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Review Article

AQUASOMES: A NOVEL DRUG CARRIER SYSTEM

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ABSTRACT
In the past few years many approaches were tried for the improvement of the drug delivery. Nanoparticulate carrier systems constitute one of the self assembling approach for the delivery of pharmaceutical agents. Aquasomes are three layered, self assembled nanoparticulate carrier systems, comprised of a solid phase nanocrystalline core coated with oligomeric film to which biochemically active molecules are adsorbed with or without modification. These structures are self assembled by noncovalent and ionic bonds. The solid core provides the structural stability, while the carbohydrate coating protects against dehydration and stabilizes the biochemically active molecules. Properties like protection and preservation of fragile biological molecules, conformational integrity, and surface exposure made it as a successful carrier system for bioactive molecules like peptide, protein, hormones, antigens and genes to specific sites. This article reviews principle of self assembly, significance of each component, properties and applications of aquasomes.

Keywords: aquasomes, self assembly, calcium phosphate, oligomers, carrier system, nanoparticles.

INTRODUCTION

Some of the challenges of most drug delivery systems include poor bioavailability, *in vivo* stability, solubility, intestinal absorption, sustained and targeted delivery to site of action, therapeutic effectiveness, side effects, and plasma fluctuations outside therapeutic window. However, nanotechnology in drug delivery is an approach designed to overcome these challenges due to the development and fabrication of nanostructures at submicron scale and nanoscale which are mainly polymeric and have multiple advantages. Nanotechnology can simply be defined as the technology at the scale of one-billionth of a meter. Generally, nanostructures have the ability to protect the encapsulated drug from hydrolytic and enzymatic degradation in the gastrointestinal tract; targeted delivery of a wide range of drugs to various parts of the body for sustained release [1-3].

Nanoscale particles can travel through the blood stream without sedimentation or blockage of the microvasculature. Small nanoparticles can circulate in the body and penetrate tissues such as tumors. Nanoparticles have already been used to deliver drugs to target sites for cancer therapeutics [4] or deliver imaging agents for cancer diagnostics [5]. In addition, nanoparticles can be taken up by the cells through natural means such as endocytosis. The reason why these nanoparticles (NPs) are attractive for medical purposes is based on their important and unique features, such as their surface to mass ratio that is much larger than that of other particles, their quantum properties and their ability to adsorb and carry other compounds. NPs have a relatively large (functional) surface which is able to bind, adsorb and carry other compounds such as drugs, probes and proteins.

Due to the size of nanostructures, they are able to penetrate into tissues and are taken up by cells, allowing efficient delivery of drugs to sites of action. The uptake of nanostructures was found to be 15-250 times greater than that of microparticles in the 1-10µm range [6]. It provides drug delivery carriers, as well as treatment and management of chronic diseases which include cancer, HIV/AIDS.

Nanoparticles can be broadly classified as organic and inorganic nanoparticles. Organic particles may include carbon nanoparticles(fullerenes) while some of the inorganic nanoparticles may include magnetic nanoparticles, noble metal nanoparticles (like gold and silver) and semiconductor nanoparticles (like titanium dioxide and zinc oxide). There is a growing interest in inorganic nanoparticles as they provide superior material properties with functional versatility. Due to their size features and advantages over available chemical imaging drugs agents and drugs, inorganic nanoparticles have been examined as potential tools for medical imaging as well as for treating diseases. Inorganic nanomaterials have been widely used for cellular delivery due to their versatile features like wide availability, rich functionality, good biocompatibility and capability of targeted drug delivery and controlled release of drugs[8].

Various methods employed for the preparation of nanoparticles use polymers and encounter difficulties such as the compatibility of solvents and other constituents and the polymers and co-polymers with the active principle and biological fluids and factors of the collection system[9]. Kossovsky proposed a system to prepare nanoparticles transporting the so-called aquasomes, whose particle size (lower than 1000 nm), is appropriate to parenteral administration because it prevents the obstruction into the bloodstream capillaries [10].

