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Review Article

An In-depth Review of Exploring the Potential of Colloidosomes in Drug Delivery

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ABSTRACT

Colloidosomes, pioneering microcapsules composed of coagulated colloidal particles assembled at the interface of emulsion droplets, have garnered significant attention due to their remarkable properties and potential applications in targeted and controlled drug delivery. Their unique core-shell architecture offers unparalleled advantages, including tunable permeability, mechanical strength and encapsulation capabilities for a wide range of therapeutic agents. These versatile carriers have demonstrated remarkable potential in delivering small molecules, biomacromolecules, genetic materials and even living cells, addressing challenges associated with conventional drug delivery systems. Colloidosomes can be fabricated through various techniques, encompassing emulsion-based, nature-of-colloids-based and emerging methods such as microfluidics and 3D printing. Comprehensive characterization, employing techniques like electron microscopy, spectroscopy and rheology, is crucial for understanding their structural, physical and functional properties. Remarkable advancements have been achieved in developing stimuli-responsive, targeted and multi-functional colloidosomes, enabling precise spatiotemporal control, selective accumulation and integrated functionalities for theranostic applications. Despite their immense potential, challenges remain in scaling up production, ensuring long-term stability, navigating regulatory landscapes and facilitating clinical translation. Addressing these obstacles through collaborative efforts, advanced characterization and the integration of emerging technologies is paramount for unlocking the full potential of colloidosomes in revolutionizing drug delivery strategies and realizing personalized medicine.

Keywords: Colloidosomes, Targeted Drug Delivery, Controlled Release, Encapsulation, Microcapsules.

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INTRODUCTION

The remarkable progress in the field of nanotechnology and material science has paved the way for the development of innovative drug delivery systems aimed at enhancing the therapeutic efficacy and minimizing the adverse effects associated with conventional formulations. Among these emerging platforms, colloidosomes have garnered significant attention due to their unique properties and potential applications in targeted and controlled drug delivery.[1,2] Colloidosomes, also known as colloidal microcapsules, are hollow, elastic shells composed of coagulated or fused colloidal particles assembled at the interface of emulsion droplets.[3,4] These microcapsules exhibit a distinctive core-shell structure, where the core can encapsulate a wide range of active ingredients, including small molecules, biomacromolecules and even living cells, while the shell provides a protective barrier and modulates the release kinetics. The concept of colloidosomes was first introduced in the early 2000s by Dinsmore *et al.*, who demonstrated the self-assembly of colloidal particles at the interface of water-in-oil emulsion droplets, forming a robust and selectively permeable shell.[5] Since then, colloidosomes have evolved rapidly, with researchers exploring different fabrication techniques, materials and applications to unlock their full potential. Figure 1 shows the key steps in the formation of colloidosomes.

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One of the key advantages of colloidosomes lies in their ability to encapsulate a diverse range of active ingredients, including hydrophilic, hydrophobic and amphiphilic compounds. This versatility is particularly advantageous in the pharmaceutical industry, where many drugs face challenges related to poor solubility, instability and rapid degradation.[6,7] Encapsulation within colloidosomes can protect these sensitive compounds from harsh environmental conditions, prolong their shelf-life and enhance their bioavailability. Furthermore, colloidosomes offer remarkable tunability in terms of their permeability, mechanical strength and compatibility. By carefully selecting the colloidal particles and modulating their interactions, researchers can tailor the properties of the colloidosome shell to achieve desired release profiles, ranging from sustained and controlled release to triggered or stimuli-responsive release. This level of control is crucial in developing personalized and patient-centric drug delivery systems.[8] Another compelling feature of colloidosomes is their potential for targeted delivery. By incorporating targeting ligands or functional moieties onto the colloidal particles or the shell surface, colloidosomes can be designed to selectively accumulate at specific sites or tissues, minimizing off-target effects and maximizing therapeutic efficacy.[9] This approach holds great promise in the treatment of various diseases, including cancer, neurological disorders and infectious diseases. Despite their numerous advantages, the translation of colloidosomes from bench to bedside has faced several challenges, including scalability, stability and regulatory hurdles.[10]

This review aims to provide a comprehensive overview of colloidosomes, encompassing their evolution, fabrication techniques, characterization methods and diverse applications in drug delivery. It will delve into the recent advancements in colloidosome engineering, such as the development of stimuli-responsive systems, targeted delivery strategies and multi-compartmental designs. Additionally, the review will critically examine the current limitations and challenges faced in the translation of colloidosomes and propose strategies to overcome these hurdles, paving the way for more effective and personalized therapies.

Evolution and Concept of Colloidosomes

The concept of colloidosomes emerged as a pioneering approach to encapsulate materials within a robust and tunable shell structure. Initially inspired by the self-assembly of colloidal particles at liquid-liquid interfaces, colloidosomes have undergone significant evolution, driven by the increasing demand for advanced drug delivery systems and the need for precise control over release kinetics. The earliest work on colloidosomes dates back to the late 1990s, when researchers explored the behavior of colloidal particles at fluid interfaces.[3,11] Velev *et al.* demonstrated the formation of hollow spherical structures by adsorbing latex particles onto the surface of emulsion droplets.[12] These particle-coated droplets, termed "colloidosomes," exhibited remarkable stability and provided a simple method for encapsulating various materials within their core.[1,4]

