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Bovine Serum Albumin Nanoparticles constructing procedures on Anticancer Activities

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Abstract

Bovine serum albumin is adaptable protein carrier, especiallyuseful for its remarkable nontoxic, biocompatibility, non-immunogenic and biodegradable properties also it is readily available. Hence; it can be considered to assemble nanoparticles for drug delivery system. Most of the anticancer drugs have some severe problems as concern their instability in a biological environment, insolubility and poor uptake into cells and tissues that can cause undesirable side effects for targeting nanoparticles. Bovine serum albumin nanoparticles can be used to overcome those drawbacks for DDSs. The significant outcomes of bovine serum albumin nanoparticles have its site-specific drug targeting using various ligands modification in the expanse of anticancer treatment. Some nanotechnological techniques to make albumin nanoparticles also have been discussed, such as coacervation, emulsification, thermal gelation, and nab-technology. Characterization and improvement of drug loading capacity in albumin nanoparticles also been addressed in this review.

Keywords: Drug delivery system , Brovine serum albumin, Desolvation Method, Emulsification, drug loading capacity.

1. Introduction

Albumin nanoparticles have a splendid future in the controlled delivery as therapeutic agents. Albumin nanoparticles indicated high drug loading capacity in a composite with biodegradability, biocompatibility, and the probability of covalent derivatization[1] with drug contemplating ligands. A superior comprehension of the components of activity of these vehicles will give a premise to their further enhancement, along with this hectic accessibility open doors in the zone of drug delivery[2].These properties, and additionally particular take-up in a tumor and inflamed tissue, prepare availability, biodegradability, and absence of toxic quality and immunogenicity, make serum albumin a perfect contender for drug delivery. Modern applications of serum albumin (human and bovine) have shown some significant points as a character and in the biocompatible and biodegradable carrier for drugs [3-5].The atomic weight of bovine serum

albumin is 69,323 Da and also having an isoelectric point (pI) of 4.7 in water (at 25°C). BSA is widely used for drug delivery system because of its features, such as it iseconomical, easy to purify, the simplicity of enhancement. Also, it has extraordinary ligand-binding properties, so it is extensively acknowledged in the pharmaceutical industry[6, 7].Bovine serum albumin (BSA) is veryhigh water dissolvable and binds drugs and inorganic substances non-covalently. Auxiliary, BSA structure is homologous to the three-dimensional structure of HSA.

The fundamental distinction lies in the number of tryptophans (Trps). BSA has two Trps, while HSA has just a single. This distinction is valuable with regards to its examination by spectrofluorimetry since this amino acid is the liable one in charge of the characteristic fluorescence of proteins[8-10].The precipitation technique can get microparticles and NPs of albumin in natural solvents, trailed by a procedure of cross-linking with glutaraldehyde molecules (desolvation technique)[11]. BSA particles can encapsulate a massive number of drug atoms per molecule, accomplishing high drug-loading efficiency. Despite, with sizes in the range within a few hundred nanometers to a few micrometers, these particles are inclined to take-up by the reticuloendothelial framework in liver and spleen. Another approach has been accounted for that can formulate hydrophobic drugs into albumin nanoparticles in size range in the vicinity of 100 to 200 nm[12, 13]. Accordingly, Abraxane, a paclitaxel-albumin nanoparticle with an average size of 130 nm, has been widely examined in animal and clinical examinations[14]. Polymeric micelles with sizes of 20-100 nm give efficaciously carriers for the delivery of hydrophobic or amphipathic compounds[15, 16]. Undeniably, the surface change of NPs is imperative to entrap drugs and suppress side effects. Modification of the NPs surface by focusing on particles can build up the drug concentration in the targeted organs or tissues, and be diminishing the dosage and adverse symptoms. A few ligands, for example, Arg– Gly– Asp (RGD)[17, 18], folate [1, 19], transferring [20, 21] and monoclonal antibodies[22, 23] have been utilized NPs as liver malignancy and different carcinomas.The copolymer, which hascontained ahydrophilic portion, usually PEG weights have within the range of 2 to 15 kD forms a coronal layer. In general hydrophobic protein comprise poly (propylene oxide),poly (D, L-lactic acid), poly (ε-caprolactone), poly (glutamic acid), orpoly (L-aspartic acid).Those make the core and acts as a reservoir for some drugs, such as doxorubicin, paclitaxel, docetaxel, camptothecin [24-27].These properties help in the particular aggregation of micelles in tumor tissue through the upgraded permeability and retention (EPR) effect [28-30], toxicity to healthy tissues and enhanced antitumor efficacy. Nonetheless, there remain worries about the conceivable toxicities of polymeric micelles, including general cytotoxicity, hematoxicity, immunogenicity, carcinogenicity, and other aspects,[31] making high biocompatibility an essential for synthetic copolymer micelles.

