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RESEARCH PAPER

Rational Design, Development, and Physicochemical Characterization of Gallic Acid- and Hyaluronic Acid-Functionalized Selenium Nanoparticles

Dhuha Al-Hasnawi [1], Dhafir Masheta [2], Asim A. Balakit [3]*

[1] *College of Pharmacy, University of Babylon, Hillah, Iraq*

[2] *Department of Pharmaceutics, College of Pharmacy, University of Babylon, Babylon, Iraq*

[3] *Department of Pharmaceutical Chemistry, College of Pharmacy, University of Babylon, Babylon, Iraq*

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ABSTRACT

Nano carriers are efficient drug delivery systems for targeting various diseases, including cancer. Selenium nanoparticles (SeNPs) have garnered significant interest due to their advantageous physicochemical characteristics and prospective applications in nanodrug delivery systems. This study involved the rational design, synthesis, and physicochemical characterization of gallic acid- and hyaluronic acid-functionalized selenium nanoparticles (GA /HA-SeNPs) by a simple aqueous reduction process. Various HA: Se and GA: Se mass ratios were examined to identify the optimal formulation for generating stable and monodisperse nanoparticles. The produced nanoparticles were evaluated using dynamic light scattering (DLS) and zeta potential analysis to assess particle size distribution, polydispersity index (PDI), and colloidal stability. HA-functionalized SeNPs demonstrated Z-average diameters between 123.6 and 130.8 nano meters (nm), with PDI values ranging from 0.085 to 0.182. Zeta potential readings varied from −12.8 to −24.8 millivolt (mV), signifying satisfactory colloidal stability. The inclusion of gallic acid further optimized the characteristics of the nanoparticles. The ideal formulation was achieved with HA: Se and GA:Se ratios of 5:1, resulting in nanoparticles with a particle size of 98.91 nm, a PDI of 0.065, and a zeta potential of −16.7 mV. These results indicate the effective creation of stable and homogenous functionalized selenium nanoparticles appropriate for prospective nanomedical applications.

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INTRODUCTION

Cancer is one of the most challenging health issues with continuous raising in incidence and mortality worldwide, even with the advances in diagnosis and therapy strategies [1]. Chemotherapy is one of effective cancer treatments, however, it has some significant limitations such as drug resistance which make no longer effective where cancer cells became able to evade drug induced cell death resulting therapeutic failure [2]. The drug resistance can occur by a variety of mechanisms, such as drug efflux and DNA repair

* *Corresponding Author Email: duha.hadi@student.uobabylon.edu.iq*

enhancement to evasion of apoptosis and cancer stem cell survival [3]. The other serious limitations are the lack of selectivity towards cancer cells, poor pharmacokinetics such as rapid systemic clearance and low solubility, resulting in dose-limiting toxicities that adversely affect patient outcomes [4]. Accordingly, there is a continuous urgent need to improve cancer treatment strategies and develop new chemotherapeutic agents with enhanced efficacy and lowered toxicity. Nanodrugs and nanodrug-drug delivery systems offer proper solutions to tackle the above limitations, due to their characteristics such as nano-size and functionalities, nanoparticles can be developed to act as effective cancer chemotherapeutics with improved drug stability and solubility, prolonging systemic circulation, and enabling enhanced accumulation in tumour tissues by the enhanced permeability and retention (EPR) effect [5]. Nanocarriers offer controlled and sustainable drug release which support maintenance of optimal therapeutic levels at cancer sites with reduced systemic toxicity [6]. Because of their outstanding properties, selenium nanoparticles have attracted the attention as multifunctional therapeutic platform, they have the ability to influence multiple cell death pathways, they can act as antioxidant and anticancer agents with low toxicity levels [7]. Functionalized selenium nanoparticles with copper, polyphenols and hyaluronic acid showed significant anticancer activities and improved biocompatibility in different cancer types [8,9]. Other surface modified selenium nanoparticles have been shown to induce apoptosis, oxidative stress modulation, and tumour suppression in vitro [10]. As targeted drug delivery systems, nanoparticles can be functionalized by targeting moieties that make them selective toward cancer cells rather than normal cells. Hyaluronic acid is one of the macromolecules used for such purpose, it facilitates active, receptor-mediated uptake by cancer cells overexpressing CD44, thereby enhancing selectivity and cellular internalization [11]. It is reported that hyaluronic acid coated nanodrug delivery systems have improved cancer targeting and therapeutic index in variety of cancer types [12]. Gallic acid, a natural polyphenol, it has been studied for its anti-cancer, antioxidant, anti-inflammatory activities, inducing apoptosis, and inhibiting cancer cells proliferation in variety of cancers [13].

