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AQUASOMES

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ABSTRACT

Aquasomes are self assembled structured particles composed of calcium phosphate or ceramic diamond covered with a polyhydroxyl oligomeric film and it is perform as nanoparticulate carrier system. Aquasomes can be considered to the most recently developed drug delivery system for therapeutics as they possess the ability to deliver active molecules such as protein, peptides, hormones, antigens, genes etc. The solid core provides the structural stability, while the carbohydrate coating protects against dehydration and stabilizes the biochemically active molecules. After synthesis of solid center of ceramic and polyhydroxyoligomeric material coating like cellulobiose and trehalose the last stage was drug loading during which the aquasomes perform as host particulates to non-covalently interact with bio-active moiety via hydrogen and cationic bonding.

KEYWORDS: Aquasomes, Self assembled, Calcium phosphate, Nanoparticulates.

INTRODUCTION

Aquasomes are nanoparticulate carrier system but instead of being simple nanoparticulates these are three layered self assembled structures, comprised of a solid phase nanocrystalline core coated with oligomeric film to which biochemically active molecules are adsorbed with or without modification.[1] Aquasomes are like " bodies of water" and their water like properties protect and preserve fragile biological molecules and this property of maintaining conformational integrity as well as high degree of surface exposure is exploited in targeting of bioactive molecules like peptide and protein hormones, enzymes, antigens and genes to specific sites.[2][3]

These carbohydrates stabilize the nonoparticulates of ceramic are known as "aquasomes" which was first developed by Nir Kossovsky.[4] The pharmacologically active molecule incorporated by co- polymerization, diffusion or adsorption to carbohydrate surface of preformed nanoparticulates.[5] The structure of aquasome was shown in the following figure - 1.

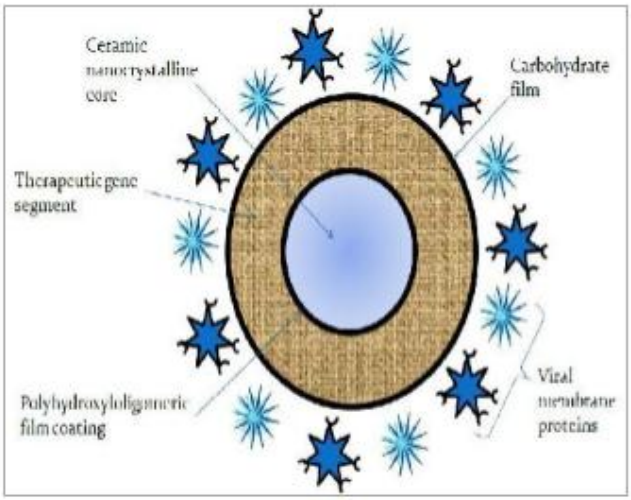

Figure 1: Structure of aquasome.

PROPERTIES

- Aquasomes water like properties provides a platform for preserving the conformational integrity and biochemical stability of bio-actives.[6]
- Aquasomes mechanisms of action is controlled by their surface chemistry. Aquasomes deliver contents through combination of molecular shielding, specific targeting, and slow and sustained release process.
- Aquasomes possess large size and active surface hence can be efficiently loaded with substantial amount of agent through ionic, non covalent bonds, vander waals forces and entropic forces. As solid particles dispersed in aqueous environment, exhibit physical properties of colloids.
- Aquasomes due to their size and structure stability, avoid clearance by reticuloendothelial system or degradation by other environmental challenges.[7]

PRINCIPLE OF SELF ASSEMBLY

Self assembly implies that the constituent part of some final product assume spontaneously prescribed structural orientation in two or three dimensional space.[8] The self assembly of macromolecules in the aqueous environment, either for the purpose of creating smart

nanostructure materials or in the course of naturally occurring biochemistry, is governed basically by three physicochemical processes: the interaction of the charged group, dehydration effect and structural stability.

a. Group interaction between charged

The interaction of charged groups such as amino, sulphate, carboxyl, phosphate group facilitates long range approach of self assembly sub units. Charged group also plays a role in stabilizing tertiary structures of folded proteins.

b. Hydrogen bonding and dehydration effect

Molecules forming hydrogen bonds are hydrophilic and this confers a significant degree of organization to surrounding water molecules. Hydrogen bond helps in base pair matching and stabilization of secondary protein structure such as alpha helices and beta sheets. In case of hydrophobic molecules, which are incapable of forming hydrogen bond. However, their tendency to repel water helps to organize the moiety to surrounding environment. The organized water decreases the overall level of disorder/entropy of the surrounding medium.[9] Since, organized water is thermodynamically unfavorable, the molecule loose water/dehydrate and get self assembled.

