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Aquasomes Nanocarriers for Delivery of Small Molecules

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ABSTRACT

Aquasomes are nanobiopharmaceutical carrier devices having a polyhydroxyl oligomeric layer surrounding them and a nanocrystalline calcium phosphate or ceramic diamond particle core. Aquasomes are spherical spheres with a diameter of 60-300 nanometers that are used to deliver medications and antigens. Because of qualities such as protection and preservation of delicate biological molecules, conformational integrity, and surface exposure, it was an excellent carrier mechanism delivering bioactive molecules such as peptides, proteins, hormones, antigens, and genes to specific sites. The most common core materials used to manufacture aquasomes are tin oxide, nanocrystalline carbon ceramics (diamonds), and brushite (calcium phosphate dihydrate). Calcium phosphate is the focus of attention due to its natural function in the body. Brushite is an acidic mineral that converts into hydroxyapatite after being stored for a long time. As a consequence, hydroxyapatite seems to be a more powerful centre for aquasome preparation. It's often used in the design of drug-delivery implants. A putative artificial oxygen-carrying mechanism has been found as hemoglobin-loaded aquasomes with a hydroxyapatite core. Because of their structural integrity, aquasomes have been employed as red blood cell substitutes, vaccines for delivering viral antigen (Epstein-Barr Virus and Human Immunodeficiency Virus) to elicit appropriate antibodies, and a targeted technique for intracellular gene therapy. Due to their enzyme activity and responsiveness to molecular conformation, aquasomes were created as a new carrier for enzymes such as DNAses and pigment/dyes. The challenges of retaining the conformational integrity and biochemical functioning of immobilised surface pairs, as well as the integration of these principles into a single functional composition, are described in this article.

Key Words: Aquasomes, Self-assembling, Carrier system, Nanoparticles, Carbohydrate, Drug Delivery

INTRODUCTION [1-8]

In the last decade, a variety of technical techniques have been proposed in order to obtain nanoparticles of a specific type, charged with drugs, which have revolutionised drug administration systems, particularly regulated release and vectoring of the active principle for release at target tissue or organs. Polymers are used in a variety of ways to manufacture nanoparticles, and they confront obstacles such as solvent stability and other ingredients, as well as compatibility of polymers and co-polymers with the active theory, biological fluids, and selection mechanism concerns. Some of the biomaterials utilised in nanobiopharmaceutics include multifunctional nanoparticles, quantum dots, aquasomes, superparamagnetic iron oxide crystals, liposomes, noisomes, and dendrimers. Cell/gene therapy was worth €3.8 billion in 2000, and the global market for advanced drug delivery systems is expected to grow to € 75 billion by 2015 (i.e., controlled release €19.8 billion, injectable/impantable polymer systems €5.4 billion, liposomal drug delivery €2.5 billion, needle-free injection €0.8 billion, pulmonary €17.0 billion, transdermal 9.6 billion, rectal €0.9 billion, transnasal €12.0 billion, transmucosal Developments in this area are increasing, notably in the realm of alternatives to injectable macromolecules, as drug formulations aim to cash in on the € 6.2 billion worldwide market for genetically engineered protein and peptide pharmaceuticals and other biological therapies. Since then, advancements in vesicular drug delivery have resulted in the development of systems that enable drug targeting, the trapping of large drug moieties, and the extended or controlled release of conventional pharmaceuticals. Several breakthroughs in the formulation and creation of small-dose dosage forms to improve pharmaceutical performance have been achieved in recent

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years. Pharmaceutical carriers are available in a wide range of sizes and forms. Examples include particulate, polymeric, macromolecular, and cellular carriers.

