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Unravelling the influence of human serum environment on drug release from nanoformulations with polyethylene glycol shell

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Nano-bio interactions remain underexplored for their impact on drug release profiles of polymeric nanoparticles. Core-shell nanoformulations from linear (PEG-*b*-PCL) and branched (PEG_2-*b*-PCL) polymers containing a multi-potent drug interact with human serum proteins. These interactions are affected by PEG shell density, leading to enhanced lipophilic cargo release without drug aggregation.

Therapeutic interventions using nanoparticles (NPs) continue to offer significant potential in addressing key challenges associated with managing high morbidity rate diseases.[1] Among various platforms explored in the development of nanomedicine, polymeric nanocarriers have emerged as highly versatile because of their tunable size, morphology, surface charge, and synthetic flexibility. The compositions of their macromolecular precursors are easily controlled through synthetic articulation to enhance nanoparticle drug-loading capacity, controlled release in response to varied internal or external stimuli, and to impart biodegradability to their constituent polymer blocks.[2-4]

Despite demonstrated progress *in vitro*, there has been limited success in the clinical translation of polymeric nanoparticles. Significant challenges still remain, including the limited understanding of the behavior and efficacy of such nanoparticles upon entering blood circulation.[5, 6] Upon exposure to biological fluids, nanoparticles rapidly interact with biomolecules and ions in blood plasma, forming a dynamic interfacial layer that has been shown to define their biological identity and cellular interactions.[7, 8] Among plasma proteins, human serum albumin (35-50 g/L, 50-60% of total protein content) is predominant. Due to its strong surface affinity, it can significantly influence the circulation, biodistribution, immune recognition, and pharmacokinetics of nanoparticles. This can lead to disparities between the *in vitro* and *in vivo* behaviour of nanoparticles.[9] Extensive studies have now been carried out to understand nanoparticle-serum interactions. However, the majority have focused primarily on characterizing protein corona formation, its composition, and the impact of the latter on the colloidal stability and biological identity of nanoparticles.[10] An important task for polymeric nanoparticles is to deliver their cargo in a controlled and sustainable manner. Far fewer investigations have examined how these nano-bio interactions impact drug release from polymeric NPs.

It has been noted that the surface charge on pullulan nanoparticles can critically govern how human serum albumin (HSA) complexes and consequently modulates drug release behavior from HSA-bound nanoparticles. This study has suggested that nano-bio interactions decrease overall mitoxantrone release in this nanocarrier.[11] Treatment of transferrin-functionalized p(HEMA-ran-GMA) polymeric nanoparticles with 55% v/v human serum was shown to lower drug release as compared to non-serum conditions.[12] Similarly, studies on PLGA nanoparticles have suggested that although cumulative doxorubicin release appeared only minimally affected by human plasma, detailed kinetic modeling uncovered subtle but significant changes in release profiles dictated by corona structure.[13] Collectively, literature shows disparity on the effect of protein adsorption on cargo release from nanoparticles, with some studies suggesting acceleration while others report a decrease in drug release kinetics.

The influence of serum protein interactions on drug release from nanocarriers containing polyethylene glycol (PEG) in the shell remains particularly underexplored. Although PEGylation has long been employed for nanoparticle stealth and to mitigate nonspecific protein adsorption, recent evidence has shown that the presence of PEG does not eliminate serum interactions, and PEG grafting density could have a role in tuning plasma protein adsorption.[14-16] There is critical need to understand how biologically relevant human serum will influence drug release

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from well explored PEG-based core-shell nanocarriers. The crucial information needed does not necessarily invoke protein-corona build-up and its characterization but instead evaluates if serum protein-nanoparticle interactions can change the release characteristics of therapeutic cargo (often small lipophilic drugs). We were intrigued to address this issue using nanoparticles from linear diblock (AB: A = polycaprolactone, PCL; B = PEG) and branched star (AB_2) polymers (Fig. 1A). Utilizing naturally occurring omnipotent curcumin (CUR) as a model drug, we have examined how presence of serum protein could affect its release in NPs from AB and AB_2 polymers. The insights can help build nanoparticle composition cargo-release structure-property relationships, and design efficient block copolymer-based core-shell formulations.

