European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 7, Issue 07, 2020

Aquasomes: Water Like Bodies Vesicular System For Therapeutics Molecules As Robust System For Delivery

Liban Dahir[1], Kajol[2], Amneet Kaur[3], Ashish Manocha[4], Sheetu Wadhwa[5], Vijay Mishra[6], Narendra Pandey[7], Rajesh Kumar[8], Sanjay Jain[9], R Narayana Charyulu[10], Kalvatala Sudhakar[11]

[1,2,3,4,5,6,8,11]*School of Pharmaceutical Science, LIT-Pharmacy, Lovely Professional University, Jalandhar, Punjab*

[8]*Department of Pharmacy, Medi-Caps University, Indore, Madhya Pradesh*

[9]*Department of Pharmaceutics, Nitte University, Mangalore, Karnataka*

Email: [2]ckbhaipharma@gmail.com, [11]Sudhakar.20477@lpu.co.in

ABSTRACT

Aquasomes are novel spherical nanovesicular drug carrier that ranges from 60 to 300 nanometer in size. They are self-organizing architectures through the action of different bonds e.g. ionic, non-covalent and van der waals forces. Aquasomes are constructed from three main components i.e. core substance, coating material and the loaded drug. The core mainly acts as a support for the polyhydroxy oligomers to enhance the structural stability of the formulations whereas the coating material is responsible for protecting the loaded pharmaceutical bioactive substances from dehydration. They are chiefly studied for delivering acid labile molecules like proteins and peptides. Nevertheless, they have potential in achieving higher solubility of poorly aqueous soluble drugs by imparting hydrophilicity to the poorly aqueous soluble drugs. Aquasomes also proved to have double targeting since sustained as well as targeted delivery approach can be achieved. Some of the mainly used sugars as coating material, different preparation techniques, applications and evaluation parameters are thoroughly discussed in the article.

Keywords: Ceramics;Water like vesicular system;Polyhydoxy oligomers; Self-organizing architecture; versatile nanocarrier,

1. INTRODUCTION

One of the most difficult and challenging tasks in drug delivery is to assure that the drug reaches its site of action in its intact form without harming the neighboring health cells (Narang, 2012). Conventional delivery of pharmaceuticalshas been experiencing prominent drawbacks such as undesired effects, high-dose requirements,lack of specific targeting, development of multiple drug resistance as well as low bioavailability.These limitations haveled to the development of a number of novel pharmaceutical delivery as well as targeted systems with improved safety, effectiveness and higher target selectivity(De and Gambhir, 2007; Gupta and Kumar, 2012; Wilczewska et al., 2012). During the past decade potentialadvancements have been disclosed in order to get vesicularnanocarrier systems with unique carrier properties of optimized drug loading and release propertiesas well as capable of protecting vulnerable drugs and bioactive substances from the different barriers of the

body systems.In general, nanocarriers can be classified into organic and inorganic nanocompound delivery systems. Examples of organic nanocompound delivery systems are nanoliposomes, dendrimers, solid lipid nanoparicles, nanoemulsions and polymeric nanoparticles whereas inorganic nanocarrier delivery systems include 2D layered double hydroxides (LDH) also known as hydrotalcitelike compounds, mesoporous silica, carbon nanotubes, Quantum dots and magnetic nanoparticles (Senapati et al., 2018). The components and the size of nanocarriers are the chief features to guarantee stability of the nanocompounds in gastrointestinal environment which plays a critical factor in case of absorption of orally administered drugs (Mukherjee et al., 2017). Vesicular drug delivery systems can be broadly classified into lipoidal e.g. liposomes, emulsomes, enzymosomes, ethosomes, transferosomes etc. and non-lipoidal carrier systems e.g. niosomes, bilosomes and aquasomes. Description and applications of various existed and novel nanovesicular drug and bioactive delivery systems are summed up in table 1.

Among the nanocarriers are theaquasomes, which was initiallyprepared in 1996 by Nir Kossovsky with the aim of controlling molecular polymorphism of bioactive substances to maintain their biological and therapeutic activity and to increase the low solubilityof poor aqueous soluble agents(Jain et al., 2012).Aquasomes are tri-layered nanoparticulate carriertechnique that made up of a central ceramic core, a carbohydrate coat and an adsorbed bioactive substance. This carrier system is a self assembled structure that is formed mainly throughnon-covalent bond between the core material and the coating solution of carbohydrate (formation of sugar ball), although ionic bond and vanderwaals forces can be involved. This preformulated nanoparticle is subsequentlyadsorbed,copolymerized or diffused to thebiochemically active substanceby interacting with the enormouspolyhydroxyl groups present on thesugar coatingsurface(Mukherjee et al., 2017).The resultant aquasomal nanoparticle will have colloidal behavior. As the name has a power, aquasomes are referred to as the bodies of wateras they possess water like properties that explain their unique special characteristics of protecting the fragile drugs and bioactive macromolecular substances such as insulin,genes and antigens(Banerjee and Sen, 2018; Cherian et al., 2000; Kossovsky et al., 1994). To put it simply, this can be demonstrated asa person relaxing in a swimming pool where the sugar coating solution represents the swimming pool and the bioactive substance can be considered as the person in the swimming pool. As the swimming in a hot day gives relaxation, the aquasome gives protection of different pharmaceutical agents from the harsh environment they face during their journey to the site of action. Sugar coating surface of polyhydroxyl oligomer is responsible for the water like properties and since it is rough and sticky in nature that will help stabilization of labile bioactive agents by preventing dehydration effects through creation of quasi-aquas environment as well as adsorption of drugs onto the surface of the coat (Mukherjee et al., 2017). Aquasomesmay also be called as carbohydrate stabilized ceramic nanoparticles due to the fact that the major core material used in their preparation is the solid ceramic core that gives the structural stability to the aquasomal system(Banerjee and Sen, 2018; Narang, 2012).

2. COMPOSITION OF AQUASOMES

Aquasomes comprises of core substance coated withpolyhydroxycarbohydrate film over which the bioactives/ molecules or drug moieties are adsorbed with orwithout modification as demonstrated in Figure (1)& (6)(Jain, 2014)

Core material

Core materials which are the building block of the aquasomes are either polymer based such as albumin, acrylate, gelatin etc or ceramics e.g. calcium phosphate (brushite), hydroxyapatite(HAP), nanocrystalline tin oxide and diamond (carbon ceramics) (Chaudhary et al., 2018; Senapati et al., 2018).Ceramicisthe chiefcore material used due to the fact that these materials offer structural regularity and elevatedlevel of surfaceenergy thatoffers effective binding of the coating material onto it.As a core material, Calcium phosphatehas extra advantages of its natural occurrence in the human body. Also,as nanorods, it is used in bone tissue engineering as well asadjuvants in bone implants. Hydroxyapatite(HAP)is alsohighly used as a basic core for preparingaquasomes. Ease of manufacturing, biodegradability, biocompatibility of ceramics gives great potential as core in the formulation of aquasomes(Mukherjee et al., 2017).The various cores are crystalline in nature and when they are used into the synthesis process, they measure 50 to 150 nanometer and provide very clean and reactive surfaces (Jain et al., 2012).

