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Review Article

AQUASOMES UNVEILED: TRANSFORMING DRUG DELIVERY WITH CUTTING-EDGE THERAPEUTIC CARRIERS AND RECENT BREAKTHROUGHS

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ABSTRACT

The study presented herein explores the groundbreaking utilization of aquasomes, which are sophisticated colloidal ceramic carbohydrate composites, as carriers for the transportation of hemoglobin. These aquasomes undergo strategic surface modification with carbohydrates, leading to the development of a protective molecular layer characterized by a resilient glassy texture. This innovative approach effectively safeguards therapeutic proteins by forming a molecular shield, thus mitigating potential structural damage during transit. Crucially, aquasomes demonstrate remarkable efficacy in preserving encapsulated drugs within aqueous environments. This is achieved by shielding the drugs from the adverse effects of fluctuating pH levels and temperature variations, which could otherwise induce denaturation. Importantly, the protective capability of aquasomes remains intact, exhibiting no alterations in swelling or porosity despite changes in external conditions.

Furthermore, this article sheds light on recent breakthroughs in aquasomes research, highlighting their diverse applications and promising future avenues. In particular, the focus is on the use of aquasomes for the transport of hemoglobin and therapeutic proteins, underscoring their potential transformative impact in the field of biomedical sciences. The incorporation of aquasomes as carriers for hemoglobin transportation represents a significant advancement in drug delivery technology. By harnessing the unique properties of aquasomes, researchers have opened up new possibilities for the safe and efficient transport of therapeutic proteins, offering hope for the development of novel treatments for a range of medical conditions. Overall, this study underscores the immense potential of aquasomes in revolutionizing biomedical research and improving patient outcomes.

Keywords: Aquasomes, Self-assembled nano-particulate carrier system, Colloidal ceramic carbohydrate composites, Drug delivery, Hemoglobin transport

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INTRODUCTION

Aquasomes, a term coined by Nir Kossovsky, ingeniously combine the essence of water ("Aqua") with cellular-like structures ("some"). These entities serve as guardians for delicate biological molecules, boasting a composition consisting of three distinct layers: a central core, a coating, and a drug component. Through a symphony of weak interactions such as noncovalent bonds, ionic bonds, and van der Waals forces, these layers harmonize into a self-assembled structure, showcasing a remarkable versatility in pharmaceutical transportation [1]. At their core lies a ceramic stronghold, providing stability to the entire construct while remaining largely unaltered. The surface of this core undergoes noncovalent modification, evolving into a sugar-coated sphere primed for medicinal substance adsorption. The outermost layer, crafted from polyhydroxy oligomers or sugar molecules like cellobiose and trehalose, serves as a platform for attaching antigens through noncovalent bonds, fostering an environment akin to a semi-liquid film [2]. Aquasomes, with their water-absorbing capability, stand apart from conventional nanoparticle systems. This unique trait not only facilitates their transport in aqueous solutions but also fosters non-covalent interactions with a myriad of molecules, including large proteins. Such interactions bolster their stability, shielding proteins from denaturation and ensuring their integrity during transportation [3]. In the realm of pharmaceutical delivery, aquasomes shine brightly. Their ability to retain structural integrity in fluctuating pH and temperature environments sets them apart [4]. Through surface modification with carbohydrates, they create a protective molecular layer, offering sanctuary to therapeutic proteins while minimizing structural damage. This shield remains unwavering, unaffected by changes in external conditions, ensuring the safe delivery of drugs without compromise [5]. In a groundbreaking application, aquasomes have emerged as a promising avenue for the delivery of hemoglobin, addressing previous limitations such as kidney toxicity and tetramer breakdown. By leveraging colloidal ceramic carbohydrate composites, hemoglobin finds refuge within aquasomes, shielded from harm while retaining its therapeutic efficacy. This innovative approach heralds a new era in pharmaceutical delivery, where aquasomes stand as stalwart guardians, navigating the intricate terrain of molecular transport with finesse and reliability [6]. The selections of articles for the current review were searched from specialized databases (Range of years: 1992-2024) such as Elsevier, Pubmed, and Cambridge using the keywords Aquasomes, self-assembled nano-particulate carrier system, and colloidal ceramic carbohydrate composites. Other selections include articles from Springer, information from Internet sources, and Online published articles resourced from The Lancet Respiratory Medicine, Medscape, Statpearls.

Structure of aquasomes

Aquasomes, with their distinctive circular morphology, showcase a remarkable range in size, spanning from 60 to 300 nanometers. These minute marvels are intricately crafted, boasting a ceramic core that has undergone meticulous noncovalent modifications on its surface. This unique structural composition renders aquasomes as a versatile nanoparticle transport system, facilitating the delivery of a myriad of biologically active substances. However, delving deeper into their composition unveils their complexity as three-layered entities. At their core lies a robust nanocrystalline structure encased within an oligomeric layer. This outer layer serves as a protective shield, preserving the integrity of the core while allowing for the adsorption of biologically active particles without altering their inherent properties. Drawing parallels to aquatic pathways, aquasomes exhibit water-like characteristics, embodying a natural affinity for safeguarding fragile organic payloads. This inherent trait is pivotal in ensuring the safe transport and preservation of delicate biomolecules [7].