The integration of bioactive components (such as gallic acid and hyaluronic acid) with selenium nanoparticles cand develop nanoplatform with enhanced selectivity, improved therapeutic efficacy and mitigated systemic toxicity. Based on that and as a part of our interest in the development of anticancer agents and bioactive selenium nanoparticles [14,15], here we report the synthesis of selenium nanoparticles stabilized and functionalized by hyaluronic acid and gallic acid (HA/GASe NPs) and studying the optimum mass ratios that achieve the best particle size and surface charge that make HA/GA-SeNPs a promising nanodrug delivery system to deliver anticancer agents such as doxorubicin.

MATERIALS AND METHODS

Materials: sodium selenite (Na_2SeO_3) purchased from LOBA CHEMIE PVT.LTD, (precursor salt), ascorbic acid (Vc), purchased from East Francis Street, Ontario, California, USA, chitosan (CS) purchased from Glentham LIFE SCIENCES, and gallic acid (GA) purchased from MAY&BAKER LTD DAGENHAM ENGLAND. Hyaluronic acid was used as acidic form with average molecular weight 25000 Da, and purchased from AVONCHEM (UK). The synthesized molecules were characterized by DLS and Zeta potential analysis which were recorded on Malvern Zetasizer.

Synthesis of GA/HA-SeNPs

In 10 ml glass tube charged with magnetic bar, ascorbic acid (2 ml; 1.8 mg/mL) was placed, gallic acid (0.5 and 1.0 mL; 2 mg/mL) was added with continuous stirring, sodium selenite (1 ml, 0.9 mg/mL) was added in dropwise manner, the solution was stirred for 30 minutes until reddish-orange colour appeared, indication the formation of SeNPs. Hyaluronic acid (0.41, 0.62, 0.82 and 1.03 ml; 5 mg/mL) was then added to the reaction mixture, deionized water was added to get final volume of 5 mL, the mixture was then further stirred for 2 hours to complete the formation of the functionalized nanoparticles. The product was purified by using dialysis bags (3500 KD) against deionized water for 24 hours.

Characterization of GA/HA-SeNPs

Dynamic light scattering (DLS) ana Zeta potential measurements by Malvern Zetasizer

Malvern Zetasizer device was used to measure the hydrodynamic diameter, PDI and zetapotential for synthesized gallic acid- and hyaluronic acid-

functionalized selenium nanoparticles (GA/ HA -SeNPs). These analyses were performed at the faculty of Education for pure sciences university of Basra. Which operates based on dynamic light scattering and electrophoretic light scattering (ELS) principles.

First, to determine the DLS, all samples are diluted with deionized water to avoid multiple scattering of light. Measurements conducted at 25°C, and each sample was analysed in triplicate to ensure reproducibility. Second, to determine the zeta potential, samples were loaded into folded capillary cells, and measurements were carried out at 25°C. The zeta potential values were calculated

