International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Uniqueness of Albumin as a Carrier in Nanodrug Delivery

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ABSTRACT

In contemporary medicine, albumin nanoparticles have become a powerful and adaptable nanodrug carrier. The ability of human serum albumin to deliver hydrophobic drugs through passive and active targeting mechanisms demonstrates its versatility in treating a variety of disorders. In addition to discussing ongoing clinical trials using albumin-based formulations, this study emphasizes the benefits of albumin-bound Paclitaxel (Abraxane) over solvent-based formulations (Taxol). Future advancements in albumin-based therapeutics are made possible by the emphasis placed on the importance of albumin in improving drug performance and its potential as a drug delivery mechanism.

Albumin nanoparticles show promise in the treatment of a variety of illnesses. This study emphasizes their use in the delivery of hydrophobic drugs, their benefits over formulations based on solvents, and their ongoing clinical trials. The medicinal potential of albuminNeutrophils, leveraging their inflammation-targeting capabilities, have emerged as innovative drug delivery carriers. Integrating neutrophils with nanotechnology enhances treatment efficacy and reduces side effects. This review explores neutrophil-based nano-drug delivery systems, including membrane-coated nanoparticles, cell-loaded nanoparticles, and chimeric antigen receptor (CAR)-neutrophils. These therapies demonstrate superior biocompatibility, targeting, and therapeutic robustness, showing promise in various disease treatments.Neutrophils, combined with nanotechnology, offer innovative drug delivery. This review covers design principles, mechanisms, and applications of neutrophil-based nano-drug delivery systems, highlighting enhanced biocompatibility, targeting, and therapeutic efficacy.

Keywords: Nanomedicine, albumin, nanoparticles, production method.

1. Introduction

The "magic bullet" notion, which is currently being suggested and centers on the development of a targeted medication, is now thought to be fully realized through the concept of nanotechnology. Among the best nanodrugs are albumin nanoparticles. They are transported by the albumin receptor's endogenous expression, which is only found on endothelial cells that are growing new blood vessels. This is a crucial feature of the tumor stroma that enhances medication delivery to the tumour cells. Thus, in the animal model of overexpressing breast cancer, albumin nanoparticles increased target effectiveness and extended survival. Additionally, the extended half-life and safety of albumin- or albumin-coupled medications are well established. Nevertheless, phage display, fluorophore-conjugated long-circulating nanoparticles, or high-dose medications were used to achieve these outcomes.Medical applications have been transformed

by nanotechnology, especially in the area of drug delivery. Complex medicinal substances can be precisely delivered, transported, and protected thanks to nanomaterials. Because of its special qualities, albumin, a naturally occurring plasma protein, has become a flexible nano delivery system:Longer lifespan; high drug binding capacity; and accurate inflammation site targeting Minimal immunogenicity and toxicity
Nanoparticles:
Improved tissue targeting; extended circulation time; improved drug solubility; and customizable surface modification for active targetingAlbumin-based nanoparticles, which can hold a variety of therapeutic substances and imaging agents, have emerged as a promising tool in nanomedicine due to their remarkable biocompatibility and degradability.Drug delivery is improved by nanotechnology using nanomaterials. One natural plasma protein that stands out for its special qualities is albumin.
Nanotechnology has revolutionized medical sciences, enabling the development of nanoparticle drug delivery systems (DDS) that overcome traditional drug delivery challenges. Nanomedicine has made significant strides in recent decades, with nanodevices offering targeted, controlled release of therapeutic agents. These nanocarriers improve drug efficacy, reduce side effects, and enhance cellular uptake. Key requirements for successful nanodevices include drug retention, immune system evasion, targeting, and controlled release.
The advent of nanomedicine has led to the development of various nanodevices, including:

- Liposomes
- Polymer conjugates
- Polymeric micelles
- Dendrimers
- Nanoshells
- Polymeric nanoparticles
- Nucleic acid-based nanoparticles