Moreover, aquasomes possess a unique ability to maintain structural integrity, owing to the meticulously structured arrangements of

atoms within their composition. Through precise chemical bonding, these nanoparticles are endowed with defined composition, connectivity, and shape. Such structural stability, coupled with enhanced surface accessibility, forms the cornerstone for targeted delivery strategies. Indeed, the application spectrum of aquasomes extends far beyond mere transport systems. Their tailored design allows for the targeted delivery of various bioactive molecules, ranging from peptides and protein enzymes to catalysts, antigens, and even genes, to specific cellular destinations. This precision delivery mechanism holds immense promise for therapeutic interventions and biomedical research. For parenteral administration, aquasome particle sizes must adhere to stringent criteria, necessitating dimensions smaller than 1000 nanometers. To ensure compliance, these nanoparticles undergo rigorous structural analyses employing techniques such as X-ray diffraction (XRD) and electron microscopy. Such meticulous scrutiny guarantees the quality and efficacy of aquasome-based drug delivery systems, paving the way for advancements in targeted therapeutics and precision medicine [8].

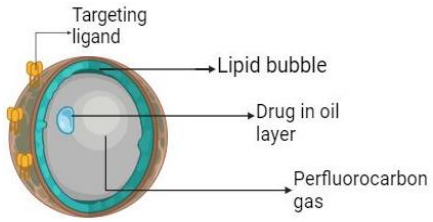

Fig. 1: Structure of aquasomes

Properties of aquasomes

Aquasomes, characterized by their water-like properties, serves as a cornerstone in maintaining the structural integrity and biochemical stability of bioactive compounds. These remarkable attributes not only provide a stable foundation but also play a pivotal role in safeguarding the conformational integrity and biochemical stability of the encapsulated bioactive substances. Their unique size and intricately designed structure enable Aquasomes to evade clearance by the reticuloendothelial system and shield against degradation induced by environmental stressors [9]. Functioning as a nanoparticle-based drug delivery system, Aquasomes comprise colloidal range biodegradable particles that exhibit enhanced accumulation in vital organs such as the liver and muscles. Remarkably, these nanoparticles possess an innate ability to attract and adhere drugs onto their surface without necessitating additional modifications. This inherent property facilitates smooth receptor recognition at the active site, thereby ensuring prompt pharmacological or biological activity upon delivery.

In contrast to conventional systems, where calcium phosphate serves as a biodegradable ceramic, Aquasomes offer a more sophisticated approach. The *in vivo* biodegradation process of calcium phosphate involves a series of orchestrated events, beginning with the intervention of monocytes and osteoclasts, multicellular cells, during the inflammatory response at the site of biomaterial implantation. Upon interaction with the biomaterial, cells exhibit two distinct modes of phagocytosis: either calcium phosphate crystals are internalized independently, subsequently dissolving within the cytoplasm following the disappearance of the phagosome membrane, or dissolution occurs after the formation of heterophagosomes. Importantly, the phagocytosis of the calcium phosphate group plays a crucial role in stabilizing tertiary structures inherent in folded proteins [10].

Composition of aquasomes

The central core part of aquasome

Aquasomes, revered for their remarkable systematic organization and consistency, embody a fusion of essential elements such as diamond flakes, brushite (calcium phosphate), and tin oxide. These elements collectively epitomize qualities of being easily manufacturable, cost-effective, biodegradable, and biocompatible, making aquasomes a coveted choice in the realm of ceramic materials. The inherent order and higher surface energy of aquasomes play a pivotal role in facilitating the effective binding of carbohydrates, as elucidated by research [11]. This characteristic not only underscores its functional efficacy but also highlights its suitability for diverse applications, particularly in the formulation of aquasomes. In the formulation process, polymers emerge as indispensable components, with options like albumin, gelatin, or acrylate being commonly employed. These polymers not only contribute to the structural integrity of aquasomes but also enhance their functional properties, further expanding their potential applications and utility in various domains.

Coating material

Cellobiose, a key player in the intricate world of polysaccharides, emerges from the partial degradation of cellulose, a structural component abundant in plant cell walls. This process involves the linkage of glucopyranosyl units, culminating in the formation of cellobiose-a disaccharide pivotal not only in biological processes but also in pharmaceutical applications. Its role as a protective agent for drug molecules against dehydration aligns with that of trehalose, another notable disaccharide composed of alpha-D-glucopyranosyl units. Trehalose, renowned for its prowess in stress resilience across diverse organisms, surpasses cellobiose in effectiveness, marking it as a superior choice for pharmaceutical formulations requiring stability under desiccation stress. The versatility of trehalose extends across various kingdoms of life, demonstrating its efficacy in preserving cell integrity and functionality in fungi, bacteria, insects, yeast, and specific plant species. Particularly during desiccation, trehalose assumes a pivotal role in maintaining cellular structures, safeguarding natural attributes such as taste, color, and texture by preserving essential biomolecules like proteins and membranes. The significance of disaccharides like sucrose and trehalose lies in their ability to interact with polar protein residues, effectively replacing water molecules and ensuring the structural integrity of biological components even in the absence of aqueous environments [12]. This phenomenon is crucial in scenarios such as lyophilization, where the removal of water necessitates the presence of stabilizing agents to prevent structural damage. Experimental evidence, notably from studies involving calcium-carrying microsomes extracted from rabbit and lobster muscles, underscores the protective role of sugars like trehalose. Findings reveal that trehalose supplementation preserves the shape and function of biological components post-lyophilization, as evidenced by maintained calcium absorption and ATP-ase activity. Conversely, vesicles lacking stabilizing sugars exhibit compromised structural integrity and functionality upon rehydration. Furthermore, beyond sugars, the inclusion of common coating ingredients such as chitosan and citrate underscores the multifaceted approach to stabilization in pharmaceutical formulations. Carbohydrates, acting as natural stabilizers, form a nano-scale glassy layer around ceramic nanoparticles and self-assembled calcium phosphate dihydrate particles. This coating mechanism serves to enhance stability and prolong the shelf-life of pharmaceutical products, ensuring their efficacy and safety for end-users. In essence, the interplay between disaccharides like cellobiose and trehalose, coupled with the synergistic action of other stabilizing agents, highlights the intricate balance required to maintain the stability and functionality of pharmaceutical formulations. These insights pave the way for the development of novel strategies aimed at enhancing the efficacy and reliability of drug delivery systems in diverse applications.

