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# The Uniqueness Of Albumin As A Carrier In Nano Drug Delivery System

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**Abstract:** With the success of several clinical trials of products based on human serum albumin (HSA) and the rapid development of nanotechnology, HSA-based nanodrug delivery systems (HBNDSs) have received extensive attention in the field of nanomedicine. However, there is still a lack of comprehensive reviews exploring the broader scope of HBNDSs in biomedical applications beyond cancer therapy.

To address this gap, this review takes a systematic approach. Firstly, it focuses on the crystal structure and the potential binding sites of HSA. Additionally, it provides a comprehensive summary of recent progresses in the field of HBNDSs for various biomedical applications over the past five years, categorized according to the type of therapeutic drugs loaded onto HSA. These categories include small-molecule drugs, inorganic materials and bioactive ingredients. Finally, the review summarizes the characteristics and current application status of HBNDSs in drug delivery, and also discusses the challenges that need to be addressed for the clinical transformation of HS.

**Keywords:** human serum albumin; drug delivery; biomedical applications;bindingsite.

## INTRODUCTION:

Nanotechnology has shown great potential in pharmaceutical applications, especially in the area of drug delivery. In particular, nanomaterials allowed the development of platforms for the efficient administration, protection, transport, and specific delivery of challenging therapeutic or diagnostic cargos, such as poorly soluble drugs, proteins, and gene therapeutics, in biological fluids toward cellular and intracellular targets.

Nanoparticles have been designed to overcome the limitations of conventional delivery and navigation through biological barriers. In fact, in several instances, nanoparticles of various chemical structures, including lipid, polymer, and inorganic nanocarriers, have shown to effectively offer control on the biodistribution and/or release of single or multitherapeutic agents and the possibility to overcome biological barriers against targeted drug delivery to the diseased site.

However, depending on their structure, such nanocarriers have also presented drawbacks restricting their success in targeted drug delivery, including nonspecific uptake by phagocytic cells, off-target distribution, nonspecific immune activation, inadequate control over drug release in biological systems, and poor intracellular internalization.

The plasmaprotein albumin has attracted attention as a natural, yet versatile, nanodelivery system due to its characteristics, including high binding capacities for both hydrophobic and hydrophilic drugs, relatively long half-life,

**Physiologic roles of albumin**

Albumin is one of the most important proteins in plasma with various vital roles. It consists 40% of the protein mass of plasma and has an amount of 35–50 g in every liter of serum . Albumin is responsible for the 80% of osmotic pressure alone . In addition, it has a role in pH maintenance through working as a buffer . Albumin is known as a carrier of numerous molecules like fatty acids, eicosanoids, biliary acid, steroid hormones, vitamin D and C, fulate, copper, zinc, calcium

**Section snippets**

**OVA**

OVA is the most common types of food proteins frequently used in the food industries. It is a glycoprotein with 47 kDa molecular weight and 365 amino acid and one disulfide bond . The main reason in choosing OVA as a drug carrier is advantages like easy access to its sources and its low price . Features like pH and temperature sensitivity makes OVA a potential drug carrier . OVA can increase MHC class I and induce lymphocytes activation. OVA can be used as a carrier

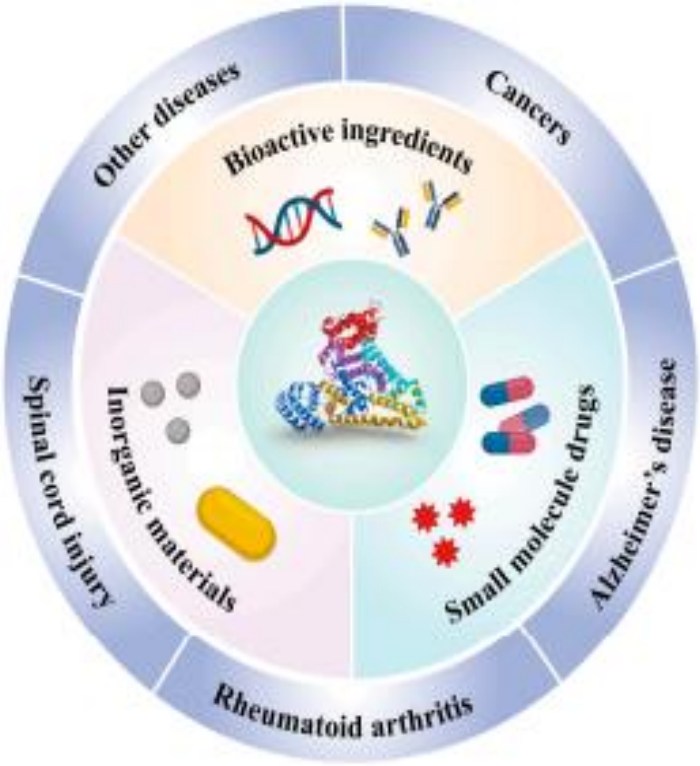
**Methods for producing albumin nanoparticles**

