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Review Article

Aquasomes as Smart Nanocarriers: A Review on Drug Delivery Potential

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ABSTRACT

Aquasomes, a novel Vesicular Drug Delivery (VDD) technology in the pharmaceutical industry, are composed of a three-layered self-assembled nanoparticle (NP) such as a ceramic core, carbohydrate coating, and drug. It adsorbs pharmaceuticals or bioactives while preserving the structural integrity of the bioactive using a carbohydrate coating. The purpose of the aquasomes is to deliver bioactive molecules, such as genes, proteins, antigens, hormones, and vaccines, to specific sites. They are spherical in shape with a size from 60 to 300 nm. Many vesicular drug delivery systems are not as good as aquasomes because their carbohydrate-coated solid core keeps the native shape and biological activity of sensitive biomolecules. This is not possible with liposomes or transferosomes, which mainly make substances more permeable and can cause structural damage. This paper encompasses the history, development, properties, benefits, drawbacks, applications, routes of administration, and research opportunities of aquasomes. Thus, researchers will benefit from this study of aquasomes, their applications, and their future with Artificial Intelligence (AI) in pharmaceutical sciences.

Keywords: Applications, Aquasomes, Artificial Intelligence, Carbohydrate Coating, Future, Self-Assembled Nanoparticle.

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INTRODUCTION

In the pharmaceutical field, the therapeutic benefits of bioactive molecules are restricted by their limited biodistribution. Drug Delivery Systems (DDS) based on nanoparticles (NPs) are ideal for diagnosis and treatment due to their small size and large surface area. The limitations of conventional forms are limited solubility, poor permeability, non-specific distribution, and short half-life. These can be eliminated by vesicular carrier technologies, which also improve drug loading and provide targeted, controlled delivery with fewer side effects. These technologies have great potential for use in DD and molecular degradation prevention. In 1995, Nir Kossovsky developed aquasomes, which blend the essence of water with the cell's structure, to protect biological molecules. The term 'aquasome' is derived from two words: 'aqua' means "water," and 'some' means "body," and consequently 'bodies of water.' It is a promising DD technique for the long-term, regulated administration of poorly soluble drugs (Prusty *et al*., 2025; Sahu *et al*., 2024). A drug, a coated layer, and a ceramic core together form aquasomes, a self-assembling three-layered structure with 60-300 nm in size and spherical in shape (Kossovsky *et al*., 1994; Khamkat *et al*., 2025). Biodegradable and biocompatible ceramics have applications in gene transport, implantable devices, genomics, and proteomics. The carbohydrate coating of ceramic NPs serves as a reservoir, protects bioactive substances (Sahu *et al*., 2024), and improves the structural integrity of aquasomes by maintaining intramolecular non-covalent interactions (Garg *et al*., 2014; Olsson *et al*., 2016; Narang, 2012). After topical application, they may develop molecular bonds, improve the permeability of bioactive substances, and penetrate the layers of the skin. As aquasomes are small and have a hydrophilic surface, they can penetrate the skin more easily, allowing them to disrupt lipid layers in the stratum corneum and diffuse through intercellular pathways (Khamkat *et al*., 2022; Shirole *et al*., 2023). Parenteral approaches of aquasomes offer greater bioavailability with fewer side effects than oral approaches (Kumar *et al*., 2024). Aquasomes permit for both passive and active targeting. The Enhanced Permeability and Retention (EPR) effect makes passive targeting possible, while ligand-mediated and receptor-specific interactions made possible by surface functionalization make active targeting possible. The structure of aquasomes is represented in Figure 1.

