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Review

PRNANO

Precis. Nanomed. 2024, 7(1):1365-1385

ANDOVER HOUSE

Nanotechnology-Enhanced Controlled-Release Systems in Topical Therapeutics

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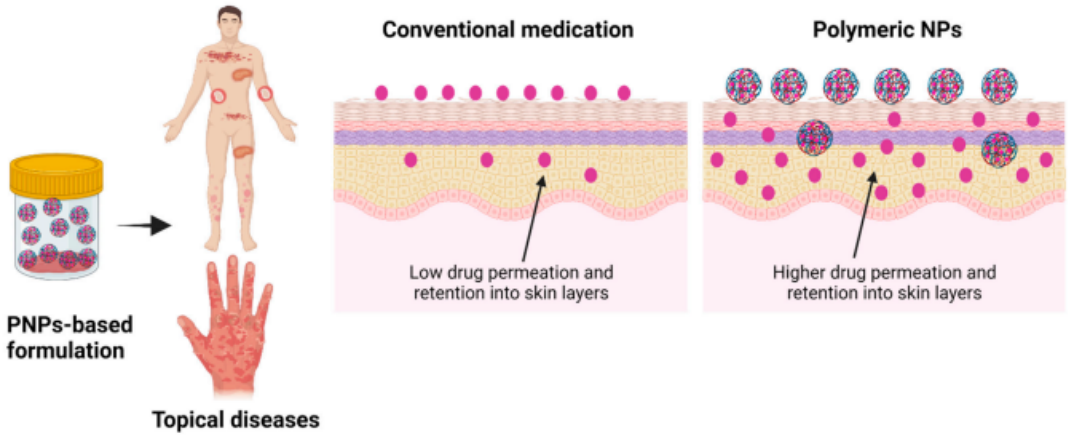
Submitted: September 20, 2024 Accepted: November 30, 2024 Published: December 12, 2024

Graphical Abstract



Abstract

Topical and transdermal drug delivery are alternative routes for medications facing challenges like solubility, stability, and first-pass metabolism. However, conventional immediate-release dosage forms delivered topically have drawbacks, including poor penetration and high side effects. Controlled-release nanoparticles offer a promising solution, improving drug permeation and providing controlled release. This review examines recent advances, challenges, and prospects of controlled-release nanoparticles for topical drug delivery. Various types of nanoparticles, including lipid nanoparticles, nanoemulsions, nanoemulgels, cubosome liposomes, polymeric nanoparticles, solid-lipid nanoparticles, lipid-polymer hybrid nanoparticles, and nanostructured lipid carriers, carbon nanotubes, nanocomposites, and protein nanoparticles have been explored for their ability to encapsulate drugs, prolong drug release, and enhance skin permeation as well as improve therapeutic outcomes. Studies have demonstrated the effectiveness of these nanoparticles in improving sustained and controlled-release topical delivery of a wide range of drugs, including poorly soluble, low degree of skin penetration, low stability, and drugs with low bioavailability and biological products. Despite their potential benefits, challenges such as scalability, reproducibility, and safety concerns remain. Future research should address these challenges and explore novel strategies to improve efficacy and safety by converging with microneedles and 3D nanoparticles. Ultimately, controlled-release nanoparticles have the potential to revolutionize dermatological and transdermal drug delivery, leading to improved therapeutic outcomes and patient care.

Keywords: nanoparticles, controlled release, topical delivery, transdermal, treatment

Purpose, Rationale, and Limitations

This study explores how nanotechnology can enhance controlled-release systems in topical therapeutics by improving drug delivery, efficacy, and patient safety. Conventional topical formulations often suffer from poor penetration, rapid degradation, and frequent dosing requirements. Nanotechnology offers solutions to these issues by enabling nanoencapsulation, which enhances drug stability, skin penetration, and controlled release.

Additionally, nanoparticles can be designed to respond to local skin conditions, offering targeted and responsive drug delivery for conditions like chronic skin diseases. However, challenges exist, including potential cytotoxicity, skin irritation, complex and costly production, scalability issues, and regulatory hurdles. This study will address these limitations to advance body and deeper tissues [1]. This route is usually reserved for the delivery of drugs for some diseases since the drug will not reach the gastrointestinal tract, thus avoiding gastrointestinal irritation and the liver first-pass effect and reaching the lesion directly to reduce unnecessary adverse reactions [2].

The employment of drug delivery through the skin has increased over time due to its convenience and cost-effectiveness. The skin serves as a crucial barrier against the penetration of various drug substances, making it an optimal site for topical and systemic drug delivery. Topical administration has emerged as a preferred method for drug delivery for genetic disorders, infections, inflammatory diseases, and skin melanoma for the past few decades [3]. However, conventional formulations with associated micronized active components, including ointments, gels, creams, and lotions, usually penetrate poorly [4]. Research on novel topical drug delivery systems has been underway to overcome these challenges, enhance safety and efficacy, and minimize side effects [5].

Novel strategies have been tested for the delivery of drugs through the skin for drugs with associated low solubility and absorption when administered by the intestinal mechanism [6]. Topical administration is known for its low side effects compared with systemic administration. However, the presence of the keratinized and the development of safe, effective, and commercially viable nano-based topical treatments.

Introduction

Topical drug delivery involves drug transport from a product on the skin to a local target site and then clearance through diffusion, metabolism, and dermal circulation to the rest of the

barrier layer of the skin, the stratum corneum, has been one of the hardest layers the drug has to pass for easy availability through the skin. Different penetration enhancement mechanisms have been implemented to reverse the above challenges, such as chemical penetration enhancers and physical techniques, including iontophoresis, electroporation, and novel drug delivery systems [7].

Researchers have explored nanotechnology as a novel transdermal and topical drug delivery device that can boost drug flow and release the drug in a controlled way [8]. Drug delivery benefits greatly from the use of nanocarriers, which are distinguished by their submicrometer size and enormous specific surface area. Their small size makes it possible to load more drugs per unit volume, which improves bioavailability at the sites of interest. Long-lasting circulation in the body via nanocarriers prevents medication deterioration and ensures prolonged release. They decrease side effects while preserving therapeutic efficacy by needing lower doses. To enable accurate distribution, their surface chemistry can also be customized for various medications and targeting compounds [9].

Drug-loaded nanoparticles frequently gather in hair follicles, making it easier for drug molecules to pass through the outer layers of the stratum corneum (SC) and then release into the skin's inner layers.

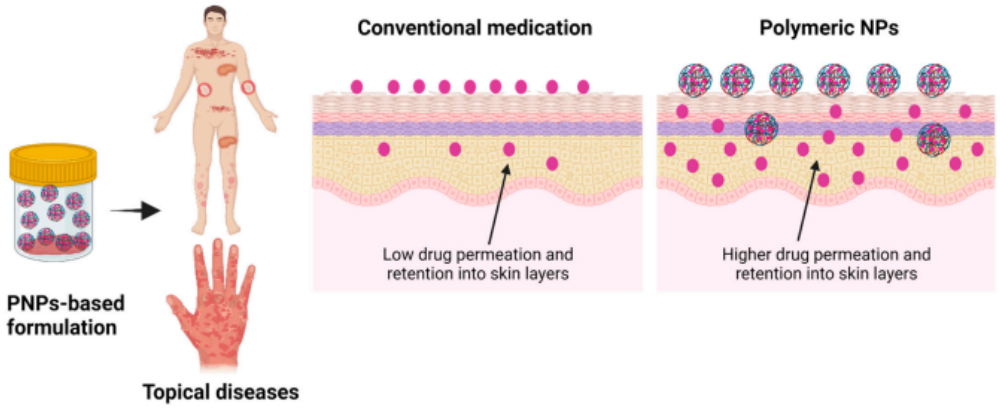


Figure 1. Comparison of conventional topical delivery and by nanoparticles[11].

