

Aquasomes: Self-assembled systems for the delivery of bioactive molecules

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Nanocarriers increase the therapeutic efficacy of the pharmaceutically active agents as they can regulate their release, improve their stability and prolong circulation time by protecting the drug from phagocytosis and premature degradation. These delivery vehicles have the potential to augment the pharmacodynamic and pharmacokinetic profiles of drug molecules, thereby enhancing the therapeutic efficacy of the pharmaceutical agents. Nanoparticles which are fabricated from ceramics consist of a hydroxyapatite core whose surface is noncovalently modified by oligosaccharide on which bioactive material/drug can be absorbed, are known as “aquasomes.” This review involves properties, advantages, preparation methods, evaluation, and applications of aquasomes.

Key words: Anthrone method, aquasomes, ceramic, hydroxyapatite, peptide delivery

INTRODUCTION

Targeting of the drug to specific site is always a challenging task. So the scientists came across some novel drug delivery systems which mainly include vesicular, colloidal, niosomal, microparticulate, nanoparticulate, and lipid-based submicron system.^[1,2] Nanoparticles are versatile nanocarriers as these can be fabricated from the polymer or ceramics. Polymeric nanoparticles can be made from biologicals such as albumin/gelatin or from organics such as acrylates. Likewise ceramic nanoparticles can be fabricated from crystalline carbon and calcium phosphate core. Ceramic nanoparticles are ceramic based, spherical, nano-size carriers that consist of a hydroxyapatite core whose surface is non-covalently modified by oligosaccharide on which bioactive material/drug are further adsorbed. These carbohydrate stabilized ceramic nanoparticles are also known as “aquasomes.” The particle size of aquasomes is lower than 1000 nm which is suitable for parenteral administration.^[3] Some researchers have extended the research about the route of administration for aquasomes from parenteral to oral, e.g., Srivani prepared the sugar coated ceramic nanocarriers of hydrophobic drug (piroxicam) for oral delivery.^[4]

Aquasomes basically have three layered and self-assembled structure which consist of a nano crystalline

core, carbohydrate coating and drug coating. 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.^[5,6]

The carbohydrate coating has the property of maintaining the conformational integrity of bioactive molecules which has led to the proposal that aquasomes have potential as a carrier system for delivery of peptide, protein, hormones, antigens, genes and hydrophobic drugs to specific sites. Outer surface of aquasomes on which antigens are noncovalently linked consists of polyhydroxyl oligomers or sugar molecules. In addition to allosteric effectors such as pyridoxal-5-phosphate and sodium citrate which creates a quasi-aqueous

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Access this article online

Quick Response Code:



Website:
www.asiapharmaceutics.info

DOI:
10.4103/0973-8398.102931

film that prevents the denaturation or degradation of the protein. The coating also protects against dehydration and stabilizes the biochemically active molecules, e.g., Trehalose has the free bond mobility with rich hydroxyl component with a unique hydrogen bonding substrate that creates a glassy aqueous state. Other disaccharides that exhibit similar dehydroprotectant activity include cellobiose, and ironically, sucrose; other oligosaccharide-type molecules such as maltose, sorbitol, lactitol also appear to exhibit dehydroprotectant activity.^[7,8]

Trehalose and related disaccharides such as cellobiose, if immobilized properly on nanoparticulate substrates could prevent the surface-induced desiccation process that tends to affect the activity of biochemical substances. Carbohydrate film on ceramic particle retains the drugs spatial properties, for example, three-dimensional conformations, a freedom of internal molecular rearrangement induced by intermolecular interactions, and a freedom of bulk movement.^[9]

Aquasomes differentiate from other nanoparticles systems by their conformation and the water absorbent nature which not only makes their aqueous transport permissible but also confers the possibility of establishing noncovalent links with distinct molecules and macromolecules promoting a major stability compared than liposomes.^[6]

Aquasomes has shown promise as an adjuvant for a variety of antigens and vaccines. Adjuvants that are currently used to enhance immunity to antigens tend to either alter the antigen conformation through surface adsorption, or shield potentially critical determinants, e.g., functional groups. As with insulin, *in vivo*, the properties exhibited by the antigen, MAP, suggest that surface modified diamond nanoparticles (5–300 nm) provide conformational stabilization, as well as a high degree of surface exposure to protein antigens.^[9]

