Optimizing Delivery Systems via Multiscale Simulations

Martina Pannuzzo [1], Paolo Decuzzi[1]

[1] Laboratory of Nanotechnology for Precision Medicine, Italian Institute of Technology, 16163, Italy

Background: Nowadays, physical, chemical, and biological properties of materials can be tailored at the nanometer scale to precisely deliver therapeutics. Computer simulations such as Molecular Dynamics provide a useful tool for predicting and understanding structure-property relations in developing novel nanomedicines while reducing extensive experimental trials.

Methods: Models at different chemical-physical resolution (e.g., coarse-grained, all-atom representation) are employed depending on the temporal and spatial scales spanned by interest phenomena.
Poly-lactic-co-glycolic acid (PLGA) and polyethylene glycol (PEG) polymers' miscibility is evaluated with all-atom simulations. Then, PLGA and PEG mixtures' mechanical strength is estimated under different regimens of miscibility to elucidate the mechanisms regulating nanoparticle deformability.
Next, the free energy profile of dexamethasone (DEX) and curcumin (CURC) molecules translocation across the polymer carrier into the aqueous solvent is derived via Umbrella Sampling method, providing insights on the drug release kinetics dependency on the physical-chemical interaction between the drug and the polymer matrix.
On a higher level of complexity, coarse-grained simulations integrate in vivo and in vitro experiments on the adsorption of blood proteins on the particle surface as a function of the polymer coating.

Results: The addition of PEG amounts comparable to that of PLGA (~50% w/w) results in heterogeneous blends with a level of phase separation that grows with the PEG's molecular weight. At low PEG concentrations, homogeneous mixtures are generated for both low and high PEG's molecular weights. The computed Young's modulus of PLGA/PEG blends is observed to decrease with the PEG content.

The higher free energy barrier associated with DEX translocation from the PLGA matrix to the aqueous solution confirms the higher affinity of this molecule for the PLGA matrix compared to CURC, supporting the experimentally documented slower release of DEX from the PLGA matrix.

Finally, nano-particle surface camouflaging with appropriate proportions of carboxyPEG2000 and methoxyPEG550 can suppress protein binding/intercalation, thereby affecting sequential dynamic processes in complement convertase assembly and nano-particle-mediated complement activation.

Conclusions: Together, these data provide the rationale to optimize delivery systems at reduced cost and experimental workload.