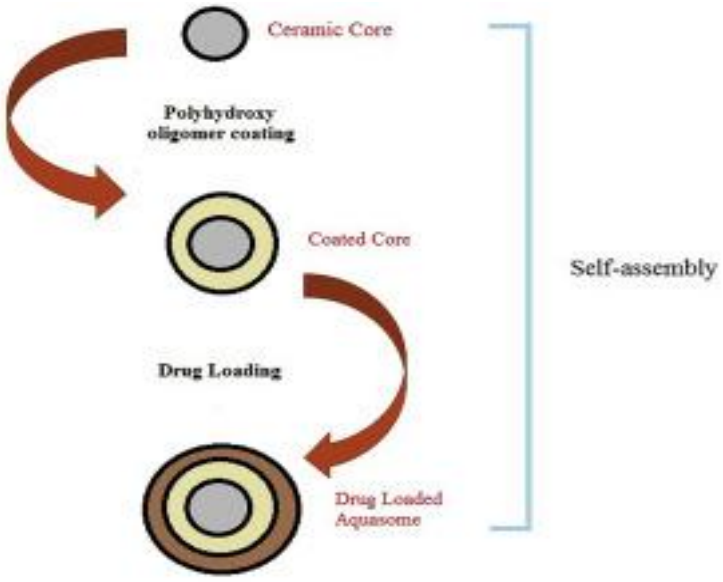

Figure 2: self assembly of aquasomes.

STRUCTURAL STABILITY

Structural stability of protein in biological environment determined by interaction between charged group and hydrogen bonds largely external to molecule and by vander waals forces

largely internal to molecule experienced by hydrophobic molecules, responsible for hardness and softness of molecules and maintenance of internal secondary structures[10], provides sufficient softness, allows maintenance of conformation during self assembly. Aquasomes are like "bodies of water" and their water like properties protect and preserve fragile biological molecules, and this property of maintain conformational integrity as well as high degree of surface exposure is exploited in targeting of bioactive molecules like peptide and protein, hormone, enzymes, antigen and genes to specific sites.[11]

COMPOSITION OF AQUASOMES

1. Core material

Polymers and ceramic are most widely used core materials. Polymers such as albumin, gelatin or acrylate are used. Ceramic such as diamond particulates, brushite(calcium phosphate)and tin oxide are used.

2. Coating material

Coating materials commonly used are cellulobiose pyridoxal 5 phosphate, sucrose, trehalose, chitosan, citrate etc. Carbohydrate plays important role act as natural stabilizer, its stabilization efficiency has been reported. Begining with performed carbon ceramic nanoparticle and self assembled calcium phosphate dehydrate particles(colloidalprecipitation) to which glassy carbohydrate are then allowed to adsorb as a nanometer thick surface coating a molecular carrier is formed.[12]

3. Bioactive

They have the property of interacting with film via non covalent and ionic interaction.

Role of Disaccharides in Aquasomes

Disaccharides like trehalose are seen to have strees tolerance in fungi, bacteria, insects, yeast and some plants. The mechanisms of action by trehalose protecting proteins and membranes within plant cell during the desiccation process and thus preserves cell structures, inherent flavors, colors and textures. The hydroxyl group on carbohydrate interact with polar and charged groups on the proteins, in a similar manner to water molecules alone and preserve the aqueous structure of proteins on dehydration.[12] These disaccharides contain a large quantity of hydroxyl group and help to replace the water around polar residues in proteins, thus maintaining their integrity in the absence of water. The studies indicated that the structure and function of cellular component could be protected by sugar during lyophilization, were

conducting with calcium transporting microsomes isolated from rabbit muscles and lobster muscles. Among three layers of aquasomes, carbohydrate fulfills the objective of aquasomes.[13]

