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Review Article

Hyaluronic Acid-Coated Niosomes: A Promising Drug Delivery System with Potential Applications

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ABSTRACT

Targeted drug delivery is a critical strategy to enhance drug efficacy while minimizing side effects. Niosomes, a versatile drug carrier system, have gained prominence in this field. Niosomes, constructed from non-ionic surfactants and cholesterol, create minute lamellar formations, providing a mechanism for the encapsulation of both hygroscopic and oleopobic drugs. These structures exhibit numerous advantages, including biocompatibility, stability, and the ability to protect labile drugs. Hyaluronic acid (HA), a natural biopolymer, is valuable in drug delivery vehicles because of its biologically inert, decomposable, and site-specificity. HA is widely distributed in the body and has significant roles in various cellular processes, making it an attractive component for drug carriers. Furthermore, HA enhances drug permeation, with its effectiveness influenced by molecular weight. HA-coated niosomes have shown promise in various applications. In ocular drug delivery, they improve bioavailability by extending drug retention in the eye, overcoming the limitations of traditional eye drops. In the treatment of inflammation, these niosomes exhibit sustained anti-inflammatory effects, offering a potential solution for addressing inflammatory conditions. For anticancer drug delivery, CD44-targeted nanoparticles designed with HA enhance drug delivery efficiency to cancer cells, showing increased cytotoxicity and tumor growth inhibition. This review underscores the potential of HA-coated niosomes as a groundbreaking approach in advanced drug delivery. Their adaptability and ability to combine the strengths of niosomes and HA hold significant promise across diverse therapeutic domains, including ophthalmology, inflammation, and cancer treatment. This synergy represents a significant step toward personalized medicine and improved patient outcomes.

INTRODUCTION

Targeted drug delivery aims to concentrate medication in specific tissues, minimizing its impact on surrounding areas. This approach maximizes drug efficacy and reduces wastage. Diverse carriers like immunoglobulins, liposomes, and niosomes have been used for effective drug targeting [1]. Niosomes are a top carrier choice. Vesicles are formed as a effect of the self-structuring of non-ionic surfactants, a concept initially investigated by researchers in the cosmetic industry during the 1970s. Niosomes are microscopic lamellar structures formed by hydrating non-ionic surfactants from the alkyl or dialkyl polyglycerol ether category along with cholesterol [2]. Hyaluronic acid stands as a widely employed biopolymer in crafting drug delivery systems. Its popularity arises from its biocompatibility, biodegradability, lack of immunogenicity, and inherent targeting capabilities [3]. HA assumes a pivotal role within the extracellular matrix, influencing diverse cellular reactions including angiogenesis, cell signalling, tissue architecture, wound healing, and tissue hydration [4, 5]. Furthermore, HA is prevalent in the vitreous humour of the eye, synovial fluid, and various connective tissues [6]. It is binding to CD44 and utilization of the EPR effect enables nanocarriers to actively target tumors, enhancing cancer cell uptake through HA-CD44 receptor-mediated endocytosis [7].

However, in the vast landscape of drug delivery systems, it becomes imperative to delineate the significance of hyaluronic acid-coated niosomes in comparison to other carriers. This review aims

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to explore and underscore the unique attributes and advantages that set HA-coated niosomes apart, making them a promising and distinctive player in the field of targeted drug delivery.

Niosomes: Structured Drug Delivery Systems

Niosomes constitute a dual-layered configuration composed of non-ionic surfactants. These bilayer structures, characterized by thermodynamic stability, manifest under specific conditions: the appropriate blending of surfactants and cholesterol, accompanied by temperatures surpassing the gel-to-liquid transition point [8, 9]. Within this bilayered configuration, a void space is present at the core. Due to their unique geometry, niosomes have the ability to encapsulate both hydrophilic and hydrophobic drugs within their structure. The entrapment of hydrophilic pharmaceuticals can transpire within the central aqueous domain or might involve adsorption onto the surface of the bilayer. Conversely, hydrophobic drugs navigate into the bilayer structure via partitioning [8, 10].

