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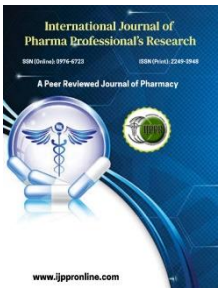

Innovative Vesicular Drug Delivery Systems: Unleashing the Power of Nanocarriers

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Abstract: "Drug delivery systems utilizing vesicular nanocarriers represent a revolutionary approach in modern pharmaceutical science. These innovative systems harness the potential of nanotechnology to enhance therapeutic efficacy, improve drug bioavailability, and mitigate adverse effects. Vesicular nanocarriers, encompassing liposomes, niosomes, ethosomes, and transfersomes among others, exhibit remarkable versatility in encapsulating diverse pharmaceutical agents, ranging from small molecules to biologics. Their unique structural properties and tunable characteristics enable precise modulation of drug release kinetics, facilitating targeted delivery and controlled release at the desired site of action. Moreover, these nanocarriers offer inherent advantages, including increased stability, reduced toxicity, and the potential to overcome biological barriers, thereby revolutionizing the landscape of drug delivery. This abstract explores the state-of-the-art advancements, promising applications, and future prospects of vesicular nanocarriers, shedding light on their transformative role in optimizing therapeutic outcomes and paving the way for personalized medicine."

Introduction: Drug delivery systems constitute a cornerstone in modern medicine, profoundly impacting the effectiveness and safety of therapeutic interventions. Their significance lies in their ability to precisely deliver medications to specific targets within the body, optimizing treatment outcomes while minimizing adverse effects. These systems enhance therapeutic efficacy by ensuring targeted delivery, thereby increasing drug concentrations at desired sites. Additionally, they improve drug bioavailability by addressing issues related to solubility and stability, ensuring optimal drug absorption and utilization.[1]

Controlled-release mechanisms embedded within these systems maintain consistent drug levels, extending drug duration and enhancing patient adherence. Importantly, they mitigate side effects

by reducing systemic exposure to drugs, thus enhancing safety profiles. Furthermore, drug delivery systems hold promise for personalized medicine, enabling tailored treatments based on individual patient needs and characteristics. By overcoming biological barriers and facilitating the delivery of diverse therapeutic agents, these systems open avenues for novel therapeutic approaches, ushering in a new era of targeted, efficient, and personalized medical treatments.[2,3]

The evolution of vesicular nanocarriers represents a transformative journey in pharmaceutical sciences, revolutionizing drug delivery strategies over decades of research and innovation. It began with the advent of liposomes in the 1960s, marking a pioneering step in encapsulating drugs within lipid bilayers. These early vesicular carriers demonstrated the potential to protect sensitive drugs, modify their pharmacokinetics, and facilitate targeted delivery. Over time, the evolution expanded to encompass various types of vesicular nanocarriers, each offering unique advantages and tailored functionalities.[4]

Niosomes emerged as a promising alternative to liposomes in the 1970s, utilizing non-ionic surfactants to form vesicles. Their improved stability, ability to encapsulate hydrophilic and hydrophobic drugs, and cost-effectiveness garnered significant attention. Ethosomes, introduced later, brought an innovative approach by incorporating high ethanol concentrations in lipid vesicles, enhancing drug penetration through the skin and enabling efficient transdermal delivery.[5,6]

Transfersomes, introduced in the 1990s, introduced a breakthrough in overcoming biological barriers. Their ultra-deformable nature enabled them to traverse through pores much smaller than their size, facilitating deeper tissue penetration and efficient drug delivery. Further advancements in nanotechnology paved the way for cubosomes and archaeosomes, offering sophisticated structures capable of encapsulating diverse drug types while providing enhanced stability and bioavailability.[7]

Throughout this evolution, the focus extended beyond mere encapsulation to tailor vesicular carriers for specific drug delivery challenges. Modifications in composition, size, surface charge, and targeting ligands aimed to optimize drug release kinetics, increase tissue specificity, and overcome physiological barriers. The evolution of these vesicular nanocarriers not only expanded the possibilities in drug delivery but also diversified their applications across various medical fields, including oncology, infectious diseases, and dermatology.[8]

As research continues, the evolution of vesicular nanocarriers persists, driving towards more sophisticated designs and functionalities. The quest for improved stability, enhanced targeting capabilities, and the ability to encapsulate a broader range of therapeutic agents remains at the forefront, promising continued innovation and breakthroughs in drug delivery systems for improved patient care and treatment outcomes.[9]

Nanocarriers represent a cornerstone in modern pharmaceuticals, wielding profound significance in revolutionizing drug delivery paradigms. Their pivotal role lies in their ability to address critical challenges associated with traditional drug formulations, offering transformative solutions that enhance therapeutic efficacy and patient outcomes. These nanoscale carriers, such as liposomes, niosomes, and other vesicular systems, provide a tailored platform for drug encapsulation, protection, and targeted delivery.[10]

One of the primary significances of nanocarriers is their capability to improve drug bioavailability. Many potent drugs encounter limitations related to solubility, stability, or rapid degradation within the body, hampering their effectiveness. Nanocarriers adeptly address these hurdles by encapsulating drugs, enhancing their solubility, stability, and protecting them from degradation,

thereby augmenting their bioavailability. Moreover, nanocarriers enable precise targeting of drugs to specific cells, tissues, or organs, minimizing systemic side effects and maximizing therapeutic impact.[11]

This targeted approach mitigates toxicity on healthy tissues, enhances drug concentrations at the intended site of action, and facilitates controlled release, optimizing treatment outcomes. Furthermore, nanocarriers hold promise for delivering a diverse range of therapeutic agents, including traditional small molecules, biologics, and genetic material. Their versatility and ability to encapsulate various drug types expand the horizons of pharmaceutical research, ushering in personalized medicine and innovative treatment modalities. In essence, nanocarriers stand as catalysts for transformative advancements in drug delivery, promising more effective, safer, and tailored therapeutic interventions.[12]

2. Types of Vesicular Nanocarriers:

Vesicular nanocarriers include liposomes, niosomes, and ethosomes, each utilizing distinct compositions and structures for drug encapsulation and delivery. Liposomes are lipid-based vesicles; niosomes employ non-ionic surfactants, while ethosomes integrate high ethanol concentrations, each offering unique advantages in drug delivery applications. These nanocarriers vary in properties, allowing tailored approaches for targeted drug delivery and enhanced therapeutic outcomes. Figure 1 shows the various types of vesicular nanocarriers.

