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Review Article

NANOTECHNOLOGY IN TOPICAL DRUG DELIVERY: ENHANCING EFFICACY AND OVERCOMING LIMITATIONS

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ABSTRACT

Topical drug delivery systems have evolved from ancient plant-based treatments to sophisticated formulations. These systems offer advantages like localized therapeutic effects, avoidance of first-pass metabolism, and circumvention of enzymatic drug degradation. However, conventional topical formulations have limitations such as poor skin penetration, limited efficacy, and potential skin irritation. Nanotechnology has revolutionized topical drug delivery by addressing these challenges using nanocarriers, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions, dendrimers, nanosponges, carbon nanotubes, mesoporous nanoparticles, and metallic nanoparticles. These nanocarriers enhance drug penetration, improve drug stability, and enable targeted drug delivery. They also offer potential for controlled release, increased bioavailability, and reduced toxicity. Nanotechnology has clinical applications in wound healing, anti-aging, cancer therapy, pain management, cosmetics, chronic skin disorders, and growth factor delivery. Despite their advantages, nanocarriers face challenges, including potential toxicity, complex synthesis procedures, and high production costs. Nanotechnology is anticipated to become increasingly significant for the development of novel and effective topical drug delivery systems.

Keywords: Topical drug delivery, Nanotechnology, Nanocarriers, Skin penetration, Targeted delivery

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INTRODUCTION

Topical drug delivery systems (TDDS) are designed to administer medications directly to the skin or mucous membranes, offering a non-invasive and localized approach to treatment. Over the years, topical drug delivery has evolved significantly since its inception in ancient times [1]. The evolution from simple plant-based treatments applied topically to refined, scientifically developed formulations. This has led to a deeper understanding of skin physiology, drug pharmacokinetics, and development of novel delivery technologies [2].

Topical formulations play a crucial role in treating a wide range of conditions, from dermatological disorders to pain management and hormone replacement therapy. These systems allow localized therapeutic effects, avoid first-pass metabolism, and circumvent enzymatic drug degradation in the gastrointestinal tract. Topical hormone replacement therapies have become increasingly popular in endocrinology because of their ability to avoid first-pass metabolism and deliver stable hormone levels [1, 3].

To support the present review, an extensive literature search was conducted using databases such as PubMed, Scopus, ScienceDirect, and Google Scholar. Keywords included “nanotechnology,” “topical drug delivery,” “nanocarriers,” “skin penetration,” and “targeted delivery.” Filters were applied to include only English-language articles published between 2014 and 2024. Preference was given to peer-reviewed original research articles, reviews, and clinical studies that focused on nanocarrier-based topical and transdermal drug delivery systems.

Advantages of topical drug delivery

Topical drug delivery offers several key benefits, making it a preferred route for both localized and systemic therapies. One of the primary advantages is its ability to bypass the gastrointestinal tract and hepatic first-pass metabolism, thereby reducing systemic side effects and improving its bioavailability. The direct application of the system at the site of action ensures enhanced therapeutic efficiency and minimizes drug loss. Additionally, topical application is non-invasive, painless, and facilitates ease of self-administration, which improves patient compliance. It also allows sustained drug release and localized action over an extended period [4, 5].

Disadvantages

However, this route also has limitations. The primary barrier to effective drug delivery is the skin itself, particularly the stratum corneum, which restricts the penetration of large or hydrophilic molecules. Interindividual variability in skin thickness, hydration, pH, and lipid content further affect the extent and consistency of drug absorption. Some formulations may cause local skin irritation or allergic reactions [1].

Conventional topical formulations

Conventional formulations are diverse and have been extensively used for local and systemic drug administration through the skin. There are a wide range of formulations, including dusting powders, poultices, lotions, liniments, solutions, emulsions, suspensions, creams, gels, ointments, and pastes.

Limitations of conventional topical formulations

- Skin barrier: The skin's natural protective barrier presents a major challenge that hinders the effective uptake and diffusion of numerous therapeutic agents into the body. The absorption and penetration of drugs into the skin are influenced by several physiological factors. These include skin thickness, moisture content, pH level, and dermatological conditions, such as eczema and psoriasis.

