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REVIEW PAPER

A review study on the application of polymeric-based nanoparticles as a novel approach for enhancing the stability of albumins

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ABSTRACT

Albumin is a liver synthesized protein and the most abundant non-glycosylated plasma protein with a molecular weight of 66 kDa and 585 amino acids. It works as a preservative to maintain plasma volume, osmotic blood pressure, and microvascular integrity. It also works as a blood carrier for endogenous and exogenous substances, improving the stability and survival of drugs and components by corona protein formation around them. However, the presence of different albumin preservatives and stabilizers that can affect other blood cells and binding of preservatives to albumin caused a lower binding capacity of commercial albumin that needs to be addressed. Nowadays nanotechnology is considered a promising field of research in biology and biological products. To the best of our knowledge, this is the first study to review the effects of polymeric nanoparticles on the stability and function of albumin products. A literature review was performed on the publications available on the subject matter from 2011 to 2021. The keywords in different combinations such as "polymeric nanoparticles", "nanoparticles", "stability", and "serum albumin" were searched in databases of PubMed and Scopus. The collected data were then analyzed. According to review results, PLGA, a negatively charged polymer, with lower molecular weight can be introduced as an effective candidate for enhancing albumin stability. Also, it can be concluded that while some cationic nanoparticles can increase the thermal stability of albumin, they have no favorable effects on the albumin structure; thus, they must be modified structurally to be applicable for the production of albumin products.

Keywords: *Nanoparticles, Polylactic scid-polyglycolic acid copolymer, Protein stability, Serum albumin*

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INTRODUCTION

Human serum albumin (HSA), the most abundant plasma protein, is a non-glycosylated globular protein (66 kDa and 585 amino acids) with an isoelectric point of 4.3–4.9 [1-3]. Under physiological conditions, each albumin has near 15 negative net charges that cause the solubility of this protein in water [4]. There are three domains in the 3D structure of albumin (I, II, and III) and each domain contains two identical subunits (A and B) [5-7] (Fig. 1). The structure of albumin is very stable due to the presence of disulfide bridges between 34 cysteine residues. These 17 disulfide bridges improve HSA stability and half-life so that this protein has a half-life of about 15-19 days [7]. This protein is synthesized by the liver and has several roles in the body, including maintaining plasma volume, osmotic blood pressure, and microvascular integrity, acting as a blood carrier for endogenous and exogenous substances, increasing the stability and survival of drugs and components by corona protein formation around them [8, 9]. Due to the importance of albumin, a decrease in the amount of it causes some diseases

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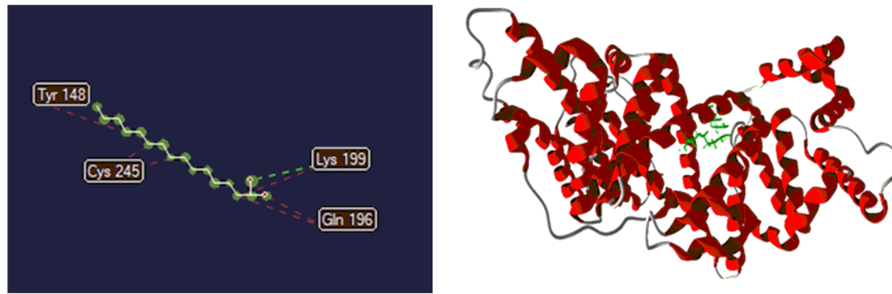

Fig. 1. Structure and binding sites of albumin. Tyrosine 148, cysteine 245, lysine 199, and glycine 196 are four critical amino acid residues in the albumin structure

Fig. 2. High cost, enzymatic degradation, immunogenicity, viral contamination, toxicity, and side effects of preservatives (e.g., inhibition of DNA/RNA, amino acid synthesis, hypoglycemia, inhibition of platelet, and degradation of muscle proteins) are some challenges in using albumin products

such as hypovolemia and hypoproteinemia [10, 11]. For almost 100 years, albumin blood products have been widely produced in high demand and used in various fields. On the one hand, these products are used to compensate for blood loss in patients undergoing surgery or chemotherapy/ radiotherapy, patients with severe burns, shocks, chronic diseases, cardiopulmonary bypass, acute liver failure, and edema [10-13]. On the other hand, albumin products are used in pharmacology to increase drug stability, prevent degradation, and target the drug delivery system [14]. They are also applied in research as a supplement to cell culture media, for protein fusion, as cryopreservation, and as a stabilizer agent for proteins [1, 15]. There are some problems in the preparation of albumin products (Fig. 2), which can be attributed to the presence of different preservatives and stabilizers that can affect other blood components of red blood cells. The two most widely used preservatives for thermal sterilization are N-acetyltryptophanate and sodium caprylate. N-acetyltryptophanate competes with bilirubin for binding to albumin. Thus, the amount of this