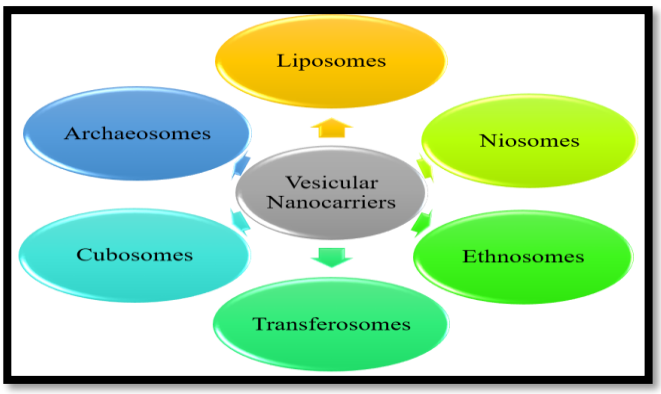

Figure 1: Types of Vesicular Nanocarriers

2.1 Liposomes:

Liposomes stand as a versatile and effective vesicular drug delivery system, playing a pivotal role in modern pharmaceuticals. These microscopic spherical vesicles, comprised of phospholipid bilayers, have revolutionized drug delivery since their inception in the 1960s. Their unique structural composition allows liposomes to encapsulate a wide range of pharmaceutical agents, varying from hydrophilic compounds within their aqueous core to hydrophobic substances within the lipid bilayers. This versatility makes them an ideal carrier for various therapeutic molecules, including drugs, nucleic acids, and imaging agents.

A primary advantage of liposomes lies in their ability to protect encapsulated drugs from degradation and clearance mechanisms. The lipid bilayer encapsulation shields drugs from enzymatic degradation and immune recognition, enhancing their stability and circulation time in the body. This protection contributes to improved drug bioavailability, ensuring a more sustained and controlled release at the target site.

Moreover, liposomes exhibit remarkable biocompatibility and low toxicity, making them well-tolerated within the body. This favorable safety profile has facilitated their extensive use in pharmaceutical formulations, particularly in delivering anticancer drugs, antimicrobials, and vaccines. Additionally, the customizable nature of

liposomes allows for modifications to their surface properties, enabling targeted delivery to specific cells or tissues. Functionalization with ligands or antibodies enhances their ability to recognize and bind to target cells, facilitating site-specific drug delivery while minimizing off-target effects.

The versatility and adaptability of liposomes have led to the development of innovative drug formulations. Advances in liposomal technology have yielded long-circulating liposomes, triggered-release systems, and actively targeted liposomal formulations. These advancements continue to expand their applications across diverse therapeutic areas, promising enhanced efficacy, reduced side effects, and improved patient outcomes. As research progresses, liposomes remain at the forefront of vesicular drug delivery systems, continually evolving to meet the demands of modern medicine and paving the way for more efficient and targeted drug therapies.[13-15]

2.2 Niosomes:

Niosomes, a type of vesicular drug delivery system, offer a promising alternative to liposomes, harnessing non-ionic surfactants to form vesicles. Their emergence in the 1970s marked a significant stride in pharmaceutical sciences, providing a versatile platform for drug encapsulation and delivery. Composed of non-ionic surfactants and cholesterol, niosomes possess structural similarities to liposomes while exhibiting distinct advantages, including enhanced stability, cost-effectiveness, and facile manufacturing processes.

The formulation of niosomes involves the self-assembly of non-ionic surfactants into bilayered structures in aqueous solutions. This formation process generates vesicles with hydrophilic heads facing the aqueous environment and hydrophobic tails oriented inward, encapsulating drugs either within the aqueous compartments or between the bilayers. This structural versatility allows niosomes to encapsulate a wide range of drug types, including both hydrophilic and hydrophobic compounds, offering potential applications across various therapeutic areas.

One of the key advantages of niosomes lies in their enhanced stability compared to liposomes. The non-ionic nature of the surfactants contributes to increased stability in various environmental conditions, making them less prone to degradation and leakage of encapsulated drugs. Additionally, niosomes exhibit robustness against pH variations and enzymatic degradation, facilitating improved drug retention and prolonged circulation in the body.

Furthermore, the relatively simple and cost-effective manufacturing processes of niosomes make them attractive for large-scale production, potentially reducing production costs in pharmaceutical formulations. Their compatibility with different routes of administration, such as oral, topical, and parenteral, further expands their versatility in drug delivery applications.

While niosomes offer significant advantages, challenges related to achieving uniform size distribution and scalability in production persist. However, ongoing research and advancements in formulation techniques continue to refine niosomal systems, enhancing their stability, targeting capabilities, and therapeutic efficacy. With their distinctive attributes and potential, niosomes stand as a promising vesicular drug delivery system, driving innovation in pharmaceutical sciences and offering a platform for diverse therapeutic interventions.[16-18]

2.3 Ethosomes:

Ethosomes, a novel type of vesicular drug delivery system, have emerged as a promising platform for enhancing transdermal drug delivery. Introduced as an innovative formulation in the late 20th century, ethosomes are characterized by

their high ethanol content, which distinguishes them from conventional liposomes and niosomes. This unique composition confers ethosomes with remarkable fluidity and penetration-enhancing properties, particularly suitable for improving drug permeation through the skin.

The formulation of ethosomes involves the combination of phospholipids, ethanol, and water to create vesicles with a high ethanol concentration. This high ethanol content imparts flexibility to the lipid bilayers, enhancing their deformability and enabling deeper penetration into the skin layers. Additionally, the fluidizing effect of ethanol on skin lipids facilitates enhanced drug diffusion through the stratum corneum, ultimately promoting increased drug absorption and bioavailability.