Bioactive molecules

Pharmaceuticals that disrupt the film through non-covalent and ionic interactions have demonstrated considerable promise as potential options for aquasomes [13].

Preparation of aquasomes

The method of preparation of aquasomes involves various steps, which are as follows.

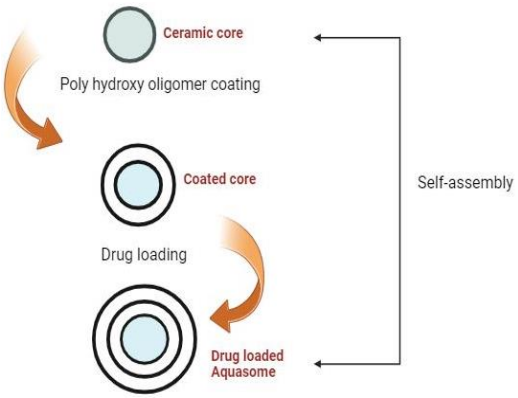

Fig. 2: Composition of aquasomes

Preparation of central-core material

The first phase in aquasome planning is the establishment of the ceramic center's structure. The selection of materials for the core guides the method of producing ceramic cores. Nanocrystalline calcium phosphate and hydroxyapatite are commonly employed as the core materials in Aquasomes, with tin oxide, carbon ceramic (diamond), and other substances also serving as potential alternatives. The ceramic cores can be produced through processes such as colloidal precipitation and sonication, inverted magnetron sputtering, plasma condensation, and similar methods. The cores formed through precipitation are subjected to centrifugation and subsequently washed with sufficient distilled water to eliminate the sodium chloride generated in the process. The resulting precipitates are then suspended in distilled water, and the particles of the desired size are collected by passing them through a fine membrane filter. The significant level of organization suggests elevated surface energy, facilitating the adherence of polyhydroxy oligomeric coatings. Diamond and calcium phosphate stand out as the prevailing ceramic cores in this context [14, 15].

Coating of ceramic core

In the second step, the surface of ceramic cores undergoes a coating with carbohydrates. Several methods are employed to facilitate the epitaxial adsorption of carbohydrate (polyhydroxy oligomers) coatings onto Nano-crystalline ceramic surfaces. Typically, these processes involve adding polyhydroxy oligomers to a dispersion of thoroughly cleaned ceramics in ultra-pure water, followed by sonication and subsequent lyophilization. This sequence promotes the predominantly irreversible adsorption of carbohydrates onto the ceramic surfaces. Various methods are employed to achieve the epitaxial adsorption of carbohydrate (polyhydroxy oligomers) coatings onto nano-crystalline ceramic cores. Typically, these techniques involve introducing polyhydroxy oligomers into a dispersion of meticulously purified ceramics in ultra-pure water, followed by sonication and subsequent lyophilization. This process ensures the most enduring adsorption of carbohydrates onto the ceramic surfaces.

Drug candidate immobilization

The ultimate stage in aquasome preparation involves loading the drug onto coated particles through partial adsorption. Surface-modified Nano-crystalline cores are integral in aquasome preparation, providing a stable foundation throughout the process. Meticulously designed for stability, these cores play a pivotal role in facilitating non-denaturing self-assembly during aquasome formation. Their unique attributes make them essential for creating aquasomes with heightened stability and improved bioavailability, as they effectively incorporate a diverse range of biochemically active molecules onto their surfaces. The tailored design of these cores renders them versatile and well-suited for various applications in pharmaceuticals and related fields [16].

Self-assembly of molecules

In the realm of constructing large atom ensembles with precise architectural designs, molecular self-assembly stands out as an advanced method that incorporates components from earlier techniques. This innovative approach relies on the strengths of sequential covalent synthesis, leading to the production of meticulously defined molecules characterized by a moderate level of structural complexity. The methodical application of sequential covalent synthesis ensures a stepwise assembly process, contributing significantly to the formation of intricate molecular architectures with well-defined features. The integration of various techniques within molecular self-assembly not only enhances overall efficiency but also allows for a controlled approach to structural complexity. By incorporating sequential covalent synthesis, the method strikes a delicate balance between precise assembly and manageable intricacy. This strategic combination enables the creation of atom ensembles that exhibit both meticulous arrangement and architectural soundness. Ultimately, molecular self-assembly, with its incorporation of sequential covalent synthesis, provides a versatile and powerful approach for developing intricate and architecturally defined molecular systems [17].

