Review Article

# Gold Nanoparticles in Transdermal Drug Delivery: A Promising Approach for Skin Therapeutics

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**ABSTRACT**

Gold nanoparticles (AuNPs) have emerged as a promising tool for transdermal drug delivery, offering a painless and non-invasive alternative to traditional methods. Their unique physical and chemical properties, such as surface plasmon resonance, redox behavior, and biocompatibility, make them ideal for delivering therapeutics across the skin barrier. This review explores the applications of AuNPs in skin drug delivery, including their ability to target specific skin layers, enhance penetration, and provide controlled release of drugs. The advantages of AuNPs, such as increased bioavailability, reduced toxicity, and improved patient compliance, are discussed, along with challenges like storage stability and potential skin irritation. The review also highlights the potential of AuNPs in treating various skin conditions, including cancer, inflammation, and infections, and their future prospects in dermatology.

**Keywords:** Gold Nanoparticles, Transdermal Drug Delivery, Skin Therapeutics, Nanocarriers, Targeted Delivery, Skin Penetration.

## INTRODUCTION

Transdermal delivery systems (TDS) or transdermal therapeutic systems (TTS) are topical formulations that comprise medications that exhibit systemic effect. The process of delivering a medication through "intact" skin such that it enters the bloodstream in enough quantity to be helpful following the administration of a therapeutic dose is known as transdermal drug delivery [1]. Since the 19th century, the medical industry has experienced tremendous expansion. Peter Paul Speise is credited with creating Nanoparticles [2]. Through the Latin nanus, which means very little, the prefix "nano" is derived from the ancient Greek vavoc. Nanotechnology is the design, characterization, manufacturing, and use of systems, devices, and structures by manipulating size and form at the Nanoparticles [3].

AuNps have distinct physical and chemical properties because to their various shapes and sizes. First, the gold core of AuNPs is chemically inert and non-toxic. Second, production of AuNPs is relatively simple, and the diameter range is relatively controlled, typically ranging from 1 to 150 nm. Third, AuNPs can be effective drug carriers because their various characteristics and sizes allow for controlled drug release in diverse areas [4].

The delivery of a medicine through the skin is a very effective method of drug administration. The transdermal drug delivery system (TDDS) is a novel strategy in the pharmaceutical profession for medication administration since it offers various advantages over traditional routes of administration. Conventional drug delivery system formulations necessitate higher dosages and longer regimens to achieve therapeutic results, and long-term regimens can result in significant side effects and, ultimately, low patient Compliance [5].

Nanoparticles are of current interest due to a growing awareness of their potential effects on human health and environmental sustainability, as well as the rising release of man-made nanoparticles into the environment [6]. All health care workers should understand the anatomy and function of human skin. Skin is also known as the cutaneous membrane [7].

NPs are employed as pharmaceutical medication carriers for diagnostics and therapy. These NPs, which include polymeric NPs, nanoemulsions, liposomes, and solid NPs, are thought to have clinical applications [8]. Gold nanoparticles (AuNPs) have been used in a wide range of biomedicines, including diagnosis and therapy, due to their unique chemical and physical properties, such as surface plasmon resonance, redox behavior, conductivity, high surface-to-volume ratio, low toxicity, and high biocompatibility. Furthermore, in aqueous solutions, AuNPs exhibit a wide spectrum of colors linked to their size and absorption peaks between 500 and 550 nm [9]. Nanoparticles and nanopharmaceuticals are divided into numerous categories of nanosystems based on their distinct features, including inorganic, organic, lipid-based, polymeric, and nanocapsules, among others [10]. Drugs are defined by FDA, in part, as "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals. It is expected that the drugs are capable of targeting the disease-causing cell with an exact therapeutic concentration in an effective Manners [11].