Coating material

Coating or overlay substancesmainly used areD-(+)-cellobiose, trehalose, citrate,saccharose, chitosan, pyridoxal-5-phosphate, etc. Carbohydrate act as a natural stabilizer with glassy nature that can adsorb the therapeutic agents. This layer of carbohydrate coating is considered the most crucial in the preparation of aquasomes due to the fact that the hydroxyl groups present on these oligomers interact with the charged and polar functional groups of the bioactivesand hence can preserve the structural integrity of the proteins in the devoid of water by providing water like environment. Carbohydrate coating also stabilize the core material byionic, non-covalent &entropic interactions. Core to coat ratio is described to be directly proportional to the particle size of the aquasome. This could be reasoned to the accessibility of free surface of core materialinrespect to coating substances(Mukherjee et al., 2017; Senapati et al., 2018).

Trehalose is a widespread non-reducing disaccharide and naturally occurring sugar consisting of two glucose molecules having 1,1-glycosidic linked (α-D-glucopyranosyl-α-D-glucopyranoside) and it is sometimes referred as mushroom sugar. Trehalose is abundantly present in various organisms such as shrimp, bacteria, fungi, yeast, insects, and plants (Elbein et al., 2003). While Trehalose is not found in mammals, a significant amount of a trehalase enzyme which cleaves trehalose into two glucose molecules is found in the human intestine (Burek et al., 2015). Among the three anomers of isomers, only a,a-trehalose has been biosynthesized in a multiplicity of living organisms. One of the main functions of trehalose is to protect some organisms against dehydration that will allow them to survive in a completely dried condition. From this perspective, researchers have utilized this property of dehydroprotectant to preserve the structure of biological materials that are labile or sensitive to the dry (Elbein et al., 2003). Bioprotective behavior of trehalose is attributed to its ability to exist in different forms of polymorphs, both in crystalline and amorphous forms. Trehalose can also undergo reversible transition between anhydrous and hydrated form without change in its structural integrity. Trehalose dehydrate has local pockets in its amorphous state that will capture residual (remaining) H_2O molecules by halting them if H_2Owater is rare. Among all other disaccharides, it has the highest glass transition (Tg) temperature (Jain and Roy, 2009) and it is considered as unique in its non-hygroscopic glass property that is stable at higher temperatures even when the glass is almost fully desiccated (Richards et al., 2002). Usually, when water is added to an amorphous material its mobility increases resulting in a decrease in Tg. Nonetheless, this expected decline does exist in case of trehalose, Tg is already significantly stronger than maltose or sucrose, neither of which show so various polymorphic behaviours. Another extraordinary property of trehalose is that interaction

between trehalose &H_2O is much higher than H_2O to H_2Ointeraction that could participate in the preservation of the molecular structure of bioactive substances (Jain and Roy, 2009). Trehalose, having the highest capacity for hydration, protects lipid bilayers via direct interaction with polar biomolecules as it organizes the water molecules around the membrane. Mainly trehalose protects biochemically active substances through water replacement, water entrapment and glass transformation (Richards et al., 2002). Water replacement mechanism is resulting from great flexibility of glycosidic bond letting trehalose to interact with the irregular polar groups of the bioactive substances whereas water entrapment is a result of entrapment of water close to the structure of bioactives maintaining their native hydration (Burek et al., 2015).

Cellobiose is a disaccharide of 2 d-glucose molecules linked by β-1,4-glycosidic link with each other. Thus, Cellobiose is differentiated from maltose in its arrangement at the glycosidic linkage. Cellobiose is formed from hydrolysis of cellulose, a polysaccharideof glucose in which all units are linked by β-l,4′-glycosidic bonds. There is no enzyme used for hydrolyzing cellobiose in humans(Robert J. Ouellette, 2015).

Chitosan is a polymeric carbohydrate having a structure similar to that of cellulose. Both are made from β- (1,4)-coupled monosaccharides. The key Sources of Chitosan are Insects, Crustaceans such as (Crab & Shrimp shell) and Fungi. After cellulose, the second most abundant biopolymer is chitin. Chitosan is obtained from deacetylation of chitin and it has noble film forming characteristics. Chitosan is utilized as a coating substance in various delivery systems of therapeutic drugs. Chitosan consists of 3 kinds of functional groups i.e. amino, primary as well as secondary hydroxyl groups. These fuctional groups act as a spacer to link drug molecules, targeting ligands and imaging agents to the carriers (Nehra et al., 2018). Chitosan-coated carriers have many advantages over the uncoated particles such as improved drug payloads, bioadhesive and sustained drug release properties (Agnihotri et al., 2004). Chitosan is extensively considered in the last few years for potential drug deliveryofa number of routes of administration due to its distinctive physicochemical features, in-vivo biodegradability, biocompatibility& antimicrobial activity(Felt et al., 1998**).** In addition to that, it has a good coagulation ability, adhesion as well as immune-stimulating activity. In opposite to all other polymeric carbohydrates, it has a monograph in the pharmacopeia. Moreover, Chitosan has a cationic character attributed to its primary amino_ group and they are responsible for most of its properties i.e. controlled release, transfection, mucoadhesive property, upsurged permeability, efflux pump inhibitory properties and in situ gellatingcapability (Bernkop and Dünnhaupt, 2012). Chitosan is characterized by high antifungal and antibacterial properties against a number of microorganisms but negligible toxicity on human cells. Bacteriastatic properties of chitosan were assessed in common skin fungus as well as some bacterial strains. Powdered chitin, entire crab shells or chitosan were ineffective in all of the tests whereas chitosan solution in acetic acid inhibited the growth of fungus as well as the bacterial strains. Its ability of inactivating fungal and bacterial mulplication, is attributed to the cationic charged amino group that may combine with anionic components such as sialic, neuraminic or N- acetylmuramic acids found on the surface of the cells, and may also inhibit microbial growth by jeopardizing exchanges with the media, chelating transition of metal ions and by inhibiting enzymes. It was also found that 1% solution of chitosan in 1% of acetic acid had fully inactivated candida tropicalis as well as candida albicans (Ranjha and Khan, 2013).

Bioactive substance

Different categories of drugs and therapeutics that face limitations in their conventional delivery approach have been used to carry in aquasomes e.g. proteins, peptides, poorly soluble drugs, hemoglobin, vaccines, antigen and gene delivery through non covalent and ionic interactions (Senapati et al., 2018).