Conformational integrity of aquasomes exploited as a red blood cell substitutes, vaccines for delivery of viral antigen (Epstein-Barr and Immune deficiency virus) to evoke correct antibody and as targeted system for intracellular gene therapy. Enzyme activity and sensitivity toward molecular conformation made aquasome as a novel carrier for enzymes like DNAses and pigment/dyes.^[10]

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 nanoparticles offer favorable environment for proteins thereby avoiding their denaturalization. This property is due to the presence of inorganic cores, which are coated with polyhydroxyl compounds and these are responsible for their hydrophilic behavior.
3. Aquasomes increases the therapeutic efficacy of

pharmaceutically active agents and protects the drug from phagocytosis and degradation.

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.
6. 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.^[11,12]

PROPERTIES OF AQUASOMES

1. Aquasomes with water like properties provides a platform for preserving the conformational integrity of bioactive substances.
2. These systems deliver their contents through a combination of specific targeting, molecular shielding and slow sustained release.
3. Calcium phosphate is biodegradable in nature and its degradation can be achieved by monocytes and osteoclasts.
4. These carriers also protect the drug/antigen/protein from harsh pH conditions and enzymatic degradation, thus requiring lower doses.
5. The structure stability of aquasomes and their size avoids its clearance by reticuloendothelial system or degradation by other environmental challenges.
6. Mechanism of aquasomes is controlled by their surface chemistry and delivers their contents through the combination of specific targeting, molecular shielding, slow and sustained release process.

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. By using the principle of self-assembly, the aquasomes are prepared in three steps, i.e., preparation of core, coating of core, and immobilization of drug molecule.^[3,7,11]

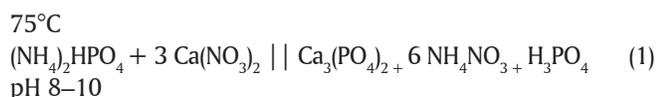
Preparation of the core

The first step of aquasome preparation is the fabrication of the ceramic core. The process of ceramic core preparation depends on the selection of the materials for core. These ceramic cores can be fabricated by colloidal precipitation and sonication, inverted magnetron sputtering, plasma condensation, and other processes. For the core,

ceramic materials were widely used because ceramics are structurally the most regular materials known. Being crystalline, the high degree of order in ceramics ensures that any surface modification will have only a limited effect on the nature of the atoms below the surface layer and thus the bulk properties of the ceramic will be preserved. The high degree of order also ensures that the surfaces will exhibit high level of surface energy that will favor the binding of polyhydroxy oligomeric surface film. Two ceramic cores that are most often used are diamond and calcium phosphate.

Preparation of ceramic core using coprecipitation:

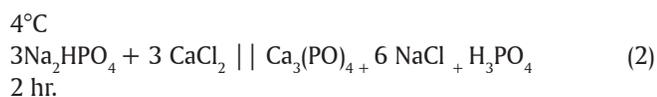
In this method, diammonium hydrogen phosphate solution is added drop wise to calcium nitrate solution with continuous solution. The temperature of the solution is maintained at 75°C in a flask bearing a charge funnel, a thermometer and a reflux condenser fitted with a carbondioxide trap. The synthesis can be described by the following equation:



During the synthesis, the pH of calcium nitrate has to maintain between eight and ten using concentrated aqueous ammonia solution. The mixture is then magnetically stirred by maintaining the temperature and pH conditions as detailed above. The precipitates are then filtered, washed and finally dried overnight. The powder was then sintered by heating to 800–900°C in an electric furnace.

Preparation of ceramic core using sonication

This method is based on the modification of procedure reported by Kossovsky.^[13] The synthesis can be described by the following equation:



Based on the above reaction stoichiometry, equivalent moles of the reagents were used.