### 1. CLASSIFICATION OF NANOPARTICLES- [12,13,14]

2.1 Organic nanoparticles

2.2 Carbon nanoparticle

2.3 Inorganic nanoparticles

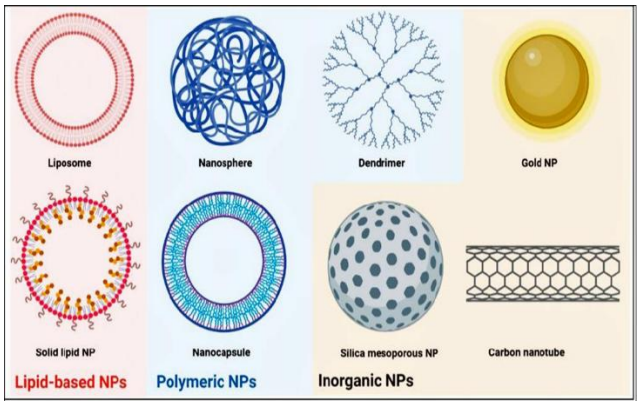


**Figure 1:** General structure of the most common Synthetic nanoparticles uses for drug delivery [15,16,17]

Nano carriers improve drug delivery by allowing for better targeting, controlled release, and bioavailability. Here are the primary types [16].

**2.1 Organic Nanoparticles-**

This article explores the advantages and disadvantages of several organic nanoparticles, including carbon nanotubes, quantum dots, dendrimers, liposomes, and polymers [18].

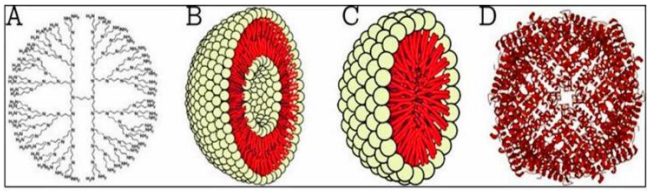


**Figure 2:** Types of organic Nanoparticles A) Dendrimers, B) liposomes, C) Micelles, D) Ferritin [19-21]

**A) Dendrimers**

Dendrimers are highly organized, branched macromolecules that resemble trees. Dendrimers have a vast surface area for binding medicines, making them useful for transporting numerous therapeutic agents or targeting ligands [12, 22]. The term "dendrimer," which accurately depicts the structure of these frequently branching molecules, comes from the Greek word "dendron," which meaning "tree" [23]. Dendrimers are an attractive class of drug delivery technologies that potentially address some of the difficulties associated with already licensed anticancer medicines [24].

**B) Liposomes**

Liposomes are single or bilayer structures composed of phospholipids that are self-contained, with the liquid core located within the bilayers and spheres. Since the 1970s, phospholipids have been employed to deliver medicinal chemicals as micro- or nanoparticles for their development [25]. Liposomes are spherical, concentric vesicles created by combining the Greek words “Lipos,” meaning fat, and “Soma,” meaning body. Liposomes are phospholipid molecules that form a circular sac. It encloses a water droplet that was artificially created to deliver the drug across the cellular barrier. Liposomes are 100-nm nanoparticles [17]. Liposomes have numerous applications in dermal and transdermal medication administration, including tailored distribution to skin appendages. Liposomes are used in dermal drug administration to improve drug penetration into the skin, resulting in localized therapeutic levels while limiting percutaneous absorption [26].

**Types of Liposome-**

1. **Traditional liposomes:** These consist of a single phospholipid bilayer.
2. **Long-circulating liposomes:** These are composed of a phospholipid bilayer with additional polymers, such as PEG, to prolong their circulation time.
3. **Cationic liposomes:** A phospholipid bilayer is supplemented with cationic lipids to facilitate gene transport.
4. **Targeted liposomes:** These are made of a phospholipid bilayer that has been mixed with targeting ligands to target specific organs or cells [27].

**Composition of Liposome-** Liposomes are bilayer vesicles that are utilized to transport drugs. Phospholipid bilayers enclosing an inner aqueous region make up their spherical formations, which vary in size from 0.02 to 10 µm. By forming a hydrophilic area inside of them, phospholipids can form sphere-shaped liposomes that can change into a water solution. About 40 years ago, Bangham and associates initially defined liposomes as tiny, spherical vesicles that contained phospholipids, cholesterol, non-toxic surfactants, and even membrane proteins. This group's research gave rise to the hypothesis that liposomes, which are known to transport a variety of compounds in the core region, might be used as delivery vehicles. Because liposomes are biocompatible and biodegradable and may contain both water-loving and water-hating medications, they are advantageous for drug delivery [28].

**C) Micelles**

Micelles are colloidal systems created when amphiphilic molecules self-assemble in aqueous environments at concentrations higher than their critical micelle concentration [29].

