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Review Article

AQUASOMES: An Overview

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ABSTRACT

Aquasomes are one of the most recently developed delivery system for bioactive molecules like peptide, protein, hormones, antigens and genes to specific sites. Aquasomes are spherical in shape with 60300 nm particles size. Aquasomes are spherical particles composed of calcium phosphate or ceramic diamond covered with apolyhydroxyloligomeric film and act as nanoparticulate carrier system but instead of being simple nanoparticle these are three layered self-assembled structures, comprised of a solid phase nanocrystalline core coated with oligomeric film on which biochemically active molecules are adsorbed with or without modification. It is widely used for the preparation of implants. Aquasomes exploited as a RBC substitutes, vaccines for delivery of viral antigen and as targeted system for intracellular gene therapy. Enzyme activity and sensitivity towards molecular conformation made aquasome as a novel carrier for enzymes like DNAses and pigment/dyes. This report reviews the principles of self assembly, the challenges of maintaining both the conformational integrity and biochemical activity of immobilized Surface pairs. The delivery system has been successfully utilized for the delivery of insulin, haemoglobin, and enzymes like serratiopeptidase etc.

Keywords: nanoparticulate, nanocrystalline

INTRODUCTION:

Aquasomes are termed as "bodies of water", since they have water like properties which protect and preserve fragile biological molecules and this property of maintaining conformational integrity as well as high degree of surface exposure is used in targeting and delivering of bio-active molecules like peptide and protein hormones, antigens and genes to specific sites where action is required. Aquasomes basically have three layered and self assembled structure which consist of a nano crystalline core, carbohydrate coating and drug coating.

Recent advances in he fields of biotechnology and genetic research have resulted in promotion of proteins and peptides as a major class of therapeutic agents. Mainly three type of core materials are used which includes brushite, i.e., Calcium phosphate dihydrate, nanocrystalline carbon ceramics, i.e., diamonds and tin oxide. The solid core provides the structural stability to aquasomes. Calcium phosphate occurs naturally and due to its instability it gets converted in to hydroxyapatite upon prolongs storage. Owing to biodegradability, cost, stability, and safety, hydroxyapatite (HA) was selected as a core for the preparation of aquasomes. Moreover, it is widely used for the preparation of implants, and for the delivery of drugs and antigens. They are particularly suitable for protein delivery because of their high adsorption capability.

Principle of "self assembly of macromolecule" is governed by three physiochemical process i.e.

1. Interaction between charged groups

2. Hydrogen bonding and dehydration effect

3. Structural stability

Self-assembly, broadly defined as the spontaneous fabrication of multi-component molecular structures, is the elegant mechanism through which the most complex biological molecules achieve their ultimate form. As an approach to macromolecular synthesis, self-assembly is appealing because biomimetic processes imply more biochemically functional products. This

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report reviews the principles of self assembly, the challenges of maintaining both the conformational integrity and biochemical activity of immobilized surface pairs, and the convergence of these principles into a single functional composition.

Preparation of Aquasomes: Aquasomes preparation is considered to be a relatively simple and straight forward approach with minimum solvent usage and no homogenization steps (to obtain the desired size). The general procedure consists of an inorganic core formation, which will be coated with carbohydrate forming the polyhydroxylated core that finally will be loaded by protein/antigen/drug .The method of preparation of aquasomes involves three steps.

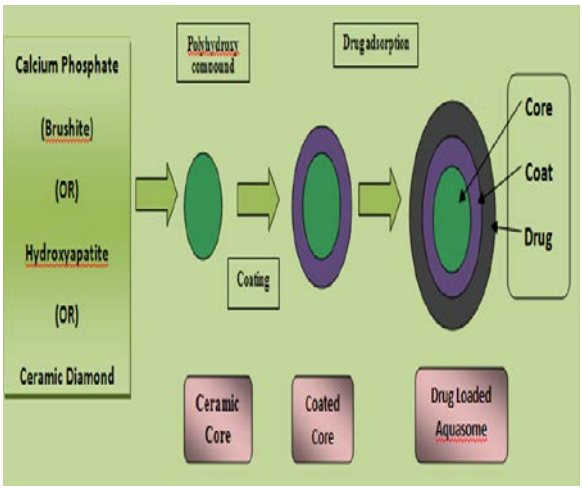

Figure 1:

Formation of an inorganic core: It involves the fabrication of a ceramic core, and the procedure depends upon the materials selected. The two most commonly used ceramic cores are calcium phosphate and diamond.

a). Synthesis of nanocrystalline tin oxide core ceramic: It can be synthesized by direct current reactive magnetr on sputtering. Here, a 3 inches diameter target of high purity tin is sputtered in a high pressure gas mixture of orgon and oxygen. The ultrafine particles formed in the gas phase are then collected on copper tubes cooled to 770K with flowing nitrogen.

b). Self assembled nanocrystalline brushite (calcium phosphate dihydrate) : These can be prepared by colloidal precipitation and sonication by reacting solution of disodium hydrogen phosphate and calcium chloride.

c). Nanocrystalline carbon ceramic, diamond particles : These can also be used for the core synthesis after ultra cleansing and sonication.The common feature of various cores is that they are crystalline and that when they are introduced into the synthetic processes, they measures between 50-150 nm and exhibit extremely clean and therefore reactive species. Ceramic materials,being structurally highly regular, are surface layer when any surface modification is being done, thus preserving the bulk properties of ceramics. This high degree of order also offers a high level of surface energy that favors the binding of pohyhydroxyl oligomeric surface film. The precipitated cores are centrifuged and then washed with enough distilled water to remove sodium chloride formed during the reaction. The precipitates are resuspended in distilled water and passed through a fine membrane filter to collect the particles of desired size. The equation for the reaction is as follows:

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

II-Coating of the core with polyhydroxy oligomer: In the second step, ceramic cores are coated with carbohydrate (polyhydroxyl oligomer). The coating is carried out by addition of carbohydrate into an aqueous dispersion of the cores under sonication. These are then subjected to lyophilization to promote an irreversible adsorption of carbohydrate onto the ceramic surface. The unadsorbed carbohydrate is removed by centrifugation. The commonly used coating materials are cellobiose, citrate, pyridoxal-5-phosphate, trehalose and sucrose.

III-Loading of the drug of choice to this assembly:

The final stage involves the loading of drug to the coated particles by adsorption. For that, a solution of known concentration of drug is prepared in suitable pH buffer, and coated particles are dispersed into it. The dispersion is then either kept overnight at low temperature for drug loading or lyophilized after some time so as to obtain the drug-loaded formulation (i.e.,aquasomes). The preparation thus obtained is then characterized using various techniques. The procedure for preparation of aquasomes is depicted in above figure.

Objective of aquasome:

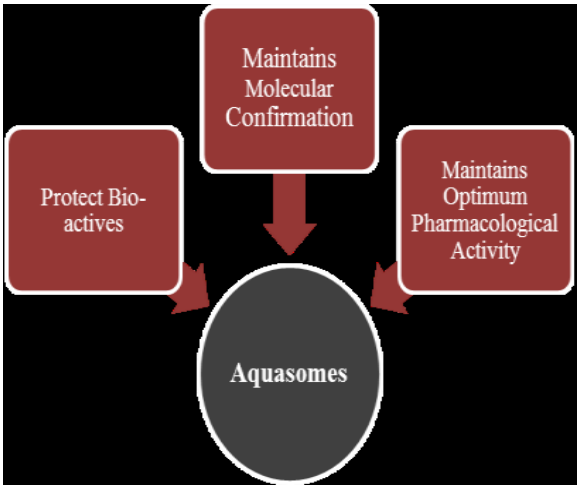

Figure 3:

1. Characterization of creamic core: Size distribution for morphological characterization and size distribution analysis, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are generally used. Core, coated core, as well as drug-loaded aquasomes are analyzed by these techniques. Mean particle size and zeta potential of the particles can also be determined by using photon correlation spectroscopy.

