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AQUASOMES- A NEWER DRUG DELIVERY SYSTEM

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Abstract:
In biomedical research Nanotechnology has emerged field in the last few decades. The present context is an attempt to present the brief information about nanobiotechnological applications. Nanobiopharmaceutics involves delivery of biopharmaceutical product through different biomaterials like multifunctional nanoparticles, quantum dots, aquasomes, superparamagnetic iron oxide crystals, and liposomes dendrimers. Of the many different types of immunopotentiating compounds that have been researched, aquasomes are of considerable promise, because of their potency and adjuvanticity. Enzyme activity and sensitivity towards molecular conformation made aquasome as a novel carrier for enzymes like DNAses and pigment/ dyes.This report reviews the principles of self assembly, the challenges of maintaining both the conformational integrity and biochemical activity of immobilized surface pairs. Discovery of Aquasomes comprises a principle from microbiology, food chemistry, biophysics and many discoveries including solid phase synthesis, supramolecular chemistry, molecular shape change and self assembly. Aquasomes have potential activity and act as a carrier system for delivery of peptide, protein, hormones, antigens and genes to specific sites. Aquasome deliver their content through specific targeting, molecular shelling and slow sustained release process. Aquasome technology represents a platform system for conformational integrality and biochemical stability of bioactives.

Key Words : *Aquasomes, Nanopotential Compounds, Biomaterial, Immunopotential*

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INTRODUCTION:

Aquasomes were first developed by Nir Kossovsky and these carbohydrate stabilize nanoparticles of ceramic are known as"aquasomes". Aquasomes are termed as "bodies of water", since they have water like properties which protect and preserve fragile biological molecules and this property of maintaining conformational integrity as well as high degree of surface exposure is used in targeting and delivering of bio-active molecules like peptide and protein hormones, antigens and genes to specific sites where action is required. The pharmacologically active molecule incorporated by co-polymerization, diffusion or adsorption to carbohydrate surface of preformed nanoparticles. Aquasomes are three layered structure having a self assembledby non-covalent bonds. Principal of "self assembly of macromolecule" is covered by three physiochemical process that are 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 protein[1,2].

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 areincapable of forming hydrogen bond, their tendency to repel water helps to organize themoiety to surrounding environment, organized water decreases level of entropy and is thermodynamically unfavourable, the molecule dehydrate and get self assembled. Self assembly leads to altered biological activity, vander waals needs to be buffered. In aquasomes, sugars help in molecular plasticization [3,4,5].

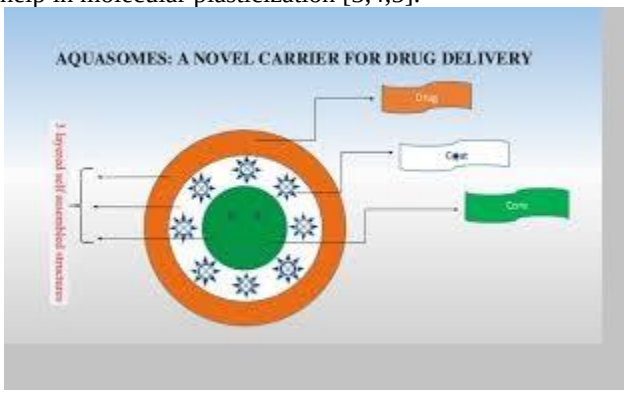

Fig.1.Aquasomal Drug Delivery system

STRUCTURE OF AQUASOMES [6,7,8]

Aquasomes are nanoparticulate carrier system but instead of being simple nanoparticles these are three layered self assembled structures, comprised of a solid phase nanocrystalline core coated with oligomeric film to which biochemically active molecules are adsorbed with or without modification. Aquasomes are first discovered by Nir Kossovsky. Aquasomes are also called as "bodies of water" andtheir water like properties protect and preserve fragile biological molecules, This property of maintaining conformational integrity as well as high degree of surfaexposure made it as a successful carrier system for bioactive molecules like peptide, protein, hormones, antigens and genes to specific sites, that is for targeting.

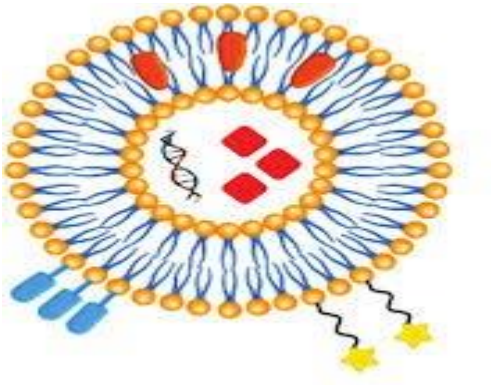

Fig No 2.Structure Of Aquasomes

Aquasomes are nanoparticulate carrier system but instead of being simple nanoparticles these are three layered self assembled structures, comprised of a solid phase nanocrystalline core coated with oligomeric film to which biochemically active molecules are adsorbed with or without modification. The soild core provides the structural stability, while the carbohydrate coating plays important role act as natural stabilizer protects against dehydration and stabilizes the biochemically active molecule

Aquasomes are spherical 60–300 nm particles. Aquasomes offer an attractive mode of delivery for drugs which having the problems such as route of delivery ,physical as well as chemical instability ,poor bioavailability and potent side effects . 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 are exploited in targeting of bio-active molecules like peptide and protein hormones, antigens and genes to specific sites .