We considered biocompatible PCL and PEG polymeric arms as hydrophobic and hydrophilic components in the design of linear (AB) and branched star (AB_2) macromolecular precursors. Nanoparticles from such polymers have been widely investigated as carriers for small lipophilic pharmaceutics. Importantly, the star polymer composition (AB_n) leads to denser PEG composition in nanoparticles.[17, 18] Core-shell (micelle) nanoparticle morphology is an easily constructed and commonly investigated system in drug delivery, and it was adapted for this study. AB (M_n= 5,600 g/mol) and AB_2 (M_n= 7,700 g/mol) polymers of controlled compositions and containing one or two polymeric arms of PEG_{2000} were synthesized using established synthetic procedures.[19-21] The relevant characterization data including NMR and GPC profiles are included in the Electronic Supporting Information.

Aqueous nanoformulations from AB and AB_2 polymeric precursors, with and without therapeutic cargo (curcumin mixture from natural sources, denoted here as "CUR"), were prepared using co-solvent evaporation, a common methodology leading to well-defined NPs (ESI 1.2.1).[22] Critical micelle concentrations of AB and AB_2 based nanoparticles (Figures S.4-S.5.) were calculated to be 0.0099 and 0.015 mg/mL, respectively. Hydrodynamic diameters and size distributions of the resulting formulations were analyzed using dynamic light scattering (DLS). Blank NPs from AB_2 (30 nm, Table S.1) were smaller and had lower PDI than their AB counterparts (35 nm). Both nanoformulations contain a similar molecular weight core-forming polycaprolactone block (with degree of polymerization ≈ 32 for both polymers) and with a 1:10 w/w drug: polymer feed ratio showed excellent CUR encapsulation efficiencies (≥85%, Table S.2). The decrease in hydrodynamic size noted upon CUR encapsulation suggests better core packing with the inclusion of lipophilic cargo (Table S.2). DLS measurements were complemented by TEM imaging, in which NPs of 26 nm and 19 nm (Blank AB and AB_2, respectively) and 22 nm and 24 nm (CUR loaded AB and AB_2, respectively) were observed (Fig. 1D). NPs from AB_2 showed mostly spherical morphology with a small number of worm like aggregates due to higher hydrophilic fraction (in the spherical to cylindrical transition threshold).[23, 24]

To evaluate the effect of human serum on NP size, CUR-loaded nanoformulations were incubated with human serum at 37°C and their hydrodynamic diameters were monitored over

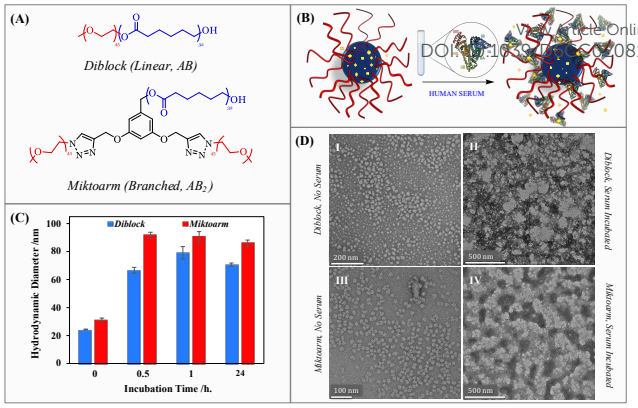

Fig. 1 (A) Chemical structures of AB and AB_2 polymers. (B) Schematic illustration of CUR loaded NP interaction with human serum proteins. (C) Serum-induced changes in hydrodynamic diameters of AB and AB_2 micelles at 37 °C. **(D)** TEM images showing CUR-loaded micelles (I: AB, III: AB_2) and serum-treated nanoparticles (II: AB, IV: AB_2). Protein image created with Biorender.com.