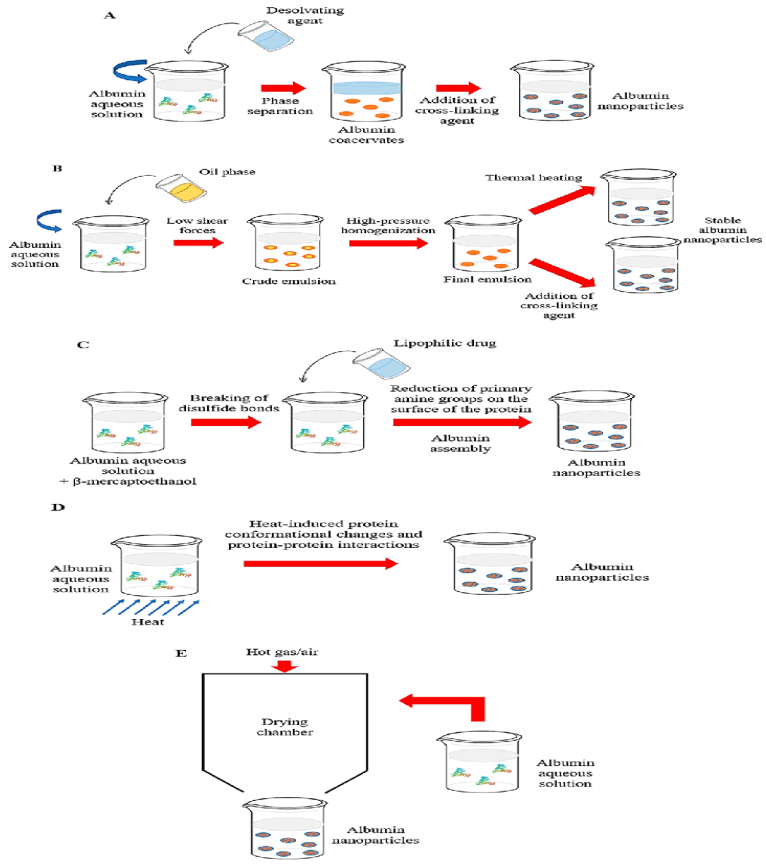
These innovative platforms aim to improve pharmacological and therapeutic properties of conventional drugs, addressing challenges such as degradation, solubility, and toxicity.
Nanotechnology has transformed medical sciences with nanoparticle drug delivery systems (DDS). Nanomedicine enhances drug efficacy, reduces side effects, and targets specific sites. Various nanodevices, including liposomes, polymer conjugates, and nanoparticles, have been developed to overcome traditional drug delivery challenges, improving treatment outcomes.

LITERATURE REVIEW

1. **Ana Loureiroa,b, Nuno G. Azoiaa, Andreia C. Gomesb and Artur Cavaco-Pauloa :**
   Nanomedicine, the application of nanotechnology to medicine, is being increasingly used to improve and exploit the advantages of efficient drug delivery. Different nanodevices have been developed in recent years, among them protein-based nanoparticles which have gained considerable interest.
2. **Alessandra Spada, Jaber Emami,* Jack A. Tuszynski, and Afsaneh Lavasanifar :**
   Albumin is an appealing carrier in nanomedicine because of its unique features. First, it is the most abundant protein in plasma, endowing high biocompatibility, biodegradability, nonimmunogenicity, and safety for its clinical application.
3. **Heng Mei a, Shengsheng Cai a, Dennis Huang c, Huile Gao b,*, Jun Cao a, Bin He a**:
   The considerable development of carrier-free nanodrugs has been achieved due to their high drug-loading capability, simple preparation method, and offering “all-in-one” functional platform features

