



A Review on Nano formulations for Transdermal Drug Delivery System

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Abstract : The transdermal route offers several advantages over traditional drug delivery methods. These include high bioavailability, avoidance of first-pass liver metabolism, consistent drug levels in the bloodstream, and a non-invasive approach to treatment. Furthermore, transdermal drug delivery systems (TDDS) offer prolonged therapeutic effects, fewer side effects, enhanced bioavailability, improved patient adherence, and easy discontinuation of therapy. TDDS is used not only in pharmaceuticals but also in skincare and cosmetics. Research has shown that the transdermal route causes minimal skin irritation and performs better in various in vivo tests compared to oral administration. This review article provides an in-depth analysis of TDDS, emphasizing its benefits over conventional dosage forms, discussing limitations, examining transdermal patch components, exploring various patch types, outlining preparation methods, and identifying ideal TDDS requirements. Additionally, it addresses regulatory factors, physicochemical evaluation methods, therapeutic applications, and recent progress in transdermal drug delivery systems

IndexTerms - Component,formatting,style,styling,insert.

INTRODUCTION

Transdermal drug delivery systems (TDDS), often called patches, offer a unique way to administer medications through the skin. These patches are designed to effectively deliver therapeutic amounts of drugs into the bloodstream, allowing for efficient treatment and prevention of various health conditions [1]. A transdermal patch is a medicated adhesive that sticks to the skin [2], releasing precise doses of medication, which can also aid in healing targeted areas [3]. Compared to oral, intravenous, subcutaneous, or transmucosal methods [4], this delivery route provides more consistent drug levels and reduces side effects, overcoming challenges linked with traditional pills or injections [5].

Transdermal systems are ideal for conditions that need long-term, frequent dosing, as they're less invasive, pain-free, and can be used independently by patients, making them both convenient and cost-effective [6]. These systems are tailored to deliver drugs through the epidermis or dermis [7], effectively managing skin-related conditions by bypassing first-pass metabolism and allowing controlled release over time [8]. The primary aim is to achieve a steady and predictable drug release rate, reducing patient-to-patient variability [9]. Historically, early transdermal systems used drug-infused patches with natural adhesives to help drugs absorb through the skin [10].

This review highlights recent progress in developing chemical permeation enhancers and carriers, such as gels, emulsions, and vesicular systems, that improve the effectiveness of transdermal drug delivery [11].

1. Advantages of TDDs

- It allows for a continuous and stable release of medication over a prolonged period, minimizing the chances of side effects and treatment failures that can occur with intermittent dosing [12].
- These systems enable patients to administer the medication on their own [12].
- Transdermal delivery prevents the variations in drug levels that occur with peak and trough cycles, permitting extended and less frequent dosing [13].
- It provides a quicker and more convenient way to administer medication [14].

- The rate of absorption can be managed through a layered design [14].
- It avoids issues related to gastrointestinal compatibility [15].
- Patients are more likely to follow their treatment plans, as they are not required to take multiple doses daily [15].
- This method allows patients to take control of their medication management independently [15].

2. Disadvantages of TDDs

- For a drug to be suitable for transdermal delivery, it needs certain physicochemical characteristics to penetrate the stratum corneum. If the required dose is over 10 mg daily, effective transdermal delivery can become difficult [12].
- At present, only small, lipophilic drugs can be effectively transported through the skin [13].
- Transdermal administration offers extended drug release, but it can be costly due to the complex formulations involved [14].
- Drugs with low solubility, limited stability, short half-lives, or sensitivity to oxidation and hydrolysis present challenges, adding to manufacturing costs [16].
- There are limitations in the amount of medication that transdermal systems can carry [17].
- Transdermal delivery might result in lower drug levels in the bloodstream [18] due to variations in skin barrier function, which can be influenced by factors like skin location and patient age [19].