There are different physical and chemical methods for producing albumin nanoparticles. Common chemical methods are desolvation, emolation and self-assembly [8,10,40]. Thermal gelation, nanoparticle albumin-bound (NAB) technology and nanospray drying are physical methods in producing albumin nanoparticles [11,41] (Table 1). Furthermore, there are different approaches for loading albumin nanoparticles on targeted drugs (for instance, covalent bonds, surface coating and electrostatic absorption).

**Albumin as a nanocarrier**

Albumin has unique features that make it a suitable option as a drug transporter. Some of them are as follow

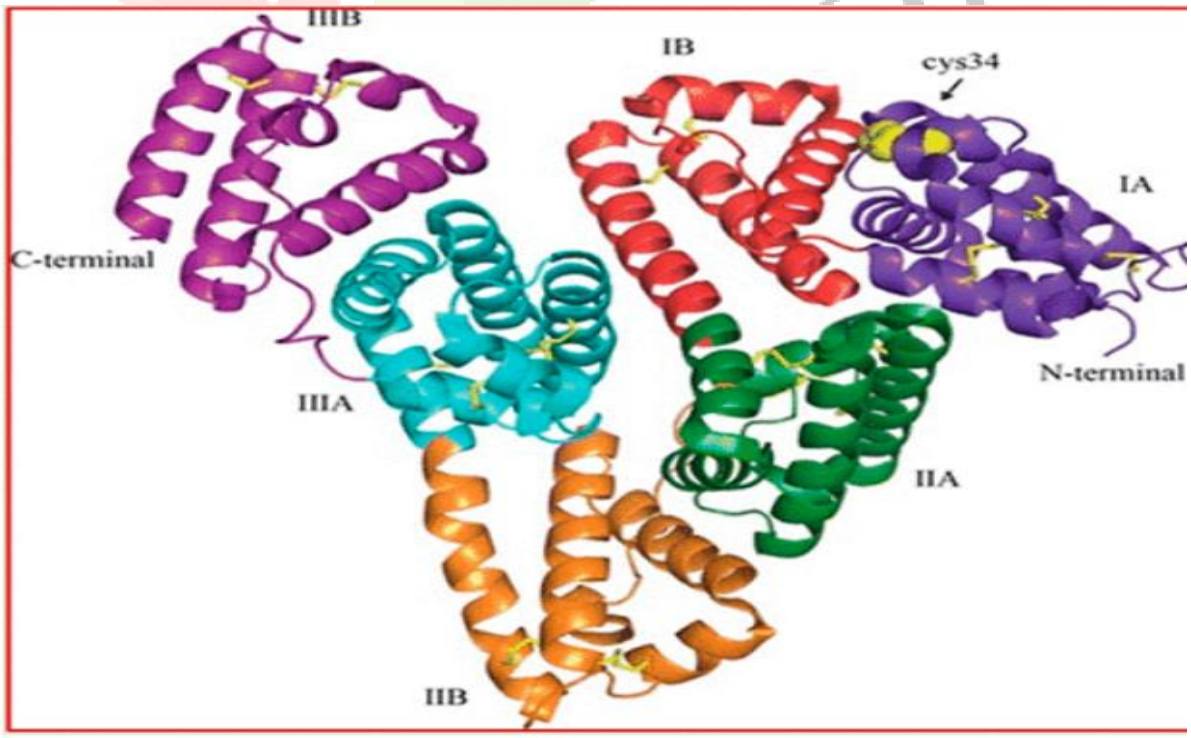
- A great amount of albumin is already in our body, therefore injecting too much albumin
- would have lower side effects than other carriers .
- Transporting therapeutic drugs with albumin not only reduces costs but also decreases drug's toxicity.
- The bond between albumin and hydrophobic substances are reversible which facilitates transporting drug in the body and releasing it onto the




