

Review on Aquasomes for Sustained and Novel Drug Delivery

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ABSTRACT

Aquasomes represent a sophisticated class of self-assembling nanoparticle drug delivery systems engineered to enhance the stability, bioavailability, and overall therapeutic efficacy of pharmacological agents through targeted, sustained release. Structurally, these nanocarriers feature a unique three-tier architecture: a solid ceramic core, a protective polyhydroxy oligomer coating, and the actively adsorbed bioactive payload. This specific configuration excels at preserving the three-dimensional conformation and biological activity of fragile molecules, making aquasomes ideal vehicles for proteins, peptides, enzymes, and poorly water-soluble therapeutics. This review comprehensively examines the formulation strategies, synthetic methodologies, and evaluation metrics associated with aquasomes, with a primary focus on their utility in sustained drug delivery. The fundamental manufacturing phases core synthesis, carbohydrate coating, and drug immobilization are detailed alongside critical physicochemical characterization parameters, including particle morphology, size distribution, zeta potential, entrapment efficiency, and in vitro release kinetics. Furthermore, this paper synthesizes recent technological advancements, clinical applications, inherent limitations, and future potential. By extending circulation half-life, minimizing dosing frequency, and ensuring active ingredient stability, aquasomes offer a highly promising platform for advanced therapeutics. Ongoing research and protocol optimization will be crucial for translating these innovative nanocarriers into viable clinical treatments for complex and chronic diseases. Recent advances in surface engineering, ligand functionalization, and targeted drug delivery have significantly expanded the therapeutic potential of aquasomes. Despite promising preclinical findings, large-scale clinical studies remain limited. Future research should focus on scalable manufacturing, regulatory approval, and clinical translation of aquasome-based formulations.

Keywords: *Aquasomes; Nanoparticles; Sustained drug delivery; Targeted drug delivery; Ceramic core; Drug delivery systems*

INTRODUCTION

Aquasomes are an advanced nanoparticulate drug delivery system designed to preserve the structural and functional integrity of bioactive molecules, that have been specifically designed to for the structural and functional integrity of bioactive molecules [1]. These systems represent a notable advancement in the field of nanotechnology based novel drug delivery, particularly for sensitive therapeutic agents such as proteins, peptides, enzymes, and phytoconstituents, which are highly susceptible to degradation under physiological and environmental conditions [2]. The ability of

aquasomes to maintain the native conformation of biomolecules distinguishes them from conventional nanoparticulate carriers and makes them highly suitable for modern pharmaceutical applications. The concept of aquasomes is fundamentally based on the principle of self-assembled nanoparticles, which is a process in which individual drug components spontaneously organize into a stable and ordered structure through non-covalent interactions. This self-assembly is driven by thermodynamic stability and involves different intermolecular forces such as hydrogen bonding, electrostatic interactions, van der

Waals forces, and hydrophobic interactions. These interactions collectively contribute to the formation of a stable supramolecular structure capable of preserving the biological activity of the drug molecule [3].

Structurally, aquasomes are composed of three distinct layers: a solid nanocrystalline core, a carbohydrate coating, and an outer layer of drug molecules. The core is typically made from ceramic materials such as calcium phosphate, hydroxyapatite, or diamond-like carbon, which provide mechanical strength, structural rigidity, and a high surface area for drug adsorption. These materials are inherently biocompatible and biodegradable, making them ideal for pharmaceutical and biomedical applications [4].

