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Aquasomes: A Promising Delivery System

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ABSTRACT

Aquasomes Are Innovative, Nanoscale Delivery Vehicles That Merge the Benefits of Nanotechnology with Biological Stability. These Three-Layered Self-Assembling Structures Comprise a Solid Core (Commonly Made of Calcium Phosphate or Tin Oxide), A Carbohydrate Coating, And an Outer Layer That Carries Bioactive Molecules Such as Proteins, Peptides, And Genetic Material. The Unique Structural Design Enables Aquasomes to Preserve the Therapeutic Integrity of Sensitive Molecules While Ensuring Targeted and Controlled Delivery. With Their Ability to Maintain Drug Stability and Functionality, Aquasomes Represent a Next-Generation Platform in Drug Delivery, Offering Promising Prospects for Clinical and Pharmaceutical Advancements.

Keywords: Aquasomes, Self assembling carrier system, Novel drug delivery, Core Material

INTRODUCTION

Recent advances in nanotechnology have revolutionized the field of drug delivery, enabled the precise transport of therapeutic agents while preserved their biological functionality. Among these innovations, aquasomes stand out as a promising nanoparticulate system designed to mimic the natural architecture and dynamics of biological membranes. Aquasomes are three-layered, self-assembling nanoparticles composed of:

- A solid core made from biocompatible materials like calcium phosphate or tin oxide, which provides structural support.
- A carbohydrate coating that stabilizes the core and prevents chemical degradation.
- An outer layer that adsorbs bioactive agents—such as proteins, peptides, enzymes, antigens, or DNA—while maintaining their native configuration and activity.

This unique arrangement allows aquasomes to protect fragile molecules from denaturation, enzymatic degradation, or hostile biological environments. Their ability to preserve molecular integrity and facilitate targeted, sustained release makes them suitable for applications in gene therapy, vaccine delivery, and enzyme replacement therapies**.**

In essence, aquasomes bridge the gap between biological compatibility and pharmaceutical precision—offering a versatile, next-generation approach to therapeutic delivery.

In nano biopharmaceutics, a diverse range of biomaterials is employed, including multifunctional nanoparticles, quantum dots, Aquasomes, superparamagnetic iron oxide crystals, liposomes, niosomes, and dendrimers. Among the different types of 'some's,' Aquasomes stand out as carbohydrate-ceramic nanoparticles designed to serve as drug delivery systems. They feature a nanocrystalline core—typically composed of calcium phosphate or ceramic diamond—coated with a polyhydroxylated oligomeric layer that stabilizes and protects biopharmaceutical agents. (1,2).

Kossovsky proposed a technique for creating nanoparticles known as Aquasomes, which are distinguished by their small size under 1000 nanometres—making them appropriate for parenteral delivery, as they reduce the risk of clogging blood capillaries. These nanocarriers are also referred to as "bodies of water" due to their structural and functional characteristics. (3,4)

Aquasomes are spherical nanoparticles ranging from 60 to 300 nanometres in size. Their development typically involves three core materials: tin oxide, nanocrystalline carbon ceramics (such as diamond), and brushite, which is a form of calcium phosphate dihydrate. These particles present a promising platform for drug delivery, especially for compounds that face challenges like limited administration routes, physical or chemical instability, low bioavailability, and strong side effects. (5) The development of aquasomes draws upon diverse scientific disciplines such as food chemistry, microbiology, and biophysics. It has been shaped by numerous advancements, including solid-phase synthesis, supramolecular chemistry, dynamic molecular structuring, and self-assembly processes. (6)

