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AQUASOMES: A POTENTIAL DRUG CARRIER FOR DELIVERING THE BIO-ACTIVE MOLECULES

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ABSTRACT

Aquasomes are spherical "water bodies" like particles which act as a nano-particulate carrier system, but instead of being a simple nanoparticle these aquasomes are three layered structures, self-assembled by both non-covalent and ionic bonds. These aquasomes are also known as "Ceramic Nanoparticles" and the three layered self-assembled structures are comprised of a solid phase nanocrystalline core fabricated from calcium phosphate or ceramic diamond and coated with polyhydroxy oligomeric materials like cellobiose, sucrose, trehalose, lactose to which biochemically active molecules/drug are adsorbed with or without modification. The solid ceramic core will gives the structural stability, and the carbohydrate coating provides protection against dehydration and stabilizes the biochemically active molecules. So, these aquasomes technology acts as a platform for protection and prevention of fragile, conformational integrity and maintaining biochemical stability of bioactives/biological molecules. This delivery system has been successfully utilized for the delivery of drugs like antiviral, anticancer agents, proteins, peptides, enzymes, antigens, hormones and genes by specific targeting, molecular shielding and slow sustained release process.

KEYWORDS: Aquasomes, ceramic, polyhydroxy oligomers, self-assembly, bioactive molecules.

INTRODUCTION

In recent years, significant efforts have been devoted for the development of new drug delivery system to improve the therapeutic efficiency and safety of the existing drugs by altering the bio-dissemination pattern of the drug, by reducing the amount and frequency of dosing. The novel drug delivery systems using colloidal particulate carriers such as liposomes, niosomes, aquasomes and carbosomes.[1-4] Aquasomes are nanoparticulate carrier systems which are completely ceramic based, spherical and nano-size carriers that consist of a hydroxyapatite core having non-covalently modified surface by oligosaccharide on which bioactive materials/drug are further adsorbed. These aquasomes are also known as "ceramic nanoparticles".[5-6]

Aquasomes were first developed by Nir Kossovsky in 1995. These are like "water bodies" and their aqueous properties protect and fallible biological molecules. The particle size of aquasomes is lower than 1000 nm.[7-9] Aquasomes are self-assembles by non-covalent and ionic bonds as three layered structures. Principle of "self-assembly of aquasomes" is directed by three physiochemical process.[10] They are

1. Interaction between charged groups
2. Hydrogen bonding and dehydration effect on molecule
3. Structural stability of proteins

1. Interaction between charged groups[11-17]

It accelerates long range approach of self-assembly. Charge group of subunits also plays a role in stabilizing tertiary structures of folded proteins. self-assembling units have long range approach because of the interaction of charged groups such as sulphate-, amino-, carboxyl- and phosphate- groups. At an intermolecular distance of 15nm, long range interactions of constituent subunits starts for first phase of self-assembly. In case of hydrophobic structure, long range up to 25nm.

2. Hydrogen bonding and dehydration effect

Hydrogen bonding assists the base pair matching and stabilization secondary protein structure such as alpha helices and beta sheets. Molecule forming hydrogen bonds are hydrophilic and this contributes a significant degree of organization to surrounding water molecules. In case of hydrophobic molecules, they dehydrate and get self-assembled, because they tend to repel water helps to organize the moiety to surrounding environment.

3. Structural stability of proteins in biological environment

It is determined by interaction between charged group and Hydrogen bonds. Vander Waal forces mostly internal to molecule and hydrogen bond mostly external to molecules which is experienced by hydrophobic molecules. Vander Waal forces in molecule responsible for hardness and softness of molecule and maintenance of internal secondary structures, allows maintenance of self-assembly and carbohydrates in aquasomes helps to molecular plasticization.

These self-assembled and three layered structure of aquasomes consist of a nano crystalline core, carbohydrate coating and drug coating. Nano crystalline core provides the structural stability to aquasomes. Carbohydrates coating is mostly done by using polyhydroxy oligomers. It has the property of maintaining the conformational integrity of bioactive molecules. Loading of drug on the surface of coated particles by adsorption is the last and final stage for the preparation of aquasomes.

