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Aquasomes: A Novel Approach in Drug Delivery System for Poorly Water-Soluble Drug

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ABSTRACT: Aquasome are novel drug delivery systems in conventional dosage forms, includes various carrier systems for developed the nanoparticles system. The aquasomes formulation are administered by oral or parenteral route. Bioactive molecules developed in delivery system like protein, hormones, vaccine, antigen, gene bind the specific site. The particle size of aquasome is 60-300 nm range with spherical shape. Structure of aquasomes comprise three layers, assembled with ceramic core coated stabilized by active biomolecules are adsorbed without modification. Carbohydrate coating provide structural stability or protect against dehydration and maintaining the property of surface exposure in targeted delivery of molecules. To enhance dose frequency of aquasomes is challenges of preparation in aquasomes, the slow antigen produces at sustained rate it has proven effective to enhance immunity against covid-19. Pharmaceutical active molecules incorporated to surface by adsorption. The sustained release process, combination of bioactive molecules and targeted molecules are delivered through aquasomes. This review article is focus on revolutionary characterization and application of aquasomes in targeted drug delivery systems.

Keywords: Conventional drug delivery, Aquasomes, carrier system, bioactive molecule, Targeted molecule.

INTRODUCTION

Aquasomes proves to be a promising drug delivery for sustained and controlled drug delivery of poorly water-soluble drugs. The conventional drug delivery has drawback with sided effect, low dose of specific targeting as well as low bioavailability for preparation. The aquasomes first developed by Nir Kossovsky (1995) for alternatively the termed as "Bodies of water'' The novel delivery system it has improved safety effectiveness, aquasomes are Nano particulate delivery system have simple nanoparticle three layered and they have potential for achieve high solubility of poorly aqueous soluble drug in hydrophilic nature. The three-layered structure comprises with ceramic core, coated core and drug loading aquasomes, it contains pharmacologically active molecules co- polymerization, diffusion or adsorption to carbohydrate coating.

The world was suffered from pandemic Covid-19 and no effective treatment to treat this, aquasome produce specific antibody in the body at sustained rate. The slow antigen produce in small quantity, it has proven effective to enhance immunity against covid-19 (Anand *et al.,* 2017). The aquasome properties like maintain the oxygen transport and protect the drug antigen, the bioactive molecules have maintain their biological and therapeutic activity and to increase the low solubility of aqueous soluble drug. In aqueous state, temperature, solvents in bioactive faces, the vesicular drug have lipid carrier system niosomes, aquasomes, bilosomes. Aquasomes is a carrier of vaccine for delivery of viral antigen or red blood substitutes for targeted system for intracellular gene therapy. Where the bioavailability is constrained by rate of dissolution, the carbohydrate stabilized in ceramic nanoparticle due to the more amount of core material used in their preparation of solid ceramic nanoparticle to the structural stability of aquasomes (Patri *et al.,* 2005).

The number of carriers utilized to deliver a drug in targeted site it includes serum, protein, polymers, or niosomes. The destructive interaction between drug and carrier in case of aquasome carbohydrate coating prevents the denaturing interaction in drug and solid carrier. The components and size and carrier have stability of Nano compounds in gastric environment which play a factor in absorption of orally administered Advanced drug delivery. (Cherian *et al*., 2000).

Many research articles aimed to increase the solubility enhance it also capable to deliver a bioactive macromolecular substance virus and vaccine. Aquasome in the field of vaccine delivery in peptide based for prevention of allergic disease in immune system. Oral delivery of protein and peptide it has challenging since coating technique may prevent against acid not in proteolytic enzyme. The natural stabilizer aquasome polyhydroxy sugar act dehydro protectant maintain molecule in dry solid state. The size of aquasome 60- 300 nm particles, the new studied suggest that aquasome are not only parenteral administered it could be administered by oral or another route (Damera *et al.,* 2019).

