Human Serum Albumin: A Novel Drug Delivery Carrier System

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Abstract: With the success of several clinical trials of products based on human serum albumin (HAS) and the rapid developments of nanotechnology, HAS-based Nano-drug delivery systems (HBNDSs) have received Extensive attention in the field of nano-medicine. 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 HAS. 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 HAS. 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 as drug delivery, biomedical applications of albumin

INTRODUCTION

Nanotechnology has shown great potential in pharmaceutical Applications, especially in the area of drug delivery. In Particular, nano- materials 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.[2] Nano-particles have been designed to overcome the limitations of conventional delivery and navigation through biological barriers. In fact, in several instances, nano-particles of various chemical structures, including lipid, polymer, and inorganic nano-carriers, have shown to effectively offer control on the bio-distribution and/or release of single or multi therapeutic agents and the possibility to overcome biological barrier. [3,4] against targeted drug delivery to the diseased site. However, depending on their structure, such nano-carriers have also presented drawbacks restricting their success in targeted drug delivery, including non specific uptake phagocytes, off-target distribution, nonspecific immune activation, inadequate control over drug release in biological systems, and poor intracellular internalization.[5] The plasma protein albumin has attracted attention as a natural, yet versatile, nano-delivery system due to its characteristics, including high binding capacities for both hydrophobic and hydrophilic drugs, relatively long half-life, specific targeting of inflammation sites, as well as virtually minimal toxicity andimmunogenicity.[6]Albumin is one of the most abundant and important proteins in the body because of its role in the maintenance of intravascular colloid osmotic pressure, neutralization of toxins, and transport of therapeutic agents.

In addition to the natural affinity of many drugs for binding to Albumin, the possibility for chemical conjugation of drugs to Albumin nano-particles has also been explored for several entities. Moreover, the surface of the albumin-based Nano-Particle can also be functionalized with legends due to the Presence of functional groups to which different type linkers or

spacers can be attached. Being recognized by theGp60 receptors and secreted protein, acidic and rich in cysteine (SPARC) pathways, it potentially can provide active targeting without the use of external legends. Albumin nano-particles have been the subject of excellent several reviews, to date.[6–9] The Purpose of the current manuscript is to provide an update on the status of albumin in the nonmedical field, emphasizing the unique features of this delivery system responsible for its Successful preclinical and clinical application for different Therapeutic entities and in various disease conditions.

Advantages of using HSA as Drug Carrier:

- Human Serum Albumin (HSA) is native to the body.
- It is biodegradable in nature, nontoxic and non-immunogenic [3].
- HSA is a robust macromolecule. It is stable over a wide pH range 4-9, could be heated at 60°C for up to 10h without deleterious effect, is unchanged by denaturing agents and solvents at moderate concentrations. Therefore, albumin could remain stable under typical processing conditions [3].
- As the most abundant protein in plasma, albumin is readily available. It has been used in clinical setting for more than 30 years[3]
- The half-life of albumin is 19 days in blood circulation [3]

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 and calcium

Advantages: Albumin-based nano-particles offer advantages are as follows

1. Poorly soluble drugs can really benefit from Being wrapped up in nano-particles this makes them more bio-available & effective.
2. When we add legends or other special targeting Bits to nano-particles, they can stick to specific Receptors on sick cells. This clever approach keeps more of the medicine away from healthy tissues, which means fewer side effects!
3. We can design nano-particles so that they slowly release their medication over time. This Leads to longer-lasting effects and means you don't Have to take doses as often.
4. Nano-particles act like tiny shields. They help protect medications from enzymes & Chemicals that might break them down, boosting their stability and effectiveness.

Disadvantage

1. It is time consuming process.
2. It requires specialized equipment.
3. Loss of protein bound to albumin.
4. Albumin modifications are known to cause systemic disease.
5. It also responsible for progressive kidney proximal tubule cell injury.

Types of albumin

1. Lactalbumin: It is also called whey protein. It is a protein fragment of milk. Essentially comprises a small part of Beta-lactoglobulin[20]
2. Ovalbumin: This type of albumin Constituents about 50% of the proteins of egg White. It is also called serpin.[21-22]
3. Plant 2s –albumin: It is the best albumin for the storage of proteins.[23]

Function of Albumin:

1. Keeping fluid balance: Imagine albumin in your blood like a tiny sponge. It attracts water molecules due to its size & negative charge. This creates a **colloid osmotic pressure** that pulls fluid from the space between cells into the blood vessels. This stops fluid from piling up in tissues & helps keep blood volume just right. Think of it like a dam that holds back water, making sure the right amount stays in the bloodstream without leaking out.

