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ALBUMIN AS A DRUG DELIVERY AND DIAGNOSTIC TOOL AND ITS MARKET APPROVED PRODUCTS

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Abstract: Albumin is one of the most extensively studied endogenous proteins which are used in the fabrication of drug delivery and diagnostic technologies during last 10 years. This review provides a summary of products involving the use of albumin as a drug delivery tool for getting better the pharmacokinetics of a drug by developing the targetted drug delivery systems and diagnosing the pathologies. Using albumin, following market approved products have been developed: Levemir® and Victoza® (antidiabetic product), Abraxane® (antimetastatic breast cancer product), and Nanocoll® and Albures® (for lymphoscintigraphy and diagnosis of cancer and rheumatoid arthritis).

Keywords: albumin, drug delivery tool, peptides, radiopharmaceutical

Albumin is likely one of the most extensively studied endogenous proteins which is used in the fabrication of drug delivery technologies. It can be used to improve the pharmacokinetic nature of drugs and also to develop targeted drug delivery tools (1). There are three types of albumin i.e., ovalbumin, bovine serum albumin, and human serum albumin. Out of these, ovalbumin is a monomeric phosphoglycoprotein. It is exceedingly used as food (2). This multifunctional protein contains 385 protein units i.e., amino acids. Its chemical structure contains a disulfide bond as well as 4 free sulfydryl groups. Its molecular weight and isoelectric point are 47,000 Da and 4.8, respectively (3). In comparison to other protein polymers, ovalbumin is selected as a drug delivery tool particularly in controlled drug delivery because of its many attractive features like low cost, ease in availability, its capability to develop gel networks, emulsion stabilization, and pH- and temperature-sensitive nature. Bovine serum albumin is also extensively employed in drug delivery systems due to its low cost, medical significance, plenty in nature, simple purification, and its extraordinary ligand-binding features (4, 5). Its molecular weight and isoelectric point in water (at 25°C) are 69,323 Da and 4.7, respectively (3). To evade a probable *in vivo* immunologic reaction, the substitute of bovine serum albumin i.e., human serum albumin is used. It is the most plentiful hydrophilic plasma protein having a mean half-life of 19 days and a molecular weight of 66,500 Da. It possesses 35 cysteinyl moieties with a sulfhydryl group and seventeen disulfide bridges (6). It is enormously vigorous towards organic solvents, pH (unstable in pH > 9 as well as < 4) and temperature (can be heated at 60°C for 10 h). Human serum albumin, produced in the liver, is also extensively employed in drug delivery systems because it is inert, biodegradable, easily available, significantly uptaken by the tumor and inflamed tissue. It is a

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hydrophilic protein which composes more than half of the blood serum protein. It helps in the maintenance of oncotic pressure, transportation of thyroid hormones, fatty acids, unconjugated bilirubin and many drugs. It undergoes competitive binding with calcium ions (Ca^{2+}) as well as buffers at the pH of body fluids. In addition, human serum albumin prevents photodegradation of folic acid (7, 8).

Collection of data

The collection of data was carried out through an easy literature survey using a combination of key word "albumin" and "drug delivery tool". The collected peer-reviewed publications belonged to the period of 1950–2012, exhibiting a gradual increase in the number of articles on this topic from 1950 to 2012. It was also ensured that there was no repetition of any article. In addition, we also came to know that some albumin-based drug delivery tools have also been approved for marketing, which exhibited the rising curiosity of researchers in the pharmaceutical use of albumin as a drug tool. Above described information encouraged us to prepare a follow-up review article covering the essential advances on this topic in the past.

RESULTS AND DISCUSSION

Human serum albumin is known as the most plentiful protein in the body which is mainly distributed in systemic circulation and the lymphatic system. It is already employed in many applications e.g., nephrotic syndrome, for substituting the blood, to treat severe burns, and to compensate the malnutrition or cachexia in cancer patients (9).