Ethosomes exhibit several advantages in transdermal drug delivery. Their ability to penetrate through the skin's lipid barrier more effectively than traditional liposomes enhances the delivery of both hydrophilic and lipophilic drugs. This feature makes them suitable carriers for a wide range of therapeutic agents, including nonsteroidal anti-inflammatory drugs, anesthetics, and even macromolecules like peptides and proteins.

Moreover, ethosomes have shown promise in improving the efficacy of topical drug delivery while reducing side effects. Their ability to enhance drug permeation allows for lower drug doses to achieve therapeutic effects, minimizing systemic exposure and potential adverse reactions. Additionally, their biocompatibility and non-toxic nature make them well-tolerated and suitable for various dermatological applications.

However, challenges such as stability issues and formulation optimization persist in ethosomal systems. Yet, ongoing research and advancements in formulation techniques aim to address these challenges, refining ethosomal formulations and expanding their applications. With their unique composition and penetration-enhancing capabilities, ethosomes continue to hold significant promise as an innovative vesicular drug delivery system for efficient transdermal drug administration.[19,20]

2.4 Transfersomes:

Transfersomes, an advanced class of vesicular drug delivery systems, represent a significant breakthrough in overcoming biological barriers for efficient drug delivery. Introduced in the 1990s, transfersomes stand out for their exceptional deformability and capability to penetrate through pores much smaller than their size, allowing for enhanced tissue permeation and deeper drug delivery. Comprising phospholipids and edge activators such as surfactants or bile salts, transfersomes exhibit remarkable flexibility, enabling them to squeeze and deform to a significant extent without rupturing, thus overcoming physiological barriers that hinder drug delivery.

The unique property of transfersomes lies in their ultra-deformable nature, allowing them to penetrate tight barriers such as the stratum corneum in the skin or the endothelial lining in blood vessels. This deformability enables transfersomes to squeeze through narrow pores or constrictions, facilitating deeper penetration into the skin layers or reaching target tissues. Consequently, transfersomes demonstrate superior potential for transdermal drug delivery and targeted delivery to specific cells or tissues.

The deformability of transfersomes is attributed to the incorporation of edge activators, which disrupt the lipid bilayers and reduce interfacial tension, enhancing membrane flexibility. This structural adaptation enables transfersomes to navigate through biological barriers more effectively than conventional vesicular systems like liposomes or niosomes. As a result, transfersomes offer improved bioavailability and

therapeutic efficacy of encapsulated drugs while minimizing systemic side effects.

Moreover, transfersomes exhibit promising applications in delivering a wide range of therapeutic agents, including small molecules, peptides, and macromolecules. Their potential to encapsulate diverse drug types and facilitate controlled release further expands their utility in various medical fields, including dermatology, oncology, and vaccination.

Despite their exceptional properties, challenges related to stability and large-scale production persist in transfersomal formulations. Nonetheless, ongoing research aims to address these challenges, refining transfersome formulations and optimizing their properties for enhanced drug delivery. With their exceptional deformability and potential to overcome biological barriers, transfersomes stand as a promising vesicular drug delivery system, offering a pathway for efficient and targeted drug administration in diverse medical applications.[21-23]

2.5 Cubosomes:

Cubosomes, a distinctive type of vesicular drug delivery system, present an intriguing structural design that sets them apart in the realm of pharmaceutical nanocarriers. These nanostructured particles, developed as innovative drug delivery platforms, exhibit a unique bicontinuous cubic phase morphology, comprising interconnected water and lipid compartments. Their intricate structure, characterized by a network of lipid bilayers arranged in a highly organized cubic lattice, distinguishes them from traditional vesicular systems like liposomes or niosomes.

The formation of cubosomes involves the self-assembly of lipid-based molecules, typically monoolein, into a cubic lattice structure in aqueous environments. This structure forms a complex three-dimensional network with a high surface area, offering an ideal platform for encapsulating hydrophilic and hydrophobic drugs within the interfacial regions or lipid domains. Cubosomes' capability to encapsulate a broad range of pharmaceutical agents, including small molecules and biologics, showcases their versatility as drug carriers.

One of the defining features of cubosomes lies in their high stability and ability to sustain the encapsulated drug's integrity over extended periods. The robust lipid bilayers provide protection to the encapsulated drugs from degradation, enhancing their stability and preserving their therapeutic efficacy. Moreover, the high surface area-to-volume ratio of cubosomes facilitates efficient drug loading, enabling higher drug payloads compared to some other vesicular carriers.

Cubosomes exhibit promise in various drug delivery applications, including oral, topical, and parenteral delivery systems. Their adaptability allows for modifications to optimize drug release kinetics, enabling controlled and sustained release profiles. Additionally, their potential to traverse biological barriers and target specific sites makes them attractive for delivering drugs to specific tissues or cells.

While cubosomes show remarkable potential, challenges in scaling up production and fine-tuning their properties for specific drug delivery needs remain areas of ongoing research. Nonetheless, their unique structural attributes and drug delivery capabilities position cubosomes as a promising vesicular drug delivery system, offering opportunities for tailored and efficient drug administration in diverse medical applications.[24,25]

2.6 Archaeosomes:

Archaeosomes, an innovative class of vesicular drug delivery systems, harness the unique

properties of archaeal lipids, derived from archaea, to offer a promising platform for advanced drug delivery. These specialized vesicles, distinct from conventional phospholipid-based carriers, utilize archaeal lipids with unusual structural characteristics, imparting remarkable stability and potential in drug delivery applications. Archaeosomes' structural design comprises ether-linked lipids, providing enhanced stability and resistance to degradation compared to conventional phospholipids.

The creation of archaeosomes involves incorporating archaeal lipids into vesicular structures through self-assembly in an aqueous environment. The unique features of these lipids, including their unique branched chains and ether linkages, enable the formation of stable bilayered vesicles with increased resistance to harsh conditions such as extreme temperatures or enzymatic degradation. This structural resilience enhances the stability and longevity of encapsulated drugs within archaeosomes, ensuring their preservation and efficacy during storage or transit in the body.

