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A BRIEF REVIEW OF SELF ASSEMBLED CERAMIC NANOPARTICLES AND THEIR APPLICATIONS

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ABSTRACT

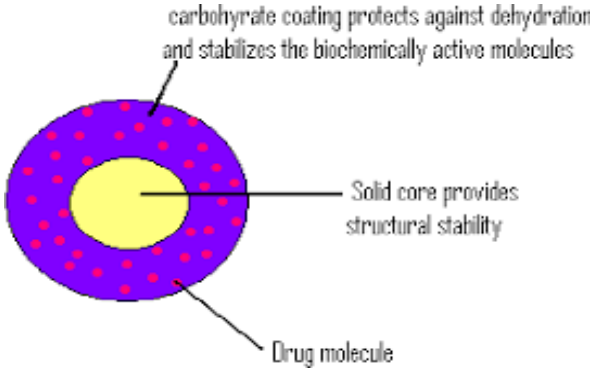
Aquasomes are nanoparticulate carrier systems. These are three layered self assembled structures composed of nanocrystalline core coated with oligomeric polyhydroxy carbohydrate film, on which biochemically active molecules of drug are adsorbed with or with out modification. Aquasomes are spherical shaped particles with a size range of 60-300nm. Generally it is given through iv route. But due to the development of Research and development it can be delivered through other routes. Aquasomes can be compressed as tablets by using multi functional excipients.Aquasomes have wide range of applications dute to the stability provided by the oligomeric film.Aquasomes can also deliver enzymes sensitive to molecular conformation (DNAases, RNAases), pigments, dyes, vaccines, RBC and fragile substances. The active surfaces provide a base to load water in soluble drugs.In this review article, principle of self-assembly, conformational integrity, preparation of aquasomes and delivery of vaccines are discussed in a brief.

KEYWORDS: Aquasomes, self-assembled carrier systems, ceramic cores, nanoparticles.

INTRODUCTION

Aquasomes are first developed by Nir.Kossovsky. Aquasome is a word derived from two words "aqua" means water and "somes" means cell like structures. So, aquasomes are known as "bodies of water". As these are water like bodies, they give protection to fragile substances there by preventing the dehydrating effect. Surface exposure, conformational integrity made them successful carriers for delivery of various substances to specific sites.

Aquasomes are defined as the self-assembled sugar coated nanoparticles on which drug are incorporated by co polymeration and adsorption. Sugar coating is responsible for providing stability and preventing denaturation. Non covalent bond is responsible for self assembly of three layered molecules.[1]



Principle of self assembly is governed by three physico chemical process[2]

1. Interaction between charged groups
2. Hydrogen bonding and dehydration
3. Structural stability of moiety

1. Interaction between charged groups

Most of the biological components and synthetic surfaces are charged due to intrinsic chemical groups or absorbed ions on it. The interaction of charged groups (amiono, carbonyl, sulphate, phosphate) helps for self assembling of sub units, they also help stabilization of territory structure.

Examples of natural interactions of charged group include crystalline lattis formations, demineralization.
Examples of ion pairs include binding of carboxylate drug to ionaised arginine lysine of proteins, bridging between proteins and ligands, metal ion coordination to proteins side chain etc.

2. Hydrogen bonding and dehydration
Hydrogen bonds are formed between electro positive hydrogen atom and electro negative donor atom (oxygen, nitrogen…) and electronegative basic acceptor (carbonyl oxygen). Either donor or receptor can be ionized more than one bond can exist between donor and acceptor. Though unshared hydrogen bonds are common, charged groups are better at donating and accepting hydrogen bonds in proteins, amino and carbonyl groups act as donor and acceptor groups respectively.

The more the electro negative nature of acceptor and the bond would be shorter and stronger. Hydrogen bonds are responsible for self-assembly of atoms, base pairing of nucleotides, stabilization of secondary protein structures such as (α-helices and β-sheets). Hydrogen bonds conifer hydrophilicity, degree of organization with surrounding water. Hydrophobic molecules are incapable of forming hydrogen bonds. Hydrophobic nature of moiety helps to organize it to surrounding environment. Organized water decreases entropy so, it is thermodynamically unfavorable and it undergoes dehydration for self assembly.

3. Structural stability of moiety in biological environment
The forces acting between the dipoles are called Vander Waals forces. The structural stability of moiety in the biological environment interaction between charged groups and hydrogen bonds external to the molecule and vanderwaal forces internal to the molecule. Vander Waal forces are observed in hydrophobic regions, shielded from water, play main role in maintaining molecular shape and conformation during self-assembly.

