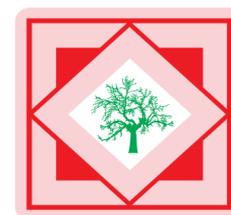




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# A review on albumin as drug carrier in treating different diseases and disorders

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## ABSTRACT

Over the past decade numerous drug delivery systems have been developed to improve the treatment of different diseases and disorders. Albumin has been widely studied as a protein carrier for drug delivery, a stable endogenous protein; albumin has been employed as a non-immunogenic delivery carrier and extensively researched in various disease therapies. To provide the prospective for future research, this review summarizes the application of albumin as drug or imaging agent carriers for treating different diseases and disorders such as diabetes, hepatitis C and rheumatoid arthritis, Cancer, Tumor, Cardiovascular disorders, Hypovolemia, Hypoalbuminemia and potential future directions. There are three major types of albumin-based carrier systems including albumin drug conjugates, albumin particles and genetic infusion albumin. Their imaging or therapeutic effects have been proved in clinic or preclinical studies.

**Keywords:** Albumin, Plasma protein, Human Serum Albumin, Nanoparticle

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## INTRODUCTION

Albumin is the most abundant protein in plasma, accounting for more than half of human plasma protein [1]. Human albumin is an essential protein found in human plasma and accounts for about 50%-60% of plasma proteins. Each molecule is composed of three units, or domains, which function together to give albumin its unique binding properties. Albumin is primarily responsible for 75%-80% of plasma's normal colloid oncotic pressure. It has solubilising long chain fatty acids, delivery of nutrients to cells, and balancing plasma pH. Albumin has been widely studied as a protein carrier for drug delivery. Serum albumin, often referred to simply as albumin, is a globular protein that in humans is encoded by the *ALB* gene. Serum albumin is produced by the liver, occurs dissolved in blood plasma and is the most abundant blood protein in mammals, several hydrophobic steroid hormones and as a transport protein for haemin and fatty acids. Too much or too little circulating serum albumin may be harmful [1, 2].

There are several advantages of using albumin as drug carrier: 1) as an endogenous protein, Human Serum Albumin (HSA) is native to the body. It is biodegradable in nature, nontoxic and non-immunogenic; 2) Albumin is a robust protein. It is stable over a wide pH range 4-9, could be heated at 60°C for up to 10 h without deleterious effect, is unaltered by denaturing agents and solvents at moderate concentrations [3,4]. 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; 4) the half life of albumin is 19 days in blood circulation. It may play an important role as a carrier in improving the pharmacokinetic property of small drug molecules, peptides or protein based drugs [4,5].

Albumin is emerging as a versatile protein carrier for drug targeting and for improving the pharmacokinetic profile of peptide or protein-based drugs. Albumin is the most abundant plasma protein (35–50 g/L human serum) with a molecular weight of 66.5 kDa. [6] Like most of the plasma proteins, albumin is synthesized in the liver where it is produced at a rate of approximately 0.7 mg/h for every gram of liver (i.e. 10–15 g daily); Human serum albumin (HSA) exhibits an average half-life of 19 days. HSA is used for treating shock, burns, hypoalbuminemia, surgery or trauma, cardiopulmonary bypass, acute respiratory distress and hemodialysis [6]. As an alternative to blood derived albumin, recombinant human serum albumin (Recombunin) has been developed and is a genetically engineered protein expressed in yeast cells that has shown comparable safety, tolerability, pharmacokinetics and pharmacodynamics to native HSA [7]. Albumin is an acidic, very soluble protein that is extremely robust: it is stable in the pH range of 4–9, soluble in 40% ethanol, and can be heated at 60 °C for up to 10 h without deleterious effects. These properties as well as its preferential uptake in tumor and inflamed tissue, its ready availability, its biodegradability, and its lack of toxicity and immunogenicity make it an ideal candidate for drug delivery.

### Basic functions of Albumin

Albumin functions primarily as a carrier protein for steroids, fatty acids, and thyroid hormones in the blood and plays a major role in stabilizing extracellular fluid volume by contributing to oncotic pressure (known also as colloid osmotic pressure) of plasma because smaller animals (for example rats) function at a lower blood pressure, they need less oncotic pressure to balance this, and thus need less albumin to maintain proper fluid distribution. The functions and binding properties of HSA are multifold [8]: a) it acts as the solubilizing agent for long chain fatty acids and is therefore essential for the metabolism of lipids; b) it binds bilirubin, the breakdown product of heme; c) it binds a great number of therapeutic drugs such as penicillins, sulfonamides, indole compounds, and benzodiazepines to name just a few; d) it binds copper(II) and nickel(II) in a specific and calcium(II) and zinc(II) in a relatively nonspecific manner and acts as the transport vehicle for these metal ions in the blood; e) it is the major protein responsible for the colloid osmotic pressure of the blood; f) when HSA is broken down, the amino acids provide nutrition to peripheral tissue. The three-dimensional structure of HSA has been elucidated by X-ray structure analysis [9, 10].