One of the notable attributes of archaeosomes is their biocompatibility and potential for stimulating immune responses. Archaeal lipids have demonstrated adjuvant properties, capable of modulating the immune system and enhancing the body's immune response. This characteristic makes archaeosomes attractive as carriers for vaccines and immunotherapies, offering opportunities to improve vaccine efficacy and stimulate robust immune reactions.

Archaeosomes exhibit promise in various drug delivery applications, including delivering both hydrophilic and hydrophobic drugs. Their stability and adaptability allow for efficient encapsulation of a wide range of pharmaceutical agents, making them versatile carriers for diverse therapeutic molecules. Moreover, their potential to target specific cells or tissues and their ability to traverse biological barriers present opportunities for precise and effective drug delivery strategies.

However, challenges related to large-scale production, standardization, and the incorporation of specific archaeal lipids persist in archaeosomal formulations. Despite these hurdles, ongoing research endeavors aim to harness the unique characteristics of archaeosomes, optimizing their properties and expanding their applications. With their exceptional stability, versatility, and potential immunomodulatory effects, archaeosomes stand as a promising vesicular drug delivery system, offering avenues for tailored and efficient drug administration in various medical contexts.[26,27]

3. Properties and Structural Features:

3.1 Size, morphology and composition:

Vesicular drug delivery systems (DDS) encompass a diverse range of structures characterized by their size, morphology, and composition, each influencing their functionality in drug delivery:

3.1.1 Size:

Vesicular DDS exhibit varying sizes, typically ranging from nanometers to micrometers. This size range profoundly impacts their behavior within biological systems. Nano-sized vesicles, such as liposomes or niosomes, offer advantages like enhanced cellular uptake and penetration due to their smaller dimensions, facilitating targeted drug delivery. Larger vesicles, like transfersomes or archaeosomes, may offer unique advantages in specific applications, such as sustained release or encapsulating larger therapeutic agents.

3.1.2 Morphology:

Vesicular DDS display diverse morphologies, including spherical shapes (like liposomes), elongated or tubular structures (as seen in transfersomes), cubic structures (cubosomes), or irregular shapes depending on their formulation

and composition. These morphological variations impact their surface-to-volume ratio, stability, and interactions with biological membranes, influencing their ability to encapsulate different types of drugs and traverse biological barriers.

3.1.3 Composition:

The composition of vesicular DDS varies widely, primarily consisting of lipids, surfactants, or amphiphilic molecules. Lipid-based vesicles like liposomes, niosomes, or archaeosomes comprise phospholipids, cholesterol, and other lipid components. Surfactant-based vesicles, such as transfersomes, include edge activators along with lipid components. The composition affects the vesicles' stability, drug-loading capacity, and interactions with biological environments, determining their suitability for specific drug delivery applications.

Each aspect size, morphology, and composition—contributes uniquely to the functionality and performance of vesicular DDS. Tailoring these parameters allows for the design of customized drug delivery systems capable of addressing diverse therapeutic needs, ranging from targeted delivery and controlled release to improved stability and compatibility with various drug types.[28-30]

3.2 Encapsulation efficiency:

Encapsulation efficiency in vesicular drug delivery systems (DDS) refers to the percentage of drug molecules successfully entrapped or encapsulated within the vesicles compared to the total amount of drug used during the formulation process. This efficiency is a crucial parameter as it directly influences the therapeutic efficacy and bioavailability of the drug. High encapsulation efficiency ensures that a larger proportion of the drug payload is retained within the vesicles, minimizing wastage and enhancing the effectiveness of the drug delivery system.[31]

Several factors impact encapsulation efficiency in vesicular DDS:

3.2.1 Formulation method:

The method used to prepare vesicles significantly affects encapsulation. Various techniques like film hydration, thin-film hydration, sonication, or extrusion influence the vesicle size, stability, and the ability to encapsulate drugs efficiently.

3.2.2 Physicochemical properties:

The physicochemical characteristics of the drug molecules, such as solubility, hydrophobicity, and molecular weight, affect their incorporation into the vesicles. Hydrophilic drugs might be encapsulated within the aqueous core of vesicles like liposomes, while hydrophobic drugs may be embedded within the lipid bilayers.[32]

3.2.3 Vesicle characteristics:

Parameters such as size, morphology, and composition of the vesicles play a vital role in encapsulation efficiency. Larger vesicles might have higher encapsulation capacity but lower stability, while smaller vesicles may offer better penetration but limited capacity.

3.2.4 Drug-to-lipid ratio:

The ratio of drug to the lipid components during vesicle preparation influences encapsulation efficiency. An optimal ratio ensures maximal drug loading without compromising vesicle stability.

3.2.5 Drug properties:

Some drugs might have specific interactions with vesicle components, affecting encapsulation. For instance, certain drugs might interact with the lipid bilayers, leading to higher or lower encapsulation efficiencies.

Achieving high encapsulation efficiency involves optimizing these factors during the formulation

process. Understanding the interplay between drug characteristics and vesicle properties is essential for designing efficient vesicular drug delivery systems with high encapsulation efficiency, contributing to enhanced therapeutic outcomes and targeted drug delivery.[33,34]

3.3 Surface modifications and targeting strategies:

Surface modifications and targeting strategies in vesicular DDS are pivotal for enhancing specificity, improving efficacy, and reducing off-target effects. These strategies involve altering the surface properties of vesicles to achieve targeted delivery to specific cells, tissues, or organs. Several approaches are employed:

3.3.1 Surface functionalization:

Chemical modifications of the vesicle surface involve attaching ligands, antibodies, peptides, or aptamers onto the vesicle's exterior. These ligands can specifically recognize and bind to receptors or antigens overexpressed on target cells, facilitating targeted delivery. For instance, antibodies or aptamers can be attached to liposomes to enhance their affinity for cancer cells, enabling precise drug delivery to tumors.[35]

3.3.2 Stealth coating:

PEGylation is a common approach involving the attachment of polyethylene glycol (PEG) chains to the vesicle surface. This stealth coating reduces recognition by the immune system, prolongs circulation time by avoiding rapid clearance, and minimizes non-specific interactions, thereby improving the vesicle's bioavailability and targeting to specific sites.

