International Journal of Pharmacy and Pharmaceutical Research (IJPPR)

Volume 31, Issue 1, January 2025 ijppr.humanjournals.com ISSN: 2349-7203

A Review on Aquasomes: A Novel Approach in Drug Delivery System for Poorly Water-Soluble Drug

Praveen Kumar N*, Daisy Chella Kumari S, Abinaya S, Theyaneshwaran P, Sandhiya M

*Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai- 600 003 India.

Received: 2025-1-07 Revised: 2025-1-19 Accepted: 2025-1-25

ABSTRACT

Nanobiotechnology has been a cutting-edge strategy for medications that are difficult to provide in traditional dosage forms throughout the past few decades. Aquasomes, liposomes, niosomes, nanoparticles, and quantum dots are a few of the main varieties of nano-biotechnologically produced carrier systems. One innovative method and great option for medication administration is the use of aquasomes, which are self-assembling nanoparticulate carriers. Aquasomes proven to be an important drug delivery mechanism in the creation of ceramic nanoparticles. Aquasomes consist of a solid crystalline core covered in three layers of carbohydrates that are used to adsorb physiologically active medicament molecules. While the polyhydroxy oligomer covering protects against dehydration and gives stability to active medicinal molecules, the solid core provides structural stability. With a length ranging from 150 to 1500μm, microneedles are a potential transdermal technique that improves medication transport across the skin by generating micron-sized holes in the epidermis. Aquasomes can be used to deliver insulin, haemoglobin, serratiopeptidase, and poorly water-soluble medications. An overview of aquasomes, their functions, the role of carbohydrates and core, their production techniques, a characterisation study, and applications are all included in this review paper.

Keywords: Nanobiotechnology, Aquasomes, Self assembled Carrier system, Nanoparticles, Novel drug delivery.

1. INTRODUCTION:

Aquasomes are nanoparticulate carrier systems, but they are three-layered self-assembled structures rather than just simple nanoparticles. They are made of a solid phase nano-crystalline core covered in an oligomeric film, to which biochemically active molecules are adsorbed either completely or partially [1]. Nir Kossovsky initially created aquasome in 1995. The term "aquasome" refers to "bodies of water" since it is derived from two words: "aqua" means "water" and "somes" means "body [2]. For bioactive compounds like peptides, proteins, hormones, antigens, and genes to target the locations, aquasomes are an effective carrier mechanism because it exhibits a high degree of surface exposure while maintaining conformal integrity [3].

Aquasomes' water-like characteristics allow them to keep and protect the delicate molecules.

Carbohydrates and techniques such as co-polymerization, diffusion, or adsorption stabilise the ceramic core aquasomes; pharmacologically active molecules are added to the carbohydrate surfaces of prepared nanoparticles. Carbohydrates are crucial in this and function as a natural stabiliser. The sugar coating creates a glassy molecular layer that adsorbs therapeutic proteins or tiny compounds without changing their three-dimensional conformations [4]. Aquasomes are made up of three layers: a solid crystalline core, a coat of carbohydrates, and the active medication, which self-assembles by means of non-covalent bonding [5].

Aqueous particle s range in size from 60 to 300 nm. For the development of aquasomes, three primary types of core materials are primarily utilised: tin oxide, brushite (calcium phosphate dihydrate), and nanocrystalline carbon ceramics (diamonds). For medications with issues like inadequate bioavailability, strong adverse effects, physical and chemical instability, and poor delivery routes, aquasomes offer an appealing mechanism of delivery [6].

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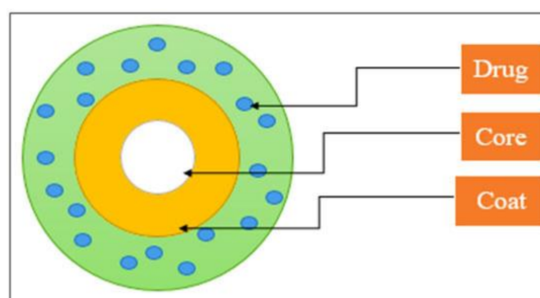

Figure 1: Schematic diagram of Aquasome. It has 3 layers. 1. Solid Crystalline Core 2. Polyhydroxy oligomer coat 3. Bioactive molecules.