compound affects the binding capacity of albumin to bilirubin and its detoxifying properties. In addition, sodium caprylate induces some adverse effects (e.g., inhibition of DNA/RNA synthesis and amino acid metabolism, hypoglycemia, endothelial permeability disorder, suppression of platelet function, and degradation of muscle protein). The binding of preservatives to albumin leads to a lower binding capacity of commercial albumin (to molecules and drugs) than natural albumin. As a result, patients using albumin products may suddenly experience large levels of free metabolites in the blood that cannot bind to commercial albumin which causes a lot of unwanted side effects [16, 17]. On the other hand, albumin injection increases albumin leakage which can cause tissue edema, albuminuria, and hypoalbuminemia. In these cases, repeated injections of albumin should be performed, which adversely increases leakage and edema. In this field, the increased hydrodynamic radius of albumin by polymers can be effective to prevent albumin leakage [4]. Also, free proteins have some drawbacks such as enzymatic degradation, immunogenicity, and cytotoxicity. To date, some studies tried to reduce these advantages without changing protein structure and function by synthetic polymers [18].

Using polymeric nanoparticles in improving the quality of blood products has received a lot of attention today [19-24]. However, few studies have been conducted to investigate the effect of these nanoparticles on albumin products. In this regard, the purpose of the present study is to review the studies on the improvement of albumin products using nanopolymers and the possible effects of polymeric nanoparticles on the structure and performance of albumin.

Polymeric nanoparticles (PNPs)
Chitosan (CS)

Chitosan is a cationic polysaccharide consisting of glucosamine and N-acetylglucosamine units linked by β (1-4) glycosidic bonds obtained from chitin deacetylation (Fig. 3B). This polymer is biocompatible, biodegradable, and non-toxic, which can be easily manipulated by nanotechnology engineering to gain more special properties [25-30]. However, the pH-dependent positive charges on the CS surface predispose it to react with negatively charged sites in the blood vessels, such as epithelial and blood cell membranes, and polar proteins [31, 32]. Since albumin makes up 60% of serum proteins and has negative charges at physiological pH, therefore, it is prone to react with CS-NPs [33]. In this regard, Bekale *et al*. evaluated the impact of CS molecular weight (15, , and 200 kDa with the same degree of deacetylation 90%) on BSA- and HSA-CS interactions. They revealed that interactions induced some changes in the conformation of native proteins. The larger CSs (200 kDa) induced

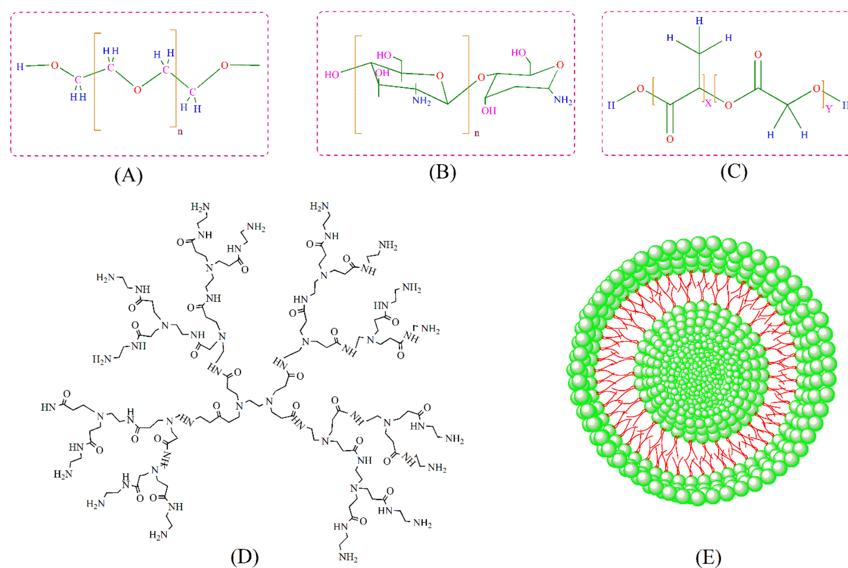

Fig. 3. Compounds such as (A) polyethylene glycol (PEG), (B) chitosan, (C) polylactic acid-polyglycolic acid copolymer (PLGA), (D) dendrimer, and (E) liposomes have been used for albumin modification

