REVIEW ARTICLE

Cutting-edge Innovations in Oleanolic Acid Formulation

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ABSTRACT

Oleanolic acid (OA), a naturally occurring pentacyclic triterpenoid, has garnered significant attention due to its broad spectrum of pharmacological activities. Despite its therapeutic potential, the clinical application of OA is limited by its poor water solubility and low bioavailability, which hinder effective systemic absorption and therapeutic efficacy. Advances in pharmaceutical formulation technologies have addressed these challenges, paving the way for enhanced delivery systems that improve OA solubility, stability, and bioavailability. Among the most promising strategies are nanoformulations, including lipid-based nanoparticles, polymer-based nanocarriers, and solid lipid nanoparticles (SLNs). Lipid-based systems such as liposomes and nanoemulsions not only protect OA from environmental degradation but also facilitate controlled release and improved skin permeability, making them suitable for topical delivery. Polymeric carriers and micelles offer targeted delivery and sustained drug release, while SLNs enhance drug loading and stability. Characterization techniques such as dynamic light scattering, zeta potential analysis, electron microscopy, and differential scanning calorimetry ensure formulation quality, stability, and performance. These advanced delivery systems significantly improve the pharmacokinetic profile and therapeutic potential of OA.

Key words: Application, Liposomes, Microemulsion, Nanoparticles, Oleanolic acid

INTRODUCTION

Oleanolic acid (OA), a naturally occurring triterpenoid, is found in numerous plants and has been recognized for its diverse pharmacological properties.[1] This pentacyclic compound is present in various fruits, vegetables, and medicinal herbs, including olive leaves, garlic, and certain species of the Lamiaceae family. Conventionally, OA has been used in folk medicine across different cultures, attributed to its beneficial effects on health.[2] In recent years, scientific research has delved deeper into its potential therapeutic applications, revealing promising results in the treatment and management of a range of diseases and conditions.

The pharmacological profile of OA is extensive. It exhibits hepatoprotective, anti-inflammatory, antioxidant, and anti-cancer activities.[3,4] Additionally, it has been shown to possess anti-diabetic, anti-microbial, and anti-hypertensive properties. These multifaceted therapeutic benefits have generated significant interest in its potential as a drug candidate. However, the clinical application of OA is challenged by its poor water solubility and low bioavailability.[5,6] These physicochemical limitations hinder its effective absorption and distribution in the human body, thus limiting its therapeutic efficacy.

Formulation science plays a critical role in overcoming these challenges. Innovative formulation strategies can enhance the solubility, stability, and bioavailability of OA, thereby maximizing its therapeutic potential. Various approaches have been explored, including the use of nanoparticles, liposomes, solid dispersions, and inclusion complexes.[7,8] Each of these strategies aims to improve the pharmacokinetic properties of OA, ensuring it reaches the desired site of action in adequate concentrations to exert its therapeutic effects.

Nanoparticle-based formulations have garnered particular attention due to their ability to improve the bioavailability of poorly soluble drugs. By encapsulating OA in nanoparticles,

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it is possible to enhance its solubility and stability, protect it from degradation, and achieve controlled release. Liposomal formulations, which involve encapsulating the drug within lipid bilayers, offer another promising approach.[9] These formulations can enhance the drug's bioavailability and provide targeted delivery, reducing potential side effects.

Solid dispersions, where the drug is dispersed in a carrier matrix, can also significantly improve the solubility and dissolution rate of OA. Additionally, inclusion complexes, particularly with cyclodextrins, have been shown to enhance the solubility and stability of OA. These complexes involve the incorporation of the drug molecule into the cavity of the cyclodextrin, improving its aqueous solubility and protecting it from degradation.[10]

The development of these advanced formulations not only addresses the solubility and bioavailability issues but also opens new avenues for the clinical application of OA. By optimizing the delivery of this potent bioactive compound, it is possible to fully harness its therapeutic potential, paving the way for new treatments and improved health outcomes.[11,12]

Given the broad spectrum of pharmacological activities exhibited by OA, its enhanced formulation holds great promise for the treatment and management of various diseases, including cancer, inflammation, metabolic disorders, and liver diseases. By providing a comprehensive overview of the latest advancements in OA formulation, this review facilitates the translation of preclinical research findings into clinical applications. It offers valuable insights for researchers, clinicians, and pharmaceutical scientists involved in drug development, guiding them towards the development of optimized OA formulations with enhanced efficacy, safety, and patient compliance.

NANO CARRIER-BASED FORMULATIONS

Enhanced delivery of OA can be crucial for maximizing its therapeutic potential due to its promising pharmacological activities. Nano formulations offer a promising strategy to improve the delivery of OA by enhancing its solubility, stability, and bioavailability.

Lipid-based nanoformulation can improve a drug solubility, stability, and permeability as well as its potential for targeted and controlled release and can be used for topical drug delivery. These nanoformulations include liposomes, nanoemulsions, and solid lipid nanoparticles (SLNs). Utilizing nanoformulations for the topical delivery of OA can offer several advantages: OA is hydrophobic in nature, which can limit its solubility in water and topical formulations.

