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MULTIFUNCTIONAL ALBUMIN NANOPARTICLES FOR TARGETED AND ADVANCED THERAPEUTIC DELIVERY

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ABSTRACT

Effective, ongoing, and safe therapies are essential in modern medicine, and they primarily depend on precise medication distribution and action. The creation of drug delivery devices with better pharmacokinetic properties and increased transport to target tissues makes progress in this field easier. A number of FDA-approved therapeutic nanoparticles, such as Abraxane for metastatic breast cancer and non-small cell lung carcinoma, Optison for ultrasound imaging, and Nanocoll for SPECT diagnostics in sentinel node location, highlight human serum albumin as a promising carrier. Significant progress is expected in the treatment of soft tissue tumors, as LadRx is working to get FDA approval for Aldoxorubicin. Theranostics, which combines medications with tumor-localizing factors to efficiently target cancer cells and initiate cytotoxicity at the diseased location, offers a promising future for oncology. In addition to discussing synthesis and surface modification methods for improved targeted delivery, this paper highlights current advancements in albumin-based nanoparticles with an emphasis on drug administration, targeting, and imaging. Innovative multimodal theranostic approaches that take advantage of albumin's characteristics to improve cancer treatments are described in the conclusion.

KEYWORDS: Albumin, Nanoparticles, Therasnostic, Drug Delivery, Novel Systems.

INTRODUCTION

Albumins are commonly used in synthesizing nanocarriers for medical applications due to their availability, low cost, biodegradability, and non-immunogenic nature. Albumin-based drug delivery systems benefit from improved pharmacokinetics, drug delivery efficiency, and low cytotoxicity. They allow for easy incorporation of therapeutic agents, high loading capacity, and controlled release, which enhances drug circulation time and targeting. Various forms exist, including nanoparticles, microspheres, albumin-coated liposomes, microbubbles, and nanocapsules.[1, 2]

Because of their low toxicity and excellent therapeutic efficacy, albumin nanostructures are being used more and more in biomedical applications, especially anticancer therapy. When chemotherapeutics are encapsulated in albumin nanoparticles, these structures

lower the need for frequent administration, fight drug resistance, and minimize systemic side effects. Furthermore, the inherent affinity of albumin for cancer cells facilitates the creation of diagnostic instruments for tumor imaging *in vivo*. Nanopharmacology and nanodiagnostics research for cancer treatment has been further accelerated by recent FDA approvals of albumin-based formulations.[3]

The FDA approved Nanocoll® for lymphoscintigraphy in 1995, marking the beginning of the commercial success of albumin-based nanocarriers. The invention of nab technology by American Bioscience, which made it possible to encapsulate medications that were not very soluble in water without the use of hazardous solvents, was a noteworthy breakthrough. Nab-paclitaxel (Abraxane®), a polymeric nanoparticle with better dosage and fewer side effects than Taxol, was the first FDA-approved medication to use this technology. Lung cancer, pancreatic adenocarcinoma, metastatic breast cancer, and other cancers are being treated with nap-paclitaxel. More new formulations, such as nab-sirolimus, have demonstrated potential in rheumatic and cancer; Nanozora® was approved in 2022 for rheumatoid arthritis, while Fyarro® was approved in 2021 for PEComa. Other albumin-based formulations have been addressed in the literature and are at different clinical phases.[4,5]

Although albumin nanoformulations are mostly researched for chemotherapy, their special qualities make them useful in a variety of medical specialties. Crosslinked albumin, for instance, works well as a surgical sealant and promotes wound healing. Furthermore, albumin can encapsulate antifungal or antibacterial substances, improving the efficacy and safety of treatment. The blood-brain barrier's albumin receptor gp60 is also being studied to enhance the way medications for neurodegenerative illnesses and epilepsy are delivered. Controlled drug delivery at pathological areas is made possible by albumin's ability to act as a drug carrier.[6,7]

PROPERTIES OF ALBUMIN NANOPARTICLES

By promoting drug accumulation in tumors via two mechanisms—passive transport, which is fueled by the EPR effect, and active transport—albumin functions as a drug carrier to increase the specificity and selectivity of chemotherapeutics. Tumors' compromised lymphatic drainage and leaky capillary network facilitate the effective uptake and retention of albumin-bound medications, increasing therapeutic efficacy while reducing damage to healthy cells. Furthermore, albumin is efficiently internalized by cancer cells, which use it as a source of energy and building blocks for development. Hypoalbuminemia in cancer is associated with the accelerated breakdown of albumin by tumor cells.[8, 9]

