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Aquasomes: A Promising Delivery Systems for Poorly Soluble Bioactives

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Abstract

Aquasomes are considered an excellent and efficient carrier system for the transport of drugs or biochemically active long chain macromolecules such as proteins and peptides, various hormones, antigens, enzymes, and genes in the recently burgeoning field of nanobiotechnology research. These are three-layer self-collecting structures composed of an oligomeric film covering a strong stage nanocrystalline centre to which biochemically dynamic particles adhere to, independent of changes in the environment and which self-assembles through non-covalent or ionic connections. Aquasomes are circular particles, 60–300 nm in size, that are used to deliver antigens and medications. The structural stability is provided by the solid core, while the active drug molecules are stabilized and protected from dehydration by the polyhydroxy oligomer covering. The most common way to distribute aquasome formulations is parenterally, however recent research indicates that there may be additional, oral, ways as well. A combination of targeted molecular shielding and prolonged release mechanism is used by aquasome to deliver their bioactive chemicals. The present paper offers an overview of the aquasome as a potentially useful medication delivery technique. It covers every facet of aquasome, such as their structure, the processes for preparing them, ways to characterize them, and medical uses as a drug delivery system.

Keywords: Aquasomes, Self-assembly, Ceramic Core, Coating material, Bioactive material, Characterization, Applications.

INTRODUCTION

The last several years have seen the development of innovative technologies that enable the functionalization of pharmaceuticals into nanoparticles with a variety of properties. This has altered the way that drugs are delivered, particularly in terms of targeted and regulated pharmacological responses. When compared to conventional dosage forms, the nanoparticulate drug delivery system offers several advantages, including better drug loading and delivery, targeted distribution of the medication to the site of action, relatively few adverse effects, and the delivery of poorly soluble medicines. Researchers face many difficulties while developing nanoparticles, including incorporating polymers, ensuring that solvents and other materials work effectively and additionally making assured polymers and copolymers function effectively with drugs and biological fluids (M Mohan *et al.,* 2021; Ibrahim Khan *et al.,* 2019).

Nir Kossovsky created aquasome for the first time in 1995. The term "aquasome," which meaning "bodies of water," is formed from words: "aqua" which means water and "somes," which means body. Aquasomes are nanoparticulate carrier systems; however, they are three layered self-assembled structures rather than simple nanoparticles (Domenico *et al.,* 2023; K Samson 2021). They are made of a solid phase nanocrystalline core (ceramic core) covered in a carbohydrate film, onto which biochemically active molecules are adsorbed, either altered or not by ionic and covalent bonds (Gulati *et al.,* 2015). Their water-like characteristics shield and preserve delicate biological molecules, and they are utilized to target bioactive molecules like peptide, proteins, hormones, enzymes, antigens, and genes to specific parts by preserving quality of conformation and an elevated level of surface exposure (Sanjay *et al.,* 2012). The unique features of aquasome involve retaining oxygen transport, shielding the drug antigen, preserving the biological and therapeutic action of bioactive substances, and enhancing the low solubility of aqueous soluble drugs. Ceramic aquasomes are stabilized by carbohydrate by the method of co-polymerization, diffusion, or adsorption approaches (Sachin *et al.,* 2020).

Principle of self-assembly:

Interactions of charged groups, dehydration effects, and structural stability, fundamentally regulate the process by which macromolecules self-assemble in a liquid medium, whether in the course of naturally occurring biochemistry or the development of intelligent nanostructured compounds (Ajay *et al.*, 2021).

Interaction between charged groups**:** Amino, carboxyl, sulfate, and phosphate groups interact to support the long-term strategy of self-assembling units.

Hydrogen groups and dehydration effect**:** The surrounding water molecules benefit greatly from the order created by hydrophilic molecules that form hydrogen bonds. Hydrophobic molecules' propensity to break down water aids in moiety organization in relation to its surroundings since they are unable to form hydrogen bonds. Because structured water reduces entropy and is thermodynamically unfavourable, the molecule becomes dehydrated and self-assembles.

