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REVIEW ARTICLE

A Review on Design Principles and Therapeutic Applications of Bioceramic Aquasomes for Drug Delivery

Arul Selvam A*[1], Suganya K[1], Dhanesh Kumar M R[1], Sathish A[2]

[1] *Department of Pharmaceutics, GRD College of Pharmacy, Thiruvallur, Tamil Nadu, India*
[2] *Department of Pharmacy Practice, GRD College of Pharmacy, Thiruvallur, Tamil Nadu, India*

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Abstract: Aquasomes consists of three-layered, self-assembling ceramic nanoparticles that function as highly efficient vehicles for the delivery of fragile bioactive molecules. These systems, typically ranging from 60 to 300 nanometers, utilize a solid nanocrystalline core often composed of calcium phosphate or carbon as a structural scaffold. A polyhydroxy oligomeric film, such as trehalose or cellobiose, is subsequently adsorbed onto this core to create a "water-like" environment. This unique coating serves to preserve the native conformational integrity of adsorbed proteins, peptides, and genetic materials, protecting them from denaturing forces often encountered in systemic circulation. Unlike conventional lipid-based vesicles, these ceramic-based particulates offer superior mechanical stability and high surface energy for drug loading. The mechanism of action relies on the ability of the carbohydrate layer to mimic the natural aqueous environment, thereby preventing the irreversible dehydration-induced aggregation of biologics. Current research highlights their utility in cancer therapy, vaccine development, and the delivery of insulin or hemoglobin. These systems achieve enhanced bioavailability and reduced systemic toxicity by integrating site-specific targeting ligands. The structural versatility and biocompatibility of the ceramic-core design provide a robust platform for addressing the limitations of traditional drug delivery. Ongoing investigations into stimuli-responsive release and hybrid theranostic models indicate a significant shift toward personalized nanomedicine. This review provides the structural engineering, stabilization mechanisms, and clinical potential of aquasome-based delivery systems.

Keywords: Aquasomes; Bioceramics; Nanoparticles; Protein Stabilization; Targeted Therapeutics.

1. Introduction

Aquasomes are categorized as multicomponent nanoparticulate systems characterized by a three-layered self-assembled architecture [1]. The size range of these particles, generally between 60 and 300 nm, allows for optimal interaction with biological membranes and facilitates efficient cellular uptake. The structural foundation consists of a solid nanocrystalline core, which is modified by a carbohydrate coating to enable the non-covalent adsorption of bioactive agents [2]. While traditional delivery systems like liposomes or niosomes rely on lipid bilayers that may suffer from oxidative degradation or leakage, aquasomes utilize ceramic materials that provide inherent physical rigidity and stability [3].

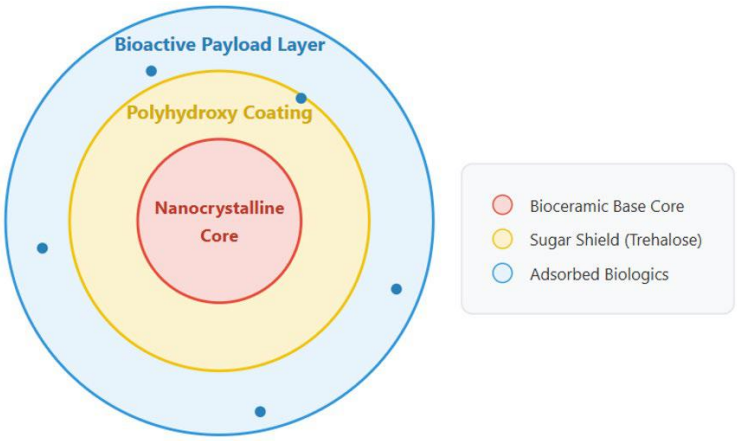

Figure 1. Structure of the Three-Layered Aquasomes

* Corresponding author: Arul Selvam A

The nomenclature is derived from the Latin "aqua" (water) and the Greek "soma" (body), signifying "bodies of water." This name reflects their primary functional characteristic: the ability to maintain an aqueous-like environment at the nanoparticle-drug interface [4]. This feature is particularly critical for the delivery of biological macromolecules, including peptides, proteins, hormones, and nucleic acids, which are sensitive to pH fluctuations, temperature changes, and organic solvents [5]. These systems protect the therapeutic payload from denaturation by acting as molecular chaperones, ensuring that the biological activity remains intact until it reaches the target site [6].