Properties of Aquasomes[18-23]

1. Aquasomes having hydrophilic properties, will provides a platform for protecting and preserving the conformational integrity of bioactive substance/bioactive molecules.[5,15]
2. Aquasomes possesses large size and active surface. So, they are effectually loaded with suitable amounts of polymers and bioactive substances through ionic, non-covalent bonds, Vander Waals forces and entropic forces.[7]
3. Aquasomes avoid clearance by reticuloendothelial system (RES) or degradation by other environmental challenges due to their size and structure stability.[5,11]
4. Calcium phosphate is biodegradable in nature and its degradation can be achieved by monocytes and osteoclasts.[5]
5. Mechanism of aquasomes occurs by specific targeting, molecular shielding and sustained release process.[7]
6. Aquasomes are mainly evaluated by structural analysis, morphological characters, drug loading efficiency and *In vivo* performance by X-ray powder diffractometry, transmission electron microscopy, scanning electron microscopy.

Advantages of Aquasomes.[24-29]

1. Aquasomes containing natural stabilizers like various polyhydroxy sugars. So, they act as dehydro protectant and help in maintaining water like state and preserves molecules from the change in the aqueous state pH, temperature, solvents salts causing denaturation.[9]
2. In aquasomes carbohydrate coating prevents destructive denaturing interaction between drug and solid carrier.[24]
3. Aquasomes-based vaccines offer many benefits as a vaccine delivery system. Both cellular and humoral immune responses are repeatedly elicited to antigens, which are adsorbed onto the surface of aquasomes.[25]
4. Aquasomes are advantageous than other drug delivery systems like prodrugs and liposomes as they are prone to undergo destructive interaction between drug and carrier.[24]
5. Three layered aquasomes are linked with self-recognition molecules such as proteins, peptides, antibodies, nucleic acid which are known as biological labels, which can be used for various imaging tests.[5]
6. Enzyme activity and sensitivity toward molecular conformation, had made aquasomes as a completely unique carrier for enzymes like DNAase and pigment/dyes.[15]
7. Aquasomes are used to avoid a multiple-injection schedule, because it acts like a reservoir to release the molecules either in a continuous or a pulsatile manner.[25]

Composition of aquasomes s.[25]

1. Core materials

Ceramic and polymers are most widely used as core materials in aquasomes preparation. Ceramic materials such as diamond particles, brushite (calcium phosphate) and tin oxide are used and polymers such as albumin, gelatin or acrylate are broadly employed. This solid core will gives structural stability to aquasomes.

2. Coating materials

Coating materials commonly used for coating are carbohydrate (polyhydroxy oligomers) like cellobiose, sucrose, lactose, trehalose, pyridoxal-5-phosphate, chitosan, citrate etc. Carbohydrate acts as natural stabilizer, they provides protection against dehydration and stabilizes the biochemically active molecules, its stabilization efficiency has been reported. Carbohydrates are adsorbed as a glassy film on ceramic core and gives protection and prevention of fragile, conformational integrity and biochemical stability of bioactives/biological molecules.

3. Bioactive compounds

Bioactive compounds have the property of interacting with coated film via non covalent and ionic interactions. These bioactive compounds like enzymes, proteins, peptides, hormones, antigens, haemoglobin, genes and drugs like antiviral, anticancer agents are delivered by specific targeting, molecular shielding and slow sustained release process. They own the characteristics to interact with glassy carbohydrate film through ionic and non-covalent bonding.

Method of preparation of Aquasomes[31-33]

Aquasomes are prepared in three steps. The general procedure consists of (1) formation of an inorganic core, followed by (2) coating the inorganic core with

polyhydroxy oligomers, and eventually (3) loading of the drug of choice to this assembly.[11]

1. Formation of an inorganic core[11]

In aquasomes preparation most commonly used ceramic cores are calcium phosphate and diamond. In this method it involves the fabrication of a ceramic core, and the procedure depends upon the materials selected.

A) Synthesis of nanocrystalline tin oxide ceramic core

Tin oxide ceramic core are synthesized by direct current (DC) reactive magnetron sputtering. Here, a 3 inches diameter target of high purity tin is sputtered during a high gas mixture of argon and oxygen. The ultrafine particles formed in the gas phase are then collected on copper tubes cooled to 77˚ K with flowing nitrogen.