Advantages of Niosomes:

- Offer unique advantages as nanocarriers, including stability, functionalization capability, and making them ideal for achieving high tumor accumulation and cellular internalization for drug release [3].
- Niosomes offer simplicity in dosage form production and administration with ready-to-use dispersions [8].
- They increase the oral bioavailability and skin penetration of drugs [10].
- They exhibit a high patient compliance, because of the water-based suspension of niosomes [10].
- The surfactants employed in niosome formulation are biodegradable, biocompatible, and non-immunogenic [11].
- The production method for niosomes doesn't involve the use of undesirable solvents, making it suitable for routine and large-scale manufacturing [11].
- Niosomes exhibit chemical stability, eliminating the need for special storage or handling conditions [11].
- Physicochemical properties of niosomes, including size, shape, and fluidity, are easily adjustable by altering their composition and production method [11].
- Niosomes have the capacity to enclose a significant quantity of material within a compact vesicular structure [11].
- The structural design of niosomes offers protection to encapsulated drug ingredients from external and internal factors, making them suitable for delivering labile and sensitive drugs [11].

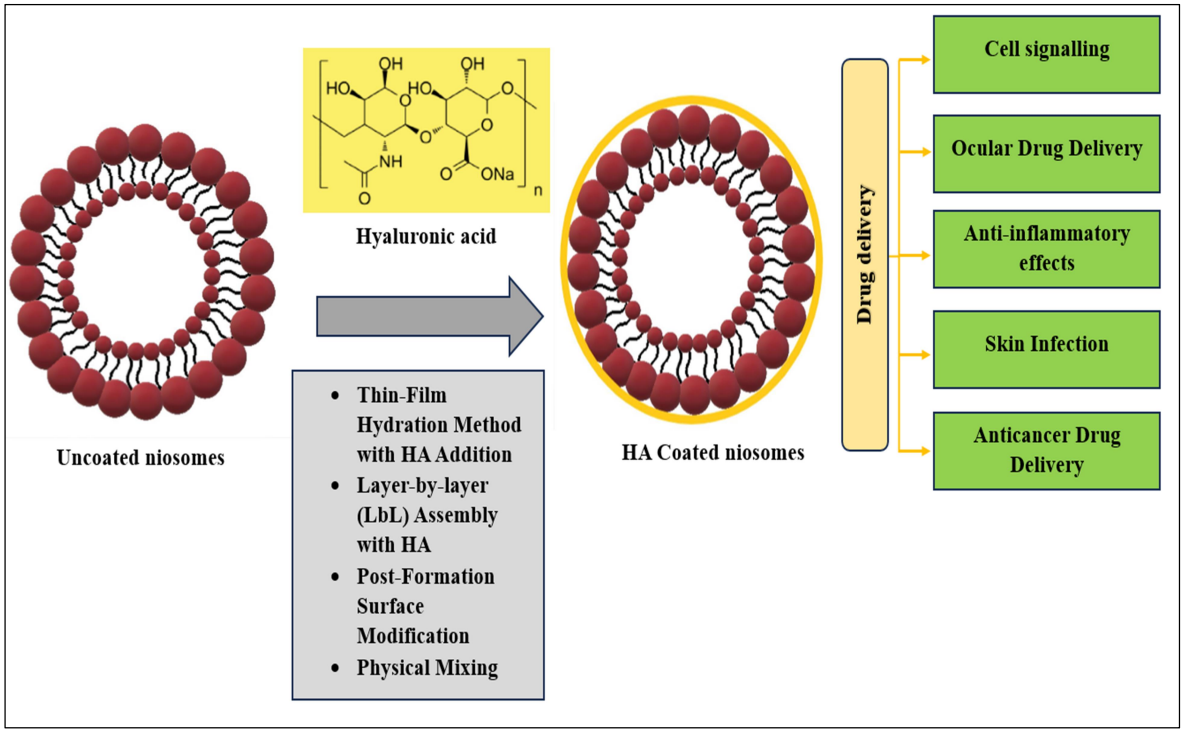

Figure 1: Nanostructured drug delivery system featuring uncoated niosomes (left) and hyaluronic acid coated niosomes (right) for enhanced drug delivery

Challenges and Opportunities of Niosomes:

- Discomes (Large disc-like niosomes) become more leakier with rising temperature, presenting a stability concern [8].
- Niosomes come with disadvantages that could affect their shelf life, including physical and chemical instability [12].
- Drawbacks also encompass concerns such as vesicle aggregation, fusion of vesicles, and the possible leakage or hydrolysis of encapsulated drugs [12].
- Methods for preparing multilamellar vesicles, like extrusion or sonication, are time-consuming and might require specialized processing equipment [12].