3.3.3 pH or temperature responsiveness:

Some vesicles are engineered to respond to changes in pH or temperature in specific tissues or environments. These stimuli trigger alterations in vesicle structure, leading to controlled drug release or enhanced uptake at the target site. pH-sensitive liposomes, for example, exploit the acidic environment of tumor tissues to release drugs selectively within tumors.[36]

3.3.4 Active targeting and triggered release:

Incorporating stimuli-responsive components or trigger molecules within vesicles enables controlled drug release at specific sites. For instance, enzymes or conditions unique to pathological environments (e.g., tumor microenvironment) can trigger drug release from vesicles, allowing for precise delivery and minimizing systemic exposure.

3.3.5 Physical targeting:

Techniques like magnetic targeting or ultrasound guidance can be utilized to direct vesicles loaded with magnetic nanoparticles or contrast agents to specific locations, offering external control over their localization and drug release.

These surface modifications and targeting strategies enable vesicular DDS to navigate biological barriers, evade clearance mechanisms, and precisely deliver therapeutic agents to desired locations, maximizing drug efficacy while minimizing side effects on healthy tissues. Tailoring these approaches enhances the therapeutic potential of vesicular drug delivery systems for various biomedical applications.[37,38]

4. Drug Loading and Release Mechanisms:

4.1 Loading methods (encapsulation, conjugation):

Drug loading methods in vesicular drug delivery systems (DDS) involve encapsulating or conjugating therapeutic agents into or onto the vesicles. These methods aim to efficiently incorporate drugs within the vesicles while maintaining stability and enhancing their therapeutic potential. The primary approaches are mentioned below:

4.1.1 Encapsulation:

4.1.1.1 Passive encapsulation:

During vesicle preparation, drugs can be entrapped within the vesicle's aqueous core or incorporated within the lipid bilayers based on the drug's physicochemical properties. For instance, hydrophilic drugs are encapsulated within the aqueous core of vesicles like liposomes, while hydrophobic drugs are incorporated into the lipid bilayers. Encapsulation relies on the self-assembly process during vesicle formation.

4.1.1.2 Remote loading:

Some drugs exhibit poor encapsulation efficiency using passive methods. Remote loading techniques involve creating a pH or ion gradient across the vesicle membrane to facilitate drug loading. This gradient-driven method enhances the encapsulation of certain drugs within vesicles by exploiting their differential solubility across the lipid membrane.[39,40]

4.1.2 Conjugation:

4.1.2.1 Surface conjugation:

Drug molecules can be covalently linked or conjugated onto the surface of vesicles. This method involves attaching drugs, targeting ligands, antibodies, or other functional molecules onto the outer surface of vesicles, often through chemical conjugation or coupling reactions. Surface conjugation allows for targeted drug delivery by enhancing the vesicles' affinity for specific cells or tissues.

4.1.2.2 Covalent attachment:

Some drugs or therapeutic agents can be chemically modified to allow covalent attachment to specific sites on the vesicle's surface or within the vesicle structure. This method ensures stable attachment and controlled release of drugs from the vesicles.

Each loading method offers distinct advantages and considerations based on the properties of the drug and the intended application. The choice of loading technique influences drug encapsulation efficiency, release kinetics, stability, and the vesicle's ability to target specific sites within the body. Optimizing these methods is crucial for designing efficient and tailored vesicular drug delivery systems for diverse therapeutic applications.[41,42]

4.2 Controlled and targeted drug release:

Controlled and targeted drug release in vesicular drug delivery systems (DDS) are essential for maximizing therapeutic efficacy while minimizing side effects. These strategies aim to regulate the release kinetics and direct drug delivery to specific sites within the body. The key approaches are mentioned below:

4.2.1 Controlled release:

4.2.1.1 Sustained release:

Vesicular DDS can be engineered to release drugs gradually over an extended period, maintaining therapeutic levels for longer durations. This sustained release is achieved by modulating vesicle characteristics such as size, composition, and membrane properties. Slow diffusion or degradation of vesicle components can also contribute to sustained drug release.

4.2.1.2 Stimuli-responsive release:

Vesicles can be designed to respond to specific environmental cues, such as pH, temperature, enzymes, or external stimuli like light or magnetic fields. pH-sensitive liposomes, for example, release drugs in response to acidic conditions in tumors, leading to targeted delivery and reduced systemic exposure.

4.2.1.3 Triggered release:

Incorporating trigger molecules or stimuli-responsive components within vesicles enables controlled drug release upon encountering

specific conditions or stimuli. External triggers like light, ultrasound, or magnetic fields can induce structural changes in vesicles, leading to on-demand drug release at targeted sites.[43,44]

4.2.2 Targeted release:

4.2.2.1 Active targeting:

Surface modifications with targeting ligands or antibodies enable vesicles to recognize and bind to specific receptors or antigens on target cells or tissues. This active targeting enhances drug accumulation at desired sites while reducing non-specific interactions, enabling precise delivery.

4.2.2.2 Passive targeting:

Vesicles can passively target specific tissues or organs based on their size, shape, or surface properties. For instance, liposomes tend to accumulate in inflamed or leaky tissues due to their enhanced permeation and retention effect, a passive targeting mechanism commonly exploited for cancer therapy.