The carbohydrate coating plays a crucial role in the functionality of aquasomes. Sugars such as trehalose, sucrose, and cellobiose are commonly used due to their ability to form extensive hydrogen bonds with both the core material and the drug molecules. This coating mimics the natural aqueous environment of biomolecules, thereby stabilizing them and preventing

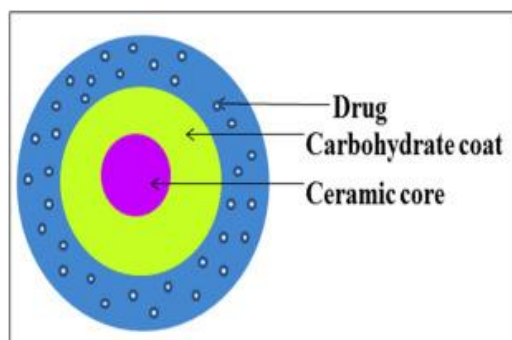
conformational changes or denaturation. The carbohydrate layer essentially acts as a molecular “water substitute,” preserving the structural integrity and biological activity of sensitive compounds. The outermost layer of aquasomes consists of drug molecules adsorbed onto the carbohydrate-coated surface through non-covalent interactions. This adsorption process ensures that the drug retains its original structure and activity, as no chemical modification or covalent bonding is involved. This is particularly advantageous compared to other delivery systems where drug conjugation may alter pharmacological properties [5].

Conventional drug delivery systems often suffer from rapid degradation, poor bioavailability, short biological half-life, and frequent dosing. Nanotechnology-based carrier systems have emerged to overcome these limitations. Among them, aquasomes have gained considerable attention because they preserve the native conformation of sensitive biomolecules while providing sustained and targeted drug release.

Table 1. Comparison of aquasomes with other nanoparticulate drug delivery systems

Feature	Liposomes	Niosomes	Polymeric NP	Aquasomes
Protein Stability	Moderate	Moderate	Good	Excellent
Sustained Release	Moderate	Moderate	Good	Excellent
Biocompatibility	High	High	High	Very High
Drug Loading	Moderate	Moderate	High	High
Structural Integrity	Moderate	Moderate	Good	Excellent

Figure 1: Structure of Aquasome



One of the most significant advantages of aquasomes is their ability to preserve the structural integrity and biological activity of drugs. Many bioactive molecules lose their activity when exposed to environmental stresses such as temperature fluctuations, pH changes, and enzymatic degradation. Aquasomes provide a protective microenvironment that shields these molecules, ensuring their stability and effectiveness throughout the delivery process [6].

Methods involved in synthesis of nano structures

The major steps involved in the production of nanostructures are described below, as aquasomes are self-assembling tri-layered nanostructures.

(i) Sequential covalent Synthesis, This approach is used to develop arrays of covalently linked atoms generated with unambiguous composition, connectivity and shape such as vitamin B12, it can originate the structures that are disproportionate from the thermodynamic minimum for that collection of the atoms [7].

(ii) Covalent polymerization This approach is used to generate molecules with high molecular weight, in this method a comparatively Low weight is enabled to react with itself to produce molecule comprising many covalently linked monomers. Example: formation of polyethene from ethylene. Covalent polymerization indirectly creates a synthetic route to stabilize nanostructures and phase separated polymers.

(iii) Self-organizing synthesis In order to arrange atoms, ions, or molecules into structures, this method depends on weaker or less directed bonds such as ionic, hydrogen, and Van der Waals interactions. Molecular crystals, ligand crystals, colloids, micelles, emulsions, phase-separated polymers, and self-assembled monolayers are among the various structures that can be produced with this technique. Self-origination is the distinctive feature of this method. (iv) Molecular self-assembly This approach combines disoriented components with their basic constituents to create an ordered structure; this is an attribute of aquasomes that is critical for self-assembly and has a number of interesting applications in the formulation development of nanoscience and nanotechnology [8].

Composition of Aquasomes

Aquasomes are nanoparticulate carrier systems rather than simple nanoparticles; these are three-layered self-assembled structures which consist of a solid phase nanocrystalline core coated with the polyhydroxyl oligomeric film onto which the effective molecules are adsorbed with or without alteration. Aquasome development occurs in three stages: Core preparation, core coating with carbohydrates and drug molecule immobilization [9].