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Method of aquasomes preparation

Three steps contribute to the self-assembled aquasome preparation method: drug molecule immobilization, core coating, and core preparation. The process of establishing an inorganic core and covering it with lactose to produce a polyhydroxylated core is known as core preparation (Ghorpade *et al*., 2024; Sahu *et al*., 2024). Common core materials include brushite, ceramic diamond, polymers, and tin oxides. The polyhydroxyoligomeric materials utilized in core coating include cellobiose, sucrose, lactose monohydrate, trehalose, citrate, chitosan, and pyridoxal-5-phosphate. The last step is adsorption, which immobilizes the drug molecule by dispersing coated particles in a solution with a known drug concentration with a suitable pH of buffer (Kallingal and Suresh, 2021; Sahu *et al*., 2024). Here, Figure 2 denotes the detailed preparation process of aquasomes.

Applications of Aquasomes

Aquasomes enhance the stability, prevent degradation, and enable controlled release of drugs. By enabling targeted delivery, gene therapy, and antioxidant transport, they enhance therapeutic efficacy and maintain the structural integrity of fragile biomolecules. Aquasomes are considered superior to many vesicular drug delivery systems due to their carbohydrate-coated solid core, which preserves the native shape and biological activity of sensitive biomolecules, unlike liposomes or transfersomes that mainly enhance permeability but may cause structural degradation. Table 1 represents marketed formulations of the aquasomes.

Delivery of Insulin

In 2000, Cherian *et al*., developed an aquasome formulation with a calcium phosphate core and various disaccharides, including cellobiose, pyridoxal-5-phosphate, and trehalose, for parenteral insulin administration. This firm, non-denaturing carrier aids in the drug's adsorption into the aquasome. Cellobiose-coated particles were found to effectively lower blood glucose levels in albino rats' *in vivo* research. Unlike cellobiose and trehalose, pyridoxal-5-phosphate-containing aquasome also reduces blood sugar levels. An insulin-entrapped alginate matrix, when administered orally in porous hydroxyapatite NPs, allows for regulated insulin release from the aquasomes (Cherian *et al*., 2000; Crowe *et al*., 1988).

Delivery of Antigen

For antigen delivery, researchers have developed aquasomes, coated with a layer of cellobiose to prevent denaturation of adsorbed antigens. This high surface area is suitable for conformational stabilisation of antigens and proteins (Pandey *et al*., 2011; Sahu *et al*., 2024). This is particularly relevant for Hepatitis B, where the surface antigen (HBsAg) can be adsorbed onto a cellobiose-coated hydroxyapatite core, facilitating immune responses through T helper cells (Jain *et al*., 2012). In vaccine research, the development of products that boost immune responses is crucial, and aquasomes are showing promise as immunopotentiating agents. These systems showed favorable properties, such as a size of about 200 nm and a Bovine Serum Albumin (BSA)-loading efficiency of 20-30%. They were made by hydroxyapatite self-assembly and coated with polyhydroxyl oligomers and BSA. Aquasomes elicited a combined T-helper 1 (Th1) and Th2 immune response, demonstrating superior immunological activity over plain BSA (Goyal *et al*., 2008).

Delivery of Enzyme

Aquasomes can deliver enzymes to particular cystic fibrosis sites using a calcium phosphate core coated with chitosan polymer. Alginate gel also ensures the structural integrity of the enzyme and improves its therapeutic efficacy (Khamkat *et al*., 2025).

Delivery of Topical formulation

Shanmugam and Srinivasan established a topical antibiotic-loaded aquasomes for Skin and Soft Tissue Infections (SSTIs) in 2024, with regulated drug release (Shanmugam and Srinivasan, 2024). For topical fungal treatment, curcumin-loaded aquasomes were created by Bwalya *et al*. and an *in vitro* study of 12 hr established. As an ideal formulation with sustained release of 98.12% curcumin to improve the solubility and stability profile (Patel *et al*., 2025; Bwalya *et al*., 2025).

Delivery of Gene

Aquasome formulation offers great gene therapy in viral vectors and a high immune response as a drug. The aquasome delivers genes inside the cells because of its five layers: a ceramic core, polyhydroxy oligomeric film, applied gene, carbohydrate coating, and viral membrane protein. This structure enhances gene delivery and the ability to target genes or viral vectors (Jagdale and Karekar, 2020).