- Molecular size: The size of drug molecules, typically measured in Daltons (Da). Larger molecules encounter significant resistance because of tightly packed lipids in the stratum corneum. Smaller molecules (<500 Da) generally exhibit enhanced penetration across the skin [4].

- Molecular Weight: The mass of drug molecules influences their ability to diffuse through the skin. To overcome this barrier, drugs with high molecular weights may require alternative delivery mechanisms. Molecules with lower molecular weights (<500 g/mol) were more likely to penetrate effectively.

- Lipophilicity: The solubility of a drug in lipids versus water is often indicated by its log P value. Highly lipophilic drugs may accumulate within lipid layers. Optimal penetration was achieved at moderate lipophilicity (log P-values of 1-3).

- Hydrophilicity: The tendency of a drug to dissolve in aqueous environments makes it difficult for hydrophilic drugs to cross the stratum corneum and often requires penetration enhancers or specialized delivery systems for effective absorption.

- Polarity refers to the distribution of electrical charges or the balance between the hydrophilic (water-attracting) and hydrophobic (water-repelling) properties within a molecule. Polar molecules face challenges when penetrating the lipophilic barrier of the skin. Nonpolar drugs typically exhibit better penetration, but may have solubility issues in the systemic circulation.

- Ionization: The degree to which a molecule is charged is influenced by the pKa of the drug and skin pH. Ionization states vary with the skin pH (approximately 5.5), which affects drug absorption. Nonionized molecules generally demonstrate superior penetration.

- Solubility: The capacity of a drug to dissolve in lipids and aqueous environments. Excessive solubility in one phase can hinder penetration across all skin layers. Drugs with balanced solubility in the lipid and aqueous phases exhibit better diffusion [21, 22].

The challenges faced by conventional formulations can be overcome by using nanotechnology. The primary challenge in topical drug delivery is the skin barrier, particularly the stratum corneum, which limits the diffusion of the drug molecules. This barrier function significantly reduces the bioavailability and efficacy of the therapeutic agents. Nanotechnology offers solutions to this problem by utilizing nanocarriers such as liposomes, polymeric nanoparticles, and gold nanoparticles to enhance drug penetration across the skin barrier.

Table 1: Conventional topical formulations

S. No.	Formulation	Description	References
1.	Dusting powders	Topical powders consist of finely divided drug particles that are applied directly onto the skin. They are useful for absorbing moisture, protecting the skin, or delivering drugs to localized areas.	[6, 7]
2.	Poultices (Cataplasm)	A mixture composed of herbs, plants, and other ingredients known for their healing effects. This mixture is placed in a warm, damp cloth and then applied to the body to alleviate inflammation and accelerate the healing process.	[8]
3.	Lotions	Lotions are liquid preparations containing suspended or dissolved drug particles.	[9]
4.	Liniments	Liniments are liquid preparations containing active ingredients dissolved or suspended in alcohol, oil, or water.	[9, 10]
5.	Solutions	Topical solutions are liquid formulations with lower viscosity, typically composed of water, alcohol, and occasionally oil, designed for application on the skin.	[11]
6.	Emulsions	An emulsion is a two-phase liquid mixture where one liquid is dispersed in the form of tiny droplets within another liquid, which acts as the continuous phase.	[12, 13]
7.	Suspensions	Suspensions are a type of biphasic liquid dosage form where tiny solid particles, measuring between 0.5 and 5.0 microns, are distributed within a liquid or semisolid medium.	[14]
8.	Creams	Creams are semisolid mixtures made up of water and oil components, stabilized by emulsifying agents.	[15, 16]
9.	Gels	Gels are semisolid systems composed of a network of colloidal particles dispersed in a liquid phase.	[17]
10.	Ointments	Ointments are semi-solid formulations designed for application on the skin or mucous membranes, offering a protective barrier and moisturizing effect.	[18]
11.	Pastes	Pastes are semisolid preparations containing a high concentration of solid particles dispersed in a suitable base, such as petrolatum	[19, 20]

Although conventional topical formulations offer many benefits, they often struggle to effectively penetrate the skin barrier, resulting in poor drug delivery and limited efficacy.