(i) Preparation of core: The initial phase of preparing an aquasome involves fabricating the ceramic core using ceramics and polymers. The ceramic materials used in this phase are diamond particle, calcium phosphate (brushite), tin oxide, Hydroxyapatite [HAP] [10].

These are utilized in this phase due to their crystallinity, biocompatibility, affordability, ease of production, and biodegradability. This leads to a higher degree of order, achieves structural regularity, and increases surface energy, which effectively binds the coating material (carbohydrate) to it. Due to this peculiar property, these are the selective ceramics which are specially enlisted to formulate aquasomes [11].

(ii) Carbohydrate coating of core: In this step, the outer core is coated with polyhydroxy oligomers, or carbohydrates. With its glassy texture, carbohydrates act as a natural stabilizer and can produce a glassy carbohydrate coating on ceramics and adsorb therapeutic agents in the nanoscale size range. The carbohydrate layer is considered as the pivotal material in the preparation of aquasomes due to the fact that the hydroxyl groups present on these oligomers interact with the charged as well as polar functional groups and they safeguard the structural integrity of the biomolecule in the absence of water by creating a water-like environment [12,13].

Coating the preformed ceramic nanoparticles or self-assembled calcium phosphate dihydrate by sonication and colloidal precipitation. The substances that are typically employed as coating materials include

cellobiose, lactose, saccharose, trehalose, chitosan, citrate, sucrose, pyridoxal 5-phosphate etc.

Loading of drug: After the Carbohydrate coating of core, the drug is loaded in the core by either mechanical stirrer or by magnetic stirring followed by centrifugation, which ensures efficient drug loading in the prepared core.

The preparation of aquasomes is relatively simple and direct synthesis with the minimal usage of the solvents. Furthermore, achieving the desired particle size does not require homogenization; instead, fabrication relies simply on core coating and drug loading. [9,11].

Step 1: Fabrication of the Solid Core

Core formulation: The primary step in formulating aquasomes is the fabrication of the solid core. The synthesis technique depends on the chosen material, with common methods including colloidal precipitation, sonication, dendrimeric approaches, plasma condensation, and inverted magnetron sputtering. Ceramics are frequently utilized as core materials. Typically, these ceramic cores are synthesized via a co-precipitation process that employs magnetic stirring under reflux conditions.

The first stage of aquasome formulation involves synthesizing the solid core. Depending on the desired characteristics, several techniques can be utilized:

(i) Co-Precipitation via Reflux

Calcium phosphate ceramic cores are commonly synthesized through a dropwise addition of 0.19 N diammonium hydrogen phosphate into a 0.32 M calcium nitrate solution. This reaction requires continuous stirring, strict temperature maintenance at 75°C, and pH regulation between 8 and 10. The resulting mixture is continuously agitated for six days to induce the precipitation of calcium phosphate. The final solid cores are isolated through filtration, washed extensively, and air-dried overnight at 100°C [14].

Alternatively, Goyal et al. documented a modified co-precipitation approach. In this method, aqueous solutions of 0.152 M calcium nitrate tetrahydrate and 0.09 M diammonium hydrogen phosphate are combined. A volume of 1440 mL of this mixture is treated with a dispersant (3 mL of 0.1 g/L methyl cellulose), followed by the addition of 115 mL of 24% ammonium hydroxide. The suspension is vigorously stirred and heated between 60°C and 70°C for three hours. The resulting precipitate is filtered, washed repeatedly, and dried overnight at 100°C. Finally, the material undergoes calcination in air at 1000°C for six hours, followed by grinding to yield the finished cores [15].

(ii) Self-Precipitation

This method relies on the incubation of a simulated body fluid (SBF) consisting of 134.8 mM sodium chloride, 5.0 mM potassium chloride, 4.2 mM sodium

hydrogen carbonate, 2.5 mM calcium chloride, 1.0 mM disodium hydrogen phosphate, 1.5 mM magnesium chloride, and 0.5 mM disodium sulfate. The SBF is adjusted daily to a pH of 7.2 using hydrochloric acid. The fluid is sealed in polystyrene bottles and incubated at a controlled temperature of $37\pm1^{\circ}\text{C}$ for one week. The resulting precipitate is collected via filtration, washed thoroughly with distilled water, and dried at 100°C .

