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Aquasomes: A Novel Drug Delivery Carrier System

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***Abstract*: Nanoparticles, Liposomes, Niosomes, Quantum dots, and Aquasomes are some major different types of Nano biotechnology based carrier system. It is a novel approach to deliver those drug which is degraded when given in conventional dosage form. Aquasomes are three layered self-assembled nanoparticulate carrier system. They are laying in size range about 60-300nm.They are made up of a nanocrystalline solid core which is coated with oligomeric film and upon this film biochemically active molecule are adsorbed with or without modification. Aquasome is colloidal range biodegradable nanoparticle, so that they will be more concentrated in liver and muscles. The strong core gives the structural stability, however carbohydrate coating provide protection against dehydration and stabilizes the biochemically active molecules.**

***Keywords*: Novel drug delivery system, Aquasomes, Oligomeric coating, Bioactive substance, Self-assembled carrier.**

1. Introduction

The word Aquasomes are made up of two words "Aqua" which means water and "Somes" which means cell. It simply means that aquasomes are nanoparticulate system which has properties like water [1]. It is a novel drug delivery system that contain nanoparticulate system which act as a carrier system for bioactive substance like protein, insulin etc. alternatively they are called as "Bodies of Water" because of water like properties [2]. They are said to be nanoparticulate system because of their size which is in nanometer. Their size range is about 60- 300nm [3].

Nanotechnology is defined as design, characterization, production and application of structure, device and systems by controlled manipulation of size and shape at nanometer scale4.

Aquasomes are spherical shaped 60-300 nm nanoparticulate system used for drug and antigen delivery [3]. They are made up of three layered structure. The innermost layer is nanocrystalline core layer made up of three types of materials like Tin oxide, nanocrystalline carbon ceramics (Diamond), and Brushite [5]. Above this, a layer of oligomeric coating is done which is called as second layer and mostly carbohydrate are used for this [4]. And lastly bioactive materials are adsorbed on the surface of oligomeric films with or without modification by co-polymerization, Diffusion, or Adsorption [5]. So "Aquasomes are carbohydrate stabilized nanoparticles of the core which was first developed by NirKossovsky in 1995 [6].

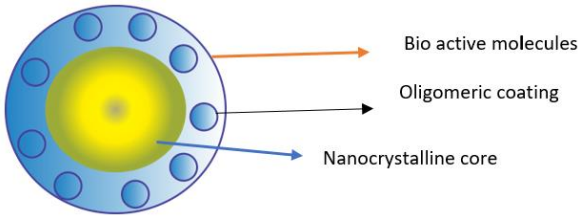

Fig. 1. Aquasomes

The solid core provides the structural stability, while carbohydrate coating protects against dehydration and stabilizes the biochemically active molecules [7]. Carbohydrate plays important role act as natural stabilizer; it's stabilization efficiency has been reported i.e. fungal spore producing alkaloid stabilized by sucrose rich solution8and desiccation induced molecular denaturation prevented by certain disaccharides [9]. These three layered structure are self-assembled by non-covalent bonds.

The property of protection, prevention of fragile biological molecules, maintaining conformational integrity made it as a successful carrier system for bioactive molecules like protein, Hormones and other drugs to specific site [10]. Aquasomes Offer an attractive mode of drug delivery for those drug who faces the problem such as route of delivery, physical as well as chemical instability [11].

Aquasomes nanotechnology represent a platform system for conformational integrity and biochemical stability of bio actives compounds [12]. The discovery of Aquasome include concept from food chemistry, microbiology, biophysics, and frequent discoveries including solid phase synthesis, supramolecular chemistry, molecular shape change and self-assembly [13].

A. Characteristics of Aquasomes

- Aquasomes can be efficently loaded with substantial amount of bioactive agent through ionic, non-covalent bond, vanderwalls forces. This is possible because of larger size and active surface provided by aquasomes [9].
- In Aquasome, the amount of the drug should be low because these nanoparticulate carrier protect the drug/bioactive material from altered environment and enzymatic degradation [14].

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- Mechanism of action of aquasomes is governed by their surface chemistry and deliver their content through combination of specific targeting, molecular shielding and sustained release process [15].
- Aquasomes avoid clearance by reticuloendothelial system and degradation by other environmental condition due to their structure stability and size [16]
- The core material is composed of calcium phosphate, which is biodegradable in nature and it's degradation can be achieved by monocyte and osteoclasts [14].
- Aquasomes provides water like environment due to oligomeric coating and due to this region it provides a platform for maintaining the conformational integrity and stability of bioactive compound.
- Carbohydrate coating of aquasomes prevent destructive denaturation interaction between drug and solid carrier.14

B. Objectives of Aquasomes

- The main region of preparing aquasomes is to prevent bioactive material from altered body environment [12].
- It avoids multiple injection schedule because this system act like a reservoir to release the content in continuous or pulsatile manner [17].
- Due to its prevention mechanism of bioactive substance aquasomes provide optimum pharmacological action in low dose concentration [14].
- Multilayered aquasomes conjugated with biorecognition mol. Such as antibodies, nucleic acid, and it can be used for imaging test.
- Both cellular and humoral immunity can be elict by delivering the antigen adsorbed aquasomes vaccine [17].