Kossovsky proposed a technique for making nanoparticles that transport so-called aquasomes (Figure 1), which have a particle size (less than 1000 nm) that is suited for parenteral delivery because it avoids capillary blockage. Aquasomes are nanoparticulate carrier systems, but they're three-layered self-assembled structures with a solid phase nanocrystalline core and an oligomeric film on which biochemically active molecules may be adsorbed with or without modification. Aquasomes resemble "bodies of water," and their watery properties help to protect and keep fragile biological components. Bio-active molecules such as peptide and protein hormones, enzymes, antigens, and genes are targeted to specific places using this feature of conformational stability and high surface visibility. These three-layered structures are self-assembled via non-covalent and ionic bonding. Aquasomes are ceramic nanoparticles stabilised by carbohydrates, in which a pharmacologically active chemical co-polymerizes, absorbs, or adsorbs to the carbohydrate surface of pre-formed nanoparticles. Aquasomes were found employing ideas from microbiology, food chemistry, biophysics, and a variety of other breakthroughs, including solid-phase synthesis, supramolecular chemistry, molecular shape-shifting, and self-assembly.

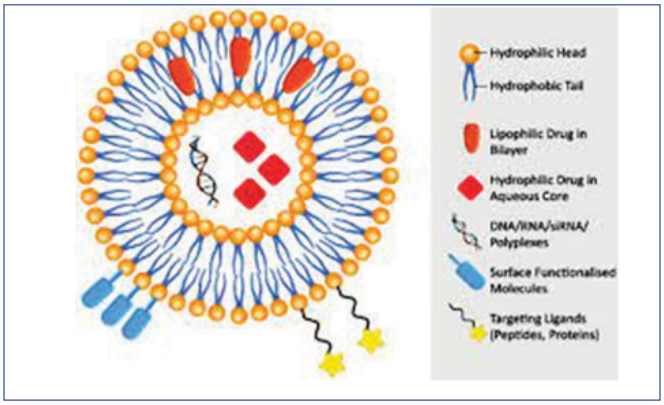

Figure 1: Basic structure of an Aquasome system.

RATIONALE [9]

Aquasomes resemble "bodies of water," and their watery properties help to protect and keep fragile biological components. Bio-active molecules such as peptide and protein hormones, enzymes, antigens, and genes are targeted to specific places using this feature of conformational stability and high surface visibility.

PROPERTIES [10,11]

1. Aquasomes can successfully load vast numbers of agents via ionic, non-covalent, van der Waals, and entropic capabilities due to their enormous size and active surface. It appears as stable particles with colloidal physical characteristics distributed in an aqueous environment.
2. Aquasomes' mechanism of action is controlled by their surface chemical. Targeted delivery, molecule shielding, and a progressive and steady release mechanism are all used by aquasomes to provide content.
3. Aquasomes' water-like properties provide a platform for preserving bio-active conformational integrity and biochemical stability.
4. Because of their size and composition stability, aquasomes defy clearance by the reticuloendothelial system and destruction by other environmental concerns.

PRINCIPLE OF SELF ASSEMBLY [12-14]

When the components of a final product spontaneously adopt preset structural orientations in two or three dimensions, this is referred to as self-assembly. Whether for the purpose of making smart nanostructure materials or in the course of naturally occurring biochemistry, the self-assembly of macromolecules in the aqueous atmosphere is governed primarily by three physicochemical processes: charged group interactions, dehydration impacts, and structural stability.

Interaction between charged groups

The interaction of charged groups such as carboxyl, amino, phosphate, and sulfate groups permits self-assembly subunits to take a long-range approach. The charged community also contributes in the tertiary structural stability of folded proteins.

Hydrogen bonding and dehydration effect

Secondary protein structures such as alpha helices and beta sheets benefit from hydrogen bonding because they increase base pair matching and stability. Hydrophilic molecules have a lot of structure because they establish hydrogen bonds with the water molecules surrounding them. Hydrophobic molecules are ones that can't make hydrogen bonds with each other. On the other hand, their capacity to resist water contributes in the arrangement of the moiety in respect to its environment. The ordered water decreases the overall degree of disorder/entropy in the underlying medium. Because structured water is thermodynamically unfavorable, the molecule loses water/dehydrates and self-assembles.