Structural analysis: FT-IR spectroscopy can be used for structural analysis. 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. Identification of sugar and drug loaded over the ceramic core can also be confirmed by FT-IR analysis of the sample.

Crystallinity: The prepared ceramic core can be analyzed for its crystalline or amorphous behavior using X-ray diffraction. In this technique, the X-ray diffraction pattern of the sample is compared with the standard diffractogram, based on which the interpretations are made.

2. Characterization of coated core:

A. Carbohydrate coating: Coating of sugar over the ceramic core can be confirmed by concanavalin A–induced aggregation method (determines the amount of sugar coated over core) or by anthrone method residual sugar remaining after coating). Furthermore, the adsorption of sugar over the core can also be confirmed by measurement of zeta potential.

B. Glass transition temperature: DSC can be used to analyze the effect of carbohydrate on the drug loaded to aquasomes. DSC studies have been extensively used to study glass transition temperature of carbohydrates and proteins. The transition from glass to rubber state can be measured using a DSC analyzer as a change in temperature upon melting of glass.

Application:

Oral delivery of acid labile enzyme: Rawat et al proposed the use of a nanosized ceramic core–based system for oral administration of the acid-labile enzyme serratiopeptidase. Thenanocore was prepared by colloidal precipitation under sonication at room temperature. The core was then coated with chitosan under constant stirring, after which the enzyme was adsorbed over it. The enzyme was protected by further encapsulating the enzyme-loaded core into alginate gel. The TEM images of particles showed them to be spherical in shape, with an average diameter of 925 nm. The enzyme-loading efficiency of the particles was found to be approximately 46%. The vitro drug release data followed the Higuchi model in acidic medium (pH 1.2) for a period of up to 2 to 6 hours, while the alkaline medium (pH 7.4) showed sustained and nearly complete first-order release of enzyme for up to 6 hours.

Insulin delivery: Cherian et al prepared aquasomes using a calcium phosphate ceramic core for the parenteral delivery of insulin. The core was coated with various disaccharides such as cellobiose, trehalose, and pyridoxal-5-phosphate. Subsequently the drug was loaded to these particles by adsorption method.

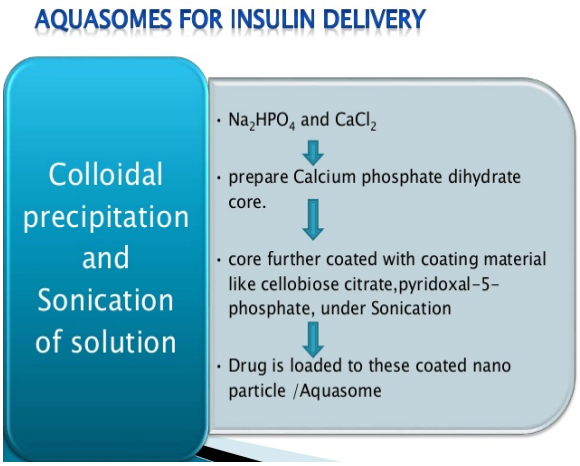

Figure 4:

Antigen delivery: The adjuvants generally used to enhance the immunity to antigens have a tendency either to alter the conformation of the antigen through surface adsorption or to shield the functional groups. So Kossovsky et al demonstrated the efficacy of a new organically modified ceramic antigen delivery vehicle. These particles consisted of diamond substrate coated with a glassy carbohydrate (cellobiose) film and an immunologically active surface molecule in an aqueous dispersion.

These aquasomes (5–300 nm) provided conformational stabilization as well as a high degree of surface exposure to protein antigen. Diamond, being a material with high surface energy, was the first choice foradsorption and adhesion of cellobiose. It provided a colloidal surface capable of hydrogen bonding to the proteinaceous antigen.

