Optimization of Hard Protein Corona Isolation on Quantum Dots Using Dynamic Light Scattering and Zeta Potential Analysis

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ABSTRACT

The adsorption of biomolecules onto nanoparticle surfaces results in the formation of a protein corona, which governs the biological identity and fate of nanoparticles in physiological environments. Accurate isolation of the hard protein corona is essential for understanding nanoparticle–cell interactions and improving nanomedicine design. This study optimized experimental conditions for hard protein corona isolation from graphene and silicon-based quantum dots (QDs) using Dynamic Light Scattering (DLS) and zeta potential measurements. QDs were incubated with multiple biological media, including cancer cell culture media, patient-derived organoid (PDO) media, and serum-containing solutions for periods ranging from 1 to 24 h. Following incubation, protein-coated nanoparticles were isolated using gentle centrifugation and characterized by DLS to determine hydrodynamic diameter and surface charge. Increasing incubation time generally promoted protein adsorption, resulting in larger hydrodynamic diameters and reduced surface charge. The most stable corona was obtained after 6–12 h of incubation, whereas prolonged incubation beyond 12 h resulted in plateauing or slight reductions in particle size, suggesting protein exchange or aggregation. Graphene QDs exhibited more reproducible protein corona formation than silicon QDs, indicating that nanoparticle surface chemistry significantly influences corona evolution. The optimized protocol provides a reproducible strategy for isolating hard protein coronas suitable for downstream proteomic characterization and biological evaluation.

Keywords: Protein corona, Quantum dots, Dynamic light scattering, Zeta potential, Nanomedicine, Cancer organoids.

INTRODUCTION

Nanotechnology has revolutionized biomedical research by enabling the development of multifunctional nanoparticles for imaging, diagnostics, biosensing, and targeted drug delivery owing to their unique physicochemical properties and tunable surface functionalities [1–4]. Among these nanomaterials, quantum dots (QDs) possess exceptional optical characteristics, including high photostability, broad excitation spectra, narrow emission bandwidths, and size-dependent fluorescence, making them highly attractive for bioimaging, biosensing, and targeted therapeutic applications [5–7]. However, once nanoparticles enter biological environments such as blood, serum, or cell culture media, they rapidly adsorb proteins and other biomolecules onto their surfaces, forming a protein corona that fundamentally alters their physicochemical characteristics, biological identity, biodistribution, cellular uptake, and immunological responses [2,3,8–10].

The protein corona consists of two distinct layers with different binding affinities and exchange kinetics. The soft corona comprises loosely associated proteins that rapidly exchange with surrounding biomolecules, whereas the hard corona consists of proteins that bind strongly to the nanoparticle surface and remain adsorbed for prolonged periods [2,8,11]. Since cells interact primarily with the protein-coated nanoparticle rather than the pristine nanoparticle surface, the hard corona largely determines nanoparticle biodistribution, immune

recognition, cellular internalization, toxicity, circulation time, and therapeutic efficacy [3,4,9,12]. Consequently, reliable isolation and characterization of the hard protein corona have become essential for understanding nano–bio interactions and for the rational design of nanomedicine platforms.

Dynamic Light Scattering (DLS) is a rapid, non-destructive, and widely adopted technique for monitoring changes in nanoparticle hydrodynamic diameter associated with protein adsorption [13,14]. When combined with zeta potential analysis, DLS provides valuable information regarding nanoparticle size distribution, colloidal stability, surface charge, aggregation behavior, and the evolution of protein corona formation under different biological conditions [13–15]. These complementary analytical techniques have become indispensable tools for investigating nanoparticle–protein interactions before downstream biochemical characterization.

Despite numerous studies investigating protein corona formation, standardized protocols for isolating the hard corona remain limited due to the dynamic nature of protein adsorption and the influence of experimental variables. Factors such as nanoparticle composition, surface chemistry, incubation time, biological medium, centrifugation conditions, and washing procedures significantly affect the reproducibility and composition of the isolated corona [3,10,11,16–18]. Furthermore, differences in nanoparticle materials, including graphene- and silicon-based quantum dots, may result in distinct protein adsorption kinetics owing to variations in surface energy, functional groups, and electrostatic interactions [19,20].

Therefore, establishing optimized and reproducible isolation protocols is essential for improving the consistency of downstream proteomic analyses and biological evaluations. In this study, we optimized the isolation of hard protein coronas formed on graphene and silicon-based quantum dots using DLS and zeta potential analysis. The optimized protocol is intended to facilitate subsequent protein identification, cytotoxicity assessment, and nanoparticle interaction studies using cancer cell models and patient-derived organoids.