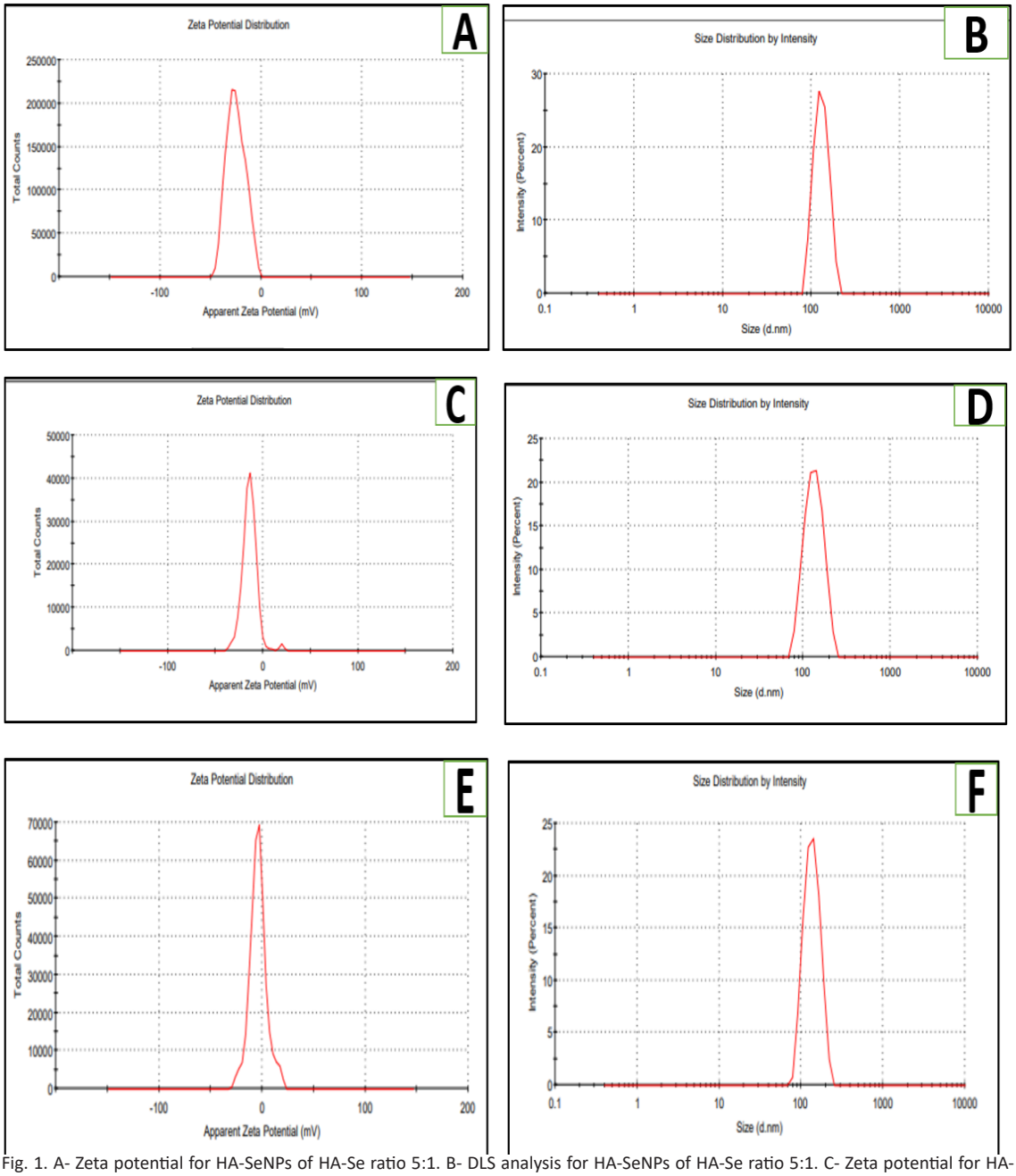

Fig. 1. A- Zeta potential for HA-SeNPs of HA-Se ratio 5:1. B- DLS analysis for HA-SeNPs of HA-Se ratio 5:1. C- Zeta potential for HA-SeNPs of HA-Se ratio 7.5:1. D- DLS analysis for HA-SeNPs of HA-Se ratio 7.5:1. E- Zeta potential HA-SeNPs of HA-Se ratio 10:1. F- DLS analysis for HA-SeNPs of HA-Se ratio 10:1.

using the Smoluchowski model, providing insight into the surface charge and stability of the HA/GA-SeNPs systems.