2. Properties:

The platform that aquasomes' water-like properties offer for maintaining the biochemical stability and structural integrity of bioactives. The surface chemistry of aquasomes regulates their mode of action. Aquasomes use a slow, sustained release mechanism, molecule shielding, and targeted delivery to deliver material[7].Aquasomes are resistant to degradation by various environmental factors and the reticuloendothelial system because of their size and because of their huge size and active surface, aquasomes can be effectively loaded with a significant amount of agents via entropic, vanderwaals, and ionic forces [5,8].Using aquasomes as a carrier also protects the medication, antigen, or protein from high pH levels and enzymatic breakdown, necessitating smaller dosages [9].Particle size, morphology, and structural analysis are the primary characteristics of aquasomes. These are assessed using transmission electron microscopy, scanning electron microscopy, and X-ray powder diffractometry [5].

3. Principle of self-assembly:

3.1. Group interaction between charged: In addition to performing a role in the balancing out of the tertiary constructions of proteins, the affiliation of charged gatherings such as amino, sulfate, carboxyl, and phosphate bunch works with the long reach approach of self-gathering subunits [7].

3.2. Hydrogen bonding and dehydration effects: Base pair matching and the stabilization of secondary protein structures like beta sheets and alpha helices are aided by hydrogen bonds. The surrounding water molecules are significantly more organized when hydrophilic

molecules form hydrogen bonds with them. In contrast, hydrophobic molecules can organize the moiety by repelling nearby water molecules, even though they are unable to make hydrogen bonds. The surrounding environment becomes less entropy when there is organized water present. Due to its unfavorable thermodynamics, the molecule undergoes dehydration and self-assembly [10].

3.3. Structural stability of protein in biological environment: Determines the hardness and softness of the molecule and the maintenance of internal secondary structures; vanderwaals forces, which are mostly internal to hydrophobic molecules and the interaction between charged groups and hydrogen bonds, largely external to the molecule, are responsible for

these properties. Sufficient softness is provided by these forces, allowing conformation to be maintained during self-assembly, which results in altered biological activity' [5,11].

4. Objectives:

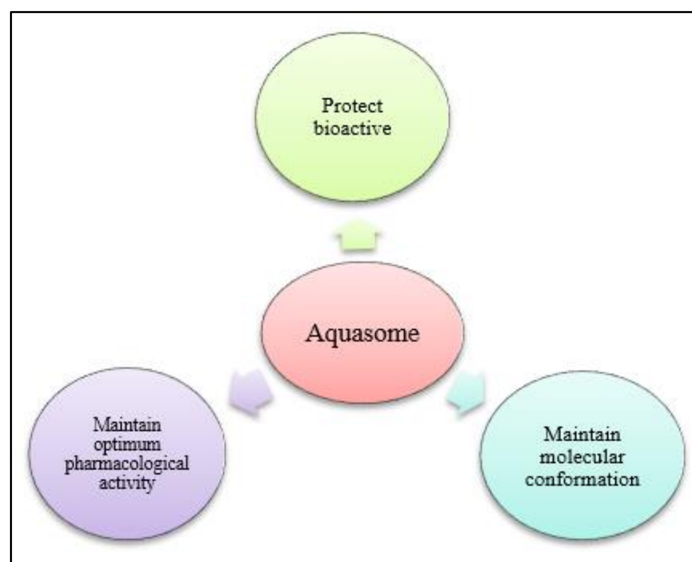

Figure 2: **Objectives of aquasomes**

Aquasomes preserve good pharmacological efficacy and molecular confirmation. Typical characteristics of active molecules include their unique three-dimensional conformation, their ability to move freely in bulk and to rearrange their molecules internally under the influence of other molecules. However, proteins undergo irreversible denaturation upon desiccation, even in unstable aqueous state [5, 12].

The pH, solvents, salts, and temperature of an aqueous solution can all cause denaturation of an active molecule. Under these circumstances, natural stabilizers found in aquasomes, such as polyhydroxy sugars, function as dehydroprotectant, keeping the molecules in their dry, solid state by maintaining a water-like condition [13].