Among nanoformulations, lipid-based nanoparticles, polymer-based nanocarriers, and SLNs are particularly noteworthy.

Lipid-based nanoparticles

Lipid-based nanoparticles, such as liposomes, nanoemulsions, and lipid nanoparticles, offer an efficient approach for delivering drugs due to their biocompatibility, ability to encapsulate both hydrophilic and hydrophobic drugs, and potential for controlled release.

Liposomes are vesicular structures composed of lipid bilayers, which can entrap OA within their aqueous core or lipid bilayers. Liposomes can protect OA from degradation and enhance its solubility, leading to improved bioavailability.[13]

Lipid-based nanoparticles provide a lipid-based environment that enhances the solubility of OA, allowing for better incorporation into topical formulations. OA can be prone to degradation in the presence of light, heat, and oxygen. Encapsulation within nanoparticles can protect OA from environmental factors, thereby improving its stability and prolonging its shelf-life in topical formulations.

Nanoparticles can improve the permeability of OA through the skin barrier. The lipid components of these nanoparticles can interact with the lipids in the stratum corneum, the outermost layer of the skin, facilitating the penetration of OA into deeper skin layers where it can exert its therapeutic effects. Lipid-based nanoparticles can be designed to achieve controlled release of OA over time. By modulating the lipid composition and structure of the nanoparticles, as well as incorporating release-controlling agents, the release kinetics of OA can be tailored to optimize its therapeutic efficacy and minimize potential side effects. Surface modification of lipid-based nanoparticles with targeting ligands or functional groups can enable targeted delivery of OA to specific skin cells or tissues, such as inflamed or diseased areas, while minimizing systemic exposure and off-target effects.

Nanoemulsions are colloidal dispersions of oil and water stabilized by surfactants. Nanoemulsions can encapsulate OA within their oil phase, providing protection against degradation and facilitating absorption across biological membranes.

Lipid nanoparticles include SLNs and nanostructured lipid carriers (NLCs), which consist of a lipid matrix that can entrap OA. SLNs and NLCs offer advantages such as controlled release, improved stability, and enhanced permeation.

Overall, lipid-based nanoparticles, including liposomes, nanoemulsions, and SLNs, offer a versatile platform for the topical delivery of OA, enhancing its solubility, stability, permeability, and targeting capabilities. This approach holds great promise for the development of effective and safe formulations for the treatment of various skin conditions, including inflammation, oxidative stress, and wound healing.

Polymer-based nanocarriers

Polymeric nanoparticles and micelles, which are polymer-based nanocarriers, provide OA with a versatile encapsulation and release profile control. These nanocarriers can help move OA to the intended location and shield it from deterioration. Colloidal particles known as polymeric nanoparticles are made of biodegradable polymers that can contain and release a drug over time, such as chitosan or poly (lactic-co-glycolic acid). Polymeric nanoparticles improve the delivery of OA by providing adjustable characteristics and an extended circulation time.[14]

Amphiphilic block copolymers create polymeric micelles, which are self-assembling structures capable of encasing OA in their hydrophobic core. The solubility and stability of OA are improved by polymeric micelles, which increase bioavailability and therapeutic efficacy.

SLNs

SLNs are colloidal carriers composed of solid lipids dispersed in an aqueous phase stabilized by surfactants. SLNs offer several advantages for delivering OA, including improved drug loading (DL) capacity, controlled release, and protection against degradation.

SLNs can encapsulate OA within the lipid matrix, allowing for higher DL compared to other nanoparticle systems. SLNs can modulate the release kinetics of OA, offering sustained drug release over an extended period.[15] This controlled release profile enhances OA bioavailability and reduces dosing frequency. SLNs provide protection to OA against degradation by enzymes or harsh environmental conditions, preserving its pharmacological activity during storage and transport.

CHARACTERIZATION OF OA NANOFORMULATIONS

Physicochemical characterization plays a critical role in the development and optimization of nanoformulations for therapeutic agents like OA. Due to its poor water solubility and low bioavailability, OA is often encapsulated in nanoscale delivery systems such as nanoparticles, nanoemulsions, lipid carriers, or micelles. To ensure efficacy, safety, and stability, these nanoformulations must be rigorously characterized using various analytical techniques.

Particle size and size distribution

Particle size significantly influences the biological fate of a nanoformulation. It affects drug dissolution, cellular uptake, biodistribution, and clearance from the body. Nano-sized particles (typically in the 10–200 nm range) exhibit enhanced permeability and retention effects in tumors and improved transport across biological membranes. Dynamic light scattering is the most commonly used technique to measure hydrodynamic diameter and polydispersity index (PDI).[16]

PDI indicates the uniformity of particle sizes within the sample. A lower PDI (<0.3) is desirable, signifying a narrow size distribution and better formulation stability. OA nanoformulations such as SLNs, polymeric nanoparticles, or self-nanoemulsifying drug delivery systems generally exhibit particle sizes in the range of 100–200 nm with low PDI values, indicating good monodispersed particles.