4. **Edidiong Udofa, Zongmin Zhao**:
   Since the inception of the concept of "magic bullet", nanoparticles have evolved to be one of the most effective carriers in drug delivery
5. **SofiaTeixeira,ORCID,Maria Alice Carvalho ORCID andElisabete M. S. Castanheira.**
   Cancer is one of the leading causes of death worldwide. In the available treatments, chemotherapy is one of the most used, but has several associated problems, namely the high toxicity to normal cells and the resistance acquired by cancer cells to the therapeutic agents.
6. **Shrawani Lamichhane, Sangkil Lee**
   Albumin is a biocompatible, non-immunogenic and versatile drug carrier system. It has been widely used to extend the half-life, enhance stability, provide protection from degradation and allow specific targeting of therapeutic agents to various disease states.
7. **Yeong L Tan, Han K Ho**
   As a natural polymer, albumin is well-received for being nontoxic,nonimmunogenic, biodegr+9adable and biocompatible. Together with its targeting potential on specific cells, albumin-based nanoparticles appear as an effective carrier for various therapeutics
8. **Ji Young Yhee, Jangwook Lee, Hyeyoun Chang, Jeewon Lee, Ick Chan Kwon, Kwangmeyung Kim**
   Albumin has been used as a popular material for carrying imaging probes and/or drugs to provide efficient biomedical imaging and therapy. It is considered as an ideal material for in vivo applications, because albumin is naturally abundant in serum to show non-toxicity and non-immunogenicity

METHED OF PRAPARATION



Desolvation or coacervation method

The desolvation process involves the continuous or intermittent dropwise addition of a desolvating agent (methanol, acetone, or ethanol) into an aqueous solution of albumin with constant stirring until turbidity appears, indicating the formation of nanoparticles . Nanoparticles thus formed are not stable and could redissolve in water or may aggregate. Therefore, the nanoparticles formed are stabilized using a cross-linker (glutaraldehyde or *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide[EDC])Glutaraldehyde hardens the nanoparticles by condensation cross-linking of the amino moieties present in the albumin side chain while EDC stabilizes the nanoparticles by forming a peptide bond between the amino and carboxyl groups of amino acids. Stirring is continued for 6 h to ensure the cross-linking of all amino acid residues

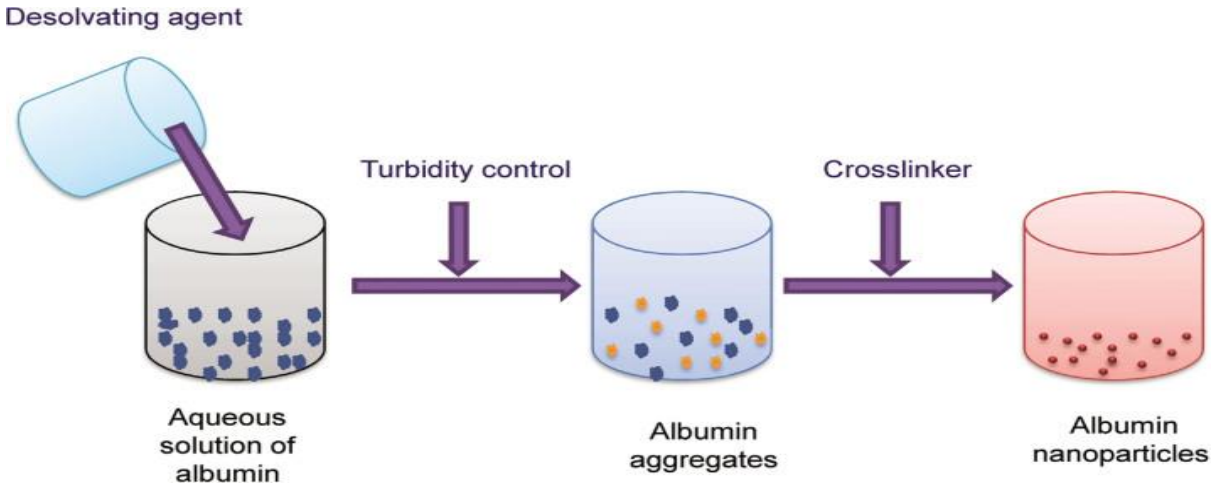
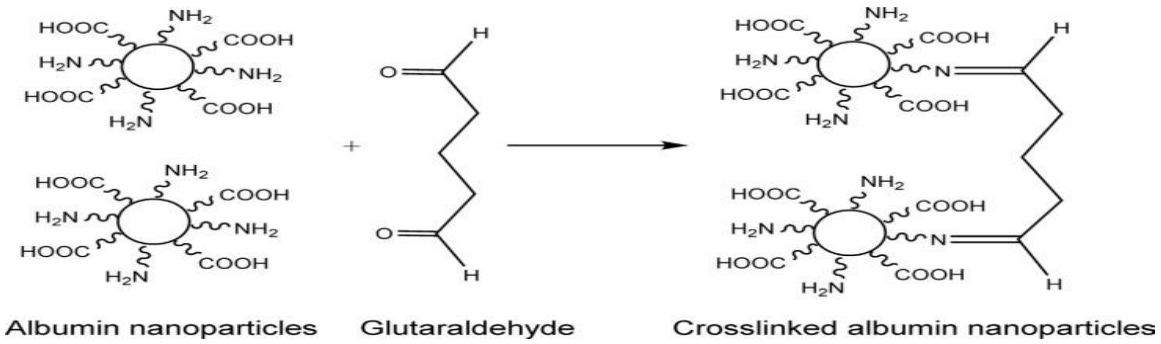