B) Self assembled nanocrystalline brushite (calcium phosphate)

Oviedo et al, had prepared indomethacin loaded aquasomes through the formation of an inorganic core of calcium phosphate on which lactose film was coated and further adsorption of indomethacin as a low-solubility drug.[36]

By reacting solution of disodium hydrogen phosphate and calcium chloride by colloidal precipitation and sonication, inorganic core can be prepared. In these the solution of both disodium hydrogen phosphate and calcium chloride are mixed and sonicated using a bath sonicator. By centrifugation ceramic core can be separated. After the decantation of supernatant, the core is washed, and re-suspended in distilled water and filtered. The core material remained on the filter medium is collected, dried and then percentage yield is calculated.

C) Nanocrystalline carbon ceramic, diamond particles

Kossovsky et al. had prepared aquasomes through formation of inorganic core of diamond for delivery of antigens and vaccines. These diamond particles presently used to enhance immunity to antigens tend to either altering the antigen conformation by surface adsorption, or shield potentially critical determinants.[41]

These diamond ceramic particles can be used for synthesis of core after ultra cleansing and sonication. The main feature of these various cores is that they are crystalline. When they are introduced into the synthetic processes they measures between 50 -150 nm and exhibit clean spectrum and therefore reactive species. For core fabrication Ceramic materials are mostly used as they are structurally highly regular. The high degree of order in crystalline ceramics ensures only a limited effect on the character of atoms below the 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 carbohydrates surface film. During the reaction the precipitated cores are centrifuged then washed with enough water to get rid of common salt formed. To collect the particles to desired size the precipitates are resuspended in distilled water and passed through a fine membrane filter. The equation for the reaction is follows:

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

2. Coating of the core with carbohydrates

In the second step, ceramic cores are coated with carbohydrates on their surface. The carbohydrates which are mainly used are polyhydroxy oligomers. The adsorption of carbohydrate occurs epitaxial on the surface of the ceramic cores. By addition of polyhydroxy oligomers (carbohydrates) into the aqueous dispersion of inorganic core, coating is carried out under sonication. Then these are subjected to freeze drying technique, which makes an irreversible adsorption of polyhydroxy oligomers onto the ceramic surface. By centrifugation the unadsorbed carbohydrates are removed. The commonly used coating materials are trehalose, sucrose, lactose, cellebiose, citrate, chitosan, pyridoxal-5-phosphate etc.

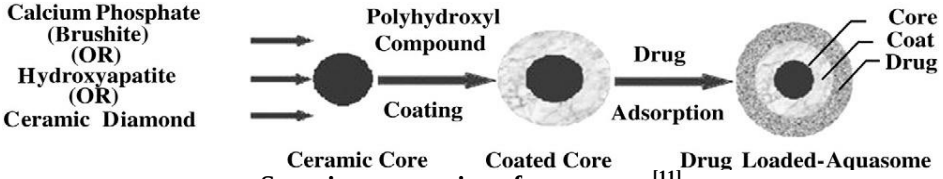
Cherian et al prepared aquasomes using cellobiose, trehalose and pyridoxal-5-phosphate as coating materials for parenteral delivery of insulin. In all formulations except cellobiose coated particles a prolong reduction of blood glucose was observed. Pyridoxal-5-phosphate coated aquasomes were found to be more effectual in reducing blood glucose levels than aquasomes coated with cellobiose or trehalose. This could be attributed to the high degree of molecular preservation by pyridoxal-5-phosphate.[28]

Aquasomes containing natural stabilizers like various disaccharides or polyhydroxyl sugars act as dehydroprotectant. These stabilizers providing protection against dehydration, maintains water like state and thereby helps to preserves the molecular conformation of bioactive molecules. The disaccharides are rich in hydroxyl group and help to replace the water around polar residues in proteins, thereby maintaining their integrity in the absence of water. Disaccharides such as trehalose are reported to have stress tolerance in bacteria, fungi, insects, yeast and some plants. Trehalose also works by protecting the plant cell proteins and its membranes during the desiccation process and also preserves cell structures, colours, inherent flavors and textures. Some Fungal spores producing ergot alkaloids were stabilized by sucrose rich solutions and desiccation induced molecular denaturation is prevented by certain disaccharides.[11]

3. Loading of drug to the coated particles

The loading of drug to the coated particles is done by adsorption and it is the final stage for the preparation of aquasomes. In this stage a solution of known concentration of drug is prepared in suitable pH buffer

and coated particles are dispersed into it. In order to get the drug-loaded formulation (i.e., aquasomes), the dispersion was either kept overnight at coldness for drug loading or lyophilized.. The preparation obtained is characterized by using various techniques.