Principles of self-assembly

The self-organizing of molecules in the aqueous environment is mainly based on 3 physicochemical doctrines; the interactions between charged groups, effect of dehydration, in addition to structural stability. Since, most of the biochemically active molecules are amphiprotic, the interactions between charged groups e.g. carboxyl, amino, phosphate & sulfate group initiate the self-assembling subunits. Charged groups stabilize tertiary structures of folded proteins whereas formation of hydrogen bonds assist in stabilizing the secondary structure of proteins. H-bond forming molecules being hydrophilic set up a major degree of assembly to neighboring water molecules. On the other hand, hydrophobic molecules are unable to form hydrogen bond. Their affinity to repel H_2O makes them organize the moieties inside adjacent surroundings. The organization of H_2O which minimizes the degree of entropy leads the molecules to dehydrate and consequently get self-organized. Vander Waals forces which are mostly seen in hydrophobic regions play crucial role in conserving molecular integrity while self-assembling (Jain et al., 2012).

3. METHODS OF PREPARATION OF AQUASOMES

The fabrication of aquasomes are comparatively simple and straight forward synthesis with minimum use of solvents. In addition to that, for getting the required size, homogenization steps are not involved in their fabrication(Narang, 2012). There are three main steps in the development of aquasomesi.e. core fabrication, coating and loading of the drug as illustrated in figure (6)(Umashankar et al., 2010).

Step 1. Core fabrication

The first basic step for the establishment of aquasomes is the fabrication of the core which is dependent on the material used for its preparation. The various core forming materials available have been discussed earlier. Core can be prepared by means ofcolloidal precipitation, sonication, dendrimeric method, plasma condensation, inverted magnetron sputtering, and other techniques. Preformulated cores are also available with different commercial suppliers(Jain et al., 2012; Narang, 2012; Umashankar et al., 2010).

Precipitation method

Ceramic core can be prepared by coprecipitation with magnetic stirring under reflux conditions and self-precipitation technique.
Coprecipitation by reflux:
Diammonium hydrogen phoshphate,$(NH_4)_2HPO_4$, solution of 0.19 N is added into a calcium nitrate, $Ca(NO_3)_2$, solution of 0.32 M under continuous stirring in a drop-wise manner, maintaining the temperature at 75 °C. Then theobtained mixture isstirred&shaked for six days. A precipitate of calcium phosphate forms. After filtering, washing thoroughly and air-drying overnight at 100 °C a powder forms. The powder is then sintered to about 800-900 °C using electric heater(Vengala et al., 2013a, 2013b). The reaction can be given as follows.

$3\ (NH_4)_2HPO_4 + 3\ Ca(NO_3)_2 \rightarrow Ca3(PO4)_2 + 6NH_4NO_3 + H_3PO_4$

(75 °C / pH 8 to 10)

Another method for coprecipitation have been reported by Goyal et al, by mixingaliquot 3 ml of 0.1 gm/L solution of methylcellulose (as a dispersant) into 1440 ml of water containing of calcium nitrate tetra hydrate (0.152 M) and di-ammonium hydrogen phosphate (0.090 M). After the addition of 115 ml of NH_4OH (24%) into the above mixture, it is heated around 60 to 70 °C with vigorous stirring for three hours. The resulted precipitate isobtained from supernatant thru filtration and subsequent washing several times with water. After overnight drying at 100 °C, the precipitate islastly calcined in an air atmosphere at 1000 °C for sixhours followed by simple grinding (Cherian et al., 2000).

Self-precipitation:

Simulated body fluid of pH 7.2 which is containing 134.8 mM of sodium chloride, 5.0 mM of potassium chloride,4.2 mM of sodium hydrogen carbonate, 2.5 mM of calcium chloride, 1.0 mM of disodium hydrogen phosphate, 1.5 mM of magnesium chloride, and 0.5 mM of disodium sulfateis daily adjusted to pH 7.2 with HCl. After shifting the solution into a series of polystyrene bottles, the bottles arefirmlyclosed& kept at a temperature of 37±1 °C for 1 week. A precipitate is formed and filtered. It is entirely washed with distilled water several times and dried at 100 °C(Vengala et al., 2013b).

Sonication method

Di-sodium hydrogen phosphate, $Na_2\ HPO_4$,is reacted with Calcium chloride, $CaCl_2$,to give a colloidal precipitate (Kossovsky et al., 1996; Vengala et al., 2013b, 2013a). Based on the reaction stoichiometry, mole equivalentsare reacted in a 120 ml volume, 1 mole of di-sodium hydrogen phosphate equivalent to 8.90 g & 1 mole of calcium chloride equivalent to 7.35 g are separately mixed with 60 ml of water. A bath sonicator is used for sonication of the mixture for 2 h at 4°C. Following sonication, it is centrifuged using a C- 24 Remi centrifuge (4°C & 15000 rpm) for one hour. After centrifugation, the supernatant is decanted and the precipitate is washed several times with distilled water. The obtained precipitate is re-suspended in 50 ml distilled water & then filtered using a membrane filter of pore size 0.22 µm. The core is dried (100°C, 2 days) to get ceramic nanoparticles. After drying, the percentage yield is calculated(Vengala et al., 2017). The chemical reaction involved is as follows,

$3Na_2HPO_4 + 3CaCl_2 \rightarrow Ca3(PO4)_2 + 6NaCl + H_3PO_4$

(2 h/4°C)

Dendrimer method

Carboxylic acid terminated half generation poly (amidoamine) (PAMAM) were used to assess calcium carbonate ($CaCO_3$) crystallization in aqueous solution and through this process spherical shaped cores consisted mainly of valerite crystals was found (Khopade et al., 2002).

Step 2. Carbohydrate coating of the core

The coating process encompasses several wet chemical analysis and lyophilization processes (Jain et al., 2012).Carbohydrate is incorporated into a dispersion containing the core substance after that sonicated and finally lyophilized to provide irreversible carbohydrate adsorption on to the surface of the ceramics. Other methods for coating process such as non-

solvent addition and direct incubation are also reported(Mukherjee et al., 2017). Excess and un-adsorbed carbohydrates are separated through stirred ultrafiltration cells (Banerjee and Sen, 2018).

Step 3. Drug immobilization

The previous two methods, core preparation and coating are common for all aquasomal formulations. In this step the drug or the bioactive substance is adsorbed on the polyhydroxy oligomers. The general steps involved in the synthesis of aquasomes are represented in figure (7).

