Doctoral Dissertation Summary
Doctoral Program in Chemical Engineering (35th cycle) – Politecnico di Torino

Production and activation of shear-responsive drug carriers for treating obstructed blood vessels: a coupled CFD-DEM approach

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The obstruction of critical blood vessels caused by clots is one of the leading causes of death worldwide, causing the development of efficient antithrombotic strategies to be of the utmost importance. Blood clots are usually treated using a tissue plasminogen activator to dissolve the clot and preventing the major consequences ischemic events lead to. However, this treatment requires a prompt administration of the active agent and a careful choice of the dosage, as the amount of freely circulating drug should not overcome a certain threshold. One of the most innovative strategies for a localized drug delivery is based on shear-responsive drug carriers, micrometric clusters of polymeric nanoparticles coated with the active agent. The carriers can be designed to travel undisturbed under normal blood flow conditions and to be activated through breakup right onto the clot, as a response to the local increase in the hydrodynamic stress caused by the lumen restriction itself. The resulting fragments are more likely to adhere to the clot, enhancing the efficiency of the thrombolytic action.

The present work aims to establish a simulation framework able to follow the production process of the carriers from the agglomeration via spray drying to the shear-inducted de-agglomeration: the formation of aggregates during spray drying is investigated and simulated through discrete element methods (DEM), while the flow field in an obstructed blood vessel is determined using computational fluid dynamics (CFD) techniques. The correlation between hydrodynamic forces and internal mechanical stresses has been studied using a refined discrete element method based on Stokesian dynamics.

A qualitative relationship between the spray drying process conditions and the morphology of the final product has been identified: compact agglomerates are obtained when the diffusion of nanoparticles in the droplet is fast with respect to its shrinkage, otherwise the resulting agglomerates are hollow (low and high Péclet number, respectively). A dataset of plausible compact and hollow carrier morphologies has been generated by DEM spray drying simulations, and CFD simulations have shown that the presence of a peak in hydrodynamic forces caused by the occlusion of the vessel can act as an internal, non-invasive activation mechanism for drug carriers.

A statistical analysis of the response of the dataset of compact and hollow carrier morphologies to the CFD-calculated flow field has been performed, thus linking the process conditions of the formation of agglomerates to their response to pathological shear stresses. Hollow agglomerates are subject to higher internal mechanical stress with respect to compact ones.