Delivery of protein and peptides

Aquasomes exhibit greater stability for proteins and peptides due to non-covalent bonding. While hydroxyapatite aquasomes coated with lactose or trehalose show significant BSA loading (40%-60%), DCPA aquasomes only produce modest loadings (8%-16%). Surface analysis and Molecular Dynamics (MD) simulations demonstrate stable interactions and energy performance at various temperatures, with optimal conditions affecting BSA loading.

Delivery of Haemoglobin

According to reports, hydroxyapatite ceramic cores are made by self-precipitation and co-precipitation methods. A study described a hemoglobin-loaded aquasome in which a carboxylic acid-terminated poly (amidoamine) dendrimer was used as a template to adsorb the hydroxyapatite core with hemoglobin and trehalose. When the formulation's oxygen-carrying capacity was

compared to fresh blood, the hemoglobin concentration stayed constant for 30 days, with a hemoglobin loading capacity of 13.7 mg per gram of core (Chauvierre *et al.*, 2004; Sahu *et al.*, 2024).

Challenges

The distribution of proteins and peptides could be revolutionized by aquasomes; however, there are several obstacles to overcome, such as their incompatibility with sterilization methods, shelf-life compliance, viability for large-scale manufacturing, and commercialization potential. Production methods and high ingredient costs are still unresolved. It enters the bloodstream, is non-specifically absorbed by phagocytic vesicles, and has stability and safety problems because of the polyethene glycol surface coating (Khamkat *et al.*, 2024; Sharma *et al.*, 2012).

Regulatory aspects and Future aspects

The regulatory requirements for Novel Drug Delivery Systems (NDDS), particularly in nanotechnology, are critical to establishing a solid foundation for nanosystems and their clinical applications (Dhar *et al.*, 2022; Sahu *et al.*, 2024). Recent research has improved the effectiveness of the antidepressant by using co-precipitation sonication to create aquasomes loaded with Mirtazapine (MRT). When paired with biosensors, aquasomes may become sophisticated diagnostic tools that enable early detection and customized treatment (Dondorp *et al.*, 2020; Sahu *et al.*, 2024).

Recent studies conducted between 2023 and 2025 have emphasized aquasomes as advanced nanocarriers that impact Artificial Intelligence (AI). By leveraging AI technology and processing power, AI companies can assist the pharmaceutical industry in discovering new drugs. AI mimics human intelligence through methods like Machine Learning (ML) and Deep Learning (DL). While ML allows computers to learn from data without explicit programming, DL uses advanced neural networks to identify complex patterns. It improves the safety and design of lipid

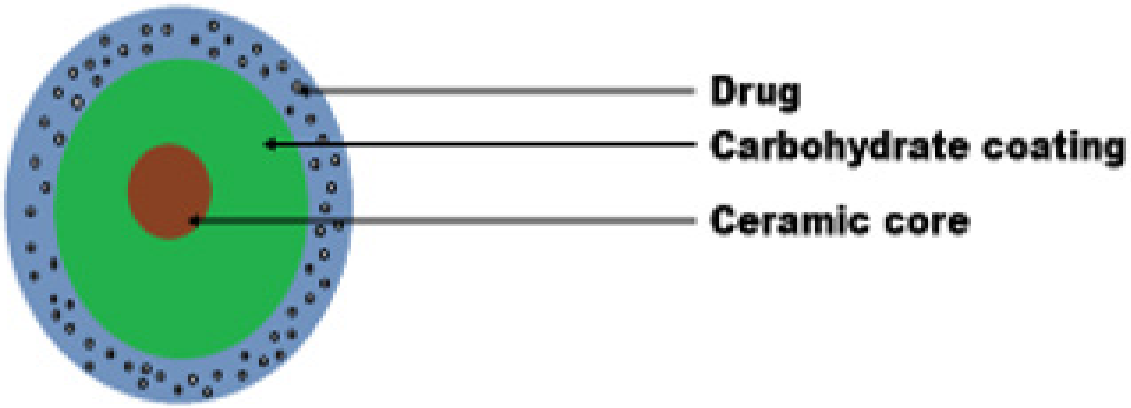

Figure 1: Structure of Aquasomes.