Structural stability

In molecules with fewer charges than formally charged groups, a dipole moment is seen. The forces aligned with dipoles are known as Van der Waals forces. Interactions between charged groups and hydrogen bonds, which

are primarily exterior to the molecule, and van der Waals powers, which are mostly inside, determine the structural stability of a protein in a biological environment. The Vander Waals forces, which are felt most commonly by hydrophobic molecule areas isolated from water, play a tiny but important effect in molecular shape and conformation during self-assembly. Van der Waals powers are the primary determinants of molecule hardness and softness. The van der Waals contact between hydrophobic side chains enhances stability in compact helical structures, which are thermodynamically unfavourable for long random coils. Small modifications are needed for effective antigen-antibody interactions, and maintaining internal secondary structures like helices provides the necessary softness and allows conformation to be maintained during self-assembly. In biotechnological self-assembly, this might lead to changes in molecular structure and biological function. As a consequence, in order to maintain optimal biological function, the van der Waals must be buffered. Aquasomes' molecular plasticization is aided by sugars.

ROLE OF DISACCHARIDES [15]

Carbohydrate is the third layer of aquasomes, and it helps the aquasomes achieve their goal. The hydroxyl groups on oligomers bind to the polar and charged groups of proteins in the same way as water does, retaining the watery structure of the proteins after dehydration. In the absence of water, these hydroxyl-rich disaccharides assist to replenish water around polar residues in proteins, maintaining their stability. A particular hydrogen binding substrate is created by the combination of free bound mobility and high hydroxyl content, resulting in a glassy aqueous state.

COMPOSITION [16-18]

Core material

Popular fundamental components include ceramic and polymers. Diamond flakes, brushite (calcium phosphate), and tin oxide are easy to produce, biodegradable, low-cost, and biocompatible ceramics. It provides a high degree of systemic order and regularity. Because of its high degree of order and increased surface energy yields, which contribute to successful carbohydrate binding, it is an excellent candidate for aquasome formation. Albumin, collagen, and acrylate polymers are some of the materials employed.

Coating material

Cellobiose is a 4-O-beta-D-glucopyranosyl-D-glucopyranosyl-D-glucopyranosyl-D-glucopyranosyl-D-glucopyranosyl-D-glucopyranosy After being partly hydrolyzed, cellulose is used to make it. It shields the drug molecule from dehydration), pyridoxal 5-phosphate, sucrose, and trehalose (a non-reducing sugar with the alpha-D-glucopyranosyl-alpha-D-glucopyranosyl-alpha-D-glucopyranosyl-alpha-D-glucopyranosyl-alpha-D-glucopyranosyl-alpha-D-glucopyranosy It was discovered to be more effective than cellobiose. It was shown to be stress-resistant in fungus, bacteria, insects, yeast, and certain plants. Trehalose maintains cell shapes, natural tastes, colours, and texture throughout the desiccation phase by maintaining proteins and membranes within plant cells. Water is replaced with polar protein residues by disaccharides with a large number of hydroxyl units, such as sucrose and trehalose. It maintains their dignity in the absence of precipitation. Sugar might protect the shape and function of biological components after lyophilization, according to experiments using calcium carrying microsomes obtained from rabbit and lobster muscles. When calcium-carrying microsomes are lyophilized without a stabiliser sugar, the rehydrated vesicles display much lower calcium absorption and uncoupled ATPase activity. When rehydrated with 0.3 g trehalose/g membrane, lyophilized vesicles vary morphologically from newly produced vesicles), chitosan, citrate, and other coating ingredients are often utilized. Carbohydrate is often employed because it serves as a natural stabilizer. Carbohydrates are adsorbed on the nanometre scale as a glassy layer covering prepared ceramic nanoparticles and self-assembled calcium phosphate dihydrate particles.

Bio-active molecules

Drugs that interfere with the film via non-covalent and ionic interactions were shown to be a promising option for aquasomes.

METHOD OF PREPARATION [19-21]

Preparation of core material

The ceramic center's building is the initial step in aquasome planning. The materials utilised for the core dictate the procedure for creating ceramic cores. These ceramic bases may be made by colloidal precipitation and sonication, inverted magnetron sputtering, plasma condensation, and other techniques. Because ceramic materials are the most structurally regular materials known, they were widely chosen for the heart. Because ceramics have such a high degree of order, any surface alteration will have only a little influence on the atoms underneath the surface layer, keeping the ceramic's bulk qualities. The high degree of order indicates that the surfaces have a lot of surface energy, which makes it easier for polyhydroxy oligomeric surface coatings to stick to them. The two most common ceramic cores are diamond and calcium phosphate.