Combining controlled and targeted release strategies allows for tailored drug delivery, ensuring therapeutic agents reach the intended site at the required dose and duration. Optimization of these release mechanisms is crucial in developing effective vesicular DDS for diverse therapeutic applications, offering enhanced treatment outcomes and reduced adverse effects.[45]

4.3 Factors influencing drug release kinetics:

Several factors influence drug release kinetics in vesicular drug delivery systems, impacting the rate, extent, and duration of drug release. These factors play a crucial role in determining the effectiveness of the drug delivery system. Some key influences include:

4.3.1 Vesicle characteristics:

Smaller vesicles typically exhibit faster release due to increased surface area-to-volume ratio, facilitating quicker diffusion of drugs. Lipid composition and bilayer characteristics influence membrane permeability and drug encapsulation, impacting release kinetics. The stability of vesicles under physiological conditions determines the integrity of the vesicle structure, affecting the controlled release of drugs.[46]

4.3.2 Drug properties:

Drug solubility in vesicle components affects its release; hydrophilic drugs tend to release faster from the aqueous core, while hydrophobic drugs from lipid bilayers. Smaller molecules generally diffuse more rapidly than larger ones, impacting release kinetics. Encapsulation efficiency and method used to load drugs into vesicles affect their subsequent release behavior.

4.3.3 Environmental factors:

pH-sensitive vesicles respond to changes in pH, triggering drug release at specific sites within the body, such as tumors with acidic environments. Changes in temperature can influence the fluidity and permeability of vesicle membranes, affecting drug release rates.[47]

4.3.4 Release mechanisms:

Controlled drug release through diffusion involves drug molecules moving across vesicle membranes, influenced by concentration gradients and membrane permeability. Some vesicular systems degrade or erode over time, leading to gradual drug release as the vesicle structure breaks down.

4.3.5 Stimuli-Responsive Systems:

Vesicles engineered to respond to external stimuli like light, magnetic fields, or ultrasound trigger drug release, offering on-demand control over drug delivery.[48]

Figure 2 describes the advantages of vesicular DDS.

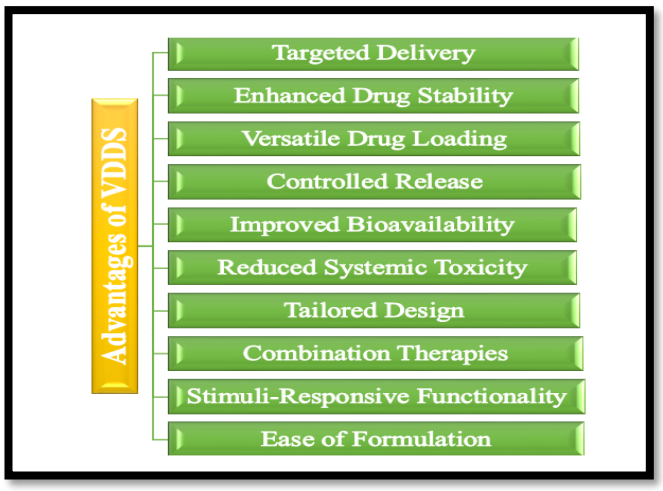

Figure 2. Advantages of Vesicular DDS

5. Challenges and Limitations:

Vesicular DDS exhibit remarkable potential, yet they encounter significant challenges. The complexity in formulating these systems demands precise control over parameters like size and composition, posing hurdles for large-scale production. Stability concerns arise, as vesicles may destabilize, leading to premature drug release or aggregation, impacting their efficacy during storage and administration. Achieving high drug-loading capacity without compromising stability remains a challenge, especially for certain drug types. Additionally, VDDS encounter barriers penetrating biological tissues effectively, limiting their application in targeted therapies. Issues regarding their in vivo longevity, rapid clearance, and degradation further impede their efficacy. Translation to clinical use demands addressing scale-up challenges, reproducibility, and meeting regulatory standards. Storage complexities, potential immunogenicity, and cost considerations also contribute to the limitations. Achieving specific targeting while ensuring safety and regulatory compliance poses a continued challenge. Addressing these hurdles requires ongoing research to refine formulation techniques, enhance stability, improve targeting efficiency, and ensure safety for realizing the full potential of VDDS in clinical applications.[49-50]

6. Current Advances and Research Trends:

Ongoing advancements and research trends in Vesicular DDS are shaping a promising landscape focused on improving their effectiveness and versatility. Innovations in formulation techniques, such as microfluidics and nano-precipitation, aim to enhance vesicle stability and scalability for larger-scale production. A key focus lies in creating smart vesicles that respond to specific triggers like pH or temperature, allowing precise control over drug release. Hybrid systems combining vesicles with other nanomaterials are emerging, offering multifunctional platforms for improved targeting and simultaneous delivery of multiple therapeutics. Moreover, theranostic applications integrating diagnostic and therapeutic capabilities within vesicles hold promise for disease diagnosis and treatment monitoring. Biomimetic vesicles designed to mimic biological entities enhance biocompatibility and targeting ability, while refined targeting strategies using ligands aid in precise drug delivery. Efforts also emphasize the translation of VDDS from lab research to clinical use, addressing challenges in scale-up and regulatory compliance. Computational tools are instrumental in optimizing vesicle design and predicting their behavior. Collectively, these trends underscore a concerted effort to overcome limitations and expand the therapeutic potential of VDDS in diverse healthcare applications.[51,52]

7. Conclusion:

In conclusion, Vesicular Drug Delivery Systems (VDDS) present a multifaceted approach with immense potential in revolutionizing drug delivery for various medical applications. While offering advantages such as targeted delivery, enhanced stability, and controlled release, VDDS encounter challenges like formulation complexity, stability issues, and limited targeting efficiency. Current research is steering toward innovative formulations, stimuli-responsive systems, and hybrid approaches to overcome

these limitations. The pursuit of smart, biomimetic, and theranostic vesicles signifies a paradigm shift towards more precise and personalized medicine. Efforts to bridge the gap between research and clinical translation highlight the necessity of scalability, safety, and regulatory compliance. As these advancements progress, VDDS are poised to offer sophisticated solutions, ushering in a new era of tailored and effective drug delivery strategies in healthcare.

8. Reference:

1. Gupta S, Kumar P. Drug Delivery Using Nanocarriers: Indian Perspective. *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences*. 2012;82:167-206.

2. Ummadi S, Shravani B, Rao NR, Reddy MS, Sanjeev B. Overview on Controlled Release Dosage Form. *System*. 2013;7(8):51-60.

