles.[25,73] Generally, the influence of the MW of PEO and PCL on the compatibility of drugs and PEO-*b*-PCL depends on the tendency of a drug to associate with PEO and/or PCL blocks.[25] The enhanced compatibility of cucurbitacin drugs were attributed to an increase in the number of hydrogen bonds and polar interactions between the drugs and PCL when the ratio of PCL/PEO was increased from 0.5 to 2.[25]

Using a similar simulation-based method, Patel et al also predicted that hydrophobic drugs that contain only hydrogen acceptor groups, such as fenofibrate and nimodipine, engage better in hydrogen bonding with linear PEO-*b*-PCL than with the branched co-polymer PEO-*b*-3PCL.[41] In contrast, cucurbitacin drugs were predicted to be more compatible with branched PEO-*b*-3PCL than with linear PEO-*b*-PCL.[41] Based on these findings, Patel et al proposed that the increase in compatibility between cucurbitacins and PEO-*b*-3PCL was due to the increase in hydrogen bonding between the drug and branched PEO-*b*-3PCL,[41] although the experimental solubilities of the investigated drugs in the PEO-*b*-3PCL are not available for validation.

Overall, these studies suggest that the compatibility between drugs and core-forming materials can be enhanced by modification of the MW, the architecture, or the hydrogen-bonding capabilities of the delivery material. The discrepancy between experimental data and predictions from the aforementioned molecular simulation studies are probably due, in part, to the absence of water and the simplification of polymer and drug components in the simulation systems. As well, the absence of evaluations of convergence in many simulation studies further complicates the resolution of such discrepancies. The primary drawback to molecular simulation is the large computational cost associated with atomistic simulations in explicit solvent. It is thus not possible to evaluate thousands of drug-material pairs by molecular simulation. However, the method remains an excellent tool for the evaluation of candidate pairs that have been prescreened by analytical models or the discerning eye of a pharmaceutical scientist.

Covalent linkage of formulation-like moieties to drugs

Drug loading and retention can be significantly improved by increasing the compatibility between the drug and the delivery material.[15,30,74] The retention of hydrophobic compounds in the core of nanoparticles is in part governed by the partition coefficient of the hydrophobic molecule between the core and the aqueous environment.[22] There are many ways to improve

drug-material compatibility, but one of the simplest and potentially least costly is to chemically conjugate a formulation-like moiety to the drug, thus generating a prodrug with enhanced delivery material compatibility (Figure 2).[22,42] To increase efficiency, computational methods have been used to direct this type of drug modification.[22,42]

Forrest et al used SPs to predict the loading of lipophilic prodrugs of geldanamycin in polymeric micelles composed of PEG-*b*-PCL. Geldanamycin is an anticancer agent that, unmodified, is insoluble in the core of PEG-*b*-PCL micelles.[42] Geldanamycin and PCL have Hansen SPs of 23.1 and 20.2, respectively. A χ_{FH} value of 1.33, calculated from Hansen SPs, was obtained for the geldanamycin-PCL pair by using Eq 2c (Table 1). The conjugation of a fatty acid to geldanamycin resulted in geldanamycin prodrugs with Hansen SPs between 20.4 and 21.6, and χ_{FH} values for the prodrug-PCL pairs that improved to 0.02 and 0.24 (Figure 2). The accuracy of these theoretical predictions varied depending on the hydrocarbon chain length of the conjugated fatty acids. Specifically, unexpectedly low drug loading was obtained when encapsulating C6 acyl conjugates in PEG-*b*-PCL micelles. Nevertheless, successful encapsulation of C12 and C16 acyl conjugates in PEG-*b*-PCL micelles were reported with experimental loading capacities up to 50-fold higher than unmodified geldanamycin.[42]

Applying similar ideas to a nanoemulsion formulation, a combination of analytically predicted SP and log*P* values were used to rationally design a prodrug of the hydrophobic anticancer agent docetaxel.[22] Theoretical results suggested that conjugation of fatty acids with chain lengths similar to the core-forming materials of a triglyceride-based oil emulsion would increase the lipophilicity of the drug, thus decreasing the difference in the SP values of the drug and the material, and enhancing the compatibility of the drug-material pair. Experimentally, conjugation of dodecyl fatty acid to docetaxel was found to increase the solubility of the drug in triglyceride by 8-fold and its loading efficiency in the nanoemulsion by 10-fold.[22] Further, theoretical and experimental log*P* values indicated that conjugates with multiple conjugated fatty acids were even more lipophilic. Nevertheless, only the monosubstituted prodrug was hydrolyzed under biologically relevant conditions to yield an activity similar to that of the parent drug.[22]

In summary, group contribution methods that compute SPs and predict the log*P* of drugs and drug derivatives appear to be excellent approaches for the selection of formulation-like moieties for chemical conjugation to drugs. These parameters provide relatively accurate physicochemical predictions for compounds with similar chemical structures. Nevertheless, kinetic properties, such as hydrolysis to release the prodrug, must still be evaluated experimentally.