**Overview of HAS-based on nano particle**

## CHARACTERISTICS OF ALBUMIN FROM DIFFERENT SPECIES*:*

is the most abundant protein in blood plasma, constituting approximately 60% of all proteins in the blood. It is a highly water-soluble small globular protein and has a molecular weight of 67 kDa and an average half-life of 19 days. It shows stability at a pH range of 4–9 and can be heated for 10 h at 60 °C. It can be extracted from Albumin many sources including human serum (human serum albumin, HSA) (Figure 1), bovine serum (bovine serum albumin, BSA), rat serum (rat serum albumin, RSA), and egg white (ovalbumin, OVA), but the two types most used for drug delivery are HSA10 and BSA of fundamental importance



**HSA-Based Multifunctional Nanocarrier:**

Due to its favorable attributes such as excellent biocompatibility, non-toxicity, nonimmunogenicity, and prolonged circulation time, HBNDSs have garnered significant attention for a wide range of biomedical applications [11]. They have emerged as crucial carriers for delivering diverse therapeutic drugs, including small-molecule drugs, inorganic materials, and bioactive ingredients, thereby enhancing both imaging performance and therapeutic efficacy across various diseases [19]. In this section, we will systematically summarize the recent advancements in HSA-based multifunctional nanocarriers within the past five years.

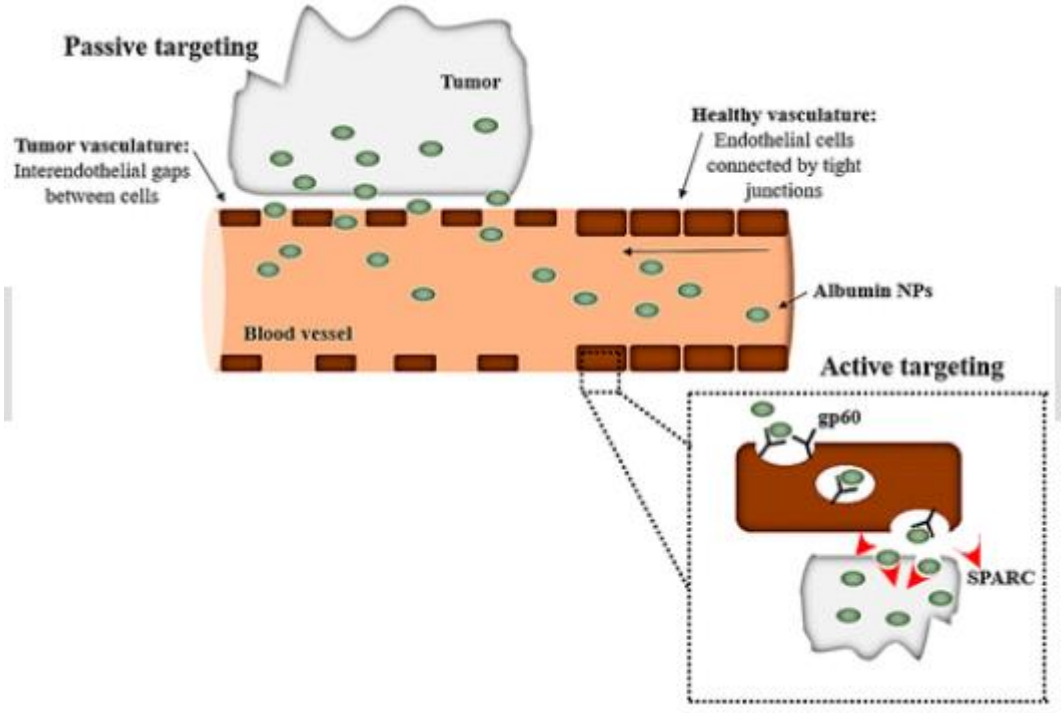
**Human serum albumin:**

serum albumin Human is made up of a single chain of 585 amino acids. Its secondary structure is highly flexible, characterized by 67% α helix and 17 disulfide bridges with 6 turns that act as cross-linkers for the three homologous domains. Human serum albumin is a protein produced by hepatocytes in the liver, at a rate of 9–12 g/day, and is one of the most abundant (levels of plasma albumin in the range from 3.5 to 5 g/dL and important proteins in blood plasma.