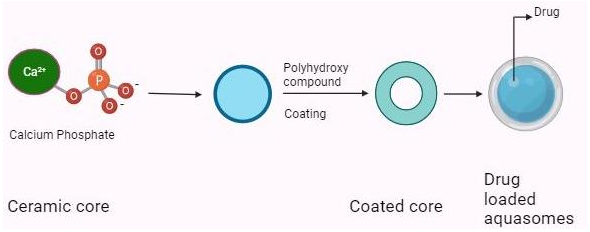

Fig. 3: Preparation of aquasomes

Evaluation parameters for aquasomes

Evaluation of core

Size distribution

Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) techniques serve as indispensable tools for investigating the particle size distribution and morphological characteristics within the realm of aquasomes. In the realm of SEM, samples are meticulously prepared by positioning them on a gold-coated specimen stub using double-sided adhesive tape. This meticulous preparation ensures optimal visualization and analysis. SEM analysis primarily revolves around discerning the particle size evident on the surface of the specimen. Through high-resolution imaging, SEM facilitates a detailed examination of aquasomes, shedding light on their surface properties and structural intricacies. Conversely, TEM delves into a different realm of analysis. Employing negative staining with phosphotungstic acid, TEM offers a distinct perspective on particle size distribution within aquasomes. This technique allows researchers to explore the internal structure of the particles, providing insights into their composition and organization at a nanoscale level. TEM serves as a powerful tool for scrutinizing the internal morphology of aquasomes, offering valuable information regarding their structural integrity and composition. Both SEM and TEM synergistically contribute to a comprehensive understanding of aquasomes. They play pivotal roles in examining the structure and properties of these innovative formulations, offering valuable insights into their morphological features. Through meticulous analysis, SEM and TEM facilitate the evaluation of coated core and drug-loaded aquasomes, providing researchers with understanding of their characteristics and potential applications. Thus, these advanced microscopy techniques are indispensable in the comprehensive analysis of aquasomes, guiding researchers towards enhanced formulations and applications in various fields [18].

Structural analysis (FTIR Characterization)

Fourier transform infrared spectroscopy (FTIR) is employed for structural analysis of aquasomes, utilizing the potassium bromide sample disk method. Both the core and coated core of aquasomes undergo analysis by recording their infrared spectra within the wavenumber range of 4000 to 400 Cm^{-1}. The examination of

characteristic peaks in these spectra is compared with reference peaks to provide insights into the structural composition. Additionally, FT-IR proves valuable in assessing the stability of the drug within the aquasome formulation. This technique contributes to a comprehensive understanding of the aquasome structure, aiding in the identification of characteristic features and ensuring the stability of the incorporated drug [19].

Crystallinity (X-Ray diffraction)

To unveil the crystalline or amorphous attributes inherent in aquasomes, a meticulous examination via X-ray diffraction analysis (XRD) is employed, with a particular focus on the hydroxyapatite ceramic core. This analytical approach involves subjecting the core to radiation emitted by copper (Cu) and potassium (K) in a wide-angle X-ray diffractometer. The resultant X-ray diffraction pattern is then meticulously juxtaposed against a standard diffractogram, forming the foundation for comprehensive interpretation. In a specific investigative endeavor, intriguing observations emerged. When scrutinizing the calcium phosphate core and lactose in isolation, distinct and sharply defined peaks characteristic of a crystalline structure were discerned. However, a significant departure was noted when studying aquasomes harboring carbohydrate-coated cores. Here, the observed peaks portrayed a distinctly different pattern, suggestive of an amorphous nature. This observation underscores the invaluable role of XRD in unraveling the intricate structural intricacies of Aquasomes. Moreover, it highlights the profound impact that coatings wield in potentially altering the crystalline or amorphous nature of the material. Through such meticulous analysis, researchers gain invaluable insights into the fundamental properties of Aquasomes, facilitating advancements in their synthesis, design, and application [20].

Evaluation of coated core

Carbohydrate coating

The confirmation of sugar coating on the ceramic core of Aquasomes is achieved through various methods, including the Concanavalin A-induced aggregation method, Anthrone reaction, and Phenol sulphuric acid method. In the context of Aquasomes, these techniques serve to validate the presence of the sugar coating. The details of these methods are outlined in table 1, providing a comprehensive overview of the approaches employed to confirm the successful coating of sugar over the ceramic core in aquasome formulations.

Table 1: Methods used for carbohydrate coating

S. No.	Method	Description	References
1.	Anthrone reaction	The calorimetric method employed for quantifying the unbound residual sugar or residual sugar left after coating involves the addition of Anthrone reagent to the sample. The mixture is then heated in a boiling water bath and rapidly cooled. In an acidic environment, carbohydrates undergo hydrolysis to form hydroxymethylfurfural, which reacts with the Anthrone reagent, producing a blue-green-colored complex. The absorbance is measured at a wavelength of 625 nm using a UV-visible spectrophotometer, with glucose serving as the standard.	[21]
2.	Concanavalin-A induced aggregation	To determine the quantity of sugar-loaded on the ceramic core in Aquasomes, a Concanavalin-A solution is introduced to suspensions containing various carbohydrate-coated cores within quartz cuvettes. The absorbance is then monitored using a UV-visible spectrophotometer at a wavelength of 450 nm at 5-minute intervals over a specified time duration. The data obtained is subsequently subtracted from the blank experiment. This method helps assess the sugar content associated with Aquasomes.	[22]
3.	Phenol sulphuric acid method	It is a colorimetric technique employed to determine the total carbohydrate content, encompassing mono-, di-, oligo-, and polysaccharides within a given sample. In this method, carbohydrates undergo dehydration to form furfural derivatives in the presence of concentrated sulfuric acid. Subsequently, these derivatives react with phenol, resulting in the development of a distinctive yellow-gold color.	[23]

Zeta potential measurement

The adsorption of sugar onto the core and the assessment of storage stability are gauged through the measurement of zeta potential. Several studies have suggested that as the saturation process involving carbohydrates on the hydroxyapatite core intensifies, there is a corresponding decrease in the zeta potential value.

Glass transition temperature

Differential scanning calorimetry (DSC) is employed to analyze the glass transition temperature of carbohydrates and proteins. In the study of drug-loaded aquasomes, DSC is utilized to investigate the impact of carbohydrates. The transition from a glass to a rubber state can be quantified by a DSC analyzer through the temperature change observed during the melting of the glass.

Evaluation of drug-loaded aquasomes

Drug loading efficiency

This process is conducted to assess the quantity of pharmaceutical substances bound to the surface of aquasomes. The determination of drug loading involves incubating the aquasome formulation, excluding the drug, in a known concentration of the drug solution for 24 h at 4 °C. Subsequently; the supernatant is separated through high-speed centrifugation lasting 1 hour at a low temperature in a refrigerated centrifuge. Following this, the clear extractive supernatant undergoes filtration, and the analysis of free drug content is performed using a UV spectrophotometer.