The Multifaceted Role of Hyaluronic Acid

Hyaluronic acid, alternatively known as hyaluronan, consists of a linear glycosaminoglycan (GAG) comprising N-acetyl-D-glucosamine and D-glucuronic acid. The repetitive disaccharide units are connected through β-1,4-glycosidic bonds [13]. HA has an extensive distribution within the extracellular matrix (ECM) of numerous vertebrate connective tissues [13, 14]. In the skin, HA constitutes 50% or more of the overall HA content within the body [15]. HA that is commercially accessible can be obtained from animal sources, such as skin, joints, the vitreous humour of the eye, synovial fluid, umbilical cord, and rooster comb, among others [13, 16]. Alternatively, HA can be obtained through bacterial fermentation, utilizing microorganisms such as *Pasteurella multocida*, *Streptococcus equi subsp*. equi, and subsp. *Zooepidemicus* [17, 18]. Using polymerizing enzymes like *Pasteurella multocida* HA synthase (pmHAS) extracted from bacteria, HA can also be synthesized through chemoenzymatic methods. This innovative approach enables the production of medical-tagged or radioactive oligosaccharides, facilitating their application within the biomedical field [19].

Hyaluronic Acid Encompasses a Wide Array of Crucial Functionalities, Including [20]:

- Cell Signaling.
- Wound Healing/Tissue Regeneration.
- Ophthalmic Surgeries.
- Treatment of Joint Disease as a Lubricant.
- Management of Bone and Skin Inflammatory Diseases.
- Tumor-Specific Delivery Systems.

HA's Impact on Drug Permeation and Delivery

The permeability of hyaluronic acid (HA) exhibits a direct correlation with its molecular weight [20]. As a permeation enhancer, and its ability to enhance the permeability of nutraceuticals and drugs is intricately linked to its molecular weight. Skin permeability follows a hierarchy: low molecular weight (In the range of approximately 5–50 kDa) > (Medium molecular weight, around 100–300 kDa) > (High molecular weight, around 600–1200 kDa) HA. For topical anti-ageing applications, HA molecules commonly utilized have a diameter of around 3000 nm [21]. Notably, high molecular weight HA (>600 kDa) demonstrates limited permeability through the skin, forming a protective hydration layer on the skin surface. Conversely, low molecular weight HA can penetrate the stratum corneum, epidermis, and even reach deeper dermal layers [20].

Methods for Coating Hyaluronic Acid on Niosomes

Coating hyaluronic acid (HA) onto niosomes involves a specialized set of methods that consider the lipid-based nature of niosomes and the need for effective coating of HA. Here are some common methods used for coating hyaluronic acid on niosomes:

1. Thin-Film Hydration Method with HA Addition:

In the niosome formulation detailed in the research article [22], our primary focus was the integration of a hyaluronic acid (HA) coating. Following the initial step of utilizing the thin-film hydration method to create niosomes, wherein Span 60 or Tween 60 was dissolved with cholesterol at a 1:1 mM ratio in 20 mL of absolute ethanol within a round-bottom flask, the thin film was then subjected to HA coating. To achieve this, various concentrations of HA (ranging from 0% to 10% w/w enhancer concerning the total lipid content) were prepared by dissolving HA powder in deionized water. Subsequently, the HA solution was incorporated into the hydration process. Notably, HA, renowned for its excellent biocompatibility and capacity to enhance drug delivery and skin penetration, played a pivotal role in tailoring the niosome surface properties. The inclusion of HA as a coating material holds significant promise for enhancing the pharmaceutical and cosmetic applications of these niosome formulations.

The assessment of average particle size in the formulations at various concentrations of HA revealed a notable rise in the mean particle size [22].

2. Layer-by-Layer (LbL) Assembly with HA:

In the study [23], the emphasis lay in creating aminated mesoporous silica nanoparticles (AMSN) with hyaluronic acid (HA) coatings. The synthesis began with mesoporous silica nanoparticles (MSN) formation, followed by maximizing HA coating efficiency using (2, 2, 6, 6-Tetramethyl-1- piperidinyl oxyl) TEMPO-mediated oxidation. The procedure involved dissolving 0.5 g of HA in 50.0 mL of distilled water, adjusting pH to neutral, and adding TEMPO and NaBr to prevent gel formation. Stirring under an inert atmosphere, followed by neutralization with 0.5 M NaOH and ethanol addition, yielded HA-coated AMSN, demonstrating potential as a stimuli-responsive drug carrier.