The shift toward ceramic-based nanoparticles is driven by the limitations of organic polymers and lipids. Polymeric systems often require the use of harsh organic solvents during fabrication, which can compromise the structural stability of delicate proteins. In contrast, the fabrication of aquasomes is predominantly an aqueous-based process, minimizing the risk of chemical degradation [7]. The high surface energy of the ceramic core allows for high loading efficiencies of hydrophilic drugs that might otherwise be poorly encapsulated in lipid-based vesicles.

2. Structural Composition of Aquasomal Systems

The functional efficiency of an aquasome is entirely dependent on the precise engineering of its three distinct layers. Each component plays a specific role in ensuring the stability, transport, and release of the therapeutic agent.

2.1. The Centralized Nanocrystalline Core

The innermost layer serves as a rigid scaffold that defines the shape and size of the nanoparticle. The selection of the core material is dictated by the requirement for high surface energy, biocompatibility, and chemical inertness.

2.1.1. Inorganic Core Materials

Commonly utilized inorganic materials include calcium phosphate (specifically brushite or hydroxyapatite), nanocrystalline carbon, and tin oxide [8]. Calcium phosphate is often preferred due to its natural presence in human bone and teeth, making it highly biocompatible and biodegradable within physiological environments [9]. The nanocrystalline nature of these cores provides a large surface area-to-volume ratio, which is essential for achieving high carbohydrate adsorption density.

Table 1. Comparison of Aquasomes vs. Conventional Lipid and Polymeric Carriers

Feature	Liposomes	Polymeric Nanoparticles	Aquasomes
Core Material	Aqueous buffer (enclosed by lipid)	Synthetic/Natural polymers	Solid nanocrystalline ceramic
Mechanical Stability	Low; prone to leakage and oxidation	Moderate to high	High; rigid structural scaffold
Preparation Medium	Often requires organic solvents	Organic solvents (e.g., DCM)	Predominantly aqueous-based
Drug Loading	Encapsulation within bilayer/core	Matrix entrapment/Adsorption	Surface adsorption on sugar film
Payload Stability	Risk of denaturation in lipids	Possible chemical interaction	High conformational integrity
Biological Mimicry	Mimics cell membranes	Limited	Mimics natural hydration shells

2.1.2. Alternative Scaffolds

Beyond traditional ceramics, researchers have explored the use of various polymers such as acrylates, albumin, and gelatin to serve as core templates. However, these materials often lack the mechanical strength and the defined crystalline lattice provided by ceramic diamond or carbon-based cores [10]. The crystallinity of the core is a vital parameter, as it influences the orientation and stability of the subsequent carbohydrate layer.

2.2. The Carbohydrate Coating Layer

The second layer consists of polyhydroxy oligomers that are adsorbed onto the ceramic core. This layer acts as a buffer between the rigid core and the sensitive bioactive molecule.

2.2.1. Stabilization Mechanism

Carbohydrates like trehalose, sucrose, cellobiose, and lactose are frequently employed. The primary role of these polyhydroxyl compounds is to replace the hydration shell of the drug molecule. When biologics are dehydrated during storage or transport, the carbohydrate hydroxyl groups form hydrogen bonds with the protein, mimicking the presence of water molecules [3]. This "water replacement" prevents the protein from unfolding or aggregating.

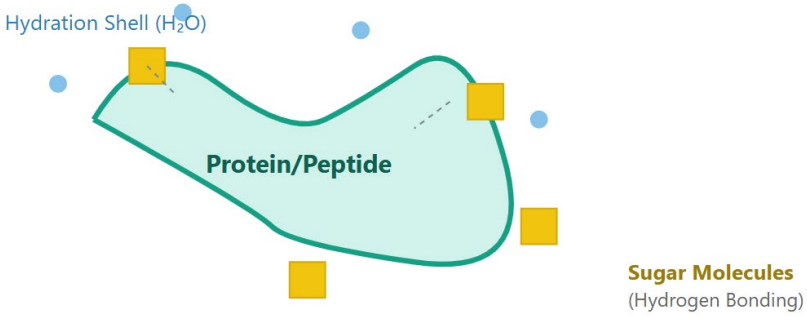

Figure 2. Biophysical Stabilization Through the Water Replacement Mechanism

2.2.2. Material Selection Criteria

Trehalose is often cited as the most effective stabilizer due to its high glass transition temperature and unique symmetry, which allows it to form a stable glassy matrix around the drug [11]. Other materials like chitosan and pyridoxal-5-phosphate are used when specific surface charges or mucoadhesive properties are required for localized delivery.