Nanotechnology for topical drug delivery

Nanotechnology involves the study of physical, chemical, and biological properties of nanoscale structures. The distinct properties observed at the nanoscale have enabled the development of new materials and devices with improved functions, making nanotechnology particularly important across various sectors, including medicine [23]. Nanotechnology has revolutionized drug delivery systems (DDS), offering numerous advantages over traditional methods. They are used to design and create nanoparticles, nanocarriers, or nanostructured materials that can carry and release therapeutic agents more effectively than traditional systems. These nanosized systems can be tailored to improve drug bioavailability, stability, and targeting [24, 25].

Nanocarriers can be engineered to incorporate both lipophilic and hydrophilic drugs and it also address the issues related to their molecular size, weight, and solubility [26]. The small size of nanocarriers (typically 1-200 nm) allows better interactions with skin structures, potentially facilitating drug passage through intercellular spaces or hair follicles. Nanotechnology-based formulations can enhance drug stability, increase residence time on the skin, and improve patient compliance through less frequent application [26–29].

Advantages of nanotechnology in topical drug delivery

Nanotechnology has revolutionized the field of topical cosmetics and pharmaceuticals by offering numerous advantages and applications. Its application addresses the challenges faced by traditional systems, such as poor skin penetration, rapid drug degradation, and short-term therapeutic effects.

Nanocarriers, including liposomes, nanoparticles, and nanoemulsions, have revolutionized topical drug delivery by enhancing skin penetration. These vehicles, ranging from 1 to 200 nm in size, can encapsulate both hydrophilic and lipophilic drugs, overcoming the limitations related to molecular size, weight, and solubility. Their diminutive dimensions enable superior interactions with skin structures, potentially facilitating drug passage through intercellular spaces or hair follicles. By localizing drug delivery and improving targeting, nanocarriers can minimize damage to normal cells and reduce systemic side effects. Furthermore, they protect drugs from degradation, enhance their solubility, and increase their bioavailability in the skin. This targeted approach not only minimizes systemic absorption and potential adverse effects but also improves drug stability, making nanocarriers a promising solution for efficient and safe topical drug administration [5, 24].

Disadvantages of nanotechnology in topical systems

Nanocarriers in topical drug delivery systems present both advantages and challenges. Although they offer enhanced drug penetration and targeting, some nanocarriers raise toxicity concerns, especially if they are non-biodegradable or lack biocompatibility. This can potentially lead to adverse effects on skin health or systemic toxicity if absorbed. In addition, stability issues during storage or application may compromise the efficacy of nanocarrier-based formulations. The complexity of developing and manufacturing nanocarrier-based topical DDS often translates to higher costs compared to conventional formulations.

Types of nanocarriers used for topical drug delivery

Conventional drugs often suffer from poor solubility, low bioavailability, and a lack of targeted delivery. Nanocarriers have been

designed to address these limitations by protecting the drugs, enhancing their delivery to specific sites, and controlling their release.

Lipid-based nanocarriers

Liposomes

Liposomes are concentric bilayer vesicles with membranous lipid bilayers that completely enclose the aqueous phase. These bilayers are mostly composed of synthetic or natural phospholipids. Their capacity to incorporate both hydrophilic and hydrophobic drugs, along with their biocompatibility, make them useful in drug delivery systems. Liposomes are classified as unilamellar (single bilayer) or multilamellar (multiple bilayers), with the number and size of the bilayers influencing drug encapsulation and circulation half-life.

Various methods are employed to prepare liposomes, including microemulsification, solvent evaporation, thin-film hydration, extrusion, sonication, solvent injection, and detergent removal [30]. In topical drug delivery systems, liposomes offer several benefits, such as improved penetration of drugs into tissues, enhanced solubility of both lipophilic and amphiphilic drugs, and sustained drug release [27]. These advantages are particularly essential for local treatment, thus reducing the need for frequent application. However, liposomes also have limitations, including the risk of oxidation and hydrolysis of phospholipids and the possibility of drug leakage, which could potentially reduce their efficacy [28].