Self assembly can be defined as the spontaneous aggregation of molecules into well-defined, stable, noncovalently bonded assemblies that are held together by intermolecularforces. Smooth curved surface of rain drops, embryo, liposomes etc are the result of self assembly. Nanoparticulate carrier systems constitute one of the self assembling approach for the delivery of bioactive agents. Nanoparticles can be fabricated from either polymers or ceramics. The pharmacologically active molecule can be incorporated into them either by co-polymerization within self assembling nanoparticulate matrix or diffusion into preassembled nanoparticulate matrix or adsorption to the surface of preformed nanoparticle[11].

Aquasomes contribute to a new drug delivery systems comprised of surface modified nano crystalline ceramic carbohydrate composites. These drug delivery systems were first discovered by Nir Kossovsky. These are nanoparticulate

carrier systems with three layered self assembled structures (Fig 1). These comprises of central solid nanocrystalline core coated with polyhydroxy oligomers onto which biochemically active molecules are adsorbed.

Aquasomes are also called as "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 made it as a successful carrier system for bioactive molecules like peptide, protein, hormones, antigens and genes to specific sites, that is for targeting[12].

In general these complex multicomponent particulate delivery systems are assemblies of simple polymers, complex lipid mixtures or ceramic materials with diameter ranging between 30 to 500 nm. As these are solid or glassy particles dispersed in an aqueous environment, they exhibit the physical properties of colloids and their mechanism of action is controlled by their surface chemistry. Aquasomes deliver their contents through a combination of specific targeting, molecular shielding and a slow and sustained release process [13].

Aquasome technology represents a platform system for conformational integrity and biochemical stability of bioactives. Their large size and inherently active surfaces facilitate them to be loaded with water insoluble drugs through non covalent processes. Their intended route of administration is parenteral and with advancement of research in this field, other routes might be contemplated.

Three types of core materials are mainly used for producing aquasomes: tin oxide, nanocrystalline carbon ceramics (diamonds) and brushite (calcium phosphate dihydrate). Polymers like albumin, gelatin or acrylates can also be used but ceramics are mainly used because they are structurally the most regular materials known, being crystalline high degree of order ensures,

(a) Any surface modification will have only limited effect on nature of atoms below surface layer and thus bulk properties of ceramic will be preserved [14].

(b) The surface will exhibit high level of surface energy that will favor the binding of polyhydroxy oligomer surface film. The freshly prepared particles possess good property of adsorbing molecules within fraction of seconds.

Calcium phosphate is the core of interest, owing to its natural presence in the body. The brushite is unstable and converts to hydroxyapatite upon prolonged storage. Hydroxyapatite seems, therefore, a better core for the preparation of aquasomes. It is widely used for the preparation of implants for drug delivery [15].

Nanoceramic crystalline core particles are coated with glassy oligomer or pyridoxal-5-phosphate. Oligomer/ carbohydrate are a substance of choice as it fulfills the objective of aquasomes. The hydroxyl groups on oligomer interact with polar and charged groups of proteins, in a same way as with water thus preserve the aqueous structure of proteins on dehydration. These disaccharides are rich in hydroxyl group and help to replace the water around polar residues in protein, maintaining integrity in absence of water. The free bound mobility associated with a rich hydroxyl component creates unique hydrogen binding substrate that produces a glassy aqueous state. In aquasomes, sugars help in molecular plasticization [16]. Commonly used sugars for coating include trehalose, lactose, cellobiose, sucrose etc.

The pharmacologically active molecule can be incorporated by co-polymerization, diffusion or adsorption to carbohydrate surface of pre formed nanoparticles. The surface modified nanocrystalline cores provide the solid phase for the subsequent non denaturing self assembly for broad range of biochemically active molecules [16].

STRATEGIES USED IN CHEMICAL SYNTHESIS OF NANOSTRUCTURES:

Aquasomes are self assembled three layered nanostructures. The strategies normally used in the chemical synthesis of nanostructures are,

1) Sequential covalent synthesis, basic strategy of nanoparticle synthesis where reversible interactions (hydrogen bonds) are used to bind the molecules. Arrays of covalently linked atoms are generated with well defined composition, connectivity and shape, ex., Vit B_{12}.

2) Covalent polymerization [17], most important strategy, used for preparing molecules with high molecular weight, low weight substance allowed to react with itself to produce molecule comprising many covalently linked monomers.

3) Self-organizing synthesis, widely used strategy, relies on weaker and less directional bonds as ionic, hydrogen and vander waals. Molecules adjust their own position to reach thermodynamic minimum, true nanostructures are prepared [18].