Polymeric nanoparticles, nanoemulsions, lipid-based nanoparticles (liposomes and solid-lipid nanoparticles), metal nanoparticles, and dendrimers are the most often used for topical and transdermal drug administration. Conventional drug administration methods, like syrups, pills, and capsules, are rapidly eliminated from the body and frequently cause variations in plasma drug levels outside of the therapeutic window. Controlled-release medicine delivery methods are crucial to solving this problem. For a prolonged time, these systems guarantee a consistent and prolonged release of the medication, keeping plasma drug levels within the therapeutic range. Thus, they yield the intended therapeutic outcome (Figure 1) [10].Liposomes, polymeric nanoparticles, solid-lipid nanoparticles, and nanostructured lipid carriers are examples of controlled-release nanoparticles (Figure 2). These particles have unique qualities that make them ideal for encasing medications, extending their release, and improving skin penetration. By carefully manipulating their physicochemical attributes, like size, shape, and surface characteristics, controlled-release nanoparticles can enhance drug delivery kinetics, augment medication bioavailability, and minimize drug toxicity. (Figure 1) [12].

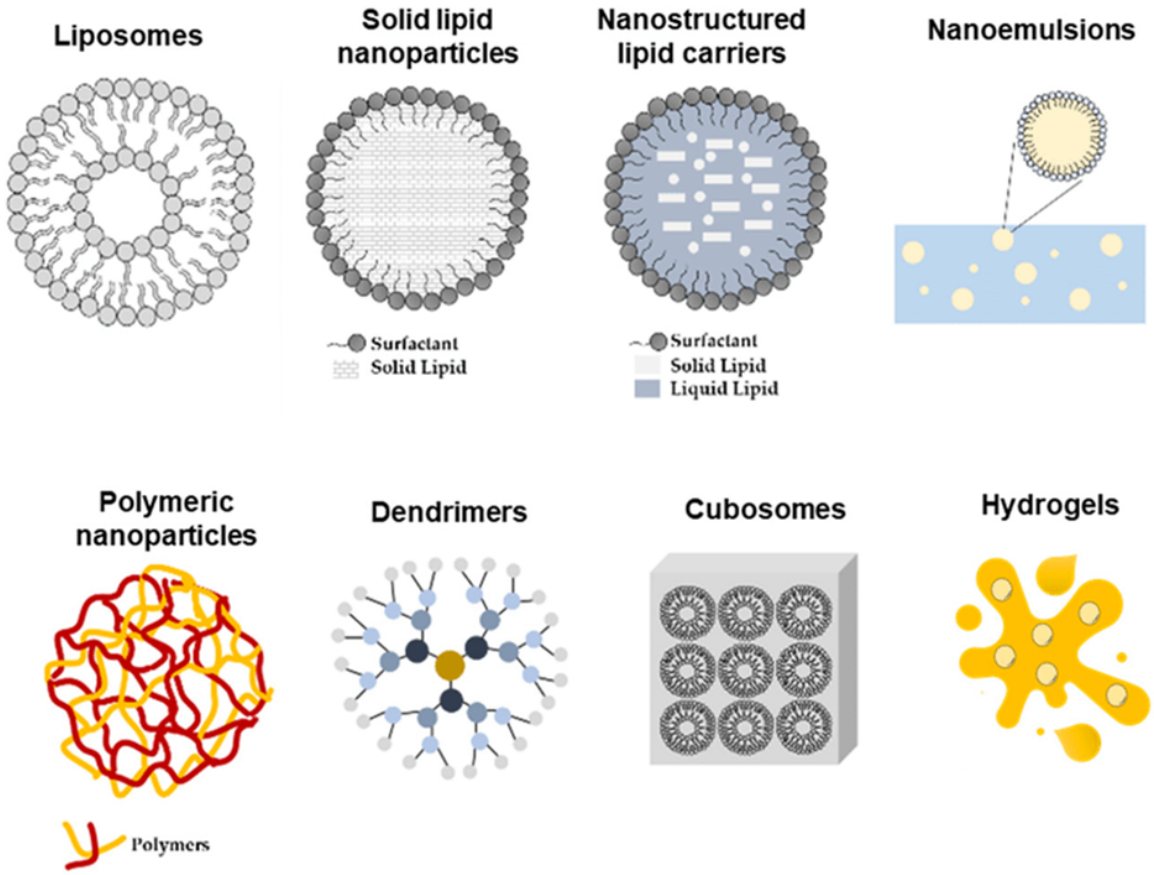


Figure 2. Commonly used types of nanoparticles for controlled-release topical administration.

This literature review discusses the prospects, difficulties, and current developments in controlled-release nanoparticles for topical medication administration. This review seeks to provide a thorough overview of the state-of-the-art topical formulations based on nanoparticles, clarify essential obstacles to their clinical translation, and outline future research directions to maximize the potential of controlled-release nanoparticles in dermatological and transdermal drug delivery. It does this by synthesizing insights from a wide range of research studies.

Discussion

The role of nanoparticles for controlled topical delivery and their advancements are discussed in detail, along with different types of nanoparticles and test drugs. It is summarized in a table (Table 1) in the Supporting File.

Polymeric Nanoparticles

Topical nanocarriers that are polymeric nanoparticles (PNPs) are showing promise in improving the skin penetration of active medications [13]. PNPs, such as nanocapsules and nanospheres, are made of biocompatible polymers such as proteins/polypeptides (such as gelatin and albumin) and polysaccharides (such as chitosan and cellulose), with a ranging size of 10 to 1000 nm [14]. Because they are biodegradable, they offer protection against degradation, high drug-loading capacity, and controlled drug release. Nanospheres distribute medications and polymers uniformly or on the surface, but nanocapsules contain drugs within a core chamber encircled by a polymer layer [15]. PNPs, with adjustable chemical and physical properties, safeguard unstable drugs, minimize side effects through controlled release, and facilitate skin permeation by enhancing concentration gradients [16]. Drug release from this type of nanoparticles is governed by (i) Standard diffusion-controlled release, (ii) Degradation of nanoparticles from biodegradable polymers, and (iii) Release triggered by environmental conditions such as pH, temperature or radiation in sensitive-to-stimuli PNs [17]. Polymeric nanoparticle drug release starts with rapid water absorption, expanding the polymer matrix. This allows drug diffusion through increasing pores, driven by concentration gradients or directly through polymeric chains. In non-degradable systems, release depends on membrane properties. Osmotic pressure aids drug transport (osmotic pumping). The drug's effective diffusion coefficient determines the release rate through the polymer. Stimuli-sensitive nanoparticles can change their chemical structure by employing heat, ultrasound, magnetic field, or light, degrading the nanostructure by erosion [14].

One study compared miconazole-loaded polymeric nanocapsules (PNCs) and lipid nanocapsules (LNCs) for topical delivery of miconazole nitrate. Both formulations exhibited sustained release compared to the solution, with LNCs showing a more prolonged release. Kinetic analysis revealed that LNCs followed a Baker model while PNCs followed a Higuchi diffusion model. PNCs relied on slow diffusion from viscous polycaprolactone, while LNCs' extended release was due to miconazole's lipophilicity and the lipid core's composition. Sustained formulations offer benefits like prolonged antifungal activity and improved treatment outcomes [18]. The paper compared polymeric and lipid nanocapsules for miconazole nitrate-enhanced topical delivery, demonstrating improved drug permeation and retention with nanocapsules. The study's rigorous evaluation of particle size, in vitro and ex-vivo performance, and statistical analysis strengthens the credibility of the findings. The research highlights the potential of nanocapsules in enhancing topical drug delivery efficacy, offering valuable insights for future developments in pharmaceutical formulations for treating fungal infections.