The primary goal of aquasome preparation is to shield bioactive material from changed bodily environments. Because this system acts as a reservoir to release the content in a continuous or pulsatile manner, it reduces the need for different injection schedules [14].

Aquasomes having many layers coupled with biorecognition molecules. For example, nucleic acid, antibodies, and imaging tests. By administering the antigen-adsorbed aquasome vaccine, both humoral and cellular immunity can be induced [15].

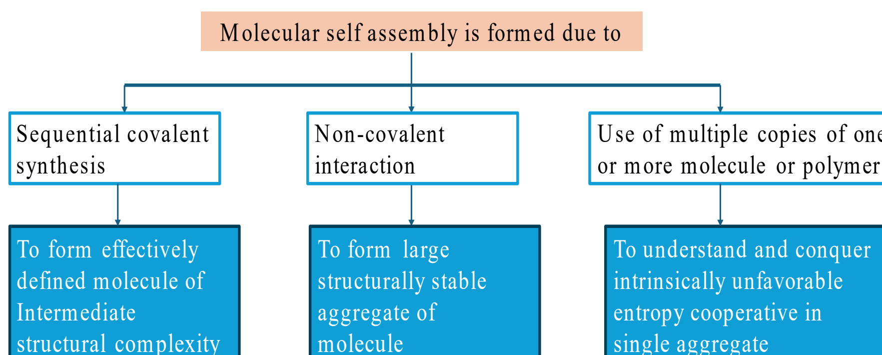

Figure 3: Formation of molecular self-assembly

5. Composition or Materials used:

5.1. Core material: Polymers and ceramics are commonly used core materials. Ceramics that are crystalline, inexpensive, biocompatible, and easily manufactured include tin oxide, brushite (calcium phosphate), and diamond particles. It offers a high level of structural regularity and order. Higher surface energy is yielded by the high degree of organization,

which facilitates the effective binding of carbohydrates onto it. These characteristics make it a strong contender for the formulation of aquasomes.17 Polymers including gelatin, albumin, and acrylate are utilized [16].

5.2. Coating material: The most favored coating materials include citrate, chitosan, cellobiose, sucrose, trehalose, and pyridoxal-5-phosphate. Soft pharmaceuticals cannot change shape when there is a carbohydrate film present as the coating material. By maintaining the molecular conformation of biochemically active molecules, supplying structural integrity, providing a water-like environment for the biochemically active molecules, and safeguarding the three-dimensional conformations of drug molecules, carbohydrates function as a natural stabilizer and dehydroprotectant [17].

5.3. Cellobiose: It is 4-O-beta-D-glucopyranosyl-D-glucopyranose reducing sugar. It is acquired from the partial hydrolysis of cellulose. It protects the drug molecule against the dehydration [15].

5.4. Trehalose: It is a non-reducing sugar that is alpha-D-glucopuyranosyl-alpha-D-glucopyranoside. Additionally, trehalose protects the medication molecule from denaturation and dehydration [18].

5.5. Bioactive molecules: Aquasomes are a suitable fit for medications with the ability to interact with films through ionic and non-covalent interactions [19].

5.6. Chitosan: It is a linear polysaccharide made up of N-acetyl D-glucosamine and β-linked D-glucosamine that are dispersed at random. Crabs, shrimp shells, and insects are the main sources of chitosan. The process of deacetylating chitin yields chitosan, which has the ability to form films. Chitosan has three different types of functional groups: amines, primary and secondary hydroxyl groups. These functional groups serve as a severance agent between medication molecules [20].

6. Role of disaccharides:

The goal of aquasomes is achieved by carbohydrates, one of the three layers of the aquasomes. Proteins' watery structure is preserved during protein dehydration because the hydroxyl groups on oligomers interact with polar and charged protein groups in the same way as they do with water. These hydroxyl group-rich disaccharides aid in replenishing the water surrounding polar residues in proteins, preserving their integrity when water isn't present. A rich hydroxyl component's free bound mobility results in a special hydrogen binding substrate that forms a glassy aqueous state [15,21,22].

7. Method of Preparation:

The preparation of aquasomes is a fairly easy technique that doesn't include any homogenization processes and just requires a small amount of solvent. The three phases in the manufacture of aquasomes—forming the core, coating the core, and immobilizing the therapeutic molecule—follow the idea of self-assembly [23].