MATERIALS AND METHODS

Materials

Graphene quantum dots (GQDs) and silicon-based quantum dots (SiQDs) were selected as representative carbon- and semiconductor-based nanomaterials to investigate their protein corona formation behavior under biologically relevant conditions. GQDs were used due to their favorable optical properties, chemical stability, and tunable surface functional groups, while SiQDs were included to evaluate the influence of different nanoparticle compositions and surface chemistries on biomolecular interactions. To simulate diverse biological environments, multiple types of conditioned biological media were employed, including colorectal cancer cell-derived media, pancreatic ductal adenocarcinoma (PDAC) media, prostate cancer media, patient-derived organoid (PDO) media, and serum-containing culture media. These media systems provided varied protein compositions and extracellular biomolecule profiles to assess the effect of biological complexity on corona formation. The selected quantum dots and biological media enabled systematic evaluation of nanoparticle–protein interactions, surface charge modification, and size evolution during incubation, providing a foundation for optimizing hard protein corona isolation protocols.

Sample Preparation

For each experiment, 1.5 mL of biological medium (including colorectal, prostate, pancreatic ductal adenocarcinoma (PDAC), or patient-derived organoid (PDO) culture media) was mixed with 0.5 mL of either graphene quantum dots (GQDs) or silicon quantum dots (SiQDs) in low-retention polypropylene centrifuge tubes. The mixtures were gently vortexed for 10–15 s to ensure uniform nanoparticle dispersion and adequate interaction between the nanoparticles and biomolecules present in the biological media. The prepared suspensions were then incubated under controlled experimental conditions for predetermined time intervals prior to protein corona isolation and subsequent characterization by Dynamic Light Scattering (DLS) and zeta potential analysis.

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Incubation Conditions

Following sample preparation, the nanoparticle–biological medium suspensions were incubated under controlled laboratory conditions to facilitate protein corona formation. To investigate the kinetics of protein adsorption and identify the optimal incubation period for hard protein corona development, samples were incubated for 1, 1.5, 2.3, 3, 6, 12, and 24 h. These time points were selected to capture the initial rapid adsorption phase, the transition from soft to hard corona formation, and the stabilization of the protein layer at longer incubation periods. After each designated incubation interval, samples were immediately subjected to centrifugation for hard protein corona isolation, followed by Dynamic Light Scattering (DLS) and zeta potential analyses.

Isolation of Hard Protein Corona

Following the designated incubation period, the nanoparticle suspensions were subjected to centrifugation at 1.5 × g for 45 min to separate protein-coated quantum dots (QDs) from unbound proteins and other soluble biomolecules. After centrifugation, the supernatant containing free and loosely associated proteins was carefully aspirated without disturbing the nanoparticle pellet, thereby preserving the hard protein corona adsorbed on the QD surface. To minimize sample loss and maintain the integrity of the protein-coated nanoparticles, low-retention polypropylene centrifuge tubes and gentle pipetting techniques were employed throughout the isolation procedure. The recovered nanoparticle pellets were subsequently used for Dynamic Light Scattering (DLS) and zeta potential analyses to evaluate the formation and stability of the hard protein corona.

Dynamic Light Scattering and Zeta Potential Analysis

The physicochemical properties of the quantum dots (QDs) before and after protein corona formation were characterized using Dynamic Light Scattering (DLS) and zeta potential analysis. Hydrodynamic diameter measurements were performed by DLS to evaluate changes in particle size resulting from protein adsorption onto the nanoparticle surface, while zeta potential measurements were conducted to assess variations in surface charge associated with corona formation.

The hydrodynamic diameter, polydispersity index (PDI), and zeta potential were recorded for samples collected at each incubation time point. Changes in these parameters were used to monitor the kinetics of protein adsorption, evaluate nanoparticle colloidal stability, and determine the formation and maturation of the hard protein corona. An increase in hydrodynamic diameter together with alterations in surface charge was considered indicative of successful protein adsorption, whereas the PDI provided information on particle dispersion and the potential occurrence of nanoparticle aggregation during incubation. These complementary measurements enabled a comprehensive assessment of protein corona evolution under different experimental conditions.

Experimental Workflow

The optimization process was systematically performed over a five-week period to evaluate the protein corona formation behavior of quantum dots (QDs) under biologically relevant conditions and to establish a reproducible experimental framework for subsequent analyses. During the first week, graphene quantum dots (GQDs) were incubated with conditioned media derived from colorectal cancer, pancreatic ductal adenocarcinoma (PDAC), and prostate cancer models to investigate initial biomolecular interactions. In the second week, the experimental scope was expanded by incorporating silicon quantum dots (SiQDs) and additional biological media conditions, while dynamic light scattering (DLS) training and cytotoxicity assessment protocols were initiated to support nanoparticle characterization and biocompatibility evaluation.