The study evaluated terbutaline sulfate (TB) transdermal delivery using nanoparticle hydrogels. The hydrogel exhibited an initial burst effect attributed to surface-localized drug leading to rapid dissolution upon contact with the release medium. TB release followed the Higuchi model, indicating hydrogel diffusion, promising sustained therapeutic effects and patient compliance. Chitosan nanoparticles in the formulation offer optimal size for skin penetration, biodegradability, and the ability to form nanohydrogels, enhancing TB release and topical bioavailability. [19]. the study developed a transdermal terbutaline sulfate nanoparticle-loaded hydrogel using chitosan and tripolyphosphate, showing high entrapment efficiency and controlled release. The evaluation revealed enhanced drug permeation, indicating nanocarriers' potential for skin delivery. Fourier Transform Infrared Spectroscopy confirmed ingredient compatibility, and statistical analysis ensured result reliability. This novel delivery system offers promise in respiratory medicine, potentially replacing oral forms with improved compliance and fewer side effects, warranting further clinical validation.

The study aimed to enhance patient compliance with ondansetron HCl (OND) by developing transdermal delivery systems. OND, an antiemetic with low oral bioavailability and short half-lives, poses adherence challenges. Prepared nanoparticles initially showed rapid OND release, followed by sustained release and a burst effect. Two Eudragit polymers, RS 100 and RL 100, known for pH-independent drug release, were selected. RL 100, with higher water permeability, facilitated better drug wetting and release due to increased water penetration.

[20]. The above study tried to accommodate some innovative and eco-friendly methodologies, good polymer selection, and particle size control attributed to topical controlled drug release. Still, it lacked in-vivo studies and comparative analysis with other formulations.

Goudon et al. investigated the controlled-release potential of retinol using co-polymeric nanoparticles for topical application with Eudragit 100 polymer. In vitro drug release studies showed the best correlation with the Higuchi model, suggesting diffusion-based release. Temperature, external medium nature, and pH influenced diffusion through the polymeric membrane. Still, identical parameters yielded different release rates based on retinol/polymer ratio, with higher ratios resulting in faster release kinetics. Kinetic studies demonstrated nanoparticle-controlled release, releasing retinol over 18 hours [21]. The researchers conducted encapsulation yield measurements, drug release tests in synthetic sweat solution, and characterization of nanoparticles using techniques like scanning electron microscopy. Using different release models, such as zero-order, first-order kinetics, and the Higuchi model, to analyze the drug release from the nanoparticles adds depth to the study. By comparing the release profiles of formulations containing different initial drug concentrations, the researchers could assess the impact of formulation parameters on drug release kinetics. The controlled release of retinol from nanoparticles could offer stability, efficacy, and prolonged action advantages when incorporated into cosmetic formulations.

Elmowafy et al. prepared indomethacin in nanosphere and nanocapsule forms for topical administration. In vitro drug release followed the Higuchi controlled-release model, indicating uniform dispersion throughout a matrix and release primarily governed by diffusion through the matrix [22]. This study focused on examining the formulation and evaluation of a polymeric nanoparticles-based topical gel for delivering a poorly soluble drug, indomethacin. By utilizing nanocapsules and nanospheres, the researchers aimed to enhance the drug's solubility and permeability for improved therapeutic outcomes. The in vitro release studies and ex-vivo permeation experiments provided valuable insights into the formulations' drug release mechanisms and skin permeability. The in-vivo evaluation demonstrated promising anti-inflammatory and analgesic effects of the topical gel. Overall, the study highlights the potential of nanotechnology in enhancing the delivery of poorly soluble drugs through topical formulations, offering a novel approach for effective drug delivery and therapeutic benefits.

Encapsulation of amphotericin B in polycaprolactone (PCL) nanoparticles showed pH-dependent drug release. At pH 7.4, 78% of the drug was released within 48 hours, indicating significant permeation. Conversely, at pH 5.5, only 22% of the drug was released, demonstrating reduced permeation. The sustained release at pH 7.4 was attributed to the cleavage of PCL ester links [23]. The research on amphotericin B-loaded polymeric nanoparticles for treating Leishmania infections presents an innovative approach with promising implications. The controlled drug release mechanism demonstrated anti-leishmanial activity, and favorable particle characteristics highlight the potential of these nanoparticles for targeted therapy. The study's findings suggest that polymeric nanoparticles could improve treatment outcomes for Leishmania infections by enhancing drug efficacy and minimizing systemic side effects. Further research and clinical validation are needed to fully assess these formulations' clinical utility and safety.

PLGA-based polymer nanoparticles encapsulating benzocaine, a local anesthetic, exhibited a biphasic release pattern in vitro. The initial rapid release occurred within approximately 90 minutes, followed by sustained release over 420 minutes, plateauing thereafter. The release rate significantly decreased over time. Combining with a hydrogel reduced the initial rapid release by about six times within the first 90 minutes while enhancing sustained release, achieving maximum release [24]. The study presents a comprehensive approach to enhancing the permeation of local anesthetics through topical application using chitosan-coated polymeric nanoparticles in thermosensitive hydrogels, along with the penetration enhancer limonene. The characterization of nanoparticles. The positive results in terms of mean diameter, zeta potential, encapsulation efficiency, and enhanced drug permeation suggest that this hybrid hydrogel-nanoparticle system could be a promising strategy for improving topical drug delivery, with implications for pain management and

other medical applications. Further research and clinical trials are warranted to validate the efficacy and safety of this innovative approach in practical settings.

Solid-Lipid Nanoparticles

Nanoparticles, including metallic, polymeric, and inorganic-clay types, are solid colloidal particles under 100 nm, capable of entrapping drugs via physical or chemical bonding, ensuring drug stability and controlled release [9]. Solid-lipid nanoparticles (SLNs) serve as emulsion-based carriers for lipophilic bioactive compounds, ranging from 50 to 2000 nm in size, offering biocompatibility and biodegradability [4]. SLNs in transdermal drug delivery systems provide occlusive and adhesive characteristics, forming a uniform coating on the SC, enhancing residence time and skin absorption [25]. Compared to other nanoparticles, SLNs are more stable, with longer drug release times, easier sterilization, and higher production scalability [26], facilitated by their distinctive structure for controlled-release profiles [27]. Understanding drug loading and release mechanisms in SLNs is vital for optimizing therapeutic efficacy. Factors like lipid composition, drug-lipid interactions, and processing conditions influence drug loading. Mechanistic insights into release kinetics involve lipid crystallinity, particle size, and surface modifications. Researchers aim to enhance targeted delivery using ligand conjugation and polymer coating techniques, while stimuli-responsive SLNs offer precise drug release control. These advancements promise to improve drug delivery and therapeutic outcomes [9].