Predicting drug loading and retention

Controlling drug release is one of the key requirements of a successful drug formulation. Premature drug release from the formulation may lead to systemic side effects due to the distribution of drug to nontarget tissues and inefficient drug accumulation at the target site.[9,75]

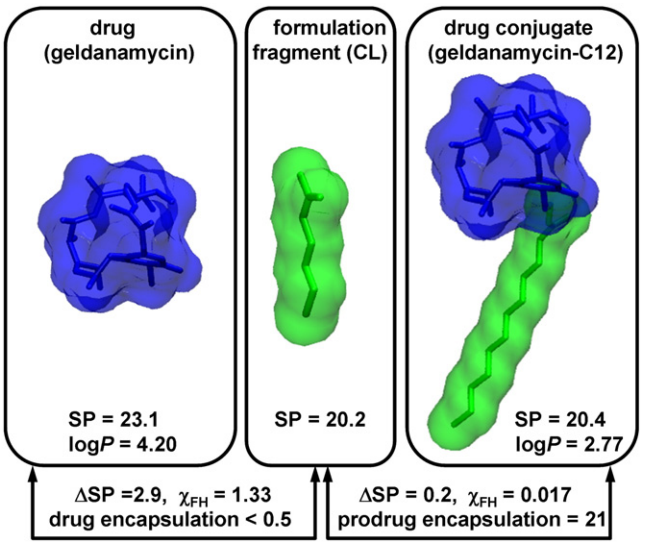


Figure 2. Schematic representation of the difference in solubility parameters (ΔSP) and Flory-Huggins interaction parameters (χ_{FH}) before and after conjugating a formulation-like moiety (C12 acyl chain) to the lipophilic drug geldanamycin. The core-forming material of polymeric micelles is represented by caprolactone (CL). The drug encapsulation was calculated based on the ratio of drug to poly(ethylene-glycol)-*b*-poly(ε-caprolactone) micelles (wt/wt %). Data obtained from Forrest et al.[42]

Recently, Costache et al used docking techniques to determine an ensemble of poses of drugs interacting with core-forming polymers of nanospheres and predicted the interaction energy of hydrophobic drugs and tyrosine-derived oligomers.[35] Before docking calculations, the aggregation state of the hydrophobic oligomer was equilibrated by performing MD simulations on hydrated single and multiple chains of ABA triblock co-polymers followed by the removal of the PEG blocks.[35] Here, A is PEG and B is oligo(desaminotyrosyl-tyrosine octyl ester suberate). In this study, Costache et al reported a correlation between the experimental maximum drug loading in the triblock co-polymer nanospheres and the theoretically calculated polymer-drug binding energies, where the model drugs were curcumin, paclitaxel, and vitamin D_3. Consistent with other theoretical studies,[38,41] the binding affinities of hydrophobic drugs to the core-forming polymers were proportional to the number of hydrogen bonds, the number of aromatic interactions between the drug-polymer pairs, and the hydrophobicity of the drug. Other features such as size and flexibility also influence binding affinities and location of the drug within the delivery system. In particular, highly hydrophobic (predicted log*P* = 7.9) and flexible vitamin D_3 was predicted to penetrate into the hydrophobic core of the nanosphere delivery system and have the most favorable docking energy, *D* (*D* = −10.3 kcal/mol).[35] This finding agreed well with experiment, where vitamin D_3 has the highest drug loading in the nanosphere. The less flexible and less hydrophobic curcumin (predicted log*P* = 3.6) was similarly found to penetrate into the hydrophobic core of the nanosphere. The predicted docking energy of curcumin (*D* = −7.2 kcal/mol) to the nanosphere was less favorable than vitamin D_3 and, experimentally, curcumin loaded less into the nanosphere than did vitamin D_3. Finally, the

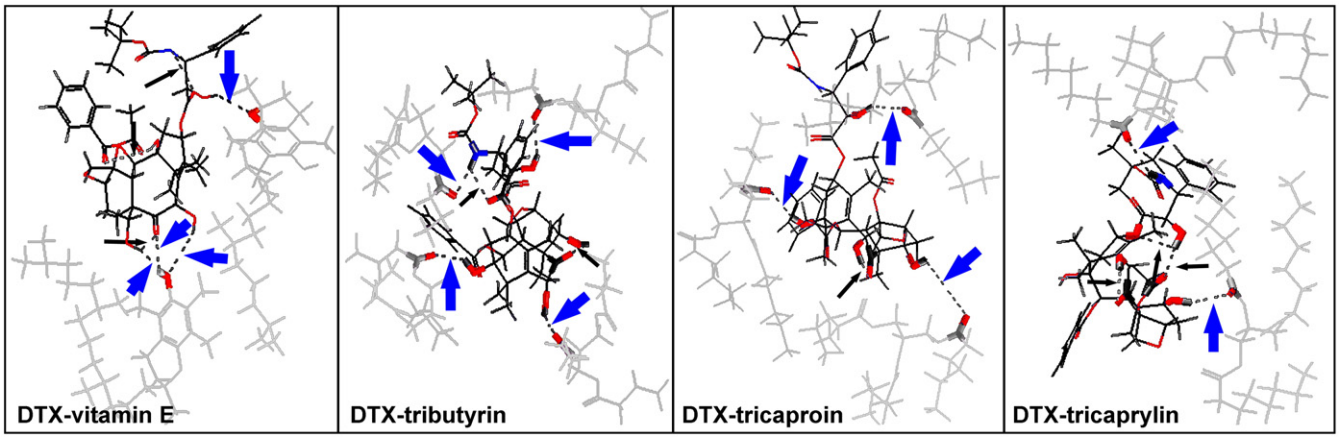


Figure 3. Hydrogen bonding between docetaxel (DTX) and small-molecule excipients from MD simulations of a DTX-excipient binary mixture. The excipient is represented in gray lines and DTX is represented in multicolored lines (carbon and hydrogen in black, oxygen in red, and nitrogen in blue). Lines are thickened to emphasize functional groups involved in hydrogen bonds. The intra- and intermolecular hydrogen bonds are indicated by thin black and thick blue arrows, respectively. Explicit solvent and excipients that do not form hydrogen bonds with DTX are omitted for clarity. Data obtained from Huynh et al.[21]

more bulky and rigid paclitaxel (predicted log$P$ = 3.2) was predicted to preferentially interact with the surface of the hydrophobic core of the nanospheres and have an even less favorable docking energy (D = −4.4 kcal/mol). In agreement with molecular simulation, paclitaxel was found to have the lowest experimental drug loading in the nanospheres.[35]