2. Transporting molecules: Albumin is like adelivery truck zooming around the body, moving important things. It has little pockets that grab onto various types of cargo, such as:

- Hormones like insulin & thyroid hormones that need to get to their target cells.
- Fatty acids, which are energy-packed, travel from the intestines or fat stores to muscles and other parts for energy.
- Bile acids help with digestion; they ride with albumin to get to the intestines and help break down fats.
- Vitamins, especially fat-soluble ones like A, D, E, & K, depend on albumin for a smooth trip through the bloodstream.
- Metals like copper, zinc, & calcium tag along with albumin to reach where they're needed.

3. Buffing pH: Our body needs a perfect pH balance slightly alkaline to work well. Albumin acts like a chemical buffer by soaking up extra hydrogen ions when the pH is too low and releasing them if it gets too high. This helps keep the pH in a happy range that's key for enzymes and cells to do their jobs properly.

4. Binding & detoxifying toxins: Albumin is kind of like a bouncer in your bloodstream. It grabs and neutralizes nasty substances such as:

- Drugs; it can hold onto drugs longer, slowing their release so they don't hit toxic levels in our tissues.
- Metals; heavy metals like mercury & lead can be really bad for us, but albumin binds them up &keeps us safe from damage.
- Toxins; from those made by bacteria to waste products our bodies produce—albumin helps neutralize & get rid of them safely.

Methods for producing albumin nano-particles

There are different physical and chemical methods for producing albumin nano-particles. Common chemical Methods are disolvation, emolation and self-assembly. Thermal gelation, nano-particle albumin-Bound (NAB) technology and nano-spray drying are physical methods in producing albumin nano-particles. Furthermore, there are different approaches for loading albumin nano-particles on targeted Drugs (for instance, covalent bonds, surface coating and electrostatic absorption).

Albumin as a nano-carrier

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

HSA-Based Multifunctional Nano-carrier:

Due to its favorable attributes such as excellent biocompatibility, non-toxicity, non-immunogenicity, and prolonged circulation time, HBNDSs have garnered significant attention for a wide range of biomedical applications. 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. In this section, we will systematically summarize the recent advancements in HSA-based multifunctional nano-carriers within the past five years.

CHARACTERISTICS OF ALBUMIN

Biocompatibility: Albumin is non-toxic, non-immunogenic, biocompatible, and biodegradable, making it an ideal carrier for drug delivery.

Targeted Delivery: Albumin can interact with receptors over expressed in diseased tissues and cells, allowing for targeted delivery of drugs.

Half-Life Extension: Albumin's extended serum half-life of around 19 days can help promote half-life extension and targeted delivery of drugs.

Nano-particle-Based Systems: Albumin nano-particles are extensively investigated for drug delivery due to their superior biocompatibility and enhanced targeting capacity.

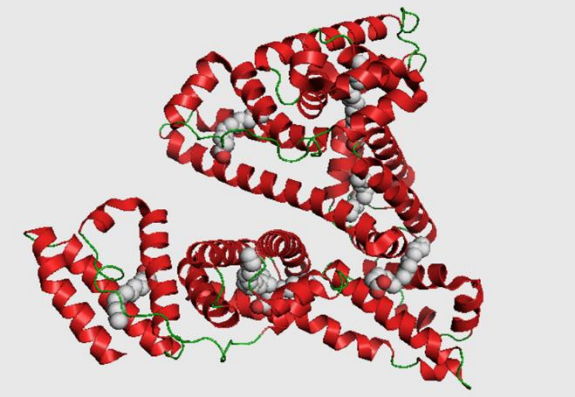
Research and Development: Research scientists are working on developing and optimizing albumin nano-

particles for therapy through conventional or alternative administration routes.

Types of serum albumin

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.[11] 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 [12]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[13]. 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 hypo-albuminemia, 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.

Bovine Serum Albumin:

It is a Bovine serum Albumin protein and it is found in animals (cow). It is also called Fraction "V". It comprises about 583 amino acids and no Carbohydrates. BSA is a small, stable, and Non-reactive protein. BSA shows no Biochemical applications. BSA is Inexpensive so it is very commonly used in Experiments. BSA is widely used for Pharmaceuticals and tissue-relatedApplications.[19]

Serum Albumin from Other Species:

Bovine serum Albumin is derived from bovine serum, and it is very similar toThe HAS. Its molecular weight is 69.323 kDa, and it has an Iso-electric point (pI) of 4.7 in water (25 °C), which makes it negatively charged at a neutral pH and positively charged under acidic conditions.[14] The presence of both negatively charged amino acids and positively charged ones in BSA can result in the binding of both positively and negatively charged substances. Because it is widely available at low cost and easy to purify and control, it has been widely used as a carrier for drug delivery in the literature. Furthermore, it has high loading capability, and it is water-soluble and can bind both hydrophilic and hydrophobic drugs, making it a very versatile carrier. The only downside could be a possible immunogenic response in vivo in humans[15]but also in mice.[16]