24 h using DLS (Fig 1C). Both AB and AB_2 NPs exhibited a significant increase in particle size by 30 min, followed by a gradual change and eventual particle size stabilization during the remaining incubation period. The initial increase is attributed to protein adsorption on the NP surface, a process typically completed within the first 10-60 min of exposure.[25] Overall, both nanoformulations followed a similar trend with an approximately 2.7 - 2.9 fold increase in hydrodynamic diameter at 30 min, after which time the particle size remained relatively stable over the 24 h period. Human serum proteins, predominantly albumin, adsorb onto the NP surface. The apparent increase in diameter by DLS is a reflection of the adsorption of serum proteins and the associated hydration shell.

After multiple washes to remove unbound and excess serum, TEM was subsequently utilized to visualize changes in NP composition. As detailed in the electronic supporting information (ESI 1.2.3), washing using a 100 kDa centrifugal filter isolates NP-protein complexes (retaining >100 kDa bound proteins while removing free albumin ~65 kDa). This was confirmed using UV-Vis with 275 nm protein peak in the eluent; and 425 nm curcumin in the retentate (Fig. S.9). Analysis of CUR loaded AB_2-based NPs incubated in serum for 60 min showed patchy structures ~100 nm in size (Fig. 1D, IV). This suggests that a stable corona layer is formed on NPs which leads to aggregated NP-protein structures, consistent with what has been reported earlier.[26-28] TEM analyses of NPs before washing showed grey backgrounds due to unbound protein preventing uranyl acetate (UA) stain penetration, while post-wash backgrounds were darker, confirming unbound protein removal (Fig. S.8). Post-serum incubation, TEM revealed amorphous protein layers around NPs. The protein adsorption was found to be denser in NPs from the AB_2 star polymer. Such individual boundaries noted here were harder to distinguish in pre-wash samples. In contrast, diblock AB-based NPs showed less extensive serum adsorption, with spherical structures visible even in pre-wash samples.

We subsequently evaluated CUR release from AB and AB_2 based nanoformulations, with and without 40% v/v human

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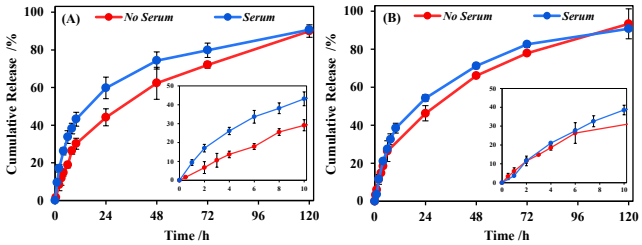

Fig. 2 CUR release profile from (A) miktoarm and (B) diblock polymer-based formulations, in the presence and absence of serum (40% v/v). Studies conducted at 37 °C in PBS buffer (pH 7.4, + 1% v/v Tween 80).

serum, under simulated physiological conditions (0.01 M PBS + 1% Tween 80, pH 7.4, 37°C) using the dialysis bag method. We noted that sample processing of release aliquots for UV-Vis analysis was complicated by the presence of serum. Dilution of in-bag collected samples with methanol (to release free CUR from the nanocarriers) resulted in protein aggregation. The presence of aggregates in methanol solution resulted in a subtle UV-Vis baseline slope most evident in the 600-800 nm region where CUR absorption is near zero (Fig. S.11). This interference, caused by light scattering from protein aggregates, required careful sample processing for quantification of CUR release. To eliminate these scattering contributions to absorbance, we introduced a simple precipitation-centrifugation protocol prior to sample analysis to enable accurate CUR quantification (ESI section 1.2.5). A control experiment comparing spectra acquired before protein addition and after sample processing confirmed negligible loss of CUR during the precipitation/centrifugation step (Fig. S.12).