**2.1.1 Polymeric Nanoparticles**

Biodegradable nanoparticles derived from polymers such as polylactic-co-glycolic acid (PLGA). These are utilized for controlled medication release and biocompatible, making them appropriate for sustained-release therapy [22]. Because of their biodegradability and biocompatibility, these polymeric nanoparticles increased bioavailability while decreasing toxicity. Polymeric nanoparticles are classified into three types: hydrogels, nanospheres, and nanocapsules, the latter of which include polymeric micelles and polymersomes. These can be derived from natural or synthetic polymers, the majority of which are biodegradable and biocompatible [17].

### 2.2 Carbon-based Nanomaterials

Fullerenes, carbon nanotubes, and graphene are examples of materials with unique physical and chemical properties that can be used in drug delivery, diagnostics, and tissue engineering [12]. Carbon nanotubes and graphene oxide have large surface areas and the potential for functionalization[30].

### 2.3 Inorganic Nanoparticles

Metal, ceramic, magnetic, and nanoshells are examples of inorganic particles, along with their sizes, descriptions, benefits, limitations, and applications. Inorganic nanoparticles are much smaller in size than organic nanoparticles. It covers a size range of 1-100 nm with improved loading efficacy [18]. These nanoparticles, which are made of metals (such as gold and silver) or metal oxides (such as iron oxide), are commonly employed for imaging and medication delivery. Cancer therapy uses gold nanoparticles for targeted delivery and photothermal therapies [22].

### 2.3.1 Metal nanoparticles

Metal Nanoparticles includes two types are as follows-

- Gold Nanoparticle
- Silver nanoparticle

**GOLD NANOPARTICLES-**

Gold nanoparticles (AuNP) are the most commonly used and have served as the standard option in various research for a variety of reasons. The most noteworthy are their physicochemical qualities, minimal cytotoxicity, enzymatic stability, and chemical resistivity (for more information on gold nanoparticle properties) [31]. Gold nanoparticles. Gold nanoparticles, with their multifunctional therapeutic modalities, can be employed as targeted delivery systems for vaccines, nucleic acids, and immunological antibodies, theranostic drugs, and in cancer therapy [29]. Gold nanoparticles may be used to deliver RNA and DNA. They protect the nucleic acid from the nucleus. Gold nanoparticles are also used for tissue regeneration [32].

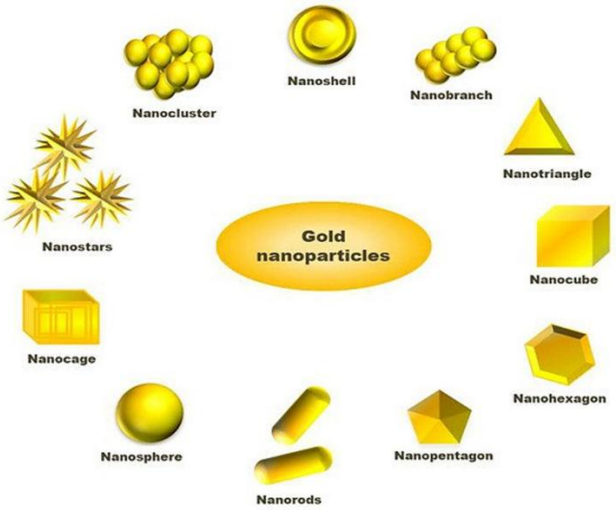


**Figure 3:** Different Shapes available for nanoparticles [31].

**Preparation of nanoparticles-**

Gold nanoparticles (AuNPs) can be produced using a variety of ways, including the Turkevich and Frens approach. The procedure is combining 100 mL of 0.1 g/L chloroauric acid (HAuCl4) and 0.7 mL of 10 g/L trisodium citrate, then heating to boiling and stirring constantly for 30 minutes. After cooling, the solution includes AuNPs ranging in size from 10 to 100 nm. The color of the mixed solution shifted from pale yellow to burgundy during this procedure, indicating that the gold nanoparticles had been properly formed [31].

**AuNps and Cytotoxicity-**

Because the utility of AuNPs is heavily influenced by their inherent toxicity, toxicological studies are considered prior to their use in cancer care. It has been established that the cytotoxicity of AuNPs is strongly related to nanoparticle size, surface charge, and functional groups [4].