ADVANTAGES[9,10]

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, peptideswhich are known as biological labels can be used for various imaging tests.
5. Enzyme activity and sensitivity toward molecularconformation 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.
7. Aquasomes conserves the structural veracity and biochemical constancy of drug particles.
8. Due to their specific size and structural stability, aquasomes evade RES (reticuloendothelial clearance) or degradation in acidic pH.
9. Receptor recognition is not difficult as the drug is easily adsorbed on the surface of aquasomes, hence sitespecific delivery of biomolecules can be achieved easily.
10. Aquasomes own large size and an active surface hence, substantial amount of drug molecules can be surface adsorbed through ionic, non-covalent bonds, van der Waals forces, and entropic forces.

DEMERITS [11]

Drug release from aquasomes can be controlled by altering their surface through combination of specific targeting, molecular shielding, and controlled release of therapeutics.

PROPERTIES OF AQUASOMES [12,13]

- Aquasomes can be efficiently loaded with substantial amounts of agents through ionic, non co-valent bonds, van der waals forces and entropic forces since they possess large size and active surface. As solid particles dispersed in aqueous environment, exhibit physical properties of colloids. Aquasomes mechanism of action is controlled by their surface chemistry.
- Aquasomes allow delivery of drug contents through combination of specific targeting, molecular shielding, and slow and sustained release process. Aquasomes have water like properties which provides a great advantage for preserving the conformational integrity and biochemical stability of bio-actives.
- Aquasomes avoid clearance by reticuloendothelial system or degradation by other environmental challenges due to their size and structure stability. 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 X-ray analysis of the samples and drug loading efficiency and in vivo performance. The chemical composition and the crystalline structure of samples can be obtained by X-ray powder diffractometry.
- 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. 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. Aquasomes water like properties provides a platform for preserving the conformational integrity and bio chemical stability of bio-actives. Aquasomes due to their size and structure stability, avoid clearance by reticuloendothelial system or degradation by other environmental challenges.

COMPOSITION OF AQUASOMES [14,15]

I- Core material

Ceramic and polymers are most widely used core materials. Ceramic such as diamond particles, brushite (calcium phosphate) and tin oxide are used. Core materials, for example, ceramic (diamond particles, brushite/calcium phosphate, and tin oxide) and polymers (gelatin, albumin, or acrylate) are broadly employed.

II- Coating material

Coating materials commonly used are cellobiose, pyridoxal 5 phosphate, sucrose, trehalose, chitosan, citrate etc. Carbohydrate plays important role act as natural stabilizer, its stabilization efficiency has been reported. Beginning with preformed carbon ceramic nanoparticle and self assembled calcium phosphate dihydrate particles (colloidal precipitation) to which glassy carbohydrate are then allowed to adsorb as a nanometer thick surface coating a molecular carrier is

formed. Cellobiose pyridoxal-5-phosphate, trehalose, sucrose, citrate, chitosan, etc., are used. Carbohydrate act as an efficient natural stabilizer. Carbohydrates is adsorbed as a glassy film in nanometer size range coating the preformed ceramic-nanoparticles and self-assembled calcium phosphate dihydrate particles.

III- Bioactive

They have the property of interacting with film via non covalent and ionic interactions . Bioactive compounds own the characteristics to interact with glassy carbohydrate film through ionic and non-covalent bonding.

PRINCIPLE OF SELF ASSEMBLY[16,17]

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- 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 surroundingenvironment. 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- 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 asubtle but critical role inmaintaining molecular shape o conformation during self-assembly. The van der waalsforces 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 ofaquasomes, sugars help in molecular plasticization.

PREPARATION METHODS OF AQUASOMES [18,19]

The general procedure consists of an inorganic core formation, which will be coated with Lactose forming the polyhydroxylated core that finally will be loaded by model 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.