Increased expression of SPARC, also called osteonectin, encourages invasiveness and albumin uptake in cancer cells, which in turn enhances albumin buildup in solid tumors. Due to tumor heterogeneity, the EPR effect's clinical usefulness varies even though it helps deliver drugs to tumors as demonstrated in animal models. Novel approaches have been developed to improve the EPR impact by altering the tumor microenvironment (TME). These efforts include enhancing perfusion, increasing vascular permeability for nanoparticles, and focusing on characteristics unique to the TME. These tactics could include anti-angiogenic drugs, vasodilators to enlarge endothelial pores, and physical changes brought about by treatments like photodynamic, sonodynamic, and radiation therapy.[10,11]

Modifying nanoparticles with certain ligands to target tumor locations specifically is known as active transport in nanosystems for drug delivery. Through receptor-mediated endocytosis, this method improves medication delivery to cancer cells by employing polypeptides or antibodies that attach to the overexpressed proteins on these cells. In addition to substances that interact with proteins overexpressed in tumor blood vessel linings, such as vascular endothelial growth factor (VEGF) and αvβ3 integrins, common ligand targets include transferrin, folic acid, and epidermal growth factor (EGF).[12]

METHODS OF SYNTHESISING ALBUMIN NANOPARTICLES

Simple techniques that don't require special conditions can be used to generate albumin nanoparticles; the method chosen will depend on the qualities of the therapeutic component, the intended particle size, and the intended use. For medication delivery, human serum albumin (HSA) is obtained from plasma or genetically modified Pichia pastoris. Ovalbumin from egg white, rat serum albumin (RSA), and bovine serum albumin (BSA) are substitutes. Desolvation, emulsification, nab technology, thermal gelation, spray drying, and green chemistry methods are some of the synthesis techniques.[13, 14]

Desolvation

The first step in the desolvation procedure is to add a dehydrating agent, such as ethanol, to a room-temperature, slightly acidic aqueous albumin solution while stirring. Albumin precipitates as colloidal aggregates as a result, creating droplets that contain more colloidal particles than the solvent. Crosslinking is then induced by the gradual addition of glutaraldehyde, resulting in stable nanoparticles with tunable sizes that are affected by temperature, mixing speed, glutaraldehyde concentration, dehydrating agent type, and solution pH. Because solvents may be eliminated during lyophilization, the process enables scalable production without the need for further purification. While temperature control can polymerize albumin without the use of chemical agents, optimization reveals that a minimum glutaraldehyde content is required for optimal crosslinking. Physical procedures and harmless

chemicals are examples of alternative crosslinking processes. Advanced control over the creation of nanoparticles has also been made possible by improvements to the desolvation process, such as the use of semi-permeable membranes for the addition of ethanol and sonication for better drug encapsulation.[15,16]

Emulsification

As a method of encapsulation, emulsification entails mixing an albumin solution with a drug-containing oil phase, then homogenizing the mixture to form nanoparticles. After that, these nanoparticles are stabilized by chemical crosslinking or thermal denaturation. The main drawback of this approach is that it is challenging to produce nanoparticles smaller than 500 nm and requires organic solvents to eliminate oil-phase residues and surfactants, which might result in unfavorable drug interactions.[17,18]

Self-assembly

By using a hydrophobic material to decrease the polarity of the albumin solution and the molecules' surface charge, self-assembly is a method for producing albumin nanoparticles. This makes it possible for albumin to create microemulsions in an aqueous medium, creating vesicles as large as 100 nm in diameter that can carry medications that are both hydrophobic and amphipathic. This method's drawbacks include variable solubility, quick *in vivo* disintegration, and poor storage stability, all of which make large-scale manufacture more difficult. The creation of cationic albumin nanoparticles as siRNA carriers for metastatic lung cancer is one such use. By altering albumin with ethylenediamine and combining it with siRNA through electrostatic interactions, these nanoparticles are created. Research has demonstrated their effectiveness in suppressing the Bcl-2 gene and lowering lung metastases and tumor size *in vivo*.[19,20]