Drug loaded aquasome have three layered structure, ceramic core, coated core (carbohydrate coating), drug loading. The characterized of aquasome in terms of size or morphology, drug loading, drug release, size distribution of ceramic core, particle size, structural analysis of core, crystalline nature. Aquasome preparation containing polymer gelatin, magnesium stearate, and ceramic core are prepared by mixing of calcium chloride and disodium hydrogen phosphate, the coating material are used chitosan, sucrose, lactose. The drug loading aquasome analysed by SEM Images shows particle drug were uniform dispersed in coating material in good content, the DSC studied are used for carbohydrates and protein determination. XRD were investigate to study the nature of material is crystalline or amorphous it was observed that crystal structure of the drug in the aquasome (De La Zerda and Gambhir 2007).

Advantages:

1. They are improved bioavailability of drug like BCS Class II (Gholap *et al.,* 2011).
2. It has overcome the difficulties of the drug insolubility or rapid degradation.
3. The aquasome preparation hydrophilic and lipophilic drug can be incorporated.
4. It enhanced the stability of formulation.
5. It reduces side effect and drug toxicity.
6. In systemic circulation prolonged existence of the drug.
7. Acts as a vaccine delivery system.

Ideal properties of Aquasomes:

1. Aquasome as a Nano carrier system it also protects the drug, antigen, protein in pH condition and require low dose of drug.
2. Water like properties preserving the bioactive molecules.
3. Prevent the reticuloendothelial system (Goyal *et al*., 2009).
4. Aquasome deliver contents through combination of specific targeting molecules in sustained release system.
5. It has maintained pharmacological activity and preserve the molecule in dry solid state.
6. Calcium phosphate is biodegradable in nature it achieved by monocytes and multicellular cells.
7. It should have stable in environmental condition.

Composition of aquasomes: Aquasomes are composed of coated material with carbohydrate coating bioactive molecules, loading of drug adsorbed in coated particles for preparation of aquasomes.

1. Core material
2. Coating material
3. Chitosan
4. Lactose
5. Trehalose
6. Bioactive molecule

1. Core material: Core material are used brushite (calcium phosphate) and disodium hydrogen phosphate or polymer are used gelatin, acrylate, albumin it has effective binding of coating material. Hydroxyapatite is also used for preparation of aquasome it has ease of manufacturing, biodegradability of ceramic as a core in formulation. High surface energy or great potential leads to carbohydrate for structural regularity. Calcium phosphate advantages for natural occurence in the human body (Kaur *et al*., 2015).

2. Coating material: Coating of aquasomes preparation material is widely used for lactose, sucrose, chitosan, pyridoxyl-5 phosphate, carbohydrate coating as a natural stabilizer plays an important role for adsorbed as glassy film in ceramic nanoparticle. The coating also stabilize the core material, and core to coat is proportional to particle size of aquasome. Bioactive can preserve the structural of protein by providing water like environment, the self-assembled calcium phosphate particles used in coating process (Khopade *et al*., 2002).

3. Chitosan: Chitosan is used for coating material of aquasome, providing for drug adsorption and it obtained from chitin. In last few years drug delivery for number of route of administration for physicochemical feature in antimicrobial, biocompability. Polymeric carbohydrate has similar structure of cellulose both are monosaccharide, chitosan contains three functional group amino, primary, secondary hydroxyl groups (Kumar *et al*., 2013). The bacteriostatic properties of chitosan are assessed in skin infection or bacterial strain, it has high antifungal or antiseptic properties against microorganisms but less amount toxicity on human cells.

4. Lactose: Disaccharide sugar containing galactose and glucose it has linked with 1, 4-glycosidic linkage and it have used for treatment of constipation. It has mild flavor and solubility is less than other sugars used in food, the addition of lactose is important for composition of milk product. Lactose used in coating material of aquasome formulation (Kumar *et al.,* 2013).

5. Trehalose: Non reducing sugar, it has naturally occurred sugar consisting two glucose molecule and shield the drug against dehydration. The main function of trehalose is protect the organism survive in completely dried condition, the researchers have utilize dehydroprotectant for preserve the biological material for sensitive to environment. The ability to polymorph both in crystalline or amorphous forms and other disaccharide it has highest glass transition state (Kutlehria *et al*., 2018). The another property of trehalose is interact with water is much higher than bioactive molecule, it has protect the lipid bilayer and protect the biochemically active substance in water. The entrapment and glass transformation resulting flexible in polar groups for maintaining the hydration process.

