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Investigating the Impact of Shear Flow on Nanoparticle-Protein Interactions

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SUMMARY

Most nanoparticle-based therapies are intended for intravenous administration, exposing them to associated hemodynamic parameters and the presence of cells and biomacromolecules post-administration. While most efforts in nanomedicine development focus on formulation stability, the range of biologically-relevant approaches probing nanoparticle stability in biological media remain limited in scope. In the present study, we examine the role of surface chemistry in nanoparticle-protein interactions using three polystyrene latex nanoparticle chemistries. These nanoparticles were treated in media mimicking cell culture conditions, and the impact of static co-incubations versus flow on nanoparticle parameters were compared. Following treatment with protein-containing media, we performed analysis of nanoparticle parameters using either the centrifugation-wash step or *in-situ* analyses to compare the effects of isolation protocols on nanoparticle physicochemical parameters. Overall, our findings show that flow and sample recovery methods significantly impacted the concentration and composition of surface-adsorbed proteins. Amine-modified latex nanoparticles showed the most pronounced susceptibility to flow and nanoparticle isolation techniques. The implications of this work lie in the development of more biologically-relevant and harmonized approaches in measuring the nanoparticle protein corona, since sample preparation techniques and analytical approaches used, may impact the translational scope and relevance of assays used to measure nanoparticle interactions with biological media

INTRODUCTION

Nanoparticles are routinely explored for the development of novel drug delivery systems. Despite the high potential of nanoparticles as novel therapies, the attrition rate from bench to clinic remains high (Mitchell et al., 2021). Nanoparticles are not inert species- following nanoparticle administration within protein-containing media, proteins will spontaneously interact and adsorb onto the particle surface- referred to as a 'protein corona'. The protein corona alters the physiochemical properties of nanoparticles, and affects their subsequent biological fate (Rampado, Crotti, Caliceti, Pucciarelli, & Agostini, 2020). For nanoparticles which are intended for intravenous administration, it's crucial to understand how physiological flow in combination with media composition impact the range and extent of nanoparticle-protein interactions. The present study aims to investigate changes in nanoparticle

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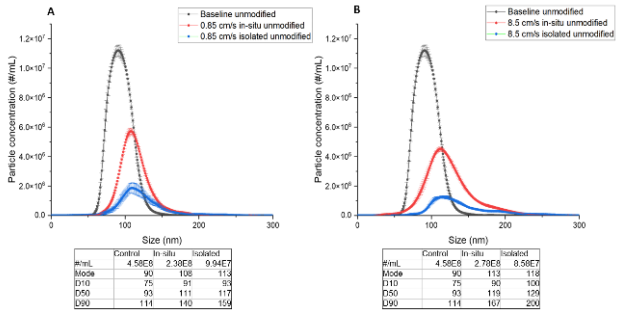
parameters following treatment with protein-containing media under various flow speeds.

MATERIALS AND METHODS

Here, we report the investigation of the impact of shear flow on nanoparticle-protein interactions using model latex polystyrene nanoparticles with different surface chemistries including unmodified, amine-modified (Merck, Dorset), and carboxylate-modified (ThermoFisher, Renfrew). Nanoparticles were incubated within 10% v/v Foetal Bovine Serum (FBS) for 2 hours at 37 ˚C (0.85 cm/s, 8.5 cm/s) to mimic physiological blood flow as seen within the median cubital vein and arteries. Physicochemical parameters of the particles were measured using electrophoretic light scattering (ELS), dynamic light scattering (DLS), and particle tracking analysis (PTA). SDS-PAGE was used to fingerprint the composition of the nanoparticle protein corona.

RESULTS AND DISCUSSION

We observed an increase in nanoparticle size following incubation within 10% *v/v* FBS. A significant increase in particle size was also seen in the presence of flow (0.85 cm/s, 8.5 cm/s).



	Control	In-situ	Isolated
#/mL	4.58E8	2.30E8	9.94E7
Mode	90	106	114
D10	75	91	93
D50	93	111	117
D90	114	140	159

	Control	In-situ	Isolated
#/mL	4.58E8	2.70E8	8.58E7
Mode	90	113	116
D10	75	90	100
D50	93	119	129
D90	114	167	200

Fig. 1. *A comparison of PTA-measured nanoparticle size (d.nm) following incubation under a) 0.85 cm/s or b) 8.5 cm/s shear flow conditions.*

This evidence is supported by previous studies (Jayaram, Pustulka, Mannino, Lam, & Payne, 2018) which show a change in protein corona composition when exposed to circulatory shear flow conditions.

In PTA analysis, a shift in particle size and loss in concentration was observed following the centrifugation-wash method of latex nanoparticles. PTA enabled *in-situ* evaluation of particle sub-populations forming due to nanoparticle-protein and protein-protein interactions.

Our results show that the centrifugation-wash approach used in nanoparticle isolation from media, leads to nanoparticle loss and perturbations in size, not reflected in *in-situ* measurements. We found that physiologically-relevant flow conditions yielded different nanoparticle parameters and protein composition when compared to static incubation conditions. Overall, our work demonstrates the importance of developing biologically-relevant assays for studying the nanoparticle protein corona.

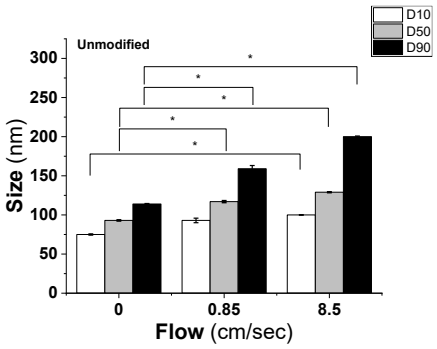


Fig. 2. *PTA-measured size comparison (d.nm) for unmodified latex nanoparticles following incubation under various shear flow conditions. Error bars: S.E.M.*

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