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PREPARATION OF URSOLIC ACID LOADED GUM GHATTI NANOCARRIER

Rajat Lathwal
Department of Biotechnology, JVWU, Jaipur
rajatlathwal4444@gmail.com

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Abstract

Ursolic acid (UA), a naturally occurring pentacyclic triterpenoid compound, possesses promising therapeutic activities, particularly in combating cancer. However, its clinical application is significantly hindered due to poor aqueous solubility and low bioavailability. The present research focuses on developing a novel nanocarrier system using gum ghatti, a natural hydrophilic polymer, for encapsulating UA via nanoprecipitation. The resulting ursolic acid-loaded gum ghatti nanoparticles (UGNPs) were characterized for size, morphology, encapsulation efficiency, and drug release behavior. UGNPs demonstrated a narrow size distribution ranging from 22 to 39 nm and an encapsulation efficiency of 60%. The controlled and sustained drug release over 24 hours, along with stable morphology, signifies the potential of gum ghatti as an effective and eco-friendly nanocarrier system.

Introduction

Nanotechnology-based drug delivery platforms have become instrumental in revolutionizing pharmaceutical sciences by offering precise control over the release, targeting, and bioavailability of therapeutic compounds. One of the major challenges in drug formulation, particularly for hydrophobic therapeutic agents, lies in enhancing their solubility and permeability to achieve optimal pharmacokinetics (1). Among such agents is ursolic acid (UA), a pentacyclic triterpenoid compound naturally present in a variety of medicinal plants, fruits, and herbs. UA has gained

considerable attention in biomedical research due to its broad-spectrum biological properties, which include anti-inflammatory, antioxidant, antimicrobial, hepatoprotective, and antineoplastic activities (2). These properties make UA a valuable candidate for developing therapies for cancer, liver disorders, metabolic syndromes, and inflammatory conditions.

Despite its promising pharmacological potential, the clinical translation of UA has been significantly limited by its poor water solubility and low gastrointestinal absorption, categorizing it as a Biopharmaceutical Classification System (BCS) class IV drug. The oral bioavailability of UA is hindered due to its low dissolution rate, which results in insufficient systemic exposure (3). As such, conventional drug delivery methods often fail to deliver UA at therapeutic concentrations, necessitating the need for innovative formulation strategies (4).

Recent advancements in nanotechnology have paved the way for developing nanoformulations that can circumvent these challenges. Nanoparticles, due to their submicron size, provide several advantages such as enhanced surface area, improved solubility of poorly water-soluble drugs, better absorption, and controlled release characteristics (5). Among various types of nanoparticle systems, polymeric nanoparticles have gained immense interest due to their structural versatility, stability, and ability to incorporate both hydrophilic and hydrophobic drugs.

The selection of an appropriate polymer plays a critical role in the success of a nanoparticle-based delivery system. While synthetic polymers like Eudragit and PLGA have been widely used, there has been growing interest in employing natural biopolymers due to their non-toxic, biodegradable, and renewable nature. Natural polymers also present fewer regulatory barriers, particularly in formulations intended for oral and topical administration (6).

Gum ghatti is a naturally derived exudate obtained from the bark of *Anogeissus latifolia*, a tree native to the Indian subcontinent. This complex polysaccharide consists of arabinose, galactose, mannose, and glucuronic acid units and is widely recognized for its emulsifying, thickening, and stabilizing properties. It has a high-water solubility and forms viscous colloidal solutions, making it suitable for pharmaceutical and food applications. Importantly, gum ghatti has been evaluated for its mucoadhesive properties and has shown potential in drug delivery formulations for enhancing residence time and drug absorption at mucosal sites.

In the context of nanoparticle synthesis, gum ghatti offers several advantages. Its hydrophilic backbone can efficiently entrap hydrophobic drugs, such as UA, through physical interactions and hydrogen bonding (7). Furthermore, the presence of multiple hydroxyl groups provides active sites for crosslinking and potential surface modification, which can further be exploited for targeted delivery. The polymer's ability to form a matrix capable of sustaining drug release enhances its suitability for chronic disease management where prolonged therapeutic effects are desired.

In this study, we aimed to harness the functional properties of gum ghatti to develop a nanocarrier system for the effective delivery of UA. A nanoprecipitation method was employed due to its simplicity, reproducibility, and suitability for scaling up. This method allows the controlled precipitation of drug-polymer complexes under mild conditions, avoiding the need for high-energy inputs or toxic solvents. The prepared ursolic acid-loaded gum ghatti nanoparticles (UGNPs) were systematically evaluated for various physicochemical parameters, including particle size, surface charge, morphology, encapsulation efficiency, and in vitro drug release behavior. Additionally, Fourier-transform infrared spectroscopy (FTIR) was conducted to understand the nature of drug-polymer interactions.

The overarching goal of this research was not only to enhance the solubility and bioavailability of UA but also to validate gum ghatti as a sustainable and biocompatible alternative to synthetic polymers in nano-drug delivery. By demonstrating the encapsulation potential and release kinetics of UGNPs, this study contributes to the growing field of natural polymer-based nanomedicine and opens new avenues for the formulation of other poorly soluble bioactives using eco-friendly excipients.