In the third week, incubation durations were extended based on preliminary observations indicating continuous protein adsorption and dynamic evolution of the nanoparticle corona over time. The fourth week focused on introducing intermediate incubation time points to identify the transition toward corona stabilization and determine the onset of equilibrium adsorption behavior. During the fifth week, the 12- and 24-hour incubation experiments were repeated to assess reproducibility and validate the consistency of the optimized protocol. Concurrently, fabrication of poly(ethylene glycol) diacrylate (PEGDA) scaffolds was initiated to establish a

platform for future three-dimensional culture studies and to enable investigation of QD–protein corona interactions within more physiologically representative tissue-like environments.

RESULTS

Effect of Incubation Time on Protein Corona Formation

Dynamic light scattering (DLS) analysis demonstrated a clear time-dependent evolution of the protein corona surrounding quantum dots (QDs) following incubation in biological media. The progressive increase in hydrodynamic diameter with increasing incubation time indicates continuous adsorption of proteins onto the nanoparticle surface, consistent with previous studies showing that nanoparticle exposure to biological fluids results in rapid formation of a biomolecular corona that defines their biological identity [2,9]. During the initial incubation phase, particle size increased rapidly, suggesting the attachment of abundant proteins and the formation of an early, loosely organized corona layer. As incubation proceeded, the rate of size increase gradually decreased, indicating progressive occupation of surface binding sites and the transition toward a more stabilized corona structure [8,10].

The most significant and reproducible increase in hydrodynamic diameter was observed between 6 and 12 h, suggesting this period represents the primary stage of corona maturation. Beyond 12 h, several samples exhibited either stabilization or a slight reduction in particle size, indicating that corona formation is a dynamic equilibrium process involving continuous protein adsorption, exchange, and rearrangement rather than simple accumulation [3,8,12]. These changes may result from displacement of weakly bound proteins, structural reorganization of the adsorbed layer, or variations in nanoparticle aggregation and colloidal stability [9,11]. The combined DLS observations highlight the importance of incubation time in regulating QD–protein interactions, while DLS and zeta potential measurements provide complementary approaches for monitoring corona evolution and nanoparticle surface modification [13,14]. The 6–12 h incubation period was therefore identified as an optimal window for reproducible protein corona characterization.

Zeta Potential Analysis

Zeta potential measurements demonstrated progressive changes in the surface charge of quantum dots (QDs) during incubation with biological media, confirming the formation and evolution of the protein corona. The initial QDs exhibited a highly negative surface potential due to their intrinsic surface functional groups and stabilizing ligands. With increasing incubation time, the zeta potential shifted toward less negative values, indicating adsorption of proteins onto the nanoparticle surface and partial masking of the original surface charge [10,13,14].

The reduction in absolute zeta potential reflects the replacement of the nanoparticle–solution interface with a biomolecular layer, which modifies the electrostatic properties and interfacial characteristics of QDs. Similar charge alterations have been reported as a consequence of protein adsorption, where corona formation changes nanoparticle surface identity and influences subsequent biological interactions [2,10]. During the early incubation period, rapid changes in surface potential correspond to initial protein attachment and corona development. Between 6 and 12 h, the zeta potential reached a relatively stable range, suggesting that sufficient protein coverage had formed and the corona structure approached equilibrium. This stabilization indicates the development of a more persistent corona dominated by strongly associated proteins [8,11].

The zeta potential results support the DLS observations by confirming that protein adsorption modifies both the hydrodynamic size and surface properties of QDs. The combined application of DLS and zeta potential analysis provides a reliable approach for monitoring nanoparticle–protein interactions and corona evolution [13,14]. The consistent charge stabilization observed after 6–12 h suggests this incubation period provides suitable conditions for reproducible protein corona characterization and subsequent biological evaluation.

Comparison between Graphene and Silicon Quantum Dots

A comparative analysis of graphene quantum dots (GQDs) and silicon quantum dots (SiQDs) revealed distinct differences in their protein corona formation behavior, highlighting the influence of nanoparticle composition

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and surface chemistry on nano–bio interactions. GQDs exhibited more reproducible hydrodynamic diameter distributions and lower experimental variability, suggesting relatively stable protein adsorption behavior and consistent corona development. This stability may be associated with the robust carbon framework and controlled surface functional groups of GQDs, which regulate biomolecular interactions at the nanoparticle interface [10,15].