Building upon this foundation, Dinsmore *et al.* in 2002 reported a groundbreaking study that introduced the term "colloidosomes" and established the fundamental principles of their formation.[5] They showed that colloidal particles could self-assemble at the interface of water-in-oil emulsion droplets, creating a robust and selectively permeable shell. This seminal work paved the way for further exploration of colloidosomes as potential carriers for controlled release applications. The early research on colloidosomes focused primarily on understanding the self-assembly mechanisms and exploring the influence of various parameters, such as particle size, charge and concentration, on the formation and stability of the colloidosome shell.[11,13] Researchers also investigated the permeability and mechanical properties of these structures, recognizing their potential as encapsulation vehicles for a wide range of active ingredients.[2-4] As the field progressed, researchers began to explore different fabrication techniques and materials to expand the versatility and functionality of colloidosomes. One significant advancement was the introduction of stimuli-responsive colloidosomes, which can undergo structural or permeability changes in response to external triggers, such as temperature, pH, or magnetic fields. These smart colloidosomes opened up new avenues for controlled and targeted drug delivery, allowing for precise temporal and spatial release of the encapsulated cargo.[14]

Another notable development was the emergence of multi-compartmental colloidosomes, which feature multiple internal compartments separated by semi-permeable membranes. These sophisticated structures enable the encapsulation of multiple active ingredients or the creation of hierarchical release profiles, where different components are released at different rates or under specific conditions. Moreover, the integration of targeting moieties, such as antibodies, peptides, or small molecules, onto the colloidosome surface has opened up opportunities for site-specific drug delivery.[15,16] By leveraging the inherent properties of colloidosomes and incorporating targeting ligands, researchers have developed targeted delivery systems that can selectively accumulate in desired tissues or cells, minimizing off-target effects and enhancing therapeutic efficacy. In recent years, the evolution of colloidosomes has been driven by the increasing demand for personalized and patient-centric drug delivery solutions. Researchers have explored novel materials, such as biopolymers, lipids and inorganic nanoparticles, to create biocompatible and biodegradable colloidosomes tailored for specific therapeutic applications.[17,18] Additionally, the integration of advanced characterization techniques, such as cryo-electron microscopy and super-resolution imaging, has provided unprecedented insights into the structure and behavior of colloidosomes at the nanoscale. As the field continues to evolve, the concept of colloidosomes has expanded beyond drug delivery,

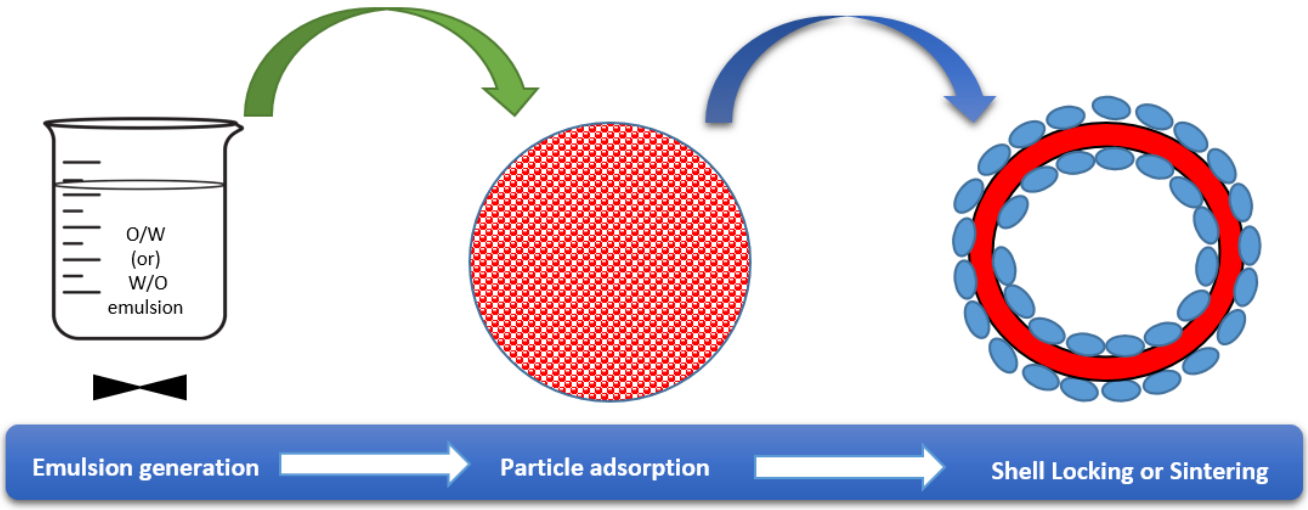

Figure 1: Key stages in the formation of colloidosomes.

finding applications in various domains, including catalysis, biosensing and energy storage.[19] This versatility underscores the remarkable potential of colloidosomes as a platform technology for encapsulation and controlled release across diverse industries

Fabrication Techniques

The fabrication of colloidosomes has been a subject of extensive research and various techniques have been developed to tailor their properties and encapsulation capabilities.[17,20] These techniques can be broadly classified into two main categories: emulsion-based and nature-of-colloids-based methods. Additionally, emerging techniques have been explored to address the limitations of traditional approaches and expand the functionalities of colloidosomes.[21]

Emulsion-based Colloidosomes

Emulsion-based techniques are the most widely used and well-established methods for colloidosome fabrication. These techniques rely on the self-assembly of colloidal particles at the interface of emulsion droplets, forming a robust and selectively permeable shell. [4,5]The emulsion type (water-in-oil or oil-in-water) and the nature of the colloidal particles determine the properties and characteristics of the resulting colloidosomes.[22]

Water-in-oil emulsion-based colloidosomes

In this approach, an aqueous solution is emulsified in an oil phase in the presence of colloidal particles.[23] The particles adsorb onto the surface of the water droplets, reducing the interfacial energy and stabilizing the emulsion. Subsequently, the particles are locked together by various methods, such as the addition of polycations, van der Waals forces, or sintering.[24,25] The water-in-oil emulsion is then transferred to an aqueous phase, typically by centrifugation or filtration, resulting in water-core colloidosomes dispersed in an aqueous medium.