4. EVALUATION OF AQUASOMES

Characterization of ceramic core
Size distribution of ceramic core
For the evaluation of morphology and size distribution of aquasomes, transmission electron microscopy (TEM) as well as scanning electron microscopy (SEM) are usually used (Umashankar et al., 2010).In transmission electron microscopy, the particlesize can be determined after negative staining with 1% phosphotungstic acid (Kossovsky et al., 1994).TEM images is carried out both in a clear & dark mode as the photographic films can be digitalized by Adobe soft wares(Oviedo et al., 2007). In case of SEM, samples areattachedon the surface of a gold coated sample holder with a two sided adhesive tapethat can be observed under suitable magnification(Mukherjee et al., 2017; Oviedo et al., 2007).
Mean particle size & zeta potential
Photon correlation spectroscopy (PCS) is used for the determination of mean particle size as well as zeta potential(Umashankar et al., 2010). Zetasizer (particle size analyzer) can also be used for the same purpose as PCS(Vengala et al., 2017).
Structural analysis of the core
FTIR spectroscopy analyses the structure of aquasomes. By using potassium bromide (KBr) sample disk method, the structure of core material can be analyzed thru comparing the observed Infra Red spectra with that of reference peaks. FT-IR not only gives structural analysis of the core but also contributes in the identification and confirmation of coating sugar as well as the loaded drug. When the polysaccharide coatings are covered over the core particles, thepeaks shift to either lower or higher wavelengths that is indicating the hydrogen bonds formed between the molecules (ceramic core particles and polyoligomer coating)(Kaur et al., 2015; Vengala et al., 2017).

Crystalline nature of the core
The ceramic core isevaluated for its crystalline lattice arrangement or amorphous characteristics by X-ray diffraction (XRD). In this method, XRD patterns of samplesarematchedwith that of reference diffractogramsaccording to which the resultis inferred(Oviedo et al., 2007; Umashankar et al., 2010). The XRD pattern of Calcium phosphate core displayed intense and sharp peaks indicating its crystalline state. After coating of the core substance with different polysaccharides of trehalose, cellobiose and pyridoxal-5-phoshphate, the sharp peaks reduced their intensity and deformed into amorphous form (Kaur et al., 2015).

Characterization of coated core

Determination of amount of remaining sugar

Anthrone method is one of the greatest methods for themeasurementof residual unreacted sugar or excess sugar remaining after coating process. After poly and disaccharides are hydrolyzed into their respective monosaccharides, they subsequently convert to hydroxyl methyl furfural and upon addition ofAnthronewill give green colored product. Aliquots of samples, prepared for calibration curve, are transferred toboiling tubes and diluted to aproper concentration. Then anthrone reagent is added, water bath boiledand rapidly cooled. When a greenish colour is observed, absorbance of UV is noted down using glucose as standard. In case of sample analysis, anthrone reagent is tagged into precisely weighed sugar coated core after being dissolved in distilled water using the same procedure already stated (Kommineni et al., 2012; Narang, 2012).

Glass transition temperatures of coating material

Differential scanning calorimetry is commonly utilized for the assessment of glass transition temperature (Tg) of carbohydrates as well as proteins. DSC study ofaquasomal formulations is done in a DSC analyzer with a formulation filled sample cell and a buffer packed reference cell. DSC gives a picture about the purity, compatibility and effect of different components on aquasomes.

Evaluation of drug loaded aquasomes

Drug loading capacity

This test is carried out to confirm the amount of drug boundon the aquasomes. The drug loading capacityisevaluated by incubating plain aquasomal formulation (i.e., not containing the drug) in a precisely weighedamount of the drug for one day at 4°C. Thenthe superfluitantis removed by using ahigh speed centrifugation for one hour. Remaining amount of thedrug in the superfluitantcan be assessed by any appropriate analyticaltechnique (Chaudhary et al., 2018).

In vitro drug release profile

The *in vitro* release profile of the loaded drug is determined by incubating a precisely weighed amount of drug loaded aquasomes in a suitable pH of buffer at 37°C with constantmixing. Samples are takenin a different time intervals and centrifuged at high speed for a period of time. After withdrawing samples, the same volume of fresh buffermust be replaced. Then the supernatants are evaluated for drug release profile (% cumulative drug release) usingspectrophotometer or any other suitable method (Chaudhary et al., 2018; Kommineni et al., 2012)

5. APPLICATIONS OF AQUASOMES

Use of aquasomal ceramic nanoparticles will also enable peroral use of acid labile pharmaceutical agents. They can also act as solubility enhancer as well as stabilizing agent for various poor soluble drugs as it is described in many research articles aimed increasing the dissolution rate (Banerjee and Sen, 2018). In addition to that they are also capable to deliver fragile bioactive macromolecular substances , haemoglobin, antigens, genes, viruses, vaccines and enzymes (Narang, 2012)

Dissolution enhancement of hydrophobic drugs

Indomethacin, a low solubility drug, was loadedin lactose coatedcalcium phosphate aquasomes. Characterization of the aquasome structure, morphology and particle size using XRD, SEM and TEM showed spherical shaped aquasomes with particle size of 60–120 nm(Jain et al., 2012).Into the bargain, cumulative release of trehalose coated ceramic nanoparticles containing piroxicam as poorly soluble drug was compared toplain piroxicam

nanoparticles andcommercial piroxicam. The drug release from ceramic core was superior to the pure piroxicam during the whole time of study. This dissolution profile improvement could be attributed to the prepared nano-sized ceramic particles (Vengala et al., 2013a).In another study, in vitro drug release of pimozide, BCS class 2 drug, was evaluated by incorporating into lactose coated ceramic nanoparticles. The results show that the aquasomes can be used as dissolution increasing method for less aqueous soluble drugs (Banerjee and Sen, 2018; Vengala et al., 2013b).Moreover, Etoposide loaded aquasomesexhibited direct proportional increase between the drug release and amount of carbohydrate coating solution. In vivo studies of etoposide suggested that aquasomal preparation of Etoposide can be used as targeted drug delivery system to some organs like liver that ensured highest percentage of the total dose injected (Nanjwade et al., 2013).The in vitro dissolution data of lornoxicam contained aquasome formulation was compared with that pure drug and enhanced results were seen. The formulated ceramic nanoparticles were spherical in shape with an average particle size ranging from 60 to 300 nm. This indicates the importance of aquasomes as a noval carrier system capable of enhancing dissolution of poorly soluble drugs(Vengala et al., 2017).

Protein and peptide delivery

Aquasomes are well known for their ability to protect and stabilize bioactive molecules that are very labile and degraded by the harsh environment of the gastrointestinal tract. Many researches has been carried out for this purpose and they have found that aquasomal system are able to deliver macromolecules e.g. proteins and peptides into systemic circulation. Insulin, the first pure protein, is a vital drug in the treatment of diabetes(Anand *et al.*, 2017; Sharma *et al*., 2019). In its initial stages of development most of the routes of administration other than parenteral was not able to produce the required therapeutic level to reduce the blood glucose due to its degradation. oral delivery of proteins and peptides are very challenging since coating techniques may prevent only against acids but not proteolytic enzymes and hence aquasomes are widely studied in the following researches for the aim of overcoming loss of therapeutic actions of bioactive agents(Brown, 2005).