Coating of core material

Carbohydrates are applied to the surface of ceramic cores in the second step. A number of approaches are used to adsorb the carbohydrate (polyhydroxy oligomers) coating epitaxially on the surface of the nano-crystalline ceramic cores. The techniques normally entail adding polyhydroxy oligomer to a dispersion of painstakingly cleansed ceramics in ultra-pure water, sonication, and then lyophilization to permit the most permanent adsorption of carbohydrate on to the ceramic surfaces. Stir cell ultra-filtration eliminates extra carbs while desorbing them fast. Coating components include cellobiose, citrate, pyridoxal-5-phosphate, sucrose, and trehalose.

Immobilization of drug candidate

Surface-modified nano-crystalline cores provide a stable platform for the non-denaturing self-assembly of a broad range of biochemically active molecules. To load the medicine, partial adsorption might be employed (Figure 2).

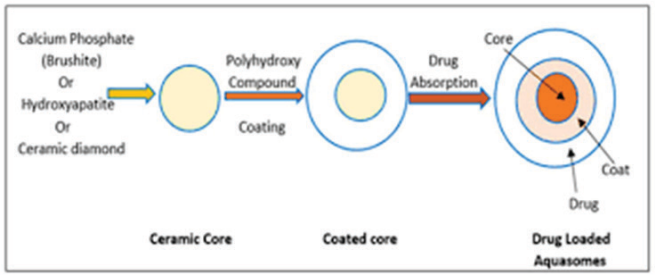

Figure 2: Method of Preparation.

Molecular self-assembly

It's the process of molecules randomly forming organized, solid, non-covalently linked aggregates. To construct huge, architecturally well-defined atom ensembles, molecular self-assembly combines components of the prior techniques: Sequential covalent synthesis yields well-defined molecules with a moderate level of structural complexity. To construct large, stable structurally defined aggregates of these molecules, ionic, hydrogen, and van der Waals contacts, as well as other non-covalent connections, are utilized. Several copies of one or more of the component molecules or of a polymer are employed to make the synthetic work simpler. The key to this kind of synthesis is to understand and overcome fundamentally unfavorable entropy in a single aggregation. For the final assembly to be stable and have a clearly defined shape, the non-covalent interactions between molecules must remain intact. Specific Van der Waals correlations and hydrogen bonds are weaker (0.1 Kcal/mol to 5 Kcal/mol) than normal covalent bonds (40 Kcal/mol to 100 Kcal/mol) yet have the same thermal energy. Self-assembled aggregates need a high number of weak non-covalent contacts, numerous hydrogen bonds, or a mix of both to maintain enough stability.

CARBOHYDRATE COATING [22-24]

Anthrone reaction

It's a calorimetric method for determining how much unbound residual sugar or residual sugar remains after coating. The sample is coated with the anthrone reagent, which is then heated in a boiling water bath and chilled quickly. In acidic situations, carbohydrate is hydrolyzed to hydroxymethylfurfural, which then reacts with anthrone reagent to form a blue-green color complex. Absorbance is measured (λmax = 625 nm) using a UV-Visible spectrophotometer with glucose as a reference.

Concanavalin-A induced aggregation

It's used to calculate the amount of sugar on the ceramic heart. The suspensions of different carbohydrate coated cores are treated with a concanavalin-A solution (in quartz cuvettes). In a UV-Visible spectrophotometer, absorbance is measured as a function of time during a 5-minute period at a wavelength of 450 nm. The findings are deducted from the blank experiment's results.

Phenol sulfuric acid method

It is also a colorimetric process for determining the overall carbohydrate content of a sample, including monosaccharide, disaccharide, oligosaccharide, and polysaccharide. Carbohydrate is dehydrated to furfural derivative in the presence of strong sulfuric acid, which is subsequently reacted with phenol to produce yellow gold pigment.

STRATEGIES USED IN CHEMICAL SYNTHESIS OF NANOSTRUCTURE [25-27]

Aquasomes are self-assembling three-layered nanostructures. As a consequence, chemical nanostructure production processes must be further enhanced. The most commonly utilized approaches for chemical production of nanostructures are mentioned below.