Structural Stability**:** A key component in keeping the molecule in a dry condition is the ability of carbohydrates to prevent dehydration. The interplay of protein and carbohydrates is also influenced by van der Waals forces, which are typically internal to the molecule. Because it's function as a natural stabilizer and dehydro-protectant, carbohydrate keeps proteins structurally stable by preventing denaturation (Ajay *et al.*, 2021; Shailender *et al.*, 2022).

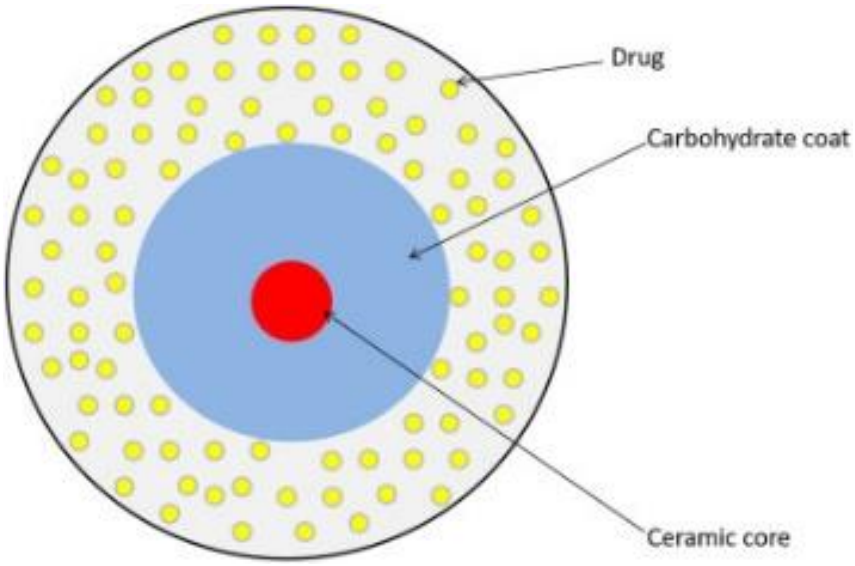

Fig-1: Structure of Aquasome

OBJECTIVES

1. Bioactives are shielded by aquasomes. For the same reason, many alternative carriers such as liposomes and prodrugs are investigated; nevertheless, it is discovered that these are vulnerable to unfavourable drug-carrier interaction. In this situation, aquasomes prove to be a noteworthy carrier because their carbohydrate covering prevents the medication and solid carrier from denaturing destructively (Suresh *et al.*, 2015).
2. Aquasomes also preserve good pharmacological efficacy and molecular confirmation. Features like unique three-dimensional conformation, freedom of bulk movement, and internal molecular rearrangement influenced by molecular interactions are typically seen in active molecules (Suresh *et al.*, 2015).

1.2 PROPERTIES

1. Since aquasomes are nanoparticles, considerable quantities of bioactive material can be placed onto their significant surface area. They function as drug release reservoirs, releasing drugs either continuously or intermittently (Marwa *et al.*, 2020).
2. Aquasomes' method of action is controlled by their surface chemistry. These involve a sustained release mechanism, molecule shielding, and targeted delivery to distribute material.
3. The bioactive compounds are preserved by their water-like qualities (Patel *et al.*, 2012).

1.3 ADVANTAGES

1. Enhance bioavailability of poorly soluble drugs
2. Both hydrophilic and hydrophobic drugs can be incorporated
3. Improved existence of drug in the systemic circulation (Rounak *et al.*, 2023).

STRUCTURE OF AQUASOME

In order to create aquasome, coating material containing particles coated with carbohydrate and drugs bound in coated particles are used.

1. **Core Material:** Acrylates, albumin, and gelatine are examples of polymers that are

utilized, while diamond (a ceramic with nano-crystalline carbon), calcium phosphate, and tin oxide are examples of ceramic materials. Since, ceramics are crystalline by nature, they offer a great degree of structural regularity and order. The primary component of aquasomes, calcium phosphate, decomposes naturally. The biodegradation of calcium phosphate occurs inside the body and is carried out by monocytes and multicellular cells called osteoclasts. Ceramics are inexpensive, easily produced, biocompatible, and naturally biodegradable. It is therefore a strong candidate for the formation of aquasomes and their use in administering drugs (Sachin *et al.,* 2020).