RESULTS AND DISCUSSION

To attain optimal drug loading, enhanced efficacy, and selectivity towards cancer cells for selenium nanoparticles (SeNPs), the natural macromolecule hyaluronic acid (HA) and gallic acid (GA) have been integrated into the synthesis process to produce functionalized selenium nanoparticles (GA /HA-SeNPs), with both biocompatible materials serving as stabilizers and functionalizing agents, that make SeNPs more effective drug delivery system

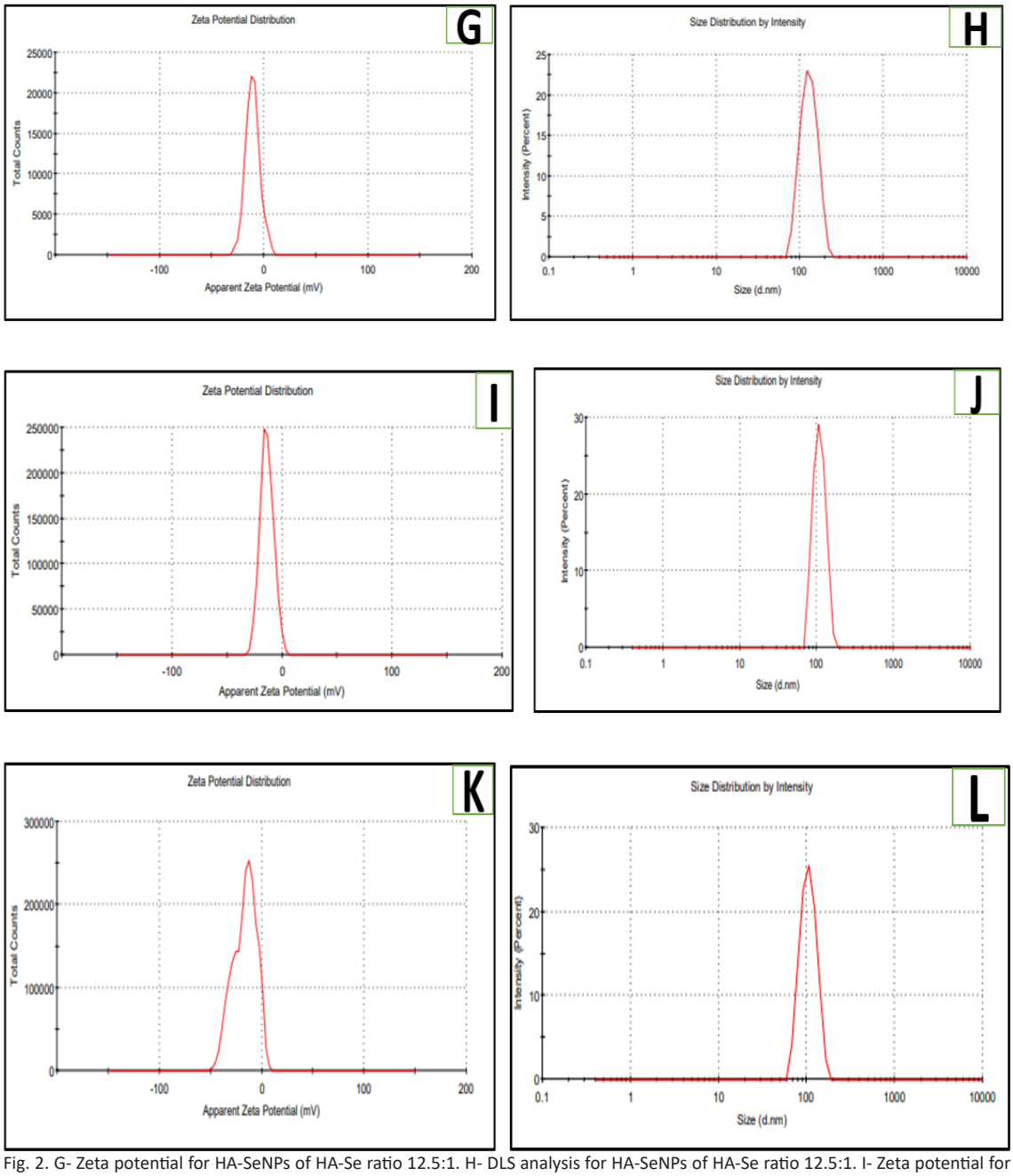

Fig. 2. G- Zeta potential for HA-SeNPs of HA-Se ratio 12.5:1. H- DLS analysis for HA-SeNPs of HA-Se ratio 12.5:1. I- Zeta potential for HA/GA-SeNPs of HA: Se 5:1 and GA: Se 2.5:1. J- DLS analysis for HA/GA-SeNPs of HA: Se 5:1 and GA: Se 2.5:1. K- Zeta potential for HA/GA-SeNPs of HA: Se 5:1 and GA: Se 5:1. L- DLS analysis for HA/GA-SeNPs of HA: Se 5:1 and GA: Se 5:1.