Advantage of Preparing Aquasomes

- The main objective of preparing aquasomes is to protect bio- actives.
- Aquasomes are advantageous than other drug delivery system like prodrugs and liposomes as they are prone to undergo destructive interaction between drug and carrier.
- In aquasomes carbohydrate coating prevent destructive denaturing interaction between drug and solid carrier.
- Aquasomes maintain molecular confirmation and optimum pharmacological activity.[14]
- In active molecule possess qualities like unit three dimensional conformation, a freedom of internal molecular rearrangement which is induced by molecular interactions and even unstable in aqueous state.
- Aquasomes containing natural stabilizers like various polyhydroxy sugar act as dehydroprotectant help in maintaining water like state and preserves molecule from the change in the aqueous state pH, temperature, solvents, salt causing denaturation.[15]

Method of preparation of Aquasomes

The method of preparation of aquasomes involves three steps.

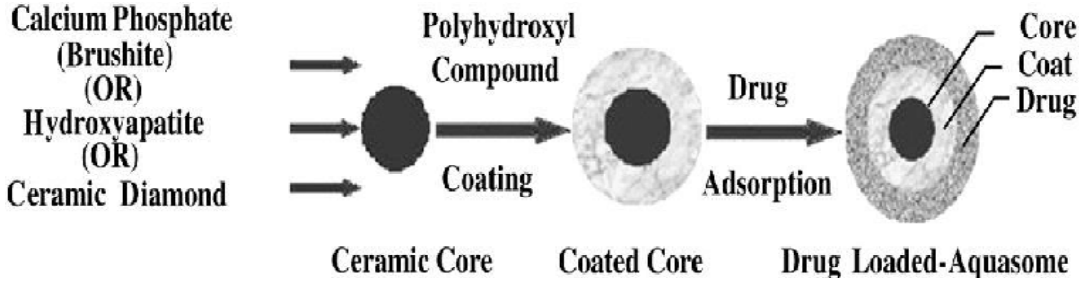

Figure 3: Method of preparation of aquasomes.

Formation of an Inorganic Core

Calcium phosphate and diamond are the two most commonly used ceramic core. This method involves the fabrication of a ceramic core, and the procedure depends upon the material selected.

Synthesis of nanocrystalline tin oxide core ceramic

It can be synthesized by direct current reactive magnetron sputtering. In a high pressure gas mixture of organ and oxygen, a 3 inches diameter target of high purity tin is sputtered. The

ultrafine particle part in the formed in the gas phase are then collected on copper tubes cooled to 770K with flowing nitrogen.

Self assembled nanocrystalline brushite(calcium phosphate dehydrate)

These can be prepared by calcium chloride colloidal precipitation and sonication by reacting solution of disodium hydrogen phosphate.

Nanocrystalline carbon ceramic, diamond particles

After nanocrystalline carbon ceramic, ultra cleansing sonication, diamond particulates can also be used for the core synthesis. The main feature of various core is that they are crystalline. Ceramic materials are structurally highly regular thus they are mostly used for core fabrication.[16] The high degree of order in crystalline ceramic ensures only a limited effect on the nature of atoms below the surface layer when any surface modification is being done, thus preserving the bulk properties of ceramic. This high degree of order also offers a high levels of surface energy that favors the binding of polyhydroxyl oligomeric surface film.[17]

Coating of the Core with Polyhydroxy oligomer

The commonly used coating material are cellobiose, citrate, pyridoxal-5-phosphate, trehalose and sucrose. It is the second step in which ceramic cores are coated with carbohydrate.[18] The carbohydrate which we mainly use can be polyhydroxyl oligomer. By addition of carbohydrate into an aqueous dispersion of the cores under sonication the coating is carried out. These are then subjected to lyophilization which make in irreversible adsorption of carbohydrate onto the ceramic surface.[19]

Charging of the drug of choice to the core

The drug is loaded to the coated particles by adsorption by dispersing the coated particles into a solution of drug prepared in apposite pH buffer. This dispersion is either lyophilized or reserved overnight at minimum temperature to gain drug laden aquasomes.