3. Elliott RO, He M. Unlocking the Power of Exosomes for Crossing Biological Barriers in Drug Delivery. *Pharmaceutics*. 2021;13(1):122.

4. Lasic DD, Barenholz Y. Handbook of Nonmedical Applications of Liposomes: Theory and Basic Sciences. *CRC Press*. 1996.

5. Arora N, Agarwal S, Murthy RS. Latest Technology Advances in Cosmaceuticals. *International Journal of Pharmaceutical Sciences and Drug Research*. 2012;4(3):168-82.

6. Godin B, Touitou E. Ethosomes: New Prospects in Transdermal Delivery. *Critical Reviews™ in Therapeutic Drug Carrier Systems*. 2003;20(1).

7. Sallam N, Sanad R, Khafagy ES, Ahmed M, Ghourab M, Gad S. Colloidal Delivery of Drugs: Present Strategies and Conditions. *Records of Pharmaceutical and Biomedical Sciences*. 2021;5:40-51.

8. Das Kurmi B, Tekchandani P, Paliwal R, Rai Paliwal S. Transdermal Drug Delivery: Opportunities and Challenges for Controlled Delivery of Therapeutic Agents Using Nanocarriers. *Current Drug Metabolism*. 2017;18(5):481-95.

9. Kumar P, Gulbake A, Jain SK. Liposomes a Vesicular Nanocarrier: Potential Advancements in Cancer Chemotherapy. *Critical Reviews™ in Therapeutic Drug Carrier Systems*. 2012;29(5).

10. Luo Y, Sun M, Tan L, Li T, Min L. Nano-Based Drug Delivery Systems: Potential Developments in the Therapy of Metastatic Osteosarcoma—A Narrative Review. *Pharmaceutics*. 2023;15(12):2717.

11. Bakhshi S, Shoari A, Alibolandi P, Ganji M, Ghazy E, Rahdar A, Fathi-karkan S, Pandey S. Emerging Innovations in Vincristine-Encapsulated Nanoparticles: Pioneering A New Era in Oncological Therapeutics. *Journal of Drug Delivery Science and Technology*. 2023;14:105270.

12. Rawat M, Singh D, Saraf SA, Saraf S. Nanocarriers: Promising Vehicle for Bioactive Drugs. *Biological and Pharmaceutical Bulletin*. 2006;29(9):1790-8.

13. Bozzuto G, Molinari A. Liposomes as Nanomedical Devices. *International Journal of Nanomedicine*. 2015;975-99.

14. Has C, Sunthar P. A Comprehensive Review on Recent Preparation Techniques of Liposomes. *Journal of Liposome Research*. 2020;30(4):336-65.

15. Li M, Du C, Guo N, Teng Y, Meng X, Sun H, Li S, Yu P, Galons H. Composition Design and Medical Application of Liposomes. *European Journal of Medicinal Chemistry*. 2019;164:640-53.

16. Kauslya A, Borawake PD, Shinde JV, Chavan RS. Niosomes: A Novel Carrier Drug Delivery System. *Journal of Drug Delivery and Therapeutics*. 2021;11(1):162-70.

17. Thabet Y, Elsabahy M, Eissa NG. Methods for Preparation of Niosomes: A Focus on Thin-film Hydration Method. *Methods*. 2022;199:9-15.

18. Muzzalupo R, Mazzotta E. Do Niosomes have a Place in the Field of Drug Delivery?. *Expert Opinion on Drug Delivery*. 2019;16(11):1145-7.

19. Kumar N, Dubey A, Mishra A, Tiwari P. Ethosomes: A Novel Approach in Transdermal Drug Delivery System. *International Journal of Pharmacy & Life Sciences*. 2020;11(5).

20. Chauhan N, Vasava P, Khan SL, Siddiqui FA, Islam F, Chopra H, Emran TB. Ethosomes: A Novel Drug Carrier. *Annals of Medicine and Surgery*. 2022;104595.

21. Chaurasiya P, Ganju E, Upmanyu N, Ray SK, Jain P. Transfersomes: A Novel Technique for Transdermal Drug Delivery. *Journal of Drug Delivery and Therapeutics*. 2019;9(1):279-85.

22. Akram MW, Jamshaid H, Rehman FU, Zaeem M, Khan JZ, Zeb A. Transfersomes: A Revolutionary Nanosystem for Efficient Transdermal Drug Delivery. *AAPS PharmSciTech*. 2022;23:1-8.

23. Oyarzún P, Gallardo-Toledo E, Morales J, Arriagada F. Transfersomes as Alternative Topical Nanodosage Forms for the Treatment of Skin Disorders. *Nanomedicine*. 2021;16(27):2465-89.

24. Gaballa SA, El Garhy OH, Abdelkader H. Cubosomes: Composition, Preparation, and Drug Delivery Applications. *Journal of Advanced Biomedical and Pharmaceutical Sciences*. 2020;3(1):1-9.

25. Barriga HM, Holme MN, Stevens MM. Cubosomes: The Next Generation of Smart Lipid Nanoparticles?. *Angewandte Chemie International Edition*. 2019;58(10):2958-78.

26. Santhosh PB, Genova J. Archaeosomes: New Generation of Liposomes Based on Archaeal Lipids for Drug Delivery and Biomedical Applications. *ACS Omega*. 2022;8(1):1-9.

27. Sedlmayr V, Horn C, Wurm DJ, Spadiut O, Quehenberger J. Archaeosomes Facilitate Storage and Oral Delivery of Cannabidiol. *International Journal of Pharmaceutics*. 2023;645:123434.

28. van der Koog L, Gandek TB, Nagelkerke A. Liposomes and Extracellular Vesicles as Drug Delivery Systems: A Comparison of Composition, Pharmacokinetics, and Functionalization. *Advanced Healthcare Materials*. 2022;11(5):2100639.

29. Pande S. Liposomes for Drug Delivery: Review of Vesicular Composition, Factors Affecting Drug Release and Drug Loading in Liposomes. *Artificial Cells, Nanomedicine, and Biotechnology*. 2023;51(1):428-40.