(iii) Sonication Method

Based on standard reaction stoichiometry, combining calcium chloride and disodium hydrogen phosphate yields a colloidal precipitate. This equimolar reaction is typically conducted in a 120 mL total volume under sonication to form the core structures [16, 17, 18].

Step 2: Carbohydrate Coating of the Core

Once the solid ceramic cores are established, they undergo a coating phase utilizing wet chemical techniques combined with lyophilization. Typical coating materials include polyhydroxy compounds such as sucrose, trehalose, lactose, cellobiose, chitosan, or pyridoxal 5-phosphate.

During this step, the chosen carbohydrate is introduced into an aqueous dispersion of the solid cores and subjected to sonication to ensure even distribution. The mixture is then lyophilized (freeze-dried), a process that drives the irreversible adsorption of the carbohydrate molecules onto the surfaces of the ceramic cores. Following lyophilization, the

formulation is centrifuged to separate and discard any unbound carbohydrate material [19, 20].

Step 3: Drug Immobilization and Loading

While the first two steps establish the foundational architecture of the aquasome, the final phase involves incorporating the active therapeutic agent. In this stage, the targeted drug or bioactive material is partially adsorbed onto the polyhydroxy oligomer coating.

To achieve this, a drug solution of a specific, known concentration is prepared in an appropriate pH buffer. The carbohydrate-coated particles are then dispersed into this buffered drug solution and incubated, allowing the therapeutic molecules to successfully bind and load onto the aquasome surface [21, 22].

Mechanism of Drug Release

Drug release from aquasomes occurs through a combination of diffusion, desorption, surface erosion, and degradation of the carrier system. Initially, the drug adsorbed on the carbohydrate-coated surface diffuses into the surrounding biological fluid. Subsequently, gradual degradation of the ceramic core and carbohydrate layer provides sustained drug release over an extended period. The release kinetics depend upon particle size, surface area, coating thickness, drug-carrier interaction, and physiological pH. Mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas are commonly used to determine the release mechanism.

Figure 2. Mechanism of Drug Release from Aquasomes

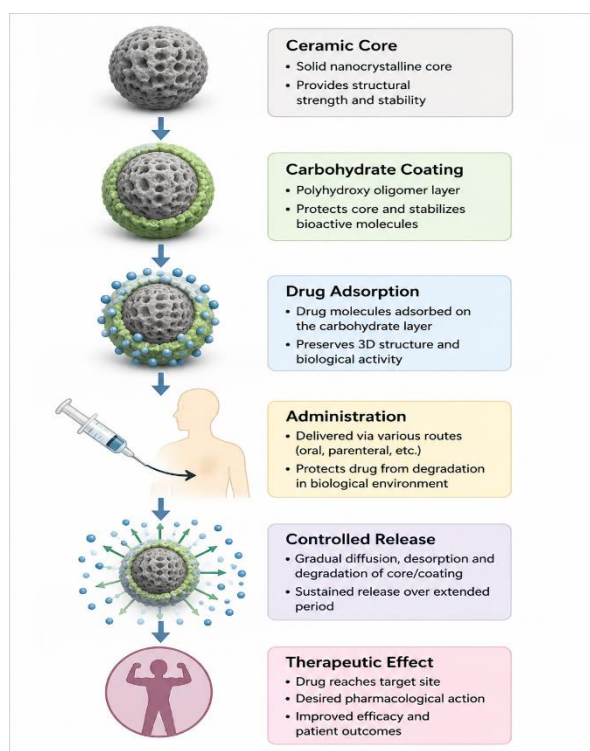


Figure 2. Schematic illustration of the mechanism of drug release from aquasomes showing ceramic core preparation, carbohydrate coating, drug adsorption, administration, controlled drug release, and subsequent therapeutic effect.