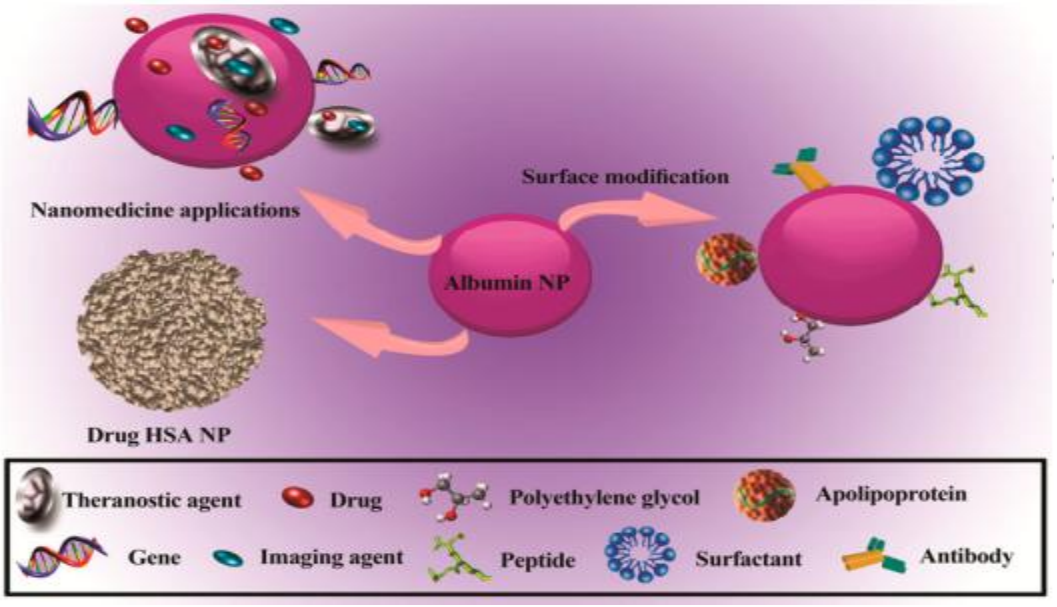


Figure 1. Versatile carrier systems based on albumin NP. Different approaches for adaptation of albumin NPs and their application for delivery of different biomolecules are displayed[32].

2. Techniques of construction BSA nanoparticles

2.1 Desolvation Method

In desolvation technique, nanoparticles are achieved by a constant dropwise adding of organic solvents like ethanol or methanol into an aqueous solution of BSA (bovine serum albumin) and continue stirring till the time, when the solutionbecame turbid. Because of the high water solubility of BSA, its phases will separate at the time of organic solvent addition[33]. After the formation of nanoparticles sufficiently, it will be stabilized and consequently redissolve in the water dispersion [34, 35]. The aldehyde group of glutaraldehyde, the amino moieties in lysine residues and arginine moieties in guanidino side chain of albumin create the crosslinking by their coacervates and coagulated by a condensation reaction[36, 37].Marty presented another strategywith his associates (1978) the establishment of this technique was utilizing a desolvation factor, for example, conventional salts or any organic solvent like alcohol (methanol, ethanol) which have to be added to protein arrangement gradually. By including this factor, third protein configuration will change. When we have come to a specific level of a desolvation, protein bunch willshape. In the following stage, nanoparticles will come about by this polymerization cluster cross-linkage with a fabrication factor that is glutaraldehyde[38].With a specific end goal to procure dispersed nanoparticles, not in a bulk frame, we should stop the framework before particles begin to accumulate. Framework turbidity willexpand inferable from this desolvation factor. Particles aggregation will shape alone with broadeningbackground's turbidity. To stop such sort of gathering and making perfect nanodispersion, we should utilize a resolvating agent[39].Figure2.Showsthe preparation of albumin nanoparticles by using a desolvatingagent.Here are some revisions on the applications ofBovine Serum Albumin (BSA) NPs to encapsulatehydrophobic drug and minerals and controlled properties[40].

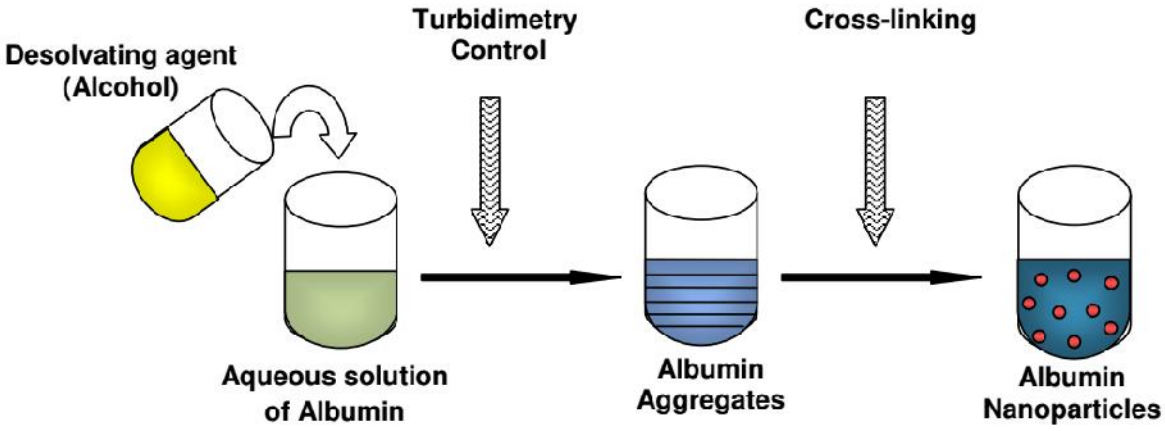


Fig 2. Preparation of albumin nanoparticles by consuming coacervation method.[41]

Table 1. The Summary of research on nanoparticulation of bovine serum albumin (BSA) by desolvation method.