1. Sequential covalent synthesis

This may be utilized to produce vitamin B12-like covalently bonded atom arrays with well-defined structure, accessibility, and shape. It has the capacity to generate configurations that are far from the thermodynamic minimum for the atom set in question.

2. Covalent polymerization

Molecules with a high molecular weight are created using this process. Allowing a low-weight material to react with itself results in a molecule with several covalently bonded monomers. Consider the case below: Ethylene is used to make polyethylene. Polyethylene has a high molecular

weight (>106 Daltons) and is straightforward to produce, but its molecular structure is simple and predictable, and the technique by which it is formed allows for only a modest amount of controlled variation in the structure or regulation of its three-dimensional shape. Polymerization provides indirect synthetic paths to stable nanostructures, such as phase-separated polymers.

3. Self-organizing synthesis

Instead of relying on weaker and less directed connections like ionic, hydrogen, and van der Waals contacts to assemble atoms, ions, or molecules into frameworks, this approach foregoes the covalent bond as the required link between atoms. Molecular crystals, ligand crystals, colloids, micelles, emulsions, phase-separated polymers, and self-assembled monolayers, among other structures, will be created using this technology. The capacity of these techniques to self-organize sets them apart. Molecules or ions adjust their locations to reach the thermodynamic minimum. Self-organization may produce true nanostructures.

MATERIAL USED AND ITS IMPORTANCE [28]

At initially, both polymers and ceramics may be employed to create the nucleus of nanoparticles. Polymers like albumin, collagen, and acrylates are among them. Ceramics included diamond flakes, brushite (calcium phosphate), and a tin oxide core. Ceramic materials were commonly used for the centre because they are the most structurally uniform materials known; their crystalline high degree of order means that (a) any surface alteration will have only a limited impact on the nature of atoms below the surface layer, preserving the bulk properties of the ceramic; and (b) any surface alteration will have only a limited impact on the nature of atoms below the surface layer, preserving the bulk properties of the ceramic; and (c) The surface would have a high degree of surface energy, allowing polyhydroxy oligomer surface film binding to occur. In a matter of seconds, the freshly produced particles have a high capacity to absorb molecules. The nanocrystalline ceramic core is covered with carbohydrate epitaxially in the second phase. Coating substances include cellobiose, pyridoxal-5-phosphate, sucrose, and trehalose. When the surface is bonded, a carbohydrate layer prevents soft medicines from changing shape and getting destroyed. Bioactive compounds are adsorbed in the third step and may communicate with the film via non-covalent and ionic interactions.

CHARACTERIZATION [29-31]

Aquasomes are defined by their structure, particle size, and shape. They are evaluated using X-ray powder diffractometery (XRD), Transmission Electron Microscopy (TEM), and Scanning Electron Microscopy (SEM). The form and size distribution may be determined using SEM pictures. Photon correlation spectroscopy may be used to determine the mean particle size and zeta potential of the particles. For organizational inquiry, Fourier-transform infrared (FT-IR) spectroscopy may be employed. The glass transition temperature of carbohydrates and proteins may be determined using differential scanning calorimetry (DSC). All materials may have their chemical composition and crystalline structure determined using XRD. The sample's X-ray scattering is measured by the following diffractogram, and the data is used to determine outcomes. Besides that, drug loading efficiency is being used to decide the quantity of drug obligated on the exterior of aquasomes; in vitro drug release kinetics can then be used to evaluate the drug's release schedule from the aquasomes; and sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) can be used to ascertain the protein's stability throughout aquasome preparation.

APPLICATIONS [32-36]

1. Viruses such as the Epstein-Barr Virus and the Human Immunodeficiency Virus are transmitted using aquasomes as vaccines. The vaccine therapy must be triggered by conformationally complicated target molecules in order to elicit the appropriate antibody.
2. Aquasomes as red blood cell substitutes, with haemoglobin fixed on the oligomer surface owing to hemoglobin's oxygen release conformational sensitivity (Table 1). This minimises toxicity, reaches 80 percent haemoglobin content, and produces blood in a non-linear manner, comparable to normal blood cells, according to the researchers.
3. Aquasomes, a five-layered composition consisting of a ceramic heart, polyoxyoligomeric film, therapeutic gene section, additional carbohydrate film, and a targeting layer of conformationally conserved viral membrane protein, have been used for effective targeted intracellular gene therapy.
4. Aquasomes for medicine distribution, such as insulin, were developed because drug action is conformationally specific. Bioactivity was recovered and activity enhanced by 60% when compared to i.v. treatment, with no verified toxicity.
5. Because enzyme activity is affected by molecular conformation, and pigment aesthetic characteristics are affected by molecular conformation, aquasomes are often utilised to transport enzymes such as DNAase and pigments/dyes.