Thermal Gelation

Two techniques for creating albumin nanoparticles include thermal gelation and spray drying. By combining another protein with an aqueous albumin solution and then exposing it to conditions that cause the protein to unfold and create nanoparticles, thermal gelation produces nano-hydrogels, which are usually spherical and have a core-shell structure. For example, spherical albumin nanoparticles with a lysozyme-filled core that retains quality and stability during lyophilization can make up a nanogel.[21]

Spray drying

Spray drying is a dehydration technique that turns colloidal suspensions into powder by atomizing the liquid product and exposing it to hot gas in a drying chamber, which causes the solvent to evaporate quickly. Electrostatic screens are used to collect the resultant powder. Large volumes of tiny particles are effectively produced by modern spray dryers using continuous processing steps.[22]

Microfluidic technology

A novel method for preparing nanoparticles, microfluidic technology (MT) uses a high-pressure pump to inject a dispersed aqueous phase into an immiscible organic phase, forming tiny droplets. Turbulence and laminar flow drive this technique, which produces a stable system for producing homogenous protein nanoparticles by precisely controlling nanoparticle size through flow and shear forces. By altering the alternating current electric field and flow velocity, these nanoparticles' characteristics can be improved. Lipid, polymeric, inorganic, and protein nanoparticles that improve drug-loading efficiency, solubility, cytotoxicity, and tumor cell internalization have all been effectively produced via MT. Notably, human serum albumin/celastrol nanoparticles have been produced using a microfluidic co-flow approach that improves solubility and lowers cellular toxicity while attaining size homogeneity, stability, and excellent encapsulation efficiency.[23,24]

NAB Technology

The Abraxis BioScience firm invented a revolutionary albumin-based nanoparticles production method called nab technology, which does not use harmful solvents or surfactants. To produce nanoparticles with a high drug-loading capacity that are 100–200 nm in diameter, a hydrophobic drug is suspended in oil, combined with an aqueous albumin solution, and then homogenized. Key procedures include fluidization, solvent evaporation, and filtration, with the resulting emulsion being lyophilized for storage. The first FDA-approved nanodrug for pancreatic cancer, non-small cell lung cancer, and metastatic breast cancer was created using Nab technology.[25-27]

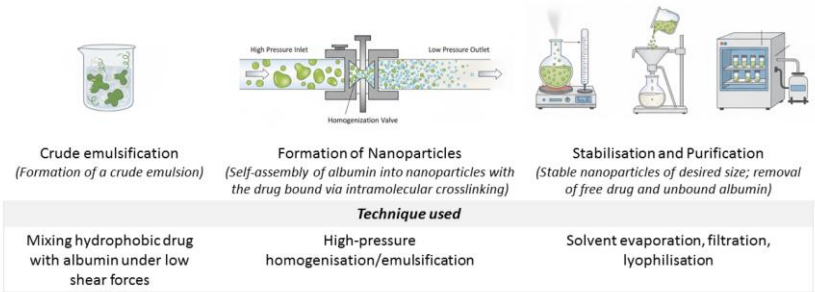

Figure 1: Schematic representation of NAB technology.

The manufacture of nanoparticles with an albumin coating and the creation of albumin nanocomplexes with radioactive metals are important research topics. Albumin complexes with radionuclides such as technetium-99m and indium-111, which are used in sentinel lymph node detection and lung and gastrointestinal imaging, are notable examples. Reducing the internal disulfide bonds in albumin, combining it with a radionuclide solution in tert-butanol, and permitting co-precipitation and complex formation at 37 °C are the steps involved in the synthesis process. The most well-known preparations are Albures, which have particle sizes ranging from 200 to 1000 nm, and Nanocoll, which has albumin aggregates that average 8 nm.[28]

SURFACE MODIFICATION OF NANOPARTICLES

The main applications of albumin-based nanoparticles are in diagnostic imaging, especially for liver and lung scans, and medication delivery in the treatment of cancer. They are also being tested for further medicinal applications, including as targeted distribution through the blood-brain barrier and mucosa, anti-inflammatory therapy, and the treatment of neurological diseases and periodontal disease. Through chemical alterations or the addition of ligands to their surfaces, albumin nanoparticles' beneficial qualities for a range of applications are frequently improved.[29]

