WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 18, 115-140. Review Article ISSN 2277–7105

AQUASOMES: A COMPREHENSIVE REVIEW OF THEIR STRUCTURE, PREPARATION, CHARACTERIZATION, AND APPLICATIONS IN DRUG DELIVERY

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Article Received on 15 August 2026,
Article Revised on 05 Sept. 2026,
Article Published on 16 Sept. 2026,

https://doi.org/10.5281/zenodo.22767107

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How to cite this Article: Ayushi Patidar*, Dr. Praveen Khirwadkar, Dr. Tanu Bhargava, Dr. Kamlesh Dashora, Kajal Gehlot (2026). Aquasomes: A Comprehensive Review Of Their Structure, Preparation, Characterization, And Applications In Drug Delivery. World Journal of Pharmaceutical Research, 15(18), 115–140.

ABSTRACT

Aquasomes are self-assembled nanocarrier systems composed of three main components: a nanocrystalline ceramic core, carbohydrate coating, and an outer layer of adsorbed drug or bioactive molecules. The therapeutic molecules are associated with the coated surface through non-covalent interactions. The hydrated microenvironment created by the carbohydrate layer may help maintain the structural integrity and biological activity of adsorbed molecules. This hydrated environment may help protect sensitive therapeutic molecules from structural changes during formulation, storage, and administration, making aquasomes a potential carrier for their delivery. Aquasomes were developed from the concept of preserving the hydrated interfacial environment surrounding sensitive biological macromolecules, particularly proteins and polynucleotides. Aquasomes have been investigated for drug delivery through several routes, including oral, topical, ocular, and parenteral administration. Their potential applications have been explored in targeted drug delivery, cancer therapy, antimicrobial therapy, vaccine delivery, and regenerative medicine. This review discusses the concept, development, components, preparation methods, characterization, pharmaceutical applications, and future prospects of aquasomes. The distinctive structural and functional characteristics of aquasomes make them a promising platform for drug and bioactive molecule delivery.

KEYWORDS: Aquasomes; Nanocarrier; Self-assembly; Ceramic core; Carbohydrate coating; Drug delivery.

1. INTRODUCTION

Rapid advances in nanotechnology have contributed to the development of novel approaches for addressing several limitations associated with conventional drug delivery systems. Many therapeutic agents face challenges such as poor aqueous solubility, limited oral bioavailability, instability under physiological conditions, rapid metabolism, and nonspecific tissue distribution, which can compromise their therapeutic performance. To address these challenges, several nanocarrier systems have been developed, including liposomes[9], niosomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, nanocrystals, and aquasomes.[2,3]

Among the advanced delivery systems, aquasomes have emerged as a unique and promising carrier because they can preserve or enhance the structural integrity of sensitive therapeutic molecules while providing efficient drug delivery.[1,10] The concept of aquasomes was introduced by Kossovsky in the 1990s, with an initial focus on preserving the biological activity of proteins and peptides during formulation and administration.[1,19] The concept was subsequently explored in a broader range of biological and therapeutic applications.[22,41] Scientific interest in aquasomes has grown due to their exceptional stability, controlled drug release characteristics, and high drugloading efficiency.[3,15]

Aquasomes are nanoscale self-assembled structures, with reported particle sizes generally falling within the nanometer range. Their three-layered architecture contributes to the structural integrity of the carrier. They are made up of three distinct layers. The innermost layer is a nanocrystalline ceramic core made up of various materials such as calcium phosphate, hydroxyapatite (which alters the shape of most porous surfaces), diamond or ceramic nanoparticles. The core provides structural support, chemical stability, and a suitable surface for subsequent coating and drug or bioactive molecule adsorption. Trehalose, sucrose, cellobiose, and other polyhydroxy carbohydrates can be used to form the carbohydrate coating. The carbohydrate layers help maintain a hydrated microenvironment around the adsorbed molecules and may reduce structural changes associated with dehydration and denaturation, which also act as a barrier between sensitive therapeutic agents and biological macromolecules.[1,19]

A layer of non-covalently adsorbed bioactive molecules or pharmaceutical drugs forms the outermost layer, bonded by hydrogen bonding, attenuated by van der Waals forces, electrostatic attraction, and hydrophobic interactions. The adsorption process ensures that the therapeutic agent's native molecular structure remains intact, while also allowing for efficient drug loading. The nanocrystalline core's highly organized surface allows for the creation of stable carbohydrate coatings. The coatings create a conducive microenvironment that allows drug molecules to be absorbed without any disruption to their biological structure. Thus, aquasomes preserve the pharmacological activity of sensitive molecules more effectively than traditional nanoparticle systems.[10,23]

Biomolecules that are otherwise susceptible to degradation can be improved in stability and therapeutic performance through the use of aquasomes, which is one of their major advantages. The biological activity of proteins, peptides, and enzymes, as well as those necessary for metabolism, reproduction, or development, is often lost due to changes in their conformation during processing, storage, or administration. The carbohydrate coating in aquasomes minimizes these structural changes by keeping the hydration shell surrounding the molecules. This is particularly useful in this process. In addition, the characteristics of aquasomes include superior colloidal stability, vast surface area, increased drug loading capability, extended circulation time, controlled drug release, and decreased immunogenicity. Together, these features improve therapeutic efficacy and decrease dosing frequency and systemic toxicity while maintaining better outcomes. Industry initially examined aquasomes for their function as delivery systems of proteins, peptide or enzyme products, vaccine agents, and hormone analogs.[10,13,23]

Even so, the application of these drugs has been broadened to encompass antimicrobial agents and other naturally occurring antibacterial or fungal compounds, as well as widely used anti-infectant drugs, anti-inflammatory medications, antioxidants, and many natural phytoconstituents. A number of studies have revealed that aquasomes can significantly increase drug solubility, dissolution rate, bioavailability, and therapeutic efficacy while facilitating targeted sustained drug release. Among the reported applications are oral, topical, ocular, and pulmonary delivery systems, as well as transdermal and parenteral drug delivery methods.[16,29,37]