2.3. The Bioactive Payload

The outermost layer comprises the active pharmaceutical ingredient (API) or biological molecule. Unlike many other systems where the drug is encapsulated within a matrix, in aquasomes, the drug is typically adsorbed onto the surface of the carbohydrate-coated core. The loading process involves non-covalent interactions, such as hydrogen bonding, van der Waals forces, and ionic attractions [12]. Because the drug is not chemically conjugated to the carrier, its native conformation is preserved, and its release at the target site is facilitated by the displacement of these weak bonds in the presence of physiological fluids.

Table 2. Stabilization of Polyhydroxy Compounds in Aquasomes

Mechanism	Description	Relevance to Aquasomes
Water Replacement	Hydroxyl groups of sugars form hydrogen bonds with protein surface.	Prevents unfolding during dehydration or processing.
Vitrification (Glassy State)	Sugars form a rigid, amorphous "glass" around the drug molecule.	Immobilizes the protein, preventing aggregation and motion.
Water Trapping	The carbohydrate layer retains a small percentage of residual moisture.	Maintains the native hydrated state of the bioactive cargo.
Exclusion Mechanism	Sugars are preferentially excluded from the protein's immediate surface.	Increases the chemical potential, favoring the compact native state.

3. Physicochemical Mechanisms and Stabilization

The success of aquasomes in drug delivery is attributed to the synergistic relationship between the ceramic core and the carbohydrate coating.

3.1. Maintenance of Conformational Integrity

Biological molecules are highly dependent on their three-dimensional structure for activity. The carbohydrate layer provides a flexible, hydrophilic environment that protects the drug from the rigid surface of the ceramic core. This prevents the "solid-state" denaturation that often occurs when proteins are adsorbed directly onto hard surfaces [13].

3.2. Controlled Release and Biodistribution

The release of the drug from the aquasomal surface is governed by the dissolution of the carbohydrate layer and the subsequent desorption of the API. The release kinetics can be modulated to achieve sustained therapeutic levels by controlling the thickness and composition of the carbohydrate film [14]. The small particle size allows the system to evade the reticuloendothelial system (RES) to a certain extent, prolonging circulation time

Table 3. Physicochemical Properties and Selection Criteria for Core and Coating Materials.

Material Category	Examples	Functional Role	Advantages
Inorganic Core	Calcium Phosphate (Hydroxyapatite)	Structural base; defines geometry	Highly biocompatible; biodegradable; high surface energy
	Nanocrystalline Carbon (Diamond)	Structural base	Exceptional chemical inertness; rigid lattice
	Tin Oxide	Structural base	High durability; suitable for specific imaging
Carbohydrate Coating	Trehalose	"Water-replacement" layer	High glass transition temperature; superior protein protection
	Cellobiose	Stabilizing film	Efficient hydrogen bonding; cost-effective
	Sucrose/Lactose	Buffer layer	Easily available; facilitates rapid drug release
	Pyridoxal-5-phosphate	Functionalized coating	Enhances loading of specific enzymatic payloads

4. Fabrication Methods and Formulation

The production of aquasomes is a sequential process that requires precise control over environmental conditions to ensure the self-assembly of the three-layered architecture. Unlike many nanoparticle formulations that rely on complex polymerization or organic phase separation, aquasome fabrication is largely conducted in aqueous media, which is instrumental in preserving the biological activity of the cargo [15].

4.1. Production of the Nanocrystalline Core

The first stage involves the formation of a solid, crystalline scaffold. The most prevalent method for creating inorganic cores, particularly calcium phosphate, is colloidal precipitation.

