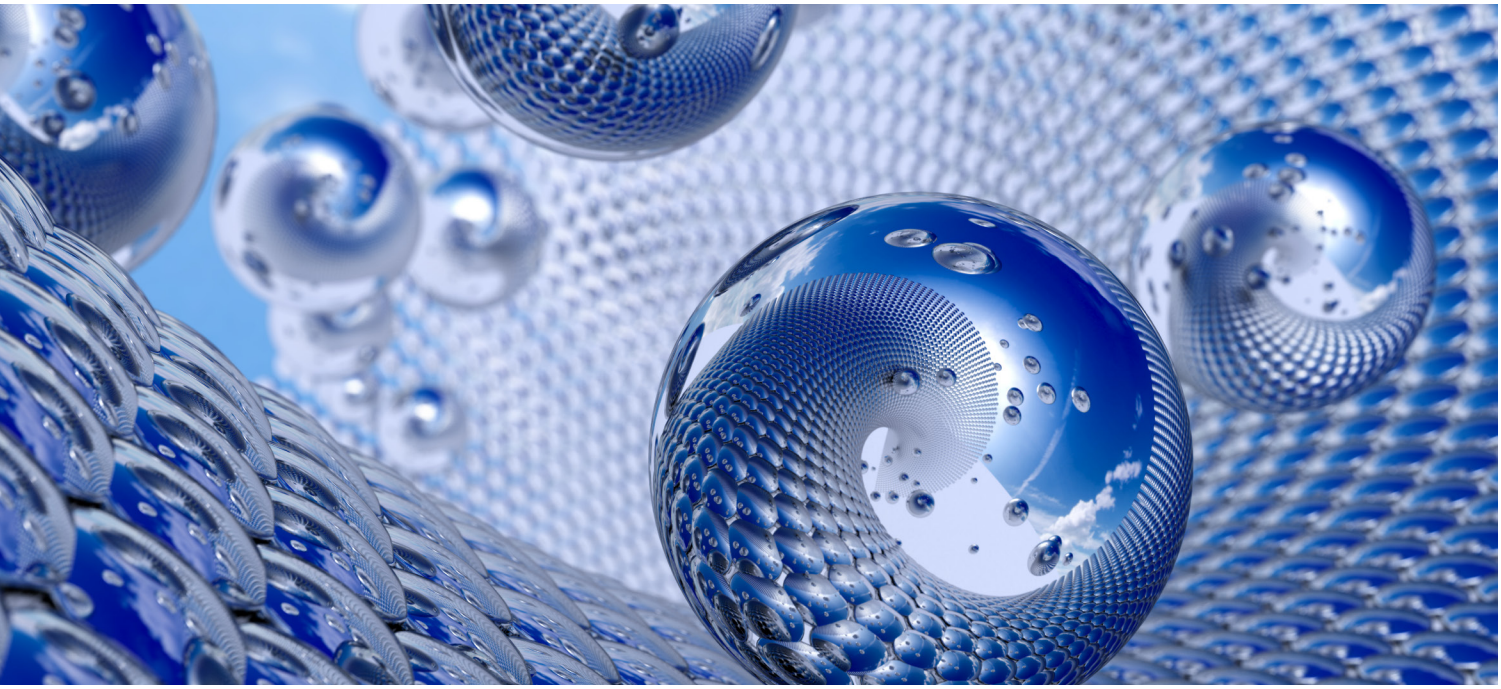
DASSAULT SYSTEMES

BIOVIA

IN SILICO DESIGN OF THERAPEUTIC NANOPARTICLES

EXPLORING DRUG DELIVERY METHODS WITH SANOFI

APPLICATION BRIEF



Since many active pharmaceutical ingredients (APIs) are hydrophobic, the usage of conventional liquid delivery methods can be difficult to implement for parenteral administration. Encapsulating drugs in copolymer nanoparticles (NPs) of poly-[D,L-lactic acid] (PLA) and Poly Ethylene Glycol (PEG) can improve their pharmacological and bio-distribution properties. Such nanoparticles present advantageous physical and biopharmaceutical properties as drug delivery systems compared to conventional liquid formulations. The present study[1] aims to predict the drug affinity for nanoparticles and their effective drug loading using in silico tools to virtually screen potential drugs for non-covalent encapsulation applications.