• ANATOMY AND PHYSIOLOGY OF SKIN

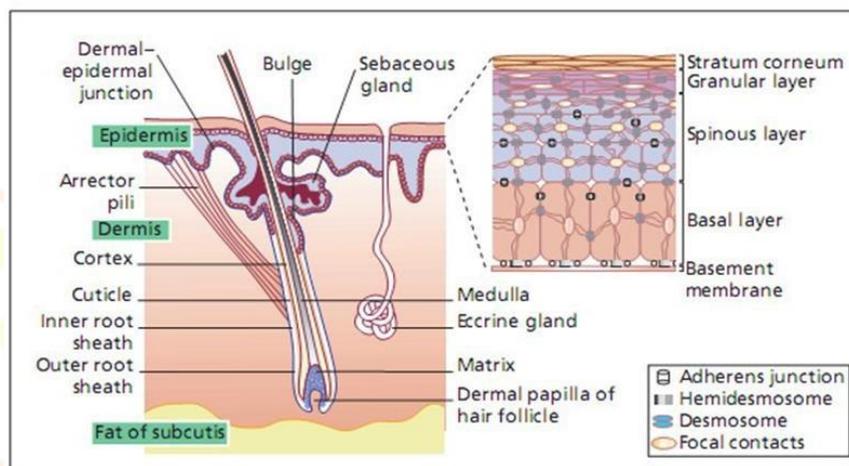


Figure 1 Anatomy and physiology of skin [20]

The skin acts as the body's main barrier against external elements [21]. As the largest organ, it makes up around 16% of the body's length, typically covering an area between 1.5 and 2.0 square meters and representing roughly 6-10% of total body weight. Composed of multiple cellular layers, human skin can be classified into two main types: hairless and hair-bearing skin. Hair-bearing skin includes both hair follicles and sebaceous glands [20].

.1. Layers of skin

2.1.1 Epidermis

The epidermis is the skin's outermost layer, functioning as a vital protective barrier. It consists of stratified epithelial cells and keratinocytes that actively multiply in the suprabasal area, with basal layers showing differentiation. The thickness of the epidermis varies, with regions like the palms and soles reaching about 0.8 mm. It is composed of several layers of epithelial cells, and the lower layers are commonly known as the viable epidermis. Keratinocytes are the dominant cells in this layer [22].

2.1.2 Dermis

Located below the epidermis, the dermis is a complex [23], fibro-elastic layer that provides the skin with structural strength. It contains an extensive network of nerves and blood vessels. Discomfort during parenteral drug administration can result from possible irritation to nerve endings within this layer [24].

2.1.3 Hypodermis

The hypodermis, or subcutaneous fat layer, supports the epidermis and dermis by storing fat, regulating temperature, and providing cushioning. It contains significant blood vessels and nerves extending to the skin and may house sensory pressure receptors. For transdermal drug delivery, medications must penetrate the epidermis, dermis, and hypodermis to enter the bloodstream, while topical applications focus on permeating the stratum corneum for retention in the skin layers [25].

- **SKIN AND DRUG PERMEATION**

Understanding Transdermal Drug Delivery Systems (TDDS) requires examining the skin's structure and biochemistry, as these factors influence its barrier properties and the rate of drug absorption. Covering roughly 2 square meters in an average adult, the skin is one of the largest organs and receives about one-third of the body's blood flow. The epidermis, the outermost skin layer, is about 150 micrometers thick, formed through the continuous movement of basal epithelial cells migrating to the surface as they differentiate. Below the epidermis, other layers include the stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum, known collectively as the viable epidermis.

The dermis lies beneath the epidermis, acting as the connective tissue foundation and originating from the mesoderm. It consists of a dense network of connective tissues, primarily collagen fibers, along with some elastic tissue in its upper layers. The dermis also houses blood vessels, lymphatic vessels, nerves, as well as structures like hair follicles, sweat glands, and sebaceous glands [26].

1. Functions of skin

- Acts as a protective shield against physical, mechanical, and thermal damage, as well as against harmful substances.
- Helps retain moisture to keep the skin hydrated.
- Minimizes the harmful effects of UV radiation from sunlight.
- Serves as a sensory organ, enabling the sensation of touch and temperature changes.
- Aids in temperature regulation by releasing sweat to cool the body as needed.
- Functions as part of the immune system, detecting and responding to potential infections.
- Contributes to vitamin D synthesis when exposed to sunlight.

[These diverse functions highlight the skin's essential and adaptable role in the human body.]

2. Barrier functions of the skin

The outermost layer of the skin, the stratum corneum, is crucial in preserving the skin's barrier function. In this layer, tightly packed and overlapping cells provide a strong defense against bacterial invasion while helping to maintain moisture. The stratum corneum is mainly composed of keratinized dead cells and contains less water than other skin layers. To reinforce this barrier, lipids are released by cells from deeper skin layers to the surface, where they form a sturdy, interlocking network similar to mortar between bricks in a wall [27].