Current research suggests that hydrogen bonding enhances drug loading and slows drug release,[35,41] although rank-ordering can be complicated by the influence of other factors, such as lipophilicity.[22] In this context, Sutton et al demonstrated that a single molecule of doxorubicin forms five to six hydrogen bonds with a hydrophobic aggregate of PCL and three to four hydrogen bonds with a hydrophobic aggregate of PLA, although water molecules were not present in this simulation.[38] The authors proposed that the increased number of hydrogen bonds formed by doxorubicin in PEG-*b*-PCL micelles is responsible for the slower drug release in this system as compared to PEG-*b*-PLA micelles.[38]

Similarly, the MD simulation of docetaxel molecules solvated by pharmaceutical excipients revealed that the experimental solubility of docetaxel in small-molecule excipients, such as triglycerides and vitamin E, increases with an increasing number of predicted hydrogen bonds between the drug and the excipients, as shown in Figure 3.[21] However, the experimental numbers of hydrogen bonds between the drug and excipients are not available for validation. Nevertheless, better experimental drug retention was observed with a highly hydrophobic excipient that formed fewer hydrogen bonds with docetaxel.[76] Similar observations were also reported based on a combination of MD simulation and molecular docking.[35] Indeed, the lipophilicity of materials has, in some cases, contributed to drug loading and retention to a greater extent than hydrogen-bonding capability,[21,35] and the number of hydrogen bonds between the drug and excipient does not always correlate with the rate of drug release,[21,75,77] especially at high drug loading where drug aggregation may occur within the formulation.[38]

Generally, analytical models can be applied to the rapid prediction of physicochemical properties that can be used to assist formulation development. Analytical models for SP and log$P$ are more accurate when predicting compatibilities for chemically similar materials, making these methods well suited to rank-order chemical libraries during selection of a formulation-like moiety for drug conjugation. Hansen SPs outperform Hildebrand SPs for molecules that form hydrogen bonds, and FH theory is more accurate for concentration-dependent interactions. Overall, analytical models excel in the early elimination of material possibilities during library enrichment. These simple models are sometimes inaccurate, however, especially when assessing the compatibility of materials with divergent chemical properties. Thus, once analytical models have been used to significantly reduce the number of materials to be evaluated, molecular simulations can be used to obtain further insight at greater computational expense. Given the large number of physicochemical properties that are thought to influence drug-material compatibility, the proper weighting of these many competing factors is one of the great challenges to theoretical methods. In this pursuit there is a strong need for systematic methodological evaluations and comparisons, which are currently lacking in the literature.

Optimizing materials

Numerous theoretical models have been developed to predict the conformation and size of polymers in various media.[55,78-82] There is thus a wealth of theoretical insight into the aggregated structures of formulation materials.[20,35,39,44,83] Within this domain, the application of analytical models is generally limited to the study of biomolecules with simple structures, whereas molecular simulations have been conducted for more complex systems, where they are capable of revealing important nanoparticle properties and their substructures (Figure 4).

Linear polymers

In the 1950s, Flory[55] put forth the random-flight model for free linear polymers, in which polymer size depends on both polymer length and solvent suitability. This model was derived

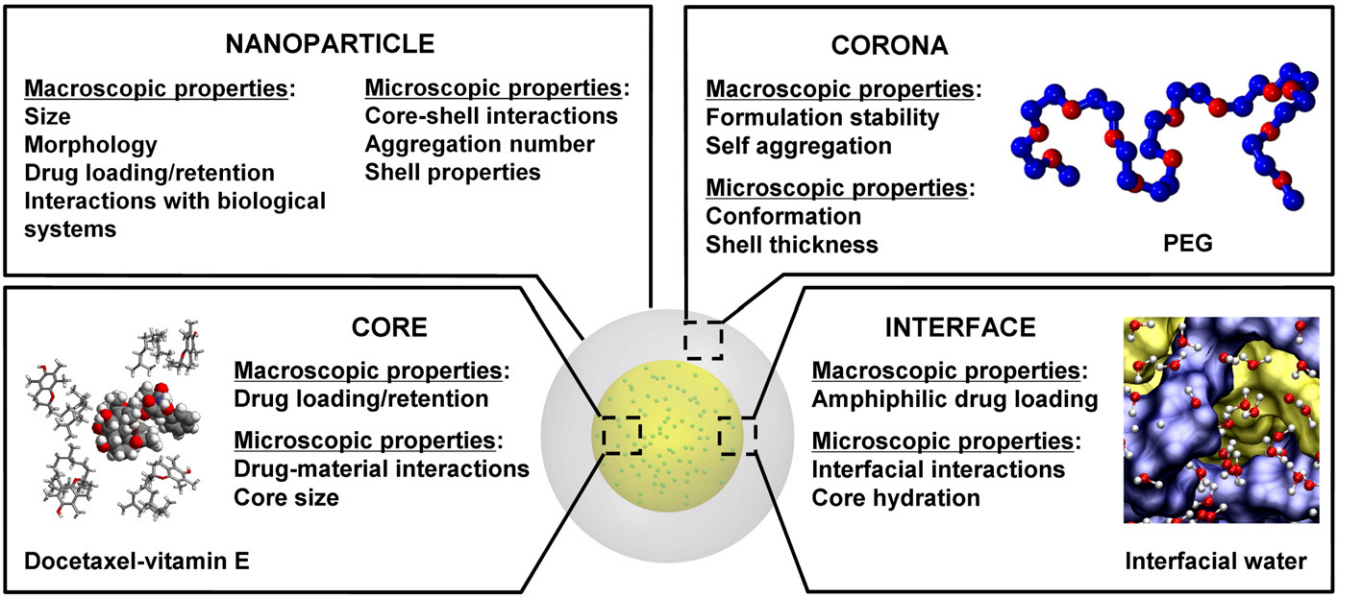


Figure 4. Performance-related properties of nanoparticles revealed by molecular simulation.