Oil-in-water emulsion-based colloidosomes

Conversely, this technique involves emulsifying an oil phase in an aqueous solution containing colloidal particles and a surfactant. The colloidal particles and surfactant stabilize the oil-water interface, enabling the formation of oil-in-water emulsions.[26,27] After the particles are locked together, the emulsion is transferred to a non-aqueous phase and the resulting oil-core colloidosomes are redispersed in an aqueous medium.

Water-oil-water emulsion-based colloidosomes

In this approach, a pendant drop of an aqueous suspension of colloidal particles is formed in an oil phase. The particles adsorb onto the surface of the pendant drop, forming a densely packed monolayer.[28,29] This particle-coated drop is then transferred through a planar oil-water interface, resulting in the formation of a giant colloidosome with a spherical water/oil/water structure.

These emulsion-based techniques offer flexibility in controlling the size, composition and encapsulation properties of colloidosomes by adjusting parameters such as emulsion droplet size, particle concentration and emulsion stability. Table 1 shows the comparison of various fabrication methods used in the preparation of colloidosomes.

Nature-of-Colloids-based Colloidosomes

In addition to emulsion-based techniques, colloidosomes can be fabricated by exploiting the unique properties and interactions of different colloidal materials. Aqueous or oily gel core colloidosomes: This approach involves emulsifying a hot aqueous or oil solution containing a gelling agent (e.g., agarose, gelatin) in the presence of colloidal particles.[30,31] Upon cooling, the gelling

agent solidifies, forming a gel core surrounded by the colloidal particles. The resulting gel-core colloidosomes are separated from the continuous phase, washed and redispersed in an appropriate medium.

Hairy colloidosomes

This technique employs rod-like polymeric particles instead of spherical particles to form the colloidosome shell. The rod-like particles assemble at the interface of water-in-oil emulsion droplets, creating a "hairy" shell structure. After the aqueous core is gelled, the oil phase is removed and the resulting colloidosomes are dispersed in an aqueous medium.[4,32]

Nanoparticle colloidosomes

These colloidosomes are fabricated using Water-in-Oil-in-Water (W/O/W) double emulsions as templates. Hydrophobic nanoparticles dispersed in the oil phase self-assemble at the interfaces, forming a colloidal shell.[33,34] Upon removal of the oil phase, nanoparticle colloidosomes with tunable permeability and size are obtained.

Layer-by-layer (LbL) colloidosomes: This technique involves the layer-by-layer deposition of polyelectrolytes onto a template (e.g., biocrystals, nanoparticles), followed by the removal of the template, resulting in hollow polymer capsules.[20,35] The encapsulation of enzymes or other active ingredients can be achieved during the LbL process.

These nature-of-colloids-based techniques offer versatility in tailoring the composition, size and morphology of colloidosomes by exploiting the unique properties of different colloidal materials and their interactions with various templates or core materials.

Emerging Techniques

While emulsion-based and nature-of-colloids-based techniques have been widely explored, researchers have also investigated emerging techniques to address the limitations of traditional approaches and expand the functionalities of colloidosomes.[36,37]

Microfluidic techniques

The use of microfluidic devices has enabled precise control over the size, morphology and encapsulation properties of colloidosomes. These techniques involve generating double emulsions (e.g., W/O/W) with controlled flow rates and geometries, allowing for the formation of monodisperse and multi-compartmental colloidosomes.[38,39]

Pickering emulsion-based colloidosomes: Pickering emulsions, stabilized by solid particles instead of surfactants, have been explored for colloidosome fabrication. This approach offers improved stability and the potential for encapsulating hydrophobic or amphiphilic compounds within the oil droplets.[40]

Electrohydrodynamic co-jetting

This technique involves the simultaneous co-jetting of two immiscible liquids (e.g., water and oil) and colloidal particles through a concentric nozzle system under the influence of an electric field. The resulting colloidosomes exhibit precise control over size, shape and encapsulation properties.[41,42]

3D printing and additive manufacturing

Researchers have explored the potential of 3D printing and additive manufacturing techniques for the fabrication of colloidosomes with complex architectures and controlled release profiles. These approaches enable the creation of intricate structures and multi-compartmental designs tailored for specific applications.[43,44]

In addition to these emerging techniques, ongoing research efforts focus on developing new materials, such as biopolymers, inorganic nanoparticles and hybrid materials, for colloidosome fabrication. The integration of stimuli-responsive components and the incorporation of targeting moieties are also areas of active investigation, aiming to enhance the functionality and specificity of colloidosomes for targeted and controlled drug delivery applications.

Characterization of Colloidosomes

Comprehensive characterization of colloidosomes is crucial for understanding their structural and functional properties, as well as ensuring their reproducibility, quality and suitability for specific applications. A wide range of analytical techniques has been employed to investigate various aspects of colloidosomes, including their size, morphology, surface properties, encapsulation efficiency and release kinetics.[8-10] Following are the common characterization methods used for colloidosomes.

Size and Morphology Analysis

Dynamic Light Scattering (DLS)

DLS is a widely used technique for determining the size distribution and average diameter of colloidosomes in suspension. This method measures the fluctuations in the scattered light intensity caused by the Brownian motion of the particles, providing information about their hydrodynamic radius.[10]

Electron Microscopy

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are powerful techniques for visualizing the morphology and structure of colloidosomes at high resolutions. SEM provides detailed information about the surface morphology and shell structure, while TEM allows for the observation of internal features, such as the core-shell architecture and encapsulated materials.[45]

Table 1: Comparison of Different Colloidosome Fabrication Techniques.