**Determination particle size of nanoparticles-**

The particle size distribution is assessed using a Particle Size Analyzer (Horiba SZ-100) and the dynamic light scattering method. The nanoemulsion solutions are dispersed in water and tested at room temperature. These measurements use a scattering angle of 90◦ [33].

**CHEMICAL PROPERTIES OF GOLD NANOPARTICLES TO SKIN DRUG DELIVER**

- **Biocompatibility of AuNps-** AuNPs biocompatibility is determined by their biological destiny in vivo, which may be assessed using pharmacokinetics, tissue distribution, toxicity, and clearance [34].
- **Targeting -**AuNPs can be targeted in two ways: passively (via increased permeability and retention (EPR) effect and MPS escape) and actively (by tumor cell targeting and stimuli-response) [34].

## 3. CHARACTERISTICS OF NANOPARTICLES [35]

- UV-visible spectroscopy.
- Analysis of X-ray diffraction.
- Electron microscopy.
- Mass spectrometry.

## 4. ANATOMY AND PHYSIOLOGY OF SKIN

The skin has developed into an extraordinarily effective barrier, preventing both excessive water loss from the body and the entry of xenobiotics. It allows us to survive a wide range of environmental obstacles. Almost all substances diffuse at a pace controlled by the stratum corneum, the skin's outer layer [1]. The skin, particularly the stratum corneum, acts as a barrier to drug penetration due to its high density (1.4 g/cm$^2$ in the dry state) and low moisture level of 15-20%. The barrier function is further enhanced by the constant renewal of the stratum corneum, which limits topical and transdermal absorption [36]. From a global

perspective, we propose that advances in transdermal delivery systems can be categorized as undergoing three generations of development, from the first generation of systems that produced many of today's patches by judicious selection of drugs that can cross the skin at therapeutic rates with little or no enhancement; through the second generation, which has yielded additional advances for small-molecule delivery by increasing skin permeability and driving [38]. The epidermis is made up of five sublayers, arranged from outermost to innermost: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. However, differentiation of keratinocytes is separate in each stratum [39].

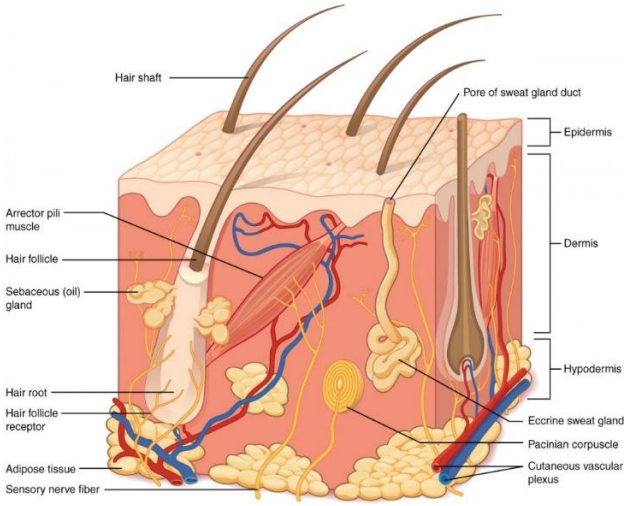


**Figure 4:** Structure of human Skin [36,37]

### 4.1 TYPES OF SKIN [40]

- Normal Skin
- Dry Skin
- Oily Skin
- Combination Skin
- Sensitive skin

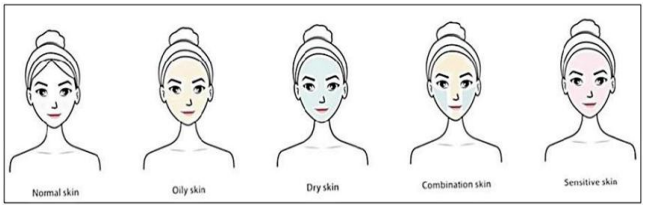


**Figure 5:** Illustrates several skin types based on moisture level and lipid content [41]

### 4.2 SKIN TYPES AND THEIR CARE

The skin is classified into 4 groups and for class appropriate ingredients should be used to maintain its natural functionality [42].