2. **Coating Material:** By maintaining the structural integrity of biochemically active molecules, supplying a water-like environment, securing the three-dimensional conformations of drug molecules, and maintaining the molecular conformation of those molecules, carbohydrates function as a natural stabilizer and dehydro-protectant. Most popular coating materials are citrate, chitosan, cellobiose, sucrose, lactose, trehalose, and pyridoxal-5-phosphate. Soft medications won't alter their form when there is a covering made of carbohydrate film.
3. **Bioactive Substances:** This system incorporates biochemically active compounds through adsorption via ionic and non-covalent interactions (Shailender *et al.,* 2022).

Role of Disaccharides:

The hydroxyl molecule on the carbohydrate preserves the structure of the watery proteins after dehydration by interacting with the polarised and cationic groups in the proteins in a manner similar to that of water atoms alone. These disaccharides' many hydroxyls' groups aid in resupplying water to proteins' polar residues so that they maintain their strength when water is restricted (Sachin *et al.,* 2020; Sritoma *et al*., 2018).

STRATEGIES FOR AQUASOME PREPARATION

1. Precisely connected, precisely formed, and precisely shaped clusters of bonded covalent atoms
2. Covalent polymerization is a technique for creating molecules with a high molecular weight and a low weight that can interact with itself to form molecules made up of several covalently bonded monomers.
3. Self-organizing synthesis requires weaker, lesser directed bonds, as those in hydrogen, ionic, and Vander Waals bonds. True nanostructures arise when molecules rearrange themselves to reach the temperature-dependent limit (Amol D *et al*., 2011).

PREPARATION METHODS

The general process is to build an inorganic core, cover it with carbohydrate to create a polyhydroxylated core, and then load the model drug into the core. The aquasomes are made in three stages: core preparation, carbohydrate coating, and drug immobilization—all based on the self-assembly concept.

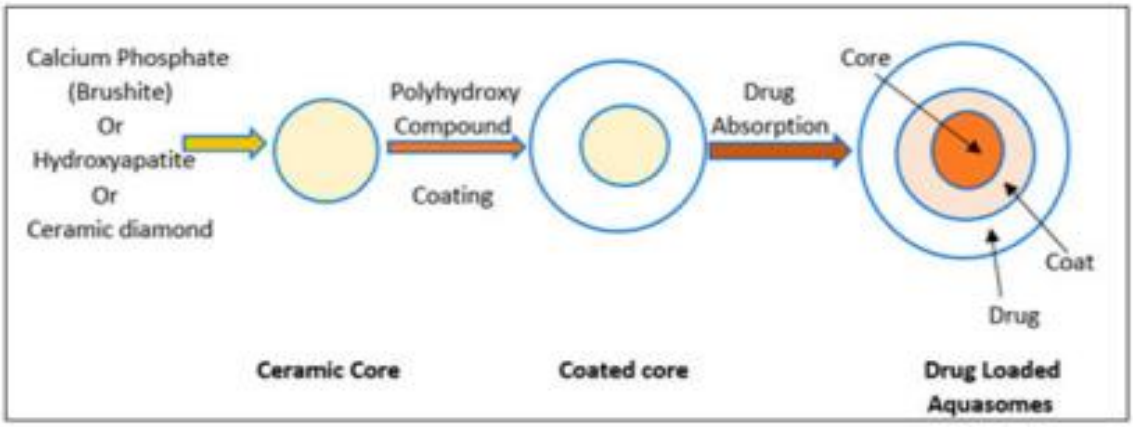

Fig-2: Preparation of Aquasome

1. Preparation of inorganic core

The type of core to be utilized determines the core preparation process. Typically, the core materials employed include hydroxyapatite, calcium phosphate, carbon ceramic (diamond), and nanocrystalline tin oxide. Hydroxyapatite and nanocrystalline calcium phosphate are two of these elements that are commonly used as aquasome core materials. These ceramic cores can be made using a variety of methods, including ultrasound treatment, colloidal precipitation, plasma condensation, and reverse magnetron-based flaring.

a. Synthesis of Tin Oxide Nanocrystal Core:

Reactive magnetron sputtering with direct current is one method of synthesis. High grade tin is extruded from a 3-inch diameter and then exposed to a

elevated-pressure of argon and oxygen combination. Nitrogen was used to chill ultrafine particles that were gaseously placed on a copper tube to 77 K (Sachin *et al.,* 2020; Sritoma *et al.,* 2018, Jitendra *et al.,* 2018).

b. Calcium phosphate dihydrate Synthesis:

It can be produced via a variety of techniques, including PAMAM approaches, sonication, co-precipitation, and self-precipitation.

i. **Co-precipitation:** The calcium nitrate solution is continuously stirred while a dropwise addition of diammonium hydrogen phosphate solution is made. The temperature is maintained using a charge funnel, thermometer, and reflux condensate. Using ammonia solution, the pH of calcium nitrate kept between 8 and 10. Magnetic stirring is used to stir the mixture in the forementioned 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 (Vishwas *et al.*, 2023; Srivani *et al.*, 2012; Irma Rojas *et al.,* 2007) $(NH_4)_2\ HPO_4$ +3Ca $(NO_3)_2 \rightarrow Ca_3(PO)_4 + 6NH_4\ NO_3 + H_3PO_4$

ii. **Sonication Method:** This procedure involves precisely measuring and thoroughly mixing 50 ml of distilled water with calcium chloride and disodium hydrogen phosphate. Temperature was kept at 4°C after mixing using an ultrasonic bath for 22 minutes of sonication. In fifteen minutes, the ceramic core is manufactured, isolate by centrifugation, and the core is cleaned with distilled water before being filtered through tiny particles. After gathering the particles on the surface, the solution is filtered, and it is subsequently dried at a temperature of 70°C in a hot air oven. The ceramic core that is frequently utilized in diamond and calcium phosphate particles

iii. **PAMAM:** PAMAM dissolves in simulated bodily fluid and is kept at pH 7.4 in a solution of poly (amidoamine), which is used to make calcium carbonate. After one week at 37°C to encourage the development of crystals, the pH of the solution was corrected by adding NaOH solution. Precipitate cores forms after which they are filtered and cleaned with water. The discharge is dried using hot air oven and then refrigerated for an entire night (Irma Rojas *et al.,* 2007)

c. Nanocrystalline carbon ceramic, diamond particle:

Following sonication and ultra-cleaning, these ceramic materials can also be utilized for core production (Jadhav *et al.,* 2022).

2. Carbohydrate Coating

It is possible to coat carbohydrates by nonsolvent addition or adsorption by active incubation.

The process of coating involves inserting carbohydrates into a mixture of core in water while it is being sonicated. In addition, it undergoes lyophilization in order to facilitate the irreversible adsorption of carbohydrates onto the ceramic surface. On studies, it has been established that the drug absorption efficiency is facilitated by the polysaccharide layer on the ceramic core. Sugars that are rapidly desorbing are eliminated through ultra-filtration of stir cells. Common materials include trehalose, cellobiose, citrate, pyridoxal-5-phosphate, sucrose, and lactose (Sachin *et al.,* 2020; Jadhav *et al.,* 2022).

Quantification of carbohydrate coating can be done by using Anthrone reagent and phenol sulfuric acid method (Pavani vengala *et al.,* 2016; Pavani vengala *et al*., 2017).

3. Immobilization of drug

When the coated particles are dissolved into a drug solution made in the appropriate pH buffer, the drug is adsorbed onto the particles and loaded onto them. To obtain an aquasome that is loaded with medication, this mixture is either refrigerated for an overnight period or lyophilized (Vishwas *et al.,* 2023; Pavani vengala *et al.,* 2013).

CHARACTERIZATION OF AQUASOMES

1. FTIR Analysis:

The confirmation of drug, ceramic core, sugar coated core and drug loading can be confirmed using FTIR spectra. The compatibility between drug and excipients can be assessed using FTIR analysis (Pavani vengala *et al.,* 2013).