Table 2: Physicochemical characterization techniques employed for aquasome evaluation

Parameter	Technique	Purpose
Particle size	DLS	Size
Zeta potential	Zetasizer	Stability
Morphology	SEM/TEM	Shape
Crystallinity	XRD	Crystal nature
Functional groups	FTIR	Drug compatibility
Thermal analysis	DSC	Stability
Drug loading	UV/HPLC	Loading efficiency
Release	Dissolution	Release profile

Characterization and Evaluation

a. Attenuated Total Reflectance: Fourier Transform Infrared Spectroscopy (ATR-FTIR) FTIR spectroscopy will be utilized to analyze and verify the chemical structures of the naked hydroxyapatite (HAP) cores, the carbohydrate-coated intermediates, and the final drug-loaded aquasome formulations [23].

b. Differential Scanning Calorimetry (DSC): The thermal properties of the samples will be assessed using a Shimadzu DSC 60 Plus instrument, which will be calibrated beforehand with an indium standard. Aliquots weighing between 5 and 10 mg will be sealed in aluminum crucibles, utilizing an empty aluminum pan as a baseline reference. The thermal scans will be conducted from 25°C to 400°C at a constant heating rate of 10°C per minute, maintained under a continuous nitrogen purge of 50 mL/min [24, 25].

c. X-ray Diffraction (XRD): Analysis To investigate structural crystallinity, potential amorphization, and drug-excipient compatibility, XRD diffractograms will be recorded. The analysis will compare the uncoated cores, sugar-coated cores, fully formulated drug-loaded aquasomes, unformulated pure drug, and a physical mixture of the raw components [26, 27].

d. Scanning Electron Microscopy (SEM): The surface morphology and topographic features of the dried formulations will be examined using a JEOL JSM-IT200 scanning electron microscope. Prior to imaging, the samples will be affixed to aluminum stubs using double-sided carbon tape and sputter-coated with gold to optimize electrical conductivity. Micrographs will be captured under high-vacuum conditions using accelerating voltages between 5 and 20 kV [28, 29, 30].

e. Evaluation of Drug-Loaded Aquasomes (DLA):

- **Percentage Practical Yield:** The practical yield will be calculated by comparing the actual recovered mass of the synthesized aquasomes against the theoretical combined mass of all starting materials used in the batch. Standard production yield formulas will be applied [31, 32].

- **Drug Entrapment Efficiency (% EE) and Drug Loading:** The finalized aquasomes will be evaluated to determine the total percentage of the drug successfully incorporated into the carrier, as well as the overall entrapment efficiency, following established analytical protocols [33, 34].

f. In Vitro Release Studies: A comparative dissolution profile of the pure drug versus the drug-loaded aquasomes will be generated using a USP Type II (paddle) apparatus. The test will be conducted in an acetate buffer medium (pH 4.5) maintained at 37 ± 0.5 °C with an agitation speed of 100 rpm. At predetermined time points, 10 mL sample aliquots will be withdrawn and immediately replaced with fresh buffer to ensure perfect sink conditions. Drug concentrations will be quantified via UV spectrophotometry. All trials will be performed in triplicate. To elucidate the release mechanism, the resulting data will be fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas mathematical models. The best-fitting model will be identified by the highest regression coefficient (R^2). Furthermore, the diffusional exponent (n) derived from the Korsmeyer-Peppas equation will be analyzed to define the specific mechanism of drug release [35, 36].

g. Stability Studies: In accordance with International Council for Harmonisation (ICH) guidelines, the optimized aquasome formulations will undergo stability testing for one and three months. The formulations will be stored under three distinct environments: refrigerated ($4-8$ °C), ambient room temperature (28 ± 2 °C), and accelerated conditions (40 °C). Post-storage, the samples will be re-evaluated for structural integrity, drug content, and in vitro release characteristics [37].