The study focused on preparing deferoxamine (DFO) nanoparticles for the topical treatment of diabetic foot ulcers, revealing promising results with SLNs. These SLN formulations demonstrated an initial burst release followed by a slow, prolonged release pattern, crucial for sustained therapeutic effects with reduced application frequency. With high drug loading and the slowest release rate among formulations, SLNs emerged as a potential candidate for further development and clinical applications. Overall, the study highlights SLNs as effective carriers for achieving sustained release of DFO, promising for treating diabetic ulcers and other conditions requiring localized drug delivery [28]. The study focuses on utilizing SLNs to develop controlled-release systems for diabetic ulcer treatment, emphasizing formulation optimization for sustained and effective drug delivery at the ulcer site. The composition of nanoparticles influences the controlled release of deferoxamine, with the observed release profile showing an initial burst followed by sustained release. This research underscores the importance of precise formulation design in achieving controlled and prolonged drug release, which is crucial for enhancing therapeutic outcomes in diabetic wound healing.

Gomes et al. developed lipid nanoparticles (LNs) to encapsulate minoxidil and finasteride for treating alopecia, targeting the dermis and hair follicles. In vitro evaluation revealed a consistent, low-release profile of minoxidil from LNs, indicating sustained drug delivery. Physiological condition assessments showed that nanolipid carriers (NLCs) loaded with minoxidil provided prolonged release due to the solid-lipid matrix. Both minoxidil and finasteride remained encapsulated within NLCs, enhancing skin penetration. This encapsulation offers sustained release advantages, particularly beneficial for cosmetic formulations, ensuring a longer-lasting effect [29]. The study on LNs for alopecia treatment demonstrates promising controlled-release capabilities through physicochemical characterization, stable particle size, and sustained drug release profiles, particularly for minoxidil. The solid-lipid matrix of the nanoparticles ensures prolonged drug release under physiological conditions while maintaining high loading efficiency and stability over 28 days. Although challenges exist with the lipophilic nature of finasteride affecting release, the study highlights the potential of LNs for controlled drug delivery to the dermis and hair follicles. These findings have significant implications for advancing controlled release formulations in dermatology, emphasizing the importance of understanding drug properties and penetration behavior for optimizing therapeutic outcomes in alopecia treatment.

SLN suspensions prepared for vitamin A exhibit both immediate and prolonged release characteristics, offering dual benefits in dermal applications. The immediate release enhances drug penetration, while sustained release manages active ingredients' potential irritation or provides prolonged delivery. Retinol SLN demonstrated controlled release within the first

6 hours, followed by an increased release rate beyond 12-24 hours, surpassing nanoemulsion release rates [30]. The study on Vitamin A-loaded SLN for topical use presents a comprehensive investigation into the controlled-release properties of SLN, focusing on burst release and sustained release aspects crucial for dermal applications. By loading glyceryl behenate SLN with vitamin A, the research demonstrates controlled release behavior over 24 hours, with initial controlled release followed by an increase in release rate. This dynamic release profile showcases the potential of SLN as carriers for dermal drug delivery, offering both burst release for improved penetration and sustained release for prolonged drug supply to the skin. The findings highlight the versatility and effectiveness of SLN in providing tailored release kinetics, making them promising candidates for controlled drug delivery in topical formulations.

Thatipamula et al. studied the formulation and in vitro characterization of domperidone (DOM), a dopamine receptor antagonist widely used for motion sickness treatment. DOM was encapsulated in nanostructured lipid carriers (NLC) and SLN. Results showed that most SLN formulations exhibited Higuchi square root release kinetics, indicating matrix diffusion-based release. Both SLN and NLC formulations demonstrated controlled release over 24 hours in vitro studies [31]. Homogenization followed by ultrasonication proved to be a reliable method for preparing SLN and NLC formulations with desirable characteristics. The controlled-release potential of the formulations was demonstrated through in vitro release studies, showing sustained drug release over 24 hours. The formulations were also evaluated for stability, with NLC formulations exhibiting better stability over time than SLN. The study highlights the importance of formulation parameters such as lipid composition and surfactant concentration in influencing the release kinetics of the drug from the lipid particles, providing valuable insights for developing controlled-release drug delivery systems.

Nanoemulsions and Nanoemulgels

A surfactant stabilizes the dispersion of either water or oil droplets within the opposing phase in an emulsion system known as a nanoemulsion. Nanoemulsions, which have droplet sizes that typically range from 0.1 to 500 nanometers [32], improve medication penetration through the skin in transdermal gels, resulting in a faster beginning of action and better therapeutic outcomes [33]. Transdermal transport is aided by their surfactant content, which enhances membrane permeability. Nanoemulsions can efficiently regulate therapeutic release, improving the bioavailability of different therapeutic molecules [34].

An investigation into the development of nanoemulsions for the efficient administration of anti-inflammatory drugs, such as aceclofenac and capsaicin, was conducted to overcome difficulties related to skin formulations and enhance controlled-release drug delivery. These medications stop side effects while addressing pain, inflammation, and the advancement of the illness. The majority of the nanoemulsion formulations demonstrated sustained release of both encapsulated medicines for more than 72 hours, demonstrating a regulated release pattern. This strategy shows promise in lowering the gastrointestinal adverse effects of taking aceclofenac orally and improving capsaicin's ability to reduce itching when paired with anti-pain and anti-inflammatory drugs [35]. The study on Nanomiemgel presents a comprehensive evaluation of a novel drug delivery system for controlled release through a combination of nano micelles and nanoemulsion. Furthermore, the skin permeation studies revealed enhanced penetration and retention of aceclofenac and capsaicin in deeper skin layers, emphasizing the efficacy of Nanomiemgel in delivering drugs to targeted sites. The research provides valuable insights into developing a promising formulation for controlled drug release applications.

Ozdemir et al. formulated an etodolac nanoemulsion to address its poor aqueous solubility, with an in vitro release profile showing sustained release via non-Fickian drug transport. Initially, a burst effect was observed from the nanoemulsion-loaded gel, followed by sustained release, likely due to etodolac adsorption on droplet surfaces or dispersion within surfactants [36]. This release pattern mirrors findings for piroxicam, another poorly soluble drug, suggesting a promising approach for enhancing drug solubility and sustained release [37]. The study demonstrates the potential of nanoemulsions in achieving sustained release

of etodolac, with initial burst effects followed by a sustained release pattern. In vitro and ex-vivo studies highlight the importance of understanding release kinetics and permeation profiles for optimizing drug delivery systems. The application of mathematical models such as zero order and Korsmeyer-Peppas further elucidates the controlled-release mechanisms involved. Overall, the findings underscore the significance of nanoemulsions as a promising carrier for controlled drug release, offering insights for developing effective topical drug delivery systems in pharmaceutical technology.

Ciprofloxacin, a drug associated with precipitation at the corneal surface, and nanoemulsion were prepared for treating ocular keratitis. In vitro release and ex-vivo trans-corneal permeation studies showed sustained release and a 2.1-fold enhancement in permeation, respectively, compared to the commercial ciprofloxacin ophthalmic solution [38]. This study demonstrated the controlled release of ciprofloxacin from the optimized nanoemulsion formulation, which was found to be diffusion-controlled, indicating a sustained release profile. The ex-vivo trans-corneal permeation studies significantly improved trans-corneal flux and permeability compared to a commercial ciprofloxacin ophthalmic solution. These findings suggest that the nanoemulsion formulation has the potential to provide more effective and sustained delivery of ciprofloxacin for the treatment of bacterial keratitis, highlighting its promising role in controlled drug release for ocular infections.