Solid lipid nanoparticles

SLNs have been developed as alternatives to conventional lipid carriers, like emulsions, liposomes, and polymeric nanoparticles, owing to their minimal toxicity and simple manufacturing processes. They are produced using various techniques, including solvent evaporation, microemulsion, high-pressure homogenization, and ultrasound-assisted synthesis [31].

SLNs offer numerous advantages, such as high biodegradability and biocompatibility, sustained and controlled drug release, and capacity to incorporate both hydrophilic and hydrophobic molecules. In addition, SLNs can be manufactured without the need for organic solvents and can enhance drug absorption and dissolution, thereby improving bioavailability. They also have limitations, including reduced drug-loading capacity and drug leakage during storage. The solid matrix creates a nearly perfect crystal lattice, which restricts the space available for drug incorporation [32, 33].

Nanostructured lipid carriers (NLCs)

Nanostructured Lipid Carriers (NLCs) are designed to overcome the limitations of Solid Lipid Nanoparticles (SLNs) by incorporating liquid lipids into the solid lipid matrix, thereby creating imperfections in the crystal structure. NLCs are a combination of lipids and solids stabilized by surfactants and cosurfactants. The composition of an NLC typically consist of approximately 0.1 to 30% lipid components in the matrix, 0.5 to 30% surfactants and cosurfactants, and 5% drug, with the remaining component being water [32, 34]. Several techniques are employed to prepare NLCs, including phase inversion, solvent injection/displacement, solvent diffusion, solvent emulsification evaporation, high-pressure homogenization, microemulsion, and probe sonication. These methods allow for the creation of NLCs with specific properties tailored to their intended use [33–35].

NLCs offer numerous benefits such as increased stability, better drug-loading capacity, and the potential to deliver both hydrophilic and lipophilic drugs. Their biocompatibility and biodegradability contribute to their reduced toxicity, making them attractive candidates for various pharmaceutical applications. However, NLCs are not without limitations. There are concerns regarding their potential for cytotoxicity, and some surfactants used in NLC formulations may cause skin irritation or other adverse effects [36].

Polymeric nanoparticles

Polymeric nanoparticles are colloidal structures composed of synthetic or natural polymers, with sizes ranging from 1 to 1000 nm. Direct polymerization of monomers and dispersion of preformed polymers are two techniques used for the preparation of polymeric nanoparticles. These nanocarriers are tailored to have specific surface properties to improve drug stability and achieve controlled release profiles [37, 38].

Furthermore, they are designed to respond to stimuli such as changes in temperature or pH, which facilitate targeted delivery to specific sites within the body. Despite their various applications, polymeric nanoparticles are limited owing to their toxicity. The toxicity profile of these nanoparticles can vary widely based on the type of polymer used in their composition, demanding thorough safety evaluations before widespread usage [39, 40].

Nanoemulsions

Nanoemulsions are dispersions of two immiscible liquids characterized by droplet sizes ranging from 20 to 200 nm. These dispersions are both thermodynamically and kinetically stable. There are two main approaches for creating nanoemulsions, each involving different energy levels [41].

High-energy methods often employ mechanical devices, such as high-pressure homogenizers or ultrasonication, to form tiny droplets. In contrast, low-energy techniques like phase inversion temperature (PIT) and phase inversion composition (PIC) rely on changing the system's temperature or composition to achieve emulsification [41, 42].

Nanoemulsions are widely used because of their potential to increase the bioavailability of drugs with poor water solubility and enhance drug penetration through the skin, leading to quicker action and improved therapeutic outcomes. They also offer versatile administration options, including oral, intravenous, and topical routes, and can effectively mask unpleasant drug taste.