Technique	Advantages	Limitations
Emulsion-based	- Well-established methods. - Versatile encapsulation capabilities. - Control over size and composition.	- Difficulty in scaling up. - Potential use of organic solvents. - Particle aggregation.
Nature-of-Colloids-based	- Tailorable shell properties.- Biocompatible materials.- Stimuli-responsive capabilities.	- Complex fabrication processes.- Limited encapsulation efficiency.- Batch-to-batch variability.
Microfluidic	- Monodisperse size distribution. - Precise control over morphology. - Multi-compartmental designs.	- Low throughput. - Specialized equipment. - Potential clogging issues.
3D Printing/Additive Manufacturing	- Complex architectures. - Controlled release profiles. - Customizable designs.	- Limited material selection. - Resolution limitations. - Post-processing requirements.

Optical Microscopy

Optical microscopy, including bright-field, phase-contrast and confocal microscopy, can be used to study the size, shape and distribution of colloidosomes, as well as to observe their behavior and interactions in real-time.

Surface Properties and Colloidal Stability

Zeta Potential Measurements

The zeta potential, a measure of the surface charge of colloidosomes, provides insights into their colloidal stability and interactions with other particles or molecules. It is typically determined by electrophoretic light scattering or laser Doppler electrophoresis techniques.[46]

Surface Characterization

Techniques such as X-ray Photoelectron Spectroscopy (XPS), Fourier-Transform Infrared Spectroscopy (FTIR) and Raman spectroscopy can be used to analyze the chemical composition and surface functionalization of colloidosomes, which is crucial for understanding their surface properties and interactions.[47]

Encapsulation Efficiency and Release Kinetics

Spectroscopic Methods

Ultraviolet-visible (UV-vis) spectroscopy, fluorescence spectroscopy and Nuclear Magnetic Resonance (NMR) spectroscopy are commonly employed to quantify the encapsulation efficiency of colloidosomes by measuring the concentration of the encapsulated cargo inside the core.[48]

In vitro Release Studies

The release kinetics of encapsulated materials from colloidosomes can be studied using various techniques, such as dialysis, centrifugation, or continuous flow systems. The concentration of the released cargo is typically monitored over time using spectroscopic methods or analytical techniques like High-Performance Liquid Chromatography (HPLC) or Mass Spectrometry (MS).[48]

Stimuli-Responsive Behavior

For stimuli-responsive colloidosomes, techniques like Differential Scanning Calorimetry (DSC), dynamic rheology and turbidimetry can be used to characterize their response to external triggers, such as temperature, pH, or magnetic fields.[48]

Mechanical and Structural Properties

Atomic Force Microscopy (AFM)

AFM can be used to study the mechanical properties of colloidosomes, including their elasticity, stiffness and deformation behavior, by measuring the force-displacement curves upon indentation of the shell.[49]

Small-Angle X-ray Scattering (SAXS) and Small-Angle Neutron Scattering (SANS)

These techniques provide information about the internal structure, particle arrangement and shell thickness of colloidosomes by analyzing the scattering patterns of X-rays or neutrons.[49]

Rheological Measurements

Rheological analysis, including oscillatory shear and flow measurements, can provide insights into the viscoelastic properties, deformation behavior and stability of colloidosome suspensions under shear stresses.[50]

In addition to these characterization techniques, advanced methods such as cryo-electron microscopy, super-resolution microscopy and in situ analytical techniques have been employed to gain deeper insights into the structure, dynamics and behavior of colloidosomes at the nanoscale level. It is important to note that the choice of characterization methods depends on the specific properties of interest, the nature of the colloidosomes and the