Vander Waal forces are responsible for hardness and softness of molecules.Vanderwaal interations in hydrophobic side chain increase the stability of the helical structure which are thermodynamically unfavourable for expanded random coils. Maintenance of internal secondary structures (helices) is responsible for the softness that maintain conformational integrity during the self-assembly, small changes are necessary for success of antigen-antibody interactions.

For maintenance of optimal biological activity vanderwaal forces are buffered in aquasomes, sugar plays the role of molecular plasticization.

Permanent dipoles interact with other permanent dipoles or with point charges. The common dipoles in proteins are formed by amide linkages to form helical structures they reinforce each other so generating a large dipole moment.

Stratagies used in chemical synthesis of nanostructures
Sequential covalent synthesis
It is used to generate arrays of covalently linked atoms with well defined composition connectivity and shape.

Ex: Vitamin B12 (wood ward 1973, Eschenmoser and winter 1977).

It generates states that are far from D minimum (thermodynamically stable moieties) (H_2 bonds) reverse interactions are used to bind molecules, pre-organization of interacting gps by covalent bond to entropy and to determine shape of the aggregate, choice of components to recognize each other, high selectivity and design of system show positive coperativity.

Covalent polymerization
It is useful strategy for preparation of molecular weight compounds (Bovey and Winslow, 1978, Seymour and Carraher, 1988). In covalent polymerisation, low molecular weight(monomers) react to form a polymer.

A polymer is a unit comprising of covalently connected monomers. Polymerization offers limited chance for controlled variation structure or 3D shape. So polymerization indirectly stabilize nanostructures.

Ex: phase separated polymers(Shull et al,1991;Frankel et al,1989).

Self organizing synthesis
It doesn't employ covalent bond. It only relies on weaker, less directional bond i.e ionic bond, H_2 bond and vanderwalls interaction to organize atoms, ions or molecules into state.

The structure prepared by thus strategy are crystals, ligand crystals, colloids, micelles, emulsions, phase separated polymers Languir blodget films and self-assembled monolyers. Self-organization is peculiar feature of these methods ions or molecules adjust their own position to reach thermodynamic minimum. By employing this method, true nanostructures are prepared.

Molecular self-assembly (MSA)
It is spontaneous assembly of molecules into a stable, non-covalently joined structure of aggregates.
MSA combines all the features of above strategies to make large structurally well defined assemblies of atoms.

- Formation of well defined molecules of intermediate state complexity through sequential covalent synthesis.
- Formation of large, stable state defined aggregates of molecules through H_2 bonds, vanderwals interactions or other non-covalent links.

- Use multicopies of a polymer to simplify the synthetic task. This helps to understand and overcome the unfavourable entropy together in single aggregate.

For the final assembly to be stable and to have a defined shape, non-covalent connection or multiple H_2 bonding between molecules must be stable.

Rational Behind Development Of Aquasomes

In last 3 decades due to development in Pharmacy field, intention of reducing toxicity and dosage requirement, enhance cellular targeting and to improve shelf life, Tinatyszyanetal (1994) have explained 3 system like prodrug or zymogen like system, simple soluble macro molecular system and complex particulate multi-component system.

The carriers like prodrugs, macromolecules and liposomes have attained the intended purpose but, prone to some bio-physical barriers. The drug may react with carrier leading to degradation of drug in such a situations, the aquasomes are promising carriers to prevent degradation by the protective poly hydroxy films, which prevent denaturation of drug.

Molecular confirmation is 3D confirmation with respect to the target or 3 activity related spatial qualities. Dehydration, degradation, decomposition can change. The spatial qualities change (many biological molecules like proteins undergo denaturation and become non-functional when desiccated) at the same time. They are not resistant to denaturation for a long time in aqueous state. In aqueous state temperature, solvents, salts can result in denaturation. So, water like circumstances should be maintained to prevent dehydration, conformational changes, degradation, alteration of the composition.[3]

So, to prevent these adverse or allergic reactions caused by drug dissolution system or carriers aquasomes with natural stabilizers (sugars) on which drug incorporated is preferred here, sugar act as dehydroprotectants.

Many scientists support the dehydro protectant action of sugars (Backetal, 1979; Timesheff 1981)

Fungal spores producing ergot were stabilized by sucrose rich solution. Dessicator induced denaturation can be prevented by trehalose.

Back-et-al (1979) reported that sugar and polyols stabilize protein against heat denaturation and it is argued that stabilization is due to the effect of sugars and polyols on hydrophobic interactions. The stability after sugar coating is explained by their different influence on state of water.