Despite these advantages, there are some drawbacks, such as limited stability under certain conditions, which can be prevented by reducing the droplet size and improving its stability against gravitational separation and aggregation. Additionally, nanoemulsions often require more emulsifiers than conventional emulsions because of their large surface areas, which can affect their toxicity and production cost [43, 44].

Dendrimers

Dendrimers are hyper-branched monodisperse macromolecules characterized by a central core, branching units, and functional surfaces. They are generally nanoscale in size, ranging from 1 to 10 nm in diameter. Their distinct characteristics, including uniform size, high surface area, and capability to encapsulate or bind molecules, make them useful in a variety of applications, especially drug delivery. The interior cavities of dendrimers can encapsulate drug molecules [45].

Dendrimers are synthesized using divergent or convergent methods. They offer several advantages, owing to their unique structural properties. Their nanoscale size allows for interactions with cells and their ability to overcome biological barriers [45, 46]. The internal cavities encapsulate drugs and their multivalent surfaces can be modified for targeted delivery, enhanced solubility, and controlled release. Dendrimers can also be used to enhance stability, permeability, and bioavailability of drugs. However, they also face challenges because of their size and surface charge, which affect their toxicity [47].

Nanosponges

Nanosponges are promising topical drug delivery systems because of their ability to provide a controlled and extended release of drugs into the skin. These solid, cross-linked, polymeric, nanoscale, and porous structures are typically hydrophilic and water-insoluble, forming three-dimensional (3D) hyper reticulated nanoporous structures. They are designed to be stable over a wide range of temperature and pH levels. Nanosponges typically range in size from 200-300 to nm and can exist in both crystalline and paracrystalline forms, depending on the synthesis and processing conditions. This crystallinity affects the drug-loading capacity [48].

Nanosponges can encapsulate drugs in two ways: as inclusion complexes (the drug forms a complex with sponge material) or as

non-inclusion complexes (the drug is entrapped in pores). Various synthetic techniques have been used for their preparation, including solvent condensation, interfacial phenomena, hyper-crosslinking, ultrasound-assisted methods, hot melting, microwave-assisted synthesis, chain-growth polycondensation, mechanochemical synthesis, and emulsion solvent evaporation [26].

These nanostructures offer high biocompatibility, biodegradability, low cytotoxicity, and the potential for targeted and sustained drug delivery. However, nanosponges have significant drawbacks, particularly for drug loading, because only small molecules with molecular weights between 100 and 400 kDa can fit into microscopic pores. Additionally, their synthesis can be expensive, posing challenges for large-scale production and affordability, and they require specific storage conditions to maintain their effectiveness [49, 50].

Carbon nanotubes

Carbon nanotubes (CNTs) are cylindrical nanostructures composed of carbon atoms arranged in a hexagonal pattern. These nanoscale structures, characterized by their carbon-based compositions, possess remarkable electrical, mechanical, and thermal properties. These attributes make CNTs highly suitable for a broad spectrum of biomedical applications [51–53].

CNTs can be produced using various techniques, including arc discharge, chemical vapor deposition (CVD), and laser ablation. These production methods allow the configuration of CNTs into different forms, such as sheets, sponges, arrays, and yarns, enhancing their versatility in different applications. In topical delivery, CNTs offer multiple benefits [54]. These include the enhanced penetration of therapeutic agents, increased bioavailability, and sustained release of active compounds. These properties make CNTs particularly promising for advancing drug delivery systems and improving the efficacy of topical treatments [54, 55].

Mesoporous nanoparticles

Mesoporous nanoparticles are characterized by pore diameters ranging from 2 nm to 50 nm. These nanoparticles, typically composed of carbon or silica, possess several attributes that make them well-suited for topical application. The synthesis of mesoporous materials involves various methods, including activation techniques, template methods, carbonization, and catalytic activation.

Among these synthesis approaches, template methods that utilize hard or soft templates are widely employed to create materials with controlled mesopores. These nanoparticles have garnered significant attention due to their unique properties, such as high specific surface area, substantial pore volume, and tunable pore sizes. These characteristics make mesoporous nanoparticles ideal for a diverse range of applications.