4) Molecular self assembly [16], spontaneous assembly of molecules into structured, stable, non covalently joined aggregates. It combines features of preceding strategies, involves

Formation of intermediate structural complexity through covalent synthesis.

Formation of stable structure through ionic, hydrogen and van der waals links.

Use of multiple copies. For final assembly, non covalent connection between molecules must be stable.

These three layered structure are self assembled by non-covalent bonds. Principal of "self assembly of macromolecule" is governed by three physiochemical process i.e.

1)Interaction between charged group: The interaction of charged group facilitates long range approach of self assembly sub units charge group also plays a role in stabilizing tertiary structures of folded proteins.

2) Hydrogen bonding and dehydration effect: Hydrogen bond helps in base pair matching and stabilization 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, which are incapable of forming hydrogen bond, their tendency to repel water helps to organize the moiety to surrounding environment, organized water decreases level of entropy and is thermodynamically unfavorable, the molecule dehydrate and get self assembled.

3) Structural stability of protein in biological environment determined by interaction between charged group and Hydrogen bonds largely external to molecule and by van der waals forces largely internal to molecule, experienced by hydrophobic molecules, responsible for hardness and softness of molecule and maintenance of internal secondary structures, provides sufficient softness, allows maintenance of conformation during self assembly. Self assembly leads to

altered biological activity, van der waals need to be buffered. In aquasomes, sugars help in molecular plasticization [16].

RATIONALE

Aquasomes maintains molecular confirmation and optimum pharmacological activity of bioactives. They protect bio-actives. Bio-actives, because of their unique three dimensional conformations, face many biophysical constraints. Aquasomes with natural stabilizers like various polyhydroxy sugars act as dehydroprotectant, maintains water like state thereby preserves molecules in dry solid state. Carbohydrate coating prevents destructive denaturing interaction between drug and solid carriers. Aquasomes help in maintaining the integrity of biological molecules in absence of water.

Many reports are there to support the dehydroprotectant activity of natural sugars, like, prevention of desiccation induced molecular denaturation of disaccharides like trehalose, protein stabilization against heat denaturation by sugars and polyols. Other sugars with dehydroprotectant property include cellobiose, sucrose, glucose, maltose, lactose and raffinose.

PROPERTIES [11, 19, 20]:

1) Aquasomes water like properties provides a platform for preserving the conformational Integrity and bio chemical stability of bio-actives.

2) Aquasomes mechanism of action is controlled by their surface chemistry. Aquasomes deliver contents through combination of specific targeting, molecular shielding, and slow and sustained release process.

3) Aquasomes due to their size and structure stability, avoid clearance by reticuloendothelial system or degradation by other environmental challenges

4) Aquasomes possess large size and active surface hence can be efficiently loaded with substantial amounts of agents through ionic, non covalent bonds, van der waals forces and entropic forces. As solid particles dispersed in aqueous environment, they exhibit physical properties of colloids.

5) The drug delivery vehicle aquasome is colloidal range biodegradable nanoparticles, so that they will be more concentrated in liver and muscles. Since the drug is adsorbed on to the surface of the system without further surface modification they may not find any difficulty in receptor recognition on the active site so that the pharmacological or biological activity can be achieved immediately. In normal system, the calcium phosphate is a biodegradable ceramic. Biodegradation of ceramic *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 phagosome membrane or dissolution after formation of heterophago-somes. Phagocytosis of calcium phosphate coincided with autophagy and the accumulation of residual bodies in the cell.

METHOD OF PREPARATION OF AQUASOMES[21-23]

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.

1. 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. The precipitated cores are centrifuged and then washed with enough distilled water to remove sodium chloride formed during the action. The precipitates are resuspended in distilled water and passed through a fine membrane, filter to collect the particles of desired size. Two ceramic cores that are most often used are diamond and calcium phosphate.

2. **Carbohydrate coatings**: The second step involves coating by carbohydrate on the surface of ceramic cores. There are number of processes to enable the carbohydrate (polyhydroxy oligomers) coating to adsorb epitaxially on to the surface of the nano-crystalline 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 by stir cell ultra-filtration. The commonly used coating materials are cellobiose, citrate, pyridoxal-5-phosphate, sucrose and trehalose.