Other areas of interest include tissue engineering, regenerative medicine, diagnostic imaging (in vivo), vaccine delivery, and gene therapy in addition to pharmaceutical drug delivery via

the socalled aquasome. They are particularly useful for advanced therapeutic applications because they can maintain the conformational integrity of biomolecules while also providing site-specific drug delivery. Aquasomes are poised to become more efficient and effective for personalized medicine and targeted therapy due to ongoing advancements in nanotechnology, material science, and pharmaceutical engineering.[3,15,41]

2. PRINCIPLE OF SELF-ASSEMBLY

When a system of individual molecules or monomers self-organizes to form a highly ordered and stable structure, it is said to undergo a process of self-assembly. Self-assembly, also referred to as self-organization, is a versatile process that can occur under physicochemical conditions resembling those of an aqueous environment. The self-assembly of aquasomes occurs spontaneously as the components tend to minimize their free energy while maintaining the structural integrity and biological activity of the therapeutic agents. During this process, the particles of interest associate in a highly ordered manner without the need for external forces or extensive chemical manipulation. In this manner, they "self-assemble" into a stable aggregate structure.[1,19]

Since the thermodynamic properties of a system are governed by interactions among its components, the major driving forces responsible for self-assembly are intermolecular forces. Several types of intermolecular forces are involved in determining the conformation and association of biomolecules in aqueous environments and may influence the self-assembly of carbohydratecoated inorganic ceramic cores onto which therapeutic molecules are adsorbed. These include: (i) electrostatic interactions between charged groups, (ii) short-range steric repulsions, (iii) van der Waals forces, (iv) hydrogen bonding, and (v) hydrophobic interactions.[10,19]

An important requirement of aquasomes is that the completed system should retain the biological activity of its constituents without significantly altering the native conformation of therapeutic agents, including proteins, peptides, and nucleic acids, following their adsorption onto the aquasome surface. Consequently, the structure and functional conformation of biomolecules adsorbed onto the aquasome surface should be preserved. The carbohydrate coating provides a highly hydrated, water-like microenvironment around the drug or bioactive molecule, which contributes to maintaining its structural integrity during delivery.[1,23]

2.1 Major Intermolecular Forces Involved in Self-Assembly

2.1.1 Electrostatic Interaction

One of the important driving forces for self-assembly is electrostatic attraction. Charged functional groups, such as amino, carboxyl, phosphate, sulfate, and other ionizable groups present in biomolecules, can interact with oppositely charged groups on the carbohydrate-coated ceramic core. Electrostatic forces can contribute to the orderly adsorption of therapeutic agents onto the carrier surface. These ionic interactions may also influence the orientation and association of biomolecules, thereby supporting the preservation of their functional activity during delivery.[19]

2.1.2 Hydrogen Bonding and Dehydration Effects

Hydrogen bonding is an important intermolecular force involved in maintaining the secondary structure of proteins, such as α-helices and β-sheets. Multiple hydrogen bonds between the carbohydrate coating of aquasomes and surrounding water molecules can form a hydration shell that resembles the natural hydrated environment of biological molecules.

During self-assembly, partial dehydration may occur at the interface between the carrier and biomolecule, in which loosely bound water molecules are displaced. This partial dehydration can facilitate closer interaction between the carrier surface and therapeutic molecule. At the same time, the hydrated carbohydrate layer can help maintain an appropriate water-associated environment, thereby supporting the preservation of the biological structure and activity of sensitive molecules after immobilization on the aquasome surface.[1,10]

2.1.3 Van der Waals Interactions

Van der Waals forces are weak, short-range attractive interactions that can contribute to the association of therapeutic molecules with the coated carrier surface. Although an individual van der Waals interaction is relatively weak, the cumulative effect of numerous interactions over a large contact area can contribute significantly to the stability of the adsorbed drug layer.[19]

2.1.4 Hydrophobic Interactions

Hydrophobic interactions can also contribute to the association of drug molecules with the aquasome surface. Nonpolar regions of therapeutic molecules may associate with compatible hydrophobic regions while minimizing their exposure to water. These interactions can influence the orientation, adsorption, and distribution of drug molecules on the

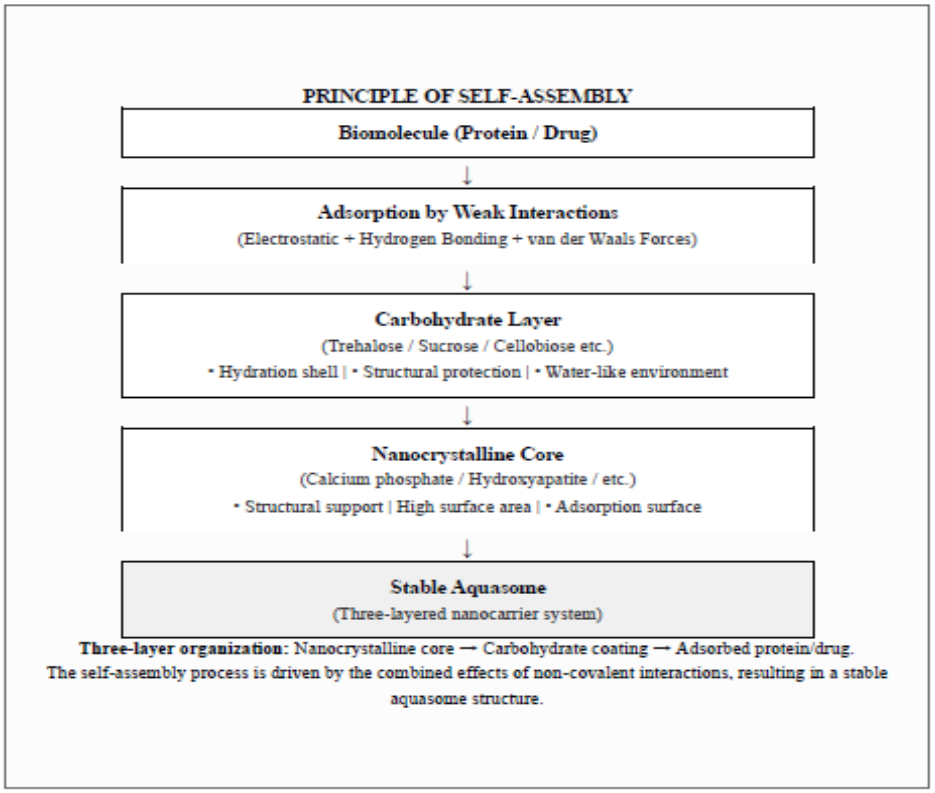
carbohydrate-coated surface.[10]