Protein	Desolvating agent	Particle size range (nm)	Polydispersity index	Cross-linking agent	Reference
BSA	Ethanol	200-300	----------	Glutaraldehyde (1.56µg/ml) protein	[37]
BSA	Ethanol	210	0.14	Glutaraldehyde (8%)	[42]
BSA	Ethanol	~200	0.04	Glutaraldehyde (0.25%)	[43]
BSA	Ethanol	~150	----------	0.235-1.175µl of Glutaraldehyde (8%) per mg of albumin	[44]
BSA	Ethanol	90-200	----------	Glutaraldehyde (25%)	[45]
BSA	Acetone	100-300	0.04-0.05	200µl of Glutaraldehyde (25%) for 1mg of BSA	[46]
Galactosylated BSA	Ethanol	120-300	0.1-0.3	Glutaraldehyde (0.5%)	[47]

Differential centrifugation led to substantially tapered size distributions after washing the particles[48, 49]. According to Nguyen and Ko, the addition of a desolvating agent such as ethanol to the albumin can increase reproducibility of albumin nanoparticles with a constricted particle size distribution[50]. Disturbed nanoparticles formation could happen because of higher aggregates of the protein with the pH values below 8.0. Monodisperse particles could be prepared between 200 nm to 300nm at the pH of above 8.0[51].

2.2 Emulsification

To make nanoparticles usually used many macromolecules, those mainly consist of proteins, for example, polysaccharides, for instance, alginate or agarose and gelatin, albumin, legumin, vicillin. These substances have broad use in the arrangement of biomaterial given their natural properties, for example, biodegradability and biocompatibility. Among of macromolecules specified, albumin and gelatin have utilized. There are two essential techniques for development of nanparticles[39].

At first, its strategy was put forward by Scheffel and his associates (1972) with a specific end goal to get ready albumin circle nanoparticles, and after that, it advanced by Gao and his Coworkers (1995). The process has appeared in Figure 2.

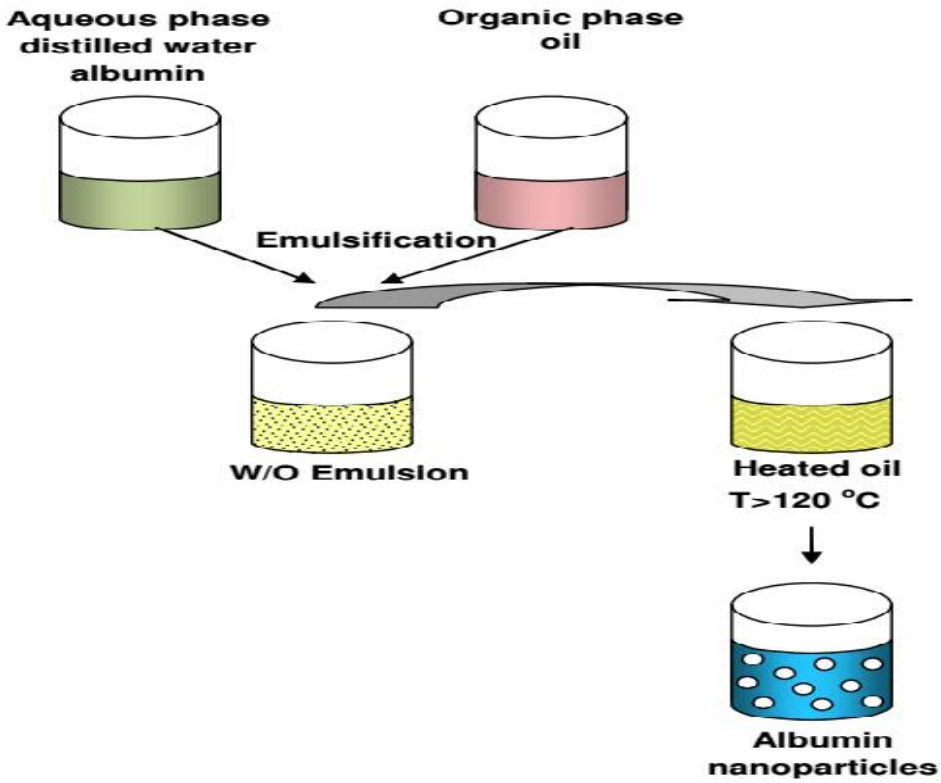


Figure 3. The procedure of bovine serum albumin nanoparticles with emulsification method.