h. In Vivo Pharmacokinetic/Pharmacodynamic: Studies To evaluate in vivo performance and therapeutic efficacy, animal trials will be conducted utilizing Wistar rats. The subjects will be randomized into designated groups and administered either the unformulated drug solution or the optimized aquasome formulation via the oral route. Blood samples will be

drawn at specific, periodic intervals. These plasma samples will undergo precipitation to extract the active compound, followed by quantification using a validated analytical method. Key pharmacokinetic parameters including maximum plasma concentration

(Cmax), time to maximum concentration (Tmax), area under the curve (AUC), and biological half-life ($t_{1/2}$) will be calculated and statistically compared across the experimental groups [39, 40].

Table 3: Clinical applications of aquasomes in drug delivery

Drug	Disease	Benefit
Insulin	Diabetes	Sustained release
Hemoglobin	Oxygen delivery	Maintains protein structure
Bromelain	Anti-inflammatory	Improved oral bioavailability
Curcumin	Cancer	Better stability
Vaccines	Immunization	Enhanced immune response
Proteins	Protein delivery	Prevents denaturation
Peptides	Hormone delivery	High bioavailability
Anticancer drugs	Cancer	Targeted delivery

Advantages of Aquasomes

- High drug loading capacity
- Excellent biocompatibility
- Protects protein conformation
- Sustained drug release
- Better bioavailability
- Reduced dosing frequency
- Minimal toxicity
- Improved patient compliance
- Suitable for peptides and proteins
- Targeted delivery potential

Limitations

- Large-scale manufacturing remains difficult.
- Higher production cost.
- Stability during long-term storage.
- Limited clinical trials.
- Regulatory approval is lacking.
- Complex manufacturing process.
- Limited commercial products available.

Future Perspectives

Artificial intelligence-assisted formulation design, ligand-targeted aquasomes, personalized nanomedicine, gene delivery, vaccine delivery, and large-scale GMP manufacturing are expected to expand the clinical applications of aquasomes. Future research should focus on regulatory approval, scalable production technologies, and long-term safety evaluation.

CONCLUSION

Aquasomes represent a highly sophisticated class of self-assembling nanoparticulate delivery systems, distinguished by their surface-engineered, solid ceramic cores. They provide an exceptionally efficient vehicle for transporting delicate bioactive agents. The

unique three-layer architecture of an aquasome is crucial for preserving the three-dimensional conformation and biological activity of therapeutic molecules throughout the formulation, storage, and physiological delivery phases. Research has demonstrated their efficacy in delivering a broad spectrum of therapeutics ranging from insulin, hemoglobin, and enzymes to various proteins, peptides, and viral antigens resulting in markedly improved clinical performance. Beyond direct drug delivery, these nanocarriers act as potent immunoadjuvants, capable of augmenting antigen presentation and boosting overall immune responses. Because they offer high biocompatibility, remarkable physical stability, and an unparalleled capacity to protect biological integrity, aquasome technology provides a promising, innovative platform for the targeted and sustained delivery of next-generation pharmaceuticals. Despite remarkable progress in formulation science, challenges related to large-scale production, long-term stability, regulatory approval, and clinical translation remain. Future multidisciplinary research integrating nanotechnology, biomaterials, and artificial intelligence is expected to accelerate the commercialization of aquasome-based therapeutics.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review article.

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Author Contributions

Dronamraju Nirmala Kumari: Conceptualization, literature search, data collection, writing – original draft, and manuscript preparation.

Lalitha Repudi: Supervision, critical review, editing, validation, and final approval of the manuscript.

Data Availability Statement

No new datasets were generated or analyzed during the preparation of this review article. All information presented is based on previously published literature cited in the references.

Ethical Approval

This article is a review of previously published studies and does not involve any human participants or experimental animals. Therefore, ethical approval was not required.

Informed Consent

Not applicable.

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