Albumin is a multipurpose drug delivery tool. It has been used to formulate various formulations as conjugates, nanoparticles and/or complexes loaded with drugs, peptides and/or antibodies. In conjugates, drugs, prodrugs or polypeptides can either be bound physically or covalently through a ligand or protein-binding group to human serum albumin. Hydrophilic micro- and nanospheres as well as micelle based intravenous formulations loaded with hydrophobic drugs or diagnostic agents can also be fabricated. Further, complex systems are synthesized by developing linkage between many targeting ligands and prodrugs and antibodies through physical bonding or fusion linkage (10). These applications of albumin-based drug delivery concepts that have advanced as commercial product and are persistently enlarging are described here.

Market approved technologies

Levemir® and Victoza® as the antidiabetic products

Levemir® is an insulin detemir, manufactured by Novo Nordisk, Denmark. It is a combination of albumin and human insulin (produced biotechnologically in *Escherichia coli*) and is indicated for the treatment of diabetes mellitus (type 1 diabetes represents the lack of insulin assembly in the islets of Langerhans in the pancreas, while the insulin resistance is termed as type 2 diabetes). Till 1999, human insulin was used to treat diabetes, while from 1960 to 1999, diabetes was treated by porcine insulin. Porcine insulin structure was similar to that of human insulin except one amino acid (11). Human insulin molecule contains 51 amino acids, out of which 21 form the A polypeptide chain and 30 constitute the B polypeptide chain. Both chains are associated to each other through a disulfide bond. The mechanism of Levemir® action depends on a straightforward theory i.e., the C-terminal amino acid threonine in recombinantly produced human insulin is substituted by lysine followed by the development of covalent bond between the myristic acid and ε-amino group of lysine.

Human serum albumin possesses 5 binding sites, due to which it exhibits high affinity with fatty acids like myristic acid. The half-life of Levemir® is 5-7 h after its subcutaneous injection to the patients with type 1 diabetes (12), which is higher than that of challenging formulations because it does not undergo microprecipitation, rather it stays soluble both before and after injection while the glargine insulin, manufactured by Sanofi-Aventis, and NPH insulin, manufactured by Novo Nordisk, do not exhibit this property.

The same theory has been applied for the improvement of pharmacokinetics of the glucagon-like 1 peptide (GLP-1) which is used for the treatment of diabetes (13). The GLP-1-(7-37) and GLP-1-(7-36) NH_2 are the biologically active moieties. The break-up of proglucagon in the gut generates these peptides, which alternatively stimulate the secretion of insulin from pancreatic cells in a glucose-dependent mode. Due to the enzymatic degradation, the half-life of GLP-1(7-37) is 1.5-2 min. Liraglutide is an albumin-binding derivative of GLP-1 and exhibits many excellent features; liraglutide resists the metabolic degradation due to albumin-binding and thus exhibits a prolonged plasma half-life (11-15 h) after subcutaneous injection. This property makes liraglutide to be appropriate for single subcutaneous dose in a day.

Victoza® was approved for marketing in 2009 in Europe and in 2010 in USA for treating the

patients suffering from type 2 diabetes. By 2011, its sale reached approximately 0.66 million US $. Victoza® treats the diabetes 2 by targeting β-cells, which allows the augmented insulin secretion for a prolonged period along with the regulation of blood sugar concentration. Some concurrently occurring effects of Victoza® are weight loss and gastrointestinal disorders (14).