**Table 1:** Skin type and their care

| Skin type | Features | Herbs | Essential oil |
|---|---|---|---|
| Oily skin | 1.Shinyand often has breakouts.<br>2. Coarse pores and pimples. | Aloe Vera, Thyme, Lemon grass | Bergamot, Lavender, Juniper |
| Dry skin | 1. Afeeling of skin tightness.<br>2. Fine lines. | Aloe Vera, olive oil, calendula | Chamomile Fennel, Geranium, Lavender |
| Combination skin | 1. Oily skin on the forehead, shine, Blackheads.<br>2. Dullness and fine lines on cheeks | WitchHazel, Menthol, Aloe Vera, Turmeric | Citrus oils, jasmine oil, sandal wood oil |
| Normal skin | 1. Neither oily nor dry<br>2. Appears smooth | Pomegranate, Herbal face pack, Gingili oil | Chamomile Fennel, Geranium, Lavender, Sandal wood |

Skin is the body's biggest multilayered organ, with a surface area ranging from 1.7 to 2.0 $m^2$. Skin has three layers: the epidermis (outer layer), dermis (middle layer), and subcutaneous tissue (inner layer) [42]

### 4.3 LAYER OF SKIN

#### 4.3.1 Epidermis

The thickness of the multilayered epidermis varies based on cell size and the number of cell layers, with palms and soles measuring 0.8 mm and eyelids at 0.06 mm. It consists of the outer stratum corneum and viable epidermis [43,44]. The epidermis is divided into four layers: stratum basale, spinosum, granulosum (also known as viable epidermis), and stratum corneum. During the keratinization process, keratinocytes create precursors of barrier components such as keratin, filaggrin, and lipids, which will eventually "seal" the skin surface [45].

#### 4.3.2 Dermis

The dermis is a 3 to 5mm thick layer made up of connective tissue that includes blood arteries, lymph vessels, and nerves. It also nourishes and oxygenates the skin while eliminating pollutants and waste materials [44]. It includes connective tissue, vascular tissue, a network of lymphatic vessels, sweat and sebum glands, hair follicles, and macrophages [37].

#### 4.3.3 Hypodermis

The hypodermis, or subcutaneous fat tissue, supports the dermis and epidermis. It functions as a fat storage area. This layer regulates temperature, provides nutritional support,

and offers mechanical protection. It carries the main blood vessels and nerves to the skin and may contain sensory pressure organization [44].

## 5. MECHANISM OF SKIN PENETRATION

### 5.1 Penetration of drug into skin

A number of medications are administered transdermally to target deeper dermal, subcutaneous, and muscle layers. For such drugs, it is critical to determine the drug level within the skin and understand the penetration behavior into deep dermal tissue layers in order to evaluate dermal bioavailability or assess bioequivalence between different formulations, for which a gold standard in vivo human skin should be used. This is not always possible, however, due to the high cost of clinical trials and concerns about introducing treatments or items with possibly hazardous effects. One of these ways is to employ in vitro penetration and permeation models [46].

### 5.2 Follicular penetration: shape dependence [47]

Gold nanoparticles (GNPs) of different shapes - rods, spheres, and stars - are applied to human skin samples. All the particles are the same size, about 100 nanometers. Gold nanorods penetrate the skin well and build up in the sebaceous glands. Gold nanostars work even better, getting into the skin and glands easily, with some building up inside.

## 6. DRUG DELIVERY APPROACHES OF SKIN DISEASE

Gold nanoparticles are exceedingly small and can enter readily and effectively, with minimal toxicity and no skin injury. As a result, they are commonly used in nanocarrier formulations for skin disorders. Nanoparticle administration for cutaneous disease treatment is preferable, with less adverse effects. Because of their limited penetration in skin tissues, typical creams, gels, and ointments are ineffective for medication delivery [48].

## 7. NANOCARRIERS AS EFFECTIVENE DIAGNOSIS AND TREATMENT FOR THE SKIN CANCER

Because of their unique chemical and physical features, nanocarrier-based delivery systems can be used as a synthetic substrate for diagnostic probes. This aids in the detection and monitoring of tumors, providing cancer patients with greater optimism [49]. Nanoparticles affect pharmacokinetics, improve bioavailability, decrease immunogenicity, extend therapeutic half-life, and increase the solubility of chemicals that are not very soluble in aqueous medicines. Furthermore, they can offer the administration of two or more medications at the same time as part of the combined treatment, as well as the adjustable release of therapeutic molecules [49].