The drug payload or drug loading (DL) is then calculated using the following formula:

$$\%\ DL = Wt\ of\ total\ drug\ added - weight\ of\ unentrapped\ drug / weight\ of\ aquasomes * 100$$

***In vitro* drug release studies**

The investigation into the *in vitro* release kinetics of the encapsulated drug aims to examine the drug's release behavior from aquasomes. A specific quantity of drugloaded aquasomes is incubated in a buffer with an appropriate pH at 37 °C while maintaining continuous stirring. Samples are periodically withdrawn and subjected to high-speed centrifugation. Following each withdrawal, equivalent volumes of fresh medium are introduced. The supernatants obtained are then analyzed to quantify the released drug amount [24].

In process stability studies

SDS-PAGE, which stands for sodium dodecyl sulphate polyacrylamide gel electrophoresis, serves as a valuable technique in evaluating the stability and integrity of proteins throughout the formulation of Aquasomes. This method involves the separation of proteins based on their molecular weight using a polyacrylamide gel and the detergent SDS, which denatures the proteins. By subjecting the aquasome formulation to SDS-PAGE, researchers can gain insights into the protein components' structural integrity, ensuring that the formulation process does not compromise the stability of the proteins [25].

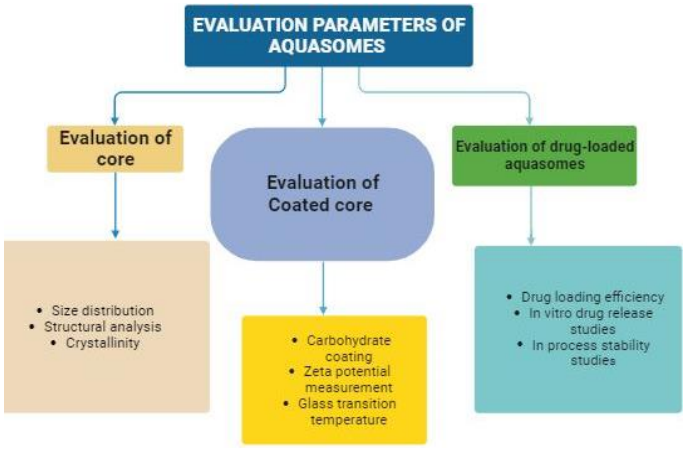

Fig. 4: Evaluation parameters of aquasomes

Application of aquasomes

Nanoparticles

Aquasomes can effectively encapsulate a wide range of substances through mechanisms such as ionic interactions, non-covalent bonds, vander Waals forces, and entropic effects. In the reaction process aided by sonication, nanocrystalline calcium phosphate ceramic core particles undergo self-assembly due to an elevation in surface-free energy. This core material is commonly composed of calcium phosphate ($CaHPO_4$). The nanocrystalline core particles made of calcium phosphate ceramic naturally come together and arrange themselves during the reaction process when exposed to sonication, primarily because the increased surface free energy promotes this self-assembly phenomenon [26].

Carbohydrate coating

Aquasomes uphold the structural integrity of biochemically active compounds with the help of the assistance of ionic, non-covalent, and entropic forces. The ceramic core stability is ensured by a polysaccharide film. The water-like characteristics of aquasomes offer a foundation for maintaining the conformational integrity and biochemical stability of bioactive substances Carbohydrate is introduced into a core dispersion, and subsequent steps involve sonication, followed by lyophilization. The coating can also be achieved through adsorption via direct incubation or by adding a non-solvent [27].

Drug incorporation

Ionic and non-covalent interactions play a role in adsorbing biochemically active molecules into this nanoparticulate system. The efficiency of encapsulating drugs is enhanced when the drug adheres to the core coated with carbohydrates [28].

Delivery of peptides

The complexity inherent in the biochemical and structural makeup of protein and peptide-based pharmaceuticals poses significant challenges in formulating effective delivery strategies, setting them apart from conventional drugs. Developing a successful systemic delivery approach requires a thorough understanding of the intricate biophysical, biochemical, and physiological properties unique to these compounds. Various factors must be carefully weighed during the formulation process. Firstly, considerations such as size, biological half-life, and immunogenicity are pivotal in ensuring the efficacy and safety of the delivery system. Moreover, maintaining conformational stability while determining appropriate dose requirements adds another layer of complexity [29].

Furthermore, the selection of the administration route is crucial. The exploration of alternative methods beyond traditional oral delivery, including buccal, nasal, rectal, vaginal, and pulmonary routes, has gained traction in recent investigations. These routes offer potential advantages such as bypassing digestive degradation and enhancing absorption rates, thereby improving therapeutic outcomes. In the quest for optimal delivery systems, variables like the site and rate of administration, as well as pharmacokinetics and pharmacodynamics, cannot be overlooked. These factors profoundly influence the design and effectiveness of delivery mechanisms for protein and peptide-based pharmaceuticals. Despite the challenges, ongoing research efforts have yielded promising results. Innovative approaches and advancements in drug delivery technologies continue to drive progress in overcoming the complexities associated with delivering these bioactive compounds. By addressing the multifaceted nature of protein and peptide-based pharmaceuticals, researchers strive to develop formulations that maximize therapeutic efficacy while minimizing adverse effects, ultimately improving patient outcomes [30].