Table 1. Aquasomes applications in drug delivery.

Drugs	Applications
Dithranol	Psoriasis
Etoposide	Anti-cancer
Indomethacin	Anti-inflammatory
Insulin	Glucose regulation
Serratiopeptidase	Proteolytic
Hemoglobin	Blood oxygen carrier
Hepatitis B vaccine	Anti-hepatitis
MSP 119	Anti-malarial
Serum Albumin	Osmotic pressure

FATE OF AQUASOMES [37]

1. Aquasomes are biodegradable nanoparticles that are mostly found in the liver and muscles. They have no problem identifying receptors on the active site since the drug is adsorbed on the system's surface without additional surface change, as with insulin and antigen distribution. This allows for quick pharmacological or biological action. Calcium phosphate is a biodegradable ceramic in most systems.
2. Ceramic biodegradation in vivo is predominantly mediated by monocytes and multicellular cells termed osteoclasts, which participate initially near the biomaterial implantation site during the inflammatory response. When cells come into contact with biomaterial, there have been reports of two types of phagocytosis: either calcium phosphate crystals were taken up alone and subsequently dissolved in the cytoplasm after the phagosome membrane vanished, or dissolution following the creation of heterophagosomes. Calcium phosphate phagocytosis coincided with autophagy and the aggregation of leftover bodies in the cell.
3. Monocytic activity may be influenced by a number of soluble factors, including IFN-γ (interferon-gamma) and 1,25-dihydroxycholecalciferol. Other cytokines may be active during the biodegradation phase, causing the inflammatory system to become activated.

FUTURE PERSPECTIVES [38]

Aquasome, a self-assembled organ, has a promising future in the reliable delivery of a broad range of therapeutic compounds, including viral antigens, hemoglobin, and insulin. The core's unique carbohydrate covering promotes biological activity while maintaining the characteristics and structural integrity of the medicine molecule. Biosensors are drugs-distribution equipment or drugs-tracking tools that aid in diagnostics. When a biosensor and an aquasome nucleus are joined, it may be used to examine soft tissue in malignant illness and improve diagnosis. The world is now stricken by the COVID-19 epidemic, and there is no effective remedy. The notion of delayed antigen release in tiny amounts using aqua some that develop specific antibodies in the body at a steady rate is employed in the instance of COVID-19. It has been proven to be effective in increasing COVID-19-specific immunity. It often exhibits mild symptoms such as difficulty breathing and low oxygen levels, which may be maintained by aquasomes' oxygen transport capability.

LIMITATIONS [39]

Modeling self-assembled aquasomes systems is challenging due to a number of disadvantages. If a medicine is poorly absorbed, it might cause toxicity in the body by producing burst release. Polyethylene glycol should be applied on its surface to prevent opsonization and phagocytic clearance of aquasomes in the body.

CONCLUSION

Built on the self-assembly idea, aquasomes are one of the most simple and novel drug carriers. When conformationally sensitive drug candidates are given through aquasomes, they have a higher biological activity. This is most likely due to the ceramic's unique carbohydrate coating. These formulations have also been demonstrated to elicit a greater immunological response, indicating that they might be employed as a proteinaceous antigen immune adjuvant. As a consequence, this approach provides medical researchers renewed hope for bioactive molecule dispersion. To evaluate their effectiveness and protection, as well as to assess their therapeutic value and commercialization, much more study on aquasomes is required in terms of pharmacokinetics, toxicity, and animal studies.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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AUTHOR'S CONTRIBUTION

All authors have equally contributed to this manuscript. All authors did the literature survey from standard databases, collected all essential elements, and wrote this manuscript collectively.

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