FIG2: DESOLUTION METHOD OF ALBUMIN



Emulsification

The emulsification process (Figure 1) involves the addition of a nonaqueous solution (oil phase) into an albumin solution (water phase), under stirring, generating a crude emulsion. The emulsion can be made uniform by homogenization using a high-pressure homogenizer. After that, there are two possible methods to stabilize the nanoparticles, thermal heating (temp >120 °C)or chemical treatment using a cross-linker, such as glutaraldehyde.Emulsification is another efficient techniques to obtain micro or nanoencapsules with different shapes, sizes and stabilities . The bioaccessability of EOs can be optimized by high-energy emulsification techniques such as ultrasonication and microfluidization in a very short time. It is important to provide a good balance between energy and time, as supplying more energy can lead to over-processing phenomenon, resulting in enlargement of emulsion droplets and poor stabilization of the formed droplets . Indeed, over-processing which can lead to re-coalescence of droplets should be avoided. Several factors such as the adsorption rate of the surface-active agent, residence time of the emulsion in

the emulsification zone, coalescence rate, and energy density can contribute to over-processing Therefore, it is essential to fine-tune the energy load or duration of the emulsification to prevent over-processing phenomenon to ensure obtaining boosted antimicrobial efficacy of EOs.

Self-Assembly Method

Self-assembly relies on the formation of albumin nanoparticles due to the increase in the hydrophobicity of the protein by breaking of disulfide bonds caused by the use of β-mercaptoethanol or reduction of primary amine groups on the surface of the protein caused by the addition of a lipophilic compound. The result is the self-assembly of albumin and the formation of nanoparticles in an aqueous environment. The self-assembly procedure is illustrated

Thermal Gelation

Thermal gelation, as can be seen from is characterized by heat-induced protein conformational change and unfolding, followed by protein–protein interactions, such as the formation of hydrogen bonds,electrostatic,hydrophobic interactions, and disulfide-sulfhydryl interchange reactions.

Nanospray Drying

Nanospraydrying is a versatile technique,commonly used to produce a dry powder from a liquid phase. One of the main advantages of this method is that particles are dried and produced in a continuous and single-step process. It ischaracterized by the spray generation of droplets from a liquid solution. The process includes different steps, such as atomization of feed into a spray, sprayair contact, drying of spray, and separation of dried product from the drying air. A liquid feedstock is atomized into a spray of droplets and brought into contact with a drying gas, at a sufficient temperature to obtain moisture evaporation.. As the moisture evaporates, the solid dried particles are formed and collected using an electrostatic particle collector. Optimization of the nanospray drying parameters allows regulating the properties of the nanoparticles, making them suitable for specific applications.