2.1.5 Steric Interactions

Short-range steric effects influence the orientation and spatial arrangement of molecules during selfassembly. The balance between attractive interactions and steric repulsion helps determine the final organization and stability of the aquasome structure.[19]

The final stage of self-assembly is therefore influenced by a combination of non-covalent interactions, including hydrogen bonding, electrostatic interactions, van der Waals forces, and hydrophobic interactions. Although each individual interaction may be relatively weak, their cumulative effect can provide sufficient stability to the assembled structure while allowing a degree of molecular mobility and appropriate orientation of the constituent molecules.

Overall, self-assembly in aquasomes involves the spontaneous organization of the nanocrystalline core, carbohydrate coating, and therapeutic molecule through coordinated intermolecular interactions. The resulting three-layered structure provides a hydrated, water-like microenvironment that can help preserve the structural integrity and biological activity of sensitive therapeutic molecules.



Three-layer organization: Nanocrystalline core → Carbohydrate coating → Adsorbed protein/drug.
The self-assembly process is driven by the combined effects of non-covalent interactions, resulting in a stable aquasome structure.

3. OBJECTIVES OF AQUASOMES

Aquasomes are being explored as nanocarrier systems with the aim of providing a protective environment for therapeutic molecules while maintaining their stability and biological function. The major objectives of aquasome-based drug delivery systems include the following:

3.1 Enhanced Stability

One of the main objectives of aquasomes is to improve the stability of sensitive therapeutic molecules. The carbohydrate layer surrounding the core can retain water and provide a hydrated environment, which may help minimize structural changes associated with dehydration. This property is particularly useful for molecules that are sensitive to changes in their surrounding environment.[1,17]

3.2 Preservation of Molecular Conformation

Aquasomes are designed to help preserve the native three-dimensional structure of bioactive molecules. Preservation of molecular conformation is particularly important for proteins, peptides, and enzymes because their biological activity is closely related to their structural integrity.[1,17]

3.3 Improvement in Bioavailability

Aquasomes may be useful for improving the delivery of drugs with poor aqueous solubility or limited stability. Their nanosized structure provides a large surface area, which can support drug adsorption and improve the dispersion of selected therapeutic agents.[11,16]

3.4 Controlled Drug Delivery

The association between the drug and the carbohydrate-coated surface can influence the rate at which the drug leaves the carrier. Therefore, aquasomes may function as drug reservoirs and provide prolonged or controlled drug release, depending on the properties of the drug and carrier.[10,11]

3.5 Protection from Environmental Stress

The carbohydrate coating can provide a protective hydrated environment around the therapeutic molecule. This may help reduce the effects of dehydration and other environmental stresses that can affect the stability of sensitive bioactive substances.[1,17]

3.6 Facilitation of Drug-Carrier Interaction

Drug molecules can associate with the carbohydrate-coated surface through different types of interactions, including ionic interactions, hydrogen bonding, van der Waals forces, and other noncovalent interactions. Such interactions allow therapeutic molecules to be incorporated without necessarily requiring chemical modification of the drug.[1,19]

3.7 Potential for Targeted Delivery

The surface of an aquasome can potentially be modified to influence its interactions with biological tissues or cells. This provides an opportunity to investigate aquasomes for site-specific drug delivery and potentially improved cellular uptake in suitable therapeutic applications.[14,15]

3.8 Development of a Versatile Nanocarrier

Another objective is to develop a carrier capable of accommodating different types of therapeutic molecules. Aquasomes have been investigated for the delivery of proteins, peptides, antigens, and selected small-molecule drugs, highlighting their potential as a versatile drug delivery platform.[10,11]

4. PROPERTIES OF AQUASOMES

Aquasomes have a characteristic three-component architecture consisting of a nanocrystalline core, a carbohydrate coating, and an adsorbed therapeutic molecule. Their properties are influenced by the nature of the core material, the carbohydrate coating, and the interactions between the drug and the carrier surface.