In this approach, solutions of calcium chloride and disodium hydrogen phosphate are reacted under controlled pH and temperature conditions. The resulting precipitate of hydroxyapatite or brushite is subjected to high-energy sonication to reduce the particle size to the nanometer range [16]. The crystalline nature of the core is essential; amorphous structures often lack the necessary surface energy to maintain a stable carbohydrate film. Carbon-based cores, such as those made from nanocrystalline diamond, are often produced via high-pressure high-temperature (HPHT) methods followed by intensive purification to remove metallic impurities [17].

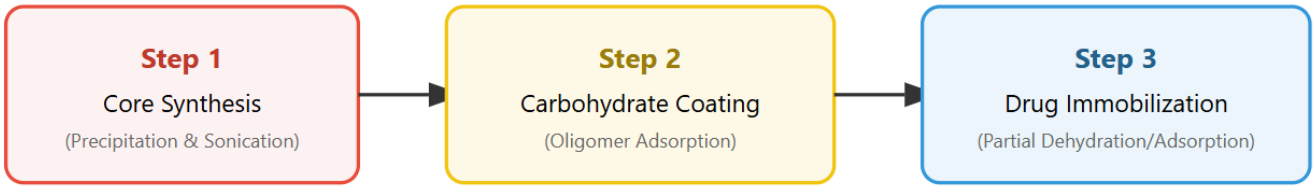

Figure 3. Preparation and Self-Assembly of Aquasomes

4.2. Application of the Polyhydroxy Coating

Once the core is prepared and cleaned of unreacted precursors, the second step involves the adsorption of the carbohydrate layer. This process relies on the high surface energy of the nanocrystalline core to attract polyhydroxyl molecules.

The ceramic particles are dispersed in an aqueous solution containing a high concentration of the chosen carbohydrate, such as trehalose or cellobiose. The mixture is typically incubated for several hours at room temperature or slightly elevated temperatures to allow for the formation of a stable film [18]. The carbohydrate molecules align on the surface of the core through hydrogen bonding and van der Waals interactions. Excess carbohydrate is removed through centrifugation or dialysis to ensure that only the adsorbed layer remains, preventing the formation of bulk sugar crystals during the final loading stage [19].

4.3. Adsorption of the Bioactive Agent

The final step is the loading of the therapeutic payload onto the carbohydrate-coated scaffold. This stage is the most sensitive, as the temperature and pH must be strictly maintained to prevent the denaturation of proteins or peptides.

The drug or biological molecule is added to the suspension of coated cores. Loading is generally performed at low temperatures, often 4ºC, to ensure maximum stability for heat-sensitive biologics [20]. The payload interacts with the hydroxyl groups of the carbohydrate layer through a process of partial dehydration, where the carbohydrate replaces the hydration shell of the protein. This non-covalent attachment allows for the drug to be released in its native state once it encounters the aqueous environment of the target tissue [21].

5. Characterization and Analytical Evaluation

Rigorous characterization is mandatory to verify the structural integrity, size distribution, and loading efficiency of the aquasomal particles.

5.1. Morphological and Structural Evaluation

The physical dimensions and surface morphology are critical parameters that influence the biological fate of the delivery system.

5.1.1. Microscopy and Particle Size Distribution

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are utilized to visualize the spherical nature and surface smoothness of the particles [22]. Dynamic Light Scattering (DLS) provides data on the hydrodynamic diameter and the polydispersity index (PDI). A narrow PDI is indicative of a homogeneous population of nanoparticles, which is essential for predictable pharmacokinetics. Zeta potential measurements are also conducted to determine the surface charge, which influences the colloidal stability and the interaction with cell membranes [23].

5.1.2. Spectroscopic and Thermal Studies

Fourier Transform Infrared (FTIR) spectroscopy is employed to confirm the presence of the carbohydrate layer and the drug on the ceramic core. Shifts in the characteristic absorption bands of the hydroxyl or amide groups indicate the formation of hydrogen bonds between the layers [24]. Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) are used to assess the crystalline state of the core and the physical state of the adsorbed drug. These techniques help in confirming that the drug remains in a molecularly dispersed or amorphous state within the carbohydrate matrix, which is beneficial for rapid dissolution and bioavailability [25].