Serum albumin is the main protein of human blood plasma.[11] It binds water, cations (such as  $\text{Ca}^{2+}$ ,  $\text{Na}^+$  and  $\text{K}^+$ ), fatty acids, hormones, bilirubin, thyroxine (T4) and pharmaceuticals (including barbiturates) - its main function is to regulate the colloidal osmotic pressure of blood. Alpha-fetoprotein (alpha-fetoglobulin) is a fetal plasma protein that binds various cations, fatty acids and bilirubin. Vitamin D-binding protein binds to vitamin D and its metabolites, as well as to fatty acids. The isoelectric point of albumin is 4-5.9g/dl.

### Structure:

The 3D structure of human serum albumin has been determined by X-ray crystallography to a resolution of 2.5 Å. [12] Albumin is a 65-70 kDa protein. The general structure of albumin is characterized by several long  $\alpha$  helices, this allows it to maintain a relatively static shape, something essential for regulating blood pressure.[13]

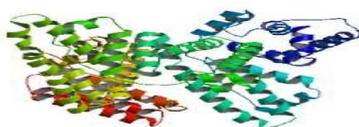


Fig.1 Basic structure of Albumin

Serum albumin contains eleven distinct binding domains for hydrophobic compounds. One haemin and six long-chain fatty acids can bind to serum albumin at the same time[13]. Each domain is a product of two sub domains that possess common structural moiety's.[14] The principal regions of ligand binding to human serum albumin are located in hydrophobic cavities in sub domains IIA and IIIA, which exhibit similar chemistry.

### Types of albumin:

Serum albumin is widely distributed in mammals. Examples include:

- The human version is human serum albumin.
- Bovine serum albumin, or BSA, is commonly used in immunodiagnostic procedures, clinical chemistry reagents, cell culture media, protein chemistry research (including venom toxicity), and molecular biology laboratories (usually to leverage its non-specific protein binding properties).[15]

**Albumin as a drug carrier:**

Albumin is playing an increasing role as a drug carrier in the clinical setting.[16] Principally, three drug delivery technologies can be distinguished:

1. Coupling of low-molecular weight drugs to exogenous or endogenous albumin
2. Conjugation with bioactive proteins
3. Encapsulation of drugs into albumin nanoparticles.

**Tumor:**

Albumin accumulates in malignant and inflamed tissue due to a leaky capillary combined with an absent or defective lymphatic drainage system. Tumour uptake in preclinical models can be easily visualized by injecting the dye Evans blue that binds rapidly and tightly to circulating albumin and makes subcutaneously growing tumours turn blue within a few hours post-injection. As an alternative to drug targeting, conjugating therapeutic peptides or cytokines with albumin is an attractive approach of improving their pharmacokinetic profile due to the long-half life of albumin in the body.[17] Clinically, a methotrexate-albumin conjugate, an albumin-binding prodrug of doxorubicin, i.e. the (6-maleimido)caproylhydrazone derivative of doxorubicin (DOXO-EMCH), and an albumin paclitaxel nanoparticle (Abraxane) have been evaluated clinically. Abraxane has been approved for treating metastatic breast cancer.

An alternative strategy is to bind a therapeutic peptide or protein covalently or physically to albumin to enhance its stability and half-life. This approach has been applied to peptides with anti nociceptive, anti diabetes, antitumor or antiviral activity. Levemir, a myristic acid derivative of insulin that binds to the fatty acid binding sites of circulating albumin, has been approved for the treatment of diabetes.

**Cancer:**

Serum proteins are potential drug carriers of antineoplastic agents due to their accumulation in tumor tissue. Uptake of these proteins in solid tumors is mediated by a number of factors including an increased metabolic activity of tumors, an enhanced vascular permeability of tumor blood vessels for circulating macromolecules, and a lack of a functional lymphatic drainage system in tumor tissue. Recently, a number of acid-sensitive albumin and transferrin conjugates with anthracyclines and the alkylating agent chlorambucil have shown promising *in vitro* activity. In addition, acid-sensitive doxorubicin conjugates with monoclonal antibodies and albumin doxorubicin conjugates prepared by glutaraldehyde cross-linking have shown promising antitumor efficacy *in vivo*.[18]