Formation of core material: The first step in the formulation of aquasomes is the development of the ceramic core. The method of ceramic core preparation depends on the choice of core materials. These ceramic cores can be built by various processes such as colloidal precipitation, sonication, inverted magnetron sputtering, and plasma condensation etc. In the preparation of core, the most regular material preferred which is ceramic. Two ceramic cores that are generally used diamond and calcium phosphate [24].

A. 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 [25].

B. Self-assembled Nanocrystalline brushite (calcium phosphate dihydrate): Numerous techniques, including co-precipitation, self-precipitation, sonication, and PAMAM approaches, can be used to synthesise it [26].

(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

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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 [26].

(ii) Sonication: The solutions of calcium chloride and disodium hydrogen phosphate were combined and subjected to sonication using an ultrasonic bath. There are equal amounts of each reagents utilised. The temperature was maintained at 4 °C for two hours. Centrifugation is used to remove the ceramic core, which is subsequently cleaned, resuspended in de-ionized water, and filtered. The core material that is kept on the filter paper is gathered and properly dried [26].

(iii) Poly (Amidoamine) PAMAM: To encourage nucleation and crystal formation, PAMAM was dissolved in a pH 7.4 simulated bodily fluid and kept at 37 °C for a week. The pH of the solution was changed by adding the NaOH solution. Deionized water was used to wash the precipitate many times. It was then filtered and let to dry overnight [27].

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

$2Na_2HPO_4 + 3\ CaCl_2 + H_2O \rightarrow Ca_3\ (PO_4)_2 + 4NaCl + 2H_2 + Cl_2 + (O)$ [28].

D. Coating of the core with polyhydroxy oligomer: Coating materials such as cellobiose, citrate, trehalose, pyridoxal 5 phosphate, and sucrose are frequently utilised. 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 unadsorbed carbohydrate is removed [29].

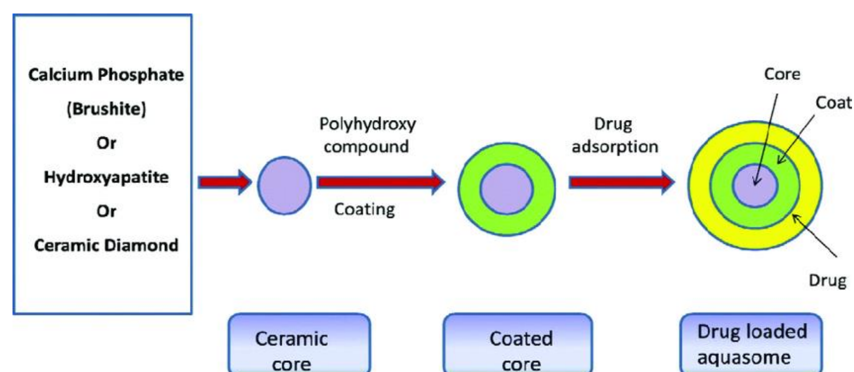

Figure 4: Preparation of aquasome.

E. Immobilization of drug molecule: The last stage in the creation of aquasomes is the partial adsorption of the medication onto coated particles. A drug solution with a known concentration is made in an appropriate pH buffer. The coated particles are mixed and left in a low temperature dispersion for the purpose of loading drugs or lyophilizing the mixture. Drug-loaded formulation was eventually obtained, and it was further characterised using a variety of methods [9,10,30].

8. Evaluation parameters of Aquasomes:

Aquasomes are primarily assessed and identified based on the diverse morphological and structural characteristics of their polyhydroxy oligomer covering structure and core.

A. Evaluation parameter for core material:

1. Size distribution: Particle size distribution and morphological examination are done using transmission electron microscopy (TEM) and scanning electron microscopy (SEM) methods. In the SEM, samples were put on the surface of a gold-coated specimen stub using double-sided sticky tape to measure the particle size; in the TEM, the particle size is measured following phosphotungstic acid negative staining. Using these methods, coated core and drug loaded also examined [31].