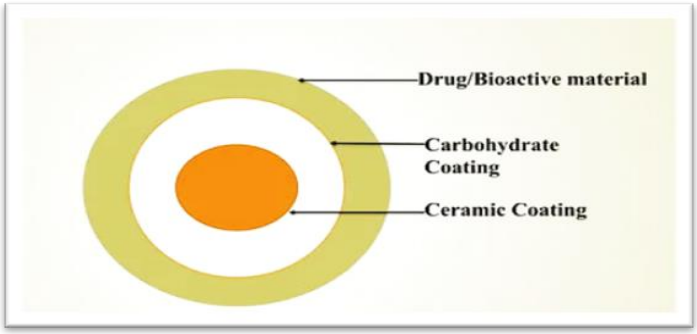

Fig. 1: Structure of Aquasomes

PROPERTIES OF AQUASOMES

Aquasomes exhibit a unique combination of physical, chemical, and biological characteristics:

Structural Properties

- Three-layered composition: Core (inorganic), carbohydrate coating, and adsorbed drug layer.
- Self-assembling nanostructure: Formation through spontaneous assembly, allowing uniform particle size.
- Nanometric size range: Typically between 60–300 nm, enabling efficient cellular uptake**.**

Biochemical Properties

- Preservation of molecular conformation: Protects proteins and peptides from structural degradation.
- Biocompatibility: Non-toxic and safe for biological systems.
- High surface area: Enhances adsorption of therapeutic agents.

Functional Properties

- Controlled drug release: Enables sustained and targeted delivery to specific sites.
- Stability in physiological conditions: Resistant to enzymatic and thermal degradation.
- Versatile payload capacity: Capable of delivering a wide range of biomolecules—vaccines, DNA, enzymes, etc.

Innovative Features

- Mimics natural biological systems, especially cell membranes.
- Allows effective delivery of delicate biopharmaceuticals without compromising their activity.
- Potential to integrate with emerging technologies like gene editing or personalized medicine.(7,8,9,10)

PRINCIPLE OF SELF-ASSEMBLY

- **Electrostatic Interactions:** Charged functional groups—such as amino, sulfate, carboxyl, and phosphate—play a crucial role in stabilizing protein tertiary structures. These groups also facilitate long-range interactions that promote the self-assembly of molecular subunits.
- **Hydrogen Bonding and Dehydration Effects:** Hydrogen bonds are essential for base-pair recognition and stabilizing secondary structures like alpha helices and beta sheets. When hydrophilic molecules form hydrogen bonds with surrounding water, the water becomes more structured. In contrast, hydrophobic

molecules cannot bond with water and instead exclude nearby water molecules, leading to molecular ordering through repulsion. This organized hydration results in lower entropy, creating an energetically unfavorable environment that encourages dehydration and drives self-assembly.

- **Protein Structural Stability in Biological Systems:** The mechanical flexibility of molecules, including their rigidity or softness, is governed by van der Waals forces (mainly within hydrophobic regions) and external interactions like electrostatic forces and hydrogen bonding. These interactions collectively enable proteins to retain their secondary structures during assembly. This structural flexibility ensures molecular integrity and supports biological activity during delivery.(11)

ADVANTAGES OF AQUASOMES

- Act as a sustained-release depot for therapeutic agents, reducing the need for repeated injections.
- Function as vaccine carriers whose surface-adsorbed antigens provoke both cellular and humoral immune responses.
- Enhance the efficacy of active drugs while shielding them from enzymatic degradation and phagocytic clearance.
- Serve as versatile vehicles for enzymes (e.g., DNase) and dyes, and, when layered with bio-recognition ligands (antibodies, nucleic acids, peptides), double as biological labels for various imaging modalities. (11)

COMPOSITION OR MATERIALS USED

1. Core Materials in Aquasome

Aquasomes commonly utilize ceramics and polymers as their core materials. Ceramics such as tin oxide, brushite (a form of calcium phosphate), and diamond particles are favored due to their crystalline nature, cost-effectiveness, biocompatibility, and ease of production. These materials exhibit high structural uniformity, which contributes to increased surface energy—a property that enhances the efficient adsorption of carbohydrate layers.