from Debye theory[78] and predicts the radius of gyration, $R_g = R/\sqrt{6}$, where R is the root-mean-squared end-to-end distance of the polymer. Here, R scales with the effective bond length of the monomer, a, and the degree of polymerization of the polymer, N, according to a power law such that $R \approx aN^{\alpha}$, where α is the swelling exponent (Eq 4, Table 1).[55,79] In a good solvent, R is known as the Flory radius, R_F, and α is equal to 0.588.[55] In a mediocre solvent (theta solvent), the polymer behaves ideally and exists as a Gaussian coil with an α value of 0.5. In a poor solvent, the polymer collapses and has an α value of 1/3.[84] Although such simplifications are useful, they are also imperfect. When α values are back-calculated from experimental measures of size, the α values of polymers in good solvents depend somewhat on the polymer composition and MW. For example, gel permeation chromatography and size exclusion techniques provide an α value of 0.571 for aqueous solutions of linear PEO with a MW of 25 kDa to 120 kDa.[85] From the same study, α values of 0.523 were obtained for linear PEG with a MW of 0.2 kDa to 7.5 kDa.[85] Similarly, Lee et al reported an α value of 0.57 for 1.63 kDa < MW_{PEO} < 7.0 kDa,[37] based on a simulation study of a series of hydrated PEO polymers with various degrees of polymerization using a coarse-grained (CG) hydrodynamic bead model.[37] In a separate CG and all-atom MD simulation study, the conformation of PEO was described as an ideal chain with $\alpha = 0.515$ for 0.44 kDa < MW_{PEO} < 1.63 kDa.[39] Here, MD simulation outperformed the hydrodynamic bead model as a tool for predicting the size of PEO molecules, yielding hydrodynamic radii and diffusion constants of PEO in better agreement with experimental results, which were obtained from three different size exclusion chromatography techniques.[39,85]

Whereas Flory's random-flight model is limited to polymers free in solution, the conformation of polymers attached to a planar surface can be predicted by de Gennes theory.[80,81] According to this theory, grafted polymers adopt so-called mushroom and brush regimes in a good solvent at low and high grafting density, respectively. In the mushroom regime, named for the predicted mushroomlike shape of each polymer, the grafted polymers are separated by a distance $D > R_F$ and occupy a "half-sphere with a radius comparable to R_F of a Gaussian coil."[80,81] In the brush regime, named for the predicted bristlelike appearance of the polymers extending outward from the surface, $D < R_F$ and the grafted polymers adopt a more extended configuration as they horizontally occlude one another.[81] Daoud and Cotton theory extends de Gennes theory to star-shaped polymer models.[86] This theory predicts that the radius of a star-shaped polymer is smaller than that of a linear polymer of the same MW.[86] Significantly, a similar prediction was obtained by molecular simulation studies of amphiphilic PEG-*b*-PCL star-shaped co-polymers in water.[20] This prediction was confirmed by size exclusion chromatography and by static and dynamic light scattering measurements of free linear PEG blocks in water.[85,87]

Even though the theories of de Gennes, and Daoud and Cotton are most often applied to curved surfaces, these theoretical models exclude the influence of the radius of the sphere–an inauspicious assumption given that deviation from planarity significantly influences the conformation of the outer layers of a core-shell nanoparticle.[82] Surface curvature may influence the adsorption of hydrophilic polymers on hydrophobic surfaces.[20] Indeed, the conformations of polymers grafted to a curved surface are theoretically predicted to depend not only on the chain length of the polymer but also on the radius of curvature of the surface.[82] Specifically, when the ratio of the radius of curvature to the thickness of the grafted polymer layer is much less than one, the R_g of grafted polymers grows as a function of the degree of polymerization

of the polymer with α equal to 3/5.[82] Clearly there is a need for extensions of available theoretical methods to explicitly account for surface curvature.

Nanoemulsions

For a nanoemulsion formulation to include stable particles of a desired size, the interactions between the core- and shell-forming materials often require optimization.[88] This can be done experimentally by selecting compatible components and determining the appropriate mixing ratio,[75,77] although this approach is very time-consuming. Current theoretical efforts are directed at understanding how nanoemulsions integrate components at the atomistic level, thus collecting information that will be useful for future rational design.

To this end, oil-in-water nanoemulsions were recently simulated by Lee et al.[45] and, separately, by Henneré et al.[71] In these studies the nanoemulsion systems were represented by a planar model, which is layered as water, phospholipid, oil, phospholipid, water.[45] The oil phase was composed of trilinoleylglycerol,[71] or perfluorooctylbromide (PFOB),[45] and the phospholipid was palmitoyloleoylphosphatidylcholine (POPC).[45,71] In these simulations, the head group of POPC was fully hydrated, and the hydrocarbon tails of POPC interacted favorably with the hydrophobic triglyceride tails, as expected.[71,89] In contrast to triglycerides, perfluorocarbons are lipophobic[70] and are expected to be immiscible with POPC. However, an experimental study by Yokoyama et al showed that the miscibility of perfluorocarbons with hydrocarbons increases when the chain length of the perfluorocarbons are significantly shorter than that of the hydrocarbons.[90] This PFOB/POPC nanoemulsion model was used to investigate the quenching mechanism of melittin tryptophan. In agreement with experiment, the tryptophan side chain of melittin was located within the POPC layer. Further, based on the radial distribution of the bromine atoms of PFOB around trytophan residues, the bromine was very close to direct contact with the trytophan. These results are consistent with the known quenching mechanism of tryptophan,[91] which is due to the collision of the tryptophan with bromine.[45] Overall, this study demonstrated that atomistic simulations can reproduce the interactions and the quenching mechanism of tryptophan within the PFOB/POPC nanoemulsion system at the molecular level.