2. Characterization (FTIR): To determine structural analysis, Fourier transform infrared spectroscopy, or FT-IR, is utilised. The technique of potassium bromide sample disc is applied. By obtaining their infrared spectra in the wavenumber range of 4000 - 400

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cm1, the core and coated core may both be examined. Observed characteristic peaks match up with reference peaks. Using this method, the drug's stability inside the formulate on may also be assessed [32].

3. X-ray diffraction: This technique is used to investigate whether a material is crystalline or amorphous. In a wide-angle X-ray diffractometer, copper (Cu) and potassium (K) radiation are applied to the hydroxyapatite ceramic core to examine it. The interpretations are then based on a comparison between the sample's x-ray diffraction pattern and the standard diffractogram. A study found that whereas lactose and calcium phosphate cores separately produced identical, sharp peaks for crystalline peaks, peaks representing an amorphous structure were seen when carbohydrate-coated cores were examined. It might be the cause of the coating process, which involves solubilizing a carbohydrate insolvent and then lyophilizing the dried product to cover the core's surface, as well as the saturation of the carbohydrate [7,33].

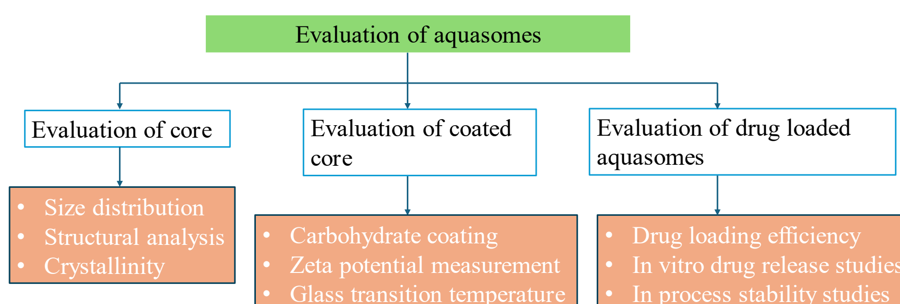

Figure 5: Evaluation parameter of aquasomes.

B. Evaluation parameter for coated core:

1. Carbohydrate coating: The Concanavalin A-induced Aggregation technique, the Anthrone reaction, and the Phenol Sulfuric Acid method can all be used to prove that sugar has been coated over the ceramic core.

2. Zeta potential measurement: This method determines the sugar's adsorption over the core and predicts the stability of storage by measuring the potential. According to some research, the zeta potential value decreased more as the saturation process by carbohydrates on the hydroxyapatite core increased.

3. Glass transition temperature: The glass transition temperature of proteins and carbohydrates was examined using differential scanning calorimetry (DSC). The impact of carbohydrates on the drug-loaded aquasomes was investigated using DSC.A DSC analyser may be used to monitor the temperature change that occurs when glass melts and turns into rubber [34,35,36].

C. Evaluation parameter of drug-loaded aquasomes:

1. Drug loading efficiency: This is carried out in order to assess the quantity of medication bound to the aquasome surface. The aquasome formulation without the drug can be incubated for 24 hours at 4°C in a solution containing a known concentration of the drug to determine the drug loading. The supernatant is then separated in a chilled centrifuge using high-speed centrifugation for one hour at a low temperature. After filtering, the clear extractive supernatant is examined using a UV spectrophotometer to determine the amount of free medicine. The following formula is used to compute the drug payload/drug loading [37,38].

$$\%\ \text{Entrapment efficiency} = \frac{\text{Actual drug loaded}}{\text{Theorotical drug loaded}} \times 100$$

$$\%\ \text{Drug loading} = \frac{\text{weight of total added drug} - \text{weight of unentrapped drug}}{\text{weight of aquasome}} \times 100$$

2. In vitro drug release studies: The purpose of the in vitro release kinetics studies is to examine the drug's release pattern from the aquasomes. A known amount of drug-loaded aquasomes should be continuously stirred at 37°C in a pH-appropriate buffer.

Occasionally, samples are removed and quickly centrifuged for a certain amount of time. Equivalent medium quantities must be added after every withdrawal. The amount of medication released is then estimated by analysing the supernatants [39,40].

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) [41].