Despite their advantages, mesoporous nanoparticles have certain limitations. These include complex synthesis procedures, high production costs, and challenges associated with scaling up the production to industrial levels. These factors may impact their widespread adoption and commercial viability in various fields [51, 56].

Metallic nanoparticles (MNPs)

Metal nanoparticles (gold and silver nanoparticles) range in size from 1 to 100 nm. MNPs have gained recognition as effective drug carriers because of their unique mechanical, electromagnetic, and optical properties. They are prepared using two main approaches: top-down, in which bulk materials are broken down into nanoparticles, and bottom-up, in which the nanoparticles are built from atoms or molecules. Biological or "green" synthesis methods using plant extracts, microorganisms, or marine organisms are gaining interest as environmentally friendly alternatives [57, 58].

Metal nanoparticles offer several benefits, such as a high surface-to-volume ratio for greater drug loading, enhanced stability, and tunable size for crossing biological barriers. They can also be functionalized to improve biocompatibility and target specific cells. However, their limitations include potential toxicity, production scale-up, and endosomal entrapment. The most commonly used metals for nanoparticle synthesis include gold, silver, and iron oxide. Other metals used include copper, platinum, zinc oxide, titanium dioxide, and palladium [59].

Clinical application

- Wound Healing: Nanomaterials can accelerate wound healing by promoting cell proliferation, reducing inflammation, and preventing bacterial infections. Curcumin-based nanosystems have demonstrated potential for wound healing [24].

- Anti-aging: Nanoencapsulated active ingredients can more effectively target the signs of aging, such as wrinkles and hyperpigmentation [60].

- Cancer therapy: Polymer-based drug delivery systems, particularly those that use polyethyleneimine (PEI), have been thoroughly studied for their ability to target tumor sites and integrate therapeutic agents with imaging technologies for cancer theranostics [61].

- Pain management: Topical nanocarriers are best for pain management. Nanocarriers loaded with non-steroidal anti-inflammatory drugs (NSAIDs) can provide localized pain relief and reduce inflammation in affected joints. Nanocarriers containing local anaesthetics or capsaicin can aid in the management of chronic neuropathic pain [36].

- Cosmetic applications: Nanotechnology enhances the efficacy and texture of skincare products, thereby improving their overall performance. The nanoparticles on sunscreen provide improved UV protection and cosmetic acceptability [62].

- Chronic skin disorders: Nanocarriers improve the penetration and absorption of active ingredients through the skin barrier, thereby increasing the treatment efficacy for various skin conditions. Nanocarriers loaded with corticosteroids or other anti-inflammatory agents can aid in the management of various chronic skin conditions, such as psoriasis and vitiligo [29].

- Growth factor delivery: Nanotechnology-based drug delivery systems protect growth factors from degradation, enhance their penetration into tissues, and allow for controlled and sustained release at wound sites. Nanocarriers can potentially accelerate wound healing and tissue regeneration by improving the stability and bioavailability of the growth factors [63].

CONCLUSION

In conclusion, nanotechnology has emerged as a transformative approach for topical drug delivery that overcomes the limitations of conventional formulations, such as poor skin penetration, low bioavailability, and rapid drug degradation. A wide range of innovative nanocarriers, including liposomes, SLN, nanoemulsions, and more drugs, can now be delivered more effectively and selectively to the targeted skin layers. These systems enhance drug stability, enable controlled release, and improve therapeutic outcomes, while minimizing systemic side effects. Although challenges like manufacturing complexity and high costs remain, the potential of nanotechnology in dermatological, therapeutic, and cosmetic applications is vast and continually expanding.

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AUTHORS CONTRIBUTIONS

Samidha S. Golatkar was responsible for conducting the literature review, organizing the content, and drafting the initial version of the manuscript. Apeksha C. Rahate and Madan D. Pomaje jointly supervised the overall work, provided critical inputs, and contributed to the review and finalization of the manuscript.

CONFLICT OF INTERESTS

Declared none

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