Controlled
Release

Targeted
Delivery

Solubility
Enhancement

POLYMER MICELLES FOR DRUG DELIVERY

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Introduction

Polymeric micelles obtained from the self-assembly of amphiphilic block copolymers are probably one of the most common drug delivery carriers among polymeric nanoparticles.[1–4] The rise of highly controlled polymerization techniques, especially processes such as ATRP[5] and RAFT,[6] has led to an extraordinary surge of new types of block copolymers fit for biomedical applications. Facile control over the polymer structure has also meant access to a large array of self-assembled morphologies including micelles, cylindrical micelles, and polymersomes. Micelles in particular are at the center of attention as potential drug carriers due to a core-shell structure that is highly water soluble while still maintaining a hydrophobic core suitable for hydrophobic drugs. This is crucial for many drugs since they are often rendered insoluble in water, and loading them into drug carriers can increase their solubility by several orders of magnitude.[4,7]

Choice of Block Copolymers

The choice of drug carriers can be daunting. In addition to a range of commercially available block copolymers, there is basically no limit to the design of amphiphilic structures thanks to advances in polymer design. Block copolymers can be further complemented by other amphiphilic polymers (such as miktoarm starpolymers, multiblock copolymers, and star polymers) to enable the formation of compartmentalized micelles. Whatever architecture is chosen, the primary consideration should be the compatibility between the drug and the polymers.[7] The polymer–drug interaction plays an important role in the drug-loading capacity of a carrier and the stability of the drug in the matrix, which ultimately affects the shelf-life of the carrier. The miscibility of a drug with the polymeric matrix can be described by the Flory–Huggins theory. This contains both entropy and enthalpy components, expressed by the Flory–Huggins interaction parameter χ, that describe the interaction between the polymer and the drug. In other words, the Flory–Huggins parameter χ is a measure of compatibility between polymer and drug.

Since many drugs have a strong tendency to crystallize, theoretical models of the polymer–drug interactions treat this like a solution where the presence of the homogenous mixture is determined by the miscibility curve of its phase diagram on the molecular level. Moreover, the models discussing the thermodynamic stability of a binary system are based on a fast equilibrium. This may not always be the case since polymers with high T_g values may trap the drug in the matrix, resulting in a kinetically stable system. Readers who are interested in the underpinning thermodynamic principles are referred to an excellent review article.[8]

How, then, can one choose the right polymer for the right drug to achieve good loading and high stability? The assumption "like dissolves like" is a good starting point. This rule of thumb is based on the Flory–Huggins parameter χ in **Equation 1**:

$$\chi = \frac{(\delta_s - \delta_p)^2 v_s}{RT} \qquad (1)$$

where δ_s and δ_p are the Scatchard–Hildebrand solubility parameter of the solute and the polymer, respectively.[7] In short, polymers that are chemically similar to the drug should enable the highest loading capacity. A good example is doxorubixin conjugated to a polymer.[9] While the drug attached to the polymer was found to be inactive, polymer micelles constructed with the polymer-drug conjugate created an environment that had the highest compatibility possible with free doxorubicin leading to an increased loading capacity. Decorating the polymer with the same drug to be loaded is an effective but cost-prohibitive option. Alternatively, subtle changes to the interior polymeric structure by altering the substitution of the polymer can maximize loading. For example, a PEO-b-PCL polymer was modified with benzyl, carboxyl, stearyl, palmitoyl, and cholesteryl functional groups with the aim of varying the hydrophobicity to tailor the polymer matrix toward the highest possible loading capacity of the chosen drug.[10]

However, not every lab has synthetic chemists capable of carefully tailoring a drug carrier to the drug. A tool is needed to help predict the best possible polymer structure for the drug. This is not easy, but an initial estimate can be obtained using the group contribution method to determine approximate partial solubility parameters. In this approach, the polymer and drug are essentially dissected into their different functional groups, which then are used to determine dispersion forces, dipole-dipole interactions, and hydrogen bonding of polymer and drug.[11] This approach frequently has been employed to predict the most suitable polymeric drug carrier,[12–13] but one also needs to exercise caution since many aspects are not taken into account resulting in unsuitable predictions. More refined approaches are based on molecular dynamics simulation,[14] which can reveal the critical role of H-bonding, an interaction that is often more crucial than hydrophobic forces to achieve high drug loading.[15] Further theories, based on a free