more secondary structure changes in proteins [34]. In another study, Li *et al*. investigated the effects of different pH values and BSA/chitosan ratio on the interaction between CS and BSA and the consequent protein conformational changes. The results showed that both of them affected CS-BSA interaction so that the protein and CS interacted with each other by electrostatic interactions that depended on the mixture's pH and the viscosity of the solution. They revealed that the addition of CS altered the microenvironment and the secondary structure of BSA via tryptophan fluorescence quenching of the protein [35]. Based on the fact that the addition of sulfate residue in the CS chain can reduce the interactions between CS and blood components by increasing the electrostatic repulsion, Moraes *et al*. prepared sulfated chitosan (SC) film, with a larger distribution of sulfate groups by substitution of three reactive groups in CS chain and then assessed its impact on albumin. They suggested that chemical modification of CS with sulfate improved the blood compatibility of CS by inhibition of BSA and fibrinogen adsorption, reduced platelet adhesion, and accelerated anticoagulant activity in the intrinsic pathway [36]. Moreover, Shagholani *et al*. synthesized a magnetic NP coated with CS and then modified that with polyvinyl alcohol (PVA) without any crosslinker and then investigated its possible effect on BSA. These NPs had low BSA protein adsorption capacity, which presented that they are a suitable candidate for drug delivery [37]. The mechanistic detail of the interaction between CS-based biocompatible silver nanoparticles (AgNPs) and HSA was investigated by Sen *et al*. Interestingly, CS-AgNPs could spontaneously attach to HSA without inducing significant conformational changes in albumin. In addition, this interaction reduced amyloid fibril formation and β-sheet content in HSA, so that amorphous and globular aggregates significantly decreased in the presence of CS-AgNPs [38]. In another study, Benghanem *et al*. prepared the hydrogels using carboxymethylcellulose (CMC) and CS with and without crosslinking agents and assessed their effects on albumin. They revealed that CMC-CS-based hydrogels exhibited an *in vitro* anti-inflammatory activity by reducing albumin denaturation in a dose-dependent manner [39]. In addition, Karpuraranjith *et al*. examined the synergistic influence of CS-zinc-tin oxide colloidal NPs on BSA. They indicated that CS-zinc-tin oxide NPs could destabilize BSA [40]. Liu *et al*. tried to develop a new approach to improve the blood compatibility of paclitaxel/chitosan (PTX/CS) nanofiber (NF) coatings using layer-by-layer (LbL) assembly with phosphorylcholine group poly (2-methacryloyloxyethylphosphorylcholine-co-methacrylicacid; PMA) polyanion and CS polycation. They could successfully synthesize multilayered PMA/CS films on the PTX/CS NF coatings, which improved hemocompatibility by 94% inhibition of platelet adhesion and 60-70% suppression of bovine plasma fibrinogen and BSA adsorptions [41]. In another study, Qashqoosh *et al*. loaded Lansoprazole, an antiulcer drug, into CS in the presence of Tween 80 and then evaluated the interaction between BSA and the synthesized NPs (NLPZ). Similar to Sen *et al*. study, they also revealed that the formation of BSA-NLPZ was exothermic, spontaneous, and enthalpically driven, based on thermodynamic parameters. However, the secondary structure of BSA was reformed by NLPZ and LPZ in this study. Based on data, the binding affinity of NLPZ with BSA was decreased compared with LPZ, meaning that drug delivery of NLPZ into tissue may be higher [42]. Manea *et al*. prepared an effective drug delivery system by ciprofloxacin-HCl-Chitosan/Tween/Tripolyphosphate (CIP@CH-TW/TPP) and reported that the interaction between CIP@CH-TW/TPP nanocomposites and BSA was spontaneous and enthalpically driven involving both hydrogen bonding and Vander Waals forces [43]. In a different study, Yun *et al*. attended to improve the hemocompatibility of the polysulfone (PSf) membrane, which is commonly used in blood purification fields but has inadequate blood compatibility. For this purpose, they grafted 4-(chloromethyl) benzoic acid (CMBA) and sulfonated hydroxypropyl chitosan (SHPCS) onto the PSf surface and then assessed the influences of SHPCS-BAPSf membrane on protein adsorption and other blood components. Based on data, the BSA adsorption of the PSf membrane was reduced after grafting. Blood compatibility tests also demonstrated that the SHPCS-BAPSf membranes were more hemocompatible than the PSf membrane [44]. The effects of various polymeric-based nanoparticles on the albumin have been summarized in Table 1.