The hydroxyl gap on sugar interacts with polar gap of biological molecules in a same manner to water molecules alone and prevent dehydration.

The OH gap replaces the water around protein thus; maintain integrity in absence of water.

Systematic biophysical constraints and intrinsic biophysical constraints destabilize the drug.

I.B.C caused by drug dissolution system can be prevented by using natural molecules stabilizers like sugar.

System bio physical constraints

Some physics, chemistry agents cause degradative which cause design by compositional changes, loss of spatial activity, breaking of bonds. Such agents include ultraviolet, heat free radicals etc. These agents promote dehydration which leads to molecular inactivation.

Degradative agent's pre in mammals can destroy poly peptides, while denaturation during dehydration can impair poly peptides on long term storage.

Intrinsic

Intrinsic are imposed by drug dissolution system. When drug is immobilized to nanoparticle substrate. It can cause surface induced dehydration and in turn molecular conformation so lead to sub-optional pharmacological activity.

Bio-chemically active molecules can loose their functional activity in both dry and wet states. At the same time water environment is essential for activity.

Therefore the challenge is to store and transport bio-molecules in the dry state without loosing activity. The solution for this challenge is formulation as aquasomes which are Nano sized water bodies. Sugar coating acts as dehydro protectant on which drug is coated. Sugar coating acts as dehydroprotectant on which drug is coated.

Role of disaccharides in preserving

Sugar acts as protectant. So this system is suitable for preserving cells, proteins, flavours, The first studies that indicate state and function of cellular components can be protected by sugar driving lyophilization were conducted on Ca^{+2} transporting microsomes isolated from rabbit muscles and lobster muscles.

Ca^{+2} transporting microsomes lyophilized without stabilizing sugar. The rehydrated vesicles show Ca^{+2} uptakes and uncoupling of ATPase.

Vescicles lyophilized with 0.3g trehalose per gram membrane are morphological distinguisghable from freshly prepared vescicles.

It was concluded that trehalose water system passes into a glassy state and there by arrests long range of molecular motion there by denaturation is thus impeded.

Method of preparation of aquasome[4,5,6,7,8]

Aquasomes are prepared by using principle of self-assembly in 3 steps

- Preparation of core
- Coating of core
- Immobilization of drug molecule

Aquasome is a aqueous colloid comprised of small solids formed from relatively few atoms clustered in solid crystals to which glassy carbohydrate are applied as surface coating it acts as dehydroprotectant for subsequent attatchment of active drug can didate.

Preparation of core

First step involved in aquasome preparation is the fabrication of ceramic core. This depends on proper selection of core materials. These ceramic cores can be fabricated by colloidal precipitation and sonication, inverted magnetron sputtering, plasma condensations and other processes.

For the core, ceramic materials were widely used. Since ceramics are crystalline, the surface modification have limited effect on the atoms below surface layer there, bulk properties are preserved. The high degree of order ensures that the surfaces exhibits high level of surface energy that favours the binding of poly hydroxy oligomeric surface film. Two ceramic cores that are most often used are diamonds and $CaPO_4$.

There is a Direct current reactive magnetron sputtering, in this a 3 inch diameter target of high purity tin is sputtered in a high pressure gas mixture of organ and oxygen. The ultra fine particles for formed in the gas phase are then collected on copper tubes cooled to 77K with flowing nitrogen.

Eg: system of nano crystalline tin oxide core ceramic colloidal precipitations and sonication by reacting solutions.

It is used for preparation of nanocrystalline brushite (Ca^{+2} poly dehydrate) here, reacting solutions are di sodium hydrogen phosphate and $CaCl_2$.

$2Na_2HPO_4+3CaCl_2+H_20$ ------- > $Ca_3(PO_4)_2+4NaCl+2H_2+Cl_2+$ (O)

Sonication

It is used for the preparation of n.c carbon ceramic, diamond particles.

Carbohydrate coatings

The carbohydrates are coated on the ceramic cores. There are number of processes for absorption of carbohydrates coating epitaxially on the surface of nano-crystalline ceramic cores.

Poly-hydroxy oligomers are generally added to the meticulously cleaned ceramics in ultra pure water, sonication and lyophilization promote irreversible absorption of carbohydrate on to the ceramic surfaces. Excess carbphydrate is removed by stir cell ultra filteration. Commonly used coating materials are cellulobiose, citrate, pyridoxal-5-phosphate, sucrose and trehalose.