6. Bioactive molecule: The drugs and therapeutic use in the conventional delivery for aquasome preparation carries protein, poorly soluble drug vaccines, antigen delivery through ionic interaction for aquasome. The carbohydrate interacts with charged groups for preserve the aqueous molecule for protein dehydration (Kossovsky *et al.,* 1994).

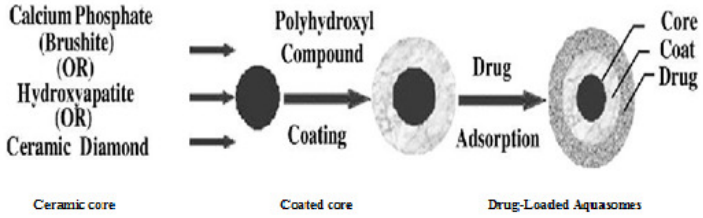

Fig. 1. Drug loaded Aquasomes.

METHOD USED FOR PREPARATION OF AQUASOMES

The aquasome preparation using principle of self-assembly, prepared in three steps, preparation of core by using sonication method, carbohydrate coating, drug load in core material. The coating material lactose, sucrose, trehalose used for fragile structure, the film prevents the drug from change the shape. By following method used in aquasome preparation one or combination (Mitragotri *et al.,* 2014)

1. Preparation of core by sonication method
2. Carbohydrate coating
3. Drug loading
4. Co- precipitation method
5. Dendrimer method (PAMAM)

1. Preparation of core by sonication method: Aquasome are prepared by using sonication method, the process of ceramic core preparation by using material of core. In this method weigh, accurately quantity of disodium hydrogen phosphate and calcium chloride mixed well in 50 ml distilled water. After mixing using ultrasonic bath for sonication for 22 minutes and temperature was maintained 4°C. The ceramic core is prepared and separated by centrifugation in 15 minutes, the core material is prepared and the washed with some distilled water and then filtered pass in fine particles. The solution is filtered after collect the particles on the surface and then dried in hot air oven under 70°C temperature. The ceramic core often used in calcium phosphate and diamond particles (Rawat *et al.,* 2008).

2. Carbohydrate coating: The commonly used coating material in aquasome is lactose, chitosan, sucrose, trehalose, pyridoxyl 5- phosphate, the various process used in carbohydrate coating to adsorb ceramic core. Take 1 mg of ceramic core is mix in distilled water resuspended into it. Stir well in beaker after add lactose in core material and make up the volume 50 ml. The mix solution of lactose and ceramic used sonicate within 20 minutes, then add non solvent (Acetone 1 ml) stir the solution 2 minutes properly, and then solution aside for 20 minutes. The irreversible adsorption of carbohydrates on the surface material and solution is well mixed then centrifuge for 15 minutes for 2000 rpm. (Nehra *et al.,* 2018) After centrifugation some unadsorbed carbohydrate is removed, then sugar coated core washed in distilled water and surface particle are collected and dried in hot air oven and maintained the temperature.

3. Drug loading: The coated particles provide solid phase for biochemically active substance, loading of drug by partial adsorption in coated material. 1 mg drug dissolve in 10% ethanol/ methanol in 50 ml distilled water then stir properly and then coated particles are mixed in it and shake vigorously for 20 minutes. The solution was stored in refrigerator, after get centrifuge the solution 1500 rpm for 10 minutes and supernatant was discarded. After centrifuge the solution filter with distilled water and then dried, the coated particles are dispersed kept the sample in refrigerator, sometime drug loaded aquasomes observed (Rojas-Oviedo *et al.,* 2007).

4. Co-precipitation method: Ceramic core prepared by co-precipitation method, use reflux condenser with magnetic stirring. Weigh 0.4 gm diammonium hydrogen phosphate is add into 0.7 gm of calcium nitrate mixture continuous stirring maintained the temperature 75 degree. The mixture is shake or aside one day then precipitate is form, calcium nitrate is maintain the pH add aqueous ammonia in it then mixture is magnetically stirred. After stirring filter the solution properly and washed with distilled water, filtered precipitate is dried overnight. The powder form in electric furnace was sintered by heating 800 -900°C (Patel *et al*., 2016).