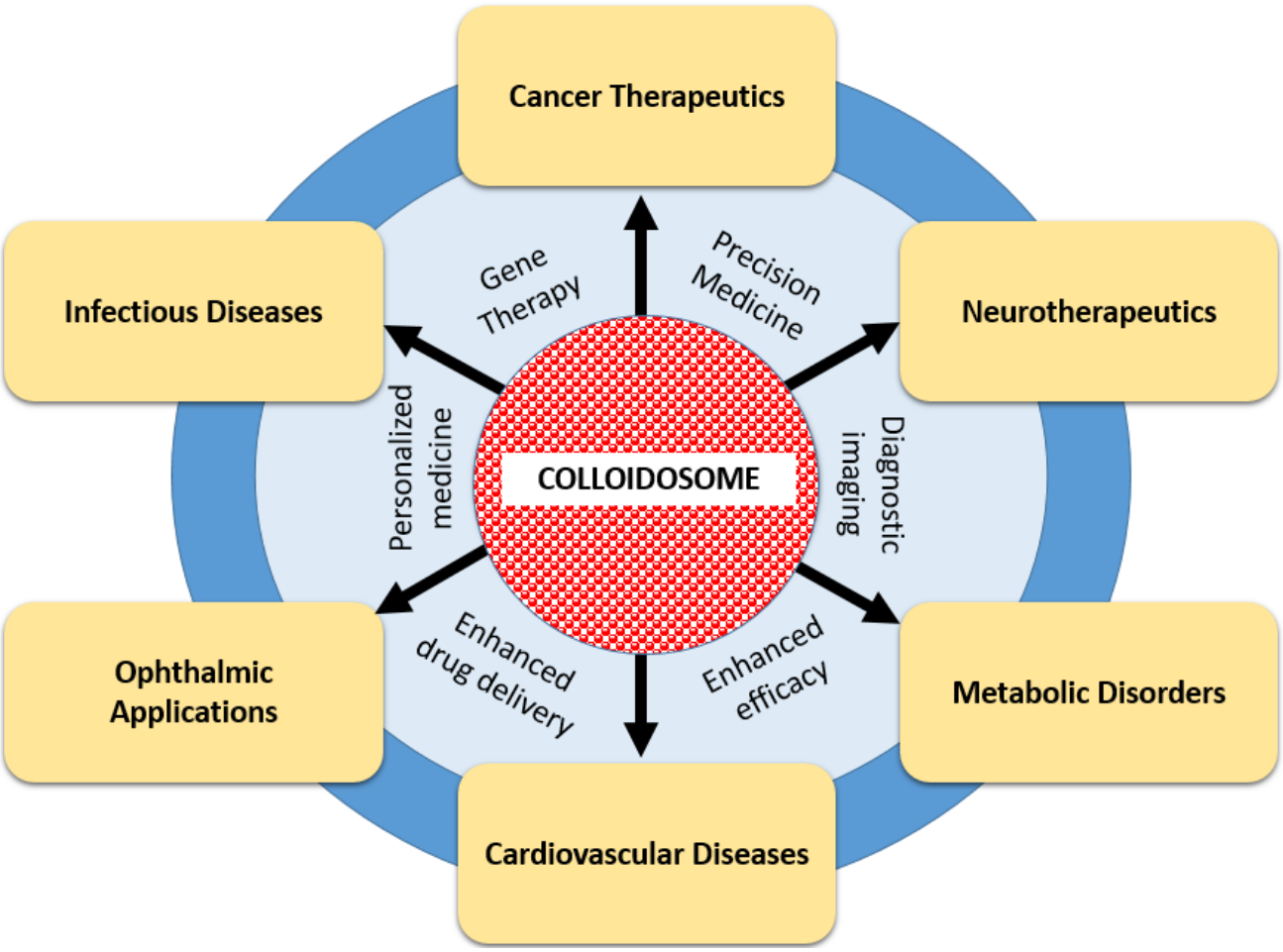

Figure 2: Applications of colloidosomes in drug delivery.

intended applications. Often, a combination of complementary techniques is required to obtain a comprehensive understanding of the structural, physical and functional properties of colloidosomes.

Colloidosomes in Drug Delivery

The unique properties of colloidosomes, including their tunable permeability, mechanical strength and encapsulation capabilities, have made them attractive candidates for various drug delivery applications. Colloidosomes have demonstrated remarkable potential in delivering a wide range of therapeutic agents, from small molecules to biomacromolecules and even genetic materials.[49] Figure 2 illustrates the applications of colloidosomes in drug delivery (Table 2), highlighting their versatility and the strategies employed to achieve targeted and controlled release.

Small Molecule Delivery

Colloidosomes have shown great promise in encapsulating and delivering small molecule drugs, particularly those with poor solubility, stability, or bioavailability issues. The core-shell structure of colloidosomes allows for the efficient encapsulation of hydrophobic or hydrophilic small molecules, protecting them from degradation and enhancing their solubility.[50]

Researchers have explored various strategies to load small molecule drugs into colloidosomes, such as incorporating them directly into the core during the fabrication process or adsorbing them onto the shell surface. The release kinetics of the encapsulated drugs can be modulated by tailoring the shell permeability, thickness, or introducing stimuli-responsive components.

For instance, Zhang *et al.* developed colloidosomes with Poly (Lactic-co-Glycolic Acid) (PLGA) shells for the controlled delivery of hydrophobic drugs like curcumin.[51] These colloidosomes exhibited sustained release profiles and enhanced cellular uptake, demonstrating their potential for cancer therapy.

Protein and Peptide Delivery

The delivery of proteins and peptides poses significant challenges due to their susceptibility to degradation, poor membrane permeability and rapid clearance from the body. Colloidosomes have emerged as promising carriers for protecting and delivering these biomacromolecules, leveraging their ability to encapsulate and control the release of sensitive cargos.[46,47] Researchers have

developed various strategies to encapsulate proteins and peptides within colloidosomes, such as incorporating them into the core during fabrication or adsorbing them onto the shell surface. The shell composition and properties can be tailored to minimize interactions with the encapsulated biomolecules, ensuring their stability and bioactivity.[44]

For example, Zhang *et al.* reported the successful encapsulation of insulin within colloidosomes composed of Poly (N-Isopropylacrylamide) (PNIPAM) nanoparticles.[51] These colloidosomes exhibited temperature-responsive release behavior, enabling controlled insulin delivery for the potential treatment of diabetes.

Gene Delivery

Gene delivery represents a promising therapeutic approach for treating genetic disorders and cancer, but it faces significant challenges due to the fragility and instability of genetic materials, as well as the need for efficient cellular uptake and intracellular trafficking. Colloidosomes have emerged as attractive carriers for gene delivery, offering protection, controlled release and the potential for targeting specific cells or tissues.[52,53]

Researchers have explored various strategies for encapsulating genetic materials, such as plasmid DNA, small interfering RNA (siRNA), or messenger RNA (mRNA), within colloidosomes. The shell composition and surface modifications can be tailored to enhance cellular uptake, endosomal escape and nuclear localization, ensuring efficient gene delivery and expression.[54] For instance, Li *et al.* developed colloidosomes composed of cationic polymers and magnetic nanoparticles for the delivery of plasmid DNA.[55] These colloidosomes exhibited efficient cellular uptake and gene transfection, while the magnetic properties enabled targeted delivery using external magnetic fields.