To further quantitatively determine the importance of constituent interactions, efficient generalized-ensemble simulation algorithms can be used to construct the free-energy profiles that govern these interactions.[92]

Micelles formed from linear block copolymers

Linear, amphiphilic diblock and triblock co-polymers have emerged as the materials of choice for use in a wide range of biomedical applications, including fabrication or coating of biomedical devices, drug delivery, and tissue engineering.[93-96] Polymeric micelles comprise a hydrophobic core, which can load and store drugs as cargo, and a hydrophilic shell, which surrounds and solubilizes the hydrophobic core and hinders interactions with components of the host mononuclear phagocytic system.[9,13] Molecular simulations have been employed to investigate the structure, dynamics, and self-aggregation properties of polymeric micelles, with or without drugs.[40,44,97]

Kuramochi et al used all-atom MD simulations to study the structure of a spherical micelle composed of 20 chains of the linear diblock co-polymer PEG_{11}-*b*-poly(γ-benzyl L-glutamate)$_9$ (PEG_{11}-*b*-$PBLG_9$) in explicit water.[40] In addition, Huang et al investigated glycyrrhetinic acid-modified PEG-*b*-PBLG micelles as drug carriers for doxorubicin.[98] According to Kuramochi et al, a slightly elliptical micelle structure is formed after 7 nsec of simulation, with a hydrophobic PBLG inner core and a hydrophilic outer PEG shell. The core-forming polymer, PBLG, is hydrophobic[40] as a result of its benzyl group side chains. Nevertheless, it has a backbone made of hydrophilic esters and amide groups, and is capable of forming hydrogen bonds with water. In agreement with nuclear magnetic resonance (NMR) and other MD studies of free linear PEG, the PEG blocks of the micelle presented in this study were highly hydrated and adopted a helical conformation. Further, this study revealed that the benzyl groups, which contribute significantly to hydrophobic interactions, were preferentially located near the center of the hydrophobic core. Based on the radial density distribution, some water molecules dynamically penetrated into the hydrophobic PBLG core and formed a hydrogen-bonded network with the ester and amide groups in the backbone of the hydrophobic core. Importantly, the transient presence of water molecules within the hydrophobic core is unlikely to have been predicted by an analytical group contribution method. Structurally, the PBLG chain adopted an α-helix conformation that was stabilized by six to eight hydrogen bonds within a PBLG block. Overall, the micelle was stabilized by multiple hydrogen bonds between water and the PEG blocks, and hydrophobic interactions within the PBLG core.[40]

In another study, Mathias et al used a combination of NMR and MD simulation to investigate the location of an electron spin-labeled hydrophobic drug, chlorambucil-tempol adduct, in fluoroalkyl-linker and fluoroalkyl-linker-PEG micelles,[44] in which the fluoroalkyl hydrophobic segment, $CF_3(CF_2)_5CH_2CH_2$-, is expected to form an inner core that excludes water. To reduce computational expense during simulations, explicit water was omitted in favor of a restraining force on the CF_3 groups to assist the formation of fluoroalkyl-linker or fluoroalkyl-linker-PEG micelles. Under this restraining force, the hydrophobic fluorocarbons cluster together and form the inner core of the micelle, whereas the relatively less hydrophobic linker, isophorone diurethane, forms an interface between the inner core and the hydrophilic PEG shell.[44] In these simulations, the system included a single drug initially placed outside the micelle or in the inner fluoroalkyl core, or at the core-PEG interface, each successively with and without distance restraints based on NMR data. During unrestrained simulation, the drug was shown to migrate to the isophorone diurethane interface region of the micelle.[44] Overall, this study provides a simplified model to capture the preferred interactions and localization of a drug among a variety of distinct chemical environments within the micellar delivery system.[44] These results can be used to rationally design a new linker between the hydrophobic and hydrophilic blocks.[44]

Water molecules have a significant influence on the conformation and aggregation morphology of many delivery materials. In many cases, therefore, simulations must be conducted in the presence of explicit molecular water so as to obtain results that are comparable to experiment. The computational acceleration that is obtained via implicit water models may result in inaccurate simulation results, as reviewed elsewhere.[99]

Micelles formed from star-shaped block co-polymers

Unimolecular micelles are inherently stable to dilution and may be prepared to be monodisperse and of a smaller size than most multimolecular systems.[100,101] Star-shaped block co-polymers are an excellent material for making unimolecular micelles, provided the molecules can be engineered to avoid self-aggregation.[20,101]

Recently, MD simulations were employed to systematically evaluate 13 star-shaped block co-polymers, each having six identical arms of methoxyPEG-*b*-PCL that vary in terms of total MW and ratio of hydrophobic to hydrophilic block length, $MePEG_x$-*b*-PCL_y, where x and y are the repeated unit of the hydrophobic and hydrophilic blocks, respectively.[20] Following 200 nsec of atomistic MD simulations for each system, the radii of the hydrophobic PCL core and the PEG blocks were found to be independent of each other and predictable over a broad MW range.[20] This information can be used to rationally design star-shaped block co-polymers of a specific size. Unique to this study, a quantitative relationship related the water-accessible surface area of the hydrophobic PCL core to the MW of PCL and PEG moieties (Figure 5). Importantly, the hydration value obtained for PEG moieties agrees well with the experimental hydration value of PEG in water, indicating a valid simulation model.[20] From this study, all the star-shaped block co-polymers investigated were predicted to self-aggregate and to form multimolecular micelles in water. Significantly, dynamic and static light scattering measurements of $[PCL_{18}$-*b*-$PEG_{113}]_6$ indicated multimolecular aggregation, in agreement with theoretical predictions (F. Li and C. Allen, unpublished results). Further, star-shaped block co-polymers with a hydrophobic PCL core $\leq$2 kDa per arm are predicted to be fully protected from water when the hydrophilic PEG blocks are $\geq$14.6 kDa per arm.[20] The authors hypothesize that these new rationally designed star-shaped block co-polymers can avoid PCL-mediated aggregation and form thermodynamically stable unimolecular micelles.