The solutions of disodium hydrogen phosphate and calcium chloride are mixed and sonicated using an ultrasonic bath. The ceramic core can be separated by centrifugation. After the decantation of supernatant, the core is washed, re-suspended in distilled water and filtered. The core material retained on the filter medium is collected, dried and then % yield is calculated.

Poly (amidoamine) (PAMAM)

Dendrimers with carboxylate terminals, i.e., half-generation dendrimers can be used to study crystallization of calcium carbonate in aqueous solution. The report shows that it

produces spherical calcium carbonate composed mainly of valerite crystals. The calcium ion binding ability, monodispersity and spherical shape suggests the possibility of the use of carboxylic acid terminated dendrimers to produce spherical hydroxyapatite. An attempt was made to produce spherical nanometric hydroxyapatite particles by using carboxylic acid terminated PAMAM dendrimers as templates or crystal modifiers. Besides studying the template directed biomineralization.^[5]

Carbohydrate coating

The second step involves coating by carbohydrate on the surface of ceramic cores can be done by different methods. Commonly used coating materials are cellobiose, citrate, pyridoxal-5-phosphate, sucrose and trehalose.

Adsorption method

The adsorption of carbohydrate occurs epitaxially on to the surface of the nanocrystalline ceramic cores. The processes generally entail the addition of polyhydroxy oligomer to a dispersion of meticulously cleaned ceramics in ultra pure water, sonication and then lyophilization to promote the largely irreversible adsorption of carbohydrate on to the ceramic surfaces. Excess and readily desorbing carbohydrate is removed either by stir cell ultrafiltration or by dialysis method. Lactose coating can also be done by adsorption by direct incubation and by nonsolvent addition.^[7]

Drug loading

The surface modified nanocrystalline cores provide the solid phase for the subsequent nondenaturing self-assembly for broad range of biochemically active molecules. The drug can be loaded by partial 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 [Figure 1].^[14]

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 after disappearance of the

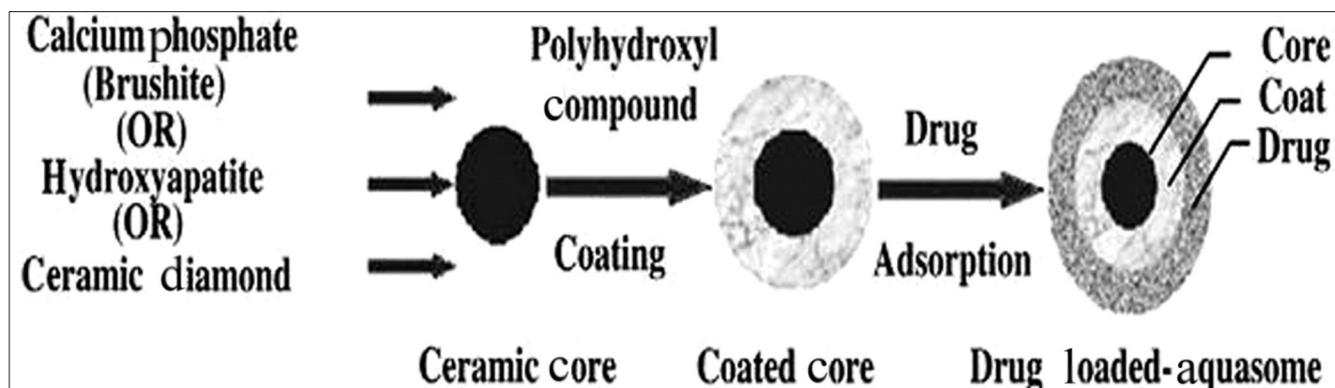


Figure 1: Preparation of aquasomes.^[15]

phagosome membrane or dissolution after formation of heterophagosomes. Phagocytosis of calcium phosphate coincided with autophagy and the accumulation of residual bodies in the cell.^[16]

EVALUATION OF CERAMIC CORES

Structure analysis

Fourier transformed infrared spectroscopy (FTIR) is used for the analysis of structure of core. The KBr sample disk is prepared using hydroxyapatite powder which is compressed and dried. Infrared spectra were recorded in the wave number range of $4000\text{--}400\text{ cm}^{-1}$ using FTIR spectrophotometer.^[11]

Phase analysis of core

X-ray diffraction (XRD) is used to analyze the phases of hydroxyapatite ceramic cores. The cores are exposed to Cu K α radiation in a wide-angle X-ray diffractometer.^[17]

Particle morphology

Transmission electron microscopy one drop of aqueous dispersion is placed over a 400-mesh carbon-coated copper grid followed by negative staining with phosphotungstic acid and placed at the accelerating voltage.