The goal of surface modification of nanoparticles is to increase the half-life of drugs. The mononuclear phagocyte system clears circulating albumin nanostructures after they are opsonized. By covering nanoparticles with biologically inert polymers and permitting the attachment of targeting ligands for targeted tissue delivery, this clearance might be lessened. Modifying agents, which include surfactants, polyethylene glycol (PEG), cationic polymers, folic acid salts, apolipoproteins, monoclonal antibodies, transferrin, and peptides, can be directly or indirectly attached to albumin via a crosslinker.[30]

Polyethylene Glycol

Key advantages of PEGylation—the process of coating nanoparticles with polyethylene glycol (PEG)—include decreased immunogenicity and a prolonged biological half-life, which improves drug retention. PEG slows drug diffusion by forming a chemical barrier, enabling sustained release. In order to improve medication transport across the blood–brain barrier, PEG and lactoferrin were used in a study to alter bovine serum albumin (BSA) nanoparticles carrying doxorubicin (DOX). Lactoferrin was adsorbed, PEG2000 was conjugated, and BSA–DOX nanoparticles were formed as part of the synthesis. When compared to unmodified BSA–DOX nanoparticles, cytotoxicity tests on BCECs/C6 glioma cells and *in vivo* investigations in rats demonstrated higher cytotoxicity, prolonged blood half-life, and greater brain tissue penetration.[31, 32]

Cationic Polymers

The manufacture of nanoparticles uses cationic polymers, such as copolymers of lactic and glycolic acids, polycaprolactone, polyethyleneimine (PEI), and poly-L-lysine (PLL), to stabilize the particles and improve their resistance to proteolytic enzymes, which postpones the release of drugs. PEI modification of HSA–doxorubicin nanoparticles enhanced surface charge, decreased opsonization, and boosted MCF-7 breast cancer cell uptake. Furthermore, by increasing the molecular weight and concentration of the PLL coating in aqueous solutions, PLL improved the durability of BSA-siRNA nanocapsules and albumin nanostructures.[33]

Chitosan Polymers

The biocompatibility of drug delivery systems is improved by the introduction of natural polysaccharide chitosan polymers. Chitosan's cationic nature helps it adhere to cell membranes by providing mucoadhesive qualities. The intestinal absorption of insulin was enhanced when chitosan was applied to the surface of insulin-loaded albumin nanostructures. This could help with the future development of oral insulin formulations.[34]

Thermosensitive polymers

In order to create drug delivery systems with controlled release, thermosensitive polymers are essential. For example, albumin nanoparticles coupled with poly(N-isopropylacrylamide-co-acrylamide-co- allylamine) (PNIPAM–AAm–AA) are used to administer Adriamycin. At temperatures higher than the sol–gel phase transition, these polymer-coated nanoparticles release the medication to HepG2 cells and exhibit a delayed *in vitro* drug release when proteolytic enzymes are present. By taking advantage of the localized hyperthermia present in malignant tissue, this method enables Adriamycin to be temperature-dependently targeted to tumor tissues.[35]

Surfactants

Prior to production, polymers can be conjugated with albumin or chemically linked to the surface of albumin nanoparticles (NPs) to stabilize them. Polysorbate 80, an emulsifier that improves the stability of medication solutions, is one example. By slowing metabolism, coating doxorubicin-loaded albumin NPs with Polysorbate 80 extended their half-life and reduced toxicity to testicular and cardiac tissues, hence reducing cytostatic quantities in healthy tissues. Furthermore, Polysorbate 80 may increase the bioavailability of oral antiviral medications and boost nanoparticle penetration across the blood–brain barrier.[36]

Folic acid salts

Because of its high affinity for folate receptors that are overexpressed on a large number of cancer cells, folate functions as a targeting ligand. The carboxyl group of folic acid and the amino group of the protein usually

form a covalent link to conjugate it to proteins. The main applications for folate alterations are in cancer imaging agents and cytostatic medication delivery systems. For example, folic acid-conjugated albumin nanospheres have been created to deliver doxorubicin to tumor tissue in a targeted manner. HeLa cancer cells may effectively internalize these nanospheres without causing damage to healthy aortic smooth muscle cells. Furthermore, *in vitro* research shown that BSA nanocapsules augmented with folate improved the stability and solubility of these nanoparticles while also enhancing the transport and release of paclitaxel to prostate cancer cells.[37, 38]

Monoclonal Antibodies (mAbs)