5. Dendrimer method (Poly (Amidoamine) PAMAM: In aqueous solution poly (amidoamine) used to calcium carbonate, PAMAM is dissolved in simulated body fluid then maintained the pH 7.4. Solution is kept for one week in 37°C to induce crystal growth, then add NaOH solution pH of solution was adjusted. After sometime precipitate cores is formed then filtered and washed with distilled water. Precipitate is dry in hot air oven and dried overnight in refrigerator, then characterized using various techniques (Patil *et al*., 2004).

EVALUATION OF AQUASOMES

1. Size distribution
2. Structural analysis
3. Crystallinity
4. Glass transition temperature
5. Mean particle size and Zeta potential
6. Drug loading efficiency
7. In vitro drug release study

1. Size distribution: The morphological analysis or size distribution of aquasomes technique used by scanning electron microscope (SEM) and transmission electron microscope (Prasanthi *et al*., 2010). The coated core is analyzed by these two techniques, The SEM particle size is placed on to the surface of gold coated sample with two sided can be observed under magnification and zeta potential is also determined by

using electron photon spectroscopy. The TEM transmission electron microscope the particle is determine negative staining in 1% phosphotungstic acid and images is carried in both clear and dark mode as photographic film by adobe soft wares.

2. Structural analysis: The structural analysis of aquasome can use FT-IR Fourier transform infrared spectroscopy to determine core material on the sample using potassium bromide disk method. The identification and conformation of coating material is analysis by FTIR, their recording wave number range 200-400 nm; the particles are shift towards lower to higher wavelength is observed hydrogen bond formed in molecules (Jain *et al.,* 2009).

3. Crystallinity: The ceramic core is analyzed by X-ray diffraction (XRD) study it evaluated for it crystalline or amorphous characteristic. It based on interpretations of diffractogram, in this method observed that calcium phosphate core is identical it coated core is crystalline when it observed. After coating core is polysaccharide contains sucrose, lactose, trehalose, pyridoxyl-5-phosphate peak reduced intensity into amorphous. Polysaccharide is hydrolyzed in monosaccharide in addition of anthrone.

4. Glass transition temperature: The carbohydrate on drug-loaded aquasomes is determine or analyzed (DSC) Differential scanning calorimetry used in glass transition temperature. Glass to rubber transition is measure in DSC for change in temperature and melting point of glass. The formulation is filled in sample cell and buffer is packed in reference cell for analyzer in differential scanning calorimetry (Rakesh and Anoop 2012).

5. Mean particle size and zeta potential: The drug loaded aquasomes or its particle size is determined by zeta potential, (Zetasizer) is particle size analyzer. The sample is dissolved in distilled water or other solvent for zeta potential measurement. The formulation is deep into zeta dip cell, The study indicate saturation in carbohydrate containing lactose process in zeta potential decrease value (Senapati *et al*., 2018).

6. Drug loading efficiency: The drug loading is carried out in aquasome formulation in known concentration of solution of drug. Weigh the properly of drug is incubating for 24 hours at 4°C, after supernatant liquid is centrifuge for 30 minutes at low temperature and kept the solution in refrigerator. The clear solution is filtered and study under the UV spectrophotometer and drug-loading formula is below.

$$\% \text{ Drug loading} = \frac{\text{Weight of total drug added - Weight of an entrapped drug}}{\text{Weight of aquasomes}} \times 100$$

7. In vitro drug release study: The in vitro release study in drug loaded aquasome formulation it utilizes the phosphate buffer pH 6.5 and dissolution media is 900 ml in USP type 1 dissolution test apparatus. Weigh the aquasome powder 50 mg fill in gelatin capsule into dissolution basket and media stirred at speed 100-rpm 37°C. Sample are 100 ml intervals at various time, then 10 ml sample are withdrawn into basket aside for few minutes for centrifugation in 15 minutes. Filtered the solution and precipitate are examined content 340 nm using UV spectrophotometer and maintained with 10 ml fresh dissolution medium (Shahabade *et al.,* 2009).

APPLICATION OF AQUASOMES

Aquasomes containing ceramic particle enable of acid labile agent, and they increase the solubility or stabilizing agent in poor soluble drug. The other research article observes increase the dissolution rate and protect the bioactive molecules via antigen, viruses, and vaccines. Following application use in aquasomes.