In addition to ceramics, biodegradable polymers like gelatin, albumin, and acrylate are also employed for core formation. Their adaptability and compatibility with biological systems make them suitable candidates in aquasome formulation, offering versatile options for therapeutic delivery.(12)

2. Coating Materials for Aquasomes

Preferred coating agents for aquasomes include citrate, chitosan, cellobiose, sucrose, trehalose, and pyridoxal 5-phosphate. These carbohydrates create a protective layer that helps maintain the structural stability of soft pharmaceutical compounds, preventing them from undergoing shape alterations.

By forming this carbohydrate-based coating, they:

- Preserve the native molecular conformation of bioactive substances
- Ensure structural integrity throughout the formulation process
- Mimic a hydrated environment, supporting biochemical function
- Protect the three-dimensional structure of drug molecules from damage

As a result, carbohydrates serve as both natural stabilizers and dehydration protectants, enhancing the effectiveness and durability of therapeutic agents within the aquasome system.(13)

3. Cellobiose

A reducing sugar composed of two glucose units, specifically 4-O-β-D-glucopyranosyl-D-glucopyranose. It is derived from the partial breakdown of cellulose and plays a vital role in shielding drug molecules from dehydration.(14)

4. Trehalose

This non-reducing disaccharide consists of α-D-glucopyranosyl-α-D-glucopyranoside. Trehalose effectively protects therapeutic agents from both denaturation and drying-related damage.(15)

5. Bioactive Molecules

Aquasomes serve as an excellent platform for drugs capable of interacting with coating films via ionic and non-covalent bonds, enhancing delivery and stability.(16)

6. Chitosan

A linear polysaccharide formed by randomly distributed N-acetyl-D-glucosamine and β-D-glucosamine units. It is sourced mainly from crab shells, shrimp exoskeletons, and insects. Produced through the deacetylation of chitin, chitosan has film-forming capability and contains three key functional groups—amines, primary hydroxyls, and secondary hydroxyls—which help separate and stabilize drug molecules.(17)

METHOD OF PREPARATION

The synthesis of aquasomes is relatively straightforward, involving minimal solvent usage and no need for homogenization techniques. The procedure unfolds in three key stages:

1. Core formation
2. Coating application

3. Loading of therapeutic agents

Each phase adheres to the principle of self-assembly, allowing the structural components to organize themselves naturally without complex mechanical intervention.(18)

The formulation of Aquasomes begins with the creation of a ceramic core. The technique used to prepare this core varies depending on the specific material chosen. Ceramic cores can be synthesized through various methods, including colloidal precipitation, sonication, inverted magnetron sputtering, and plasma condensation. Among the available options, ceramic materials are most commonly preferred, with diamond and calcium phosphate being the two frequently utilized types.(19)

Synthesis of nanocrystalline tin oxide core: Nanocrystalline tin oxide core can be synthesized by direct current reactive magnetron sputtering. To prepare a tin oxide core, the high purity tin is blown from a diameter of 3 inches in a high-pressure gas mixture of argon and oxygen. The ultrafine particles gathered on a copper tube that were established in a gas phase and are cooled to 77 k with flow of nitrogen. (20)

Self-assembled Nanocrystalline brushite (calcium phosphate dihydrate): Numerous techniques, including co-precipitation, self-precipitation, sonication, and PAMAM approaches, can be used to synthesis it.

(i) **Co-precipitation:** Calcium nitrate solution is mixed continuously while drops of diammonium hydrogen phosphate solution are introduced. A flask with a charge funnel, thermometer, and reflux condenser with a carbon dioxide trap is used to maintain the temperature at 75°C.Using the concentrated aqueous ammonia solution, the pH of calcium nitrate is maintained between 8 and 10. Magnetic stirring is used to stir the mixture under the aforementioned condition. After that, the precipitates are cleaned, filtered, and then left to dry overnight. The powder was sintered by heating it to 800–900°C in an electric furnace

(ii) **Sonication-Based Ceramic Core Preparation:** To prepare the ceramic core, equal volumes of calcium chloride and disodium hydrogen phosphate solutions are mixed and treated using an ultrasonic bath—a process known as sonication. The mixture is maintained at a temperature of 4 °C for two hours to support proper reaction conditions. Following sonication:

- The resulting ceramic core is isolated via centrifugation
- It is then washed thoroughly, resuspended in de-ionized water, and filtered
- The core material collected on the filter paper is carefully dried for final use.(21)

(iii) **Poly (Amidoamine) PAMAM:** To initiate nucleation and crystal development**,** PAMAM was dissolved in a simulated body fluid with a pH of 7.4 and incubated at 37 °C for one week**.** The solution's pH was adjusted by adding NaOH**,** promoting optimal crystallization conditions.