Nanoemulgels, on the other side, are a different type of nanoemulsions. A hydrogel complexed with the nanoemulsion converts the formulation to a more convenient one that enhances skin penetration, stability, viscosity, and spreadability. The passage and delivery of drugs to the SC are improved, which may be attributed to the interaction of the oil droplets on the nanoemulgels and the lipids on the outer and superficial layer of the skin, stratum corneum. Nanoemulgels, with their unique characteristics of site-specific drug delivery and controlled drug release over an extended period, enhance topical drug administration's overall efficacy [39]. NEGs enhance the permeation of the drug as they can utilize all three pathways, the transcellular route, the paracellular route, and the transappendageal route, to transport the drug through the epidermis (Figure 3). The formulation consists of oils and surfactants alone or in combination with the cosurfactant, which acts as an inherent permeation enhancer and gelling agent that aids in increasing the permeability by enhancing the formulation's adhesion to the skin [34].

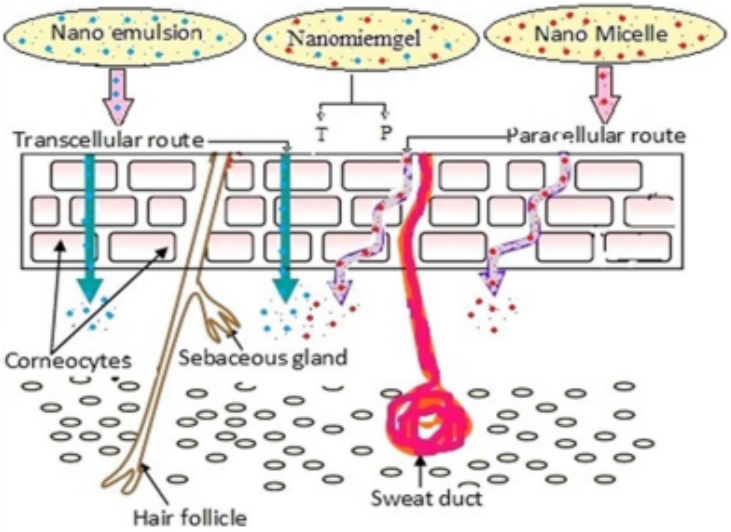


Figure 3. Possible ways of penetration and absorption of nanoemulsion as compared with nanoemulgels and nano micelles.

Nanoemulgels containing the antifungal drug posaconazole, known for its low oral bioavailability, were formulated. The emulgel demonstrated zero-order release, confirmed by Higuchi matrix kinetics, indicating drug release from

the polymer gel matrix through a diffusion mechanism. The constant rate of drug diffusion is attributed to solvent-induced relaxation and swelling in the polymer [40]. By optimizing the formulation using the Box-Behnken design, the researchers achieved a transparent nanoemulsion with enhanced drug content and desirable particle size. The in vitro drug release studies demonstrated sustained release behavior, with the optimized formulation showing a release of 79.40% at 24 hours. The drug release kinetics analysis indicated zero-order release with a diffusion mechanism, highlighting the controlled and sustained drug delivery potential of the nanoemulgels. Overall, this research significantly contributes to the field of controlled-release systems, emphasizing the efficacy and potential of nanoemulgels for sustained drug delivery applications.

Mao et al. formulated nanoemulgels containing eprinomectin, known for its hydrophobic nature, for transdermal application. In vitro transdermal penetration experiments revealed that eprinomectin permeated the skin constantly, with diffusion behaviors following zero-order kinetics [41]. This study showed that by combining eprinomectin with a nanoemulgel formulation, enhanced bioadhesive properties and prolonged retention on the skin were observed. The in-vivo evaluation demonstrated effective transdermal delivery, with the nanoemulgel allowing for sustained drug release into the dermis. This controlled-release mechanism, facilitated by the emulsion-hydrogel combination, shows promise for treating endo- and ectoparasites. The findings suggest that eprinomectin nanoemulgel could be a valuable tool in veterinary medicine for targeted and prolonged therapeutic effects against parasitic infections.

The authors developed an oxybutynin (OXB) nanoemulgel to address its systemic side effects and improve patient compliance for treating hyperhidrosis. Nanoemulgel synthesis resulted in sustained release properties and enhanced skin permeation compared to conventional gels [42]. The study on Oxybutynin-Nanoemulgel formulation for hyperhidrosis management combines nanoemulsions and gels to enhance the skin permeation of oxybutynin. Natural and semisynthetic polymers, particularly CMC-based nanoemulgels, were used in the formulation, which showed sustained drug release over 8 hours with significant skin permeation potential. Optimization with Design-Expert software highlighted key variables for stable nanoemulsions. Ex-vivo studies supported the efficacy of Oxybutynin-Nanoemulgel, suggesting its potential as a novel drug delivery system for hyperhidrosis. Further, in-vivo studies are needed to confirm clinical efficacy and safety.

Liposomes

Liposomes are microscopic spheres made from fatty materials, predominantly phospholipids. These tiny vesicles usually range in size between 10 to 1000 nm or more; an interior aqueous volume encased in an amphipathic lipid bilayer is part of these vesicles [43]. Liposomes are a regulated transdermal delivery technique because they can function as rate-limiting membrane barriers for modifying systemic absorption. When administered topically, the liposome's lipid bilayer can fuse with other bilayers (e.g., cell membrane), thus delivering the liposome contents and releasing the active ingredients within the cells. Thus, it is a long-acting delivery system, and the liposomes used have been surface-modified with active targeting ligands to improve the delivery of therapeutics to target cells [44]. This steady and regulated release of the medication from the liposomes is crucial [45].

Dapsone was formulated as a liposomal gel, and the drug's release was evaluated in vitro, indicating that the drug was released in a sustained manner [46]. In another liposomal formulation, a combination of 5-fluorouracil (5FU) and tretinoin treats actinic keratoses and skin warts. Tretinoin enhances the effectiveness of 5FU by aiding in skin exfoliation, thus shortening the duration of treatment. These drugs were formulated into liposomes, prolonging their release in vitro. For 5FU, release followed Korsemeyer-Peppas, Hixson, and zero-order kinetics, while tretinoin formulations followed Korsemeyer-Peppas, zero, and Higuchi kinetics. Lipophilic agents within liposomes exhibited delayed release due to their location within lipid bilayers. Increasing the phospholipid concentration reduced the drug release rate in dissolution studies [47]. The researchers optimized liposome formulations to achieve the desired drug entrapment efficiency and release profiles. The results demonstrated that varying

the concentrations of tretinoin and phospholipids significantly influenced drug release kinetics, with formulations showing sustained release patterns over time. The study's emphasis on characterizing the liposomes' properties, such as particle size and zeta potential, highlights the importance of these factors in controlling drug release behavior. The research provides valuable insights into designing liposomal systems for controlled drug delivery, particularly dermatological applications.

Lipid-Polymer Hybrid Nanoparticles

The most researched and thoroughly characterized nanoparticles are liposomes and polymeric nanoparticles. Lipid-polymer hybrid nanoparticles (LPHNPs) are designed to solve the drawbacks of polymeric and liposome nanoparticles, including drug leakage, limited circulation times, and structural instability, while also leveraging their positive attributes. Their potential in controlled-release formulations and targeted medication delivery has been assessed [48]. Owing to the combined properties of polymeric and liposomes, it has become a stable drug delivery platform with a wide range of uses, including gene delivery, cancer diagnosis and treatment, and vaccine adjuvants [49, 50]. Slow drug diffusion, better drug-loading, avoidance of nonspecific release, reduction of dose-dependent toxicity, improved stability, and regulated drug administration are all made possible by the lipid-polymer hybrid system [51].