Although albumin is the most abundant plasma protein, the majority of albumin is not in blood circulation. As much as 60% of albumin is stored in the interstitial space. Even though its biological half-life is 19 days, it only lasts 16–18 h in circulation. The transcapillary movement of albumin is reversible, as it can return inside the plasma through the lymphatics to maintain constant plasma protein concentrations. Its production is modulated by the body's needs In particular, the synthesis is stimulated by insulin, thyroxine, and cortisol or conditions like hypoalbuminemia, whereas it is hindered by potassium and exposition of hepatocytes to excessive osmotic pressure. Furthermore, an adequate supply of nutrients is fundamental to trigger albumin production. In fact, poor adsorption of nutrients reduces the liver's ability to produce protein. Degradation of albumin can take place in any tissue, but it occurs mainly in the liver and kidney. The balance between albumin production, degradation, and movement between intravascular and interstitial spaces determines the effective plasma albumin concentration.

**The Unique Properties of Albumin Nanocarrier in Drug Targeting**

1. The Natural Ability of Albumin in Targeting Cancer and Other Proangiogenic Environments. The hyper-permeability of blood vessels and the impaired lymph drainage, the well-known enhanced permeation and retention (EPR) effect in solid tumors has been proposed as a responsible mechanism for passive targeting of many nano carriers in solid tumors However, the defining role of the EPR effect as a responsible mechanism for passive targeting of nanocarriers in solid tumors, even in preclinical animal models, has been questioned recently. Although it constitutes a paradigm in cancer nanomedicine, Chan et al. demonstrated that 97% of the nanoparticles under their study enter into solid tumors by endothelial cells through an active process of transcytosis and that the interendothelial gaps, which characterize the EPR effect,




the case of dog albumin, a defect might exist at the location corresponding to site I. The hydrophobic interactions between DZ and BSA, rabbit serum albumin and RSA are weakened as a result of the tertiary structure change in cavity size, rather than the loss of hydrophobic residues.

In conclusion, it can be stated that RSA and rabbit serum albumin contain a drug binding site, corresponding to site I on HSA, and dog albumin contains a specific drug binding site corresponding to site II on HSA .

One of the unique features that make albumin such a powerful and effective drug carrier is that it binds to receptors, which are overexpressed by the tumor.

The main pathway that albumin relies on for the internalization inside the tumors is receptor-mediated endothelial transcytosis.

. Albumin binds with high affinity to the gp60 receptor, a 60 kDa glycoprotein (albondin).43 This receptor is found on the surfaces of endothelial cells of the tumors, and after the connection with albumin, it binds to caveolin-1, an intracellular protein that gives rise to an invagination of the cell membrane, leading to the formation of transcytosis vesicles (caveolae) transporting albumin inside the tvesicles (caveolae) transporting albumin inside the tumor.

. Moreover, SPARC (secreted protein acidic rich in cysteine), also known as antiadhesin, osteonectin, BM-40, and 43K protein, which is overexpressed by many types of tumors and absent in normal tissues, attracts albumin and contributes to its accumulation inside the tumor. These two main mechanisms allow the protein to be actively internalized by the tumor.

