MICROFLUIDIC AND NANOTECHNOLOGY BASED ASSAYS FOR THE DEVELOPMENT OF SAFE BIOPHARMACEUTICALS

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Protein stability towards aggregation represents a potential challenge for the production and administration of pharmaceuticals. In particular, aggregation can compromise the developability and shelf-life of the products, with consequences for yield and safety, respectively. In this work, we discuss two novel approaches for the analysis of the stability of protein formulations:
(1) A microfluidic diffusion-sizing platform to analyze protein sizes and interactions at high protein concentration directly in the solution state with minimal perturbation of the sample. The limited dilution of the sample during the analysis and the possibility to characterize properties directly in the solution state make the technique suitable for the analysis of heterogeneous solutions of proteins under dynamic equilibrium. We show how the platform represents an attractive tool for the analysis of sizes and interactions of proteins in both diluted and high-concentration solutions during development, manufacturing, and formulation.
(2) A highly controlled assay of surface-induced protein aggregation based on nanoparticles. Protein aggregation is often due to heterogeneous nucleation events occurring at interfaces, including air/water interface, impurities and leachable particles. However, the development of screening tools against surface aggregation has been hindered by the difficulty in generating a controlled amount of surface stress in the formulation as well as in decoupling the surface effect from the contribution of hydrodynamic flows. In our assay, we leverage the flexibility of polymer chemistry to finely tune the properties and amount of surfaces provided by the nanoparticles, inducing aggregation of soluble peptides and proteins, including antibodies, in a time scale of a few hours. This platform represents i) an attractive tool for fundamental studies of heterogeneous nucleation events under stagnant and flow conditions, and ii) a high-throughput screening assay of the effect of intrinsic and extrinsic variables on protein stability towards interface-induced aggregation.

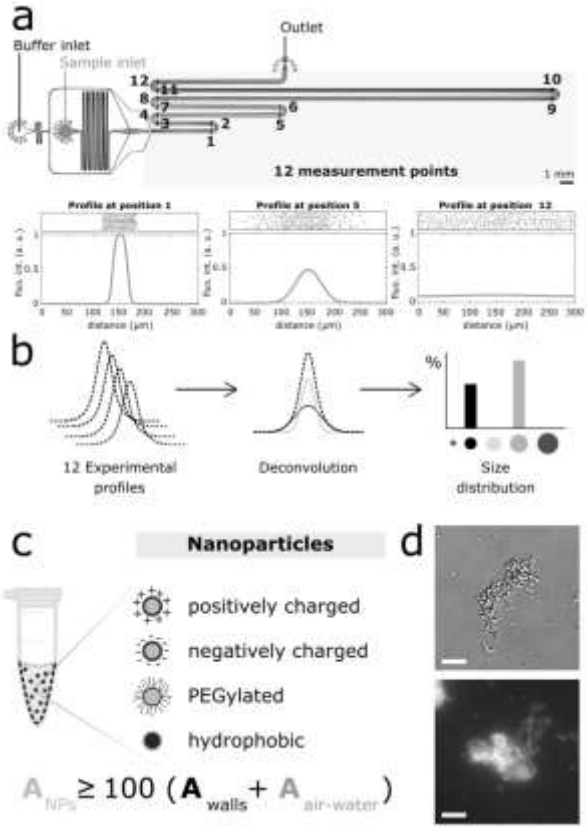

Figure 1 – a,b) Microfluidic diffusion sizing platform, allowing the measurement of size distributions. c,d) Polymeric nanoparticles library to screen for interface interactions in protein solutions.

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