Albumin nanospheres (0.3– 1 μm) were shaped by homogenizing the oil stage (e.g., cottonseed oil) containing the albumin beads at a rapid at that point thermally balanced out by warming at 175 to 180 °C for 10 min[39]. This blend was cooled and weakened with ethyl ether to lessen the oil consistency to encourage detachment by centrifugation. On the other hand, in compound adjustment, egg whites fluid arrangement was emulsified in cottonseed oil at 25 °C at that point denatured by resuspension in ether containing the cross-connecting operator 2,3-butadiene or formaldehyde [39, 52, 53]. Crisante et al. arranged cefamandole nafate-stacked BSA nanoparticles by w/o single emulsion-compound crosslinking with glutaraldehyde. BSA fluid stage was added dropwise to a constant phase comprised of cyclohexane containing glutaraldehyde and afterward homogenized at a fast [54]. A reformative emulsion-warm adjustment procedure was utilized by Yang et al. to plan BSA nanoparticles entangling the ineffectively dissolvable 10 Hydroxycamptothecin (HCPT) keeping in mind the end goal to enhance its soundness principally in its dynamic lactone frame [55]. In this examination, concoction crosslinking was supplanted by warm adjustment by including the w/o single emulsion dropwise to castor oil at 140±5 °C [55]. The likelihood of consolidating a w/o/w numerous emulsion-based ovalbumin nanoparticles in mucosal immunizations was researched[2]. The nanoparticles contained luminous markers showed the take-up and consequent inner trafficking inside macrophage cell societies [2].

2.3 Thermal Gelation Method

Thermal gelation is a successive procedure that includes warm instigated unfurling took after by protein-protein cooperation's including hydrogen holding, electrostatic, hydrophobic associations, and disulfide– sulfhydryl trade response [56-58]. In an investigation performed by Yu et al., round core-shell structure nanogels (around 100 nm) were made utilizing warm gelation technique. Where ovalbumin and lysozyme arrangements blended at pH 5.3, the pH of the blend 10.3 and the agreement changed the settlement was in this manner also mixed, warmed [56].

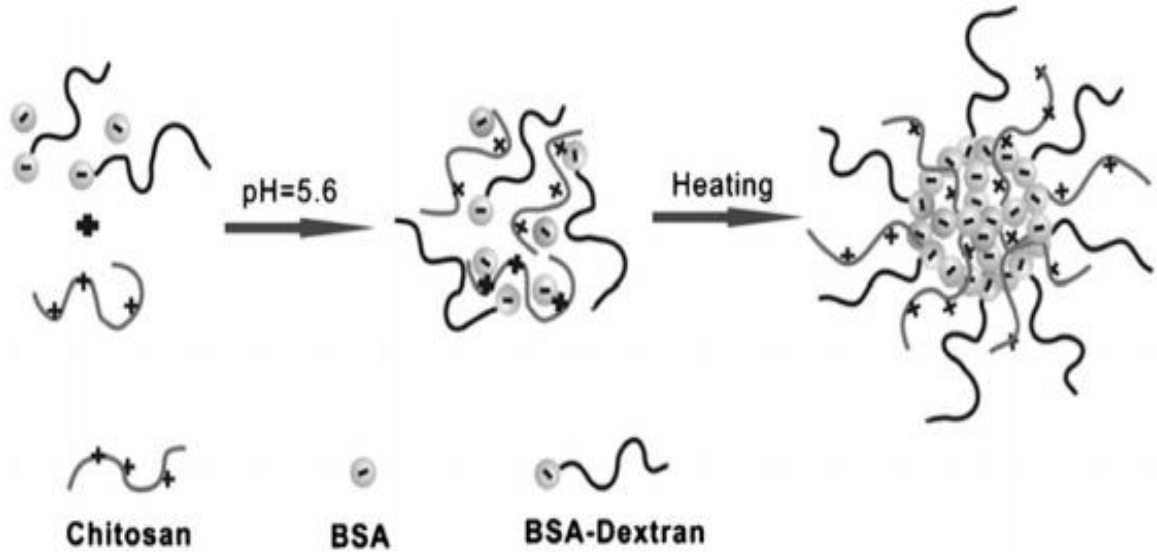


Figure 4. The construction of BSA–dextran–chitosan nanoparticles[57].

The gelation property of BSA on warming has been additionally detailed [59]. By warming a blend of chitosan and BSA– dextran conjugates, biocompatible BSA– dextran– chitosan nanoparticles were framed [57]. BSA atoms gelate framing the center of the nanoparticles through chitosan chains are somewhat caught in the nanoparticle center due to the electrostatic fascination amongst chitosan and BSA (Fig. 4). Rest of the chitosan and the dextran stretch out in the nanoparticle shell. Doxorubicin could be adequately stacked into the nanoparticles by dispersion in the wake of changing the pH of their blend to 7.4 by ethicalness of the electrostatic and hydrophobic communications between the nanoparticles also, doxorubicin [57].