. Among the albumin receptors, apart from gp60, there are also gp18 and gp30, which are cell surface glycoproteins characterized by molecular weights of 18 and 30 kDa, respectively.44 They are expressed in endothelial cell membranes of the liver and peritoneal macrophages. They are scavenger receptors that have a high affinity for damaged albumin. MHC-class I-like heavy chain, characterized by three extracellular domains (α1, α2, α3), which is noncovalently associated with a β2-microglobulin light chain, necessary for the function of the receptor.

| technique | advantages | disadvantages | size (nm) | morphology |
|---|---|---|---|---|
| desolvation | robustness, reproducibility, absence of toxic organic solvents, simplicity, possibility to obtain smaller size nanoparticles | use of toxic cross-linkers, demand for strict purification steps and removal of unreacted cross-linker, not appropriate for highly water-soluble drugs | 150−300 | spherical shape with a smooth surface |
| emulsification | higher drug entrapment efficiency | use of toxic chlorinated solvents, use of toxic cross-linkers or thermal stabilization, demand for removal of both the surfactants and oily residues, harmful to heat-sensitive drugs (if thermal stabilization is used), high energy requirement in homogenization, larger size nanoparticles, difficulty of controlling the albumin particles' size | 100−800 | albumin nanospheres |
| self-assembly | high loading of poorly water-soluble drugs | use of only lipophilic drugs, difficulties in scaling-up the technology, insufficient storage stability, different solubility protocols for different drugs | 130−160 | spherical shape and core−shell structures |
| thermal gelation | possible fabrication of nanoscale hydrogels | encapsulation only of drugs that are not heat sensitive | 100−200 | spherical core−shell structure nanogels |
| nanospray drying | single-step continuous and scalable process, versatile technique, useful for heat-sensitive samples, control for particle size | production of larger particles | 500−3000 | smooth spherical nanoparticles |
| microfluidic mixing | tunable size, structure, and surface, narrow size distribution, controlled release profile, high versatility and reproducibility, smaller size nanoparticle, ow reagent consumption, better mixing, better drug loading capability | risk of fouling and channel clogging, complex device design, not fully automated, labor-intensive, sometimes requiring special equipment, such as cleanroom facilities | 100−160 | versatile shape, from nanofibers to spherical core−shell nanoparticles |
| NAB-technology | ideal for encapsulating lipophilic drugs, safe and suitable for intravenous usage of poorly soluble drugs, no requirements for surfactants or polymeric materials for preparation, disulfide formation induced by homogenization does not substantially denature HAS, higher drug content, smaller size | demand for high pressure, use of hydrophobic drugs only | 100−200 | spherical nanoparticles with a smooth surface |

It is found in many tissues including vascular endothelium, gut, lungs and kidney.46 This receptor can determine a different fate for albumin-based nanoparticles after internalization, playing a vital role in maintaining high levels of albumin. Usually, as already pointed out, HSA is nonimmunogenic and it is not recognized as a foreign element, but, if altered or damaged, it is immediately targeted by the immune system and degraded. However, the protein is well-known for its prolonged half-time, which makes it a useful carrier in drug delivery.

The long half-life of albumin is due to the escape from intracellular degradation by FcRn receptor, which recycles internalized albumin back to the bloodstream through a pH-dependent mechanism.

## CONCLUSIONS:

The field of nanomedicine is becoming more and more appealing as it provides efficient and smart solutions for the delivery of therapeutics in the treatment of cancer, inflammatory diseases, and other conditions. Over the past few years, the great potential of albumin as a drug delivery system attracted the attention of many researchers due to its biocompatibility, biodegradability, nonimmunogenicity, and nontoxicity. It is not a foreign body; it is not rejected by the immune system since it is the most abundant protein in the plasma, and that makes it even more appealing. Its high affinity for hydrophobic drugs, the possibility for surface modification, and the high loading capability allow us to overcome the great barriers imposed by the nature of many compounds available in the market nowadays. It is a versatile drug carrier, which could be used not only for the transport of therapeutics but also for imaging applications and gene therapy. Moreover, its binding affinity for specific receptors on the surface of endothelial cells and other cells in diseased organs permits the active targeting and the specific recognition of the albuminbased formulation by the target site. This is the most important and unique feature of albumin, which makes it different and unique compared to the other nanocarriers. This feature, perhaps, has provided the inspiration for the use of albumin as a preformed corona over several other nanodelivery systems. With several albumin-based formulations already in clinical trials and the already approved Abraxane formulation, which has shown outstanding results in cancer patients, albumin nanobased formulations provide a safe and potentially effective strategy for the formulation of many existing and emerging drugs with enhanced therapeutic index

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