Other groups are working on blending star-shaped and linear block co-polymers so as to control the morphology of micelles. For example, Xin et al used dissipative particle dynamics simulations to investigate the morphology of multicompartment micelles formed by binary mixtures of star-shaped $A_aB_bC_c$ and linear $B_bA_aC_c$ triblock co-polymers.[102] In this study, polyethylethylene, PEO, and poly(perfluoropropylene oxide) are polymers A_a, B_b, and C_c, respectively, in which a, b, and c represent the block lengths.[102] Here, the dissipative particle dynamics model reproduced the experimental morphology of diblock co-polymers (spherical micelles), star-shaped triblock co-polymers (wormlike micelles), and blends of diblock and star-shaped triblock co-polymers (hamburger-shaped micelles). Further, the morphologies of blended linear and star-shaped triblock co-polymers were systematically investigated with various blending ratios and procedures.[102] Various new morphologies were obtained, including toroidal multicompartment micelles with ring/cogwheel cores and so-called sphere-on-onion micelles. Finally, the mechanisms of formation of these morphologies were also identified.[102]

Molecular simulations are the most suitable techniques for quantitative measurement of interactions at the molecular level and for the rational design of new drug delivery materials. The influence of conformation, absent or incomplete in analytical models, is simply too important.

Dendrimers

Dendrimers are branched macromolecules in which each level of branching is classified as a generation. Generally, dendrimeric polymers developed for drug delivery have a multifunctional hydrophobic inner core that is conjugated to outer hydrophilic moieties, such as PEG. Similar to star-shaped block co-polymers, dendrimer micelles can be rationally designed to be unimeric.[103] Dendrimeric polymers are promising drug delivery materials because they possess narrow polydispersity and can be designed with many combinations of size, shape, and surface chemistry.[103]

For the past decade, poly(amidoamine)-PEG conjugates (PAMAM-PEG) have been investigated for biomedical applications.[103] Lee and Larson rationally designed stable PAMAM dendrimer-PEG conjugates using CG simulations based on the MARTINI parameterization.[23] In this study, a total of 11 dendrimers were simulated in CG water and counterions.[23] Systems included single dendrimers of generations 3 to 5 (G3 to G5) and dendrimers conjugated to 0.55-kDa or 5.0-kDa PEG blocks. The simulated R_g of dendrimer-PEG conjugates with 30, 60, and 88 arms of 5.0-kDa PEG (G3P5000-30, G4P5000-60, G5P5000-88) agreed well with the R_g values obtained from neutron scattering for dendrimer conjugates with similar MW. Next, binary aggregation was studied for G4 dendrimer-PEG conjugates with 60 arms of 0.55-kDa or 5-kDa PEG (G4P5000-60, G4P550-60). Two identical dendrimer-PEG conjugates were placed in contact and simulated for a total of 400 nsec. During these simulations, the dendrimers drifted apart. Nevertheless, the G4P5000-60 simulation box was too small to allow complete PEG disentanglement. The authors proposed that 5-kDa PEG can act as a stabilizer for the PAMAM G4 dendrimer.[23] This result contradicts the experimental study by Yang et al, which suggests that interpenetration of the PEG arms from two adjacent dendrimer conjugates may exist when the MW of PEG increases from 2 to 5 kDa.[104]

Although CG methods are unable to provide information on interactions at the atomistic level, such as hydrogen-bonding interactions, they provide excellent insight into large systems such as those investigating the aggregation of complex materials.

In summary, analytical models can provide insight into the structural properties of drug delivery materials. These models excel at rapidly predicting the gross morphology of weakly interacting molecules and, in some cases, simple self-aggregated