Targeted Delivery

One of the key advantages of colloidosomes is their ability to facilitate targeted delivery, minimizing off-target effects and enhancing therapeutic efficacy. Researchers have employed various strategies to impart targeting capabilities to colloidosomes, such as incorporating targeting ligands, antibodies, or peptides onto the shell surface.[4,46,56] These targeting moieties can selectively bind to specific receptors or markers expressed on target cells or tissues, enabling the selective accumulation and internalization of the colloidosomes at the desired site of action.[57] For example, Wang *et al.* developed colloidosomes functionalized with folic acid for targeted delivery of doxorubicin to folate receptor-overexpressing cancer cells.[58] These targeted colloidosomes exhibited enhanced cellular uptake and cytotoxicity towards cancer cells while minimizing off-target effects on healthy cells. The targeted delivery and the mechanism of cellular uptake through colloidosomes is illustrated in Figure 3.

Stimuli-responsive Colloidosomes

Stimuli-responsive colloidosomes have garnered significant attention due to their ability to undergo controlled and triggered release in response to specific environmental cues or external stimuli. These stimuli can include changes in temperature, pH, redox potential, magnetic fields, or light irradiation, among others.[59,60] By incorporating responsive components into the shell or core of colloidosomes, researchers have developed smart delivery systems that can release their cargo in a precise and controlled manner, either at a specific location or in response to specific physiological conditions.[61,62]

For instance, Hu *et al.* developed pH-responsive colloidosomes composed of Poly(Acrylic Acid) (PAA) and Poly (N-isopropylacrylamide) (PNIPAM) for the delivery of doxorubicin.[15] These colloidosomes exhibited pH-triggered swelling and disassembly in the acidic tumor microenvironment, leading to enhanced drug release and improved therapeutic efficacy. In another example, Zhang *et al.* reported the development of light-responsive colloidosomes containing up conversion nanoparticles and mesoporous silica shells for controlled drug delivery.[51] Upon near-infrared light irradiation, the up conversion nanoparticles generated reactive oxygen species, leading to the disruption of the mesoporous silica shells and triggered release of the encapsulated cargo.[63-65] The integration of stimuli-responsive components into colloidosomes offers exciting opportunities for achieving precise spatiotemporal control over drug release, enabling more effective and personalized treatment strategies [66,67]

Multi-Compartmental and Multi-Functional Colloidosomes

The versatility of colloidosomes has enabled researchers to explore more sophisticated designs and architectures, leading to the development of multi-compartmental and multi-functional colloidosomes. These advanced structures offer unique advantages and opportunities for encapsulating multiple components, achieving hierarchical or sequential release profiles and integrating various functionalities within a single carrier system.[68]

Multi-compartmental Colloidosomes

Multi-compartmental colloidosomes are characterized by the presence of multiple internal compartments or sub-compartments separated by semi-permeable membranes or barriers. These complex structures allow for the encapsulation of different active ingredients or therapeutic agents within distinct compartments, enabling their simultaneous or sequential release based on specific environmental conditions or stimuli.[68,69] The fabrication of multi-compartmental colloidosomes typically involves the use of advanced techniques such as microfluidics, 3D printing, or templating methods. For instance, researchers have employed double emulsion templates or multi-phase flow