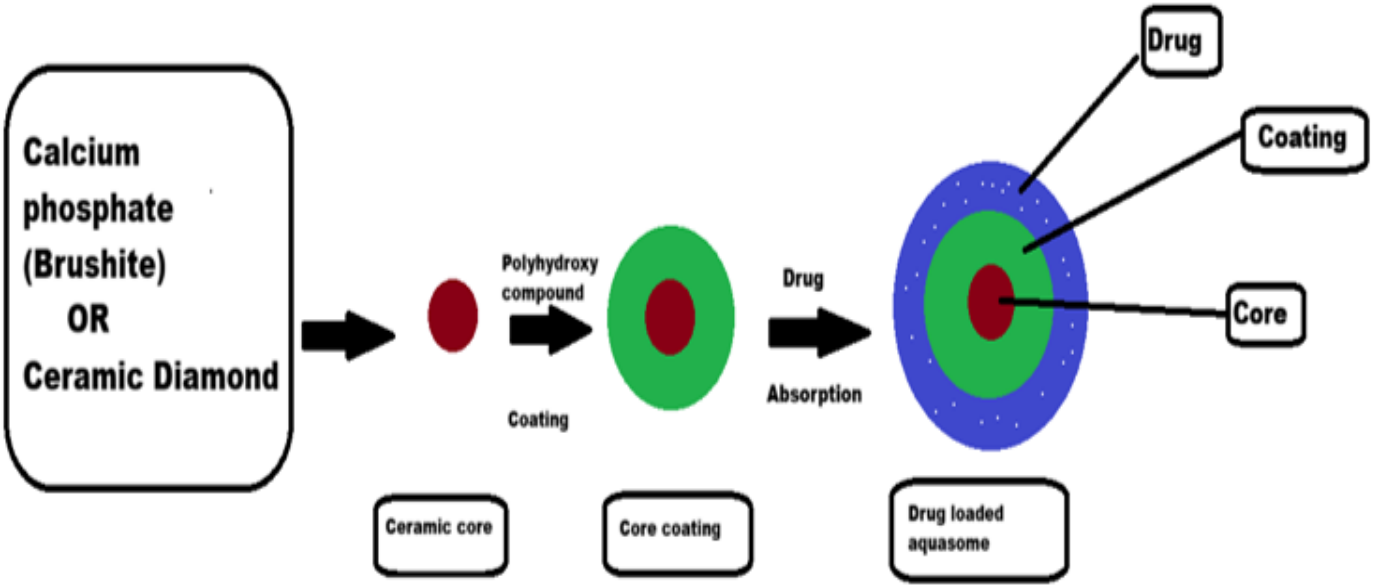

Figure 2: Method of aquasomes preparation.

Table 1: List of available marketed formulations of aquasomes.