4.1 Nanoparticulate Nature

Aquasomes are nanosized carrier systems with a relatively high surface-area-to-volume ratio. The relatively large surface area available at the nanoscale can facilitate the adsorption of therapeutic molecules onto the coated surface.[10,14]

4.2 Three-Layered Structure

A typical aquasome consists of three main components: a solid nanocrystalline core, a carbohydrate coating, and a therapeutic molecule adsorbed onto the coated surface. The core provides structural support, whereas the carbohydrate layer acts as an interface between the core and the drug molecule.[1,10]

4.3 Structural Stability

The ceramic core contributes to the structural stability of the carrier. Materials such as calcium phosphate and hydroxyapatite have been investigated as aquasome core materials because of their favorable structural and biological properties.[17,18]

4.4 Hydrated Surface Environment

The carbohydrate coating contains several hydroxyl groups that can interact strongly with water. As a result, the coated surface can maintain a hydrated, water-like environment around the carrier. This characteristic is particularly relevant for protecting molecules that are sensitive to dehydration.[1,17]

4.5 Preservation of Conformational Integrity

A notable property of aquasomes is their potential to preserve the structural integrity of bioactive molecules. This is particularly important for proteins and peptides because changes in their threedimensional structure may lead to a loss of biological activity.[1,17]

4.6 Large Surface Area for Drug Adsorption

The nanoscale size of aquasomes provides a relatively large surface area for interaction with therapeutic molecules. Therapeutic molecules may associate with the carbohydrate-coated surface through hydrogen bonding, ionic interactions, van der Waals forces, and other non-covalent interactions.[14,15]

4.7 Protection Against Degradation

The carbohydrate layer may act as a protective barrier around the adsorbed therapeutic molecule. By providing a hydrated microenvironment, the carbohydrate layer may help reduce the effects of environmental stresses, particularly those associated with dehydration and structural instability.[1,17]

4.8 Potential for Controlled Drug Release

Drug release from aquasomes is influenced by the strength and nature of the interaction between the drug and the coated surface. The gradual desorption of the drug may allow aquasomes to function as reservoirs for sustained or controlled delivery of suitable therapeutic agents.[11,14]

4.9 Potential Biocompatibility

Calcium phosphate and hydroxyapatite are commonly investigated as core materials because

of their established use in biomedical applications. However, the biocompatibility of a complete aquasome formulation depends on several factors, including its composition, particle characteristics, surface properties, drug characteristics, and route of administration. Therefore, the safety of each formulation should be experimentally evaluated.[15,18]

4.10 Versatile Drug-Loading Capacity

Aquasomes have been investigated for the loading and delivery of macromolecules as well as selected small-molecule drugs. In many cases, drug incorporation occurs through adsorption onto the carbohydrate-coated surface. The extent of drug loading depends on the physicochemical properties of both the drug and the carrier.[10,11]

5. ADVANTAGES OF AQUASOMES

5.1 Enhanced Stability

Enhanced stability is one of the major advantages of aquasome-based delivery systems. The carbohydrate coating can maintain a hydrated environment around the therapeutic molecule and may help minimize structural changes associated with dehydration. This feature is particularly relevant to proteins, peptides, and other sensitive bioactive molecules.[1,17]

5.2 Preservation of Biological Activity

Aquasomes may help preserve the molecular conformation required for biological activity. This is particularly relevant to proteins and peptides because changes in their molecular structure can affect their biological activity.[1,17]

5.3 Improved Delivery of Poorly Soluble Drugs

The small particle size and relatively large surface area of aquasomes can facilitate the incorporation and dispersion of selected poorly water-soluble drugs. Consequently, aquasome-based systems have been investigated for improving the delivery of selected hydrophobic therapeutic agents.[11,16]

5.4 Controlled and Sustained Drug Release

Aquasomes can act as drug reservoirs in which the therapeutic molecule remains associated with the carbohydrate-coated surface and is gradually released into the surrounding medium. The release profile is influenced by drug-carrier interactions, coating properties, and formulation conditions.[11,14]

5.5 Protection Against Dehydration

The carbohydrate coating has a strong affinity for water and can maintain a hydrated environment around the incorporated bioactive molecule. This may help minimize dehydration-induced changes in molecular structure and activity.[1,17]

5.6 High Surface Area for Drug Adsorption

The nanosized nature of aquasomes provides a relatively large surface area for drug adsorption. When a drug has sufficient affinity for the carbohydrate-coated surface, this property may contribute to efficient drug incorporation.[14,15]

5.7 Potential for Targeted Delivery

The surface characteristics of aquasomes can be modified according to the intended application. Such modifications may alter interactions with cells or tissues and could support the development of targeted delivery systems.[14,15]

5.8 Minimal Need for Chemical Modification of the Drug

In suitable formulations, therapeutic molecules can be incorporated by adsorption onto the carbohydrate-coated surface without forming covalent bonds with the carrier. This may be advantageous when preservation of the original structure and biological activity of the drug or bioactive molecule is important.[17,20]

5.9 Suitable Ceramic Core Materials

Calcium phosphate and hydroxyapatite have been investigated as aquasome core materials because of their established biomedical applications and favorable biological properties. Their use can provide structural support to the nanocarrier.[18,19]

5.10 Versatility

Aquasomes have been explored for the delivery of several classes of therapeutic molecules, including proteins, peptides, enzymes, antigens, hemoglobin, insulin, and selected small-molecule drugs. These studies demonstrate the potential of aquasomes as a versatile nanocarrier platform.[10,13]

6. DISADVANTAGES AND LIMITATIONS OF AQUASOMES

Although aquasomes have several promising characteristics, their development and application involve formulation, manufacturing, and translational challenges.

6.1 Complex Preparation Process

Preparation of aquasomes generally involves multiple steps, including formation of the nanocrystalline core, deposition of the carbohydrate coating, and subsequent drug loading. Each step requires careful optimization, which can increase the time and complexity of formulation development.[10,14]

6.2 Drug-Dependent Loading Efficiency

Drug loading is strongly influenced by the interaction between the therapeutic molecule and the carbohydrate-coated surface. Therefore, some drugs may exhibit poor adsorption or low loading efficiency, particularly when they have limited affinity for the carrier surface.[10,11]

6.3 Possibility of Particle Aggregation

Like other nanoparticulate systems, aquasomes may undergo aggregation during preparation or storage if suitable formulation and stabilization conditions are not maintained. Aggregation can affect particle size, surface area, drug loading, and drug-release behavior.[14,15]