Abraxane® as an antitumor product

Abraxane® was approved for marketing and prescription by the Food and Drug Administration (FDA) in 2005 and then in 41 other countries. In 2010, sales for Abraxane® were about US $ 430 million. It is indicated for the management of metastatic breast cancer. Abraxane® is a nanoparticulate formulation consisting of albumin and paclitaxel which was fabricated by the American Bioscience department (5, 15). Moreover, Abraxane® is usually well tolerated after a 30 min intravenous infusion showing no hypersensitivity reactions. Currently, Abraxane®, frequently combined with conventional chemotherapeutic agents, is also being evaluated by treating patients suffering from the cancer of head, neck, pancreas, and lungs (16-18). For instance, diagnosis of metastatic pancreatic cancer is a difficult effort, till today only two approved drugs, gemcitabine and 5-fluoururacil, are being practiced showing a poor response rate (10-20%) and slow tumor suppression (16). To date, in phase I/II study (phase III trial is in progress), a combination of Abraxane® (equivalent to 125 mg/m^2 paclitaxel) and gemcitabine (1000 mg/m^2) has been tested in 44 patients with metastatic pancreatic cancer by administering on days 1, 8, and 15 which showed high response rate (80%) (17).

The mode of action of Abraxane® involves its rapid dissolution after intravenous infusion, which results in the formation of hydrophilic paclitaxel loaded albumin complexes. Since the size of these complexes is comparable to that of endogenous albumin, the paclitaxel loaded albumin complexes mount up in the tumor *via* enhanced permeation effect (18-20).

Nanocoll® and Albures® as diagnostic products

Technetium 99m (^{99m}Tc), a metastable nuclear isomer, has been used as radiopharmaceutical since last one decade which has resulted in the enormous growth of nuclear medicine, especially in diagnostics. Its half-life is 6 h (21). In order to deliver ^{99m}Tc to its target site (like heart, liver, bones, kidneys and lungs) in the body, various transporting mechanisms have been introduced.

For approximately thirty years, ^{99m}Tc aggregated albumin has been used in nuclear medicine (22). ^{99m}Tc aggregated albumin is a sterile hydrophilic injectable radiopharmaceutical which consists of a γ-emitting radionuclide and is used for imaging. Its pH is in a range of 3.8-8.0. Aggregated albumin complexes are presently available as kits with many trade names like ^{99m}Tc-Albures® and ^{99m}Tc-Nanocoll®. They are unlike from each other in respect of the amount of human serum albumin, concentration of $SnCl_2$, particle size and preserving substances. The size (diameter) of ^{99m}Tc aggregated albumin is in a range of a few to 1000 nm. Albures® is in a size (diameter) range of 200-1000 nm and is used for the screening of primary cancers, while the size (diameter) of Nanocoll® is 8 nm and is used for the detection of metastasis. It is used in the scanning of bone marrows, swelling, perfused lungs, and isotope venography. The diseases which are diagnosed by using ^{99m}Tc aggregated albumin are breast cancer (23), lymphomas (24), leg edema (25), rheumatoid arthritis (26), esophageal squamous cell carcinoma (27), and other solid tumors (28). It is also employed in protein-losing gastroenteropathic evaluation (29) and cardiac function tests (22).

The routes of administration of ^{99m}Tc aggregated albumin include intravenous, interarterial, subcutaneous, intradermal, and intratumoral pathways. Its dose is in a range of 10-200 MBq on the basis of diagnostic objective. Poel et al. (30) developed a new hybrid multimodal tracer, ICG-^{99m}Tc-Nanocoll®, possessing two properties, radioactive and fluorescent, coupled with γ camera and/or near infrared fluorescent. Recently, ICG-^{99m}Tc-Nanocoll® has been successfully used in eleven patients with prostate carcinoma in a dose of 280 MBq (0.4 mL) by injecting into the marginal area of prostate gland to improve the surgical accuracy of competently getting rid of primary tumors and infiltrating malignant lymph nodes.

CONCLUSIONS

Albumin is a promising drug delivery and diagnostic tool. Its most successful commercial products include Levemir® (long-acting insulin), Victoza® (glucagon-like peptide), Abraxane® (antitumor formulation), as well as Nanocoll® and Albures® (diagnostic products). In the near future, it is extremely probable that there will be a new generation of albumin-based sustained and targeted drug delivery systems. These formulations will not only improve the bioavailability of loaded drugs (particularly anticancer drugs) but also will develop

the EPR effect to decrease undesired effect but with augmented anticancer efficacy.

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