C. Composition of Aquasomes

Aquasomes are Three layered self-assembled structure in which innermost layer is made up of ceramic core and above this layer carbohydrate coating is placed and lastly drug depositionis done on the carbohydrate layer [18]. The composition of the materials are discussed below,

1) Core material

Core material is the building block of aquasomes, they are made up of either polymer based e.g. Albumin, acrylate, gelatin. And ceramic e.g. calcium phosphate, hydroxyappetite, nanocrystalline tin oxide, Diamond [19].

Ceramic is used as chief core material because of their structural regularity and elevated level of surface energy that offer effective binding of coating material [20]. Calcium phosphate is also used because of their natural occurance in the human body and it Is also biodegradable in nature.

Hydroxyappetite is also used in the formation of core material in aquasome [21].

2) Coating material

Material used in coating of core layer are cellobiose, trehalose, citrate, chitosan, pyridoxal-5-phosphate etc. [22]. Carbohydrate act as natural stbabilizers and plays a crucial role in adsorbing bioactiv molecule. Carbohydrate posseses hydroxyl group that interact with charged and polar functional group present on bioactive substance and preserve the structural integrity of protein. Core material is also stabilized by carbohydrate by non-covalent interaction [23].

- *Cellobiose*

Celllobiose is a diasaccharide with the molecular formula (C6H7(OH)4O)2O). It is classified as a reducing sugar.it is a white crystalline water soluble disaccharide made up of two mol. Of glucose joined by Beta(1-4)glycosidic linkage. It protects the drug molecule from dehydrate. cellobiose is obtained by hydrolysis of cellulose [24].

- *Trehalose*

Trehalsoe is a sugar consisting of two molecule of glucose. It is widespread non-reducing disaccharide having 1,1 glycosidic linkage and it is sometime referred as mushroom sugar [25]. Trehalose is cleaved by enzyme trehalase which convert trehalose into glucose molecule. This enzyme is found in the intestine of human [26]. Trehalose possess 3 isomer, among of three anomer of isomer, only α, α-trehalose has been biosynthesized in a multiplicity of living organism. The main function of trehalose is to protect some organism against dehydration that will allow them to survive in a completely dried condition.

By using this ability of trehalose, researchers used it to preserve the structure of bioactive material that are labile or sensitive to dried condition. Bioprotectant behaviour of trehalose is attributed to its ability to exist in different form of polymorphs, Both in crystalline and amorphous form [25].

- *Chitosan*

It is a linear polysaccharide composed of randomly distributed β-linked D-glucosaamine and N-acetyl D glucosaamine. The key source of chitosan are insects, crabs, shrimp shell. Chitosan is obtained from deacetylation of chitin and it has a nobel film forming character. There are 3 functional group present in chitosan i.e. amine, primary and secondary hydroxyl group. These functional group act as a spacer to link drug molecule [27].

- *Role of Disaccharide*

To preserve the structure of protein on dehydration, polar and charged group are interact with water similar the hydroxyl group present on czrbohydrate interact with polar and charged group to preserve the structure [28]. Disaccharide like trehalose have the ability to stress tolerance in fungi, bacteria, insect and yeast. The disaccharide rich in hydroxyl group and help to replace the water around polar residue in protein, thereby maintaining their integrity in the absence of water [29].

3) Bioactive substance

Certain molecule of drug like, protein, insulin are deliver to the specified target site through Aquasomes. Bioactive substance are placed on the carbohydrate layer by the process of diffusion, adsorption etc. They have the property of interacting with film via non-covalent and ionic interaction [30].

D. Principle of self-Assembly

The three layered structure of aquasomes are self-assembled by non-covalent bond. Self-assembly of bioactive substance in

the aqueous environment is a special property for designing of nanotechnology which is primarily Governed by 3 physicochemical properties: [31].

(a) Interaction between charged group

Functionl group present in the bioactive material such as amino, carboxylic, sulphate, phosphate group.it facilitate the long range approach of self-assembling unit. Charge group stabilizes tertiary structure of protein [32].

(b) Hydrogen bonding and dehydration effect

Hydrogen bond are formed between H+ of one molecule and electronegative atom of other molecule. Formation of hydrogen bond helps in the stabilizing the secondary structure of protein. Hydrogen bond are formed by hydrophilic molecule and this confer a significant degree of organization to surrounding water molecules. On the other hand, hydrophilic molecule are unable to form hydrogen bond.

(c) Structure Stability

Structure stability of protein in biological environment is determined by interaction between charged group and hydrogen bond largely external to molecule and by vanderwall forces to internal molecule.

The vanderwal forces most often experienced by hydrophobic molecular region that are shielded from water play a subtle but critical role in maintaining molecular shape or conformation during self assembly [32].