6.4 Possibility of Premature Drug Release

Because the drug is generally associated with the outer coated surface rather than completely enclosed within a conventional vesicular structure, weak drug-surface interactions may result in rapid desorption. This may lead to an initial burst release and reduce the desired sustained-release effect.[11,20]

6.5 Scale-Up Difficulties

Moving from laboratory-scale preparation to industrial production can be challenging. Maintaining consistent particle size, crystallinity, coating characteristics, drug loading, and surface properties during scale-up requires stringent process control.[10,14]

6.6 Storage-Related Stability Concerns

The physical and chemical stability of aquasomes may be affected during prolonged storage. Factors such as particle aggregation, moisture, changes in the carbohydrate layer, and alteration of drug- surface interactions can influence the performance of the formulation. Therefore, appropriate long-term stability studies are essential.[10,14]

6.7 Limited Clinical Evidence

Although several experimental studies have reported promising results, aquasome-based systems still require further pharmacokinetic, toxicological, long-term safety, and clinical

investigations.

Further evidence is required before their widespread clinical application can be established.[10,14]

6.8 Formulation-Dependent Biocompatibility

The biological safety of an aquasome cannot be determined solely from the individual components used in its preparation. Particle size, core composition, surface characteristics, carbohydrate coating, incorporated drug, and route of administration may all influence its biological response. Hence, the complete formulation must be evaluated for safety.[15,18]

6.9 Drug-Carrier Compatibility

The physicochemical properties of a drug, including molecular size, charge, polarity, and functional groups, can influence its interaction with the aquasome surface. Therefore, the core, coating, and drug-loading conditions may require optimization for individual drugs.[11,14]

6.10 Manufacturing and Regulatory Challenges

Before clinical translation, aquasome formulations require detailed evaluation of reproducibility, purity, particle characteristics, drug loading, stability, toxicity, and pharmacokinetic behavior. Establishing consistent manufacturing and quality-control procedures may therefore remain a significant challenge during further development.[10,14]

7. STRUCTURE OF AQUASOMES

Aquasomes are novel self-assembly nanocarrier systems with a three-layered structure designed to provide a stable surface for the adsorption of drugs or bioactive molecules while helping to maintain the activity of sensitive molecules and structural stability of the adsorbed biological macromolecules in various physiological environments. The three structural elements of an aquasome are as follows.

7.1 Nanocrystalline Core

The core of the aquasome is a solid nanocrystalline material that provides the fundamental structural framework of the system. Calcium phosphate, hydroxyapatite, brushite, and some other ceramic materials have been evaluated as possible core materials due to their crystallinity, surface characteristics, and biocompatibility. The core also serves as a high-energy surface for subsequent coating with polysaccharide or polyhydroxy carbohydrate

materials.[1,18]

7.2 Carbohydrate Layer

The core is coated with a thin layer of a polyhydroxy carbohydrate such as sucrose, trehalose, or other carbohydrates with similar properties. This layer creates a very hydrated, water-like microenvironment surrounding the core and helps to maintain the stability of the adsorbed therapeutic molecules. In particular, the carbohydrate coating can help to reduce the structural changes associated with dehydration, thereby helping to maintain the conformational stability of bioactive molecules.[1,17]

7.3 Bioactive Drug Layer

The drug or bioactive molecule is adsorbed onto the carbohydrate-coated core and forms the outermost functional layer. Normal adsorption principles apply in this layer; depending on the physicochemical properties of the drug and the coating surface, adsorption may involve ionic, hydrogen-bonding, van der Waals, or other non-covalent interactions. This surface-loading strategy is expected to enhance the exposure of the active molecule and thus complete the three-layered aquasome structure.[1,17]

Nanocrystalline core → Carbohydrate coating layer → Adsorbed drug/bioactive molecule[1,19]

This is the characteristic structural feature of aquasomes, which distinguishes them from many conventional drug-delivery nanocarrier systems.

8. METHOD OF PREPARATION OF AQUASOMES

Aquasomes are typically formulated by a three-stage self-assembly process comprising (i) preparation of the inorganic/ceramic core, (ii) coating of core with a polyhydroxy carbohydrate layer, and (iii) immobilization or adsorption of therapeutic molecule onto the coated surface. The core material and the conditions employed in each stage have an impact on the physicochemical properties and loading capacity of the aquasomes.

8.1 Preparation of the Ceramic Core

The first step of the process is the formation of a nanocrystalline inorganic core. Aquasomes have been prepared with calcium phosphate, hydroxyapatite, brushite, and nanocrystalline carbon/ diamond as the core materials. The core material may be prepared by co-precipitation, selfprecipitation, sonication, plasma condensation, and other similar processes

for creating nanoparticles. Calcium phosphate-densified cores are especially suitable owing to their unique crystallographic structure and biocompatibility.[17,20]

In a typical precipitation-based approach, appropriate calcium and phosphate salts are allowed to react under controlled conditions to produce calcium phosphate particles. The resulting suspension is then sonicated, centrifuged, washed, filtered, and dried to obtain purified particles of the desired size. The conditions will differ depending on whether the target product is brushite, hydroxyapatite, or some other calcium phosphate phase.