Active Ingredients	Brand Names	Mechanism of Action	Applications	References
Indomethacin	Indocin, Tivorbex	Inhibits COX-1 and COX-2 enzymes, reducing prostaglandin synthesis to lower inflammation, pain, and fever.	Used to treat arthritis, gout, and headaches	(Rojas-Oviedo *et al.*, 2007)
Dexamethasone	DexPak, Decadron	Binds to glucocorticoid receptors, altering gene expression to suppress inflammation and immune activity.	Used to treat inflammatory and immune disorders	(Mittal *et al.*, 2012)
Bromelain	Nexobrid	Breaks down proteins; inhibits pro-inflammatory cytokines, reduces leukocyte migration, and decreases inflammatory mediators.	Used to treat soft tissue injuries, sinusitis	(Kutlehria *et al.*, 2018)
Calcitonin	Miacalcin, Calcimar	Inhibits osteoclast activity to reduce bone resorption and promotes renal calcium excretion.	Used to treat disorders of calcium metabolism	(Diociaiuti *et al.*, 2006)
Doxorubicin	Doxil, Caelyx	Intercalates DNA and inhibits topoisomerase II, inducing DNA damage and ROS formation, leading to cell death.	Used in cancer therapy	(Bhadran *et al.*, 2025)
Docetaxel	Taxotere	Stabilizes microtubules, inhibiting mitosis and causing apoptosis of rapidly dividing cells.	Used in cancer treatment	(Beheshtizadeh *et al.*, 2024)
Etoposide	Vepesid	Inhibits topoisomerase II, preventing DNA strand rejoining, leading to DNA breaks and apoptosis in dividing cells.	Used in cancer therapy	(Nanjwade *et al.*, 2013)
Cyclosporine	Gengraf, Neoral	Forms a complex with cyclophilin to inhibit calcineurin, blocking NFAT activation and IL-2 production, thus suppressing T-cell activation.	Used to treat autoimmune diseases	(Sahu *et al.*, 2024)
Insulin	Humalog (Insulin lispro), Apidra (Insulin glulisine)	Binds to insulin receptors, activates PI3K/Akt pathway, promotes glucose uptake (via GLUT4), glycogen synthesis, and inhibits hepatic glucose production.	Used to treat diabetes mellitus	(Jagdale and Karekar, 2020)

NPs and helps to create personalized medicinal nanocarriers for every patient. The use of AI in the classification and analysis of nanocarrier interactions through highly sensitive and specialized diagnostics enables precise cancer treatment. ML is a state-of-the-art technique for improving the outcomes of cancer treatment by utilizing a large library of inorganic NPs (Kapoor *et al.*, 2024). Gupta *et al.* (2023) utilized ML algorithms to forecast stability and encapsulation efficacy based on input variables such as surface modifiers and polymer composition, aiming to enhance NP formulations for protein delivery. Aquasomes can be made using the same method, but they are not the only things that can be made this way. It's particularly relevant when deciding which carbohydrate coatings (like trehalose or sucrose) will perform best and how they will affect the stability of the structure and the way it releases (Gupta *et al.*, 2023).

CONCLUSION

Aquasomes, nanostructured DDS, preserve the structural integrity and improve the therapeutic activity of drugs. They can be utilized in the pharmaceutical sector for delivering insulin, hemoglobin, genes, enzymes, peptides, and proteins. The unique carbohydrate coating prevents pharmacological action and enzymatic breakdown without altering structural shape. However, this DDS overcomes challenges like batch variation management, and increased target effectiveness. The application of AI and aquasomes will have an intense impact on the pharmaceutical research field.

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ABBREVIATIONS

AI: Artificial Intelligence; **BSA:** Bovine Serum Albumin; **COX:** Cyclooxygenase; **DDS:** Drug Delivery System(s); **DD:** Drug Delivery; **DL:** Deep Learning; **DCPA:** Dicalcium Phosphate Anhydrous; **EPR:** Enhanced Permeability and Retention; **GLUT4:** Glucose Transporter Type 4; **HBsAg:** Hepatitis B Surface Antigen; **IL-2:** Interleukin-2; **MD:** Molecular Dynamics; **ML:** Machine Learning; **MRT:** Mirtazapine; **NDDS:** Novel Drug Delivery Systems; **NFAT:** Nuclear Factor of Activated T-cells;

NP: Nanoparticle; **NPs:** Nanoparticles; **PI3K:** Phosphoinositide 3-Kinase; **ROS:** Reactive Oxygen Species; **SSTIs:** Soft Tissue Infections; **Th1:** T-helper 1; **Th2:** T-helper 2; **VDD:** Vesicular Drug Delivery.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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