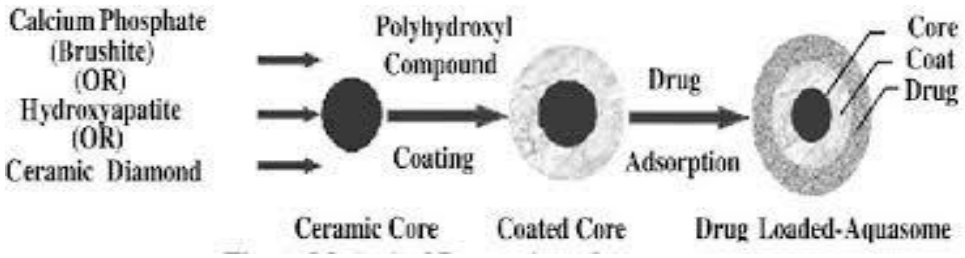

Fig.No.3. Preparation Stages Of Aquasomes

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. **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 rnagnetron 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.

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 (polyhy-droxy 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 nondenaturing self assembly for broad range of biochemically active molecules. The drug can be loaded by partial adsorption.

CHARACTERIZATION OF AQUASOMES[19,20]

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.

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.

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.

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 .

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 .

Characterization of drug-loaded aquasomes

Drug payload

The drug loading can be determined by incubating the basic aquasome formulation (i.e., without drug) in a known concentration of the drug solution for 24 hours at 4°C. The supernatant is then separated by high-speed centrifugation for 1hour at low temperature in a refrigerated centrifuge. The drug remaining in the supernatant liquid after loading can be estimatedby any suitable method of analysis .In vitro drug release studiesThe in vitro release kinetics of the loaded drug isdetermined to study the release pattern of drug from the aquasomesby incubating a known quantity of drug-loaded aquasomes in abuffer 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 .

In-process stability studies

SDS-PAGE (sodium dodecyl sulphate

polyacrylamide gelelectrophoresis) can be performed to determine the stability and integrity of protein during the formulation of the aquasomes.

APPLICATIONS OF AQUASOMES

I- Insulin delivery[21,22]

Cherian et al prepared aquasomes using a calcium phosphate ceramic core for the parenteral delivery of insulin. The core was coated with various disaccharides such as cellobiose, trehalose, and pyridoxal-5-phosphate. Subsequently the drug was loaded to these particles by adsorption method. The in vivo performance of various aquasome formulations of insulin was evaluated using albino rats. Prolonged reduction of blood glucose was observed with all formulations except cellobiose-coated particles. Pyridoxal-5-phosphate coated particles were found to be more effective in reducing blood glucose levels than aquasomes coated with trehalose or cellobiose. This could be attributed to the high degree of molecular preservation by pyridoxal-5-phosphate. The prolonged activity was attributed to slow release of drug from the carrier and structural integrity of the peptide . The utility of nanocarriers for effective delivery of insulin was also proved by Paul and Sharma. They prepared poroushydroxyapatite nanoparticles entrapped in alginate matrix containing insulin for oral administration. The optimum controlledrelease of insulin was also achieved in this study .

II- Oral delivery of acid labile enzyme

Rawat et al proposed the use of a nanosized ceramic core–based system for oral administration of the acid-labile enzyme serratiopeptidase. The nanocore was prepared by colloidal precipitation under sonication at room temperature. The core was then coated with chitosan under constant stirring, after which the enzyme was adsorbed over it. The enzyme was protected by further encapsulating the enzyme-loaded core into alginate gel. The TEM images of particles showed them to be spherical in shape, with an average diameter of 925 nm. The enzyme-loading efficiency of the particles was found to be approximately 46%. The in vitro drug release data followed the Higuchi model in acidic medium (pH 1.2) for a period of up to 2 to 6 hours, while the alkaline medium (Ph 7.4) showed sustained and nearly complete first-order release of enzyme for up to 6 hours. These aquasomes were found to be protecting the structural integrity of enzymes so as to obtain a better therapeutic effect .

III- As oxygen carrier

Khopade et al prepared hydroxyapatite core by using carboxylic acid–terminated half-generation poly(amidoamine) dendrimers as templates or crystal modifiers. These cores were further coated with trehalose followed by adsorption of hemoglobin. The size of the particles was found to be in the nanometer range, and the loading capacity was found to be approximately 13.7 mg of hemoglobin per gram of the core. The oxygen-binding properties of the aquasomes were studied and compared to those of fresh blood and hemoglobin solution. Hill coefficient values determined for fresh blood, for hemoglobin solution, as well as for the aquasome formulation indicated that the properties of hemoglobin including its oxygen-carrying capacity were retained by the aquasomes. Studies carried out in rats showed that aquasomes possess good potential for use as an oxygen carrier. Moreover, the formulation was found to retain its oxygen-binding characteristics over a period of 30 days . In another study Patil and co-workers prepared hydroxyapatite ceramic cores by co-precipitation and self-precipitation. These cores were coated with various sugars including cellobiose, trehalose, maltose, and sucrose. Subsequently, hemoglobin was adsorbed over the coated ceramic core, and the percentage drug loading was estimated by the benzidine method. The oxygencarrying capacity of aquasome formulation was found to be similar to that of fresh blood. Also, the Hill coefficients were found to be good for its use as an oxygen carrier. The aquasome formulations neither induced hemolysis of the red blood cells nor altered the blood coagulation time. The hemoglobin loading to various sugarcoated particles was found to be approximately 7.4%. The formulation was able to retain the hemoglobin over a period of 30 days. No significant increase in arterial blood pressure and heart rate was observed in rats transfused with aquasome suspension on 50% exchange transfusion .