Steps in preparation of aquasomes[11]

Characterization of Aquasomes

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

Characterization of ceramic core

Structural analysis[26,30]

Fourier transform infrared spectroscopy (FT-IR) is used to analyse the structure of core by employing potassium bromide sample disk method. In this method the KBr sample disk is prepared by using hydroxyapatite powder which is compressed and dried. By recording their IR spectra in the wave number range of 4000-400 cm^{-1} the core and coated core can be analysed by the peaks arise and the recorded peaks of sample were compared with reference peaks. By using FT-IR spectroscopy, sugar and drug loaded on the ceramic core can also be analysed.

Raman spectroscopic techniques is used to characterize the structure of aquasomes as they provide very specific signals for functional groups like phosphate ($-PO_4$), hydroxide (−OH) and carbonate ions. Raman scattering measurements were done using a Micro-Raman Spectrometer with an excitation laser source of required wavelength using a TE cooled CCD detector. In this sample was placed on a glass slide and observed under microscope. These raman scattering is advantageous as it is less susceptible to interference from water due to less absorptivity of water in visible region. Thus, Raman is a suitable technique to characterize drug delivery systems like aquasomes, which are dispersed in aqueous solution.

Crystallinity[34-35]

Crystallinity or amorphous behaviour of prepared ceramic core can be analysed by using X-ray diffraction technique. In this technique, X-ray diffraction pattern of the sample is compared with the reference diffractogram based on which the interpretations are built.

Size Analysis[5,26]

By scanning electron microscopy (SEM) and transmission electron microscopy (TEM) Core, coated core, as well as drug-loaded aquasomes morphological characterization and size distribution can be analysed.. The particle size, hydrodynamic diameter, polydispersity and zeta potential of the particles can also be determined by using photon correlation spectroscopy.

Characterization of coated core

Colorimetric analysis of sugar coating[5,37]

For colorimetric analysis of sugar coating on to the ceramic core and to quantify the residual sugar unbound or residual sugar remaining after coating, anthrone method is the best method used. Anthrone is a tricyclic aromatic ketone (it can be synthesized from several reagents like sodium hydrogen sulphite, tin chloride, or tin by partial reduction of anthroquinone). Anthrone forms green colored product, when carbohydrates are hydrolysed into simple sugar. To examine sample, calibration curve was made then required amount carbohydrate coated core is dissolved in distilled water, to this solution anthrone reagent is added and the solution is heated in a boiling water bath and cooled rapidly. When a greenish solution is obtained, then its absorbance was recorded by using UV-Visible spectrophotometer.

Carbohydrate coating[5,38]

By concanavalin A- induced aggregation method, Coating of sugar over the ceramic core can be determined (determines the amount of sugar coated over core). In these method concanavalin-A solution is added to different sugar coated core suspensions in quartz cuvettes and absorbance is determined at required wavelength as a function of time of 5 min interval using UV-Visible spectrophotometer. The data obtained is subtracted from blank experiment which was conducted in the absence of concanavalin-A.

The sugar coated particles can be further examined by transmission electron microscopy, powder X-ray diffraction, FTIR, Doppler electrophoretic light scatter analysis.

Differential Scanning Calorimetric Analysis[34]

In this study, differential scanning calorimetric (DSC) was used to study the interaction and examine the effect of polyhydroxy oligomers (carbohydrates) on the drug loaded aquasomes. And also used for the determination of storage stability of aquasomes. DSC analyser is having a sample cell containing formulation and a reference cell by which aquasomes formulations can be analysed.

Aquasomes formulations can be analyzed by DSC analyser, which is having a sample cell containing formulation and a reference cell.

Characterization of drug-loaded aquasomes

Drug loading [11, 36]: The drug loading can be determined by incubating the basic aquasomes formulation (which does not contain drug) in a known concentration of drug solution for 24 hours. And the solution was centrifuged by high-speed centrifugation for 1 hour at low temperature in a refrigerated centrifuge. And supernatant is separated. And absorbance is determined by using UV-Visible spectrophotometer. By using any suitable method of analysis the drug remaining in the supernatant liquid after loading can be estimated.