1. Viral antigen delivery or vaccine
2. Enzyme delivery
3. Oxygen delivery
4. Aquasomes for insulin delivery
5. As a red blood cell substitutes
6. Gene delivery

1. Viral antigen delivery or vaccine: The viral antigen or vaccine delivery in aquasome usually boost the immunity system against viral infection, the stimulation of B- cell in protein antigen for conformation state. The size range of aquasome is 5- 600 nm is protecting the high degree of antigen delivery; ceramic core coated is with disaccharide cellobiose for viral protein in drug delivery vehicle. The hydroxyapatite core contains antigen for hepatitis B development of immunity system against T helper cells. In case of Epstein- Barr virus aquasome is produce specific antibodies for targeting molecules for viral antigen or immune deficiency virus. as antigen (Shirsand *et al.,* 2012).

2. Enzyme delivery: The therapeutic delivery of enzymes like DNAse or dyes use in conformation in cosmetic properties, the enzyme (proteolytic) has high antiseptic or anti-inflammatory properties in nano-preparation. Aquasome are deliver the drug to specific site the enzyme is anti-inflammatory take orally administration for protect gastric acid or enzyme degradation. The biological activity of enzyme observed on immobilized DNAse in calcium phosphate aquasome core. The treatment of cystic fibrosis effective against aquasome formulation was therapeutic efficacy is produced (Shukla *et al*., 2016).

3. Oxygen delivery: The aquasome preparation particle size or drug efficacy is studied in formulation; the oxygen is binding properties of prepared formulation. The hemoglobin delivery is carried of artificial blood and it has new technique or model for transport of oxygen. Great potential as oxygen binding or maintain the properties for period of one month, to maintain the toxicity in 80% of hemoglobin concentration due to stability of drug loaded aquasomes. It has good binding capacity; pharmaceutical scientist develops synthetic oxygen carrier based on aquasome preparation for future perspective (Sutariya and Patel 2012).

4. Aquasomes for insulin delivery: The drug was formulated in aquasomes used sugar coating include sucrose, trehalose, lactose; the coated particles are adsorbed in loading of drug molecule in formulation. Formulating insulin delivery in ceramic core dispersed in alginate polymer provide high amount of insulin for oral route of administration. The nanoparticle has high bioavailability for avoid barriers in gastrointestinal tract in the stomach; Insulin has low toxicity, high drug

loading capability. For synthesis of new method will give prospect for insulin production (Tiwari *et al.,* 2012).

5. As a red blood cell substitutes: The surface of carbohydrate coated particles are encapsulated in a mixture of phospholipid, aquasome are deliver complex molecule hemoglobin produce synthetic blood material. At the time biological activity is preserved and reduced toxicity of hemoglobin in aquasome preparation. The concentration of hemoglobin 85% is observe for deliver oxygen in red blood cell natural. The major problem in blood substitutes is incompatibility for administration of blood in body and it can be stored in refrigerator for easily dried (Umashankar *et al*., 2010).

6. Gene delivery: Aquasome studies protect the integral gene in segment, the core of ceramic or film containing aquasome have preserved in membrane protein. The formulation has great gene therapy in viral vector to overcome challenges in gene delivery, it has high immune response as drug in bioactive molecules for future perspective. The novel drug delivery system has focus to studied on aquasome as gene carrier system related to delivery to pharmaceutical agents, the different method is used solubility enhancing for targeted approach (Wilczewska *et al.,* 2012).

CONCLUSIONS

The aquasomes deliver shows better biological activity and it has great solubility or enhancing property to the targeted side. The carbohydrate coat is preserving the bioactive molecules or drug interaction in formulation, it has focus on novel drug delivery system for drawbacks related in pharmaceutical agent. The crystalline nature core gives aquasome stability as broad range of molecules and better immunological response in immune system or it carries antigen, insulin or enzyme delivery, blood substitutes in hemoglobin.

FUTURE SCOPE

Recent development of aquasome in case of drug delivery has paid intention to reduce the drug toxicity, enhances the targeting molecule, and improved shelf life.

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Conflict of Interest. None.

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