2. Particle Size and Zeta Potential Analysis:

The aquasomes' size and zeta potential were assessed at 25°C using disposable sizing cuvettes and a zetasizer (Malvern Instruments, UK). For the purpose of the particle size analysis, a 1 ml sample was taken, and each sample was taken in three duplicates. To check the performance of the instrument, polystyrene beads were employed as a reference. A measure of homogeneity known as the polydispersity index (PI) was established. A homogenous population is indicated by small values of PI (<1) (Abhilash *et al.,* 2018).

3. Morphological Studies:

Images of secondary electrons in a SEM and TEM were used to determine the shape and size distribution (Irma Rojas *et al.,* 2007; Akshay *et al.,* 2020).

4. Differential Scanning Colorimetry:

A thermal study was performed on the formulations using a differential scanning calorimeter. Samples were heated from different temperature ranges (Sritoma *et al.,* 2020).

5. X-ray diffraction study (XRD):

Using an X-ray diffractometer, an XRD investigation was conducted to examine the structural nature of extract-loaded nanoparticles (Sritoma *et al.*, 2020).

6. Drug Loading Efficiency:

This is carried out in order to assess the quantity of medication bound to the aquasome surface. The drug charge is calculated by immersing the product in the absence of medication for 24 hours at 4°C at an established amount of the solution containing the medication. After that, the supernatant is separated for an hour at a low temperature in a chilled centrifuge. After filtering the clear extractive supernatant, the amount of free medication is measured using a UV spectrophotometer (Nikhil Shrivastava *et al.*, 2023).

$$\textit{Drug Loading efficiency (\%)} = \frac{\textit{Actual drug content}}{\textit{Theoretical drug content}} * \mathbf{100}$$

7. *In vitro* dissolution study:

To further understand extract release from formulation over time, an in vitro release study was conducted. To study drugs release, several dissolving media were used, depending on the substance (Nikhil Shrivastava *et al.*, 2023).

APPLICATIONS

1. Enzyme delivery:

For the purpose of administering the acid-labile enzyme serratio-peptidase orally, Rawat *et al*., created a nanosized ceramic core-based system. The enzyme was synthesized by colloidal precipitation under sonication at room temperature and coated with chitosan under continuous stirring (Manju Rawat *et al.*, 2008).

2. Insulin Delivery:

Albino rats were used to evaluate the in vivo activity of insulin aquasome formulations. Particles coated with pyridoxal-5-phosphate were shown to be more successful in lowering glucose levels than those coated with cellobiose or trehalose (Marwa Hasanein *et al.*, 2020).

3. Antigen Delivery:

These particles have an immunologically active surface molecule and a glassy layer of carbohydrates (cellobiose) covered in an aqueous dispersion. The substrate was diamond. It offered the proteinaceous antigen a colloidal surface that can form a hydrogen bond with it. The disaccharide lessens the denaturation of adsorbed antigen caused by the surface (Damera DP *et al.*, 2019).

4. Oxygen Transporter:

In one work, half-generation poly (amidoamine) dendrimers ended with carboxylic acid were used to create the hydroxyapatite core. Trehalose was then applied, followed by the adsorption of haemoglobin. In vivo experiments have shown that aquasomes are a promising oxygen carrier that can effectively maintain oxygen-binding properties for a duration of 30 days (A J Kopade *et al.*, 2002).

5. Delivery of Gene:

Research has shown that aquasomes shield and preserve the gene segment's structural integrity. A five-layered structure made up of a polyhydroxy oligomeric film, a therapeutic gene segment, an extra carbohydrate film, a ceramic core, and a targeting layer made of viral membrane protein that has been conformationally conserved (Nanjwade *et al.*, 2013).

LIMITATIONS OF AQUASOME

The simulation of the self-assembled aquasome system is hampered by a few issues. The medicine may produce toxicity in the body by burst release if it is not absorbed well. Its surface might be coated with polyethene glycol to prevent aquasomes from opsonizing and being cleared by the body's phagocytic process (Mitragotri *et al.*, 2014).

CONCLUSION

Aquasomes have emerged as a potentially useful method for efficiently delivering active chemicals to the intended location. Pharmaceutical experts now have new hope for the delivery of a wide range of bioactive compounds and the successful treatment of a variety of diseases by utilizing aquasomes-based strategies.

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