Hesperidin, a bioflavonoid with notable wound-healing effects, has limited bioavailability in topical applications due to its poor solubility and absorption. In a study where it was formulated into lipid-polymer hybrid nanoparticles, the drug's release profile was evaluated in vitro. An initial burst release of hesperidin occurred, likely due to its rapid diffusion from the nanoparticle's lipid outer layer. This phase enhances early drug availability. Subsequently, a sustained release followed, likely driven by the lipid-drug interaction, which slowed hesperidin's release from the polymer core. These results suggest that lipid-polymer hybrid nanoparticles are a promising system for the prolonged release of hesperidin in skin delivery applications [52]. Utilizing a lipid-polymer hybrid system, the researchers achieved slow drug diffusion, improved drug loading, and controlled release, addressing key challenges in traditional drug delivery methods. Response surface methodology and Box-Behnken design allowed for optimizing HLPHNs, leading to stable formulations with sustained drug-release properties. The findings suggest that HLPHNs have the potential to serve as an effective delivery system for bioactive drugs, offering controlled-release benefits that could enhance therapeutic outcomes and minimize potential side effects. Further research could pave the way for developing advanced controlled-release formulations with improved efficacy and safety profiles.

In another study, norfloxacillin was formulated as a lipid-polymer blend nanoparticle for topical delivery. The results of this study have shown that burst release of the drug at the beginning of the dissolution test then followed by a sustained release for a relatively longer time, which is attributed to the presence of a lipid bilayer made up of lipid and stearyl amine, which acts as a rate-limiting membrane for the release of the encapsulated drug. It was also concluded that the polymer and the lipid concentration modified drug release [53]. The findings reveal that the formulation with a higher lipid concentration exhibited sustained drug release, attributed to the lipid bilayer acting as a rate-limiting membrane. The study also highlights the importance of kinetic modeling, with the Korsmeyer-Peppas model fitting well to the release data, indicating a diffusion-controlled drug release mechanism. Overall, the research provides valuable insights into optimizing lipid-polymer hybrid nanoparticles for controlled drug delivery, emphasizing the significance of formulation parameters in achieving desired release profiles.

Alasidan and colleagues' research on the preparation of lipid-polymer hybrid nanoparticles for topical hydrocortisone delivery also revealed that all formulated batches of hydrocortisone release demonstrated a biphasic release behavior, with an initial burst release occurring within the first 4 hours and a sustained release occurring over the remaining 8 hours. While the sustained terminal release of hydrocortisone was thought to be caused by the encapsulated drug slowly diffusing through a similar matrix (both hydrocortisone and the lipomer matrix are hydrophobic), the rapid initial release of the drug may have been caused by drug molecules adsorbed onto the surface of nanoparticles [54].

The study on hydrocortisone-loaded lipid-polymer hybrid nanoparticles for controlled topical delivery demonstrates a systematic approach to optimizing a nanoparticle formulation for efficient drug release. The researchers achieved a controlled-release profile of hydrocortisone. The in vitro release studies showed a biphasic release pattern with an initial burst followed by sustained release, indicating the potential for prolonged drug action. Furthermore, the formulation exhibited promising anti-inflammatory effects in an in-vivo model, highlighting its therapeutic potential. Overall, the study provides valuable insights into designing nanoparticle systems for controlled drug release, with implications for enhancing the efficacy and safety of topical drug delivery.

Cubosomes

Cubosomes, nanostructured particles made of a bicontinuous cubic liquid crystalline phase, are also called liquid crystal nanoparticles. These nanoparticles form a unique microstructure by self-assembling from certain surfactants and water. Cubosomes have rheological characteristics comparable to those of solid materials, exhibiting traits of both liquids and solids [55]. Drug release that is regulated or prolonged can be achieved by cubic-phase liquid crystals [56]. The distinct microstructure of the cubic phase is thought to regulate the release of trapped molecules since the active component needs to diffuse through the extremely porous morphology—which has varying pore sizes and water channel tortuosity—to reach the external solution [57].

Shi and his colleagues designed and characterized topical gel-based oleanlic acid (OA) nanoparticles in a controlled release form. OA is a terpenoid extracted from plants and used for its diverse pharmacological activities, including antioxidant, hypoglycemic, anti-inflammatory, antibacterial, and hepatoprotective. It has a very limited oral bioavailability of approximately 0.7%. An attempt has been made to improve its bioavailability, including the formulation of this extract by solid dispersion and nanoemulsions for topical administration. The optimized OA nanoparticle demonstrated in vitro drug release characteristics more accurately described by Higuchi's equation. This implies that both diffusion and swelling may have played a role in controlling the release of the drug [58]. The optimized gel formulation showed uniform texture, suitable pH, and efficient drug release characteristics, with up to 87.89% release over 12 hours. The biphasic release profile, with an initial burst effect followed by sustained release, indicates the formulation's ability to provide immediate therapeutic effects while maintaining prolonged drug concentrations at the target site. The in-vivo anti-inflammatory studies further support the efficacy of the LCNP-based gel in delivering oleanolic acid for therapeutic benefits. Overall, the study highlights the significance of LCNP-based systems in achieving controlled and sustained drug release for enhanced therapeutic outcomes.

Acyclovir, known for its poor ocular bioavailability, was formulated as cubosomes and thoroughly characterized. The release profile demonstrated rapid release in the initial hours of the experiment, with approximately 81.60%±3.45 % of the total Acyclovir content released after 8 hours, mainly from the precursor lamellar phase. The data were analyzed using four release kinetic models (zero order, first order, Higuchi, and Korsmeyer-Peppas) to delve deeper into the release mechanism. The Higuchi model exhibited the best fit, with a high linear correlation coefficient (R2) of 0.9944, suggesting a diffusion-controlled-release mechanism [59]. The study demonstrates the potential of lyotropic liquid crystals in addressing the challenges of traditional ophthalmic drug delivery systems by providing sustained drug release and enhanced corneal retention. The controlled-release profile of Acyclovir from the cubic-phase matrix, analyzed through various kinetic models, highlights the diffusion-controlled-release mechanism with a high correlation coefficient. The comparison with negative and positive controls further validates the efficacy of the proposed system. Overall, the research offers valuable insights into the controlled-release capabilities of bioadhesive liquid crystals for ophthalmic applications, emphasizing their potential for improving drug delivery efficiency and therapeutic outcomes.

Silica Nanoparticles

As nanocarriers, silica nanoparticles are now widely used to deliver various medications with different physicochemical, pharmacokinetic, and pharmacodynamic properties. Their main

uses in drug delivery are to enable targeted drug administration, facilitate regulated release, and increase the rate at which poorly soluble medicines in water dissolve [60]. Highly promising silica nanoparticles (SNPs) have shown promise in augmenting drug penetration through the skin, improving therapeutic effects. It has been demonstrated that these therapeutic SNPs can function as transdermal formulations or as local delivery systems for bioactive substances to reach the skin. They enable encapsulated actives to be released under control and, in some situations, on demand. Drugs with limited stability and water solubility can have their physicochemical stability, and apparent solubility increased by nanoencapsulation [61].

A group of researchers in the USA formulated and encapsulated curcumin using nanoparticles for topical antimicrobial and wound healing, and the formulation's in vitro drug release profile was studied. The characterized nanoparticle formulation exhibited prolonged-release curcumin delivery for an extended period in a controlled and sustained release manner (Table 1) and better therapeutic efficacy [62]. Nanoparticles have been shown to cross the skin barrier, and the high drug-loading capacity of these carriers can be used as a strategy to control the retention and release of therapeutics [63]. The study demonstrates enhanced drug release profiles under specific stimuli like low pH and near-infrared laser irradiation. These modifications improve the stability of the nanocarrier and biocompatibility and enable targeted and sustained drug release, making Curcumin-loaded mesoporous silica nanoparticles (MSNs) a promising platform for controlled drug delivery systems. Incorporating environment-responsive elements, such as glutathione and guanidine functional groups, further enhances the specificity and efficiency of drug release, showcasing the potential of MSNs in precision medicine and personalized therapy strategies.