The disaccharide, being a dehydroprotectant, helps to minimize the surface-induced denaturation of adsorbed antigens (muscle adhesive protein, MAP). For MAP, conventional adjuvants had proven only marginally successful in evoking an immune response. However, with the help of these aquasomes a strong and specific immune response could be elicited by enhancing the availability and in vivo activity of antigen (Kossovsky et al. 1995). Vyas et al prepared aquasomes by sel-assembling of hydroxyapatite using the c-precipitation method. The core was coated with cellobiose and trehalose, and finally bovine serum albumin was adsorbed as model antigen onto the coated core.

Delivery of drug: Oviedo and co-workers prepared aquasomes loaded withindomethacin through the formation of an inorganic core of calcium phosphatecovered with a lactose film and further adsorption of indomethacin as a low-solubility drug.

The aquasomes were characterized for their structural analysis, particle size, and morphology by using X-ray powder diffractometry, TEM, and SEM. Particle size of drug-loaded aquasomes was found to be in the range of 6–120 nm. SEM and TEM techniques confirmed the spherical shape of aquasomes. However, results of drug (indomethacin) release studies from these carriers are yet to be determined.

As oxygen carrier: Khopade et al prepared hydroxyapatite core by using carboxylic acid–terminated half-generation poly(amidoamine) dendrimers as templates or crystal modifiers. These cores were further coated with trehalose followed by adsorption of hemoglobin. The size of the particles was found to be in the nanometer range, and the loading capacity was found to be approximately 13.7 mg of hemoglobin per gram of the core. The oxygen-binding properties of the aquasomes were studied and compared to those of fresh blood and hemoglobin solution. Hill coefficient values determined for fresh blood, for hemoglobin solution, as well as for the aquasome formulation indicated that the properties of hemoglobin including its oxygen-carrying capacity were retained by the aquasomes. The oxygen-carrying capacity of aquasome formulation was found to be similar to that of fresh blood. Also, the Hill coefficients were found to be good for its use as an oxygen carrier. The aquasome formulations neither induced hemolysis of the red blood cells nor altered the blood coagulation time. The hemoglobin loading to various sugar-coated particles was found to be approximately 7.4%. The formulation was able to retain the hemoglobin over a period of 30 days. No significant increase in arterial blood pressure and heart rate was observed in rats transfused with aquasome suspension on 50% exchange transfusion.

For delivery of gene: Aquasomes can be studied for the delivery of genes. It illustrates the attractive delivery system loaded with genetic material. Studies reveal that aquasomes protect and maintain structural integrity of the gene segment. A five layered composition comprised of the ceramic nanocrystalline core, the polyhydroxyl oligomeric film coating, the non covalently bound layer of therapeutic gene segment, an additional carbohydrate film and a targeting layer of conformationally conserved viral membrane proteins, have been proposed for gene therapy. The aquasome vehicle would afford all of the potential advantages of viral vectors and simultaneous overwhelming the risk of irrelevant gene integration

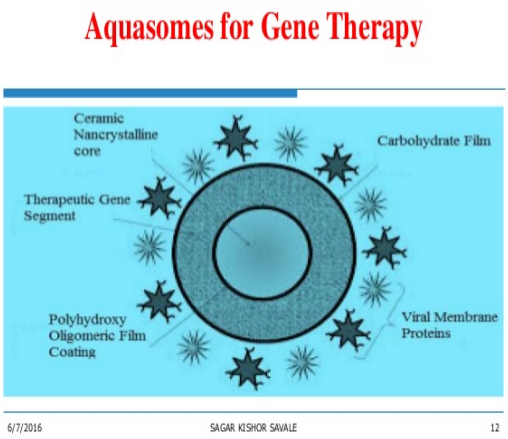

Figure 5:

For delivery of enzymes: Aquasomes also used for delivery of enzymes like DNAase and pigment/dyes because enzymes activity fluctuates with molecular conformation and cosmetic properties of pigment are sensitive to molecular conformation. DNAase a therapeutic enzyme used in the treatment of cystic fibrosis was successfully immobilized on aquasomes and targeted to the specific site and elicited significan therapeutic effect as desirable. A marked retention of biological activity was observed with surface immobilized DNAase on the solid phase of a colloidal calcium phosphate nanoparticle coated with polyhydroxyl oligomeric films.