Poly(D,L-lactic-co-glycolic acid) (PLGA)

This biocompatible and biodegradable copolymer is synthesized through ring-opening polymerization of poly lactic acid (PLA) and

Table 1. Summarized effects of nanopolymers on albumin

NPs	Characteristics	Induction of structural changes	Other effects on Albumin	Ref.
CS	Interaction between BSA/HSA and 15, 100, and 200 kD chitosan (90% deacetylation)	Size-dependently induced	For BSA: the affinity order was 200> 100> 15 kD and mostly hydrophobic For HSA: 100> 200> 15 kD and mostly electrostatic	[34]
	Interaction between BSA and Water-soluble chitosan (92% deacetylation)	Induced	Interaction depended on pH values and BSA/CS ratio	[35]
	2-N-3,6-O-sulfated chitosan films		Improved protein compatibility by inhibiting the adsorption of BSA and fibrinogen	[36]
	Negatively charged PVA-CS-coated magnetic NPs (10.62 nm)	No effect	low BSA protein adsorption capacity	[37]
	CS-AgNPs	No effect	This interaction reduced amyloid fibril formation and β-sheet content in HSA	[38]
	CMC-CS based hydrogels		Anti-inflammatory activity by reducing albumin denaturation in a dose-dependent manner	[39]
	CS-zinc-tin oxide NPs (20 nm)	Induced	hydrophobic interaction with BSA and destabilized it	[40]
	PTX/CS-PMA NF		Improved protein compatibility by inhibiting the adsorption of BSA and fibrinogen	[41]
	CIP@CH-TW/TPP nanocomposites	Induced	Interacted with BSA by hydrogen bonding and Vander Waals forces	[43]
	SHPCS-BAPSf membranes		Suitable for protein separation with low adsorption capacity	[44]
PLGA	HSA-loaded PLGA-NPs (142 nm, negatively charged) PF68- HSA-loaded PLGA-NPs (192 nm, negatively charged)		Decreased protein adsorption may prolong the half-life of HSA-loaded NPs in the bloodstream	[48]
	Different PLGA functionalized NPs		All NPs adsorbed BSA and saturation degree was nanoparticle loading/functionalization-dependent	[78]
	Three different surface modification approaches (physisorption, interfacial embedding, and dopamine polymerization) for PLGA-NPs	No effect in dopamine polymerization	Native albumin on PLGA-NPs interacted with albumin-binding proteins and their transport was facilitated into tumor cells	[49]
	Loading of morin into PLGA-NPs	Induced	Binding of HSA to NPs induced a delayed-release response of morin	[79]
	PEG-PLGA-NPs		Low PEGylation of PLGA-NPs can be applied to extend circulation and rapid drug release, while high PEGylation can be useful for retarding hydrophobic drug release	[50]
Dendrimers	NH2-G4 PAMAM Hydrophobic-functionalized G4 PAMAM	No effect Induced	Interaction with hydrophobic, electrostatic, and hydrogen bonding forces. The dendrimers binding sites on BSA were near domains I and domain II	[58]
	PAMAM-G4	Induced	Hydrophobicity played an important role in PAMAM-protein interaction. Interacted with BSA and HSA by H-bonding and van der Waals forces	[59]
	cationic, neutral, and anionic PAMAM-G4		Could not entirely suppress the immunochemical activities of albumin	[60]
	PAMAM-G4-FU complex	Induced	Dendrimer positive surface charges were decreased after exposure to BSA	[61]
	GO-PAMAM-BSA	Induced	Formed a twisted β-sheet structure in albumin, had high thermal stability	[62]
	Cationic G4 PPI dendrimers	Negligibly induced by 5K-PEG	Bonded to PEGylated BSA depending on the molecular weight of PEG and salt concentration, 20k-PEG induced a collapse of the PEG chain onto the BSA surface	[63]
	(G1, G2, and G3) amino-terminated Carbosilane dendrimers	No effect at acidic pH and pH: 7.4-9. Negligibly induced at basic pH.	Slight interaction of amino-terminated dendrimers with some proteins at neutral and basic pHs, they are not proper for protein preparation	[65]
	(G1-G4) trimethylammonium-terminated dendrimers	No effect at acidic pH by G1-G3 and induced by G4. Induced by all generations at higher pH.	At acidic pH: the higher size of dendrimer branches made an opportunity to trap proteins.	[65]
	The dimethylamino-terminated dendrimers	Induced at all pH		[65]
	AuNP dendronization with G2 and G3-carbosilane dendrons	Reduced AuNPs-induced structural changes	Effect of AuNPs on secondary structure, immunochemical activities, and unfolding of HSA significantly reduced by the demonization.	[66]
	(G1-G3) Glucose-modified carbosilane dendrimers		Most and the least interactions were related to G2 and G1, respectively	[67]
	(G1-G5) DGL		An increase of generations was proportional to the stronger binding constants with HSA and lower free ligand concentrations	[68]
	Hybrid carbosilane-viologen-phosphorus dendrimers	Induced at higher concentration	A single HSA could bind to several dendrimers, changed the zeta potential HSA from negative to positive, NH2 interacted with HSA by H-bonding contacts	[69]
	Anionic dPGS dendrimers	No effect	No or weak interaction was formed under physiological conditions	[70]
	PGLyD		Interacted with IIA sites of HSA by hydroxyl, polar, and apolar groups. Hydrophobic forces and hydrogen bonds stabilized the HSA–PGLyD complex	[71]
Lipid-polymeric nanoparticles	DPPC and DMPC (the less prehydrated liposomes) DOPC and POPC (prehydrated liposomes)		HSA formed a big complex with liposomes by penetrating them. The less prehydrated liposomes were penetrated by HSA more than others	[74]
	PEGylated fluid-phase liposomes		HSA could not bind	[75]
	PEGylated gel phase liposomes		HSA strongly bonded	[75]
	Liposome interaction with FBS		Binding was associated with the presence of PEG, cholesterol, concentration, lipid composition, and surface charge	[76]