Mehemood et al. [64] synthesized mometasone furoate in MSNs for nasal delivery; the release profile of mometasone from silica nanoparticles in vitro displayed a biphasic sustained release pattern. The synthesized formulations demonstrated an initial slow-release phase followed by a continuous-release pattern. The initial release was relatively high because of the presence of the weakly entrapped drug. Subsequently, sustained release was observed due to slow diffusion and release of drugs from the polymer matrix [64]. The study demonstrates the potential of the nano-nasal spray formulation to sustain drug release for up to 8 hours, with a biphasic release pattern observed in vitro. By employing kinetic modeling, the formulation was found to follow anomalous zero-order and Korsmeyer-Peppas release kinetics, indicating controlled drug release behavior. These results suggest that the developed formulation offers a promising approach for improving localized cytokine release syndrome treatment through enhanced drug delivery efficiency, prolonged drug action, and potentially reduced systemic side effects, highlighting the significance of controlled-release mechanisms in optimizing therapeutic outcomes for nasal drug delivery applications.

In another study by Mo et al., who formulated erianin, an active molecule used in psoriasis for its inhibitory effect on keratinocyte proliferation, in the form of dendritic mesoporous nanospheres for topical delivery, silica nanoparticles were able to release erianin in a controlled-release manner. Initially, there was a burst release of erianin within 24 hours due to some deposition of erianin on the outer surface of the dendritic mesoporous nanoparticles. Subsequently, erianin sustained release within 4 hours, indicating strong hydrogen bonding interactions between silanol groups from mesopore channels and erianin molecules [65].

Carbon Nanotubes

Carbon nanotubes (CNTs) are cylindrical molecules composed of carbon atoms. They are formed by rolling a graphene sheet into a seamless tube, which can be capped or open-ended. CNTs exhibit a high aspect ratio, with diameters as small as 1 nanometer and lengths extending to several micrometers [66]. The two commonly used carbon nanotubes are single-walled carbon nanotubes (SWCNT) consisting of a single graphene sheet wrapped around to form a cylinder, and multi-walled carbon nanotubes (MWCNT) are concentrically nested cylinders of graphene sheets [67].

Carbon nanotubes (CNTs) are highly valued in biomedicine for their large surface area, strength, biocompatibility, high drug-loading capacity, and targeted release capabilities.

However, concerns remain regarding their toxicity and biodegradability [68]. Carbon nanotubes' potential has been elucidated well for most routes, but little is known for topical delivery. In transdermal delivery, CNTs are designed to stay on the SC, releasing the drug to cross skin barriers and enter the bloodstream. Various polymers are typically used to disperse CNTs and form a thin film [69].

A study exploring carbon nanotube (CNT) gels for topical delivery of fluconazole, an antifungal drug characterized by low solubility and poor dermal absorption, achieved a high drug-loading efficiency of 89% and superior release of 91.93% after 8 hours with the optimized formulation. Stability tests showed consistent pH and drug content over three months, indicating robust formulation stability. With favorable spreadability and viscosity, CNT gels demonstrate significant potential for enhancing the bioavailability and targeted delivery of poorly soluble drugs, warranting further clinical investigation. Its efficacy cannot be predicted, so clinical studies are needed to understand its biological metabolism [70].

Quercetin, an antioxidant drug characterized by low solubility and stability, was formulated as a carbon nanotube for cancer treatment through topical delivery. The study introduces a controlled drug delivery system using modified single-walled carbon nanotubes (SWNTs) for quercetin, highlighting its pH-sensitive release. Quercetin release was significantly higher at acidic pH (61.5% at pH 5.5) compared to neutral pH (32% at pH 7.4) due to the disruption of hydrogen bonds in acidic conditions. With a loading efficiency of approximately 38%, this system enhances quercetin's therapeutic potential by ensuring higher drug concentrations in the tumor microenvironment while minimizing systemic exposure, thereby improving its efficacy in cancer treatment [71].

Protein-Based Nanoparticles

Protein-based nanomaterials, including those from albumin, collagen, silk, and gelatin, offer advantages like biodegradability, non-antigenicity, metabolic compatibility, stability during storage, ease of availability and preparation, and high drug-loading capacity (Figure 4). These nanoparticles can be modified for targeted drug delivery and are used in cancer and tumor therapies, vaccines, and pulmonary delivery. They can also be incorporated into biodegradable polymers as microspheres for controlled, sustained release and can covalently bond with drugs and ligands for precise targeting [72].

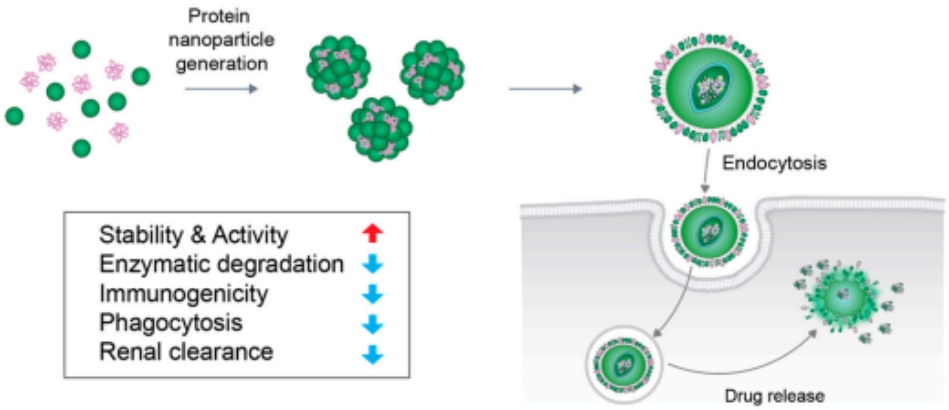


Figure 4. Delivery of protein nanoparticles to the cell and typical advantages of protein nanoparticles as a drug delivery system.

Protein nanoparticles can be embedded within biodegradable polymers in a microsphere structure to enable controlled and sustained drug release. The primary goal of designing nanoparticles as a drug delivery system is to optimize particle size, surface area, and surface properties. This ensures that nanoparticles carrying adequate drug doses can achieve targeted pharmacological effects by releasing active agents for site-specific action [73].

Asprin was formulated using albumin nanoparticles to combat diabetic retinopathy. Conventional ophthalmic dosage forms suffer from poor bioavailability in the eye's posterior chamber. Nanotechnology offers a solution: by adjusting aspirin-albumin ratios (0.06 to 1.0), we created stable, pharmacologically active aspirin-loaded albumin nanoparticles (<200 nm diameter, low polydispersity). In vitro studies showed sustained aspirin release (90% over 72 hours) and a targeted 11% release in the posterior chamber under simulated conditions. The formulation remained stable for six months and retained stability for 24 hours post-reconstitution. The coacervation method was used, resulting in 81% drug entrapment [74].

In a study by Kanazawa et al., an oligopeptide nanocarrier was developed to deliver siRNA and manage atopic dermatitis. Due to the low delivery efficiency of siRNA alone to target tissues and cells, achieving a strong therapeutic effect is challenging. However, protein nanoparticles were shown to enhance delivery efficiency. Specifically, the nanocarrier delivered anti-RelA siRNA, targeting RelA—the key NF-κB subunit involved in producing inflammatory cytokines. It suppresses TNF-α and IL-6 production, effectively alleviating atopic dermatitis-like symptoms in model mice [75].