Table 4. Analytical Techniques for Characterization of Aquasomes

Parameter	Analytical Method	Information Provided
Morphology & Size	Scanning Electron Microscopy (SEM)	Surface topography and particle shape
	Transmission Electron Microscopy (TEM)	Internal structural layers and core dimensions
	Dynamic Light Scattering (DLS)	Mean hydrodynamic diameter and size distribution (PDI)
Surface Chemistry	Zeta Potential Analysis	Surface charge; prediction of colloidal stability
	FTIR Spectroscopy	Confirmation of carbohydrate adsorption and drug binding
Crystallinity	X-Ray Diffraction (XRD)	Verification of core crystalline lattice and drug state
Thermodynamic State	Differential Scanning Calorimetry (DSC)	Physical state of drug; glass transition of sugar layer
Loading & Release	HPLC / UV-Vis Spectroscopy	Quantitative payload analysis and release kinetics

5.2. Loading Efficiency and Release Kinetics

The capacity of the system to carry a therapeutic dose and its ability to release it in a controlled manner are the ultimate measures of performance.

Loading efficiency is typically determined by separating the nanoparticles from the loading medium via centrifugation and analyzing the supernatant using High-Performance Liquid Chromatography (HPLC) or UV-Visible spectroscopy [26]. In vitro release studies are conducted in simulated physiological fluids (e.g., phosphate-buffered saline at pH 7.4) to mimic the conditions of systemic circulation. These studies often reveal a biphasic release pattern, characterized by an initial rapid desorption followed by a more controlled, slower release phase [27].

6. Therapeutic Applications and Clinical Relevance

The versatility of aquasomes allows for their application across various medical disciplines, particularly where the stabilization of sensitive molecules is required.

6.1. Delivery of Oxygen Carriers

One of the most significant applications of aquasomes is in the development of blood substitutes. Hemoglobin, when delivered in its free form, is toxic and rapidly cleared from the circulation. Researchers have developed artificial oxygen carriers that maintain the oxygen-binding affinity of the protein by adsorbing hemoglobin onto trehalose-coated hydroxyapatite cores [28]. The carbohydrate layer prevents the oxidation of hemoglobin to methemoglobin, which is inactive. These systems have shown potential in treating hemorrhagic shock and providing temporary oxygenation during surgical procedures [29].

Table 5. Therapeutic Applications of Aquasomal Payloads in Clinical Research

Bioactive Payload	Therapeutic Target	Therapeutic Outcome
Hemoglobin	Systemic circulation (Blood substitute)	Sustained oxygen delivery; reduced nephrotoxicity
Insulin	Gastrointestinal epithelium (Diabetes)	Protection from proteolysis; improved oral bioavailability
Hepatitis B Surface Antigen	Immune system (Vaccination)	Robust antibody production; potent adjuvant effect
Doxorubicin	Malignant tumors (Oncology)	Targeted cytotoxicity; minimized cardiac side effects
Lornoxicam / Piroxicam	Inflammatory sites (NSAID delivery)	Enhanced solubility; reduced gastric irritation
Plasmid DNA / siRNA	Intracellular targets (Gene therapy)	Protection from nucleases; efficient cellular uptake

6.2. Immunotherapy

Aquasomes are effective as immunological adjuvants, particularly for the delivery of viral and bacterial antigens. The particulate nature of aquasomes facilitates their uptake by antigen-presenting cells (APCs) such as macrophages and dendritic cells. For instance, aquasomes loaded with Hepatitis B surface antigen or HIV-1 proteins have shown the ability to elicit robust immune responses without the need for traditional, often toxic, aluminum-based adjuvants [30]. The rigid core ensures that the antigen is presented to the immune system in a stable, repetitive geometry, which is highly effective for B-cell activation [31].

6.3. Delivery of Insulin and Hormonal Therapy

The oral delivery of insulin remains a significant challenge due to proteolytic degradation in the gastrointestinal tract. Aquasomal formulations of insulin have been investigated to improve its stability and bioavailability. The carbohydrate coating acts as a shield against gastric enzymes, while the small size of the particles may facilitate paracellular or transcellular transport across the intestinal epithelium [32]. Similar strategies are being explored for the delivery of calcitonin and growth hormones, where maintaining the native peptide conformation is essential for receptor binding and therapeutic efficacy [33].