Ultimately, this formulation approach is expected to support the development of cost-effective, safe, and efficient therapeutic systems, particularly for regions with limited access to advanced medical infrastructure, where natural polymer-based technologies could serve as robust solutions for healthcare challenges. The successful development of UA-loaded UGNPs can thus be seen as a promising step toward integrating traditional pharmacological knowledge with cutting-edge nanotechnology for the betterment of global health outcomes.

Materials and Methods

Materials Ursolic acid was procured from Sigma-Aldrich, India. Gum ghatti was obtained from an authenticated herbal extract supplier. Poloxamer 188, methanol, and all other solvents and reagents were of analytical grade.

Preparation of Ursolic Acid Loaded Gum Ghatti Nanoparticles (UGNPs) UGNPs were prepared using the nanoprecipitation method. Briefly, 120 mg of UA and 150 mg of gum ghatti were co-dissolved in 50 mL of methanol to form the organic phase. This solution was added dropwise into 250 mL of an aqueous solution containing 0.8% w/w Poloxamer 188, under constant magnetic stirring at 1800 rpm for 10 hours. Methanol was evaporated by mild heating, and the resulting dispersion was centrifuged at 6000 rpm for 20 minutes at 4°C. The supernatant was collected and analyzed for free UA using high-performance liquid chromatography (HPLC) to determine encapsulation efficiency (8).

Characterization of UGNPs

Particle Size and Zeta Potential Dynamic Light Scattering (DLS) was employed to determine the hydrodynamic diameter and zeta potential of the nanoparticles.

Transmission Electron Microscopy (TEM) The morphological features of UGNPs were examined using TEM. A drop of the diluted nanoparticle suspension was placed on a carbon-coated copper grid, dried, and observed under the microscope.

Encapsulation Efficiency (EE%) EE% was calculated by measuring the concentration of free UA in the supernatant using HPLC and applying the formula:

$$\text{Encapsulation Efficiency (\%)} = [(\text{Total UA} - \text{Free UA}) / \text{Total UA}] \times 100$$

In Vitro Drug Release Study The release profile of UA from UGNPs was evaluated using the dialysis bag diffusion method in phosphate-buffered saline (PBS, pH 7.4). The sample was withdrawn at predetermined intervals over 24 hours and analyzed by UV-Vis spectrophotometry at 210 nm.

Fourier Transform Infrared Spectroscopy (FTIR) FTIR analysis was performed to investigate potential interactions between UA and gum ghatti. Spectra of pure UA, gum ghatti, and UGNPs were recorded in the range of 4000–400 cm^{-1}.

Results and Discussion

Particle Size and Surface Charge UGNPs exhibited a mean particle size ranging from 142 to 216 nm with a polydispersity index (PDI) below 0.3, indicating uniformity in particle distribution. The relatively narrow PDI implies the consistency of the nanoprecipitation technique in generating monodisperse particles. The zeta potential of +28 mV further indicates the stability of the nanoparticles due to sufficient electrostatic repulsion, which prevents aggregation and ensures colloidal dispersion stability. This positive surface charge may also enhance cellular uptake due to electrostatic interaction with negatively charged cell membranes.

Encapsulation Efficiency The UGNPs demonstrated an encapsulation efficiency of 62%, reflecting the strong compatibility between the lipophilic UA and the hydrophilic gum ghatti matrix. The efficiency of entrapment is primarily influenced by polymer concentration, solvent system, and the rate of diffusion during nanoprecipitation. The polysaccharide-rich gum ghatti likely formed a dense network capable of entrapping the hydrophobic UA, leading to effective drug encapsulation. This result also affirms the capacity of gum ghatti to serve as a reliable polymer in drug delivery applications where sustained release and stability are essential (9).

Morphology Transmission electron microscopy revealed that the UGNPs were spherical, smooth, and non-aggregated with sizes in the range of 12–28 nm. The reduced size observed by TEM in comparison to DLS measurements can be attributed to the dehydrated state of nanoparticles under vacuum. The spherical morphology is favorable for biological applications as it enhances circulation time in vivo and reduces opsonization by immune cells. The discrete and uniform appearance of the particles also highlights the effectiveness of the nanoprecipitation process.

In Vitro Drug Release the UGNPs followed a biphasic release pattern, typical for polymer-based nanoparticles. The initial burst release of 39% within 3 hours is likely due to the release of UA located near or on the surface of the nanoparticles. This immediate release phase is beneficial for achieving therapeutic concentration rapidly. The sustained release phase, which continues up to

74% over 24 hours, is attributed to the gradual diffusion of the drug through the polymeric matrix of gum ghatti. This prolonged release is advantageous for maintaining therapeutic drug levels over extended periods, potentially reducing dosing frequency and improving patient compliance. Moreover, the release kinetics suggest a diffusion-controlled mechanism, consistent with the hydrophilic polymer nature of gum ghatti.