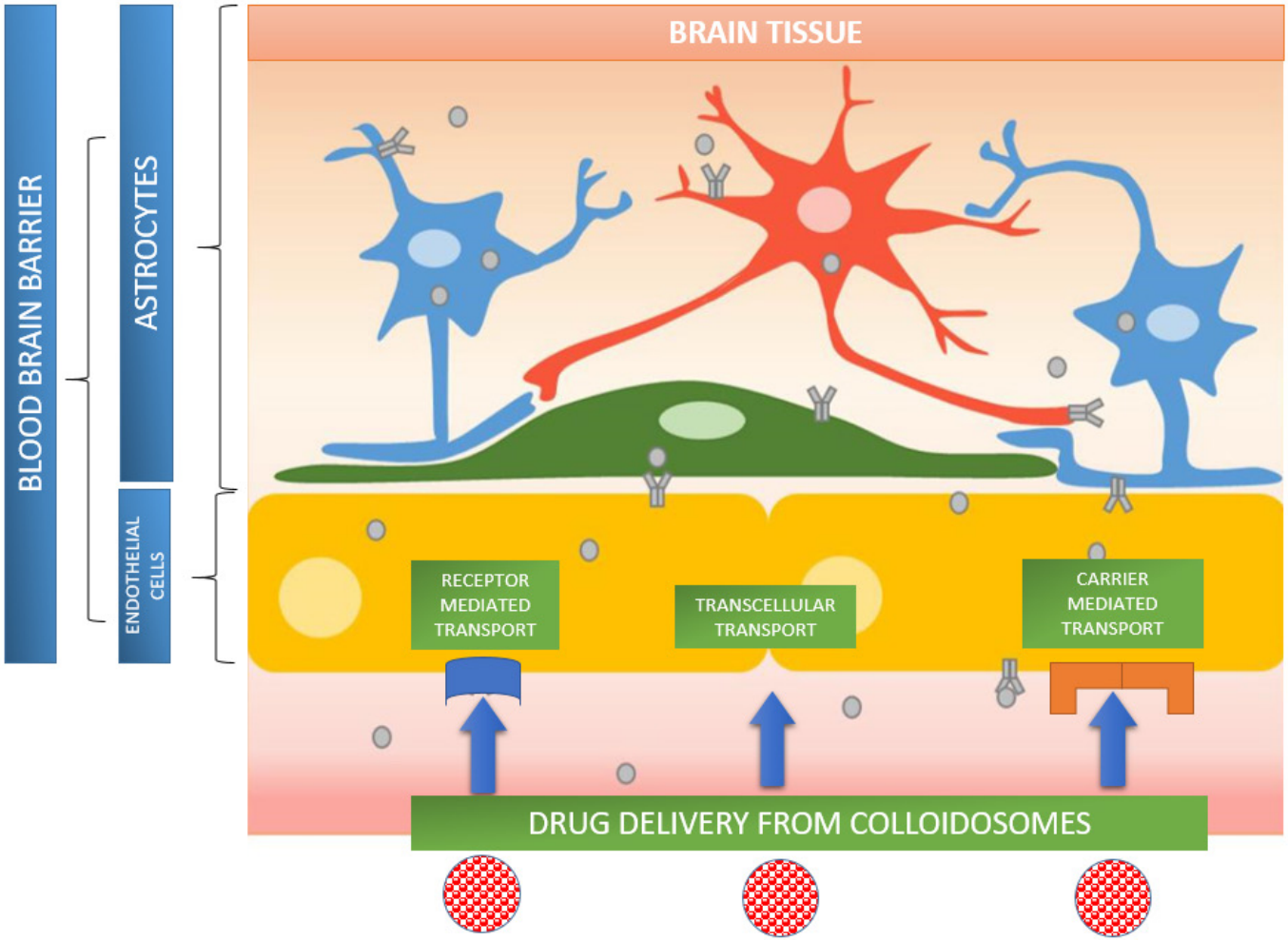

Figure 3: Targeted drug delivery to brain using colloidosomes.

focusing microfluidic devices to generate colloidosomes with multiple aqueous or oil compartments within a single shell. One of the key advantages of multi-compartmental colloidosomes is their ability to achieve hierarchical or sequential release profiles. By encapsulating different therapeutic agents in separate compartments, each with distinct release kinetics or triggers, these colloidosomes can provide a controlled and targeted delivery of multiple drugs or bioactive molecules at specific sites or time points.[70,71] For example, Zhou *et al.* developed multi-compartmental colloidosomes with an aqueous core and multiple oil compartments for the co-delivery of hydrophilic and hydrophobic drugs.[72] This design allowed for the simultaneous release of the hydrophilic drug from the aqueous core and the controlled release of the hydrophobic drug from the oil compartments, enabling synergistic therapeutic effects.

Multi-functional Colloidosomes

In addition to multi-compartmental designs, colloidosomes can be engineered to incorporate multiple functionalities within a single carrier system. These multi-functional colloidosomes combine the encapsulation and delivery capabilities with additional features such as imaging, sensing, or therapeutic modalities, creating integrated platforms for theranostic applications. [73,74] One approach to creating multi-functional colloidosomes involves incorporating functional components or materials into the shell or core during the fabrication process. For instance, researchers have incorporated magnetic nanoparticles, fluorescent dyes, or contrast agents into the shell or core of colloidosomes, enabling magnetic guidance, imaging, or diagnostic capabilities.[14,45] Another strategy involves the surface functionalization of colloidosomes with various moieties or ligands to impart additional functionalities. For example, researchers have conjugated targeting ligands, cell-penetrating peptides, or therapeutic antibodies onto the surface of colloidosomes, enhancing their targeting abilities, cellular uptake, or therapeutic efficacy.[42,75]

Multi-functional colloidosomes have shown great potential in various biomedical applications, such as simultaneous imaging and drug delivery, combined diagnosis and therapy (theranostics), or multi-modal cancer treatment. For instance, Zhang *et al.* developed multi-functional colloidosomes containing iron oxide nanoparticles and doxorubicin for combined

Table 2: Potential Applications of Colloidosomes in Drug Delivery.

Application	Description
Targeted Drug Delivery	Incorporation of targeting ligands or antibodies for selective accumulation in diseased tissues or cells, improving therapeutic efficacy and reducing off-target effects.
Controlled Release	Tunable release kinetics through shell permeability or stimuli-responsive components, enabling sustained, pulsatile, or triggered drug release.
Protein and Peptide Delivery	Encapsulation and protection of sensitive biomacromolecules, enhancing their stability and bioavailability.
Gene Delivery	Efficient encapsulation and delivery of genetic materials (e.g., DNA, siRNA, mRNA) for gene therapy and genetic engineering applications.
Theranostics	Integration of imaging agents or diagnostic probes for simultaneous imaging and drug delivery, enabling real-time monitoring and personalized treatment strategies.
Catalysis	Encapsulation of catalytic materials or enzymes within colloidosomes for applications in chemical synthesis, biocatalysis, or environmental remediation.
Biosensing	Incorporation of sensing elements or reporters within colloidosomes for the detection and quantification of specific analytes or biomarkers.
Energy Storage	Encapsulation of electroactive materials or energy storage components for applications in batteries, supercapacitors, or fuel cells.

Magnetic Resonance Imaging (MRI) and chemotherapy.[51] These colloidosomes exhibited efficient tumor accumulation, enabling real-time tracking and simultaneous drug delivery. [76]

Furthermore, multi-functional colloidosomes have been explored for applications in biosensing, catalysis and environmental remediation, showcasing their versatility and potential impact beyond the biomedical field. The development of multi-compartmental and multi-functional colloidosomes represents a significant advancement in the field of drug delivery and encapsulation technologies. By integrating multiple components, functionalities and release profiles within a single carrier system, these advanced colloidosomes offer opportunities for more precise, effective and personalized therapeutic interventions, as well as potential applications in various other domains.

Challenges

While colloidosomes have demonstrated remarkable potential in drug delivery and encapsulation applications, their translation from bench to bedside and commercial viability face several challenges.[34,49,71] Addressing these challenges is crucial for the successful implementation of colloidosome technology in clinical and industrial settings.

