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The Application of Field-Flow Fractionation to the Analysis of Nanomedicines

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SUMMARY

The combination of field-flow fractionation with powerful leading-edge detectors can be applied to the measurement of nanomaterial physicochemical properties, and the creation of harmonized robust measurement protocols. The Multi-scale Metrology Suite (MMS) at the University of Strathclyde is a unique internationally leading facility combining multiple leading-edge field flow fractionation modalities (electric, asymmetric and centrifugal) with in-line Raman, inductively-coupled plasma (ICP) mass spectrometry and multimodal detector capability. One of the goals for the MMS is to raise the standards of traditional academic analytical support underpinning pioneering academic engineering, physical and life sciences research exploring novel materials as diagnostics and therapeutics.

INTRODUCTION

Nanomedicines include medicinal products where the active pharmaceutical ingredient (API) is loaded into biocompatible nanoparticles. Since the approval of the first nanomedicine, Doxil®, the field of nanomedicine has seen a significant expansion in global commercial investment, with >50 nanomedicines in the clinic, and a new wave of next-generation products entering the arena.

Nanomedicine physicochemical attributes including size distribution, drug loading and interactions with biological media are generally unique to each nanomedicine type and are known to contribute to the safety and efficacy profile of the drug. In recent years regulatory bodies (e.g., Food and Drug Administration) have issued guidance on early pre-clinical characterization of nanomedicine drug products, which include the comprehensive analysis of their critical quality attributes in three stages that include i) preliminary low-resolution analysis of stability ii) orthogonal high-resolution analysis in buffers, and iii) high-resolution analysis in complex biological media.

Field flow fractionation hyphenation with multiple detectors has emerged as a high-resolution technique addressing step ii and iii analytical needs, through gentle high-resolution separation of materials and characterization of sample fractions (Caputo *et al,* 2021). The EPSRC Multi-scale Metrology suite (www.mms.ac.uk) hosts a fully integrated first of its kind system internationally. This system combines the latest in multiple leading-edge field flow fractionation modalities (electric, centrifugal and electric) with multiple online detectors. This combination of high-resolution separation with multimodal detectors, enables the high-resolution analysis of polydisperse samples and novel

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nanomaterials. Here, we present the setup of the EPSRC Multiscale Metrology Suite and exemplar case studies demonstrating its applications for the analysis of sample stability in buffer and biological media.

MATERIALS AND METHODS

Here, we present example case studies where the stability of model nanoparticles (e.g. polystyrene latex) in buffer and biological media (fetal bovine serum mimicking cell culture conditions for cellular uptake) are characterized using the FFF, comparing these findings in the presence and absence of FFF with conventional approaches such as dynamic light scattering and nanoparticle tracking analysis techniques.

RESULTS AND DISCUSSION

Corresponding principles for FFF are presented in Figure 1.

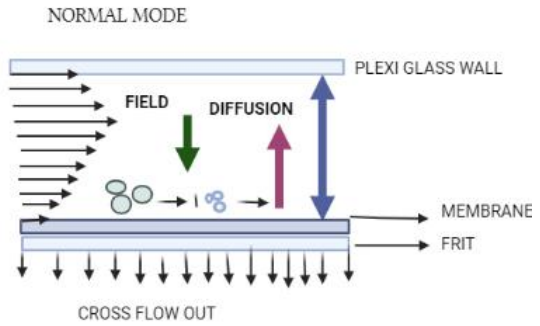

Fig. 1. *The principle of field flow fractionation (Muller et al, 2015).*

FFF is associated with material loss due to interaction with membranes; therefore, the use of fret inlet methods have gained popularity in recent years.

The configuration presented in figure 2, enables high-resolution separation of species within polydisperse samples and coupling chemical and physical detectors for high resolution analysis. The inclusion of inline Raman analysis is both a unique and novel concept in this setup.

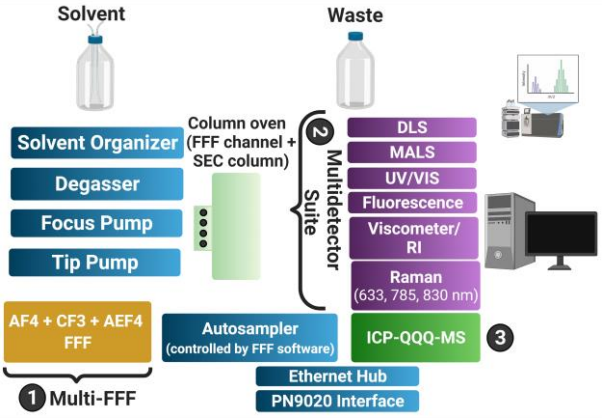

Fig. 2. *The multiscale metrology suite system configuration.*

CONCLUSIONS

The development of robust and harmonized protocols using FFF requires joint cross-sector efforts to generate standard operating procedures and robust reference standard materials aligning with nanomedicine drug product needs. Successful protocol harmonization will ultimately reduce product development costs associated with in the long-term and offer a powerful platform for the evaluation of complex nanomedicine drug products.

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