Significantly, we found that release kinetics were altered upon introduction of human serum in both nanoformulations (Fig. 2). Serum proteins accelerated CUR release from both nanoformulations, with a more slightly pronounced effect observed for miktoarm polymer-based NPs. During the initial 24 h, AB_2 NPs exhibited faster release, reaching ~30-35% in 6 h and ~55-60% after 24 h, representing ~10% higher release compared to serum-free conditions (Fig. 2A). In contrast, AB (linear diblock) NPs showed minimal differences during the first 10 h (~15-20% release), but an increased release at later times, reaching ~50-55% after 10 h compared to ~35-40% without serum (Fig. 2B). Beyond 72 h, the release profiles for both systems converged to a similar plateau. Our results suggest that serum, in general, accelerates CUR release in nanoparticles developed from both branched and linear diblock copolymers. This enhancement may be attributed to interaction of serum proteins with the PEGylated shell of such NPs. Although PEG is generally associated with "stealth" behaviour, neutral PEG chains can still weakly interact with serum proteins such as HSA through hydrogen bonding and hydrophobic contacts.[14, 29, 30] Branched AB_2 based NPs present higher PEG density in the shell, which may promote higher protein adsorption, compared to those from the linear AB polymer. This indicates that PEG density in the corona of nanoparticles may influence nanoparticle-protein interactions/adsorption, which will subsequently alter drug diffusion and release. Additionally, analysis of release kinetics using DD Solver revealed that the release profiles of CUR from AB and AB_2 NPs are best described by the Weibull model (R^2 = 0.989-0.999, Table S.3), both in the absence and presence of serum.[31] This may suggest a complex release mechanism governed by diffusion rather than zero-order kinetics.[12, 32] Fitting to the Higuchi and Korsmeyer-Peppas models (with R^2 > 0.90 and exponent n = 0.35-0.50) also supports Fickian or quasi-Fickian diffusion, indicating that drug release mainly occurred through diffusion.[33, 34] The model best describing CUR release (Weibull) in the presence of 40% v/v serum was unchanged and diffusion remained the dominant pathway with or without serum exposure.

Fluorescence spectroscopy was then utilized to assess the possibility of interactions between encapsulated CUR and human serum. It is well established that human serum albumin (HSA) contains hydrophobic pockets that can bind a wide range of small lipophilic molecules (including polyphenols such as curcumin), and the latter can play a central role in drug pharmacokinetics. We sought to quantify the binding of HSA (from our human serum solution) with CUR. Curcumin used in drug-delivery studies is often derived from natural sources and consists of a mixture of curcuminoids, including methoxy- and bis-methoxy-curcumin, whose structural variations are known to influence albumin binding and biological activity.[35, 36]

We quantified the interactions between HSA and CUR using the standard fluorescence quenching experiment. The fluorescence from tryptophan residues located in the hydrophobic pocket of domain II of human serum albumin (HSA) has been shown to be quenched upon curcumin binding.[37-39] Excitation of an aqueous solution of serum at 280 nm yielded a HSA emission band at 338 nm that was progressively quenched upon CUR titration along with a slight blue shift at higher CUR concentrations (Fig. 3A). Log-log analysis using the modified Stern Volmer equation gave a binding constant of 1.25×10^5 M^{-1} and a binding site number of n = 1.16, consistent with reported HSA-curcumin affinities and the presence of multiple binding sites on HSA (Fig. 3B).[40, 41] This