The SEM micrographs of HA, particles exhibited aggregation leading to a clumped mass. This highlights potential challenges associated with achieving uniform size and well-defined particle morphology using this methodology [23].

3. Post-Formation Surface Modification:

In the study [24], the focus was on preparing HA-modified cationic niosomes (Hyaluronic Acid-modified cationic niosomes). The HA-DOPE (Hyaluronic Acid-1,2-dioleoyl-sn-glycero-3-phosphoethanolamine) conjugate used was synthesized with modifications. Briefly, Hyaluronic Acid (HA) was preactivated with EDC (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide) at pH 4 and combined with a DOPE (1,2-dioleoyl-sn-glycero-3-phosphoethanolamine) suspension. After 24 hours at 37°C, the conjugate was purified and stored. HA-C-niosomes (Hyaluronic Acid-modified cationic niosomes) were prepared via an ethanol injection method, combining surfactants and lipids in ethanol, and then injecting the mixture into distilled water. After ethanol removal, cationic niosomes (C-niosomes) were created. HA-C-niosomes were formed by adding 10% and 20% HA-DOPE to C-niosome solutions and incubating for 40 minutes at 37°C.

The primary challenge observed in this method revolves around achieving precise control over the size and characteristics of niosomes during the ethanol injection process. Key factors influencing the final outcome include the injection rate and the ratio of Tween 80 to squalene. Maintaining optimal control over these parameters is crucial to avoid issues such as unfavorable size distribution, aggregation, and suboptimal surface modification post-formation. Thus, the primary challenge lies in finely tuning the injection rate and formulation ratios to consistently obtain niosomes with the desired attributes [24].

4. Physical Mixing and Entrapment with HA:

In the preparation of niosomal vesicles following the method outlined by [3], non-ionic surfactants, Span 20 or Tween 20, were combined with cholesterol. Hepes buffer was introduced to create multilamellar vesicles, followed by sonication. Purification was achieved through gel permeation chromatography with Hepes buffer as the eluent. The HA-Chol derivative, as described by Hanieh, was synthesized with a modification of a previously described method. Cholesterol was derivatized with 4-bromo-butyric acid to create Chol-Br, followed by the addition of HA. The reaction resulted in the HA-Chol derivative, which was dialyzed and freeze-dried, yielding 80%. For coating niosomes with the HA-Chol Derivative, solutions of HA-Chol with varying concentrations, as per Hanieh's procedure, were tested. These solutions were added to the niosomal dispersion. The resulting preparations were stirred at room temperature, monitoring functionalization progression.

The addition of HA to the results gives rise to an increase in the size of all niosomal specifics. The measured mean hydrodynamic fringe enlarges as a function of HA [3].

Hyaluronic Acid (HA) Coated Niosome Formulations:

Table 1 provides a comprehensive overview of research efforts focused on Hyaluronic Acid (HA)-coated niosome formulations. These innovative delivery systems aim to enhance drug delivery efficiency, particularly in topical and transdermal applications. The table summarizes key findings and insights from studies utilizing HA-coated niosomes, shedding light on their diverse applications in the field of drug delivery.

Applications:

1. Cell Signalling:

A dual advantage emerges when nanocarriers are endowed with coatings of anionic polysaccharides such as HA or alginate.

Table 1: Comparative Analysis of Hyaluronic Acid (HA)-Coated Niosome Formulations

Sr. No.	API/Drug	Niosome Components	Method of HA Coating	Significance of HA Coating on Niosomes	References
1	*Centella asiatica*	Span 60, Tween 60 and Cholesterol	Thin-Film Hydration Method with HA Addition	To enhance dermal absorption, permeation and accumulation in viable epidermis and dermis layers.	[22]
2	Tacrolimus	Poloxamer 188, Soybean phosphatidylcholine and Cholesterol	Physical Mixing	Improved its ophthalmic bioavailability, and corneal permeability enhancement	[25]
3	Epirubicin	Span 20, Span 60, Span 80, Cholesterol	Physical Mixing	Enhance cellular uptake	[26]
4	5-flurouracil	Tetraethylorthosilicate (TEOS), Cetyltrimethylammoniumbromide (CTAB), 3-aminopropyltriethoxysilane	Layer-by-Layer	Enhanced efficiency of drug loading and controlled drug released	[23]
5	Calcein	Tween 20, Span 20, Cholesterol	Physical Mixing	Reinforced active tumor targeting by nanocarriers, improving drug uptake	[3]
6	Fluorescein isothiocyanate (FITC)	Tween 80, Span 20	Physical Mixing	Efficiency of transdermal permeation	[27]
7	*Centella asiatica*	Span 60, Span 40, Tween 60, Cholesterol	Post-Formation Surface Modification	Enhancing cellular uptake, sustained drug released	[28]