In contrast, SiQDs demonstrated greater variations in hydrodynamic diameter and zeta potential during incubation, indicating a more dynamic interaction with proteins present in the biological environment. Such differences may arise from variations in surface oxidation, charge distribution, and chemical reactivity, which can influence protein binding affinity and corona composition [3,11]. Previous studies have demonstrated that nanoparticle physicochemical properties, including surface chemistry, size, and charge, play critical roles in determining protein adsorption patterns and the resulting biological identity of nanoparticles [2,10,16].

The observed differences between GQDs and SiQDs emphasize that protein corona formation is highly dependent on nanoparticle-specific characteristics rather than being solely governed by the surrounding biological medium. Furthermore, the combination of DLS and zeta potential measurements provides valuable insight into temporal changes in nanoparticle size and surface charge associated with corona evolution [13,14]. These findings highlight the importance of optimizing nanoparticle surface properties to achieve predictable biological performance in biomedical applications.

Identification of Optimal Isolation Conditions

The optimal conditions for protein corona isolation were determined by integrating DLS and zeta potential measurements to evaluate time-dependent changes in nanoparticle size and surface charge. Incubation periods shorter than 3 h resulted in incomplete corona formation, as indicated by limited changes in hydrodynamic diameter and zeta potential, suggesting insufficient protein adsorption and incomplete coverage of the quantum dot (QD) surface [10,13]. In contrast, incubation between 6 and 12 h resulted in stable and reproducible changes in both hydrodynamic diameter and surface charge, indicating the establishment of a mature protein corona with relatively stabilized nanoparticle–protein interactions. Previous studies have demonstrated that nanoparticle coronas undergo rapid initial protein adsorption followed by structural rearrangement and equilibration, with the final corona composition being influenced by incubation time and surface properties [2,8,11].

Extending incubation beyond 12 h produced limited additional changes in particle size and surface charge while increasing experimental variability. This behavior is consistent with the dynamic nature of the protein corona, where continuous adsorption, desorption, and exchange of proteins occur even after apparent stabilization [8,9,16]. Therefore, a 6–12 h incubation period combined with gentle centrifugation was selected as the optimal protocol for hard corona isolation, providing sufficient corona maturation while minimizing disruption of weakly associated biomolecules and maintaining nanoparticle stability.

Complementary Validation and Statistical Considerations

Although DLS and zeta potential measurements provided useful physicochemical evidence for protein corona formation, these techniques do not directly identify the proteins adsorbed to the quantum dot surface or confirm the morphology of the corona layer. Therefore, complementary analytical approaches are warranted to validate the composition and structural characteristics of the isolated hard protein corona. SDS-PAGE could initially be employed to assess the protein profile and molecular-weight distribution of proteins associated with the quantum dots. For more comprehensive identification and characterization, liquid chromatography–tandem mass spectrometry (LC-MS/MS) could be used to determine the protein composition of the hard corona and identify proteins with preferential or persistent binding to the nanoparticle surface. In addition, transmission electron microscopy (TEM) could provide morphological information on the quantum dots before and after biological exposure and help evaluate changes in particle morphology or aggregation associated with protein adsorption. Combining these complementary techniques with DLS and zeta potential measurements would provide a more comprehensive characterization of both the physicochemical and biochemical properties of the protein corona.

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The statistical robustness of the experimental findings should also be strengthened through clearly defined biological and technical replicates. For each experimental condition, independent biological replicates should be analyzed alongside technical replicate measurements to distinguish biological variability from instrumental variation. Quantitative DLS parameters, including hydrodynamic diameter and polydispersity index (PDI), together with zeta potential values, should be reported as mean ± standard deviation (SD) or mean ± standard error of the mean (SEM), with the number of independent replicates explicitly stated. Where appropriate, 95% confidence intervals should also be reported to provide an estimate of the precision of the measurements. Statistical comparisons among incubation times, quantum-dot types, and biological media should be performed using an appropriate statistical test, such as one-way or two-way analysis of variance (ANOVA), followed by a suitable post-hoc multiple-comparison test. Statistical significance should be defined a priori (e.g., $p < 0.05$), with exact p-values reported where possible.

Importantly, because the present dataset does not provide the number of biological/technical replicates, confidence intervals, or statistical test results, these values should be added after the raw experimental data are analyzed rather than estimated or fabricated. This additional validation would substantially improve the reproducibility, statistical credibility, and mechanistic interpretation of the optimized hard-corona isolation protocol.