polyglycolic acid (PGA) (Fig. 3C) [45]. Based on earlier studies, there are some drawbacks to the delivery of proteins and peptides with PLGA-based NPs: (i) they rapidly release a large part of encapsulated proteins (the high initial burst), (ii) they have an incomplete release either due to protein aggregation or protein strongly adsorb to the hydrophobic surface of PLGA, and (iii) following the decomposition of PLGA during drug delivery, lactic and glycolic acids are formed, which reduces the pH of protein microenvironment leading to protein denaturation. In general, the interaction between PLGA-NPs and proteins is associated with PLGA molecular weight, lactide/glycolide ratio, terminated groups, morphology, drug distribution, etc [46, 47]. Accordingly, many studies attended to alter these properties in PLGA-NPs to achieve suitable PLGA-based NPs for protein delivery applications. In this regard, Shubhra *et al*. tried to modify the surface of the PLGA NPs co-encapsulating HSA and magnetic NPs by poloxamer (Pluronic F68, PF68) and determine the properties of NPs-BSA interaction. The data indicated that adsorption of albumin on the NP surface was decreased after modification. They proposed that the decreased protein adsorption may prolong the half-life of HSA-loaded NPs in the bloodstream [48]. In another study, Fornaguera *et al*. prepared some PLGA-NPs through various loadings and functionalizations and then evaluated their effects on albumin. They loaded coumarin 6 (C6), to use NPs in bio-imaging, and loperamide hydrochloride (LOP), to use as nano-carriers. In addition, they functionalized PLGA-NPs with carbosilane cationic dendrons of the second generation (G2SN) and the anti-transferrin receptor monoclonal antibody (8D3) for passively and actively vectorizing of NPs to the blood-brain barrier. They revealed that all NPs could adsorb BSA and the BSA saturation concentration was nanoparticle loading/functionalization-dependent. Furthermore, Hyun *et al*. applied three different surface modification approaches (physisorption, interfacial embedding, and dopamine polymerization) and then studied their impacts on binding, conformation, and biological activities of the albumin-coated NPs. They showed that the type of surface modification methods largely affected the albumin structure. The dopamine polymerization method could preserve the conformation of albumin, while interfacial embedding could not. Albumin remained native in the first method and this approach was able to create a surface layer of native albumin on PLGA-NPs, which could interact with albumin-binding proteins such as SPARC, and their transport was facilitated into tumor cells. On the other hand, the second method induced denaturation of albumin on NPs which had no beneficial effects on cancer cells. However, the denatured albumin on these NPs contributed as a substrate for scavenger receptor A and could directly or indirectly accelerate the mononuclear phagocytic system via interaction with receptors. This study revealed that the interaction way of albumin with NPs can also affect the surface-bound albumin [49]. Additionally, the effect of PEGylation on HSA-PLGA-NPs interaction was determined by Samkange *et al*. study. The results depicted that Stern–Volmer (Ksv) protein binding constants were reduced upon PEGylation of PLGA-NPs, and A 2% w/w PEG was adequate to remarkably decrease HSA binding capacity to NPs and maintain particle size distributions (PSD). They proposed that low PEGylation of PLGA-NPs can be applied to extend circulation and rapid drug release, while high PEGylation can be useful for retarding hydrophobic drug release [50, 51].