- **BASIC COMPONENTS OF TDDS**

- Drug
- Polymer matrix
- Permeation enhancers
- Adhesives
- Backing membrane
- Release Linear [28]

.1. Drug

- For effective transdermal absorption, drugs must have specific physicochemical properties, such as low irritation potential, molecular weights under 1000 Daltons, low melting points, short half-lives, and a balanced affinity for both lipophilic and hydrophilic environments [29]. Selecting suitable drugs for TDDS is crucial to successful system development[30].

.1. Polymer matrix

Polymers play a vital role in TDDS by controlling the drug's release rate. The polymer matrix can incorporate the drug in a solid or liquid form. In intramuscular drug delivery, biodegradable polymers, either natural or synthetic, are essential for matrix formation, where the drug is dispersed. For targeted injectable delivery, the polymer must be stable and compatible with the drug and other system components, ensuring a safe and controlled release. In TDDS, various polymers are utilized, including:

- Synthetic elastomers: polybutadiene, polyisobutylene, silicone rubber, etc.
- Synthetic polymers: polyvinyl alcohol, polyvinyl chloride, polyethylene, etc.
- Natural polymers: cellulose derivatives, waxes, gums, and eudragits, among others [30].

.2. Permeation enhancers

These agents can temporarily modify the structure of the stratum corneum, which enhances drug penetration from the skin into the bloodstream [31]. They work by disrupting the organized lipid layers in the stratum corneum, either by inserting amphiphilic molecules or removing lipids. This temporary change lowers the skin's barrier resistance, promoting better drug absorption.

An ideal permeation enhancer should be inert, non-toxic, non-allergenic, non-irritating, and function in a one-way manner. It should also be compatible with both the drug and other components in the formulation. The effectiveness of these enhancers depends on the drug type, skin properties, and concentration used [26]. A diffusion cell is used to measure how much drug penetrates the skin [32]. These compounds increase stratum corneum permeability to achieve therapeutic drug levels by directly interacting with the skin barrier [33].

.3. Adhesives

Unlike multi-layer or single-layer adhesive systems, the reservoir transdermal system has a unique drug reservoir within a compartment made from a drug-impermeable metallic laminate, featuring a rate-controlling membrane on one side. To keep layers separated, a specialized adhesive, such as polyacrylates, polyisobutylenes, or silicone derivatives, is used to secure the system in place [31].

.4. Backing membrane

The backing layer in a transdermal patch serves to protect the system from external factors. This layer is impermeable to both drugs and penetration enhancers, providing structural support for the patch and shielding the drug reservoir from environmental exposure. Common backing materials include polyester, aluminized polyethylene terephthalate, and siliconized polyethylene terephthalate [34]. These backing laminates are crucial for supporting the patch [35], preventing drug loss through the top layer, and allowing for printing on the patch [36].

.5. Release Liner

To protect the transdermal patch during storage, a liner is placed over it and removed just before application. While not an integral part of the drug delivery system, this liner serves as primary packaging [37]. Common materials for release liners in transdermal systems include polyester foil and metalized laminate [38].

- TRANSDERMAL SYSTEMS CAN BE DIVIDED INTO TWO-LAYER SYSTEMS:

1. The single-layer drug in adhesive
2. The multi-layer drug in adhesive

.1. Single Layer Drug in Adhesive

In the Single-Layer Drug-in-Adhesive system, the drug is contained in a single layer that adheres directly to the skin. A typical transdermal patch has three main layers: the backing membrane, an adhesive layer with the drug, and a protective liner [39]. The adhesive layer lies between the temporary liner and the backing layer, ensuring proper adhesion to the skin [40].