Insulin delivery

The procedure for enhancing drug stability, solubility, or targeted delivery involves a meticulous series of steps designed to optimize the efficacy of pharmaceutical compounds. At its core lies the application of a specialized coating, comprising a blend of disaccharides such as cellobiose, trehalose, and pyridoxal-5-phosphate, onto a central material. This coating serves as the protective shield for the drug, safeguarding its integrity throughout various physiological environments. The process begins with the careful selection and preparation of the core material, ensuring compatibility with both the drug compound and the subsequent coating. Once the core is prepared, a precise application of the disaccharide blend ensues, meticulously covering the surface with a uniform layer. This coating not only shields the drug from external factors but also plays a crucial role in influencing its release kinetics and bioavailability. Next comes the crucial step of drug introduction into the coated particles. Employing an adsorption method, the drug molecules are carefully absorbed onto the surface of the coated core material. This method allows for controlled loading of the drug, ensuring optimal distribution and adherence to the particle surface. The significance of this technique in pharmaceutical research cannot be overstated. By encapsulating the drug within the protective matrix of the coated core, researchers can enhance its stability, prolong its shelf life, and mitigate degradation caused by environmental factors. Moreover, the controlled release properties of the coated particles enable precise modulation of drug delivery, ensuring therapeutic efficacy while minimizing potential side effects. Overall, this method represents a sophisticated approach to controlled drug delivery systems, offering a versatile platform for optimizing drug performance across a myriad of therapeutic applications. Through meticulous coating and precise drug-loading techniques, pharmaceutical researchers continue to push the boundaries of drug delivery, unlocking new possibilities for improved patient care and treatment outcomes.

Table 2: Applications of aquasomes in drug delivery

Active ingredient	Therapeutic application	References
Insulin	Blood sugar regulation	[31]
Dithranol	Psoriasis healing	[32]
Serratiopeptidase	Optimal peptidase activity	[33]
Haemoglobin	Oxygen carrying chromoprotein	[34]
Hepatitis-B vaccine	Anti-Hepatitis Immunogen	[35]
Indomethacin	Enhance drug release	[36]

Table 3: Applications of aquasomes based on the drug loading

Category	Product name	Drug loaded	Mechanism	Targeting area	Ref.
Non-steroidal anti-inflammatory drug (NSAID)	Indocin and Tivorbex.	Indomethacin	It helps to reduce inflammation in the body. It does this by stopping certain enzymes called COX-1 and COX-2 from working. These enzymes play a role in making prostaglandins, which are chemicals that cause inflammation, pain, and fever. When indomethacin blocks these enzymes, it decreases the amount of prostaglandins made, which in turn helps to lower inflammation, provide relief from pain, and reduce fever.	arthritis, gout, and specific kinds of headaches.	[37]
Polylactic acid (PLA)	DexPak and Decadron.	Dexamethasone	Dexamethasone attaches to glucocorticoid receptors, altering genetic expression to reduce inflammation and immune reactions, which helps in the treatment of different inflammatory ailments and inhibiting immune-related disorders.	Immune cells, Inflammatory pathways	[38]
Anthralin (Anti-inflammatory)	(Dithrocream, Micanol, Psorlin)	Dithranol	Dithranol addresses psoriasis by slowing down the growth of skin cells and regulating the immune system's reaction	Epidermal keratinocytes	[39]
Proteolytic enzyme	Nexobrid.	Bromelain	Bromelain functions by breaking down proteins, resulting in anti-inflammatory, anti-swelling, and clot-dissolving effects. It may reduce inflammation by inhibiting pro-inflammatory cytokines, reducing white blood cell movement, and disrupting the production of inflammatory substances, making it helpful in conditions like arthritis and injuries to soft tissues.	Soft tissue Injuries, sinusitis	[40]
Peptide hormone	Miacalcin and Calcimar	Calcitonin	Calcitonin inhibits bone resorption by osteoclasts, lowering blood calcium levels, while also promoting calcium excretion by the kidneys, contributing to overall calcium homeostasis in the body.	Bone tissues, Thyroid gland	[41]
Liposome	Doxil/Caelyx	Doxorubicin	Doxorubicin kills cancer cells by interacting with DNA and blocking topoisomerase II activity, resulting in DNA damage and increasing the production of reactive oxygen species, which exacerbates cellular injury.	Cancer cells, Normal cells	[42]
PLGA nanoparticle	Taxotere	Docetaxel	Docetaxel, a medication used in cancer treatment, works by stabilizing tiny tubes inside cells, which disrupts the important cell division process called mitosis. By interfering with the movement of these tubes, it stops cells from dividing properly, causing cancerous cells to die off. This process helps slow down the growth of tumors. However, it can also affect normal cells that are growing quickly, leading to side effects like low blood cell counts, stomach problems, and hair thinning.	Cells in bone marrow,hair follicles, and GIT	[43]
Topoisomerase II Inhibitor	Vepesid	Etoposide	Etoposide, a chemotherapeutic drug, works by inhibiting topoisomerase II, an enzyme required for DNA replication and repair. Etoposide disrupts the rejoining of DNA strands after cutting by binding to topoisomerase II, resulting in the buildup of DNA breaks. This disruption interferes with DNA replication and transcription, resulting in cell cycle arrest and apoptosis in rapidly dividing cancer cells. Nonetheless, it can harm good cells that are rapidly dividing, resulting in side effects such as bone marrow suppression, gastrointestinal difficulties, and hair loss.	Top 2 alpha and Top 2 beta cells	[44]
Immunosuppresant	Gengraf® and Neoral®.	Cyclosporine	Cyclosporine functions as a strong immune system suppressor by blocking the function of a vital enzyme called calcineurin, which plays a key role in activating T-cells. When administered, cyclosporine combines with cyclophilin to form a complex that binds to calcineurin, preventing it from carrying out its usual functions. This disruption hinders the activation of a protein known as NFAT (nuclear factor of activated T-cells) by stopping its dephosphorylation process. NFAT is responsible for activating genes that are crucial for the immune response, including interleukin-2 (IL-2). By interfering with this process, cyclosporine effectively reduces the production of IL-2 and the growth of T-cells, thereby dampening the immune response. This mechanism is essential for preventing rejection of transplanted organs and managing autoimmune conditions. However, it also increases the risk of infections and other potential side effects, which highlights the importance of close monitoring and medical supervision.	T cells	[45]
Polypeptide Hormone	Humalog (Insulin lispra), Apidra (Insulin glulisine)	Insulin	The hormone insulin, which is produced by the pancreas, has a crucial role in regulating levels of sugar in the blood and maintaining a balance in the body's metabolism. Once it is released into the blood, insulin attaches to specific receptors on the surface of target cells, setting off a series of internal signaling processes. By activating pathways like the PI3K/Akt pathway, insulin helps in the absorption of glucose into cells, especially those in muscles, fat, and the liver. This involves moving glucose transporter proteins, mainly GLUT4, to the cell membrane, allowing glucose to enter the cell. Within the cell, insulin promotes the transformation of glucose into energy through glycolysis, as well as encouraging the creation of glycogen, triglycerides, and proteins, which aid in storing energy and promoting tissue growth. Furthermore, insulin hinders the liver's production of glucose and the breakdown of stored glycogen, thus preventing an excessive release of glucose into the blood.	Various tissues and B cells	[46]