Afterwards:

- The formed precipitate was washed multiple times with deionized water
- Then, it was filtered and left to dry overnight, yielding purified crystals. (22)

(iv) **Nanocrystalline Carbon ceramic, diamond particle:** Following ultra-cleaning and sonication, diamond particles and nanocrystalline carbon ceramic may also be utilized for the core production. For this reaction, the equation is presented as follows:

$$2\ a2HPO4 + 3\ CaCl2 + H2O \rightarrow Ca3\ (PO4)2 + 4\ aCl + 2H2 + Cl2 + (O)$$

(v) **Coating of the core with polyhydroxy oligomer:** Coating materials such as cellobiose, citrate, trehalose, pyridoxal 5 phosphate, and sucrose are frequently utilized. This is the second stage of the carbohydrate coating process for ceramic cores. The coating process involves adding carbohydrates to an aqueous dispersion of the cores while they are being sonicated. Subsequently, they undergo lyophilization, resulting in the irreversible adsorption of carbohydrates onto the ceramic surface. Using centrifugation, the unabsorbed carbohydrate is removed. (23)

(vi) **Immobilization of Drug Molecules in Aquasomes:** The final step in aquasomes synthesis involves partially adsorbing the drug onto the previously coated nanoparticles. A drug solution is prepared at a known concentration using a buffer solution at an optimal pH. These coated particles are then combined with the drug solution and maintained in a low-temperature suspension to facilitate either drug loading or lyophilization of the mixture. The resulting drug-loaded aquasomes formulation is subsequently subjected to various characterization techniques to assess its properties and performance. (24)