6.4. Oncology and Targeted Chemotherapy

The application of aquasomes in cancer treatment addresses the critical need for systems that can deliver highly potent cytotoxic agents while minimizing off-target effects.

6.4.1. Enhancement of Drug Solubility and Permeability

Many chemotherapeutic agents, such as paclitaxel or doxorubicin, exhibit poor aqueous solubility and significant systemic toxicity. Aquasomal formulations utilize the high surface area of the ceramic core to achieve high drug loading. For instance, doxorubicin-loaded aquasomes have shown superior tumor suppression in preclinical models compared to free drug administration [34]. The carbohydrate layer provides a protective shield that reduces the interaction of the drug with healthy cardiac tissues, thereby mitigating cardiotoxicity.

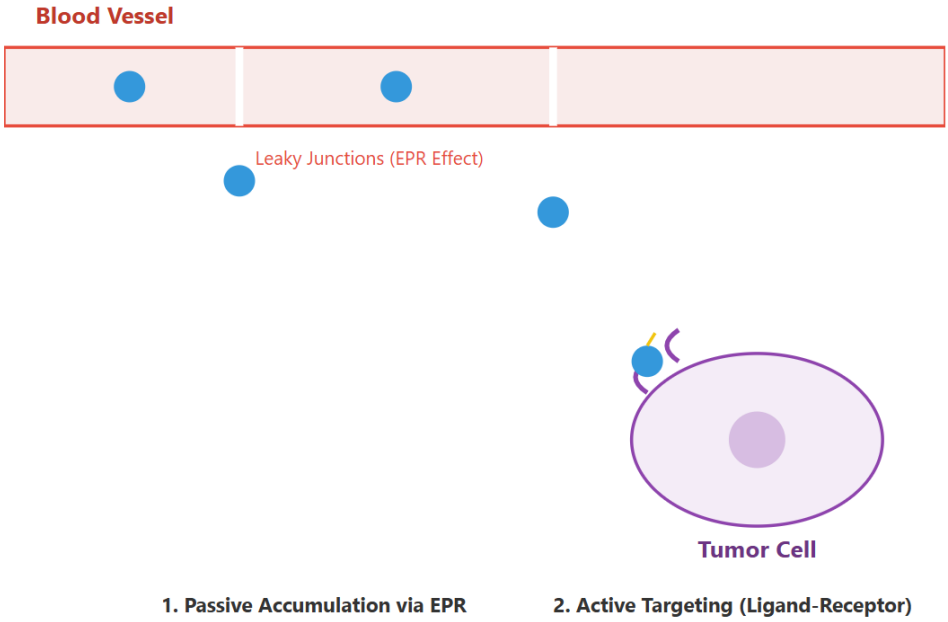

Figure 4. Targeted Accumulation and Cellular Uptake in Tumors

6.4.2. Active Targeting

The surface of aquasomes can be modified with targeting ligands, such as folic acid or monoclonal antibodies, to recognize receptors that are overexpressed on tumor cells. This site-specific delivery ensures that the therapeutic payload is concentrated within the malignant mass, enhancing the efficacy of the treatment [35]. The small size of these nanoparticles allows them to exploit the enhanced permeability and retention (EPR) effect inherent in the leaky vasculature of solid tumors.

6.5. Gene Delivery and Molecular Medicine

Gene therapy requires a delivery vehicle that can protect nucleic acids from enzymatic degradation while facilitating cellular entry and endosomal escape. Aquasomes offer a robust alternative to viral vectors and cationic lipids for the delivery of plasmid DNA, siRNA, and antisense oligonucleotides. The carbohydrate coating mimics the natural environment of the cell, reducing the immunogenicity often associated with synthetic polymers [36]. Aquasomes ensure that a higher fraction of the dose reaches the target nuclei or cytoplasm by shielding the genetic material from nucleases in the systemic circulation.

7. Recent Technological Advancements

Modern developments in aquasome technology focus on creating "smart" delivery systems that respond to internal or external stimuli.

7.1. Stimuli-Responsive Systems

Recent research has explored the integration of pH-sensitive or temperature-responsive polymers into the aquasomal architecture. These systems are designed to trigger drug release in response to the acidic microenvironment of a tumor or the elevated temperatures of inflamed tissues [37]. This level of control further refines the therapeutic profile and reduces the risk of premature drug leakage.