Advantages of aquasomes

Aquasomes are specialized colloidal drug delivery systems with unique properties that offer several advantages in various applications. Some of the advantages of aquasomes are:

Encapsulation efficiency

Aquasomes exhibit high encapsulation efficiency, allowing for the encapsulation of a variety of drugs, peptides, or bioactive molecules.

Improved bioavailability

Aquasomes can enhance the bioavailability of poorly water-soluble drugs by improving their solubility and dissolution rate.

Targeted delivery

Aquasomes can be designed for targeted drug delivery, ensuring the release of the encapsulated substance at a specific site or within a particular cell type.

Stability

Aquasomes provide stability to labile drugs, proteins, or peptides, protecting them from degradation due to environmental factors or enzymatic activity.

Biocompatibility

Aquasomes are often biocompatible and well-tolerated, making them suitable for biomedical applications.

Controlled release

Aquasomes allow for controlled and sustained release of the encapsulated substance over time, providing a prolonged therapeutic effect.

Versatility

Aquasomes can be tailored for various applications, including drug delivery, cosmetics, and food industries, making them versatile carriers for different types of formulations.

Reduced toxicity

The use of aquasomes can help reduce the toxicity associated with certain drugs by controlling their release and distribution in the body.

Ease of formulation

Aquasomes can be easily formulated into different dosage forms, such as powders, capsules, or creams, providing flexibility in product development.

Enhanced stability of active ingredients

Aquasomes can protect active ingredients from degradation, oxidation, or other chemical changes, enhancing the stability of the encapsulated substances.

Biodegradability

Some formulations of aquasomes are designed to be biodegradable, minimizing their impact on the environment.

It's important to note that the specific advantages of aquasomes may vary depending on the formulation, intended application, and the nature of the encapsulated substance. Researchers continue to explore and optimize the properties of aquasomes for various therapeutic and industrial aspects [47-49].

Limitations of aquasomes

The formulation of self-assembled aquasome systems faces certain limitations. One notable challenge arises when dealing with drugs that exhibit poor absorption, as this may lead to an undesirable burst release in the body, posing potential toxicity concerns. It is crucial to carefully assess the absorption characteristics of the drug during aquasome formulation to minimize the risk of unintended and harmful releases within the body. Additionally, to overcome another limitation, strategies can be employed to prevent the opsonization and phagocytic clearance of aquasomes within the body. One approach involves coating the surface of aquasomes with polyethylene glycol, aiming to enhance their stability and evade clearance mechanisms [50].

Recent advancements related to aquasomes

The Aquasomes have been recently undergone so my research as well as outcomes,Here are some of the important advancements regarding Aquasomes which are as follows, Improving the effectiveness of Mirtazapine (MRT) as an antidepressant by developing MRT-loaded Aquasomes using the co-precipitation sonication technique. Aquasomes represent novel delivery systems designed for transporting bioactive molecules such as peptides, proteins, hormones, antigens, and genes to targeted locations. This delivery system has demonstrated effective application in delivering various substances including insulin, hemoglobin, and enzymes such as serratiopeptidase. Aquasomes themselves are nanoparticles composed of either calcium phosphate or ceramic diamond, enveloped by a polyhydroxyoligomeric film. Recent advancements in the creation of baicalein-filled water clusters for the treatment of diabetes have led to improvements in perfecting production techniques to boost the efficiency and stability of encapsulation. Innovative methods like small-scale fluid dynamics and ultrafine precipitation have been examined to achieve precise management over the size of water clusters and drug incorporation. The analysis techniques have also progressed to include complex assessments such as freezing electron microscopy and strong-state NMR spectroscopy, offering deeper insights into the structure and connections of water clusters. Laboratory studies now include evaluations of cell absorption mechanisms and internal movement, enhancing the comprehension of water cluster pharmacokinetics and availability. Moreover, improvements in computational modeling allow for more precise forecasts of drug-target relationships, assisting in optimizing water cluster formulation for improved therapeutic impact. These advancements set the stage for the design of highly effective and focused nanomedicines for the management of diabetes.