Microfluidic Mixing

Even though less investigated, another technique used to produce albumin nanoparticles is the microfluidic technology. It provides an effective alternative for the fabrication of lipid, polymeric, and serum albumin nanoparticles. This technique is a controllable preparation process, which results in particles with tunable size and narrow size distribution. Furthermore, it provides a unique opportunity for automatized large-scale, pharmaceutical production. In the literature, there are few studies on the production of albumin nanoparticles underflow conditions. Successful results have been obtained in a recent study conducted in 2020, which was focused on the preparation of core–shell type, drug-loaded albumin-based nanoparticles. The stabilizer poly(allylamine hydrochloride) (PAH) was added to channel 1 (v1) in the first syringe pump, while the solution containing the carrier and the drug (BSA/KYNA) was filled into the channel 2 (v2) in the second syringe pump. After passing through the syringe pumps, the two solutions were mixed in the μ-mixer cell, with a volume of 250 μL, and a pressure controller apparatus. After that, the sample was collected in defined time intervals. The schematic representation of the preparation of the core–shell NPs by this microfluidic device is presented

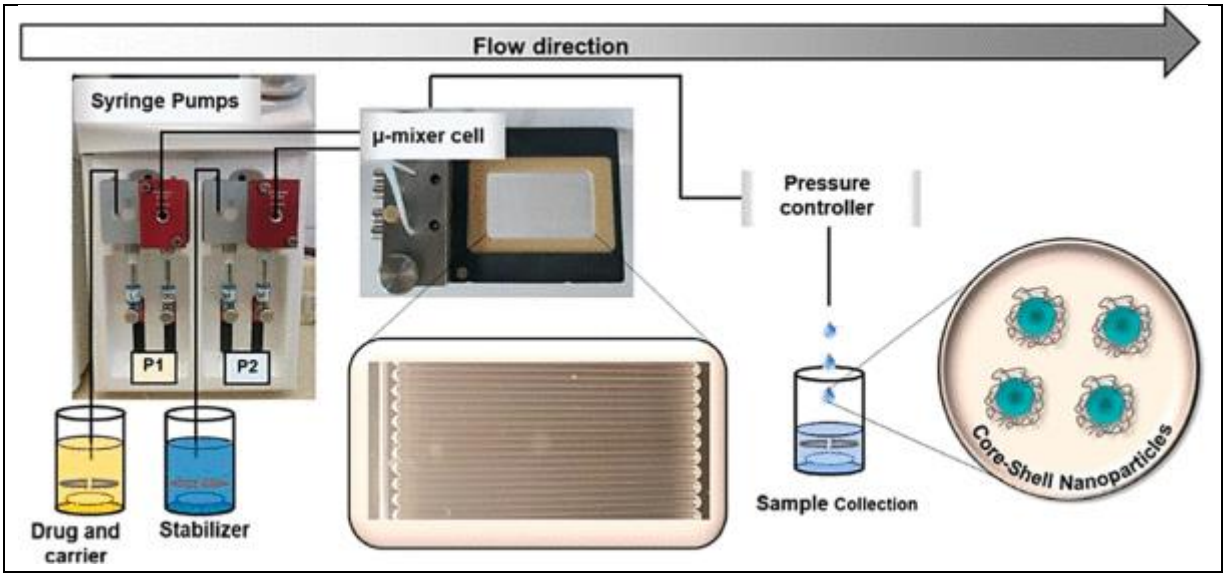


FIG. 3:Microfluidic Mixing

Here are some nanodrugs that have been used in albumin carriers:

- **Abraxane® (nab-paclitaxel)**

This FDA-approved drug is used to treat tumors. It's made of albumin-bound paclitaxel, and is known for its long drug residence time in tumors, short infusion time, and reduced risk of hypersensitivity reactions.