***In vitro* drug release studies**

Method 1[1]

Required amount of aquasomal powder was filled in the hard gelatin capsules and dissolution was carried out by using USP type 1 dissolution apparatus (basket type) at 37.5ºC temperature of in suitable buffer at suitable rpm for specific time period. Samples were withdrawn at various time intervals, sink condition was maintained and absorbance is determined at suitable wavelength by using UV-Visible spectrophotometer.

Method 2[11,34]

Drug Release pattern of aquasomes can be studies by incubating a known quantity of drug-loaded aquasomes in buffer of suitable pH at 37ºC with continuous stirring. Samples are withdrawn periodically and centrifuged at high speed for specific period of time. Sink conditions are maintained. The supernatants are collected and are analysed for the amount of drug released by using spectroscopic methods.

Method 3

In vitro release of drug from aquasomes can be studied by dialysis method by employing open tube, invert test tube method or by franz diffusion cell.

Entrapment efficiency and drug loading[1]

Entrapment efficiency is the percentage of actual amount of drug entrapped in the carrier relative to the initial amount of loaded drug. The % entrapment efficiency is calculated by

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

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

In-process stability studies[11,38]

In-process stability studies using sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) can be performed to determine the stability and integrity of protein during the formulation of the aquasomes.

Application of aquasomes

Aquasomes are able to maintain and increases the therapeutic efficacy of active pharmaceutical ingredients and also protects them from degradation and phagocytosis. The ceramic nanoparticals are also used as carrier for delivery of gene, insulin, haemoglobin, antigens, enzymes, vaccines and adsorption of protein.[40]

Insulin delivery[11,28]

Aquasomes are used to increase the bio availability of insulin. Aquasomes employing a phosphate ceramic core for the parenteral delivery of insulin was prepared by cherian et al. The core was coated with various disaccharides like cellobiose, trehalose, and pyridoxal-5-phosphate and the drug was loaded by adsorption method. The *In vivo* performance of varied aquasomes formulations of insulin are evaluated by using albino rats. Prolonged reduction of blood sugar was observed with all formulations except cellobiose coated aquasomes. Aquasomes coated with Pyridoxal-5-phosphate were found to be simpler in reducing blood sugar levels than aquasomes coated with trehalose or celliobiose. The prolonged activity was assigned to slow release of drug from the carrier and structural integrity of the peptide.

For delivery of gene[11,31]

Aquasomes can be studied for the delivery of gene. Studies reveal that aquasomes can protect and maintain structural integrity of the gene segment and prevention of risk of irrelevant gene integration. A multi layered composition consists of five layers they are ceramic nanocrystalline core, the polyhydroxy oligomeric film coating, the non-covalently bound layer of therapeutic gene, an extra polyhydroxy oligomers film and a targeting layer of viral membrane proteins, are proposed for gene therapy. The aquasomes vehicle would afford all of the potential advantages of viral vectors and simultaneous overwhelming the danger of irrelavant gene integration.

For delivery of enzyme[11,40]

Aquasomes are having the capability to delivering the enzymes (e.g: DNAase) and pigments or dyes. Cosmetic properties of pigments are susceptible to molecular conformation and the activity of enzymes may alter due to molecular confirmation. A remarkable biological activity as observed with surface immobilized DNAase on the solid phase of a core is coated with polyhydroxy oligomeric films. DNAase is a therapeutic enzyme which was utilized in the treatment of cystic fibrosis was successfully immobilized on aquasomes and targeted to the target site and elicited significant therapeutic effect.

For allergen immunotherapy[39]

Aquasomes are being a promising approach in allergen specific immunotherapy due to their ability to act as adjuvants, transport the allergens to tissues and immune-

competent cells and reduces the number of administrations. Pandey et al., prepared aquasomes as adjuvants for delivery of ovalbumin (OVA) as an allergen model without altering the antigenic and immunogenic properties of the protein/allergen. And his report demonstrates that OVA adsorbed aquasomes seems in a mixed Th1/Th2-type immune response, and also able to induce a strong T cell specific proliferative response with a cytokine profile suggestive of a Th1 response, inhibition of anaphylactic reactions and maintenance of low levels of IgE, without abrogation of Th2-mediated responses. And also suggests that aquasomes can be a possible implications in the future of peptide-based vaccines against allergic disorders.