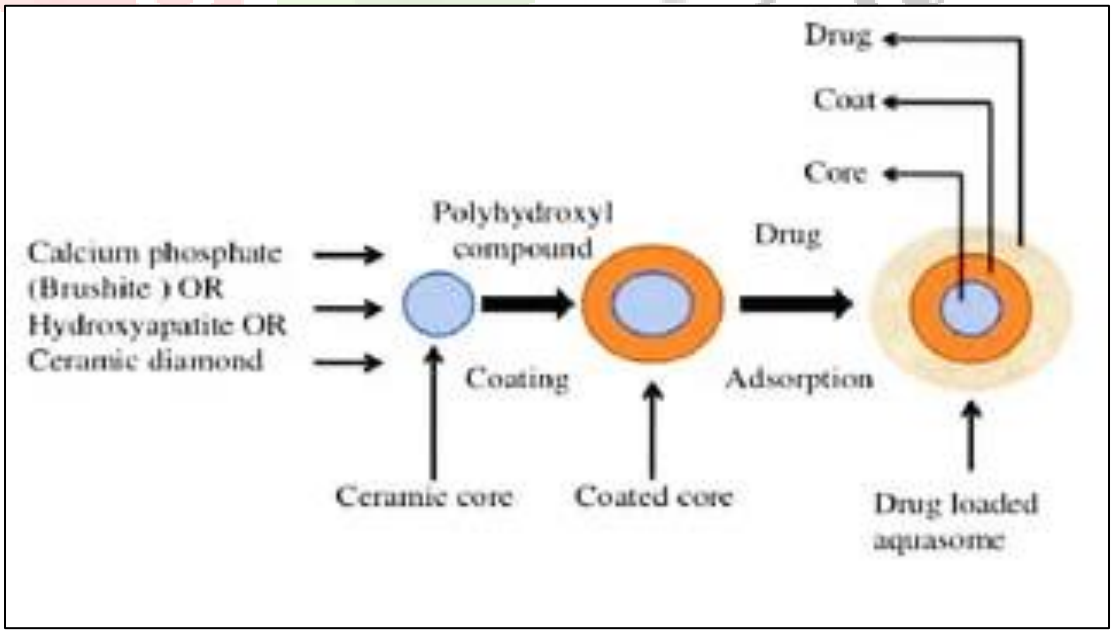

Fig.2: Preparation of Aquasomes

EVALUATION PARAMETERS OF AQUASOMES

Aquasomes are chiefly characterized and distinguished by the varied morphological and structural features of their polyhydroxy oligomer coating and underlying core.

A. Evaluation parameter for core material

1. Size distribution

Particle size and morphology were determined by transmission electron microscopy (TEM) and scanning electron microscopy (SEM). For SEM analysis, samples were affixed to gold-coated stubs with double-sided tape before size measurement. For TEM, particles were negatively stained with phosphotungstic acid to enable size assessment. Both techniques were also applied to the coated cores and drug-loaded formulations.(25)

2. FTIR Characterization

Structural analysis was performed using Fourier transform infrared spectroscopy (FT-IR). Samples were pressed into potassium bromide discs and scanned over the 4000–400 cm^{-1} range to analyze both the uncoated core and the coated core. The resulting absorption bands were matched to reference peaks, and this method also allowed evaluation of the drug's stability within the formulation.(26)

3. X-ray Diffraction

A wide-angle X-ray diffractometer using copper and potassium radiation was employed to assess the crystallinity of the hydroxyapatite ceramic core. Interpretation relied on comparing each sample's diffraction pattern against a standard reference diffractogram. Uncoated lactose and calcium phosphate cores both displayed sharp, well-defined peaks indicative of a crystalline lattice.

In contrast, carbohydrate-coated cores produced broad, diffuse peaks characteristic of an amorphous phase. This transition is attributed to the coating process—dissolving the carbohydrate, applying it to the core, and subsequent lyophilization—which saturates the carbohydrate and disrupts its crystalline order.(27)

B. Evaluation parameter for coated core

1. **Carbohydrate coating confirmation:** Concanavalin A–induced aggregation, the Anthrone assay, and the phenol–sulfuric acid test are employed to confirm the presence of a sugar layer on the ceramic core.

2. **Zeta potential analysis:** Surface charge measurements quantify carbohydrate adsorption onto the core and predict storage stability. Studies report a more negative zeta potential as the hydroxyapatite core becomes increasingly saturated with carbohydrate.
3. **Glass transition temperature:** Differential scanning calorimetry (DSC) is used to determine the glass transition temperature of proteins and carbohydrates. DSC also evaluates how carbohydrate coatings alter the thermal behavior of drug-loaded aquasomes by tracking the shift from a glassy to a rubbery state.(28,29,30)

C. Evaluation parameter of drug-loaded aquasomes

1. Drug Loading Efficiency: This assessment quantifies how much drug binds to the aquasome surface.

- Incubate blank aquasomes in a drug solution of known concentration at 4 °C for 24 hours.
- Centrifuge the mixture at high speed in a chilled centrifuge for one hour to pellet the particles.
- Filter the supernatant to remove any residual particulates.
- Measure the concentration of unbound drug in the clear supernatant using UV spectrophotometry.
- Calculate loading efficiency by comparing the initial drug amount with the measured free drug.(31,32)

2. In vitro drug release studies: In vitro release kinetics studies are conducted to characterize how the drug is liberated from aquasomes. A defined amount of drug-loaded aquasomes is suspended in a pH-appropriate buffer and maintained at 37 °C with constant stirring.

At predetermined intervals, aliquots are withdrawn and immediately centrifuged; an equal volume of fresh buffer is added each time to preserve sink conditions. The concentration of drug in each supernatant is then measured to map the release profile.