3. **Immobilization of drugs**: The surface modified nano-crystalline cores provide the solid phase for the subsequent non-denaturing self assembly for broad range of biochemically active molecules. The drug can be loaded by partial adsorption.

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

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 [19, 24].

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 [25, 26].

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 [26, 27].

Characterization of coated core

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 (Determines the residual sugar unbound or residual sugar remaining after coating). Furthermore, the adsorption of

sugar over the core can also be confirmed by measurement of zeta potential [25, 26, 27].

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 [27].

Characterization of drug-loaded aquasomes

Drug payload

The drug loading can be determined by measuring the drug remaining in the supernatant liquid after loading which can be estimated by any suitable method of analysis [19].

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 [27].

APPLICATIONS OF AQUASOMES:

Aquasomes has got a quite versatile application potential as a carrier for delivery of vaccines, hemoglobin, drugs, dyes, enzymes and even genetic material (Table 1).

1) Aquasomes used as vaccines for delivery of viral antigen i.e., Epstein-Barr and Immune deficiency virus 31 to evoke correct antibody, objective of vaccine therapy must be triggered by conformationally specific target molecules [28].

2) Aquasomes as red blood cell substitutes can effectively deliver the large, complex labile molecule, haemoglobin. By incorporating in aquasome carriers, the toxicity of haemoglobin is reduced, biological activity is preserved, haemoglobin concentration of 80% can be achieved and is reported to deliver oxygen in a non linear manner like natural red blood cells [29].

3) 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 .

4) Aquasomes for pharmaceuticals delivery i.e. insulin, developed because drug activity is conformationally specific. Bio activity preserved and activity increased to 60% as compared to i.v. administration and toxicity not reported [24].

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

6) Aquasomes are used for oral delivery of acid labile enzyme, serratiopeptidase. Enzyme loaded aquasome was further protected by encapsulating in alginate gel. They protected structural integrity of enzymes and better therapeutic efficacy was observed [30].

CONCLUSION

Aquasomes, the self-assembling surface-modified nanocrystalline ceramic cores, represent one of the simplest yet a novel drug carrier. The drug candidates delivered through the aquasomes show better biological activity even in case of conformationally sensitive ones. The crystalline nature of the core gives structural stability and overall integrity. The molecular plasticizer, carbohydrate prevents the destructive drug carrier interaction and helps to preserve the spatial qualities. Hence these appear to be promising carriers for the delivery of broad range of molecules including viral antigens, heamoglobin and insulin, and other bioactive molecules, thus promoting a better therapeutic effect. This approach thus provides pharmaceutical scientists with new hope for the delivery of bioactive molecules.

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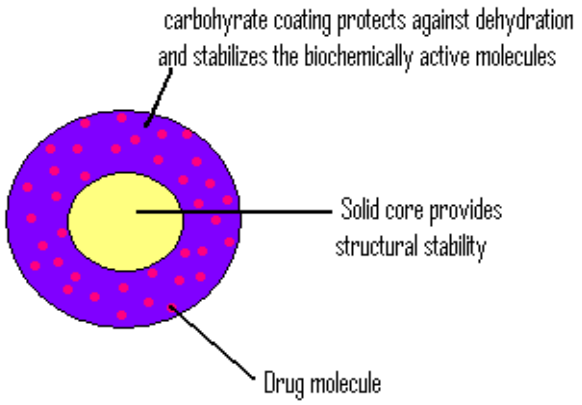

Fig 1: Three layered structure of aquasome

Table 1: Applications of Aquasomes

USE	PROTEIN/SURFACE	RATIONALE MACROMOLECULES
Vaccines	Antigenic envelope	To be effective protein protective antibodies must be raised against conformationally specific target molecules
Blood substitutes	Haemoglobin	Physiological binding and release of oxygen by haemoglobin is conformationally sensitive
Pharmaceuticals Pigments / dyes	Active drug Dye agent	Drug activity is conformationally specific wavelength absorption and reflection/ cosmetics properties of natural pigments are sensitive to molecular conformation
Enzymes	Polypeptide	Activity fluctuates with molecular conformation. Gene therapy Genetic Targeted intracellular material delivery