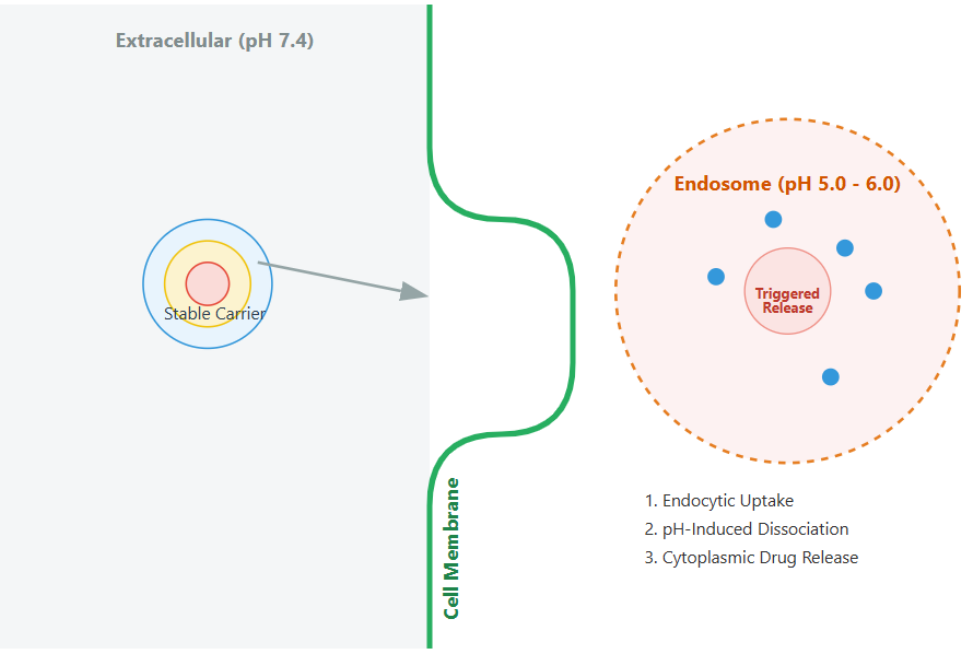

Figure 5. Stimuli-Responsive Drug Release and Intracellular Trafficking

7.2. Theranostic Applications

The incorporation of magnetic nanoparticles (such as iron oxide) or fluorescent dyes into the ceramic core has paved the way for theranostic aquasomes. These hybrid systems allow for simultaneous diagnostic imaging and targeted therapy, enabling clinicians to monitor the biodistribution of the drug and the progression of the disease in real-time [38].

8. Challenges and Future Perspectives

Despite the significant potential shown at lab scale, several hurdles remain before aquasome-based systems can be widely adopted in clinical practice.

8.1. Scalability and Manufacturing

The multi-step self-assembly process, while effective at a small scale, poses challenges for industrial-scale production. Maintaining batch-to-batch consistency in particle size and drug loading requires highly standardized protocols and specialized equipment [39]. Additionally, the long-term stability of the carbohydrate coating in liquid formulations needs further investigation to ensure a sufficient shelf-life for commercial products.

8.2. Toxicological Evaluation

While the components of aquasomes (e.g., calcium phosphate and trehalose) are generally regarded as safe, the long-term metabolic fate of the ceramic nanocrystals requires extensive toxicological profiling. The knowledge about how these particles are cleared from the body and whether they accumulate in organs such as the liver or spleen is crucial for obtaining regulatory approval [40].

9. Conclusion

Aquasomes represent a sophisticated advancement in the field of nanomedicine, providing a unique solution for the stabilization and delivery of fragile biological molecules. These systems safeguard the conformational integrity of proteins, vaccines, and genetic materials by combining the structural rigidity of a ceramic core with the protective properties of a polyhydroxy coating. Their diverse applications ranging from artificial oxygen carriers to targeted oncology treatments highlight their versatility as a therapeutic platform. While challenges regarding large-scale manufacturing and long-term safety persist, the integration of stimuli-responsive features and targeting ligands offers a promising path toward personalized and highly effective treatment modalities. Continued innovation in bioceramic engineering will likely establish aquasomes as a cornerstone of next-generation drug delivery.

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