The mean hydrodynamic diameter, polydispersity, zeta potential of core can also be measured by photon correlation spectroscopy (PCS) after appropriate dilution with PBS pH 7.4 prior to analysis.

EVALUATION OF SUGAR COATING

Colorimetric analysis of sugar coating on to the ceramic core

Anthrone method is one of the best methods used to quantify the residual sugar unbound or residual sugar remaining after coating. Anthrone forms green colored product when carbohydrates are hydrolyzed into simple sugars and subsequently to hydroxyl methyl furfural. After the preparation of calibration curve aliquots of samples are transferred to boiling tubes and diluted to an appropriate concentration.

After the addition of anthrone reagent the samples are heated in a boiling water bath and cooled rapidly. When a greenish solution is obtained, then its absorbance is recorded (λ_{max} of 625 nm) using a UV-visible spectrophotometer using glucose as standard. For the analysis of sample; sugar coated core is accurately weighed and dissolved in distilled water. From this, solution is treated with the anthrone reagent using the procedure as already mentioned.^[7]

Concanavalin-A-Induced aggregation

The amount of sugar coated over core can be confirmed by concanavalin A-induced aggregation method. Concanavalin-A solution is added to different sugar-coated HA core suspensions (in quartz cuvettes and absorbance is determined at 450 nm as a function of time of 5 min interval using UV-visible spectrophotometer. The obtained data is subtracted from blank experiment conducted in the absence of concanavalin-A.

Zeta potential and polydispersity can be calculated by photon correlation spectroscopy using PCS. The sugar coated particles can be further characterized by FTIR, transmission electron microscopy, powder X-ray diffraction, Doppler electrophoretic light scatter analysis.^[17]

AQUASOMES EVALUATION

Size and shape

The morphological examination of prepared systems is performed using a transmission electron microscope following the negative staining of phosphotungstic acid solution. The mean particle size and size distribution are determined by a photon correlation spectroscopy using a Autosizer II C apparatus and SEM. Aquasomes are mainly characterized for structural analyses, particle size, and morphology. The chemical composition and the crystalline structure of all samples were obtained through X-ray powder diffractometry.^[3]

Glass transition temperature

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.^[4]

In-process stability studies using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) can be performed to determine the stability and integrity of protein during the formulation of the aquasomes. (heparin coated nanoparticles coupled with hemoglobin.)^[11]

OTHER EVALUATION PARAMETERS

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 the amount of drug released by any suitable method.

Drug loading efficiency

This test is done to ensure the amount of drug which is bound on the surface of aquasomes. Spectrophotometric analysis of hydrophobic drugs like indomethacin and piroxicam are done by using 0.1 N methanolic hydrochloric acid solutions.^[6,7]

The Hb loading capacity

It is estimated by the difference between the control sample (HbA solution) and the free hemoglobin contained in all fractions without nanoparticles. The spectrophotometric measurements of hemoglobin are done according to Drabkin's method.

The antigen-loading efficiency for the aquasomes

The formulation's loading efficiency can be determined as reported in literature. Accurately weight antigen-loaded aquasome formulations were suspended in Triton X-100 and incubated in a wrist shaker for 1 h. Then, samples are centrifuged at and absorbance is determined using micro-BCA methods with set a blank of unloaded aquasomes formulation. Antigen loading is expressed as per unit weight of aquasomes particles (g of antigen/mg of sample).^[10]

Effect of cellobiose and trehalose on antigen

DSC analysis of aquasome formulations is done by DSC analyzer having a sample cell (containing formulation) and a reference cell (filled with buffer only).

