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AQUASOMES: A NOVEL APPROACH IN DRUG CARRIER SYSTEM

Snehal Patel*[1], Chintan Aundhia[1], Avinash Seth[1], Nirmal Shah[1], Kartik Pandya[1] and Darshika Patel[2]

*[1]Deparatment of Pharmacy, Sumandeep Vidhyapeeth, Vadodara.
[2]Deparatment of Pharmacy, Pioneer Pharmacy Degree College, Vadodara.

***Correspondence for Author: Snehal Patel**

Deparatment of Pharmacy, Sumandeep Vidhyapeeth, Vadodara.

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ABSTRACT

Aquasomes are round particles made up of calcium phosphate or ceramic diamond coated with a polyhydroxyloligomeric film and perform as nanoparticulate carrier system but despite of being simple nanoparticle these are three layered self-assembled structures, made up of a solid phase nanocrystalline core coated with oligomeric film on which biochemically active molecules are adsorbed with or without changes. The strong center core gives the structural stability, however the carbohydrate coating provides protection against dehydration and stabilizes the biochemically active molecules. After synthesis of solid center of ceramic and polyhydroxyoligomeric material coating like cellulobiose and trehalose the last stage were drug loading during which the aquasomes act as host particles to non-covalently interact with bio-active moiety via hydrogen and cationic bonding. It facilitates delivery of various protein molecules like liable enzymes and insulin via non covalently adsorption over polysaccharide layer and conforms the stability and remain orally active.

KEYWORDS: Aquasomes, calcium phosphate, Nanoparticles.

INTRODUCTION[1, 2]

Within the last decade diverse technological strategies have been proposed in order to obtain nanoparticles of a distinct nature, charged with drugs which in turn have revolutionized the systems of drug administration, particularly those of controlled release and the ones oriented at the vectoring of the active principle for release at target tissue or organs. Various methods used 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 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. Aquasomes are nanoparticulate carrier system but instead of being simple nanoparticle these are three layered self assembled structures, comprised of a solid phase nanocrystalline core coated with oligomeric film on which biochemically active molecules are adsorbed with or without modification. Aquasomes are like “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 is exploited in targeting of bio-active molecules like peptide and protein hormones, enzymes, antigens and genes to specific sites. These three layered structures are self-assembled by non covalent and ionic bonds. These carbohydrate stabilize nanoparticles of ceramic are known as “aquasomes”. The pharmacologically active molecule incorporated by co-polymerization, diffusion or adsorption to carbohydrate surface of pre formed nanoparticles. Aquasomes discovery comprises a principle from microbiology, food chemistry, biophysics and many discoveries including solid phase synthesis, supramolecular chemistry, molecular shape change and self assembly.

OBJECTIVES[3]

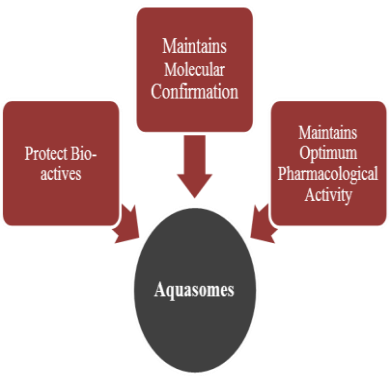

Figure 1: Objective of Aquasomes

RATIONALE[4]

Aquasomes are like “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 is exploited in targeting of bio-active molecules like peptide and protein hormones, enzymes, antigens and genes to specific sites.

PROPERTIES[3, 5]

1. Aquasomes possess 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.

PRINCIPLE OF SELF ASSEMBLY[6, 7]

Self assembly implies that the constituent parts of some final product assume spontaneously prescribed structural orientations in two or three dimensional space. The self assembly of macromolecules in the aqueous environment, either for the purpose of creating smart nanostructure materials or in the course of naturally occurring biochemistry, is governed basically by three physicochemical processes: the interactions of charged groups, dehydration effects and structural stability.

I- Interaction between charged groups

The interaction of charged groups, such as amino, carboxyl, sulphate, phosphate groups facilitates long range approach of self assembly sub units. Charged group also plays a role in stabilizing tertiary structures of folded proteins.

II- Hydrogen bonding and dehydration effect

Hydrogen bond helps in base pair matching and stabilization of secondary protein structure such as alpha helices and beta sheets. Molecules forming hydrogen bonds are hydrophilic and this confers a significant degree of organization to surrounding water molecules. In case of hydrophobic molecules, which are incapable of forming hydrogen bond. However, their tendency to repel water helps to organize the moiety to surrounding environment. The organized water decreases the overall level of disorder/ entropy of the surrounding medium. Since, organized water is thermodynamically unfavorable, the molecule loose water/dehydrate and get self assembled.