Scaling-up and Manufacturing

One of the major challenges in the development of colloidosomes is the scaling-up of production processes from laboratory-scale to industrial-scale manufacturing. Many of the fabrication techniques employed for colloidosome synthesis, such as microfluidics or emulsion-based methods, can be challenging to scale up while maintaining consistent product quality, reproducibility and cost-effectiveness.[76] Researchers are exploring alternative manufacturing strategies and process optimization to address this challenge.[25] For instance, continuous flow microfluidic systems and parallelized microfluidic devices have been investigated to increase the throughput and scalability of colloidosome production. Additionally, the development of automated and robotic systems for emulsion generation and colloidosome assembly could potentially enable large-scale manufacturing while minimizing batch-to-batch variability.[77,78]

Stability and Storage

The long-term stability and storage of colloidosomes are critical factors that need to be addressed for their successful commercialization and clinical translation. Colloidosomes are often susceptible to degradation, aggregation, or leakage of encapsulated cargo over time, which can compromise their efficacy and shelf-life.[79] Researchers are investigating various strategies to enhance the stability of colloidosomes, such as optimizing the shell composition, incorporating stabilizing agents or excipients and exploring different storage conditions (e.g., lyophilization, cryopreservation).[26,28] Additionally, the development of advanced characterization techniques and accelerated stability testing methods can aid in understanding the degradation mechanisms and identifying potential stabilization approaches.

Regulatory Considerations

The introduction of novel drug delivery systems like colloidosomes into clinical practice requires rigorous regulatory evaluation and approval processes. Colloidosomes present unique challenges in terms of their complex composition, potential batch-to-batch variability and the need for comprehensive characterization and standardization. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency

(EMA), have established guidelines and frameworks for the evaluation of nanomedicines and novel drug delivery systems.[29,33] However, the specific requirements and considerations for colloidosomes may need further clarification and guidance. Close collaboration between academic researchers, industry partners and regulatory bodies is essential to establish standardized methodologies for colloidosome characterization, quality control and safety assessment. Additionally, the development of well-defined analytical techniques and reference materials can facilitate the regulatory evaluation process and ensure the consistent quality and performance of colloidosome-based products.

Clinical Translation

Translating colloidosome technology from preclinical studies to clinical trials and eventual commercialization presents significant challenges. These challenges include navigating the complex regulatory landscape, ensuring scalable and cost-effective manufacturing processes and demonstrating the safety and efficacy of colloidosome-based formulations in human studies. Preclinical studies, including *in vitro* and *in vivo* evaluations, are crucial for assessing the pharmacokinetics, biodistribution, toxicity and therapeutic efficacy of colloidosomes. However, the translation of these findings to human clinical trials can be challenging due to interspecies differences and the complexity of the human physiological environment. [35,37] Collaboration between academia, industry and clinical research organizations is essential to overcome these translational hurdles. Establishing robust preclinical models, optimizing formulation design and conducting well-designed clinical trials are paramount for the successful clinical translation of colloidosome technology.[22,80]

Furthermore, addressing the challenges related to manufacturing, storage and regulatory compliance will play a crucial role in enabling the widespread adoption of colloidosome-based therapeutics in clinical settings. Looking ahead, the future of colloidosomes lies in the continuous exploration of novel materials, fabrication techniques and functionalization strategies. The integration of advanced characterization methods, such as cryo-electron microscopy and super-resolution imaging, will provide deeper insights into the structure and behavior of colloidosomes, enabling further optimization and design improvements. Additionally, the integration of colloidosomes with emerging technologies, such as gene editing, immunotherapy and regenerative medicine, could open up new avenues for innovative therapeutic approaches and personalized medicine.[81]

CONCLUSION

Colloidosomes have emerged as a pioneering platform in the realm of targeted and controlled drug delivery, offering remarkable versatility, tunability and encapsulation capabilities. The unique core-shell structure of colloidosomes, coupled with their tunable permeability, mechanical strength and compatibility, has opened up exciting opportunities for addressing challenges associated with conventional drug delivery systems, such as poor solubility, instability and rapid degradation of therapeutic agents. Additionally, the development of stimuli-responsive, targeted and multi-functional colloidosomes has paved the way for more precise, effective and personalized therapeutic interventions. Despite the remarkable progress in colloidosome technology, several challenges remain, including scaling-up and manufacturing, ensuring long-term stability, navigating regulatory hurdles and facilitating clinical translation. Addressing these challenges will require concerted efforts from academia, industry and regulatory bodies, as well as the integration of advanced characterization techniques and the exploration of novel materials and fabrication strategies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

W/O/W: Water-in-oil-in-water; **LbL:** Layer-by-layer; **DLS:** Dynamic Light Scattering; **SEM:** Scanning Electron Microscopy; **TEM:** Transmission Electron Microscopy; **XPS:** X-ray Photoelectron Spectroscopy; **FTIR:** Fourier-Transform Infrared Spectroscopy; **UV-vis:** Ultraviolet-visible; **NMR:** Nuclear Magnetic Resonance; **HPLC:** High-Performance Liquid Chromatography; **MS:** Mass Spectrometry; **DSC:** Differential scanning calorimetry; **AFM:** Atomic Force Microscopy; **SAXS:** Small-Angle X-ray Scattering; **SANS:** Small-Angle Neutron Scattering; **PLGA:** Poly(lactic-co-glycolic acid); **PNIPAM:** Poly(N-isopropylacrylamide); **siRNA:** Small interfering RN; **mRNA:** Messenger RNA; **DNA:** Deoxyribose nucleic acid; **PAA:** Poly(acrylic acid); **PNIPAM:** Poly(N-isopropylacrylamide); **MRI:** Magnetic resonance imaging; **FDA:** Food and Drug Administration; **EMA:** European Medicines Agency.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No animals and humans have been used for the study. Authors are giving consent to publisher that publisher shall have the exclusive right throughout the world to publish and sell the contribution in all languages.

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