Key steps:

- Disperse a known quantity of drug-loaded aquasomes in buffer (correct pH) at 37 °C under continuous stirring.
- At set time points, remove samples and centrifuge immediately.
- Replace withdrawn volume with fresh buffer to maintain constant volume.
- Analyze the supernatant to quantify the amount of drug released.(33,34)

3. **In process stability studies:** When the aquasomes are being formulated, the stability and integrity of the protein may be evaluated using SDS-PAGE (sodium dodecyl sulphate polyacrylamide gel electrophoresis)(35)

APPLICATIONS OF AQUASOMES

1. Sustained Drug Delivery

Aquasomes can encapsulate small-molecule drugs and release them gradually over time, reducing dosing frequency and improving patient compliance. Their multilayered coating allows for controlled diffusion rates tailored to therapeutic needs.(36)

2. Vaccine Delivery

By adsorbing antigens onto their surface, aquasomes act as effective adjuvant carriers that stimulate both cellular and humoral immune responses. This platform enhances antigen stability and presentation without the need for harsh chemical conjugation.(37)

3. Enzyme Stabilization and Oral Delivery

Aquasomes protect acid-sensitive or easily degraded enzymes—such as serratiopeptidase—through their ceramic core and sugar-based shell. This shielding enables oral administration of enzymes that would otherwise denature in the gastrointestinal tract.(38)

4. Diagnostic Imaging

When conjugated with imaging labels (fluorescent dyes, radionuclides, or contrast agents), aquasomes serve as targeted probes for various imaging modalities. Their surface can be functionalized with antibodies or peptides to home in on specific tissues or biomarkers.(39)

5. Gene and Nucleic Acid Delivery

The polyhydroxy oligomer layer on aquasomes can be modified to bind DNA, siRNA, or mRNA, facilitating their protection from nucleases and promoting cellular uptake. This makes them promising vehicles for gene therapy and RNA-based vaccines.(25)

6. Targeted Therapy

Surface ligands—such as antibodies, aptamers, or peptides—can be conjugated to aquasomes to direct payloads selectively to diseased cells (e.g., tumors or inflamed tissues). This targeting reduces off-target effects and enhances therapeutic indices.

7. Cosmetic and Nutraceutical Applications

Aquasomes have been explored for the controlled delivery of antioxidants, vitamins, and natural extracts in skin-care and dietary supplement formulations. Their biocompatible components ensure minimal irritation and sustained release of active compounds.(39)

LIMITATIONS OF AQUASOMES

- Time-consuming and complex multi-step preparation limits productivity and makes large-scale manufacturing challenging.
- Difficulty in scaling up with consistent batch-to-batch reproducibility, affecting quality control and regulatory approval.
- Propensity to aggregate and undergo opsonization, leading to rapid clearance by the reticuloendothelial system and shortened circulation half-life in vivo.
- Incomplete understanding of immunogenicity and complement activation for different carbohydrate coatings necessitates further biocompatibility studies.
- No aquasome-based products have reached the market so far, reflecting unresolved stability, storage, and long-term safety hurdles(17)

CONCLUSION

Aquasomes represent a versatile and innovative platform in the realm of nanocarrier systems, combining a ceramic core with biomimetic carbohydrate coatings to protect and deliver therapeutic molecules with high stability and bioactivity. Their unique tripartite structure enables sustained or targeted release of drugs, proteins, vaccines, and genetic material, addressing critical challenges in solubility, degradation, and immunogenicity. Extensive preclinical evidence underscores their potential to enhance efficacy while minimizing off-target effects, positioning them as a front-runner for next-generation drug delivery strategies.

Despite formidable hurdles in large-scale manufacturing, reproducibility, and long-term safety assessment, ongoing advances in process optimization, stealth surface engineering, and lyophilization techniques promise to bridge the gap from bench to bedside. With concerted efforts in standardized formulation protocols, comprehensive in vivo evaluations, and regulatory alignment, aquasomes stand poised to transform therapeutic regimens across oncology, infectious diseases, and beyond—realizing their promise as a powerful, clinically translatable nanomedicine platform.

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