E. Method of Preparation of Aquasomes

In the preparation of aquasomes Three main steps are involved,

1) Preparation of ceramic core

Core fabrication is the first and the basic steps in the preparation of aquasomes. It depens totally on the material used for its preparation. Different types of core material are discussed previous. Method by which aquasomes are prepared are [33],

- Colloidal precipitation
- Sonication
- Inverted magnetron sputtering
- Plasma condensation

2) Coating of ceramic core with carbohydrate

Material like cellobiose, Citrate, pyridoxal 5-phosphate, trehalose and sucrose are used for the coating of ceramic core. This is coating carried out by addition of carbohydrate into an aqueous dispersion of core under sonication. These are then subjected to lyophilization to promote an irreversible adsorption of carbohydrate onto the ceramc surface. The unabsorbed carbohydrate is removed by centrifugation [34].

3) Loading of drug of choice on carbohydrate layer

This is the final steps in the aquasomes preparation.in this steps loading of drugs to the coated particles by adsorption. For doing this a solution of known concentration is prepared in suitable pH buffer, and coated particle are dispersed into it. The dispersion is the leave for overnight at low temperature to obtain drug loaded formulation [35].

F. Evaluation of Aquasomes

1) Evaluation of ceramic core

- *Size distribution*

Size determination is an important parameter for the evaluation of ceramic core of aquasomes. They are analyzed by scanning electron microscopy, transmission electron microscopy [36].

- *Structure analysis*

For the structure analysis, fourier transform infrared spectroscopy can be used. By using potassium bromide sample disk method, the core as well as the coated carbohydrate layer are also be analyzed by recording their infrared spectra in the wave no. range 4000 to 400 cm-1.the characteristic peak observed are then matched with reference peak [37].

- *Crystallinity*

X-ray diffraction method is used for the analysis of crystalline and aorphous nature of ceramic core. In this technique diffraction pattern of the sample is compared with the standard diffractogram, based on which the interaction are made [38].

2) Evaluation of coated core

Concavalin A induced aggregation method are used for the confirmation of coating of sugar over ceramic core. It determines the amount of sugar coated over core.

Anthrone method is used to determine residual sugar unbound remaining after coating. Also the zeta potential is used for the measure of adsorption of sugar over the core [39].

3) Evaluation of drug loaded Aquasomes

- In vitro drug release studies

In vitro means outside the body, in this method a known amount of drug loaded aquasome are incubating into a buffer of suitable pH at 37^{o}C with continuous stirring. Sample are withdrawn periodically and centrifuged at high speed for a certain time period. The suprantant are then analyzed for the amount of drug released by any suitable method [38].

G. Application of Aquasomes

1) Delivery of acid-labile enzyme by oral route

The delivery of acid labile enzyme by oral route through aquasome was developed by Rawat et al. who developed a nanosized ceramic core based system by colloidal precipitation under sonication at room temperature. The ceramic core is coated with disaccharide chitosan with continuous stirring. By further encapsulating the enzyme loaded core into an alginate gel, the enzyme was secured. It's Spherical shape and average diameter (925nm) was determined by TEM [40].

2) Delivery of insulin and insulinomimetic agent

By using a calcium phosphate ceramic core cherian et al. Done the parenteral delivery of insulin via aquasomes. Disaccharide used for coating of core material are trehalose, cellobiose, pyridoxal 5-phosphate. The drug is loaded to the coated core by adsorption process [41].

The in-vivo studies of insulin loaded aquasomes are done by using albino rats. Pyridoxal 5-phosphate coated particle found more effective in reducing blood glucose level as compared to trehalose or cellobiose [42].

Insulinomimetic aquasomes is formulated by colloidal

precipitation. Disodium hydrogen phosphate and calcium chloride solution is sonicated at low temperature and then core was coated with disaccharide and immediate loaded with polypeptide k [32].

3) Delivery of Antigen

Aquasome used as a vaccine for delivery of viral antigen i.e. Epstein Barr and immunodeficiency virus to evoke correct antibody [43]. A new ceramic antigen delivery vehicle is there by formed and evaluated by kossovsky et al. These particles were diamond substrate wrapped in aq. Dispersion with coating of carbohydrate mainly cellobiose and the immunologically active surface mol. Are placed over it [39].

The size of antigen loaded aquasomes are 5-300nm, provides both conformation stabilization and a high degree of surface exposure to protein antigen [32].

4) Oxygen carrier

Aquasomes are also used as transporter of oxygen. Khopade et al. prepared a hydroxyappetite core by using carboxylic acid terminated half-generation polydendrimers, which was coated with carbohydrate like trehalose and finally haemoglobin as placed by adsorption process [44].

In vivo studies carried out in albino rat and by this studies particle size, drug loading capacity, and oxygen binding properties of formulation was determined [45].

5) Gene Delivery

Aquasomes have been used for effective targeted intracellular gene therapy. Five-layer composition composed of ceramic core, polyhydroxy oligomeric film, therapeutic gene segment, additional carbohydrate layer and a viral membrane protein layer is used for delivery of gene through aquasomes. Aquasome protect and maintain the structural integrity of gene segment [46].

2. Conclusion

Aquasome represent one of the simplest yet a novel drug delivery system based on fundamental principle of self-assembly. Thus Aquasome based strategy provides pharmaceutical scientist with new hope for the delivery of wide range of bioactive molecule and in the effective possible treatment of various disease. The drug candidate delivered through the aquasome show better biological activity even in case of conformationally sensitive ones.

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