APPLICATIONS

Oxygen carrier

Patil *et al.*, made an attempt to deliver hemoglobin using colloidal ceramic carbohydrate composites termed aquasomes. This study demonstrates that the hemoglobin-

adsorbed aquasomes can carry the oxygen satisfactorily, and it also establishes the superiority of hemoglobin aquasomal formulation over the other methods acting as artificial blood substitute. The self-assembling surface modified nanocrystalline ceramic core capable of nondenaturing attachment can be used for various applications like delivery of bioactive molecules as well as viruses.^[3]

For immunotherapy

Pandey *et al.*, prepared aquasomes for delivery of model allergen without altering the antigenic and immunogenic properties of the protein/allergen. His report demonstrates that OVA adsorbed aquasomes are able to induce a strong T cell specific proliferative response with a cytokine profile suggestive of a Th1 response, prevention of anaphylactic reactions and maintenance of low titers of IgE, without abrogation of Th2-mediated responses. This suggests that aquasomes could have possible implications in the future of peptide-based vaccines against allergic disorders.^[4]

For oral route

Kommineni *et al.* carried out a technological innovation for the delivery aquasomes via the peroral route. Piroxicam loaded aquasomes with their nanometric dimensions, low drug dose, and water like properties were prepared by using two techniques; namely, coprecipitation by refluxing and coprecipitation by sonication.^[7]

For immunopotiation

Goyal *et al.*, 2008 prepared aquasomes that develops immune responses to recombinant or synthetic epitopes which is of considerable importance in vaccine research for immunopotiation. Bovine serum albumin-immobilized aquasomes were around 200 nm in diameter and spherical in shape and had approximately 20–30% BSA-loading efficiency. The formulated aquasomes was compared with plain bovine serum albumin (BSA) and transport of immunogen to APCs was found to be a promising target for gene therapy. Thus, the enhanced transport of conformationally stable antigen leads to better presentation to APCs. APCs contain both MHC-I and MHC-II molecules leading to processing and presentation of antigen via both endocytic and cytosolic pathways leading to elicit both humoral and cellular responses. Aquasome formulations could elicit combined T-helper 1 (Th1) and Th2 immune response and proved to be slightly better carrier system compared with other ceramic-based antigen nano-carriers.^[10]

Anti thrombic activity

Leclerc *et al.*, 2003 formulated nanoparticles based on heparin-poly (isobutylcyanoacrylate) copolymers to carry hemoglobin. His work constitutes the demonstration of hemoglobin loaded on nanoparticle surface, rather than being encapsulated. Antithrombic activity of native nanoparticles was evaluated by anti-Xa factor activity assay using a coagulometer ST1. Binding of nanoparticles to von

Willebrand factor (vWF) was measured. Results have shown that the heparin on the nanoparticles surface preserved most its antithrombic activity and its capacity to recognize the vWF. The bound hemoglobin also maintained its capacity to bind ligands. One ml of nanoparticles (with a size of 100 nm) suspension can be loaded with up to 2.1 mg of hemoglobin, which preserves its ligand binding capacity as well as make suitable tools in the treatment of thrombosis oxygen deprived pathologies. These nanoparticles maintain the heparin antithrombic properties and inhibit complement activation.^[18]

Antigen delivery

The immunity can be increased by adjuvants which have a tendency either to shield the functional groups or to alter the conformation of the antigen through surface adsorption or to. So Kossovsky *et al.* demonstrated the efficacy of a new organically modified ceramic antigen delivery vehicle. 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 for adsorption and adhesion of cellobiose. It provided a colloidal surface capable of hydrogen bonding to the proteinaceous antigen. The disaccharide, being a dehydro-protectant, 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.^[19]

CONCLUSION

Aquasomes have given a new hope for the pharmaceutical Scientists to deliver bioactive molecules. Within the large pool of peptide drugs are a considerable number of candidates with the potential for delivery via these carriers. 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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How to cite this article: Narang N. Aquasomes: Self-assembled systems for the delivery of bioactive molecules. *Asian J Pharm* 2012;6:95-100.

Source of Support: Nil. **Conflict of Interest:** None declared.