[16,17]. The findings of this study indicate that the integration of HA and GA markedly affected the physicochemical properties of SeNPs, underscoring their prospective use as targeted nanodrug delivery systems for cancer treatment, specifically regarding particle size, polydispersity index (PDI), and zeta potential. To achieve the optimal synthesis process for generating monodisperse nanoparticles with perfect size and surface charge crucial attributes for nanodrug delivery systems various HA: Se and GA: HA ratios were employed, and the resulting products were analysed using DLS and zeta potential assessments. The obtained results are illustrated in Tables 1 and 2, and Figs. 1-3.

The produced GA/HA -SeNPs demonstrated

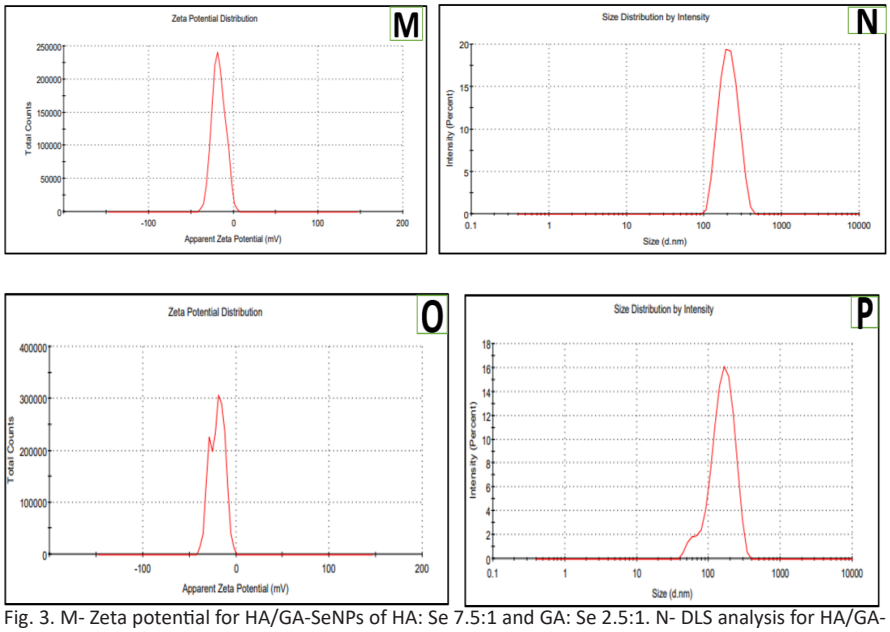

Fig. 3. M- Zeta potential for HA/GA-SeNPs of HA: Se 7.5:1 and GA: Se 2.5:1. N- DLS analysis for HA/GA-SeNPs of HA: Se 7.5:1 and GA: Se 2.5:1. O- Zeta potential for HA/GA-SeNPs of HA: Se 7.5:1 and GA: Se 5:1. P- DLS analysis for HA/GA-SeNPs of HA: Se 7.5:1 and GA: Se 5:1.

Table 1. Dynamic light scattering (DLS) and Zeta analysis for hyaluronic acid-selenium nanoparticle (HA-SeNPs), the results involve size average (Z-average), polydispersity index (PDI), standard deviation (St Dev) and zeta potential for hyaluronic to selenium ratio (HA: Se) Entries 1-4.

Entry	HA: Se	DLS			Zeta	
		Z-Average (nm)	PDI	St Dev (nm)	Zeta Potential (mV):	St Dev (mV)
1	5:1	128.6	0.107	24.85	-24.8	9.24
2	7.5:1	128.7	0.085	33.08	-13.8	6.99
3	10:1	130.8	0.126	30.88	-16.7	8.28
4	12.5:1	123.6	0.182	30.21	-12.8	6.83

Table 2. Dynamic light scattering (DLS) and Zeta analysis for hyaluronic acid/ gallic acid -selenium nanoparticle (GA/HA-SeNPs), the results involve size average (Z-average), polydispersity index (PDI), and Zeta analysis for gallic to selenium ratio (GA: Se), Entries 5-10.