- **Doxorubicin-albumin nanoparticles**

These nanoparticles are self-assembled and have TRAILs chemically linked to their surfaces. The TRAILs help cancer cells undergo apoptosis.

- **Gemcitabine-loaded albumin nanoparticles (FA-Gem-BSANPs)**

Folic acids are conjugated to the surface of these nanoparticles to help them be taken up by tumors that overexpress folate receptors.

- **Wpep-HSA-PTX NPs**

These nanoparticles have a stimuli-responsive drug release pattern and enhanced cellular uptake.

- **Transferrin-conjugated TRAIL/DOX HSA-NPs**

These nanoparticles are used to treat multi-drug resistant (MDR) cells.

- **Albumin microbubbles**

These spherical carriers are about the same size as red blood cells and can be used for imaging and therapy.

Albumin is a promising drug delivery approach because it's the most abundant plasma protein in the body and has multiple binding sites. It's made up of a single polypeptide with 585 amino acids that form a heart-shaped protein.

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.

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

Nanoparticles (NPs)

The International Organization for Standardization (ISO) defines nanoparticles as nano-objects with all external dimensions in the nanoscale, where the lengths of the longest and the shortest axes of the nano-object do not differ significantly. If the dimensions differ significantly (typically by more than three times), terms such as nanofibers or nanoplates maybe preferred to the term NPs.

NPs can be of different shapes, sizes, and structures. They can be spherical, cylindrical, conical, tubular, hollow core, spiral, etc., or irregular . The size of NPs can be anywhere from 1 to 100 nm. If the size of NPs gets lower than 1 nm, the term atom clusters is usually preferred. NPs can be crystalline with single or multi-crystal solids, or amorphous. NPs can be either loose or agglomerated .

NPs can be uniform, or can be composed of several layers. In the latter case, the layers often are: (a) The surface layer, which usually consists of a variety of small molecules, metal ions, surfactants, or polymers. (b) The shell layer, which is made of a chemically different material from the core layer. (c) The core layer, which is the central portion of the NP

Organic NPs

This class comprises NPs that are made of proteins, carbohydrates, lipids, polymers, or any other organic compounds . The most prominent examples of this class are dendrimers, liposomes, micelles, and protein complexes such as ferritin (shown in Fig. 2). These NPs are typically non-toxic, bio-degradable, and can in some cases, e.g., for liposomes, have a hollow core. Organic NPs are sensitive to thermal and electromagnetic radiation such as heat and light . In addition, they are often formed by non-covalent intermolecular interactions, which makes them more labile in nature and offers a route for clearance from the body . There are different parameters that determine the potential field of application of organic NPs, e.g., composition, surface morphology, stability, carrying capacity, etc. Today, organic NPs are mostly used in the biomedical field in targeted drug delivery and cancer therapy .

Carbon-based NPs

This class comprises NPs that are made solely from carbon atoms . Famous examples of this class are

fullerenes, carbon black NPs, and carbon quantum dots (shown in Fig. 3). Fullerenes are carbon molecules that are characterized by a symmetrical closed-cage structure. C_{60} fullerenes consist of 60 carbon atoms arranged in the shape of a soccer ball , but also other types of fullerenes such as C_{70} and C_{540} fullerenes have been described . Carbon black NPs are grape-like aggregates of highly fused spherical particles . Carbon quantum dots consist of discrete, quasi-spherical carbon NPs with sizes below 10 nm . Carbon-based NPs unite the distinctive properties of sp^2-hybridized carbon bonds with the unusual physicochemical properties at the nanoscale. Due to their unique electrical conductivity, high strength, electron affinity, optical, thermal, and sorption properties , carbon-based NPs are used in a wide range of application such as drug delivery , energy storage , bioimaging , photovoltaic devices, and environmental sensing applications to monitor microbial ecology or to detect microbial pathogens . Nanodiamonds and carbon nano onions are more complex, carbon-based NPs. Due to their characteristic low toxicity and biocompatibility, they are used in drug delivery and tissue engineering applications.