9. Advantages:

The use of aquasomes as a reservoir to release molecules either continuously eliminates the need for multiple injection schedules [42]. Aquasome-based vaccines provide numerous benefits as a vaccine delivery system. Antigens adsorbed on aquasomes can elicit cellular and humoral immune responses [41]. Aquasomes enhance the therapeutic effectiveness of pharmaceutically active agents and protect them from phagocytosis and degradation [41].

Aquasome-based vaccines are a novel carrier for enzymes like DNase and pigment/dyes. Multi-layered aquasomes conjugated with biorecognition molecules like antibodies, nucleic acids, peptides which are known as biological labels can be used for various imaging tests [42].

10. Applications:

1. Aquasomes are used as vaccines to spread viruses including the Human Immunodeficiency Virus and the Epstein-Barr Virus. For the vaccination treatment to elicit the correct antibodies, conformationally complex target molecules must act as a trigger.

2. Using aquasomes as a red blood cell replacement, where haemoglobin is bound to the oligomer surface due to its conformational sensitivity to oxygen release. The researchers found that this reduces toxicity, achieves an 80% haemoglobin concentration, and makes blood in a non-linear way that is similar to that of regular blood cells.

3. Targeted intracellular gene therapy has been successfully employed with aquasomes, a five-layered composition made up of a ceramic heart, polyoxyoligomeric film, therapeutic gene section, extra carbohydrate film, and targeting layer of conformationally conserved viral membrane protein.

4. Aquasomes for medicine distribution, such as insulin, were developed because drug action is conformationally specific. Bioactivity was recovered and activity enhanced by 60% when compared to i.v. treatment, with no verified toxicity.

5. Because enzyme activity is affected by molecular conformation, and pigment aesthetic characteristics are affected by molecular conformation, aquasomes are often utilised to transport enzymes such as DNase and pigments/dye [43-47].

Table 1: Aquasomes application in drug delivery

Sl No.	API/Bio-actives	Application
	Dithranol	Treatment of psoriasis
	Insulin	Blood Sugar regulation
	Etoposide	Anticancer targeting
	Bromelain	multi-particulate drug carrier for oral delivery
	Hepatitis B Vaccine	Antigen for prevention of jaundice
	Haemoglobin	carrier for oxygen
	Merozoite Surface Protein-119 (MSP-119)	To improve immune adjuvant property for antimalarial antigen
	Polypeptide-k	Blood sugar regulation
	Pimozide Piroxicam Lornoxicam Indomethacin	To enhance the aqueous solubility on oral administration and improve their efficacy

11. Limitations:

The aquasome systems' utility in medication delivery is impacted by a few constraints. Inadequate and insufficiently strong medication adsorption might lead to rupture release, which can be hazardous. Aquasomes are non-specifically taken up by opsonization after entering the systemic circulation, and phagocytic clearance may take place. This can be avoided by coating its surface with a substance such as polyethylene glycol (PEG), which inhibits opsonin binding through steric hindrance. It also raises concerns about safety, biocompatibility, and stability. Size, shape, and surface charge are examples of surface characteristics that have a significant impact on stability, drug release, and targeting abilities [48,49].

12. Fate of aquasomes:

The drug's pharmacological or biological activity can be completed instantly because self-assembled aquasomes are biodegradable nanoparticles that accumulate more in the liver and muscles. In vivo studies predict that monocytes and multicellular cells called osteoclasts will biodegrade ceramic because they will intervene first at the biomaterial implantation site during an inflammatory reaction. Two types of phagocytosis processes were observed when cells come into contact with biomaterial: either calcium phosphate crystals were taken up alone and then dissolved in the cytoplasm after the phagosome membrane disappeared or dissolution occurred after the biomaterial was incorporated. Phagocytosis of calcium phosphate coincided with autophagy and the deposition of residual bodies in the cell [50].

13. Conclusion:

Pharmaceutical scientists now have new optimism for the delivery of a wide range of bioactive compounds and the successful treatment of a variety of diseases due to the aquasomes-based technique.

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How to cite this article:
Praveen Kumar N et al. Ijppr.Human, 2025; Vol. 31 (1): 178-187.

Conflict of Interest Statement: All authors have nothing else to disclose.

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