Zeta potential

Zeta potential reflects the surface charge of the nanoparticles and is a key indicator of colloidal stability. It predicts the likelihood of particle aggregation due to electrostatic repulsion. Electrophoretic light scattering is used to measure the zeta potential. A value greater than ±30 mV typically indicates a stable colloidal system due to sufficient repulsive forces among particles. OA nanoparticles stabilized with surfactants like Tween 80 or polymers like chitosan show zeta potentials around –20 to –40 mV, which support stability under physiological conditions.

Surface morphology and shape

The shape and surface characteristics of nanoparticles influence their cellular interaction, circulation time, and ability to evade the immune system. Transmission electron microscopy (TEM) and scanning electron microscopy are used to visualize the morphology. Atomic force microscopy offers additional data on surface topography and roughness.[17] OA-loaded nanoparticles typically exhibit a spherical shape with smooth surfaces, favorable for intravenous or oral delivery routes.

DL and encapsulation efficiency (EE)

These parameters measure how effectively OA is incorporated into the nanocarrier system and affect dosage requirements and therapeutic performance. DL% indicates the amount of drug per unit weight of nanoparticles. EE% depicts the percentage of total OA successfully encapsulated versus the amount initially used.[18] Free OA is separated from the loaded particles using ultracentrifugation or dialysis. Quantification is usually done by high-performance liquid chromatography or ultraviolet-visible spectroscopy. EE is typically high (70–90%), especially in lipid-based carriers and hybrid nanoparticles, enhancing sustained drug delivery potential.

Crystallinity

Knowing whether OA exists in an amorphous or crystalline state within the formulation is essential, as amorphous drugs

usually dissolve faster. X-ray diffraction (XRD) identifies crystalline structures. Differential scanning calorimetry (DSC) measures thermal transitions and confirms the physical state.[19] XRD and DSC analyses often reveal a reduction or complete disappearance of OA crystalline peaks, indicating a transition to the amorphous state or complete encapsulation.

pH and viscosity (for topical/oral use)

For oral liquids or topical gels containing OA nanoparticles, pH and viscosity are crucial for patient comfort and proper drug release. pH is measured using a calibrated pH meter. The viscosity is assessed using a Brookfield viscometer.

Physicochemical characterization is a cornerstone in the development of OA nanoformulations. By examining parameters such as particle size, zeta potential, morphology, DL, and crystallinity, researchers can ensure that the nanoformulation not only improves OA solubility and bioavailability but also maintains stability, reproducibility, and safety.[20,21] As nanoformulation technologies evolve, integrating characterization with *in vitro* and *in vivo* data will further enhance the precision and reliability of OA-based therapeutics.

THERAPEUTIC APPLICATION

Traditional OA formulations often face challenges related to poor solubility and limited absorption, which can hinder their therapeutic potential. However, advanced formulations can be developed by employing innovative strategies such as nanoparticle encapsulation, lipid-based carriers, and complexation with cyclodextrins.[23]

Nanoparticle-based formulations represent a cutting-edge approach to enhance the delivery of OA. Nanoparticles, typically in the range of 10–200 nanometers, offer several advantages including increased surface area, improved stability, and controlled release kinetics.[23]

Lipid-based formulations another offer excellent biocompatibility and versatility in drug delivery. These lipid formulations can encapsulate OA, improving its solubility in biological fluids and promoting sustained release, which may lead to prolonged therapeutic effects and reduced dosing frequency.

Complexation with cyclodextrins is yet another strategy to enhance the solubility and stability of oleanolic acid.[17] This approach enables the formulation of OA into various dosage forms such as tablets, capsules, or oral solutions, expanding its potential applications in pharmaceutical and nutraceutical products.

OA exhibits diverse pharmacological activities, including anti-inflammatory, antioxidant, hepatoprotective, anticancer, and antimicrobial properties. By harnessing the advantages of advanced formulations, delivery of OA can be optimized to target tissues or organs, maximize its therapeutic effects, and minimize potential side effects.[24,25]

CONCLUSION

Despite its potential, the clinical utility of OA has been historically limited by its poor solubility and low bioavailability. Recent advances in formulation science have significantly improved the delivery and therapeutic performance of OA through the development of nano-based drug delivery systems. These include lipid-based nanoparticles, polymeric carriers, and SLNs, which enhance solubility, protect OA from degradation, and enable targeted and controlled drug release. Lipid-based systems such as liposomes and nanoemulsions offer enhanced biocompatibility and stability, while polymeric nanoparticles and micelles allow for sustained release and efficient tissue targeting. Comprehensive physicochemical characterization is essential to ensure the safety, stability, and efficacy of these advanced OA formulations. As nanotechnology continues to evolve, these innovative systems hold great potential to overcome existing pharmacokinetic limitations, offering improved therapeutic outcomes. Overall, the formulation and delivery advancements discussed in this review highlight the promising future of OA in the treatment of various chronic and acute diseases, contributing significantly to the development of effective, patient-friendly therapies.

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