IV- Antigen delivery

The adjuvants generally used to enhance the immunity to antigens have a tendency either to alter the conformation of the antigen through surface adsorption or to shield the functional groups. So Kossovsky et al demonstrated the efficacy of a new organically modified ceramic antigen delivery vehicle. These particles consisted of diamond substrate coated with a glassy carbohydrate (cellobiose) film and an immunologically active surface molecule in an aqueous dispersion. 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 dehydroprotectant, 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. Vyas et al prepared aquasomes by self-assembling of hydroxyapatite using the co-precipitation method. The core was coated with cellobiose and trehalose, and finally bovine serum albumin was adsorbed as model antigen onto the coated core. The aquasomes were found to be spherical in shape with diameter around 200 nm. The coating of carbohydrate over the surface of the core was confirmed by concanavalin A–induced aggregation assay method as well as IR spectroscopy. The antigen-loading efficiency was found to be approximately 20–30%. When the immunological activity of the prepared formulation was compared to plain bovine serum albumin, the former was found to exhibit a better response. In view of these results, aquasomes were proposed to have superior surface immutability, in that they protect the conformation of protein structure and present it in such a way to immune cells that it triggers a better immunological response .

V- Delivery of drug

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

VI- For delivery of gene

Aquasomes can be studied for the delivery of genes. It illustrates the attractive delivery system loaded with genetic material. Studies reveal that aquasomes protect and maintain structural integrity of the gene segment. A five layered composition comprised of the ceramic nanocrystalline core, the polyhydroxyl oligomeric film coating, the non covalently bound layer of therapeutic gene segment, an additional carbohydrate film and a targeting layer of conformationally conserved viral membrane proteins, have been proposed for gene therapy. The aquasome vehicle would afford all of the potential advantages of viral vectors and simultaneous overwhelming the risk of irrelevantgene integration.

VII For delivery of enzymes

Aquasomes also used for delivery of enzymes such as DNAase and pigment/dyes because enzymes activity fluctuates with molecular conformation and cosmetic assets of pigment are subtle to molecular chains. DNAase a therapeutic enzyme used in the treatment of cystic fibrosis was successfully immobilized on aquasomes and targeted to the specific site and elicited significant therapeutic effect as desirable. A marked retention of biological activity was observed with surface immobilized DNAase on the solid phase of a colloidal calcium phosphate nanoparticle coated with polyhydroxy oligomeric films).

VIII For vaccine delivery

Aquasomal-based vaccine delivery presents several benefits such as both cellular and humoral immune retorts can be provoked to antigens adsorbed on the aquasomal surface. For vaccine delivery, outer surface of aquasomes to which antigens are covalently linked comprises of polyhydroxyl oligomers or sugar molecules such as cellobiose, trehalose, maltose, sorbitol, and lactose along with substances which stimulate allosteric effects such as pyridoxal-5-phosphate and sodium citrate which protects the protein from denaturation and degradation. The carbohydrate sheath on ceramic particles confirms the surface characteristics of aquasomes, for example, three-dimensional conformations, a freedom of internal molecular rearrangement initiated by intermolecular interactions and autonomous bulk movement.[23,24]

IX Miscellaneous

Mizushima et al. prepared spherical porous hydroxyapatite particles by spray drying. These particles were tried as a carrier for the delivery of drugs such as interferon α (IFN-α), testosterone enanthate, and cyclosporine A.

CONCLUSION:

Aquasomes, are the self-assembling and surface-modified nanocrystalline ceramic cores, seem to have potential and promising carriers capable of preserving the structural integrity of protein pharmaceuticals and carrier for delivery of broad range of molecules including viral antigens, heamoglobin and insulin, thus promoting a better therapeutic effect. Also, these formulations have been found to evoke a better immunological response and could be used as immunoadjuvants for proteinaceous antigens. This approach thus provides pharmaceutical scientists with new hope for the delivery of bioactive molecules. We can see better biological activity even in case of conformationally sensitive drug candidates because of the presence of the unique carbohydrate coating the ceramic. This strategy may be beneficially extended to the novel delivery of other bioactive

molecules.The molecular plasticizer , carbohydrate prevent the destructive drug-carrier interaction and helps to preserve the spatial qualities. The structural stability and overall integrity is controlled by crystalline nature of the core. We can say aquasomes can be used as a potential carrier for the delivery of a broad range of molecules including viral antigens, hemoglobin and insulin.

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