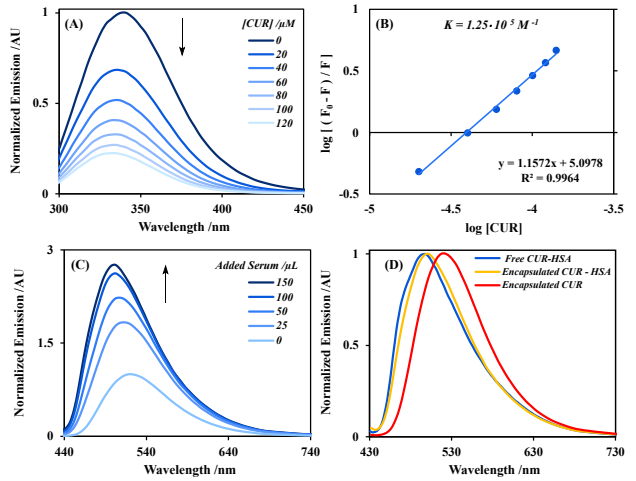

Fig. 3 (A) Normalized HSA fluorescence (λ_{ex} = 280 nm) with quenching by free CUR. (B) Resulting log/log plot for binding constant determination. (C) Normalized fluorescence emission of encapsulated CUR (AB_2 formulation, λ_{ex} = 415 nm) with addition of human serum (Initial volume = 1.00 mL). (D) Normalized fluorescence emission of AB_2 encapsulated CUR before and after the addition of 150 µL of human serum, in comparison to a free CUR-HSA (serum) complex.

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value confirms that like pure curcumin, CUR displays high binding affinity for HSA in serum.

The subsequent investigation of the effects of serum on CUR nanoformulations yielded surprising results. Encapsulated CUR was seen to emit at 522 nm in both formulations, a marked difference from free CUR in aqueous solution (λ_{em} = 553 nm, Figure S.17). Curcumin emission is highly sensitive to polarity and solvation changes, as a result offering insights into the microenvironment of the chromophore. Moving from a polar aqueous medium to the relatively non-polar core region of the micelle is expected to induce a significant blueshift in emission due to reduced hydrogen bonding. The observed emission shift (31 nm) indicates that a majority of the CUR cargo localizes in the polycaprolactone interior region of the micelle. Upon addition of human serum, pronounced and systematic changes in fluorescence spectra were observed. The addition of human serum led to progressive enhancements in emission intensity accompanied by clear hypsochromic shifts. As depicted in Figure 3C, 25 µL of serum ([HSA] = 26 µM) doubled CUR emission intensity. Higher concentrations of serum continued to increase CUR emission intensity and induce blueshifts. With respect to the miktoarm nanoformulation, the final solution (containing 150 µL of serum) was seen to emit at 502 nm, representing a total hypsochromic shift of 20 nm. These collective observations indicated a stark shift in CUR microenvironment from the moderately non-polar micellar core to a region of particularly low polarity. Significantly, the emission profile of encapsulated CUR exposed to human serum was seen to be nearly identical to that of free CUR bound to HSA from human serum (Figure 3D). Rather than remaining isolated and exempt from particle interactions with serum, it appears that encapsulated CUR participates in binding with the introduced proteins, leading to transfer or partial redistribution of the drug into the hydrophobic binding domains of HSA. These regions likely provide another favourable microenvironment for curcumin (as indicated by the high binding constant for CUR and serum HSA) in addition to the micellar core. Notably, this redistribution does not lead to any free CUR aggregation, but rather it is kept solubilized through inclusion into HSA pockets. The PEGylated nanoparticles interact with HSA, inducing serum-mediated changes in drug mobility. These transient interactions facilitate CUR migration into HSA hydrophobic pockets and ultimately promote its release from micelles.

Our findings suggest that polymeric micelles with PEGylated surfaces and their cargo interact with serum proteins. Nanoformulations from linear and branched architectures differ in terms of hydrophilic shell density, and increased PEG content seems to enhance nanoparticle-serum protein interactions. Moreover, the identity of the cargo and its affinity for serum proteins also plays an important role in this regard. These interactions do not destabilize the nanoparticles but instead facilitate drug release by easing its passage from micelle core to the aqueous environment *via* binding into serum hydrophobic pockets and preventing any aggregation. Overall, these results demonstrate that polymer architecture and protein-mediated nano-bio interactions together govern drug-release behavior.

Conflicts of interest

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There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available.

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Data availability

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