These coatings result in a reduction of both protein adsorption and the pace of macrophage uptake. The observed effects are attributed to the presence of the HA coating on the nanocarrier's surface, introducing a negative charge that hinders protein adsorption. This unique attribute allows for precise targeting, specifically to cells possessing CD44 receptors, circumventing the indiscriminate cell-uptake mechanisms associated with unmodified nanoparticles. This strategic application of anionic polysaccharide coatings on nanocarriers not only curtails undesired interactions but also enhances the potential for targeted and effective drug delivery [29].

Niosomes composed of Tween 20 and Span 20 can be effectively coated with HA-Chol. The derivatization of cholesterol enables a secure attachment of the HA molecule to the niosomal surface, as evidenced by various characterization techniques. The specifics of the coating process depend on the initial concentration of HA-Chol. In our preliminary cell-free interaction studies, it is observed that the concentration of HA-Chol seems to influence the interaction between niosomes and cell-mimicking membranes. Specifically, a favorable interaction with the cell-mimicking membrane occurs when the initial HA-Chol content in niosomes is relatively low. Subsequent focused studies with cell-supported models will address the stability of HA-Chol-coated niosomes *in vivo*, their selectivity for CD44-bearing cells, and their bioavailability [3].

2. Innovations in Ocular Drug Delivery: HA-Coated Niosomes

The predominant approach for treating various ophthalmic diseases involved topical eye drops to the lower cul-de-sac of the eyes. Nonetheless, owing to the eye's physiological and anatomical limitations, a mere 5% of the administered drug could successfully traverse the cornea and achieve therapeutic levels within intraocular tissues following eye drop application.[30,31] An approach aimed at enhancing ocular drug bioavailability involved the utilization of mucoadhesive polymers as carriers within eye drop formulations [32].

These mucoadhesive polymers lengthened the medication's residence duration on the ocular surface, reduced drug loss, and ultimately enhanced bioavailability because of their interaction with the precorneal mucin layer via non-covalent bonding which is HA, [33]) has received increasing consideration in the administration of ocular drugs since it is a natural part of the vitreous body and aqueous humour of the eye [34].

The promise of HA-based viscoelastic solutions as a mucoadhesive adjuvant has led to their widespread application in ocular medication delivery systems [33, 35]. The mucoadhesive feature of HA, when added to aqueous ophthalmic formulations, enhanced the compositions' six ocular contact times, which in turn increased the drug bioavailability [36-38].

Researchers developed FK506 HA-coated niosomes, merging niosomes with HA to enhance ophthalmic drug delivery. HA-coating improved adhesion to mucin, extended drug retention in the eye, and increased drug presence in the aqueous humour. Bioavailability was significantly enhanced, by demonstrating a 2.3-fold or 1.2-fold increase compared to non-coated niosomes or suspension. This innovative approach holds promise for effective ocular drug delivery, with the potential to transform treatment outcomes [39].

3. Innovations in Therapeutic Strategies: HA-Coated Niosomes for Inflammation

In a recent study, the *in vivo* anti-inflammatory effects of niosomes containing hyaluronan were assessed and found to surpass the performance of conventional niosomes and plain suspensions of curcumin and quercetin at all-time intervals. Both hyaluronan-containing niosomes and conventional niosomes exhibited more potent anti-inflammatory effects when compared to plain suspensions. Interestingly, while the effects of plain suspensions decreased over 24 hours, hyaluronan-containing niosomes and conventional niosomes showed increasing effects, except for a slight dip in niosome effects after 4 hours. The study also included empty hyaluronan-containing niosomes as a negative control, which consistently demonstrated an 8-10% anti-inflammatory effect over time. These findings highlight the potential of hyaluronan-containing niosomes as a robust and sustained approach for addressing inflammation. This research holds promise for advancing targeted anti-inflammatory therapies using innovative delivery systems [40].