Insulin as a model drug was formulated into aquasomes by using different types of sugar coatings including cellobiose, trehalose and pyridoxal-5-phosphate to assess their effect on delivering the therapeutic drug. After performing in vivo studies, they have concluded that pyridoxal-5-phosphate have showed highest degree of adsorption and hence delivered the highest amount of insulin followed by trehalose and cellobiose. The highest decrement in the level of glucose in the blood that is obtained from pyridoxal-5-phosphate aquasomal formulation is attributed to its higher ability of molecular protection. Although Pyridoxal-5-phosphate, trehalose and cellobiose protected the drug from degradation, only pyridoxal-5-phosphate and trehalose have shown prolonged release pattern due to their higher effect against denaturation and dehydaration of insulin. It is also reported that formulating insulin into hydroxyapatite core dispersed alginate matrix has also achieved high amount of insulin conveyance by means of oral route(Banerjee and Sen, 2018; Jain et al., 2012). Another example iscoating of PEG on hydroxyapatite with further loading of the acid labile molecules i.e. insulin and gallic acid. This nanoparticle formulation was able to achieve high bioavailability by avoiding the digestive barriers of gastrointestinal tract, more specifically stomach. It has been described that PEG has stability enhancement role in this development as it also proved to have prolonged release. The advantageous features given by this strategy of non-toxicity, low cost, pronounced biocompatibility, high drug loading capability as well as easy method of synthesis will give a new prospect for providing insulin(Zhang et al., 2018).

Vaccine delivery

Ovalbumin, a model allergen widely used for the study of IgE mediated reactions, was incorporated into aquasome system without changing immunogenic features of the allergen. A strong immune response of specific T cell proliferation was observed. In addition to that the formulation has ensured low titers of IgE and prevented anaphylaxis which accentuates potential implications of aquasomes in the field of vaccine delivery especially peptide-based one for the prevention of allergic diseases by educating the immune system(Pandey et al., 2011). Cellobiose coated nanodecay approach of hydroxyapatite core containing surface antigen of hepatitis B (HBsAg) was also developed to enhance the immune system against hepatitis B. The nanodecay based aquasomal formulation was able to enhance the immune response of both T helper cells (Th1 & Th2)(Goyal et al., 2006).In another study, cellobiose was adsorbed on diamond based ceramic nanoparticle over which immunologically active surface molecule (muscle adhesive protein) was dispersed. The formulated aquasome which was ranged from 5 to 300 nm in size, has shown great advantages of a strong and specific immune response over conventional adjuvant that could produce higher availability and affordability of vaccines in the market. Aquasomes can successfully evoke specific immune response through targeting molecules and hence can be used as a strategy for developing viral antigens such as Immune deficiency virus and Epstein-Barr(Kossovsky et al., 1994).In another instance, Aquasomal formulation of BSA exhibited higher presentation to the Antigen Presenting Cells (APC) than pure Bovine Serum Albumin. APC which contains both major histocompatibility complex (I&II) leads to presentation of antigen through cytosolic and endocytic pathways giving stimulation to both of cellular and humoral response. The superior presentation and uptake of polyhydroxy oligomericaquasomes to the Antigen Presenting Cells is attributed to the ability of the formulation to protect molecular conformation of BSA.Moreover, the aquasomal nano carriers developed well-sustained titer value and the that is probably due to the fact that aquasomesbecomes the rate determining barrier giving prolonged release of the adsorbed antigens. The uptake of pure BSA is stated as minimum & contains only a minor ratio of these cells. As antigen nano-carriers, Aquasomes demonstrated to be relatively better delivery method compared to other ceramic based (Goyal et al., 2008).

Enzyme delivery

Aquasomes are being utilized for delivery of therapeutic enzymes e.g.DNAase, Serratiopeptidase& many others. Serratiopeptidase is a proteolytic enzyme with higher anti-inflammatory properties against both types of cyclooxygenases thereby inhibiting different kinds of inflammatory processes such as prostaglandin, interleukin, thromboxane and others (Tiwari, 2017). This enzyme based therapeutic agent is an acid labile and hence need to be protected from the gastric acids as well from enzymatic degradation. This anti-inflammatory enzyme was formulated into aquasomes for oral administration. The ceramic core was synthesized through precipitation by sonicating at room temperature and chitosan was used as coating material. The enzyme was adsorbed on the chitosan with further encapsulation into alginate gel. The formulation of enzyme loaded ceramic based aquasome has exhibited low release in the acidic buffer for about two to six hours whereas the alkaline medium exhibited complete and sustained 1^{st} order release for about six hours with loading efficiency of 46%. The reservoir properties could be attributed to the alginate gel that was encapsulated on the aquasome whereas the ceramic core gives stability to the enzyme (Banerjee and Sen, 2018; Rawat et al., 2008).Another enzyme, DNAase, used in the management and treatment of cystic fibrosis has been effectively formulated intoaquasomes and as result a desirable as well as significant therapeutic efficacy was achieved. A noticeable prolonged biological actionis seen in DNAase incorporated colloidal ceramic core (calcium phosphate) nanoparticle coated with polyhydroxy oligomeric film(Jain et al., 2012).

Peroral route

Piroxicam was loaded into aquasomes for oral administration by coprecipitation technique. Due to the nanosize of formulation the required dose was comparatively less than that of conventional method and the water like properties of the aquasomes enabled protection of the loaded therapeutic drug, Piroxicam(Kommineni et al., 2012; Narang, 2012).

As oxygen carrier

Aquasomes has showed a superiority in terms of hemoglobin delivery over other available carriers of artificial blood substitutes and hence can act as a new model approach for the transport of oxygen [75]. For instance, PAMAM dendrimer template as a core was covered with trehalose and further adsorbed with hemoglobin and the O_2binding properties of the prepared aquasomes were evaluated and compared to that of freshly obtained blood as well as to hemoglobin solution. Hill coefficient values indicated a great potential of aquasomes as oxygen carrier as they are capable to maintain its O_2binding properties over a period of one month. By this toxicity is minimized with 80% haemoglobin concentration & it is reported to transport blood in non linear pattern similar to natural blood cells. Due to stability of the Hb loaded aquasomes and its good oxygen binding features, this may attract pharmaceutical scientists and industries to develop potential synthetic oxygen transport system based on aquasomal formulations(Banerjee and Sen, 2018; Khopade et al., 2002).