CONCLUSION

Drug carriers for various therapeutic purposes are becoming more significant and promising thanks to albumin-based nanodevices. Nanoparticles based on al bumin offer many benefits as medication carriers: Because of their high content of charged amino acids, which enable the electrostatic adsorption of positively and negatively charged molecules, carry reactive groups on their surfaces that can be used for drug/ligand conjugation and/or other surface modification; are simple to prepare and reproducible in defined sizes, which can be accomplished using various production methods; and exhibit an enhanced uptake in solid tumors mediated by binding to albu min-binding proteins, gp60, and SPARC.

The EPR effect, which is particularly effective with tumors, and the hypoalbuminemia in cancer patients, along with all of these features of albumin nanoparticles, enhance their use in cancer treatment. The albumin nanodevices have therefore become a viable drug carrier for the administration of chemotherapeutic drugs, increasing the anticancer efficacy, even though they can be used in more therapeutic applications. As a result, there is increasing interest in using albumin-based nanodevices in pharmaceuticals as promising delivery systems for medicinal substances, with a particular focus on cancer treatment.

REFERANCE

1. Sahoo SK, Parveen S, Panda JJ. The present and future of nanotechnology in human health care. Nanomedicine 2007; 3(1): pp 20-31.
2. Lohcharoenkal W, Wang L, Chen YC, Rojanasakul Y. Protein Nanoparticles as Drug Delivery Carriers for Cancer Therapy. Bio med Res Int 2014; 2014: 12.
3. Mahapatro A, Singh DK. Biodegradable nanoparticles are excellent vehicle for site directed in-vivo delivery of drugs and vaccines. J 1Nanobiotechnol 2011; 9.
4. Suri S, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. J Occup Med Toxicol 2007; 2(1): 16.)
5. Estanqueiro M, Amaral MH, Conceição J, Sousa Lobo JM. Nanotechnological carriers for cancer chemotherapy: The state of the art. Colloids Surf B Biointerfaces 2015; 126(0): 631-48.
6. MaHam A, Tang Z, Wu H, Wang J, Lin Y. Protein-Based Nanomedicine Platforms for Drug Delivery. Small 2009; 5(15): 1706-21.