INTRODUCTION

Polymers offer a substantial opportunity for small molecule dosage forms due to their wide range of chemistry; however, an atomistic understanding of the interactions between an API and any excipient polymers is required to optimize their usability. Additionally, the polymer constituents of the NP should ideally be both biocompatible and biodegradable for medical use, further increasing the need for these optimized interactions. In silico modeling can help lay a foundation for such studies and support more rapid screening of potential formulations on a drug-by-drug basis. In the present study, block copolymers of PLA, a synthetic biodegradable polymer, and PEG – see Fig. 1 – are modeled by computer simulations. Such systems typically form micelles in water and other polar solvents, with PLA acting as a reservoir for the API; this makes them useful as drug carriers by enhancing drug solubility in water. Additionally, the surrounding PEG layer creates a "stealth effect," shielding the nanoparticles from macrophage capture and lowering the API's clearance from the bloodstream. As a result, these types of nanoparticles are becoming increasingly utilized in nanomedicine. For this study, a set of pharmaceutically interesting compounds,

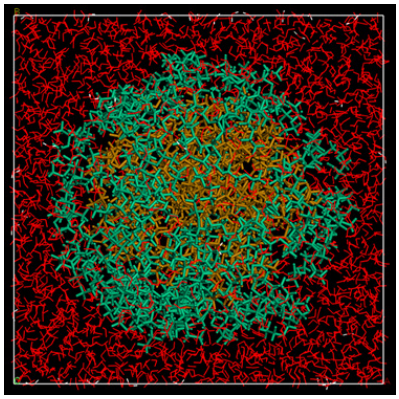


Figure 1. Solvated PLA-PEG Nanoparticle Simulated Model. **Red:** Water, **Green:** PEG segments, **Brown:** PLA segments

for which experimental data regarding drug loading in PLA-PEG NPs exists, were selected (structures depicted in Fig. 2). In addition, two Sanofi molecules (named SAR and RA), whose structures are undisclosed, were included.

The goal of this study is to develop a fast and accurate technique to predict APIs loading in PLA-PEG NPs and improve upon reported comparable methodologies. The highly validated Compass II Forcefield, a revised version of COMPASS,[2] was employed in all ab initio simulations in this study, and Monte-Carlo based docking procedures were used on realistic PLA surfaces to estimate drug binding energies. Many different simulation tools have been utilized and compared to predict the affinity of the drugs for the PLA matrix, such as a new solvation free energy tool – the BIOVIA Materials Studio Forcite Plus module.[3]

METHODOLOGY

Various atomistic and QSAR/QSPR simulations techniques have been employed in the present study. The COMPASS II Forcefield was employed for all atomistic simulations.

Using the Adsorption Locator module of BIOVIA Materials Studio, Monte-Carlo "docking" algorithms estimated the drug binding energies onto models of PLA surfaces. Validation was performed against known publication data for similar drug-like organic compounds.[4] Atomistic molecular dynamics simulations computed both the Hildebrand and Flory-Huggins (FH) solubility parameters. These computed parameters were used to predict the affinity of the drugs studied for the polymer matrix- and subsequently their potential maximum loading. A novel Free Energy Solvation (SFE) task of the Forcite Plus module predicted the reversible work required to bring a drug molecule from the gas phase into the polymer matrix. QSAR/QSPR correlations were used to obtain the compounds LogP values. Such

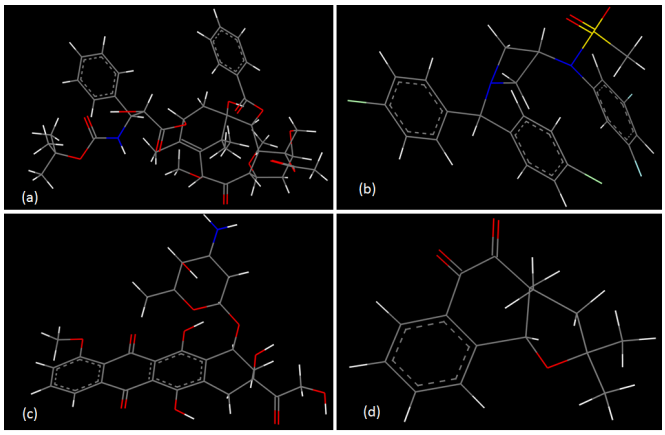


Figure 2. Selected Active Pharmaceutical Ingredients.