The Unique Properties of Albumin Nano-carrier In Drug Targeting

The natural ability of albumin in targeting cancer and other pro-angiogenic environments:

The hyper-Permeability of blood vessels and the impaired lymph drainage, the well-known enhanced permeation and Retention (EPR) effect in solid tumors[7]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 nano-carriers in solid tumors, even in preclinical animal models, has been Questioned recently .[17]Although it constitutes a paradigm in cancer nano-medicine, Chan et al. demonstrated That 97% of the nano-particles under their study enter into solid tumors by endothelial cells through an active Process of transcytosis and that the inter endothelial gaps, which

characterize the EPR effect, to overcome problems of insufficient. Nitric oxide has a very short blood residence time, and this creates a limitation for its usage. For this reason, Kinoshita etAl.[18]developed a NO drug delivery system, S-nitrosated HAS Dimer (SNO-HAS dimer), which was able to deliver NO efficiently to the tumor site. The combination of an albumin-Based drug delivery system (nab-paclitaxel) with SNO-HASDimer, enhancing the passive targeting, showed significantly higher suppression of the tumor growth (even the ones with low vascular permeability) than the drug delivery system used alone. One of the unique features that make albumin such a powerful and effective drug carrier is that it binds to receptors, which are over expressed 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).[18]

CONCLUSIONS

The field of nano-medicine 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, non-immunogenicity, and Non toxicity. 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 albumin based 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 nano-carriers. This feature, perhaps, has provided the inspiration for the use of albumin as a preformed corona over several other nano-delivery 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 Nano based formulations provide a safe and Potentially effective strategy for the formulation of many existing and emerging drugs with enhanced Therapeutic index

REFERENCE

[1] Emeje, M. O.; Obidike, I. C.; Akpabio, E. I.; et al.Nanotechnology in Drug Delivery. In Recent Advances in Novel DrugCarrier Systems; Sezer, A. D.; IntechOpen, 2012; pp 1−38.

[2] Lombardo, D.; Kiselev, M. A.; Caccamo, M. T. SmartNanoparticles for Drug Delivery Application: Development ofVersatile Nanocarrier Platforms in Biotechnology and Nanomedicine.J. Nanomater. 2019, 2019, 1−26.

[3] Mitchell, M. J.; Billingsley, M. M.; Haley, R. M.; et al.Engineering precision nanoparticles for drug delivery. Nat. Rev. DrugDiscovery 2021, 20 (2), 101−124.

[4] Wang, S.; Su, R.; Nie, S.; et al. Application of nanotechnology inImproving bioavailability and bioactivity of diet-derived phytochem-Icals. J. Nutr. Biochem. 2014, 25 (4), 363−376.

[5] Toy, R.; Roy, K. Engineering nanoparticles to overcome barriersTo immunotherapy. Bioeng. Transl. Med. 2016, 1 (1), 47−62.

[6] Karimi, M.; Bahrami, S.; Ravari, S. B.; et al. AlbuminNanostructures as advanced drug delivery systems. Expert Opin.Drug Delivery 2016, 13 (11), 1609−1623.

[7] Loureiro, A.; G. Azoia, N.; C. Gomes, A.; Cavaco-Paulo, A.; et al.Albumin-Based Nanodevices as Drug Carriers. Curr. Pharm. Des.2016, 22 (10), 1371−1390.

[8] An, F.-F.; Zhang, X.-H. Strategies for Preparing Albumin-basedNanoparticles for Multifunctional Bioimaging and Drug Delivery.Theranostics 2017, 7 (15), 3667−3689.

[9] Elzoghby, A. O.; Samy, W. M.; Elgindy, N. A. Albumin-basedNanoparticles as potential controlled release drug delivery systems. J.Controlled Release 2012, 157 (2), 168−182.

[10] Larsen, M. T.; Kuhlmann, M.; Hvam, M. L.; Howard, K. A.Albumin-based drug delivery:

harnessing nature to cure disease. Mol.CellTher. 2016, 4, 3.
[11] Kouchakzadeh, H.; Safavi, M. S.; Shojaosadati, S. A. EfficientDelivery of Therapeutic Agents byUsing Targeted AlbuminNanoparticles. Adv. Protein Chem. Struct. Biol. 2015, 98, 121−143.
[12] Caraceni, P.; Tufoni, M.; Bonavita, M. E. Clinical use ofAlbumin. Blood Transfus. 2013, 11 (4), s18−s25.
[13] Carvalho, J. R.; Machado, M. V. New Insights About AlbuminAnd Liver Disease. Ann. Hepatol. 2018, 17 (4), 547−560.
[14] Phan, H. T. M.; Bartelt-Hunt, S.; Rodenhausen, K. B.; et al.Investigation of Bovine Serum Albumin (BSA) Attachment onto Self-Assembled Monolayers (SAMs) Using Combinatorial Quartz CrystalMicrobalance with Dissipation (QCM-D) and SpectroscopicEllipsometry (SE). PLoS One 2015, 10 (10), e0141282.
[15] Elzoghby, A. O.; Samy, W. M.; Elgindy, N. A. Albumin-basedNanoparticles as potential controlled release drug delivery systems. J.Controlled Release 2012, 157 (2), 168−182.
[16] Hilton, J.; Dearman, R. J.; Sattar, N.; et al. Characteristics ofAntibody responses induced in mice by protein allergens. Food Chem.Toxicol. 1997, 35 (12), 1209−1218.
[17] Sindhwani, S.; Syed, A. M.; Ngai, J.; et al. The entry of Nanoparticles into solid tumours. Nat. Mater. 2020, 19 (5), 566−575.
[18] Desai, N. Nanoparticle Albumin-Bound Paclitaxel (Abraxane).In Albumin in Medicine; Otagiri, M., Chuang, V. T. G., Eds.; Springer:Singapore, 2016; pp 101−119.
[19] Topală, T, Bodoki, A, Oprean, L, Oprean, R, Clujul medical, 87, 215 (2014).
[20] Brew, K, α-Lactalbumin. In Advanced DairyChemistry—1 Proteins (387), (Springer,Boston, MA, 2003)
[21] Sugino, H, Nitoda, T, &Juneja, L R, GeneralChemical composition of hen eggs, In Hen eggs (13,CRC press, 2018)
[22] Hu, H, & Du, H N, Journal of ProteinChemistry, 19 , 177 (2000).
[23] Moreno, F. J, Clemente, A, The openBiochemistry journal, 2, 0 (2008).
[24] Wang, W.; Huang, Y.; Zhao, S.; et al. Human serum albumin(HAS) nanoparticles stabilized with intermolecular disulfide bonds.Chem. Commun. (Cambridge, U. K.) 2013, 49 (22), 2234−2236.
[25] Bronze-Uhle, E.; Costa, B. C.; Ximenes, V. F.; et al. SyntheticNanoparticles of bovine serum albumin with entrapped salicylic acid.Nanotechnol., Sci. Appl. 2017, 10, 11−21.
[26] Langer, K.; Balthasar, S.; Vogel, V.; et al. Optimization of thePreparation process for human serum albumin (HAS) nanoparticles.Int. J. Pharm. 2003, 257 (1−2), 169−180.
[27] Parodi, A.; Miao, J.; Soond, S. M.; et al. Albumin NanovectorsIn Cancer Therapy and Imaging. Biomolecules 2019, 9 (6), 218.
[28] Li, R.; Zheng, K.; Yuan, C.; et al. Be Active or Not: theRelative Contribution of Active and Passive Tumor Targeting ofNanomaterials. Nanotheranostics. 2017, 1 (4), 346−357.
[29] Alken, S.; Kelly, C. M. Benefit risk assessment and update onThe use of docetaxel in the management of breast cancer. CancerManage. Res. 2013, 5, 357−365.
[30] Sulkes, A.; Smyth, J.; Sessa, C.; et al. Docetaxel (Taxotere) inAdvanced gastric cancer: results of a phase II clinical trial. EORTCEarly Clinical Trials Group. Br. J. Cancer 1994, 70 (2), 380−383.
[31] Qu, N.; Sun, Y.; Li, Y.; Hao, F.; Qiu, P.; Teng, L.; Xie, J.; Gao,Y.; et al. Docetaxel-loaded human serum albumin (HAS) nano-Particles: synthesis, characterization, and evaluation. Biomed. Eng.Online. 2019, 18 (1), 11.
[32] Ertugen, E.; Tuncel, A.; Yurt, F. Docetaxel loaded human Serum albumin nanoparticles; synthesis, characterization, andPotential of nuclear imaging of prostate cancer. J. Drug Delivery Sci.Technol. 2020, 55, 101410.
[33] Tang, X.; Wang, G.; Shi, R.; et al. Enhanced tolerance andAntitumor efficacy by docetaxel-loaded albumin nanoparticles. DrugDelivery 2016, 23 (8), 2686−2696.
[34] Cheng, K.; Sun, S.; Gong, X. Preparation, characterization,Andantiproliferative activities of biotin-decorated docetaxel-loadedBovine serum albumin nanoparticles. Braz. J. Pharm. Sci. 2018, 54 (2),E17295