2.4 Nab-technology

Seize innovation is a particular strategy used to plan albumin NPs and can equally utilize for the epitome of lipophilic medications into the NPs. The medication and BSA blended in a watery dissolvable. Drug–albumin NPs incorporated by going the arrangement through a fly spout under high weight. The size scope of the NPs delivered is around 100– 200 nm [2]. A current report framed a lapatinib-stacked BSA NPs (LHNP) planning by including a Lapatinib-chloroform– ethanol blend to the BSA arrangement, and after that, the method was subjected to high shear powers to shape a coarse emulsion. This emulsion was gone through a smaller scale fluidizer and took after by vanishing and sifting of the NPs suspension to accomplish the last emulsification. From that point, the NPs were solidified, lyophilized, and put away. The medication can add to the chloroform and ethanol before the procedure of emulsification. In this investigation, the LHNP indicated high cytotoxicity is bringing about apoptosis of tumor cells and valuable harm to tumor spheroids illustrated (Figure 5(a)) [60].

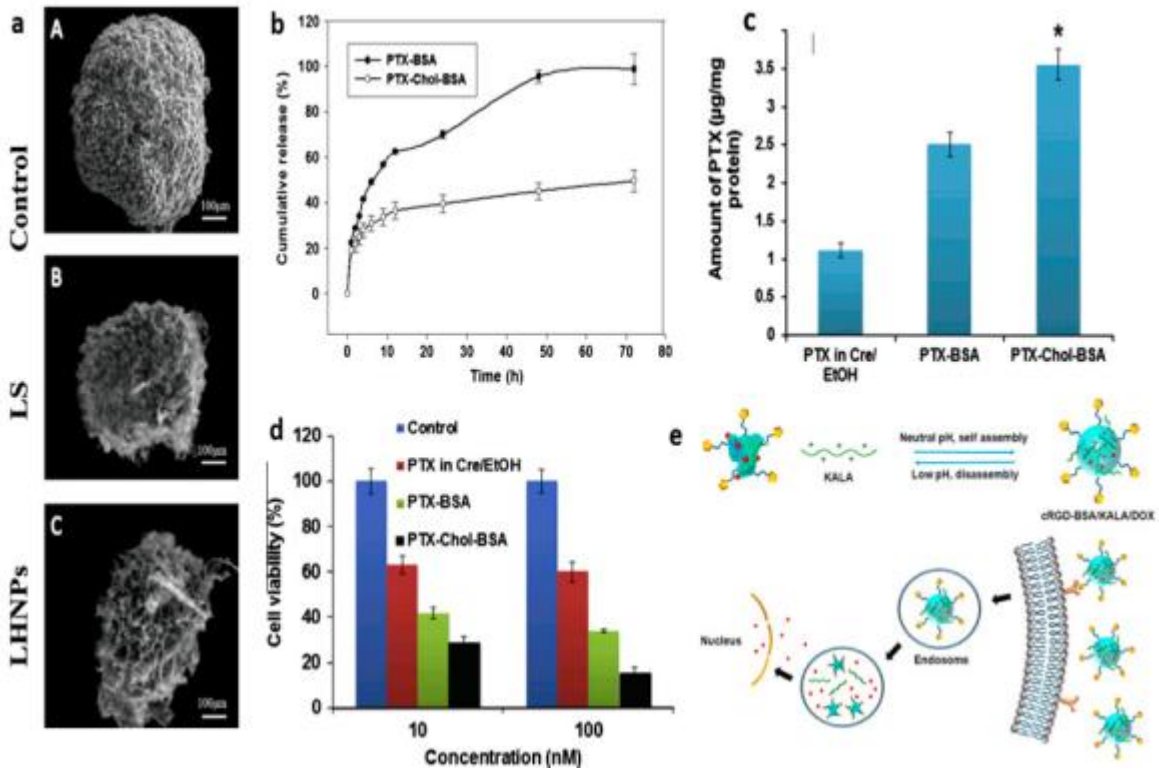


Figure 5.(a) Scanning electron micrographs of 4T1 carcinoma spheroids, after incubation with lapatinib solution (LS) and LHNP in comparison to control group[60].(b) The cumulative release profileof paclitaxel from paclitaxel-BSA and paclitaxel-Chol-BSA[61]. c) Cellular uptake quantification ofpaclitaxel after incubation in MCF-7 cells for 1h[61]. d) MCF-7 cell viability results after exposureto the formulations indicated[61]. e) Schematic illustration of the cRGD-BSA/KALA/DOX NP andtheir pH-triggered assembly and disassembly[62].

This technique fabricated grasp paclitaxel (the first FDA-affirmed nanotechnology-based medication) for the treatment of metastatic bosom tumor and as of late for different kinds of growths [61, 62]. This item has particles of around 130 nm width and shows expanded medication tumor amassing and better antitumor viability thought about than regular medications as discovered utilizing this plan in preclinical and clinical trials [63].