Dendrimers

Dendrimers are hyperbranched, monodisperse, and multifunctional PNPs that are composed of a central core, branches, and some functional residues (Fig. 3D). A large number of external functional groups and internal cavities in these NPs, along with their high ability to form multivalent bonds have led to the widespread use of dendrimers in the field of gene and drug delivery systems, medical imaging, and antimicrobial and antiviral agent preparation [52-54]. These NPs can be classified into three categories according to their surface charges: (i) cationic, (ii) anionic, and (iii) zwitterionic. However, their surface charges are a function of environmental pH. The positive charges on the surface of cationic dendrimers such as polyamidoamine (PAMAM), linear poly-L-lysine (PLL), polyethyleneimine (PEI), and hyperbranched polylysine (HBPL) have increased the possibility of the binding of these NPs to negatively charged surfaces in blood vessels such as cells and proteins [55]. As a result, these dendrimers have received more attention in the drug delivery systems than anionic and neutral dendrimers [56]. However, their blood compatibility has always been a challenge due to the induction of some

undesirable effects on the blood components. Although some studies prior to 2014 have shown that cationic dendrimers interacted with albumin more than other dendrimers, some others have suggested that neutral dendrimers could also bind to albumin via hydrogen bonding. In addition to surface charge, other factors such as dendrimer generation (size), hydrophobicity, and the functional groups can also affect the dendrimers-BSA interaction. Therefore, various studies have been conducted to determine the effects of different types of dendrimers on albumin proteins. PAMAMs are composed of a large number of surface amidoamine residues that extend outward from a central core (ethylene diamine (EDA) or ammonia) [57]. In order to investigate the impact of PAMAM hydrophobicity on the dendrimer-BSA interaction, Zhang *et al*. replaced the terminated −NH2 of the fourth generation (G4) PAMAM dendrimer with 25% acyl groups to prepare a hydrophobic-functionalized PAMAM dendrimer. They showed how a hydrophobic-functionalized G4 PAMAM influenced the structure and stability of BSA. They reported that this dendrimer could disrupt the stable helical secondary structure of BSA, while the unmodified dendrimers could not exert this effect. In addition, the NPs acted as a structure destabilizer for BSA based on the thermal denaturation test of this protein. The formation of the NP-BSA complex was related to hydrophobic, electrostatic, and hydrogen bonding forces [58]. In order to investigate the impact of the type of protein on protein-dendrimer interaction, Chanphai *et al*. carried out a thermodynamic analysis of protein-dendrimer interaction on different proteins (HSA, BSA, and milk beta-lactoglobulin (b-LG)) conjugated with G4 PAMAM dendrimers in aqueous solution at physiological pH. They revealed that hydrophobicity played an important role in PAMAM-protein interaction so that b-LG with more hydrophobic content formed stronger polymer-protein conjugates. The stability order of complexes was b-LG>HSA> BSA and the induction of conformational changes by PAMAMs in b-LG was more than in other proteins. In addition, all proteins induced remarkably morphological alternations in the polymer upon conjugation [59]. In another study, Serchenya *et al*. assessed the influences of cationic, neutral, and anionic G4 PAMAM dendrimers and newly synthesized piperidine-based cationic phosphorous dendrimers of G2 on immunochemical functions of HSA and alpha-1-microglobulin (A1M) proteins. Based on this study, none of the piperidinium-terminated phosphorus and cationic, natural, and anionic PAMAM dendrimers could induce a significant impact on the immunoreactivity of HSA and A1M in the case of equimolar complexes because they did not occupy all binding sites on the macromolecules and the regions for MAbs/Abs binding were free. However, a partial reduction in protein immunoreactivity occurred when the proteins were fully bound to dendrimers. Interestingly, this dendrimer-mediated reduction in immunoreactivity was never completed, even if the proteins were completely bound using the dendrimers. This finding showed that these NPs cannot entirely suppress the immunochemical activities of these proteins in vivo [60]. In addition, Tokarczyk *et al*. prepared a G4 PAMAM dendrimer complex with 5-Fluorouracil (5-FU), as a therapeutic drug, and then evaluated the interaction between BSA and this drug nanocarrier. Based on the results, significant reduction of α-helix, an increase of β-sheet, and random elements were observed upon contact with the G4-FU complex. In addition, under physiological pH, dendrimer surface charges were decreased after exposure to BSA, and zeta potential changed from 61 mV to 16.9 mV [61]. Onas *et al*. attempted to generate a graphene oxide-PAMAM (GO-PAMAM) complex and determine its interaction with BSA. According to data, GO-COOH had a larger size than GO-PAMAM and GO-PAMAM-BSA. Inconsistent with Tokarczyk *et al*. they also showed that BSA reduced the zeta potential of GO-PAMAM. Additionally, although GO-COOH in an aqueous solution could not affect protein folding, GO-PAMAM dendrimers induced some secondary structure rearrangement into BSA. This interaction accelerated the assembly of a strongly twisted β-sheet structure in albumin. The GO-PAMAM-BSA had higher thermal stability than GO-COOH or GO-PAMAM [62].