Using monoclonal antibodies (mAbs) in delivery systems, which improve targeted cytostatic transport by taking advantage of overexpressed antigens in cancerous cells, drugs can be directed to particular organs. Notable monoclonal antibodies include Abituzumab for prostate and colon malignancies, Cetuximab for a variety of cancers, and Trastuzumab for breast cancer. By conjugating avidin-modified albumin nanoparticles with trastuzumab, a humanized antibody against the HER2 antigen seen in many breast malignancies, antisense oligonucleotides were delivered to BT-474 cells, successfully silencing the Plk-1 proto-oncogene. When cetuximab and abituzumab were employed to functionalize albumin carriers for drug delivery in models of melanoma and colon cancer, comparable outcomes were obtained.[39, 40]

FUTURE OF ALBUMIN NANOPARTICLES

The creation of theranostic platforms that combine therapeutic medicines, such as light-activated chemicals, with tumor imaging is the focus of current research. Usually, isotope-enriched aggregates of cytostatics and transporters are used to create these theranostic nanoparticles. By making it easier to track their action *in vivo*, imaging methods like magnetic resonance imaging (MRI) enable the verification of drug uptake by cancer cells. These multi-component systems are designed to provide image-guided therapy and provide focused treatment.[41]

One technique uses albumin nanocomplexes with dyes that absorb near-infrared (NIR) light and photosensitizing substances to promote resonance energy transfer through the Förster mechanism. By transferring energy from the photosensitizer to the dye in an excited state, the system causes fluorescence and the production of reactive oxygen species. The dye then returns energy to the photosensitizer when exposed to near-infrared light. This feature successfully inhibits tumor growth and minimizes the negative skin reactions that are common with traditional phototherapy by enabling real-time tracking of medication distribution and spatially controlled activation by infrared light at tumor sites.

Nanoparticles made of gold-albumin aggregates, like Au-BSA-DOX, have demonstrated potential in the treatment of cancer. Two-photon confocal imaging confirmed that these nanoparticles successfully internalized and delivered the medication doxorubicin to the cell nucleus when tested on HeLa cervical cancer cells. Doxorubicin fluoresces to monitoring drug release, and the nanoparticles produce luminescence for tracking.[42] They are safe for human usage when excited and emitted at near-infrared (NIR) wavelengths (650–900 nm). Additionally, conjugating gold–albumin aggregates with a cisplatin derivative and folic acid enhanced drug transport and cytotoxicity in breast cancer models, inhibiting tumor growth and metastasis in mice. Additionally, non-invasive *in vivo* monitoring via NIR imaging is made possible by the integrated theranostic system.

By adding non-fluorescent inorganic molecules to the surface of albumin nanocomplexes, theranostic characteristics can be obtained. For example, albumin and ferromagnetic gadolinium (Gd) combine to form nanoparticles that are useful for MRI-based tumor imaging. When exposed to radiation, additional modification with cyanine dyes improves photothermal and photoacoustic properties, which increases tumor accumulation and reduces cancer tissue through photothermal effects. Furthermore, Gd ions enable simultaneous *in vivo* nanoparticle monitoring via MRI/NIRF and coupled photodynamic treatment.[43]

For photodynamic cancer treatment, recent research has concentrated on creating metal aggregates with photosensitizing qualities utilizing an albumin matrix. The capacity of several metal-based nanoparticles, including silver, palladium, and gold, to produce reactive oxygen species when activated by light and harm cancer cells has been studied. In particular, albumin-templated nanoclusters—including ultrasmall silver nanoclusters—have demonstrated a notable ability to generate singlet oxygen, enabling the monitoring of drug accumulation *in vivo*. The most promising strategy is albumin nanoparticles made for combination therapy, which, under certain circumstances, enable targeted drug release.[44]

CONCLUSION

Albumin-based therapeutic nanosystems have shown remarkable biocompatibility and enhanced medication efficacy in a number of medical specialties, such as neurology, rheumatology, and oncology. These formulations improve drug accumulation in targeted tissues while reducing side effects, making them particularly advantageous for medications with poor pharmacokinetics. There are still issues with large-scale manufacture, variability, and possible toxicity even though a number of albumin-based preparations have been approved for use in therapy or imaging. Furthermore, problems like non-specific immune response absorption and blood–brain barrier penetration need to be addressed. Targeted therapy has a bright future, but it will only be possible if these significant

obstacles are removed before albumin-based nanosystems can be widely used.

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