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Assembly properties of complex drug delivery systems

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SUMMARY

The interaction of materials within the context of a formulation and its manufacturing process can have a defining impact on a parenteral drug product performance. Therefore, establishment of methodologies to investigate the interactions of drug substance with itself and other components can be a critical aspect of developing a product and understanding its potential failure modes. This paper will discuss some of the methodologies used to investigate assembly properties of different delivery systems, including separation techniques combined with on-line multiple detectors, and nanoscale imaging. Examples where the data are combined with modelling the morphology demonstrate the strength of combining multiple experiments with calculations to provide deeper insight into functionality for e.g. polymeric nanoparticles and drug dendrimer conjugates.

INTRODUCTION

The modern pharmaceutical development portfolio is comprised of a variety of different modalities of drug substance and delivery systems. As such the way these materials interact within the context of a formulation and its manufacturing process can have a defining impact on a parenteral drug product performance. Therefore, establishment of methodologies to investigate the interactions of drug substance with itself and other components can be a critical aspect of developing a product and understanding its potential failure modes.

This paper discusses some of the methodologies used to investigate assembly properties of drug delivery systems, including Size Exclusion Chromatography with multiple detectors (MD-SEC), Asymmetric Flow-Field Flow Fractionation with Multi-Angle Light Scattering (AF4-MALS), Cryoscopic Transmission Electron Microscopy (c-TEM). Systems including drug-dendrimer conjugates (DDC) and polymeric nanoparticles (PNP) is discussed. Furthermore, the combination of complex measurements with theoretical models of morphology using salient examples demonstrates the relationship between structural features and function of the drug product.

MATERIALS AND METHODS

Where possible the characterisation of drug product was performed in media simulating the composition of the drug product. MD-SEC protocols are given in (Akhtar et al., 2023; England et al., 2022; Sonzini et al., 2023). AF4-MALS: Postnova AF2000 and PN3621 were used with 1mM Phosphate buffer pH 6.8, elution step was performed using a 1 $mL.min^{-1}$ constant X-flow for 5 min then 0.1 exponential for 20 min ending at 0 $mL.min^{-1}$. Radius of gyration (R_g) per retention volume was determined using NovaFFF software. c-TEM was performed on a FEI Talos L120C G2 TEM instrument on samples in deionised water, crash-cooled in liquid ethane on lacey carbon grids.

RESULTS AND DISCUSSION

Data on the MD-SEC analysis of 3 variants of the DDC AZD0466 is shown in Fig 1. The data show a

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clear difference between the size and molecular weight of a drug free dendrimer, small scale, and the optimised larger scale batch. The results demonstrate that the attachment of drug substantially affects the degree of self-association, and that the technique can easily identify differences between batches. Additional data obtained on intrinsic viscosity and hydrodynamic radius demonstrate that degree of solvation and thus the density of the system also varies across the three variants studied.

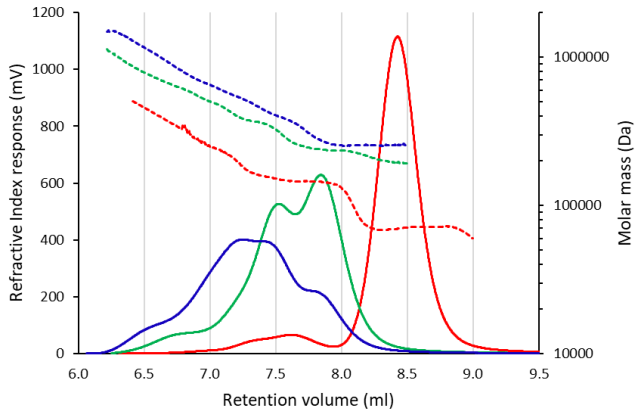

Fig. 1. *SEC chromatograms (solid lines) and resultant molecular weight data (dashed lines) for a drug free batch (red), and two active batches (small scale, green, optimised larger scale, blue) of DDC AZD0466, measured in 25 mM aqueous phosphate/citrate buffer at pH 5+glucose 5%w/w.*

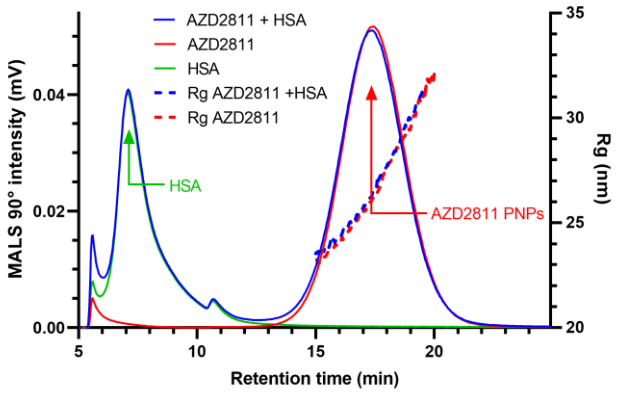

Fig. 2. *Interaction study of PNP AZD2811 and HSA using AF4-MALS*

A second drug delivery system studied a PNP using AF4-MALS, see ***Fig. 2***. The data show the PNP system incubated with and without human serum albumin (HSA) and demonstrate the capability of the formulation to prevent protein adsorption as no shift in retention time (17.5 min), nor detectable change in the radius of gyration (Rg) are observed. Furthermore c-TEM image analysis, exemplified in ***Fig. 3***, has been performed on a large population of particles of batches with different properties. Utilising both a machine learning (ML) algorithm and morphological digital twin (based on Rg calculation) developed on the results has enabled much greater insight into the formation, structure and function of the PNPs.

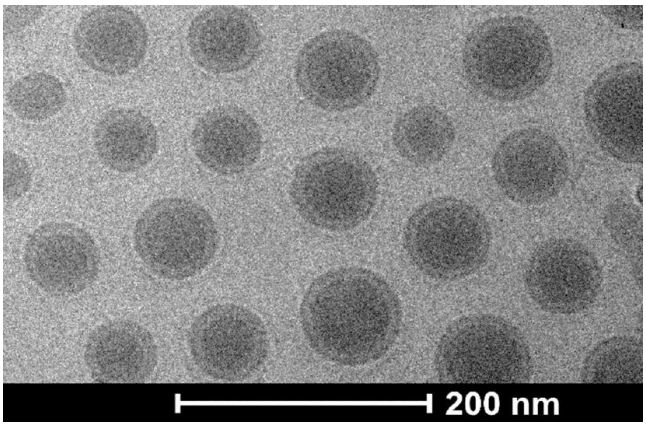

Fig. 3. *Exemplar c-TEM image of AZD2811 PNPs.*

CONCLUSIONS

The characterisation of drug-dendrimer conjugates and polymeric nanoparticles by separation with multiple detectors and nanoimaging, combined with ML analysis and a morphological digital twin provide enhanced insight into structure and function of these complex drug delivery systems.

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