While the current literature presents limited studies on the anti-inflammatory effects of the formulated niosomes, our findings are supported by the work of (Ghadi et al., 2019), as detailed in [40]. This study demonstrated a significant reduction in inflammatory markers, providing valuable insights into the potential anti-inflammatory properties of the niosomal formulation. However, due to the scarcity of available research on this specific aspect, further investigations are warranted to comprehensively understand and validate the anti-inflammatory effects.

4. Leveraging HA for Enhanced Transdermal Penetration in Skin Infection

Clinical signs of skin and soft tissue infections (SSTIs), which entail microbial invasion of the skin and underlying soft tissue, are quite prevalent. Infections can cause symptoms that are mild or severe. Infections may spread to subcutaneous tissue, necessitating complicated medical care [41-43].

Centella asiatica is a valuable medicinal herb with wide-ranging applications in alternative therapeutic treatments, including anti-tumor, anti-psoriasis, eczema, anti-inflammation, anti-aging, and burn and wound healing formulations. In a recent study, niosomes loaded with *Centella asiatica* extract (CAE-Nio) and hyaluronic acid-coated niosomes (CAE-Nio-HA) were developed to improve transdermal penetration. Niosomes formulated with Tween 60 exhibited optimal characteristics for encapsulating CAE, resulting in high encapsulation efficiency and drug loading capacity. The incorporation of hyaluronic acid influenced particle size and zeta potential while preserving encapsulation efficiency. Notably, CAE-Nio-HA demonstrated improved dermal absorption and permeation of asiaticoside, a polar compound, compared to CAE-Nio and CAE solution. This innovative approach presents a promising delivery system for enhancing the efficacy of hydrophilic natural active compounds in transdermal applications [22].

5. Anticancer Drug Delivery with HA-Coated Niosomes

With the exception of nonmelanoma skin cancers, breast cancer is presently the most often diagnosed cancer in women [44]. Chemotherapy, surgery, endocrine (hormone) therapy, radiation therapy, and targeted therapy are the major kinds of treatment for breast cancer [45]. Chemotherapy is still regarded as the primary modality for cancer treatment, despite improvements in cancer treatment methods over the previous few decades. However, there are several restrictions on the use of chemotherapeutic medicines, such as multidrug resistance (MDR), limited effectiveness, nonspecific biodistribution, and severe adverse effects [46-47].

In a recent investigation, this study represents a significant advancement in the field of anticancer drug delivery, with a specific focus on CD44-targeted nanoparticles designed to improve the delivery efficiency of Epirubicin to breast cancer cells. Through meticulous synthesis, the resulting Epi-Nio-HA nanoparticles consistently maintain a nanoscale size, display sustained release profiles, and remain stable under physiological conditions. Remarkably, the Epi-Nio-HA group exhibits substantial internalization within breast cancer cells, facilitated by CD44-mediated pathways. Notable findings indicate that both the Epi-Nio and Epi-Nio-HA groups enhance the impact of Epirubicin on breast cancer cells, resulting in increased cytotoxicity, apoptosis, and inhibition of metastasis. Encouragingly, *in vivo* assessments using Epi-Nio-HA nanoparticles demonstrate both safety and effective suppression of tumor growth in mice. These collective outcomes underscore the potential of this nanoparticle-based system as a promising avenue for developing safe and efficient therapeutic strategies against breast cancer [26].

While studies highlight the benefits of hyaluronic acid-coated niosomes in anticancer therapy, discussions on challenges are notably scarce. This underscores the need for further research to fully grasp considerations in using these niosomes for anticancer applications.

CONCLUSION

The integration of niosomes and hyaluronic acid-coated nanocarriers represents a revolutionary approach to targeted drug delivery. Niosomes offer versatility and protection for various drugs, while hyaluronic acid brings biocompatibility and enhanced permeability to the table. These HA-coated niosomes show promise across multiple applications, including ocular drug delivery, inflammation treatment, and anticancer therapy. They extend drug retention in the eye, offer sustained anti-inflammatory effects, and improve drug delivery efficiency to cancer cells. This synergy between niosomes and HA-coated nanocarriers holds great potential for personalized medicine, elevating drug delivery precision and efficacy while minimizing side effects. It represents a significant advancement in patient care across diverse medical fields. While the current findings demonstrate the promise of hyaluronic acid-coated niosomes, future research could explore potential advancements and novel applications in drug delivery. Investigating further into the optimization of formulations, Long-term Safety Studies, Patient-Specific Approaches and Combination Therapies would be essential for advancing the field of hyaluronic acid-coated niosomes in drug delivery systems.

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