8.2 Carbohydrate Coating of the Core

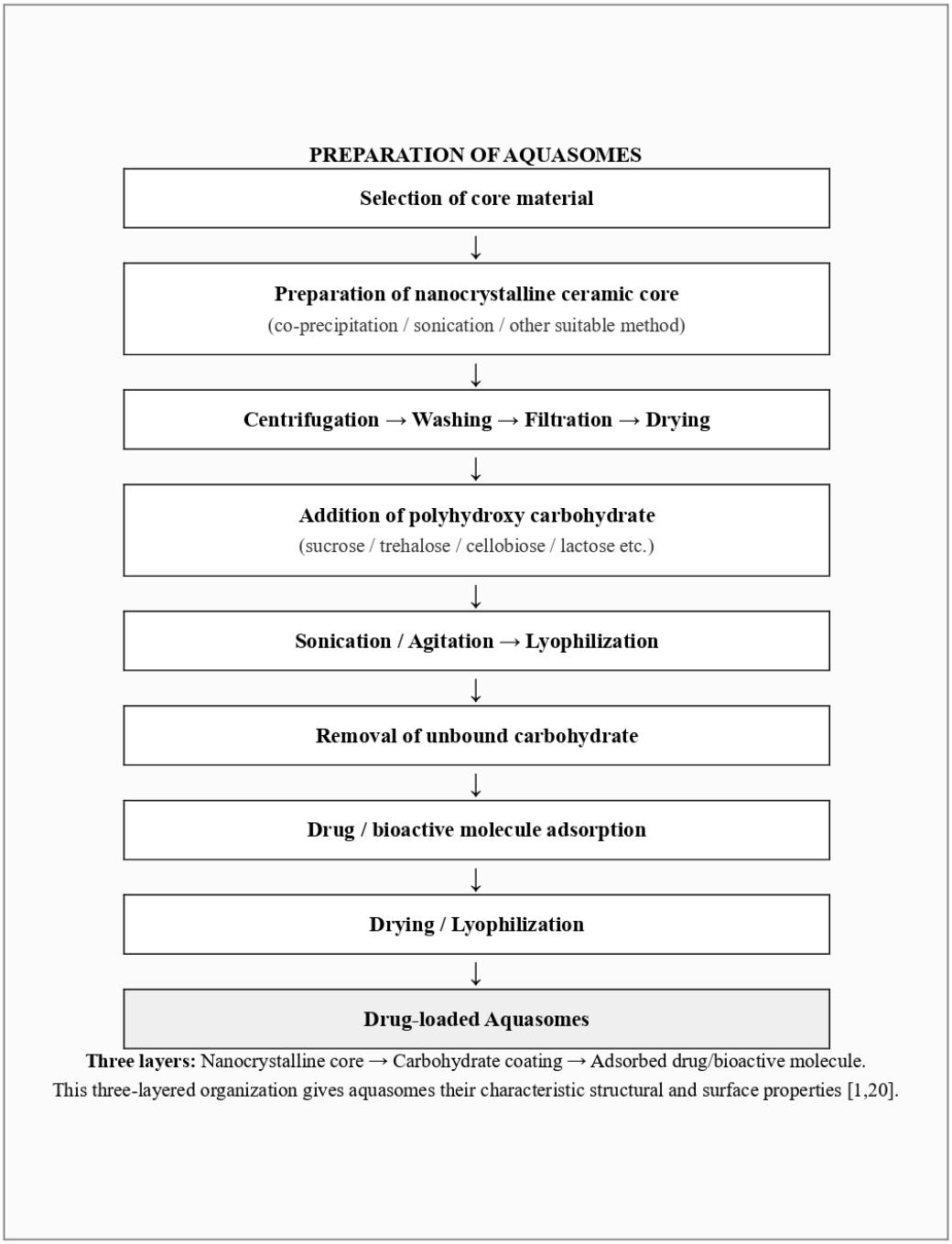
The purified ceramic particles are then coated with a polyhydroxy oligomer/carbohydrate layer. Examples of carbohydrate coating agents include sucrose, trehalose, cellobiose, lactose, citrate, and pyridoxal-5-phosphate. The carbohydrate is dispersed in an aqueous medium together with the ceramic core, generally while being agitated or sonicated, in order to facilitate adsorption onto the surface of the core. It may then be beneficial for the core and carbohydrate to be lyophilized (freeze-thawed and vacuum-dried) in order to enhance adsorption or to form a stable layer, although this is not normally necessary. Unbound carbohydrate can then be removed by means of centrifugation or filtration.[29,37]

The carbohydrate layer is an essential part of aquasomes because it provides a hydrophilic, waterassociated microenvironment around the solid core. Besides the ease of adsorption, the presence of the carbohydrate layer also serves to preserve the stability of sensitive bioactive molecules as it reduces unspecific interaction with the inorganic surface and also protects stabilized molecules from any possible dehydration.

8.3 Adsorption of the Drug

The last stage of the procedure is the adsorption of the drug onto the carbohydrate-coated nanocrystalline core in a suitable drug solution. The drug solution is prepared at a predetermined concentration in an aqueous medium or buffer and the carbohydrate-coated nanocrystalline core is dispersed in it. The distribution of the drug in the dispersant microspheres is achieved by adsorption, which occurs naturally by the suitable intermolecular interaction of the drug and the carbohydrate-coated nanocrystalline core. After drug adsorption, the drug-loaded aquasomes are separated from the dispersant medium and dried or initially lyophilized to yield the final drugloaded aquasome.

Our process of aquasomal formulation results in a three-layer system that features a nanocrystalline core that is coated on its surface with a suitable carbohydrate, and that adsorbs and contains the selected drug or bioactive molecule within or at the surface of this carbohydrate-coated nanocrystalline core.



Three layers: Nanocrystalline core → Carbohydrate coating → Adsorbed drug/bioactive molecule.
This three-layered organization gives aquasomes their characteristic structural and surface properties [1,20].

9. CHARACTERIZATION OF AQUASOMES

The characteristics of aquasomes should be investigated to confirm the formation of the ceramic core, carbohydrate coating and subsequent adsorption of the drug. Characterization

usually involves studies on particle size and morphology, structural characteristics, crystallinity, surface charge, thermal properties, carbohydrate coating, drug-loading efficiency, and in-vitro drug-release characteristics. The specific analytical methods used may vary from aquasome to aquasome depending on the aquasome composition and the therapeutic agent to be loaded.