Gene delivery

Aquasomes have shown attractive features that could act as gene therapy approach. It has been designed a five layered structure of aquasome for delivery of genes that comprised of a core of ceramic nanocrystalline, coating layer of polyhydroxy oligomer film, a layer of therapeutic gene segment, an extra carbohydrate film & a targeting layer of structurally preserved membrane of viral proteins. Aquasomes have great potential for gene therapy over viral vector and at the same time it will overcome the challenge of irrelevant gene integration (Jain et al., 2012).

Different researches carried on Aquasomes with different therapeutic molecules are demonstrated in table (2).

6. CONCLUSION

Aquasomes are mainly studied for proteins, peptides and related molecules but they are versatile compounds that can have great reproducibility and robustness to be used in different ways e.g. solubility enhancing, targeting approach and many others.They are also biocompatible and biodegrablenanocarrires having high surface area to volume ratio. In contrast to many delivery systems, e.g. liposomes and prodrugs,aquasomes are not seen to induce destructive interaction between the drug molecules and carrier.Aquasomes proved to have higher ability to produce enhanced immune response. Hence, Aquasomes are having great future potential applications as a drug and bioactive delivery system. Thisis enlightening the need for further focus and studies to give full picture of this novel drug delivery system. Aquasomes are giving hope for scientists to tackle various drawbacks related to conventional delivery of pharmaceutical agents.

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Table 1:

Different types of nanovesicular delivery systems with theirapplications

Carrier	**Description**	**Application**	**Reference**
Aquasome	Tri-layered self-assembly system consisting of central core on which polyhydroxy oligomer film is coated over which the drug is loaded	Oral delivery of labile bioactives, poorly soluble drugs and sustained release e.g. Piroxicam	(Wadhwa et al., 2018; Vengala et al., 2013a)
Archeasome	Lipid based delivery system composed of archaebacterial membrane lipids containing diether or tetraether lipids	Oral delivery of macromolecules e.g. ovalbumin	(Agrahari et al., 2016)

Bilosome	Bile salt linked vesicular lipid bilayer e.g. monopalmitoyl glycerol, cholesterol and dicetyl phosphate)	Oral delivery of vaccines e.g. Hepatitis B Vaccine	(Shukla et al., 2016; Wilkhu et al., 2013)
Colloidosome	Hollow shell microcapsules comprising of colloidal particles e.g. silica nanoparticles on the boundary of emulsion droplets	Delivery of vitamins, proteins and food supplements as well as targeted specific areas in the body e.g. kanamycin	(Rossier-Miranda et al., 2009; Thompson et al., 2014)
Cubosome	square and rounded nanostructured particles with internal cubic crystalline lattices	Targeting and controlled release of bioactive agents e.g. Capsaicin	(Peng et al., 2015; Ramya et al., 2017)
Discosome	Giant niosomes solubilized with nonionic surfactant solution	Ligand mediated ocular drug targeting e.g. ganciclovir	(Baranowski et al., 2014)
Emulsome	Lipoidal vesicular nanoparticles comprising of microscopic lipid assembly having a polar core	Parentral use of lipophilic drugs e.g. silybin	(Zhou and Chen, 2015)
Enzymosome	Novel nanocarrier in which an enzyme is linked & encapsulated to the surface of liposomes	Cancer cells targeting in a specific fashion e.g. surface-exposed superoxide dismutase	(Gaspar et al., 2007)
Erythrosome	Lipid bilayer is coated on human erythrocytes (RBC) cytoskeletons as a support	Targeting of molecules e.g. capecitabine	(Kavita et al., 2016)
Ethosome	lipid-based elastic vesicular systems composing mainly of phospholipids, ethanol (high concentrations up to 50%) & water	Deep dermal and transdermal drug delivery e.g. cromolyn sodium	(Ainbinder et al., 2010; Rakesh and Anoop, 2012)
Genosome	Artificial macromolecular complexes containing cationic lipids; highly biodegradabile and stable in blood stream	Functional cell specific gene transfer e.g. siRNA and DNA	(Rafael et al., 2017)
Hemosome	Encapsulation of haem or hemoglobin with in lipid vesicles or liposomes (Liposome-encapsulated hemoglobin-LEH)	Oxygen carrier e.g. Hemoglobin (Hb)	(Idris and Hundekar, 2014)

Liposome	Spherical vesicles of lipid consisting of one or more lipid bilayers enclosing internal water droplet	Carrier for both lipophilic and hydrophilic drugs e.g.Daunorubicin	(Yadav et al., 2017)
Niosome	Spherical structures that are made up of cholesterol and nonionic surfactants	Improvement of oral bioavailability as well as upsurging skin penetration of molecules e.g. Ketoconazole	(Shirsand et al., 2012; Yeo et al., 2017)
Pharmacosome	Colloidal dispersion of drugs covalently bound to the lipids	Drug targeting in controlled release e.g. Rosuvastatin	(Kumar et al., 2016; Supraja and Mulangi, 2019)
Photosome	Microwave dependent drug release from thermo-sensitive liposomes	Ophthalmic drug delivery e.g. sunscreen	(Lajunen et al., 2016; Stege et al., 2000)
Phytosome	Vesicular carrier of phospholipid and an individual phytoconstituent in the ratio of 1:1 or 2:1 depending on the substance	Increases the bioavailabilty of phytoconstituents e.g. Gingerol	(Pratap et al., 2018; Purkayastha and Ghosh, 2018)
Sphingosome	Colloidal concentric vesicles in which aqueous compartment entirely encloses a bilayer membrane.	Enzyme and targeted tumor therapy e.g. Vinorelbine	(Fathima et al., 2016; Kunwarpuriya et al., 2015)
Transfersome	Artificial, ultradeformable, stress responsive vesicle with an aqueous core enclosed by a complex lipid bilayer.	Transdermal drug delivery giving controlled release e.g. Miconazole	(Gupta et al., 2012; Qushawy et al., 2018)
Ufasome	Ssuspensions of bilayer of lipids encompassing of unsaturated fatty acids and their soap (ionized species).	Transdermal drug delivery e.g. Methotrexate	(Patel et al., 2011; Sharma and Arora, 2012)
Vesosome	Compartmentalized structure of liposome encapsulated liposomes, which upsurges their applicability as model cells.	Enhancement of delivery systems (synergism) e.g. Doxorubicin and 5-fluorouacil (5FU)	(Jang et al., 2013; Zhang et al., 2019)
Virosome	Phospholipid membrane vesicles of reconstituted viral envelope after exclusion of inner nucleic acid core & genetic information	Targeted drug delivery as well as delivery of vaccines e.g. Influenza virus	(Kalra et al., 2013; Pluschke and Tamborrini, 2010)

Table 2:

Different therapeutics application of Aquasomes in drug delivery

Bioactive / molecules	**Application**	**Result outcomes**	**References**
Mussel Adhesive Protein	Antigen delivery	Antigen stabilization	(Kossovsky et al., 1994)
Non-nuclear substance from HIV-1	Immunization	Elicit both humoral and cellular immunity	(Kossovsky et al., 1995)
Insulin	Insulin delivery	Protection of peptides	(Cherian et al., 2000)
Hemoglobin	Oxygen carrier	High potential as artificial blood substitute	(Khopade and Jain, 2002)
Haemoglobin	Hemoglobin carrier	Stable formulation having upsurged oxygen carrying capacity	(Patil et al., 2004)
Hepatitis B serum Antigen	Vaccine delivery	Eliciting combined immune response	(Goyal et al., 2006)
Indomethacin	Dissolution enhancement	Developed indomethacin aquasomes& structurally analysed	(Oviedo et al., 2007)
Bovine serum albumin	Antigen delivery	Structurally preserved BSA and improved presentation to Antigen Presenting Cells	(Goyal et al., 2008)
Serrapeptase	Enzyme delivery	Sustained release profile	(Rawat et al., 2008)
Ovalbumin (OVA)	Allergen immunotherapy	Induces a strong T cell specific proliferative response (Th1) without abrogation of Th2 responses	(Pandey et al., 2011)
Piroxicam	Oral delivery of hydrophobic drugs	Enhanced oral delivery of piroxicam & reduces the systemic side effects	(Kommineni et al., 2012)
Piroxicam	Lipophilic drug use	controlled release of piroxicam	(Vengala et al., 2013a)
Pimozide	Dissolution improvement of hydrophobic drug	Improved dissolution profile of aquasomes	(Vengala et al., 2013b)
Etoposide	Dissolution upsurging of poor soluble drug	Highest % of the dose was found in spleen& liver.	(Nanjwade et al., 2013)
Interferon	Protein delivery	Prolonged release	(Kaur et al., 2015)
Lornoxicam	lipophilic drug delivery	Enhanced the dissolution with better release profile	(Vengala*et al.*, 2017)
Insulin	Insulin delivery	Enhanced Insulin delivery	(Zhang et al., 2018)