30. Witika BA, Mweetwa LL, Tshiamo KO, Edler K, Matafwali SK, Ntemi PV, Chikukwa MT, Makoni PA. Vesicular Drug Delivery for the Treatment of Topical Disorders: Current and Future Perspectives. *Journal of Pharmacy and Pharmacology*. 2021;73(11):1427-41.

31. Breitsamer M, Winter G. Vesicular Phospholipid Gels as Drug Delivery Systems for Small Molecular Weight Drugs, Peptides and Proteins: State of the Art Review. *International Journal of Pharmaceutics*. 2019;557:1-8.

32. Zacheo A, Bizzarro L, Blasi L, Piccirillo C, Cardone A, Gigli G, Ragusa A, Quarta A. Lipid-Based Nanovesicles for Simultaneous Intracellular Delivery of Hydrophobic, Hydrophilic, and Amphiphilic Species. *Frontiers in Bioengineering and Biotechnology*. 2020;8:690.

33. Kooijmans SA, de Jong OG, Schiffelers RM. Exploring Interactions Between Extracellular Vesicles and Cells for Innovative Drug Delivery System Design. *Advanced Drug Delivery Reviews*. 2021;173:252-78.

34. de Jong OG, Kooijmans SA, Murphy DE, Jiang L, Evers MJ, Sluijter JP, Vader P, Schiffelers RM. Drug Delivery with Extracellular Vesicles: From Imagination to Innovation. *Accounts of Chemical Research*. 2019;52(7):1761-70.

35. Mohammadi AH, Ghazvinian Z, Bagheri F, Harada M, Baghaei K. Modification of Extracellular Vesicle Surfaces: An Approach for Targeted Drug Delivery. *BioDrugs*. 2023;24:1-22.

36. Raza A, Rasheed T, Nabeel F, Hayat U, Bilal M, Iqbal HM. Endogenous and Exogenous Stimuli-Responsive Drug Delivery Systems for Programmed Site-Specific Release. *Molecules*. 2019;24(6):1117.

37. Tiwari P, Yadav K, Shukla RP, Gautam S, Marwaha D, Sharma M, Mishra PR. Surface Modification Strategies in Translocating Nano-Vesicles Across Different Barriers and the Role of Bio-Vesicles in Improving Anticancer Therapy. *Journal of Controlled Release*. 2023;363:290-348.

38. Gaurav I, Thakur A, Iyaswamy A, Wang X, Chen X, Yang Z. Factors Affecting Extracellular Vesicles Based Drug Delivery Systems. *Molecules*. 2021;26(6):1544.

39. Wang N, Cheng X, Li N, Wang H, Chen H. Nanocarriers and Their Loading Strategies. *Advanced Healthcare Materials*. 2019;8(6):1801002.

40. Liu Y, Yang G, Jin S, Xu L, Zhao CX. Development of High-Drug-Loading Nanoparticles. *ChemPlusChem*. 2020;85(9):2143-57.

41. George D, Maheswari PU, Begum KM. Chitosan-Cellulose Hydrogel Conjugated with L-Histidine and Zinc Oxide Nanoparticles for Sustained Drug Delivery: Kinetics and In-vitro Biological Studies. *Carbohydrate Polymers*. 2020;236:116101.

42. Rezk AI, Obiweluozor FO, Choukrani G, Park CH, Kim CS. Drug Release and Kinetic Models of Anticancer Drug (BTZ) from a pH-responsive Alginate Polydopamine Hydrogel: Towards Cancer Chemotherapy. International journal of biological macromolecules. 2019 Dec 1;141:388-400.

43. Kauscher U, Holme MN, Björnmalm M, Stevens MM. Physical Stimuli-Responsive Vesicles in Drug Delivery: Beyond Liposomes and Polymersomes. *Advanced Drug Delivery Reviews*. 2019;138:259-75.

44. Marchianò V, Matos M, Serrano-Pertierra E, Gutiérrez G, Blanco-López MD. Vesicles as Antibiotic Carrier: State of Art. *International Journal of Pharmaceutics*. 2020;585:119478.

45. Ashique S, Sandhu NK, Chawla V, Chawla PA. Targeted Drug Delivery: Trends and Perspectives. *Current Drug Delivery*. 2021;18(10):1435-55.

46. Maritim S, Boulas P, Lin Y. Comprehensive Analysis of Liposome Formulation Parameters and Their Influence on Encapsulation, Stability and Drug Release in Glibenclamide Liposomes. *International Journal of Pharmaceutics*. 2021;592:120051.

47. Ghosh R, Dey J. PH-responsive Vesicle Formation by PEGylated Cholesterol Derivatives: Physicochemical Characterization, Stability, Encapsulation, and Release Study. *Langmuir*. 2020;36(21):5829-38.

48. Joy R, George J, John F. Brief Outlook on Polymeric Nanoparticles, Micelles, Niosomes, Hydrogels and Liposomes: Preparative Methods and Action. *ChemistrySelect*. 2022;7(6):e202104045.

49. Hernando S, Santos-Vizcaíno E, Igartua M, Hernandez RM. Targeting the Central Nervous System: From Synthetic Nanoparticles to Extracellular Vesicles—Focus on Alzheimer's and Parkinson's Disease. *Wiley Interdisciplinary*

Reviews: Nanomedicine and Nanobiotechnology. 2023:e1898.

50. Omidian H, Babanejad N, Cubeddu LX. Nanosystems in Cardiovascular Medicine: Advancements, Applications, and Future Perspectives. *Pharmaceutics*. 2023;15(7):1935.

51. Hernandez-Oller L, Seras-Franzoso J, Andrade F, Rafael D, Abasolo I, Gener P, Schwartz Jr S. Extracellular Vesicles as Drug Delivery Systems in Cancer. *Pharmaceutics*. 2020;12(12):1146.

52. Burnouf T, Agrahari V, Agrahari V. Extracellular vesicles as nanomedicine: Hopes and hurdles in clinical translation. International journal of nanomedicine. 2019:8847-59.