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Aquasomes: A novel nanoparticulate drug carrier

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ABSTRACT

Aquasomes are three layered self-assembled nanoparticulate carrier system. This three layered system contains a core coated with polyhydroxy oligomer upon which biochemically active molecules are adsorbed. Ceramics are mainly used as core material because of high degree of order and structural regularity. Polyhydroxy oligomer coating provides water like environment & protect biochemically active molecule from dehydration. As a whole aquasomes provide stability to biochemically active molecule. Poorly water soluble drugs, insulin, hemoglobin, serratiopeptidase can be delivered through aquasomes. This review article includes brief introduction of aquasome, role of core & carbohydrate, properties, methods of preparation, characterization study and application of aquasomes.

1. Introduction

Potential application of nanoparticulate system as drug carrier was first proposed by Dr. Gregory Gregoriadis on 1974. He proposed liposomes as nanoparticulate drug delivery system [1]. Liposomes, solid lipids nanoparticles, dendrimers, polymers, niosomes, silicon nanoparticles, gold nanoparticles, carbon nanotubes, and magnetic nanoparticles are the examples of nanocarriers for drug delivery system. Drug is adsorbed, covalently linked on nanocarrier system or it may be encapsulated inside nanocarrier system. Nanoparticles are the ideal choice for drug delivery nowadays [2–6]. The advantages of nanoparticulate drug delivery system are improved drug loading and delivery [7,8], delivering drug to the site of action which can be called as targeted delivery [9–13], delivering very less side effects comparing to conventional dosage form [14] & delivering drugs which are poorly soluble [15–18]. Due to small amount of drug is delivered to the site of action thus toxicity due to large dose is eliminated. Often they are called as nano carriers in drug delivery science. Aquasome is a self-assembled nanoparticulate carrier system which was first developed by Nir Kossovsky in 1995 whose surface can be non-covalently modified with carbohydrates [19]. It is comprised of ceramic core coated with poly hydroxyl oligomer & upon this coated core biochemically active molecule are introduced by co polymerization, diffusion or adsorption method. Presence of calcium phosphate in bones makes it an ideal biomaterial with ideal biocompatibility, biodegradability, absence of toxicity and stability to use it as drug carrier. Calcium phosphate and hydroxyapatite are used as ceramic core in aquasomes. Generally aquasomes assemble through non-covalent bonds, ionic bonds and Van der Waals forces [20]. Sugar coating produces glassy molecular layer that adsorbs therapeutic protein or small molecule without modification in three-dimensional conformations. Ceramic core superimposed with carbohydrates improved the cellular uptake in cancer cells [21,22]. Hence, aquasomes have been extensively investigated for delivery of both small and high molecular weight, pharmaceuticals [23,24]. Main advantage of aquasomes over other nanoparticulate carrier system is that there is no interaction between drug and carrier. Drug molecule remains stable in water like environment provided by oligosaccharide coating.

1.1. Role of core & carbohydrate

Materials used as core are nanocrystalline tin oxide, brushite (calcium phosphate dehydrate), carbon ceramic (diamond particles). Ceramics are mainly used as core material. Since ceramics are crystalline in nature these materials provide structural regularity and high degree of order. High degree of order provides high degree of surface energy which leads to efficacious binding of carbohydrate onto it. Another advantage of using calcium phosphate as core material is because of its natural presence in body. Calcium phosphate is widely used in the form of nanorods [25–27], nanorods [28–30], biocomposites [31–33], nanoparticles [34–37], scaffolds [38–41], hydroxyapatite whiskers [42,43]. Calcium phosphate is also used in bone tissue engineering [44,45], stem cell technology [46], as coating on bone implants [47], as adjuvants [48–52]. Hydroxyapatite was selected as a core for the preparation of aquasomes. Poorly crystalline form of hydroxyapatite found in bone is stable at physiological pH [53].

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Biocompatibility, easy to manufacture and low cost makes ceramic materials a good candidate for drug delivery applications [53,54]. Ceramics are biodegradable in nature. Monocytes and osteoclasts are responsible for biodegradation of calcium phosphate inside body. During biodegradation two kinds of phagocytosis takes place, one is only calcium phosphate crystals taken up and dissolved in cytoplasm upon disappearing of phagosome membrane and the other is dissolution of calcium phosphate crystals when incorporated with large volume of culture medium happens after forming heterophagosome [55,56].

Commonly used carbohydrates are pyridoxal-5-phosphate, cellobiose, trehalose, sucrose, lactose. Carbohydrates act as natural stabilizer & dehydroprotectant by providing structural integrity, preserving molecular conformation of biochemically active molecule, delivering water like environment to the biochemically active molecule while keeping it in dry solid state and protecting three-dimensional conformations of drug molecule [57,58]. Main principle of coating is adsorption of carbohydrate onto core.