Entry	HA: Se	GA: Se	Z-Average (nm)	PDI	Zeta Potential (mV):
5		0:1	128.6	0.107	-24.8
6	5:1	2.5:1	108.0	0.146	-13.9
7		5:1	98.91	0.065	-16.7
8		0:1	128.7	0.085	-13.8
9	7.5:1	2.5:1	185.5	0.251	-17.3
10		5:1	141.5	0.203	-20.1

particle sizes in the nanometres range (98.91–130.8 nm), a low polydispersity index (PDI), and negative zeta potential values, signifying effective stabilization and homogeneous nanoparticle production. These findings are significant because nanoparticle size and surface charge are essential factors affecting biodistribution, cellular uptake, circulation duration, and tumour formation via the increased permeability and retention (EPR) effect [18].

The DLS analysis revealed that increasing the HA:Se ratio affected both particle homogeneity and surface charge. Of the formulations examined, the HA:Se ratio of 7.5:1 exhibited the lowest PDI value (0.085), signifying exceptional monodispersity and uniform particle dispersion. Low PDI values (<0.1) are typically linked to very homogenous nanoparticle populations and enhanced formulation repeatability. The enhancement in nanoparticle homogeneity is due to the stabilizing influence of HA, which creates a hydrophilic protective shell around the selenium core, thereby inhibiting nanoparticle aggregation via steric repulsion. Comparable results were observed with HA-coated nanocarrier systems, where HA markedly improved colloidal stability and diminished particle aggregation in aqueous environments [19]. Moreover, HA has exceptional biocompatibility and biodegradability, rendering it very appropriates for biomedical applications, particularly in cancer-targeted drug delivery systems [20].

The zeta potential tests indicated negative surface charges between −12.8 and −24.8 mV, signifying moderate to good colloidal stability of the synthesized nanoparticles. The pronounced negative charge detected at reduced HA concentrations may stem from the heightened exposure of carboxylate groups on the nanoparticle surface. Conversely, elevated HA content probably induced multilayer adsorption and partial occlusion of these ionizable groups, leading to diminished negative zeta potential values. Prior research indicated that negatively charged selenium nanoparticles display increased serum stability and less nonspecific interactions with plasma proteins, therefore enhancing systemic circulation and mitigating toxicity [21].

The addition of gallic acid enhanced the physicochemical properties of the produced nanoparticles. The optimized formulation (GA: HA: Se ratio of 5:5:1) demonstrated the smallest particle size (98.91 nm), the lowest PDI (0.065), and an appropriate zeta potential (−16.7 mV), indicating the effective synergistic stabilization impact of both HA and GA. Gallic acid likely facilitated nanoparticle stabilization via hydrogen bonding and antioxidant-mediated surface protection, inhibiting nanoparticle aggregation during synthesis. These findings correlate with prior studies [22].

The obtained particle size of approximately 100 nm is particularly favourable for cancer-targeted drug delivery [23]. Furthermore, HA functionalization enables active targeting by interacting with CD44 receptors, which are overexpressed in numerous cancer cells. This receptor-mediated uptake can augment cellular internalization and elevate drug accumulation in tumour tissues while minimizing exposure to normal cells [24].

Overall, this study effectively established a stable and monodisperse GA/HA - functionalized selenium nanoparticle system, characterized by physicochemical features that provide it a promising candidate for nanodrug delivery in effective and selective cancer therapy for future research.

CONCLUSION

Gallic acid- and hyaluronic acid-functionalized selenium nanoparticles (GA /HA-SeNPs) were successfully synthesized by chemical reduction method and the physicochemical assessment tests revealed that a GA: HA: Se ratio of 5:5:1 produced the most favourable formulation, distinguished by minimal particle size, a low polydispersity index, and sufficient surface charge stability. The results suggest that the proposed nanoplatform may serve as an efficient drug delivery method for future anticancer applications, particularly for doxorubicin.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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