9.1 Particle Size and Morphological Studies

Particle size and morphology are additional parameters that can affect the physical stability, surface area, drug loading, and biological performance of aquasomes. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are generally used to characterize the shape and surface morphology of the ceramic core, the carbohydrate-coated core, and the drug-loaded aquasomes. Measurement of particle-size distribution may also be performed by dynamic light scattering or photon correlation spectroscopy when the formulation is in dispersion.

SEM provides information about the external morphology and surface characteristics, whereas TEM can provide more detailed information regarding particle dimensions and internal morphology. In an investigation of indomethacin-loaded aquasomes, electron microscopy together with X-ray analysis was used to demonstrate the formation of the calcium phosphate core and the subsequent carbohydrate and drug-associated layers.[20]

9.2 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy is used to investigate the structural characteristics and possible interactions among the ceramic core, carbohydrate coating, and drug. The spectra of the uncoated core, carbohydrate-coated core, pure drug, and drug-loaded aquasomes can be compared to identify characteristic functional groups and changes in their vibrational bands. Generally, the spectra are recorded over an appropriate infrared range, commonly around 4000-400 cm^{-1}. Changes in characteristic peaks or the appearance of additional bands can provide evidence for carbohydrate adsorption and drug association with the coated core.

FTIR analysis is useful in the characterization of drug-loaded aquasomes as it may be used to confirm that the drug is chemically intact and identify possible interactions between the drug and carrier components by detecting functional groups through their characteristic absorption bands in the spectra. Changes in peak position or intensity should be analyzed together with other characterization data and should not be considered alone as proof of chemical

interaction between the drug and components of the formulation.[34]

9.3 X-ray Diffraction (XRD)

X-ray diffraction analysis is used to identify the crystalline or amorphous nature of the components of the aquasome. The diffraction pattern of the ceramic core and drug-loaded formulation can be compared with the diffraction pattern of the corresponding reference materials. The characteristic diffraction peaks may be altered by coating the ceramic core with carbohydrate and by loading the drug into the aquasome. These alterations may reflect changes in crystallinity and/or the physical state of the drug. XRD has also been used to study the formation of calcium phosphate-based aquasomes.[20,34]

9.4 Zeta Potential

Zeta potential is a measure of the surface charge of an aquasome and is a key attribute associated with its colloidal stability. It can be measured by a particle-charge measurement method or electrophoretic light scattering. The surface charge of a particle can be modified by coating it with carbohydrate or by drug adsorption. The zeta potential of the uncoated core, coated core, and drugloaded aquasome can be compared to assess the significance of each step in aquasome formation. A higher magnitude of zeta potential generally indicates greater colloidal stability.[34,39]

9.5 Thermal Analysis

Thermal analysis of the carbohydrate coating, drug, and drug-loaded carbohydrate-coated aquasome can be performed by differential scanning calorimetry (DSC), which provides information on characteristic thermal transitions. The thermal properties of the coating, drug, and aquasomes can also be compared to evaluate changes in the physical state of each component during formulation. DSC can be used to evaluate the glass-transition behavior of carbohydrate-containing systems and to investigate changes in drug-excipient interactions during formulation.

The thermograms of the pure drug and the formulation should be compared to identify the characteristic endothermic or exothermic transitions of each component and to determine whether these transitions are maintained, shifted, broadened, or lost after formulation.

9.6 Carrier Coating Characterization

Carbohydrate deposition onto the carrier can be examined by suitable analytical techniques.

Colorimetric estimation of carbohydrate using the anthrone method can be used to quantify the unbound or residual carbohydrate after coating. Alternatively, the amount of carbohydrate coated onto the ceramic carrier can be estimated by measuring Concanavalin-A-induced aggregation of coated ceramic particles. Changes in surface charge due to carbohydrate adsorption can also be used to support successful coating.[17]

9.7 Drug-Loading Efficiency

Drug-loading efficiency is an important parameter that indicates the amount of drug associated with the carbohydrate-coated ceramic core. A known quantity of coated aquasomes is mixed with the drug solution under predetermined conditions and allowed to adsorb the drug. The particles are separated from the medium, and the unadsorbed drug remaining in the supernatant is quantified using an appropriate analytical method, such as UV-visible spectrophotometry or HPLC.

The drug-loading efficiency can be calculated using the following equation.

Drug Loading Efficiency (%) = &left;[/(Amount of drug adsorbed onto aquasomes) / (Initial amount of drug added)&right;] × 100

Alternatively, when the amount of unadsorbed drug is measured.

Drug Loading Efficiency (%) = &left;[/(Initial amount of drug - Amount of unadsorbed drug) / Initial amount of drug&right;] × 100

The appropriate calculation should be selected according to the experimental design adopted in the study.[20,35]

9.8 In-vitro Drug Release Study

The release pattern of the drug from aquasomes can be estimated using an appropriate technique, such as dissolution or diffusion, under controlled experimental conditions. In this study, a known mass of drug-loaded aquasomes is placed into a suitable release medium, usually maintained at physiological temperature (37 ± 0.5 °C). Samples are withdrawn at predetermined intervals, and the concentration of the released drug is measured using a suitable and validated analytical method. The withdrawn samples are then replaced with an equal volume of fresh medium to maintain sink conditions.

The release data can be further analyzed by fitting them to several established kinetic models, such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, to understand the

probable mechanism and kinetics of drug release. Aquasome formulations may provide controlled drug release depending on their composition, surface characteristics, drug-carrier interactions, and formulation conditions.[27,35]

9.9 Stability Studies

The aim of aquasome stability studies is to assess whether the physicochemical properties of aquasomes remain unaffected during storage under specified conditions. Particle size, zeta potential, drug content, loading efficiency, overall appearance, and drug-release behavior may be evaluated at regular intervals under defined storage conditions.