Kaushik et al., 2003 [59] analyzed the thermal stability of proteins in presence of trehalose. They used RNase A as a model enzyme & investigate the effect of trehalose on the retention of enzymatic activity upon incubation at high temperatures. They observed that 2 M concentration of trehalose increases the transition temperature (Tm) of RNase A to 18 °C (maximum) at pH 2.5. Trehalose remained inert to protein surfaces and stabilized the proteins at different pH which indicated it's applicability as universal stabilizer. Researchers have reported the effect of sugar on protein, enzyme stabilization [60,61]. Goyal et al., 2008 [58] found strong evidence from the data of Fourier transform infrared (FTIR), zeta potential and differential scanning colorimetry (DSC) study that there is a biochemical interaction between hydroxyapatite, sugars, and BSA (protein). It increased stabilization protein in formulation.

Goyal et al., 2008 [58] identified the presence of mannose-like binding lectins (MLBLs). Polyhydroxyl oligomers or carbohydrates present in aquasomes are recognized by the carbohydrate recognition domains of MLBLs. These domains recognize carbohydrates present on the target cells and bind to them. This is one of the important mechanism of antigen delivery with the help of aquasomes.

2. Properties of aquasomes

2.1. Nanoparticle

Since aquasomes are nanoparticles, they have large surface area thus can be loaded with significant amount of biochemically active molecule through van der waals forces, entropic forces, ionic and non-covalent bonds. The core material widely used is calcium phosphate ($CaHPO_4$). The nanocrystalline, calcium phosphate ceramic core particles self-assemble during the reaction process under sonication due to augmentation of surface free energy [23].

2.2. Calcium phosphate

Calcium phosphate which is used as core material in aquasome, is biodegradable in nature. Inside the body, monocytes and multicellular cells called osteoclasts are responsible for biodegradation of calcium phosphate. It is prepared from the precipitation of a monobasic sodium phosphate solution and calcium chloride solution with mechanical agitation. Researchers have shown that the process variables like the level of ultrasound frequency and the effect of the sonication on the particle size of the inorganic cores [62].

2.3. Carbohydrate coating

Aquasomes provides water like environment due to presence of carbohydrate coating and preserves conformational stability of biochemically active molecule. Polysaccharide film stabilizes the ceramic core through ionic, non-covalent, and entropic forces. Studies have demonstrated that particle size of aquasomes increases as a function of concentration of core to coat ratio. This may be credited to availability of free surface of the core particles with the coating material [23,62].

2.4. Drug incorporation process

Biochemically active molecules are incorporated in this nanoparticulate system by adsorption through ionic and non-covalent interactions. Adsorption of drug on carbohydrate coated core increases the drug encapsulation efficiency [62].

2.5. Self-assemble

This three layered structure is based on the principle of self-assembly which is achieved by non-covalent & ionic bonds. It was observed in the research works [23,63] that sonication process, during the reaction of disodium hydrogen phosphate and calcium chloride in order to prepare calcium phosphate influences self-assembly of crystalline calcium phosphate. Soniction process increased the surface free energy of calcium phosphate which was also reported by Vengala et al., 2013 [64]. This surface free energy influenced self-assembly.

3. Methods of preparation

3.1. Core preparation

Preparation technique of core depends on the type of core to be used. Generally nanocrystalline tin oxide, carbon ceramic (diamond), calcium phosphate, hydroxyapatite are used as core. Among these materials nanocrystalline calcium phosphate and hydroxyapatite are widely used as core material for aquasomes.

3.1.1. Self-assembled nanocrystalline brushite (calcium phosphate dihydrate)

Self-assembled nanocrystalline brushite is prepared by different methods which are described in Table 1.

Vengala et al., 2013 and Patil et al., 2004 [62,65] studied the effect of pH, duration & sintering on size, nature of particle & percentage yield. Uncontrolled pH leads to formation of large, elongated particles with micrometer size range. When pH was maintained in between 8 and 10 & no sintering took place, it caused formation of elongated to spherical particles (≤ 1.0 μm) but with sintering it caused formation of spherical particles in nanometer range. From the findings of Vengala et al., 2013 [62], both the uncontrolled and controlled without sintering process gave similar less percentage yield (37% in uncontrolled pH & 36% in controlled pH) while the process with controlled pH & sintering gave percentage yield of 60%. When the slurry was stirred for one day with maintaining the pH in between 8 and 10, it caused formation of large, elongated particles with less percentage yield (33%) & sintering caused formation same kind of particle with 500–1000 nm of size with same percentage yield. When the slurry was stirred for 4–6 days it improved particle size (250–1000 nm), type (elongated to spherical) & percentage yield (61%) & sintering caused formation of spherical particles (100–200 nm) & percentage yield of 60%. So, while maintaining pH in between 8 and 10 sintering process caused formation of spherical particle in nanometer size range with increased percentage yield and if duration of stirring is increased with subsequent sintering it also led to formation of spherical nanoparticle with increased percentage yield. Patil et al., 2004 [65] found that the self-precipitation method produced spherical particles (1–5 μm), with a very less yield due to formation of monolayer precipitate which occurred on container surface. The seeding caused increase in crystallization rate with production of particles of irregular size and shape. It indicates that pH, duration of stirring & sintering has effect on particle size, shape & percentage yield of ceramic core.