Nanocomposites

A nanocomposite is a multi-phase solid material in which one phase has one, two, or all three dimensions below 100 nm. This advanced material features nano-scale fillers dispersed within a matrix. The structure of a nanocomposite consists of a matrix-filler configuration, where fillers such as particles, fibers, or fragments are distributed and bonded as distinct units within the matrix. Nanocomposites are known for their advantages, including being highly dispersible in an aqueous medium. Uniform distribution of the active agent over an extended time, controlled drug release, and reduced administration frequency [76].

Molybdenum disulfide nanosheet-based nanocomposite is used for the topical delivery of umbelliferone, a potent anti-inflammatory, antioxidant, and analgesic drug with limited water solubility. The Carbopol 934 gel loaded with nanocomposite exhibited a biphasic drug release pattern, with a rapid initial release (about 65.7 ± 3.6% within the first 3 hours), followed by a slower, more gradual release in subsequent stages. A more sustained release profile was achieved, with up to 94.8 ± 4.7% of the drug released over 24 hours. In contrast, the conventional gel showed a similar release pattern to F1 for the initial 3 hours, reaching 34.7 ± 1.9%, but the overall release was lower at all-time points thereafter. The in-vivo anti-inflammatory test restricted the edema by 27% beyond other formulations. The in-vivo analgesic test also showed that the nanocomposite gel exhibited analgesic activity superior to all other treated groups [77].

Pros, Cons, and Translational Challenges of Nanotechnology Toward Topical Drug Delivery

Nanotechnology in topical drug delivery offers enhanced penetration and absorption, allowing drugs to reach deeper skin layers effectively for localized treatments of skin disorders. Nanoparticles provide controlled drug release, improving efficacy and patient adherence by reducing application frequency. Their targeted delivery to specific cells or tissues minimizes side effects and maximizes therapeutic outcomes. Additionally, nanotechnology improves drug stability by protecting compounds from environmental degradation, and nanoparticles' versatility allows formulation in creams, gels, and patches suitable for various skin types. Reduced systemic absorption is another advantage, lessening systemic side effects, particularly for toxic drugs. However, nanotechnology also presents challenges, including potential skin irritation or toxicity, high production costs, and regulatory hurdles. Environmental concerns arise as nanoparticles can accumulate in water, affecting aquatic life, and stability issues may complicate storage. There is also a risk of unintended systemic exposure, especially through damaged skin, underscoring the need for careful safety evaluation [78].

The translational challenges associated with nanomedicines (NNMs) are multifaceted and significant. Key hurdles include the complexity of large-scale manufacturing that meets Good Manufacturing Practice standards, which involves issues related to reproducibility, infrastructure, techniques, expertise, and cost. Additionally, ensuring biocompatibility and safety for human use requires thorough preclinical

evaluations, including validated assays for early toxicity detection and understanding of in-vivo behavior. Regulatory hurdles and intellectual property issues further complicate market entry, regardless of the therapeutic benefits of NNMs. Moreover, a lack of understanding of the pharmacokinetics and pharmacodynamics of NNMs can lead to limited specificity and stability in biological systems, resulting in unsatisfactory preclinical outcomes that do not translate to human efficacy. Finally, the overall cost-effectiveness of NNMs compared to existing therapies is a crucial consideration that can impact their adoption in clinical settings. These challenges underscore the need for ongoing research and development to facilitate the successful translation of nanomedicines from the laboratory to clinical practice [79, 80].

Perspectives

Nanomedicine is becoming an exciting field when it comes to drug delivery. Several research studies are underway at the laboratory and clinical trial levels. Future research in the field of controlled-release nanoparticles for topical drug delivery should focus on addressing existing challenges and exploring novel strategies to improve efficacy and safety. Advanced drug delivery systems, such as stimuli-responsive nanoparticles and microfluidic-based synthesis techniques, hold promise for personalized and precision medicine.

Close collaboration between researchers, clinicians, and industry stakeholders is essential to accelerate the translation of nanoparticle-based topical formulations from the bench to the bedside. Innovative solutions can be developed using synergistic expertise in materials science, pharmacology, and dermatology to meet the unmet needs of patients and improve healthcare outcomes.

Ongoing research emphasizes the potential benefits of Smart Nanoparticles (NPs), which are capable of providing sustained, extended-release drug delivery that offers advantages from both clinical and physiological perspectives. There is increasing recognition of the value of localized treatment and prolonged drug release in achieving therapeutic results while minimizing adverse effects, especially by reducing drug interactions and drug level fluctuations. Consequently, developing NPs with combined extended-release and targeted-delivery properties remains a prominent area of intense investigation. The convergence of nanoparticles with microneedles and 3D-printed materials presents a transformative approach to topical drug delivery by enabling precise, controlled, and minimally invasive treatments. Microneedles allow nanoparticles to bypass the outer skin layers, achieving deeper penetration and reducing systemic side effects. 3D printing further enhances customization, enabling patient-specific microneedle patches that deliver sustained and complex drug formulations. Hybrid systems could integrate sensors for "smart" responsive drug release, but challenges remain in scalability, cost, and regulatory approval. As materials science and precision engineering evolve, these combined technologies could lead to advanced, accessible topical therapies tailored to individual patient needs.

Conclusion

Topical and transdermal administration remain as alternative routes for the administration of drugs with problems such as poor solubility, stability, first-pass metabolism, and others. The route is also suitable for administering controlled-release formulations, including nanoparticles, which have been tested by many studies, as indicated in this review. Controlled release has been shown to enhance solubility and therapeutic activity, reduce toxicity, and provide sustained release of the drugs when administered topically. A range of nanoparticle products, including polymeric nanoparticles, LNs, nanocapsules, nanospheres, SLNs, silica nanoparticles, carbon nanotubes, nanocomposites, and protein nanoparticles loaded with antiemetic, anti-inflammatory, antifungal, antiasthmatic, anti-pain, antimicrobial, antioxidant drugs and biological products has been tested as controlled-release delivery systems for topical drug delivery. Despite challenges such as scalability and safety concerns, ongoing research efforts continue to drive innovation in nanoparticle design, formulation, and manufacturing processes. When these challenges are addressed and emerging technologies are leveraged, controlled-release nanoparticles have the potential to revolutionize the field of dermatological and transdermal drug delivery, paving the way for improved therapeutic outcomes and enhanced patient care. Novel formulations can

be developed by combining these nanoparticles with other delivery instruments, including micro needles and 3D-printed materials. Integrating nanoparticles with microneedles and 3D-printed materials represents a promising future for nanotechnology in drug delivery, enabling precise, customizable, and minimally invasive treatments. As materials and 3D printing advancements continue, this approach could revolutionize personalized medicine, allowing for responsive, effective, and accessible topical therapies tailored to individual needs.

Author's note: The author designed the review, acquired, analyzed, and interpreted the data and wrote the article. The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Funding: This research did not receive specific grants from public, commercial, or non-profit funding agencies.

Conflicts of Interest: The author declares no conflict of interest. For a written statement please write to the journal office..

Quote this article as Mengesha Y, Nanotechnology-Enhanced Controlled-Release Systems in Topical Therapeutics, Precis. Nanomed. 2024, 7(4):1365-1385, https://doi.org/10.33218/001c.127336.

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