Figure 1:Different Components of Aquasomes

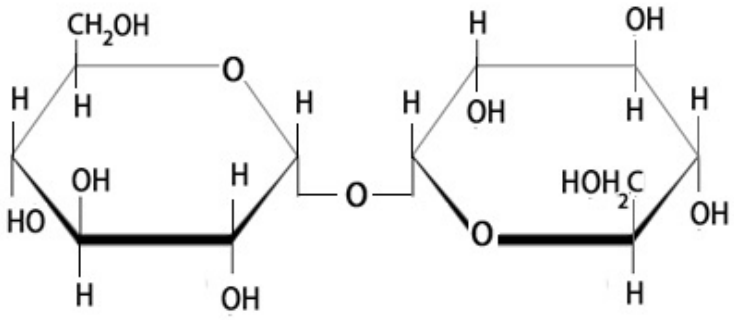

Figure 2: Chemical structure of trehalose

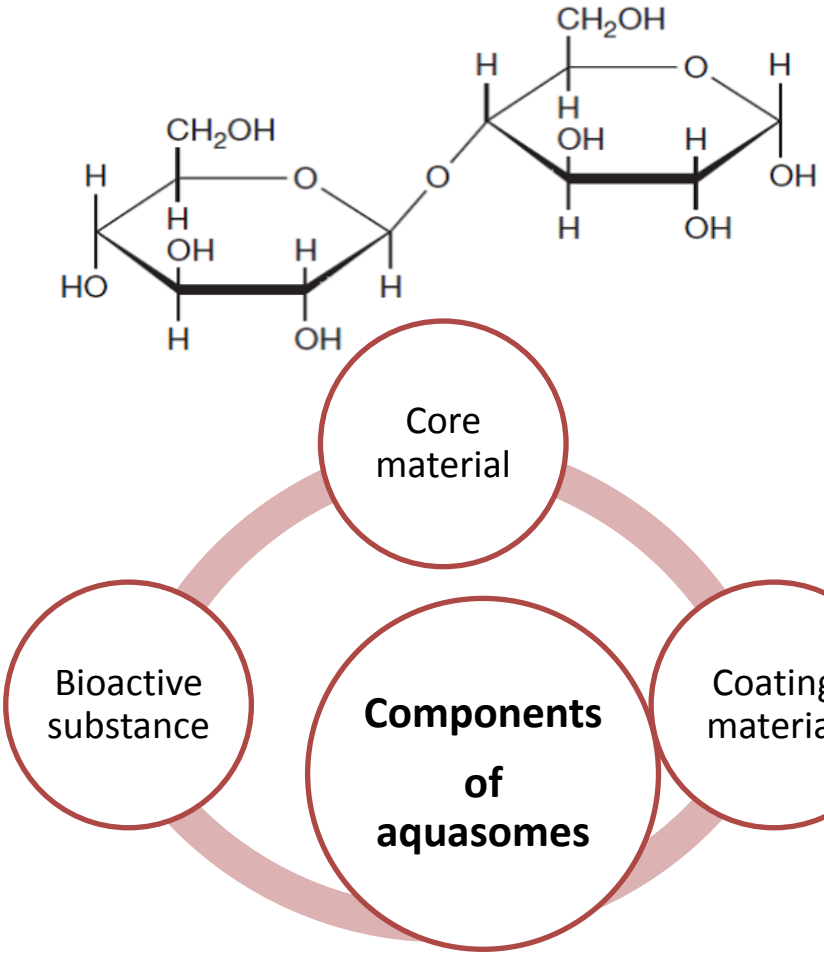

Figure 3: Chemical structure of cellobiose

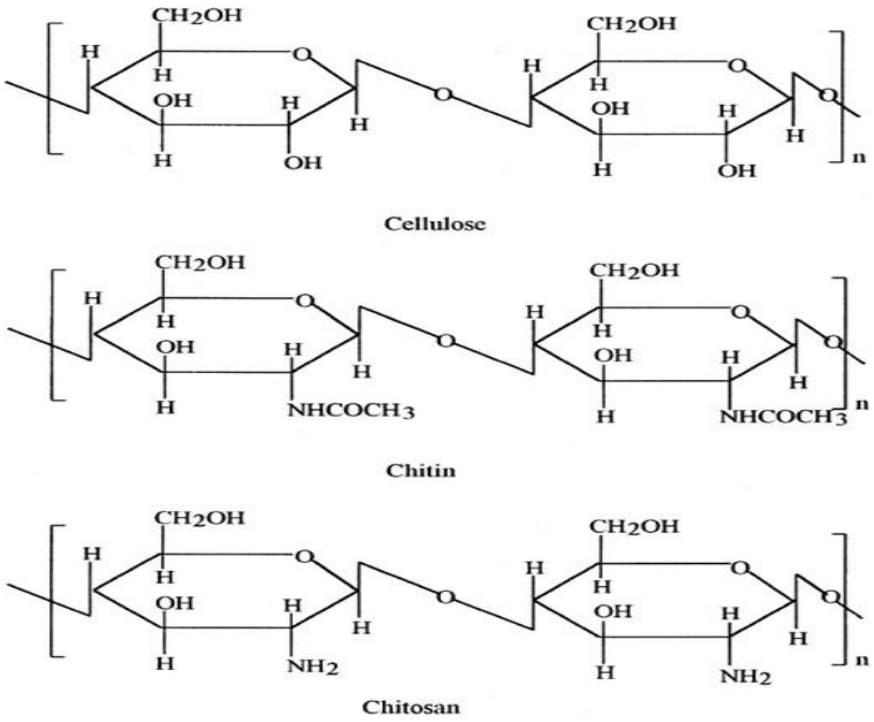

Figure 4: Chemical structure of chitosan (Ranjha and Khan, 2013)

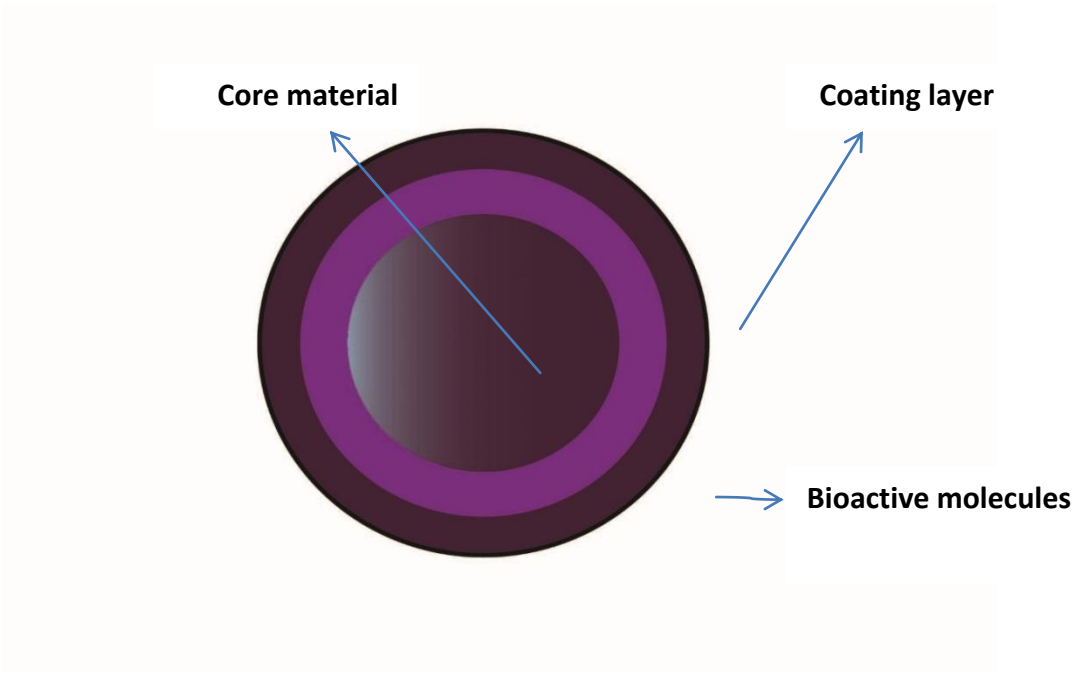

Figure 5:Three body concept of Aquasomes vesicular system

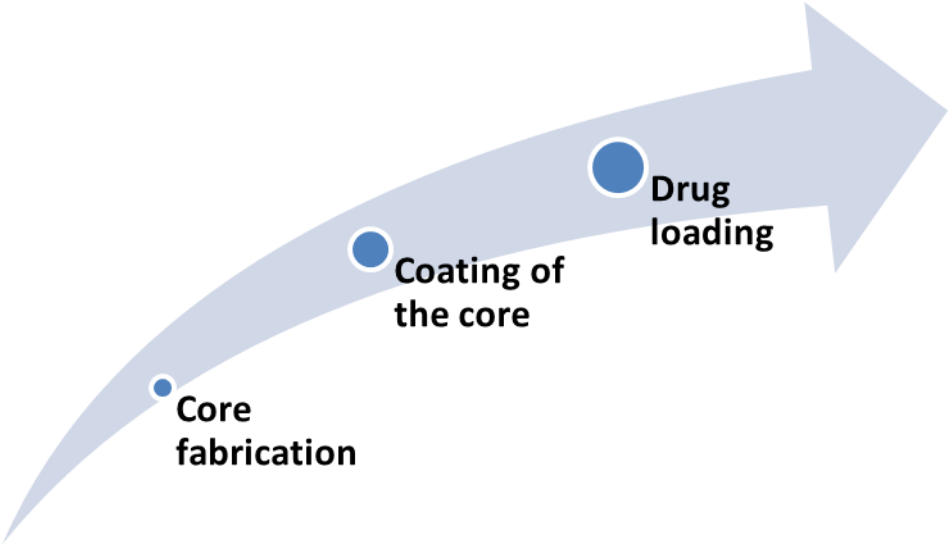

Figure 6:Steps involved in preparation of Aquasomes

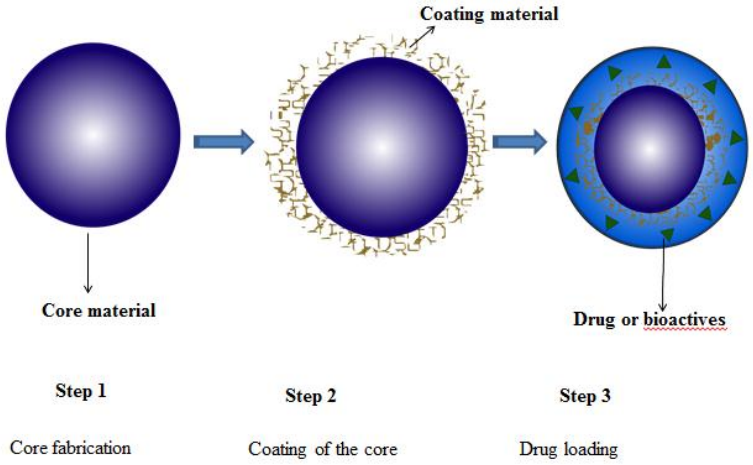

Figure 7. Graphical representation of Aquasomes preparation