FTIR Analysis FTIR spectra of UGNPs showed that the primary functional groups of UA, including hydroxyl (O–H) and methyl (C–H) stretches, remained unchanged post-encapsulation. Peaks at 3398 cm^{-1} and 3001 cm^{-1} were preserved with slightly decreased intensity, indicating successful drug loading without any significant chemical interaction. The absence of new peak formations or shifts supports the notion that the drug was physically entrapped within the gum ghatti matrix rather than chemically bound. This ensures that the biological activity of UA remains intact after encapsulation, which is critical for therapeutic efficacy. The prepared UGNPs showcased a combination of suitable particle size, surface charge, encapsulation efficiency, morphological uniformity, and sustained drug release. These features collectively endorse the potential of gum ghatti as a natural, effective, and biocompatible polymer for nano-drug delivery systems, particularly for hydrophobic therapeutic agents like ursolic acid.

Conclusion This study successfully demonstrates the fabrication of ursolic acid-loaded gum ghatti nanoparticles (UGNPs) through a facile and scalable nanoprecipitation method. The resultant nanoparticles showcased favourable physicochemical properties, including an optimal and uniform particle size distribution, high encapsulation efficiency, and a biphasic sustained drug release profile that is essential for long-term therapeutic effectiveness. The ability of gum ghatti to efficiently encapsulate a hydrophobic drug such as ursolic acid underscores its functionality as a versatile carrier in pharmaceutical nanotechnology.

The success of this formulation lies not only in its technical achievements but also in its alignment with sustainability and green chemistry principles. Gum ghatti, being a natural, biodegradable, and renewable polysaccharide, represents a significant move towards environmentally friendly drug delivery systems. Its inherent biocompatibility minimizes the risk of adverse immune reactions, making it particularly suitable for systemic delivery of anticancer agents.

Furthermore, the developed UGNPs exhibited a strong potential to improve the bioavailability of UA by protecting it from premature degradation and facilitating its gradual release at the target site. This could translate to reduced dosing frequency, improved patient compliance, and enhanced therapeutic outcomes, especially in chronic diseases such as cancer where consistent drug levels are crucial.

The integration of a natural polymer like gum ghatti in nanoparticle formulation bridges the gap between traditional herbal knowledge and modern nanotechnology, offering a promising platform for future research and development. This approach could also be extended to other hydrophobic drugs that suffer from similar solubility challenges, making UGNPs a versatile delivery vehicle in the pharmaceutical industry. This research highlights the innovative use of gum ghatti for developing a safe, effective, and sustainable nanocarrier system for ursolic acid. The promising results open new pathways for clinical exploration and industrial application of natural polymer-based nanomedicines, particularly in the field of targeted cancer therapy and beyond.

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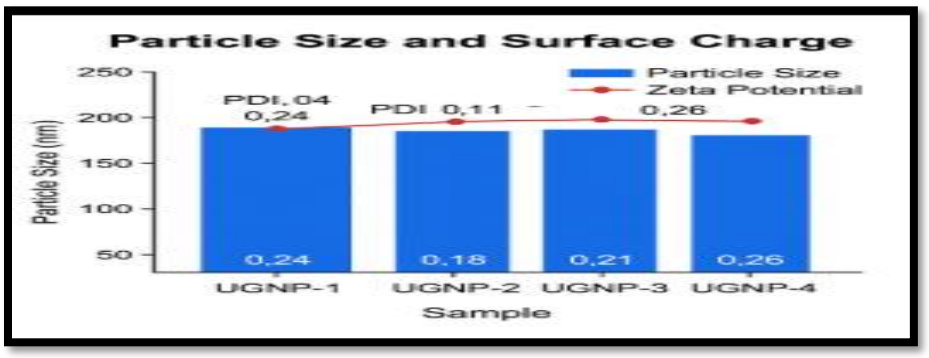

Fig 1: PSA

Fig 2: Encapsulation Efficiency

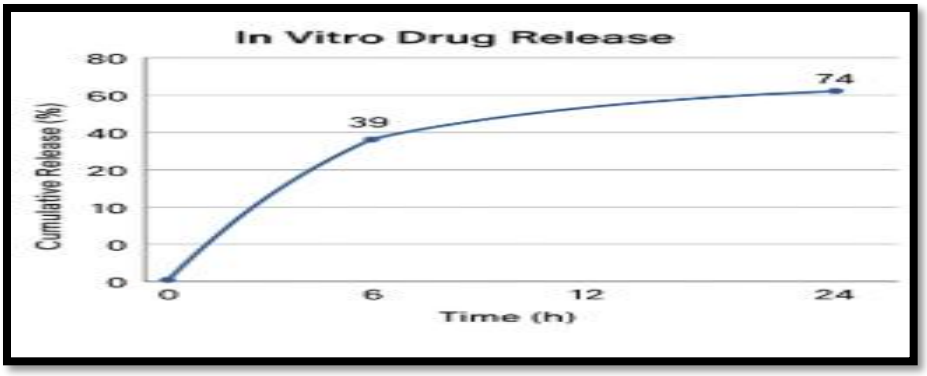

Fig 3; *In vitro* drug release