3. Nano-carrier of BSA and drug loading capacity

Two-dimensionally (2D) refined tumor cells utilized as the standard model for investigations of nanoparticulate conveyance in vitro. Notwithstanding, the 2D cell models cannot wholly mirror positive tumors[64, 65]. MCTS show higher similitude to specific tissues as far as 3D structure, cell digestion, and quality profiles when contrasted with monolayer cells, and hence have as of late increased expanding acknowledgment as a 3D tumor model to research the viability of nano medicate carriers[66-73]. Given that medicate conveyance utilizing sedate nano transporters in the tumor tissue is not wholly comprehended, the utilization of MCTS (multicellular tumor spheroids) to assess the conveyance effectiveness of medication stacked albumin particles will give interpretive signs for the outline and use of different albumin based medication bearers. The glycoprotein SPARC, otherwise called osteonectin, is overexpressed in tumor and assumes vital parts in the control of tumor attack and metastasis [74-76]. SPARC indicates the high proclivity to albumin[76, 77], and clinical examinations firmly propose that SPARC(secreted protein, acidic and rich in cysteine) is a crucial piece. The system of activity of albumin nanoparticles, for example, Abraxane[78-80].However, the part of SPARC in the infiltration and development of albumin nanoparticles in vitro 3D tumor models, e.g., MCTS, is as yet misty. While the growth of albumin nanoparticles into MCTS is a prescient imperative model of the in vivo study, albumin nanoparticles were stacked to pancreatic MCTS with/without against SPARC antibodies and the infiltration, aggregation, relocation, and development hindrance impacts of ABZ-loaded albumin nanoparticles explored (Fig. 6).

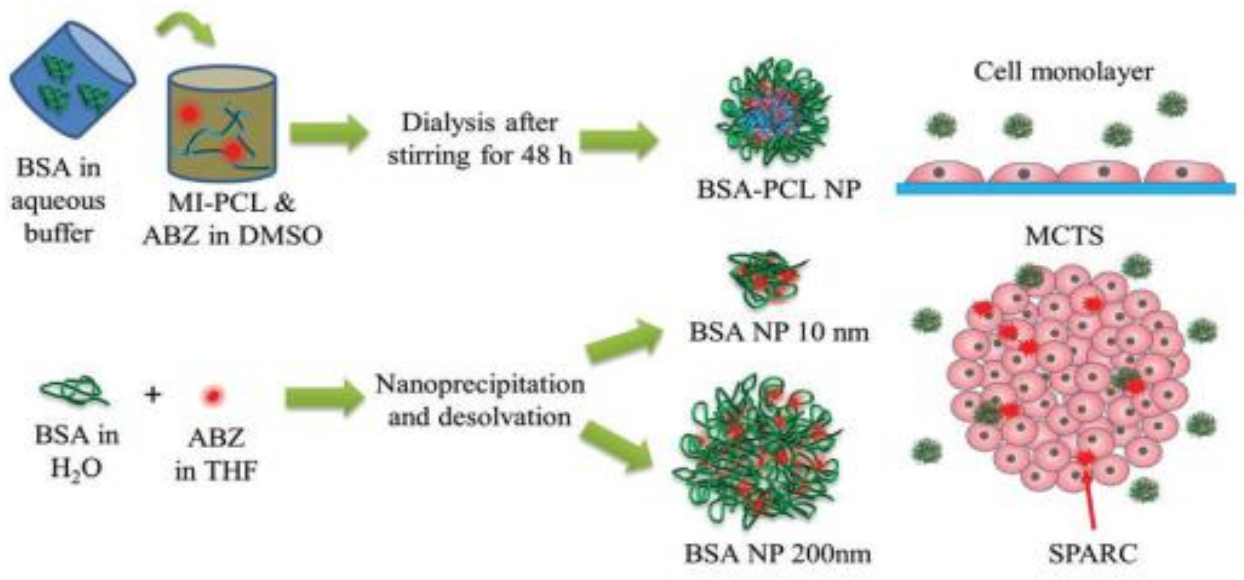
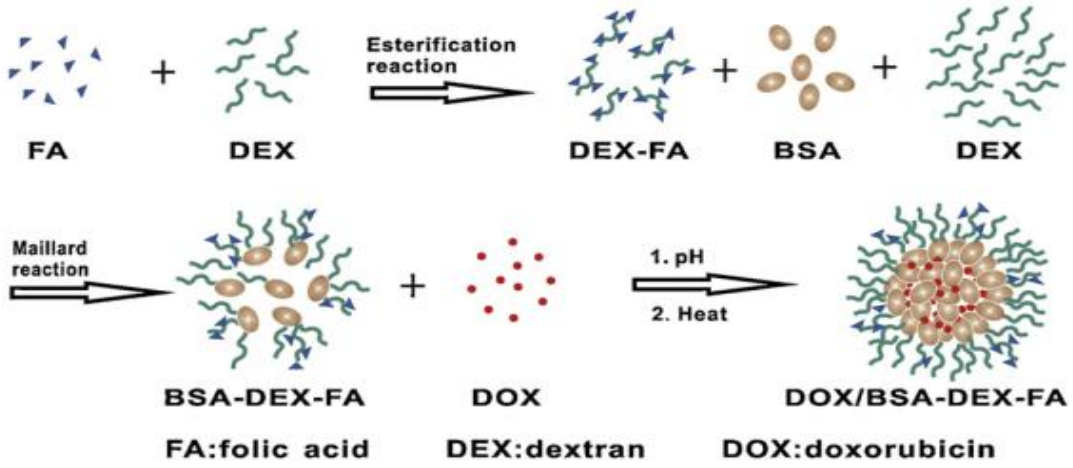


Figure 6. Schematic representation of the synthesis and evaluation in 2D and3D cellular models of ABZ-loaded BSA nanoparticles[81].