7. Couvreur P, Vauthier C. Nanotechnology: Intelligent Design to Treat Complex Disease. Pharm Res 2006; 23(7): 1417-50.
8. Shimanovich U, Bernardes GJL, Knowles TPJ, Cavaco-Paulo A. Protein micro- and nano-capsules for biomedical applications. Chem Soc Rev 2014; 43(5): 1361-71.
9. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev 2012; 64, Supplement(0): 24 36.
10. Wilczewska AZ, Niemirowicz K, Markiewicz KH, Car H. Nanoparticles as drug delivery systems. Pharmacol Rep 2012; 64(5): 1020-37.
11. Y. Shen, N. Li, S. Sun, L. Dong, Y. Wang, L. Chang, X. Zhang, F. Wang, Non- invasive, targeted, and non-viral ultrasound-mediated brain-derived neurotrophic factor plasmid delivery for treatment of autism in a rat model, Front. Neurosci. 16 (2022) 986571.
12. X. Zhou, X. Deng, M. Liu, M. He, W. Long, Z. Xu, K. Zhang, T. Liu, K.-F. So, Q.-L.Fu, L. Zhou, Intranasal delivery of BDNF-loaded small extracellular vesicles for cerebral ischemia therapy, J. Control. Release 357 (2023) 1–19.
13. S. Rosenblum, T.N. Smith, N. Wang, J.Y. Chua, E. Westbroek, K. Wang, R. Guzman, BDNF pretreatment of human embryonic-derived neural stem cells improves cell survival and functional recovery after transplantation in hypoxic–ischemic stroke, Cell Transplant. 24 (2015) 2449–2461.
14. B. Zhang, J. Zhao, Z. Wang, L. Xu, A. Liu, G. Du, DL0410 attenuates oxidative stress and neuroinflammation via BDNF/TrkB/ERK/CREB and Nrf2/HO-1 activation, Int. Immunopharmacol. 86 (2020) 106729,.
15. A.H. Nagahara, M.H. Tuszynski, Potential therapeutic uses of BDNF in neurological and psychiatric disorders, Nat. Rev. Drug Discov. 10 (2011) 209–219.
16. Q. Qi, Y. Wei, X. Zhang, J. Guan, S. Mao, Challenges and strategies for ocular posterior diseases therapy via non-invasive advanced drug delivery, J. Control. Release 361 (2023) 191–211.
17. W.L. Wong, X. Su, X. Li, C.M.G. Cheung, R. Klein, C.-Y. Cheng, T.Y. Wong, Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis, Lancet Glob. Health 2 (2014) e106–e116.
18. L. Mattern, K. Otten, C. Miskey, M. Fuest, Z. Izsv´ak, Z. Ivics, P. Walter, G. Thumann, S. Johnen, Molecular and functional characterization of BDNF- overexpressing human retinal pigment epithelial cells established by sleeping beauty transposon-mediated gene transfer, Int. J. Mol. Sci. 23 (2022) 12982.
19. D.V. Telegina, N.G. Kolosova, O.S. Kozhevnikova, Immunohistochemical localization of NGF, BDNF, and their receptors in a normal and AMD-like rat retina, BMC Med. Genet. 12 (2019) 48.
20. M. Inanc Tekin, M.A. Sekeroglu, C. Demirtas, K. Tekin, S. Doguizi, S. Bayraktar, P. Yilmazbas, Brain-derived neurotrophic factor in patients with age-related macular degeneration and its correlation with retinal layer thicknesses, Invest. Ophthalmol. Vis. Sci. 59 (2018) 2833–2840.
21. S. Ateaque, S. Merkouris, S. Wyatt, N.D. Allen, J. Xie, P.S. DiStefano, R.M. Lindsay, Y. Barde, Selective activation and down-regulation of Trk receptors by neurotrophins in human neurons co-expressing T RK B and T RK (2022) 463–477, C, J. Neurochem. 161
22. H. Han, S. Li, M. Xu, Y. Zhong, W. Fan, J. Xu, T. Zhou, J. Ji, J. Ye, K. Yao, Polymer- and lipid-based nanocarriers for ocular drug delivery: current status and future perspectives, Adv. Drug Deliv. Rev. 196 (2023) 114770.

23. A controlled trial of recombinant methionyl human BDNF in ALS: the BDNF Study Group (Phase III), Neurology 52 (1999) 1427–1433.
24. C. Miranda-Lourenço, L. Ribeiro-Rodrigues, J. Fonseca-Gomes, S.R. Tanqueiro, R. F. Belo, C.B. Ferreira, N. Rei, M. Ferreira-Manso, C. de Almeida-Borlido, T. Costa- Coelho, C.F. Freitas, S. Zavalko, F.M. Mouro, A.M. Sebasti˜ao, S. Xapelli, T. M. Rodrigues, M.J. Di´ogenes, Challenges of BDNF-based therapies: from common to rare diseases, Pharmacol. Res. 162 (2020) 105281.
25. M. Dąbkowska, K. Łuczkowska, D. Rogi´ nska, A. Sobu´ s, M. Wasilewska, Z. Ula´ nczyk, B. Machali´nski, Novel design of (PEG-ylated)PAMAM-based nanoparticles for sustained delivery of BDNF to neurotoxin-injured differentiated neuroblastoma cells, J. Nanobiotechnol. 18 (2020) 120.