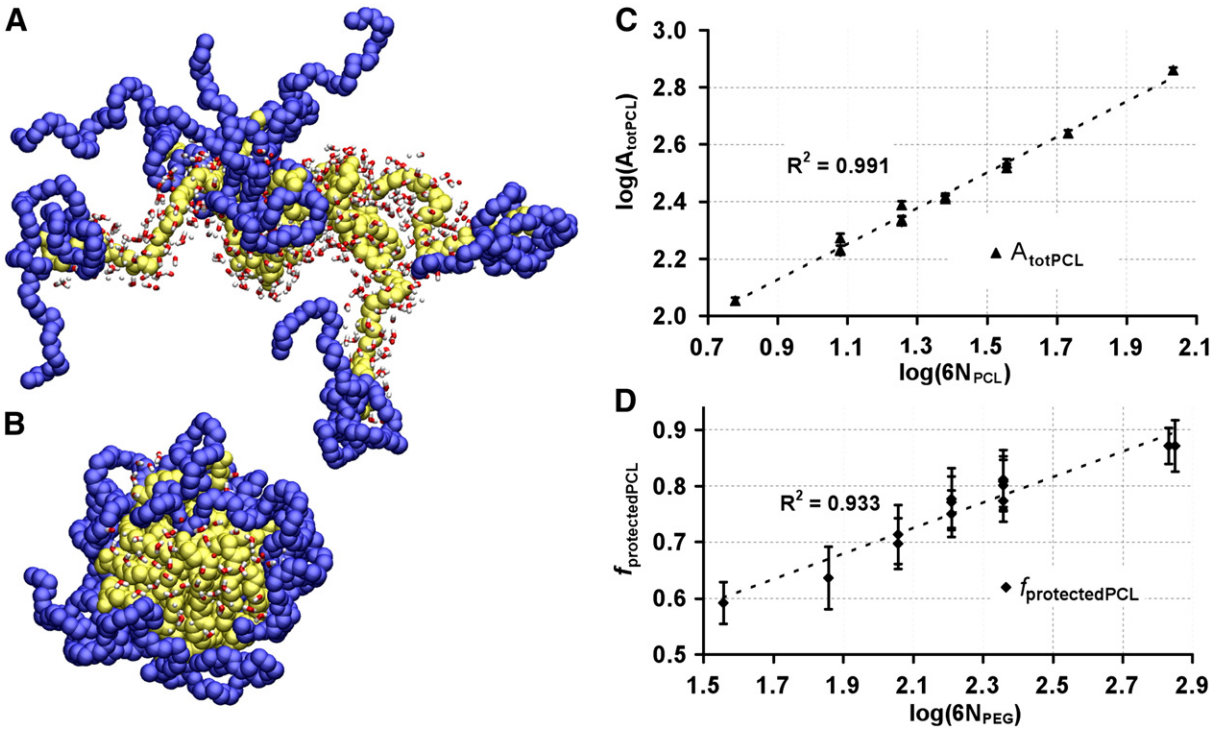


Figure 5. Snapshot of the [MePEG$_{38}$-*b*-PCL$_9$]$_6$ star-shaped block co-polymer at **(A)** 1 nsec and **(B)** 200 nsec highlighting the conformations of PCL (*yellow*) and PEG (*blue*) blocks, and water molecules within 3.5 Å of PCL. Bulk water and hydrogen atoms are omitted for clarity. Solvation properties of various star-shaped block co-polymers, obtained by calculating the number of water molecules within 3.5 Å of the polymers. **(C)** Double-logarithmic scales of total surface area of PCL core assuming zero protection by PEG versus the total number of PCL units. **(D)** Fraction of PCL at the core surface that is protected from water by PEG, $f_{\text{protectedPCL}}$, versus a logarithmic scale of the total number of PEG units. Data are evaluated from the last 160 nsec of the molecular dynamics simulations. The dashed lines are the linear fit functions. (Adapted from Huynh et al.[20] Reproduced by permission of the Royal Society of Chemistry.)

structures. In many cases, however, structures predicted from these theoretical models are inaccurate, especially in the presence of other components. In comparison, molecular simulation models can provide representations of the conformational ensemble adopted by the investigated materials while explicitly accounting for intermolecular interactions in heterogeneous mixtures. The main drawback of molecular simulation is the significant computational expense that it requires. To circumvent this limitation, many studies have attempted to predict the properties of complex formulation systems based on simulations of simplified systems, such as those using single-polymer chains, implicit water, or CG models. Unfortunately, these simplifications may reduce the accuracy of the predictions. Most importantly, each type of simplification has its own limitations that must be understood when selecting the methodology to apply to a given system. For example, CG simulations, similar to Hildebrand SPs, are not well suited to the characterization of materials that form dense networks of hydrogen bonds.

Predicting biological performance

Nanoparticle development has produced a variety of stable and efficient drug delivery systems. Their application in vivo, however, requires additional consideration of pharmacokinetics and distribution including accumulation at the target site as well as biocompatibility and toxicity. In this section we briefly highlight relationships between the physicochemical properties of nanoparticles and their biological performance both in vitro and in vivo.

Nanoparticles can be tailored to undergo enhanced cell uptake, bloodstream retention, and organ targeting based on their size and surface properties.[75,77,105] Importantly, theoretical methods are capable of predicting the behavior of these particles in biological systems. For example, the structural properties of nanoparticles have been investigated using MD simulation and related to their biological performance. These theoretical evaluations are capable of providing guidance during the rational design of drug delivery systems.

Cytotoxicity and biodistribution

The structural properties of polymers used in nanoparticle drug delivery formulations can significantly influence their cytotoxicity.[24,106-108] Metullio et al used atomistic MD simulation to predict the shape, size, R_g, and density of 18 PAMAM dendritic molecules in explicit water.[108] Because PAMAM can be toxic,[109] these properties were then compared to the cytotoxicity of various generations of dendrimers. Based on simulation analysis and experimental evaluation of cytotoxicity,[110] nontoxic dendrimers had low fractions of internal surface area and low internal volumes (from 8% to 19% of the dendrimer).[108] In contrast, cytotoxic dendrimers had much higher internal surface

areas and internal volumes (from 33% to 86% of dendrimer).[108] Radii of gyration and surface fractal dimensions (i.e., the degree of irregularity of a surface) were also related to the cytotoxicity of the dendrimers. In agreement with other findings, nontoxic dendrimers were those that had surface regularity and were densely packed with a small R_g.[108]