Characterization of aquasomes

Aquasomes are characterized chiefly for their structural and morphological properties, particle size distribution, and drug loading capacity.

Characterization of ceramic core size distribution

a. For morphological characterization and size distribution analysis, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are generally used. Core (uncoated and coated) and drug-loaded aquasomes are assessed by SEM and TEM. Mean particle size and zeta potential of the particles are analyzed using photon correlation spectroscopy.

b. Structural analysis: Fourier-transform infrared (IR) spectroscopy can be used for organizational investigation. Using the potassium bromide sample disk method, the core as well as the coated core can be analyzed by recording their IR spectra in the wave number range 4000–400 $cm^{-1;}$ the characteristic peaks observed are then matched with reference peaks.

c. Crystallinity: The core is analyzed for its crystalline or amorphous behavior by means of X-ray diffraction. The X-ray diffraction design of the trial core is equated with the reference diffractogram, based on which the interpretations are made.

Characterization of coated core

a. Carbohydrate coating

Coating of sugar over the ceramic core can be established by concanavalin A-induced aggregation process or by anthrone method. Moreover, the adsorption of sugar over the core can also be established by measuring zeta potential.

b. Glass transition temperature

Differential scanning calorimetry (DSC) studies are used to study glass transition temperature of carbohydrates and proteins and their effect on aquasomes. The transition from glass to rubber state can be measured using a DSC analyzer as a change in temperature on melting of glass.

CHARACTERIZATION OF DRUG-LOADED AQUASOMES

Drug payload

The drug loading can be determined by incubating the basic aquasome formulation (i.e., without drug) in a known concentration of the drug solution for 24 h at 4°C. The supernatant is then separated by high-speed centrifugation for 1 h at low temperature in a refrigerated

centrifuge. The drug remaining in the supernatant liquid after loading can be estimated by any suitable method of analysis.

In vitro drug release studies

The in vitro release kinetics of the loaded drug is determined to study the release pattern of drug from the aquasomes by incubating a known quantity of drug-loaded aquasomes in a buffer of suitable pH at 37°C with continuous stirring. Samples are withdrawn periodically and centrifuged at high speed for certain lengths of time. Equal volumes of medium must be replaced after each withdrawal. The supernatants are then analyzed for drug released by any suitable method.

APPLICATIONS OF AQUASOMES

1) Aquasomes have been used for successful targeted intracellular gene therapy, a five layered composition comprised of ceramic core, polyoxyoligomeric film, therapeutic gene segment additional carbohydrate film and a targeting layer of conformationally conserved viral membrane protein.[20]

2) Aquasomes used as vaccines for delivery of viral antigen i.e., Epstein-Barr and Immune deficiency virus to evoke correct antibody, objection of vaccine therapy must be triggered by conformationally specific target molecules.

3) Aquasomes as red blood cells substitutes, haemoglobin immobilized on oligomer surface because release of oxygen by haemoglobin is conformationally sensitive. By this toxicity is reduced, haemoglobin concentration of 80% achieved and reported to deliver blood in non linear manner like natural blood cell.

4) Aquasomes also used for delivery of enzymes like DNAase and pigment/dyes because enzymes activity fluctuates with molecular conformation and cosmetic properties of pigments are sensitive to molecular conformation.[21]

CONCLUSION

Aquasomes based on self assembled novel drug delivery system is having good future prospects due to its provision of providing better biological activity of conformational sensitive drug candidates and also drugs such as peptide and protein hormones, antigens. This is probably due to the presence of the unique carbohydrate coating the ceramic. Also these formulations have been found to evoke a better immunological response and could be used as immune adjuvant for proteinaceous antigens. This approach thus provides pharmaceutical scientists with new hope for the delivery of bioactive molecules. Still, considerable further

study of aquasomes is necessary with respect to pharmacokinetics, toxicology and animal studies to confirm their efficiency as well as safety, so as to establish their clinical usefulness and to launch them commercially.

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