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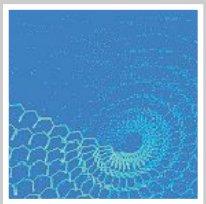

Polymer and Colloid Highlights

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Validation of a Novel Molecular Dynamics Simulation Approach for Lipophilic Drug Incorporation into Polymer Micelles

Aliya O. Kasimova[ac], Giovanni M. Pavan[b], Andrea Danani[b], Karine Mondon[a], Andrea Cristiani[d], Leonardo Scapozza[d], Robert Gurny[a], and Michael Möller*[a]

*Correspondence: Dr. M. Möller[a], E-Mail: michael.moeller@unige.ch; [a]Department of Pharmaceutics and [d]Pharmaceutical Biochemistry, School of Pharmaceutical Sciences, University of Geneva and University of Lausanne, 30 Quai E. Ansermet, 1211 Geneva 4; [b]Laboratory of Applied Mathematics and Physics (LamFI), Department of Innovative Technologies, University for Applied Science of Southern Switzerland (SUPSI), Manno; [c]CAPE Faculty, Mendeleyev University of Chemical Technology of Russia, Moscow, Russia

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To date the majority of newly developed drugs possess poor water solubility, which renders them difficult or even impossible to simply apply them in tablets or aqueous pharmaceutical formulations. The formulation of such drugs with sufficient drug concentrations is a major and challenging problem in pharmaceutical technology. Approaches to solve this problem are to incorporate these drugs in nanoparticles, liposomes, emulsions or polymer micelles in order to compensate for their poor solubility.[1] Polymer micelles, formed by amphiphilic block-copolymers, are promising drug carriers since they allow for high drug loadings and tend to have typical sizes in the nanometer range.[2,3] The novel biodegradable and biocompatible micelle-forming poly(ethylene glycol)–poly(hexyl-substituted lactide) (PEG-hexPLA) excipient has an increased lipophilicity of the micelle core in comparison to standard PEG-PLAs, and facilitates the incorporation of lipophilic drugs.[4] Here, molecular dynamics (MD) simulations were applied as a support for the understanding of the formulation of poorly water soluble drugs with these polymer micelles.[5] The novel MD simulation strategy is outlined in Fig. 1. The approach was adopted to characterize the interactions of significantly different drugs inside the polymer matrix in a time-dependent manner by Flory-Huggins interaction parameters χ_{FH} from the MD trajectories, taking into account the whole amphiphilic diblock copolymer chains, as well as a small amount of water molecules. The concept is analogous to the χ_{FH}-calculations of solutes in classical solvents, whereby χ_{FH}-values which tend to zero, or even have consistent negative values, identify drug solubilization (here potential drug incorporation into the polymer micelles) – in general, the more negative the χ_{FH}-value, the better the solubilization, and the higher the incorporation into the micelles. The calculated χ_{FH}-values for cyclosporine A–MPEG-hexPLA, griseofulvin–MPEG-hexPLA, ketoconazole–MPEG-hexPLA and quercetin dehydrate–MPEG-hexPLA were –1.080, –0.598, –0.177, and –0.028, respectively. The data reveal the MPEG-hexPLA polymer micelles' ability to incorporate the drugs. The plot in Fig. 1 presents the χ_{FH} parameters with respect to the experimental micellar drug loading (drug–polymer weight fraction expressed in mg/g), and demonstrates an almost perfect linear trend (R = 0.9977) between theory and experiment. Importantly, this trend in the calculated absolute χ_{FH}-values reflects the experimental reality – *i.e.* cyclosporin A shows the lowest χ_{FH}-value which corresponds to the highest incorporated drug amount into the micelle, and, *vice versa*, drugs with less negative χ_{FH}-values have the lowest incorporation. The results demonstrate the exceptional reliability of this method for the prevision of drug solubility into a determined polymer micelle, and allow the assumption that the presented strategy could be transferred onto other polymer micelle–drug systems.

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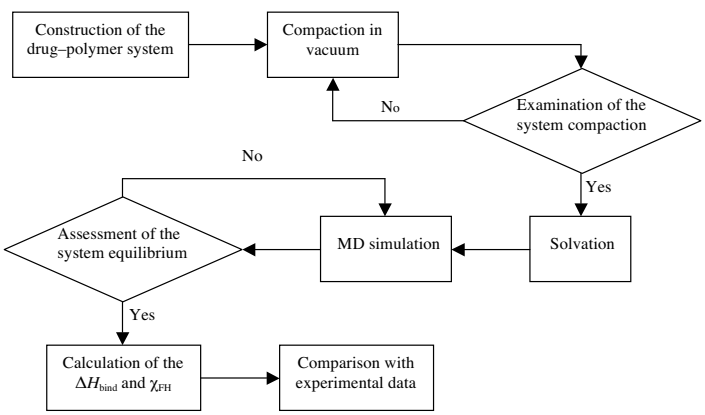

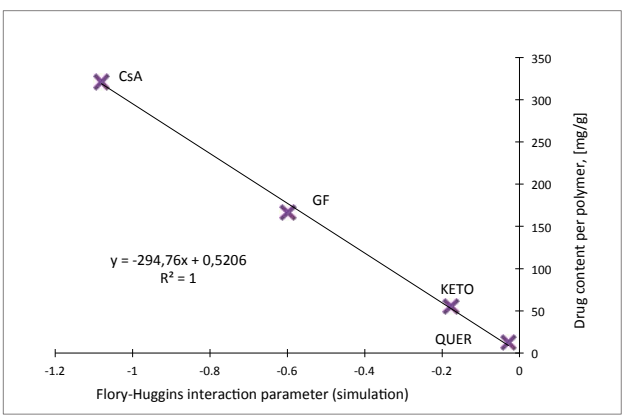

Fig. 1. (Left) Strategy of MD simulation for the assessment of drug incorporation into micelles. (Right) Relationship between the Flory–Huggins interaction parameter χ_{FH}, and the micellar drug loading, in terms of the drug/polymer mass ratio (mg/g) determined by experiment. Key: CsA=cyclosporin A; GF=griseofulvin; KETO=ketoconazole; QUER=quercetin dehydrate; ×=experimental drug content per polymer (mg/g).