DISCUSSION

Protein corona formation is a dynamic and time-dependent process regulated by competitive protein adsorption, molecular rearrangement, and continuous exchange between nanoparticle surfaces and surrounding biological fluids. The observed increase in hydrodynamic diameter during the initial incubation period indicates rapid adsorption of proteins onto quantum dot (QD) surfaces, consistent with previous studies demonstrating the spontaneous formation of biomolecular coronas immediately after nanoparticle exposure to biological environments [2,8,9].

The stabilization of particle size after approximately 6–12 h suggests the transition from an initially unstable soft corona to a more established hard corona dominated by strongly associated proteins. The subsequent stabilization or slight decrease in hydrodynamic diameter at longer incubation times may be attributed to corona remodeling processes, including displacement of weakly bound proteins by higher-affinity species, commonly described by the Vroman effect [3,8]. These observations highlight that corona formation is not a static adsorption process but a continuously evolving equilibrium between protein association and dissociation.

The progressive shift of zeta potential toward less negative values further confirms protein adsorption by demonstrating surface charge masking and modification of the nanoparticle–solution interface. Similar changes in surface charge have been reported for various nanomaterials and demonstrate that DLS combined with zeta potential measurements provides a reliable approach for monitoring corona formation and nanoparticle surface transformation [10,13,14].

The higher reproducibility observed for graphene quantum dots (GQDs) compared with silicon quantum dots (SiQDs) suggests that nanoparticle composition, surface functionalization, and chemical stability strongly influence corona formation behavior [10,11,15]. These findings emphasize the importance of considering nanoparticle-specific properties when establishing standardized protein corona isolation protocols. Although DLS and zeta potential analyses cannot directly identify the molecular composition of adsorbed proteins, they provide rapid and sensitive evaluation of corona development and serve as valuable preliminary screening tools prior to advanced proteomic characterization [13,16]

Challenges and Troubleshooting

Several technical challenges were encountered during protocol optimization.

Initial experiments showed inconsistent protein binding, necessitating repetition with extended incubation periods. An anomalous increase in particle size observed near the 1.5 h time point highlighted the dynamic nature of early soft corona formation. Sample recovery after centrifugation required careful pipetting to minimize

nanoparticle loss. The use of low-retention centrifuge tubes substantially improved reproducibility. PEGDA scaffold fabrication also required optimization due to incomplete polymerization during initial printing trials.

CONCLUSIONS

This study established an optimized protocol for isolating hard protein coronas formed on graphene and silicon quantum dots using dynamic light scattering (DLS) and zeta potential analysis. Systematic evaluation of incubation time revealed that a 6–12 h incubation period followed by gentle centrifugation provided the most stable and reproducible corona formation while minimizing sample loss, aggregation, and experimental variability. The combined analysis of hydrodynamic diameter and surface charge demonstrated progressive protein adsorption, corona maturation, and stabilization of nanoparticle–protein interactions over time.

Graphene quantum dots exhibited more consistent corona characteristics and lower variability compared with silicon quantum dots, emphasizing the critical influence of nanoparticle composition, surface chemistry, and interfacial properties on protein adsorption behavior. These findings highlight the importance of optimizing nanoparticle-specific conditions when developing standardized protein corona isolation strategies. Although DLS and zeta potential measurements do not provide direct identification of corona proteins, they offer rapid and sensitive assessment of corona formation and stability, serving as valuable preliminary tools before advanced proteomic analysis. The optimized workflow provides a reliable platform for future investigations of nanoparticle–protein interactions, biological responses, and the development of quantum dot-based biomedical applications.

Future Perspectives

Future work should focus on identifying the molecular composition of the isolated hard corona using SDS-PAGE and liquid chromatography–mass spectrometry (LC-MS/MS). Cellular uptake, intracellular trafficking, and cytotoxicity should be evaluated in pancreatic, colorectal, and prostate cancer models. Integration of PEGDA-based three-dimensional organoid platforms will provide physiologically relevant microenvironments for investigating nanoparticle behavior and improving translational nanomedicine.

Significance

Standardization of protein corona isolation remains a major challenge in nanobiotechnology. The protocol developed in this work improves reproducibility while preserving tightly bound protein layers suitable for downstream characterization. The findings contribute to the rational design of nanoparticle-based therapeutics and imaging agents by enhancing understanding of nanoparticle–protein interactions within complex biological environments. Ultimately, these optimized methodologies may facilitate the development of safer, more effective nanocarriers for precision oncology and targeted drug delivery.

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Conflict of Interest

The authors declare that they have no competing financial interests.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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