Future perspectives of aquasomes

In envisioning the future of healthcare, aquasomes stand as a beacon of promise, heralding a new era in drug delivery systems. These self-assembled structures hold within them the potential to revolutionize the way we administer medications, offering a sophisticated platform for the efficient delivery of a myriad of drug molecules. At the heart of Aquasomes lies their unique capability to encapsulate various compounds, from viral antigens to insulin, within a protective carbohydrate coating. This feature not only ensures the preservation of the structural integrity of these molecules but also enhances their biological activity, promising more effective therapeutic outcomes. Moreover, when integrated with biosensors, Aquasomes transcend mere drug delivery mechanisms, evolving into sophisticated diagnostic tools. By enabling the examination of soft tissue in conditions like cancer, they open new avenues for early detection and personalized treatment strategies. Amid the ongoing COVID-19 pandemic, where the search for effective therapies remains a pressing global concern, the potential of aquasomes shines even brighter. Their ability to facilitate slow antigen release could hold the key to combating the virus. By stimulating the production of specific antibodies at a sustained rate within the body, Aquasomes offer a tantalizing prospect for bolstering immunity against COVID-19. Furthermore, the oxygen transport property inherent in Aquasomes adds another layer of utility, particularly in cases where respiratory distress is a hallmark symptom. By helping to maintain vital oxygen levels, they could offer much-needed relief to patients struggling with breathing difficulties, potentially mitigating the severity of their condition. As we look ahead, the horizon brims with possibilities for aquasomes. From targeted drug delivery to cutting-edge diagnostics and even combating global health crises, their versatility and efficacy hold the promise of transforming the landscape of modern medicine. As researchers continue to unlock their full potential, aquasomes stand poised to usher in a future where healthcare is not just about treating symptoms but about delivering tailored solutions with precision and efficacy [46, 47].

Table 4: Emerging types of carrier related to aquasomes

Type of carrier	Characterization	Properties	Reference
Aquasomes	These pieces showcase a three-tier self-assembly layout, including a ceramic nanocrystalline particulate core. This center is surrounded by a glassy layer infused with polyhydroxy compounds. This configuration presents a fascinating mix of traits, showing potential for applications across materials science, nanotechnology, and biomedicine. The combination of ceramic nanoparticles with a polyhydroxy-infused glassy layer provides customizable features and enhanced performance across a range of applications, ranging from advanced coatings to innovative medication delivery platforms.	Molecular protection, Site-specific targeting	[51]
Aracheosomes	Vesicles containing glycerolipids sourced from Archaea demonstrate considerable adjuvant potential, indicating their suitability for various biomedical applications. These vesicles, crafted from the distinct lipid makeup characteristic of Archaea, exhibit a remarkable capacity to amplify immune responses when employed as adjuvants. This robust adjuvant activity underscores their promising role in vaccine development and immunotherapy. Leveraging the innate immunostimulatory properties inherent in Archaeal glycerolipids, these vesicles present an opportunity to enhance the effectiveness of vaccines and therapeutic strategies, potentially leading to heightened immune defenses and increased efficacy against infectious diseases and cancer.	Active adjuvant enhancement	[52]
Cryptosomes	Fat bubbles, distinguished by a surface layer made of phosphatidylcholine (PC) along with a fitting polyoxyethylene version of phosphatidylethanolamine, are a notable creation in medical study. These bubbles display special characteristics thanks to the mix of PC and the polyoxyethylene version, providing possible uses in medicine transportation systems.	Targetting drugs using ligands	[53]
Discomes	Liposomes, which are fat bubbles, are scattered within a mixture of a nonionic detergent, specially polyoxyethylene cetyl ether. This mixture provides a way of dissolving liposomes, improving their durability and possible uses, especially in medication distribution systems.	Targetting drugs using ligands	[54]
Ethosomes	These are fat-based vesicles that are pliable and bendable, containing a penetration enhancer. They are made of phospholipids, ethanol, and water, providing a flexible platform with potential uses in different areas, especially in medication transport systems.	Delivery aimed at attaining the deeper layers of the skin with accuracy.	[55]
Enzymosomes	These vesicles are designed to create a small bioenvironment where enzymes are either covalently fixed within the vesicle structure or connected to the vesicle surface. This creative layout enables the inclusion of enzymatic function within the vesicular composition, providing possible uses in different medical and drug fields, especially in focused medication delivery systems and biological processes.	Delivery targeted precisely at tumor cells.	[56]
Novasomes	The mixture is made of glyceryl dilaurate, cholesterol, and polyoxyethylene 10-stearyl ether, with the elements present in a particular weight-percent ratio. More accurately, the mixture consists of 57% glyceryl dilaurate, 15% cholesterol, and 28% polyoxyethylene 10-stearyl ether.	Delivery of medications to the hair follicle compartment.	[57]
Vesosomes	Layered-bilayer chambers, presenting an "intertwined" bilayer stage, are created by the inclusion of alcohol to a variety of saturated phospholipids. This distinct arrangement improves the structural intricacy and adaptability of these fat-based systems, providing possible uses in different areas like medicine distribution and biology.	Multiple sections of the vesicles provide improved protection to the inner contents in plasma.	[45]

CONCLUSION

Adopting aquasome-based strategies marks a significant leap forward for pharmaceutical scientists, ushering in a new era of optimism and potential in drug delivery. The unique three-layered configuration and water-like properties of aquasomes provide a versatile and robust platform for delivering a wide range of bioactive molecules. With their protective molecular layer and ability to withstand fluctuations in pH and temperature, Aquasomes offer unparalleled stability and protection for therapeutic proteins, ensuring minimal structural damage and maximizing drug efficacy. This innovative methodology holds the promise of revolutionizing the pharmaceutical industry, offering novel solutions for treating a diverse array of diseases. As researchers continue to explore and harness the capabilities of aquasomes, they pave the way for transformative advancements in drug delivery, ultimately improving patient outcomes and quality of life.

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AUTHORS CONTRIBUTIONS

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CONFLICTS OF INTERESTS

The authors declare no conflict of interest

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