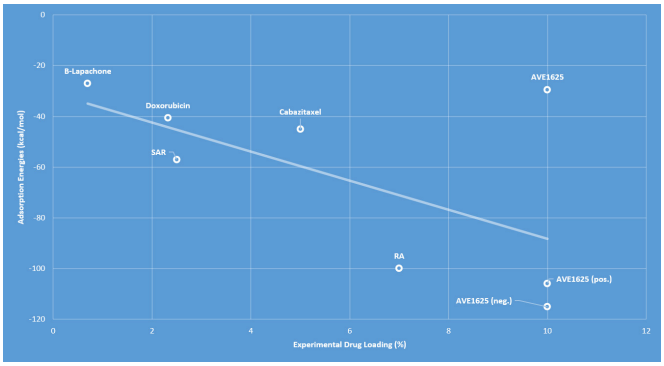


Figure 3. Drug Adsorption energies (kcal/mol) versus experimental Drug loading (%).

LogP values are used to predict the partition coefficient of small molecules in solvents and are therefore good measure of the compounds solubility.

All methods were tested against experimental data when possible using known dataset. Sanofi's proprietary drug compounds were then run against the various methods to predict their loading affinity.

RESULTS

All simulations methods employed in the present study are accessible through the Materials Studio user interface. The results of the chosen drug compounds were reported after the presentation of a validation study, consisting of results for test sets (pigments, known drugs, etc.). In all cases, the simulated adsorption energies using the COMPASS II Forcefield correlated well with reported experimental drug loading (Fig. 3). In addition, the COMPASS II Force-field performed well for predicting key physical properties of the PLA polymer (e.g. the density).

Solubility parameters and Flory-Huggins interaction parameters were estimated by molecular dynamics runs using the FORCITE PLUS module. The simple Hildebrand approach was found to be unsatisfactory, whereas the FH approach gave good results for the drugs test set.

Computing the solvation free energies as implemented in the new FORCITE PLUS module of the various drugs in both water and octanol allowed for the prediction of the water/octanol (so called LogP) partition coefficient of the chemicals. Again, a statistically relevant correlation could be demonstrated between the experimental drugs loading and the predicted SFE values. This method showed good potential albeit computationally the most demanding.

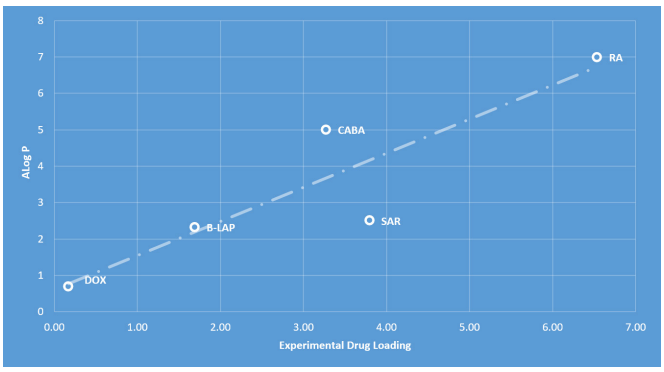


Figure 4. AlogP versus experimental Drug loading (%).

A published ALogP correlation[5] as implemented in BIOVIA Pipeline Pilot was also used to predict the drug loading in PLA NPs as seen in Fig. 4. This last method has the advantage of being very fast – however, it is more limited in the chemical space.

CONCLUSIONS

Using in-silico tools to predict potential drug loading prior to any experimental study is of great importance to the pharmaceutical industry. Molecular modelling techniques such as molecular dynamics or Monte-Carlo algorithms (all implemented in the user interface of Materials Studio) can predict drugs affinity for polymer matrices such as the PLA-PEG used in Sanofi's nanoparticles technology. From this, drugs loadings inside the NPs can be estimated saving valuable time and resources to the experimentalists.

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