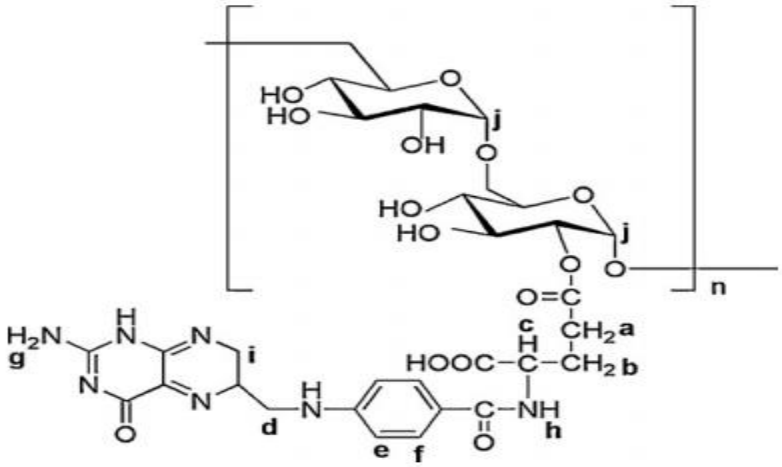
4. Characterization of BSA nanoparticles for cancer treatment

Synthesis and characterization of DEX–FA conjugate

DEX–FA conjugate synthesized by an esterification reaction between the carboxyl group of FA and the hydroxyl group of DEX with DMAP as an activator and DCC as a coupled agent. It reported that the -activated carboxyl group of FA is more manageable [82-84]. Therefore, it is possible that the esterification reaction happened in -carboxyl group then the -activated derivative was produced. The structure of DEX–FA is illuminated in Scheme 2, in which the protons labeled with bold lowercase letters correspond to the characteristic peaks in 1H NMR spectra (Fig. 6). The frequency of DEX–FA in DMSO-d6 presents the characteristic peaks of DEX and FA. In Fig.7C. The peaks at 3.1–5.0 ppm attributed to the DEX protons. The weak signals at 6.75ppm (2H in phenylene), 7.63 ppm (2H in phenylene). Moreover, 8.77 ppm (1H in pteridine) are ascribed to the FA protons, confirming that the FA hasmagnificently grafted onto the DEX. The FA graft degree in DEX–FA is about 5.0%, calculated by the peak area ratio of 7.63 ppm (2H in phenylene) to 4.9 ppm (1H of anomeric carbon in glucose unit). There are about 61.7 glucose units in each DEX chain on average. That is to say, in DEX–FA conjugate, each DEX chain is conjugated with 3.0 FA molecules on average. Fig.4 shows the FTIR spectra of DEX and FA, as well as DEX–FA conjugate. The range of DEX–FA also presents the characteristic absorption peaks of FA and DEX. The 1736 cm-1 of CO stretching vibration absorption in ester group of DEX–FA is weak due to the low FA graft degree. The FTIR spectra further confirm the formation of DEX–FA conjugate[85].



Scheme 1. Illustration of the preparation of DOX/BSA–DEX–FA nanoparticles[85].



Scheme 2. Chemical structure of DEX–FA conjugate. The protons labeled with bold lowercase letters correspond to the characteristic peaks in 1H NMR spectra (Fig. 5)[85].

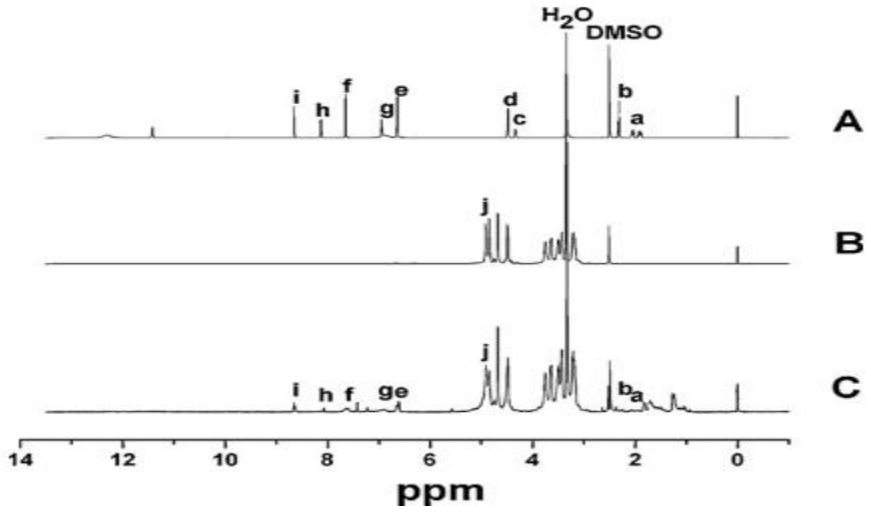


Fig. 7. 1H NMR spectra of FA (A), DEX (B), and DEX–FA conjugate (C) in DMSO-d6.
The peaks labeled with bold lowercase letters correspond to the protons shown inScheme 2[85].