Poly (propylene imine) (PPI) is another cationic dendrimer composed of a core (EDA and diaminobutane (DAB)) and the interior structure of alkyl and tertiary amine groups [57]. Ciepluch *et al*. used PEGylated albumin to carry G4 PPI dendrimers and then investigated the influence of PEG length on PPI-albumin interaction. They revealed that cationic G4 PPI dendrimers could bind to PEGylated BSA at PEG and BSA surface. This interaction was strongly related to the molecular weight of PEG and salt concentration

and no secondary structural changes exerted on albumin. However, although 20k-PEG induced a collapse of the PEG chain onto the BSA surface, these aggregates were still hydrated and could prepare a hydrophilic environment for Trp134. They proposed that dendrimer transport may be increased in the body using this collapse of the PEG-dendrimer complex on albumin as a protective way [63].

Carbosilane dendrimers, another class of cationic dendrimers, are silicon-based and have perfect kinetic and thermodynamic stability because of strong C-Si bonds. Nowadays, they are used for protein sample preparation during protein analysis because of some advantages over conventional methods; because they (i) are hydrophobic in nature, but easily can functionalize with polar materials without requiring high amounts of organic solvents or hazardous reagents, (ii) can reduce the protein extraction/purification times, and (iii) can strongly interact with proteins without requiring to remove solvents and reagents in protein sample preparation [64, 65]. In order to investigate the effects of surface modification, Shcharbin *et al*. functionalized gold NPs (AuNPs) with carbosilane dendrons and then compared the effects of NP dendronization and pure carbosilane dendrons on altering the structure and immunoreactivity function of HSA at different pHs and in the presence of protein unfolding agent (guanidine hydrochloride). They demonstrated that the effect of AuNPs on secondary structure, immunochemical activities, and unfolding of HAS was significantly reduced by the dendronization with G2 and G3 carbosilane, despite any increase of the metallic part. They concluded that the dendronization of AuNPs efficiently covers them, thus it can prevent their undesirable interaction with blood proteins [66]. In another study, Wrobel *et al*. investigated the impact of glucose-modified G1-3 carbosilane dendrimers on HSA because glycodendrimers have been proposed as low cytotoxic subtypes of cationic dendrimers. They revealed that all generations of glucose-modified carbosilane dendrimers could weakly interact with HSA so that the most and the least interactions were related to G2 and G1, respectively [67]. Dendrigraft poly-L-lysine (DGL) is another important cationic dendrimer that has a linear core and is more flexible. High water solubility and its globular structure with various capacities of functionalizing make it suitable for drug or gene delivery [68]. Sisavath *et al*. examined the influences of dendrimer generation on HSA-DGL interaction. They showed that increase of generations was proportional to the stronger binding constants with HSA and lower free ligand concentrations under physiological conditions. G3 and G4 were the same size as HAS, and a 2:1 stoichiometric ratio of HSA:DGL was related to the presence of two negative domains on the HSA at physiological pH. On the other hand, upon the size of DGL becoming more than HSA (in G5), a 1:1 stoichiometric ratio of HSA: DGL was seen, indicating only one G5 may fill both domains and the electrostatic repulsion inhibited the adsorption of a second G5. High cooperativity was shown for G1 and G2 which was related to alteration in the protein conformation that triggered the interaction with other DGL molecules. This cooperativity reduced with growing generation. In another study, Moreno *et al*. synthesized a novel hybrid carbosilane-viologen-phosphorus dendrimer using an "onion peel" approach and evaluated its possible effects on HSA. Based on this study, a single HSA could bind to several hybrid carbosilane-viologen-phosphorus dendrimers. This interaction changed the zeta potential of HSA from negative to positive. In addition, they showed that increasing concentration induced significant secondary structure changes in HSA. The terminal $NH3^+$ groups interacted with HSA by hydrogen bonding and exerted some changes in the secondary structure of the protein [69].