**Rheumatoid arthritis (RA)**

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects a large number of people throughout the world. Uncontrolled active rheumatoid arthritis causes joint damage, disability. Methotrexate (MTX) is a common used drug for treating RA and cancer. To overcome the lack of specificity with regard to the inflamed tissue as well as increasing the half life, methotrexate-albumin conjugate (MTX-HSA) was developed by directly coupling MTX to lysine residues of HSA. Compared with equivalent dosage of MTX, MTX-HSA was more effective in a collagen-induced arthritis mouse model. Meanwhile; MTX-HSA has shown to significantly reduce synovial fibroblast invasion and cartilage degradation in a humanized rheumatoid arthritis.[19]

**Hypovolemia:**

Hypovolemia is a possible indication for albumin. Its effectiveness in reversing hypovolemia depends largely upon its ability to draw interstitial fluid into the circulation. It is most effective with patients who are well hydrated.[19] When hypovolemia is long standing and hypo albuminemia exists accompanied by adequate hydration or edema, 25% albumin is preferable to 5% protein solutions. However, in the absence of adequate or excessive hydration, 5% protein solutions should be used or 25% albumin should be diluted with crystalloid.[20]

**Burns:**

An optimum regimen for the use of albumin, electrolytes and fluid in the early treatment of burns has not been established; however, in conjunction with appropriate crystalloid therapy, albumin may be indicated for treatment of

oncotic deficits after the initial 24 hour period following extensive burns and to replace the protein loss which accompanies any severe burn. [20,21]

#### **Adult Respiratory Distress Syndrome (ARDS):**

A characteristic of ARDS is a hypoproteinemic state, which may be causally related to the interstitial pulmonary edema. Although uncertainty exists concerning the precise indication of albumin infusion in these patients, if there is a pulmonary overload accompanied by hypoalbuminemia, 25% albumin solution may have a therapeutic effect when used with a diuretic.

#### **Cardiopulmonary Bypass Surgery:**

A recent meta-analysis focussed on the usage of albumin in priming solution for cardiac surgery showed favourable results of albumin in keeping the colloid oncotic pressure on a physiological level as compared with that of crystalloid hence albumin has been recommended prior to or during cardiopulmonary bypass surgery, although no clear data exist indicating its advantage over crystalloid solutions.[22]

#### **Hemolytic Disease of the Newborn (HDN):**

Hemolytic Disease of the Newborn (HDN), also known as erythroblastosis fetalis, isoimmunization, or blood group incompatibility, occurs when fetal red blood cells (RBCs), which possess an antigen that the mother lacks, cross the placenta into the maternal circulation, where they stimulate antibody production. The antibodies return to the fetal circulation and result in RBC destruction. Albumin may be administered in an attempt to bind and detoxify unconjugated bilirubin in infants with severe HDN.

#### **Albumin Microspheres:**

To present an alternative way of developing NSAIDs as microspheres specifically using albumin polymers, which are playing an increasing role as drug carriers in the clinical setting, hence there is a prolonged release of the drug along with minimized side effects. A brief overview of the methods developed for the preparation of albumin microspheres and the most suitable techniques for optimum entrapment of drug is emphasized.[23]

#### **Recombinant Human Serum Albumin**

Human serum albumin (HSA) is used clinically as an important plasma expander. Albumin infusion is not recommended for critically ill patients with hypovolemia, burns, or hypoalbuminemia because of the increased leakage of albumin into the extravascular spaces, thereby worsening edema. In the present study, we attempted to overcome this problem by producing a recombinant HSA (rHSA) dimer with decreased vascular permeability and an increased half-life. (24)

#### **Application on new horizon:**

Over the past decades, albumin has emerged as a versatile carrier for therapeutic and diagnostic agents, primarily for diagnosing and treating diabetes, cancer, rheumatoid arthritis and infectious diseases. Market approved products include fatty acid derivatives of human insulin or the glucagon-like-1 peptide (Levemir® and Victoza®) for treating diabetes, the taxol albumin nanoparticle Abraxane® for treating metastatic breast cancer. Physical or covalent attachment of antiviral, antibacterial, and anticancer drugs to albumin that are permanently or transiently attached to human serum albumin (HSA) or act as albumin-binding prodrugs.(25)

#### **Marketed Formulation:**

Dosage form	Drug	Uses
Albumin Microspheres	Paclitaxel, Cisplatin	Lung cancer
Albumin Nanoparticle	Abraxane, Tamoxifen	Breast cancer
Albumin Nanoparticle	Albendazole	Ovarian cancer
Magnetic Albumin Microspheres	5-fluorouracil and Cyclophosphamide	Breast cancer
Albumin Solution	Levemir	Diabetes

### **CONCLUSION**

The above presentation gives an overview of the expanding field of preclinical and clinical drug applications and developments that use albumin as a protein carrier to improve the pharmacokinetic profile of the drug or to target the drug to the pathogenic site addressing diseases with unmet medical needs.

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