As oxygen carrier[11,35]

Khopade et al prepared aquasomes as oxygen carriers. For this the core is prepared by carboxylic acid-terminated half generated poly (amidoamine) dendrimers as templates or crystals modifier. These cores were again coated with trehalose followed by adsorption of haemoglobin. The oxygen binding sites of aquasomes were studied by using rats. For this Hill coefficient values are determined for haemoglobin solution, for fresh blood, as well as for the aquasomes formulations indicated that the properties of haemoglobin including its oxygen carrying capacity were retained by the aquasomes.

Delivery of drug[36]

Oviedo and co-workers, prepared aquasomes for delivery of indomethacin drug through the formation of a solid ceramic core of calcium phosphate covered with a lactose film and further adsorption of indomethacin as a low-solubility drug. And the aquasomes were characterized for their particle size, structural analysis and morphology by using SEM, TEM and X-ray powder diffractometry. Particle size of aquasomes with drug loaded was found to be within the range of 60–120 nm. Spherical shape of aquasomes are confirmed by SEM and TEM techniques. However, results of drug (indomethacin) release studies from these carriers are yet to be determined

Delivery of antigen[41]

Kossovsky et al. demonstrated that aquasomes has ability to act as an adjuvant for delivery of antigens and vaccines. In this antigens are noncovalently linked to outer surface of aquasomes on which it consists of polyhydroxy oligomers or sugar molecules. These are presently used to enhance immunity to antigens tend to either altering the antigen conformation by surface adsorption, or shield potentially critical determinants. Conformational stabilization as well as a high degree of surface exposure to protein antigens, are provide by these surface modified diamond nanoparticles (aquasomes 5–300 nm). As diamond is a, high surface energy material, so it was the first choice for adsorption and adhesion of cellobiose. A colloidal surface capable of hydrogen bonding was provided to the proteinaceous antigen. The disaccharide, are being a dehydro-protectant in nature, helps to reduce 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 these aquasomes a strong and specific immune response could be evoked by enhancing the availability and *In vivo* activity of antigen

Delivery of protein and peptides[38]

Umashankar et al demonstrated that aquasomes are effective mode of delivery for therapeutic agents belonging to the class of proteins and peptides. They are able to overcome some inherent problems associated with these molecules like poor bioavailability, physical as well as chemical instability, route of delivery and potent side effects. The surface modification on aquasomes with polyhydroxy oligomers creates a glassy molecular stabilization film that adsorbs therapeutic proteins with minimal structural denaturation. So, these particles provide complete protection of an aqueous nature to the adsorbed drugs against the denaturing effects of external pH and temperature, because there are no swelling and porosity changes with change in pH or temperature

Anti-thrombic activity[5,42]

Leclerc et al, formulated nanoparticles based on heparin-poly (isobutylcyanoacrylate) copolymers to carry hemoglobin. By anti-Xa factor activity assay using a coagulometer ST1, an antithrombic activity of native nanoparticles was evaluated. Binding of nanoparticles to von Willebrand factor (VWF) was measured and 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 maintains its ligand binding capacity and also make suitable implements in the treatment of thrombosis oxygen deprived pathologies. These nanoparticles preserve the heparin antithrombic properties and inhibit complement activation.

CONCLUSION

Aquasomes represent one of the simplest and completely unique drug carrier based on the principle of self-assembly. The drug candidates delivered through the aquasomes show better biological activity even in conformationally sensitive ones. This is probably because crystalline nature of the core gives structural stability and overall integrity. The unique carbohydrate coating prevents the destructive drug carrier interaction and helps to preserve the spatial qualities. Also these formulations are found to evoke a far better immunological response and can be used to delivery of insulin, enzymes, haemoglobin, hormones, peptide, protein, antigen. Thus this approach provides pharmaceutical scientists with a new hope for the

delivery of bioactive molecules. Still, further study of aquasomes is important regarding pharmacokinetics, toxicology, and animal studies to justify their safety and efficiency, and so on establish their clinical usefulness and to launch them commercially.

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