## 8. FUNCTION OF SKIN [50]

- Provides a protective barrier against mechanical, thermal, and physical injury, as well as hazardous substances.
- Prevents the loss of moisture, helping to maintain skin hydration.
- Reduces the harmful effects of UV radiation from the sun.

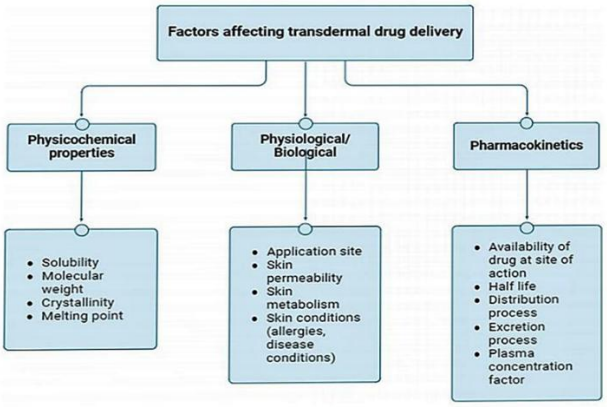


**Figure 7:** General factors responsible for transdermal system [51]

## 9. ADVANTAGES OF NANOPARTICLES

- Advantages of Nanoparticles: Nanosponge drug delivery methods reduce the risk of unwanted side effects by ensuring only minimal amounts of the drug come into touch with healthy tissue [2].
- Increased formulation flexibility, elegance, and stability [52]. They are biodegradable, non-toxic, site-specific, and can be stored for at least a year [6].
- The ability to penetrate tissues and reach even the smallest capillary veins. Via transcellular or paracellular pathways [53].
- Nanoparticles can be administered by multiple methods, including oral, nasal, parenteral, and intra-ocular [25].

## 10. DISADVANTAGED OF NANOPARTICLES

- Storage Stability: Liposomes can become unstable during storage, resulting in aggregation, leaking of encapsulated contents, or changes in size and structure[54].
- A percentage of the particles are micrometers in size [53].
- Nanoparticles are highly reactive in the biological environment due to their small size and huge surface area [12].
- When employing nanosponge drug delivery systems, there is a risk of dose dumping because the crosslinker dissolves too quickly [2].

## 11. APPLICATION IN SKIN DRUG DELIVERY

- Gold Nanoparticles Encapsulated in Lipids [55].
- NPs are also utilized as gene delivery methods, and they have demonstrated efficacy in replacing specific defective genes involved in cancer, viral infections, and other genetic illnesses [8].
- The application of lipid-polymer hybrid nanoparticles is confined to the removal of methods, and they have

demonstrated efficacy in replacing specific defective genes involved in cancer, viral infections, and other genetic illnesses [8].

- The application of lipid-polymer hybrid nanoparticles is confined to the removal of microbubbles with ultrasound [55].

## 12. APPROACHES OF TRANSDERMAL DRUG DELIVERY SYSTEM

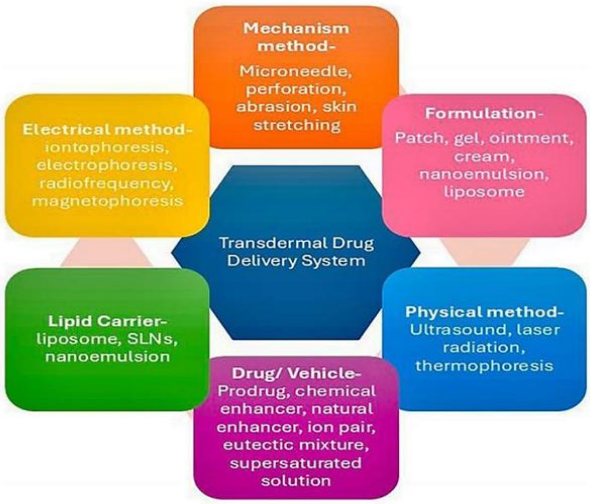


**Figure 8:** A scheme representing the approaches for the development of transdermal drugs delivery system [25]

## CONCLUSION

Gold nanoparticles offer a promising approach for transdermal drug delivery, addressing the limitations of traditional methods and improving treatment outcomes for skin conditions. Their unique properties enable targeted delivery, enhanced penetration, and controlled release of therapeutics, enhancing drug stability and bioavailability while minimizing systemic side effects. AuNPs can also be functionalized for applications.

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