For aquasomes containing proteins or other sensitive biological molecules, the biological activity or structural integrity of the incorporated molecule may also be evaluated using suitable analytical techniques, such as SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis), where appropriate.[23,39]

10. APPLICATIONS

Aquasomes have attracted considerable interest as a nanocarrier system because their three-layered architecture combines a rigid nanocrystalline core, a carbohydrate-based surface layer, and an adsorbed therapeutic molecule. The carbohydrate coating provides a hydrated environment that can help preserve the structural and functional characteristics of sensitive biomolecules. Consequently, aquasomes have been investigated for the delivery of proteins, peptides, enzymes, antigens, vaccines, genes, and certain conventional drugs.

10.1 Protein and Peptide Delivery

Protein and peptide therapeutics are often associated with poor stability, enzymatic degradation, and loss of biological activity during formulation and administration. Aquasomes can provide a relatively protective surface environment for these molecules through adsorption onto the carbohydrate-coated core. The hydrated carbohydrate layer may help minimize structural alterations and maintain the biological activity of the adsorbed molecules. Therefore, aquasomes have been explored as carriers for proteins and peptides requiring improved stability and controlled delivery.[10,23,34]

10.2 Insulin Delivery

Insulin is one of the extensively investigated biomolecules in aquasome-based delivery. Cherian et al. developed carbohydrate-stabilized calcium phosphate ceramic nanoparticles for

parenteral insulin delivery. In their system, a nanosized calcium phosphate dihydrate core was coated with carbohydrates such as cellobiose, trehalose, or pyridoxal-5-phosphate, followed by adsorption of insulin.[17] The formulation demonstrated improved performance compared with conventional insulin solution in an animal study, supporting the potential of aquasomes for preserving and delivering insulin.

10.3 Enzyme Delivery

Aquasomes have also been investigated for the delivery of therapeutic enzymes. Enzymes are highly sensitive to environmental conditions and may undergo conformational changes that reduce their biological activity. The hydrated carbohydrate coating of aquasomes can provide a favorable microenvironment around the adsorbed enzyme. Studies have therefore explored aquasomes for enzymes such as serratiopeptidase and DNase, indicating their potential for maintaining enzyme activity and improving therapeutic performance.[40]

10.4 Antigen and Vaccine Delivery

Aquasomes can be used as carriers for antigens because their surface can accommodate biomolecules through adsorption and non-covalent interactions. The carbohydrate-coated surface may help preserve the structural characteristics of antigenic molecules while facilitating their presentation to the immune system. This has led to investigations of aquasomes as potential vaccine delivery systems, particularly for protein and viral antigens. Their particulate nature may also contribute to enhanced interaction with antigen-presenting cells and stimulation of immune responses.[13,21,24]

10.5 Gene Delivery

The potential of aquasomes has also been investigated in the delivery of genetic materials. Their multilayered structure can be modified to accommodate nucleic-acid-based therapeutic molecules. Aquasome systems have been explored for the delivery of genes and viral vectors, with the objective of improving protection and facilitating intracellular transport. Such applications indicate that aquasomes may have future utility in gene-based therapeutic approaches.[25]

10.6 Delivery of Conventional Drugs

Although aquasomes were initially explored mainly for sensitive biological molecules, their application has also been extended to conventional pharmaceutical drugs. The surface characteristics of the carbohydrate-coated ceramic core can facilitate adsorption of selected

drug molecules. For example, indomethacin-loaded aquasomes based on a calcium phosphate core coated with lactose have been investigated, demonstrating the possibility of using aquasomes for poorly soluble drug delivery.[20,27,35]

10.7 Oxygen Transport

Aquasomes have been investigated as artificial oxygen-carrying systems using hemoglobin as the therapeutic cargo. In these systems, hemoglobin can be associated with carbohydrate-coated ceramic cores. Such formulations are intended to preserve the functional characteristics of hemoglobin and facilitate oxygen transport. This application highlights the broader potential of aquasomes beyond conventional drug delivery.[18,36]

10.8 Topical and Cosmetic Applications

The hydrated surface characteristics of aquasomes have also generated interest in topical and cosmetic formulations. Their ability to maintain a water-rich microenvironment may be useful for delivering active ingredients to the skin. Consequently, aquasome-based systems have been proposed for applications involving skin hydration and delivery of cosmetic or dermatological actives. Further research is required to establish their long-term stability, safety, and clinical effectiveness.[15,16]

11. CONCLUSION

Aquasomes represent a distinctive class of self-assembled nanocarriers characterized by a nanocrystalline core, a carbohydrate coating, and an adsorbed therapeutic molecule. Their major advantage lies in the ability of the hydrated carbohydrate layer to provide a favorable environment for sensitive therapeutic substances while maintaining the structural characteristics of the loaded molecules. This feature makes aquasomes particularly interesting for the delivery of proteins, peptides, enzymes, antigens, vaccines, and other biologically active compounds.

Research conducted so far has demonstrated the potential of aquasomes in insulin delivery, enzyme delivery, antigen and vaccine delivery, gene delivery, oxygen transport, and delivery of selected conventional drugs. The system may also offer advantages such as controlled drug release, improved stability of sensitive molecules, and the possibility of surface modification for specific delivery applications.

Despite these promising characteristics, aquasomes remain primarily an investigational

drugdelivery platform. Important challenges include optimization of formulation variables, drug-loading capacity, physical and chemical stability, reproducibility of preparation, in vivo behavior, toxicity evaluation, and large-scale manufacturing. Therefore, systematic pharmacokinetic, toxicological, and clinical studies are required before the technology can be widely translated into pharmaceutical products.[3,39]

Overall, aquasomes provide an interesting approach for the development of advanced nanocarriers, particularly when preservation of the structural integrity and biological activity of the therapeutic molecule is an important formulation requirement. Continued research and optimization may expand their applicability to both biological and selected conventional therapeutic agents.

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