ADVANTAGES:

1. These systems act like a reservoirs to release the molecules either in a continuous or a pulsatile manner,avoiding a multiple-injection schedule.
2. These nano particles offer favorable environment forproteins thereby avoiding their denaturalization. This property is due to the presence of inorganic cores, which are coated with polyhydroxyl compounds and these areresponsible for their hydrophilic behavior.
3. Aquasomes-based vaccines offer many advantages as a vaccine delivery system. Both cellular and humoral immune responses can be elicited to antigens adsorbed onto the surface of aquasomes.
4. Multilayered aquasomes conjugated with biorecognition molecules such as antibodies, nucleic acid, peptides which are known as biological labels can be used for various imaging tests.
5. Enzyme activity and sensitivity toward molecular conformation made aquasome as a novel carrier for enzymes such as DNAses and pigment/dyes.

Fate OF AQUASOME: The drug delivery vehicle aquasome is colloidal range biodegradable nanoparticles, so that they will be more concentrated in liver and muscles. The pharmacological or biological activity of the drug can be achieved immediately, as it is adsorbed on to the surface of the system without any surface modification and may not find any difficulty in receptor recognition on the active site. Biodegradation of ceramic (calcium phosphate) *in vivo* is achieved essentially by monocytes and multicellular cells called osteoclasts because they intervene first at the biomaterial implantation site during inflammatory reaction.

Two types of phagocytosis were reported when cells come in contact with biomaterial; either calcium phosphate crystals were taken up alone and then dissolved in the cytoplasm formation of heterophagosomes.

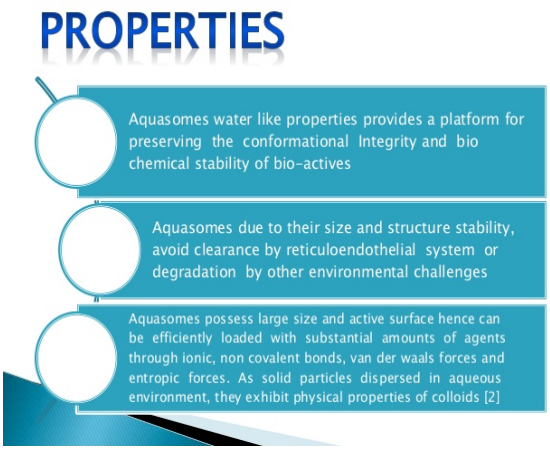

Figure 6:

Principle of self assembly: Self assembly implies that the constituent parts of some final product assume spontaneously prescribed structural orientations in two or three dimensional space. The self assembly is governed basically by three physicochemical processes:

Interaction between charged group: The interaction of charged groups, such as amino, carboxyl, sulphate, phosphate groups facilitates long range approach of self assembly sub units.

Charged group also plays a role in stabilizing tertiary structures of folded proteins.

Hydrogen bonding and dehydration effect: Hydrogen bond helps in base pair matching and stabilization of secondary protein structure such as alpha helices and beta sheets.

Molecules forming hydrogen bonds are hydrophilic and this confers a significant degree of organization to surrounding water molecules. In case of hydrophobic molecules**.**

CONCLUSION:

Aquasome is colloidal range biodegradable novel drug delivery carrier, which is based on the fundamental principle of self assembly. The drug candidates delivered through the aquasomes show better biological activity even in case of conformationally sensitive ones. This is probably due to the presence of the unique carbohydrate coating the ceramic. Furthermore, carbohydrate coating on aquasomes prevent destructive interaction between drug and carrier and thus it helps to preserve the spatial qualities. In conclusion, aquasomes appear to be promising carriers for the delivery of a broadrange of molecules including viral antigens,hemoglobin and insulin. This approach thus provides pharmaceutical scientists with new hope for the delivery of bioactive molecules.

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