III- Structural stability

Molecules that carry less charge than formally charged groups exhibit a dipole moment. The forces associated with dipoles are known as van der waals forces. 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. The Vander Waals forces, most often experienced by hydrophobic molecular regions that are shielded from water play a subtle but critical role inmaintaining molecular shape or conformation during self-assembly. The van der waals forces are largely responsible for hardness or softness of molecules. The van der waals interaction among hydrophobic side chain promotes stability of compact helical structures which are thermodynamically unfavorable for expanded random coils. It is the maintenance of internal secondary structures, such as helices which provides sufficient softness, and allows maintenance of conformation during self assembly, small changes are necessary for successful antigen- antibody interactions. In biotechnological self-assembly, this can lead to altered molecular function and biological activity. Thus, the van der waals need to be buffered for maintaining the optimal biological activity. In case of aquasomes, sugars help in molecular plasticization.

METHOD OF PREPARATION OF AQUASOMES[8]

1. Preparation of core material
2. Coating of core material
3. Immobalization of drug candidate

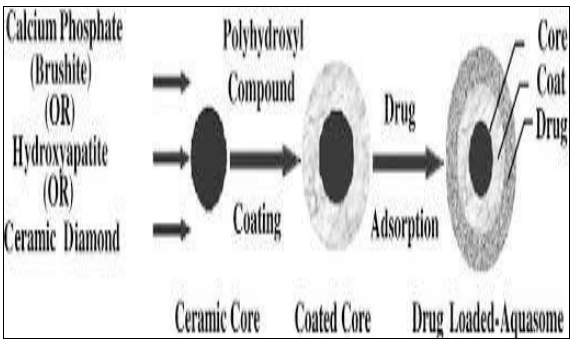

Figure 2: Method of Preparation of Aquasomes

Material used and its importance

Initially for preparation of nanoparticles core both polymers and ceramic can be used. Polymers used are albumin, gelatin or acrylates. Ceramics used are diamond particles, brushite (calcium phosphate) and tin oxide core. For core, ceramic materials were widely used because ceramics 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. (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. Second step followed by coating of carbohydrate epitaxially over nanocrystalline ceramic core. The commonly used coating materials are cellobiose, pyridoxal-5-phosphate, sucrose and trehalose, presence of carbohydrate film prevents soft drug from

changing shape and being damage when surface bound. Third step bioactives molecules adsorbed which possess property of interacting with film via non-covalent and ionic interactions.

CHARECTERIZATION OF AQUASOMES[2, 6]

a. X-ray powder diffractometry
b. Transmission electron microscopy
c. Scanning electron microscopy
d. Drug Loading Efficiency
e. Particle size distribution
f. Zeta Potential
g. In-vitro drug release

APPLICATIONS[9, 10]

1. Aquasomes used as vaccines for delivery of viral antigen i.e., Epstein-Barr and Immune deficiency virus to evoke correct antibody, objective of vaccine therapy must be triggered by conformationally specific target molecules.
2. Aquasomes as red blood cell substitutes, haemoglobin immobilized on oligomer surface because release of oxygen by haemoglobin is conformationally sensitive. By this toxicity is reduced, haemoglobin concentration of 80% achieved and reported to deliver blood in non linear manner like natural blood cells.
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.
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.

FATE OF AQUASOMES

1. Since aquasomes are 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 as in case of insulin and antigen delivery, 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
2. 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 cytoplasm after disappearance of the phagosome membrane or dissolution after formation of heterophagosomes. Phagocytosis of calcium phosphate coincided with autophagy and the accumulation of residual bodies in the cell.
3. Monocytic activities can be modulated by many soluble factors and are increased by IFN-g (interferon gamma) or 1, 25 dihydroxy cholecalciferol. Other cytokines can also contribute to inflammatory mechanism and may be involved in the biodegradation process.

CONCLUSION

Aquasomes represent one of the simplest yet a novel drug carrier based on the fundamental principle of self assembly. The drug candidates delivered through the aquasomes show better biological activity even in case of conformationally sensitive ones. This is probably due to the presence of the unique carbohydrate coating the ceramic. Also these formulations have been found to evoke a better immunological response and could be used as immune adjuvant for proteinaceous antigens. This approach thus provides pharmaceutical scientists with new hope for the delivery of bioactive molecules. 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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