The qualities of albumin NPs make them a suitable contender for tumor focused on medicate conveyance to various phases of malignancy. In such manner, multifunctional nanostructures given albumin have given another worldview to cutting-edge tranquilize conveyance and theranostic applications. For instance, a current report presented a composite nanoparticle comprising of Au nanoclusters installed in BSA NPs for DOX conveyance to cervical tumor HeLa cells, and for cell imaging through photonic excitation (Figure 8-a)[86]. The nanostructures indicated great soundness and maintenance of their glow and were well taken up by cells. Moreover, additional properties of NPs included great biocompatibility, appropriate quantum yield, and capacity to track sedate discharge. Figure 8-b delineates the cytotoxicity evaluation of HeLa cells treated with Au nanoclusters inserted in BSA NPs stacked with DOX through an MTT-based cell suitability measure. The non-poisonous quality of the void composite NPs and the harmfulness of the DOX-stacked NPs has appeared. Another investigation created HSA NPs stacked with attaching demonstrating particular poisonous excellence towards bosom malignancy cells (MCF-7)[87].

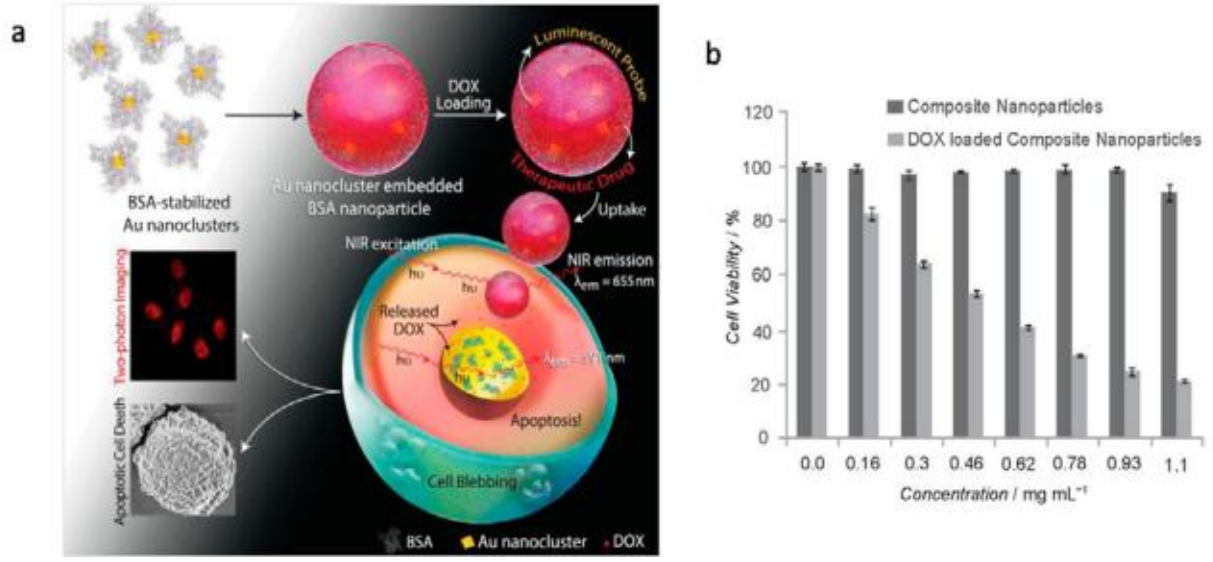


Figure 8. a) Schematic illustration of the combination nanoparticles composed of Au nanoclustersembedded in BSA NPs and the consequent cancer cell uptake and DOX release inducing cellDeath. Cellular apoptosis and related two-photon imaging are also demonstrated, b) HeLa cellviability evaluation via MTT assay after treatment with various concentrations of Au nanoclusterembedded BSA NPs and DOX-loaded Au nanocluster embedded BSA NPs for 36 h [88].

5. Conclusion

Recently bovine serum albumin based nano and microparticles have established for the drug delivery system (DDS_s) on cancer therapy. DDSs has an extensive wide range of application for the future use in therapeutic biomedical solicitations including anticancer treatment. The arrangements of nanostructures in Bovine serum albumin have many desirable properties that provide biodegradability, biocompatibility, and improvement in the water solubility for poorly water-soluble drugs and informal surface adaptation for the drug delivery system on tumor cells.Also, it has the possibility for drug targeting ligands on covalent derivatization. Because of its surface modification mechanisms and various preparation methods exploited the specific targeting sites for DDS_s. Hence, the nanostructures of bovine serum albumin providedistinct binding sides that can improve the drug compatibility for water-insoluble drug and enhance the therapeutic effect.

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Conflict of interest

The author declare no conflict of interest.

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