Numerous experimental studies have shown that the shape and size of drug delivery systems can influence the access of the drug to the target site.[111,112] In a recent study, Peng et al combined all-atom and CG simulations to systematically investigate the size and shape of a polymer-drug conjugate: a 130-mer poly-γ-glutamyl-glutamate-paclitaxel conjugate (PGG_{130}-paclitaxel).[97] In this study, various fractions of paclitaxel were conjugated to six different positions of the PGG backbone, making a total of 18 different PGG_{130}-paclitaxel conjugates. Due to limited computer resources, the MD simulations of PGG_{130}-paclitaxel conjugates were first carried out in implicit water. Following 100 nsec of MD simulation under these conditions, a CG model was used for the simulation of PGG_{130}-paclitaxel conjugates in explicit solvent for an additional 800 nsec. From an initial linear conformation at 0 nsec, 89% of PGG_{130}-paclitaxel conjugates adopted a coil shape by 900 nsec, indicating that the drug-loading fraction and the position of conjugation have only a minor influence on the conformation of the conjugates.[97] A previous study on the delivery of paclitaxel using diblock co-polymer micelles showed that wormlike and filamentous micelles exhibit prolonged circulation half-lives in comparison to spherical micelles.[111] Further, discoidal particles seem to have relatively greater tendency to accumulate at tumors in comparison to spherical particles.[112] Peng et al postulated that the PGG_{130}-paclitaxel conjugates with various coil subtypes are structurally similar to the shapes of the wormlike and filamentous micelles, and discoidal particles.[97] Therefore, they proposed that the investigated PGG_{130}-PTX conjugates may have a relatively long circulation half-life in vivo and result in significant accumulation of the drug at the tumor site.[97]

Interaction with lipid bilayers

Computational techniques have been used to investigate drugs and nanoparticles in biomimetic environments at the atomistic level.[19,113] Specifically, the application of MD simulations to study drug- or nanoparticle-membrane interactions provides significant insight into the thermodynamic and kinetic processes that govern the permeability of lipid bilayers to drugs or nanoparticles.[19,113] Such information plays an important role in the rational design of drugs and formulation materials.

Recently, gold nanoparticles (AuNPs) have been investigated for the delivery of drugs and diagnostic agents. In many cases nanoparticles must cross cell membranes so as to deliver the drug to its target site within the cell. Understanding the mechanism of AuNP uptake at the molecular level can therefore provide insight that is useful for the rational design of AuNPs for biomedical applications. In a study by Lin et al, a combination of atomistic and CG MD simulations was employed to investigate the interactions between a AuNP and a cell membrane mimetic.[113] Hydrophobic (neutral), cationic, and anionic AuNPs were simulated successively in the presence of an electronegative and of an electroneutral bilayer. AuNPs were charged by functionalizing alkyl thiol ligands with ammonium and carboxylate groups. The negatively charged bilayer contained a mixture of dipalmitoylphosphatidylcholine (DPPC) and dipalmitoylphosphatidylglycerol (DPPG) in a ratio of 3:1 (PC/PG), whereas the neutral layer contained only DPPC. Based on the free-energy profiles obtained from CG simulations, adhesion of anionic and cationic AuNPs onto the neutral DPPC bilayers was favorable.[113] Surprisingly, the anionic AuNPs showed strong affinity for the negative PC/PG bilayers. In contrast, the neutral AuNPs repelled the DPPC and PC/PG bilayers. Importantly, in agreement with the experimental data, the cationic AuNPs penetrated into the negative PC/PG bilayer with the free-energy minimum located within the bilayer, indicating that the penetration of AuNPs into the membrane is favorable.[113] Overall, Lin et al revealed that the surface charge of the AuNPs mainly contributed to the penetration of the AuNP and disruption of the membrane.[113]

From these studies it is clear that structural properties of nanoparticles, such as shape and internal structure, can influence cytotoxicity. Importantly, the shape of nanoparticles also influences pharmacokinetics and tumor accumulation. Further, the permeability of lipid bilayers to nanoparticles is theoretically predictable. Overall, atomistic and CG simulations are excellent methods for investigating nanoparticle structure, which can then be correlated to experimentally determined biological responses. Correlations between molecular or physicochemical properties and biological behavior may also be conducted with group contribution-based methods.

Conclusions and outlook

Analytical models are useful for fast prescreening during the development of delivery systems and drug derivatives. Available tools include group contribution methods for the calculation of SPs and lipophilicity, and statistical methods such as FH pairwise interactions. However, there are errors associated with the theoretical calculation of SP, log$P$, and χ_{FH}, especially when comparing compounds with different chemical properties. Nevertheless, these theoretical models are suitable for guiding early material design.

In contrast, molecular simulations produce more reliable results. Molecular simulations are more computationally expensive, however, and are thus more suitable for re-scoring materials that were highly ranked by more rapid theoretical screening methods. Molecular simulations are also capable of assessing complex molecular structures found within nanoparticles. Further, molecular simulations can be used to evaluate performance-related properties of drug delivery systems, including the size and morphology of nanoparticles.

This review discusses many publications that apply a range of theoretical and experimental methods. In many cases, however, systematic studies that evaluate and compare methodological options are unavailable. Further, very few studies test the predictive abilities of the models. As well, likely problems associated with theoretical methods include overfitting and the under-reporting of theoretical predictions that do not match experimental evaluations.

In many studies, simulation systems were simplified by removing explicit water or using an implicit water model so as to accelerate the simulation. It is however unclear if these simulations are capable of representing the correct equilibrium distribution of conformations as they would exist in aqueous solution. Here again, systematic methodological evaluations are lacking.

In comparison to atomistic models, simulations with CG models can sample much larger systems for much longer times and are excellent methods for investigating aggregation morphologies and other thermodynamic quantities that are slow to converge. However, CG models fail to capture important atomistic effects such as hydrogen-bonding interactions and may therefore require re-parameterization for each system of interest. Combinations of atomistic and CG simulation can be used for guiding the design of new delivery materials such as dendrimers and star-shaped block co-polymers. To further quantify the propensity toward aggregation, efficient generalized-ensemble simulation algorithms can be used to construct the free-energy profile governing the association of these materials.

The continuing advances in computer performance are allowing atomistic simulations of macromolecules over ever-growing time scales. Concurrently, analytical methods can be applied to larger libraries of drugs and materials. This promises a bright future for the role of theoretical methods in the development of drug delivery materials.

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