On the other hand, some studies evaluated the effects of anionic dendrimers on albumin. Dendritic polyglycerol sulfate (dPGS) dendrimers are anionic dendrimers that Ran *et al*. assessed the interaction of different sizes of them with HSA. Despite the net negative charge, the anisotropy in charge distributions on HSA proteins could lead to binding positively charged sites of them to the negative charge on dendrimers. They reported that no change was induced on HSA secondary structure by dPGS-G2 and they formed a 1:1 complex with HSA. In addition, the binding constant reduced with increasing ionic strength, and dPGS did not or very weakly interacted with albumin under the physiological condition [70]. In another study, Santos *et al*. evaluated polyglycerol dendrimer (PGLyD)-HSA interaction by fluorescence quenching and computational modeling analysis. They showed that hydroxyl, polar, and apolar groups in microenvironment

PGLyD tended to react with subdomain IIA sites of HSA. In addition, the fluorescence inhibition after PGLyD-HSA interaction indicated a complex formation in the ground state which in dendrimer transferred inside the protein cavity of the protein and Trp residue. Based on thermodynamic parameters, hydrophobic forces and hydrogen bonds stabilized the HSA–PGLyD complex [71].

Lipid-polymeric nanoparticles

Liposomes are specialized nano-vehicle structures with a lipid bilayer that creates a hollow sphere encompassing an aqueous phase (Fig. 3E) [72, 73]. Thakur *et al*. evaluated the binding of HSA and liposomes of saturated (1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC)] and unsaturated (1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) and 2-oleoyl-1-palmitoyl-snglycero-3-phosphocholine (POPC)] phosphocholines with various phase transition temperatures. They showed that the liposomes stabilized HSA based on circular dichroism (CD) measurement. Additionally, hydrophobic interaction led to albumin fractional penetration from liposomes by destabilizing the packing order of the lipid bilayer. The less prehydrated liposomes (DPPC and DMPC) at room temperature were penetrated by HSA more than more prehydrated liposomes (DOPC and POPC) [74]. In another study, Kristensen *et al*. investigated the interaction between HSA and PEGylated fluid-phase liposomes and PEGylated gel-phase liposomes with different PEG chain surface densities. Based on the results, HSA could not bind to PEGylated fluid-phase liposomes, while it strongly interacted with the PEGylated gel phase liposomes. However, the number of incorporated HSA into liposomes was very low (~2–5 per liposome) [75]. In addition, Papageorgiou *et al*. carried out a physicochemical study on the interaction between FBS (contains BSA) and liposomes and determined the impact of liposome composition and concentration on it. They demonstrated that the protein binding to liposomes was associated with the presence of PEG, cholesterol, concentration, lipid composition, and surface charge [76].

CONCLUSION

In this study, the applications of polymeric nanoparticles in preparation of albumin products and enhancing the quality of albumin during stability were reviewed [77]. According to the results, positively charged polymeric nanoparticles (such as chitosan and PAMAM dendrimers) can alter the secondary structure of this protein. In contrast, negatively charged polymers with low molecular weight could alter the structure and function of albumin less than positively charged nanoparticles. The results of this study showed that although some cationic nanoparticles can increase the thermal stability of albumin, they usually do not have favorable effects on albumin structure. As a result, they are not recommended for the production of albumin products unless their specific derivatives are created through structural modifications. As a result, PLGA with low molecular weight can be introduced as a promising preservative for albumin. Despite the net negative charge on HSA proteins, PLGA could bind to the positively charged sites of the proteins. It seems that hydroxyl, polar, and apolar groups in the microenvironment of nanopolymer tended to react with subdomain IIA sites of HSA. In addition, upon binding of nanopolymer to HSA, a complex is formed in the ground state which in nanopolymer transferred inside the protein cavity of the protein and Trp residue. Based on thermodynamic parameters, hydrophobic forces and hydrogen bonds stabilized the HSA - nanopolymer complex.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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