Cellulobiose

It is prepared from cell-free enzymatic hydolyzate of cellulose. It is H-O-B-D-glucopyranosil-D-glucose [$C_{12}H_{22}O_{11}$ molecular weight-342.30]

Pyridoxal-5-PO_4

It is 3-hydroxy 2 methyl-5-[(phosphonoxy) methyl]-4-ester or 3 hydroxy 5-(hydroxy methyl)-2-methyl isonicotinaldehyde 5-phosphate [$C_8H_{10}NO_6$ molecular weight-247.14]. It is prepared by the action of phosphorous oxy chloride on pyridoxalin aqueous solution and by phosphorylation of pyridoxamine with 100% H_3PO_4.

Trehalose

It is alpha-D glucopyranosil alpha-D glucopyranoside [$C_{12}H_{22}O_4$ molecular weight-342.30]. It is found in parasite beetle; larin us. Species and in fungi a manita muscaria. It can be isolated from compressed bakers yeast.

Sucrose: (non-reducing sugar, undergo muta rotation**)**

Sucrose is a cane sugar extracted from sugar cane, beetroots. It is a di-saccharide composed of one molecule of alpha D-glucopyranose and one molecule of BD-fructofuranose.

Immobilization of drugs

The sugar coated nano-crystalline core provides the solid phase for the subsequent non-denaturing self-assembly for broad range of bio-chemically active molecules. The drug can be loaded by partial absorption.

Fate of aquasome[9]

Aquasome is a Drug delivery vehicle; colloidal range biodegradable nanoparticles. So, highly concentrated in liver and muscles. Since the drug is adsorbed on the surface of system, they maynot be any difficulty in receptor recognition on the active state. So that pharmacological (or) biological activity can be achieved immediately.

Properties of aquasomes[10]

1. Aquasomes have large size and active surface hence can be efficiently loaded with substantial amounts of agents through ionic, non co-valent bonds, van der waals forces and entropic forces. As solid particles dispersed in aqueous environment, exhibit physical properties of colloids.
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 water like properties provides a platform for preserving the conformational integrity and bio chemical stability of bio-actives.
4. Aquasomes due to their size and structure stability, avoid clearance by reticuloendothelial system or degradation by other environmental challenges.

Characterization of aquasomes[10]
Aquasomes are mainly characterized for structural analyses, particle size, and morphology these are evaluated by X-ray powder diffractometry, transmission electron microscopy, and scanning electron microscopy. The morphology and the size distribution were obtained through images of scanning electron microscopy. The chemical composition and the crystalline structure of all samples were obtained through X-ray powder diffractometry.

Applications of aquasomes
Aquasomes as RBC substitutes[11]
Aquasomes can deliver large complex labile molecules like haemoglobin by overcoming many biological hurdles.
Core : Diamond
Coating material : Biodegradable carbohydrate
Encapsulation : with standard mixture of phospholipids by incorporating haemoglobin in aquasome carriers.
Aquasomes as RBC substitutes can achieve an 80% concentration of haemoglobin it can deliver oxygen in a non linear manner like natural RBC.

Aquasomes for viral antigen delivery or Vaccine[13]
Aquasomes can deliver Epstein Barr virus and HIV for the B-cell stimulation.

Aquasomes to deliver HIV vaccine
Core : Surface modified carbon, calcium phosphate ceramic particles.

Non-nuclear material extracted from HIV is immoblised.

Coating material: Disaccharide cellobiose emulsified viral proteins and dialyzed in to final delivery vehicle.

Aquasomes to deliver Epstein Barr Virus
Core : Tincoxide
Coating material : Cellobiose emulsified with gp 350 of envelope of Epstein Barr Virus.

Aquasomes for the delivery of mussel adhesive protein
Core : Diamond
Coating material : Cellobiose
Mussel adhesive protein has more avidity to hydrophilic than hydrophobic group so, the preferred coating material should be hydrophilic.

Aquasomes for insulin delivery[14]
Core : Calcium phosphate di hydrate
Coating material : Cellobiose, citrate, pyridoxal-5-phosphate, and trehalose.
Method for loading insulin is by partial adsorption method at low temperature and lyophilization.
Aquasomes show 60% increased pharmacological activity with the same dose of insulin delivered through intravenous route.
Aquasomes can deliver other substances like DNA, genetic material, pigments, dyes and cosmetics.

CONCLUSION
Aquasomes are novel drug delivery systems based on principle of self-assembly. The drugs delivered through aquasomes show increased biological activity even in case of conformational sensitive ones. Due to unique carbohydrate coating, destructive interaction between the drug and carrier is prevented. The aquasomes appear to be promising carries for broad range of molecules including viral antigens, insulin. Role of carbohydrates can further extend the applications of aquasomes.

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