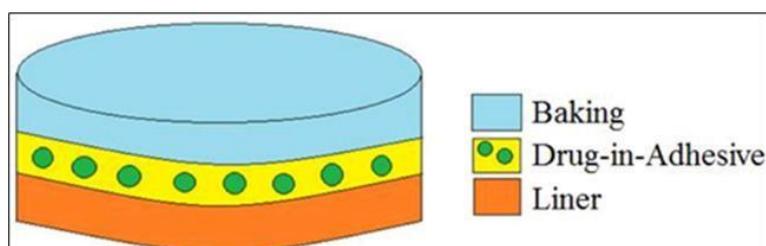


Figure 1 Single layer drug in adhesive [39]

.2. Multi-layer drug in adhesive

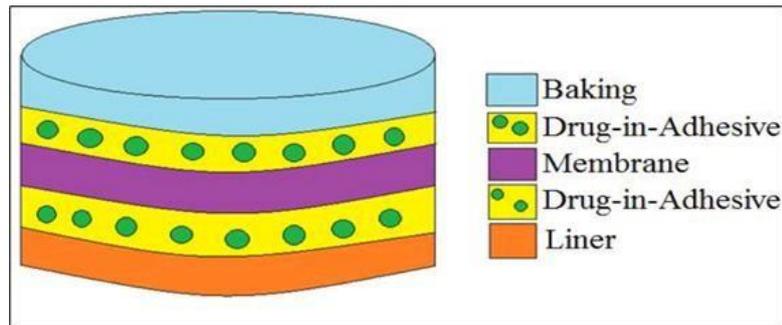


Figure 2 Multi-layer drug in adhesive [39]

Similar to the single-layer system, the multi-layer drug-in-adhesive patch delivers the drug through both adhesive layers. It includes one layer for immediate release and another layer for sustained release from a reservoir.

The multi-layer system differs by having an additional drug-in-adhesive layer, often separated by a membrane. Known as the Multi-Layer Drug-in-Adhesive system, it also includes a permanent backing layer and a removable liner [41].

5.2.1. Reservoir

In transdermal drug delivery, reservoir systems are characterized by a compartment that holds a drug solution or suspension, separated from the release liner by a semi-permeable membrane and adhesive layer. The adhesive, which secures the patch to the skin, may form a continuous layer between the membrane and the liner or be arranged concentrically around the membrane [42].

A key feature of reservoir systems is their ability to provide zero-order drug release, delivering the drug at a steady and predictable rate throughout the treatment period [43].

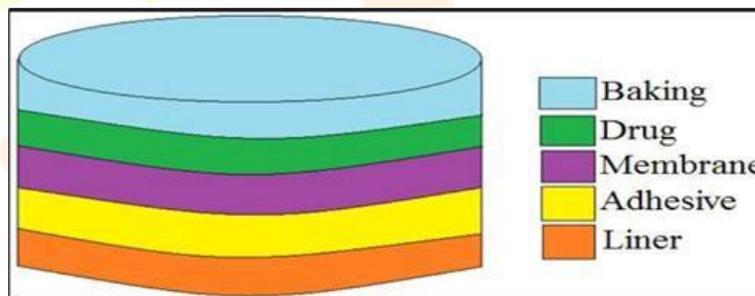


Figure 3 Reservoir [39]

5.2.2. Matrix

A basic transdermal patch design includes three main elements: the drug, an adhesive, and a structural support layer for the patch. In this setup, the drug is embedded within a polymer matrix, simplifying the manufacturing process. Unlike reservoir systems, this design does not include a rate-controlling membrane. However, these patches may be less flexible compared to reservoir systems. In this design, the drug release rate is mainly governed by the permeability of the skin [44].

Figure 4 Matrix [39]

.3. Route of drug penetration across skin

When a molecule comes into contact with unbroken skin, it encounters various substances such as cellular debris, microorganisms, and sebum. This interaction provides the diffusant with three potential pathways to access viable tissue: it can enter through the hair follicles and their associated sebaceous glands, navigate through sweat ducts, or pass through the intact stratum corneum that separates these skin structures [45].

5.3.1. Transcellular Route

Drugs that penetrate the skin via the transcellular route move through the corneocytes. These corneocytes, abundant in hydrated keratin, create a water-rich environment that facilitates the passage of hydrophilic drugs. The transcellular pathway requires not only partitioning into and diffusing through the keratin "bricks" but also infiltrating and traversing the intercellular lipids [46].

5.3.2. Intercellular Route

The intercellular route allows drugs to diffuse through a continuous lipid matrix. Solutes navigate through the lipid regions by diffusing between the horny cells of the stratum corneum, the viable cells of the epidermis, and into the dermis [47].

This pathway presents notable challenges for two primary reasons:

[i] According to the "bricks and mortar" model of the stratum corneum, the interlocking structure of the corneocytes creates a complex pathway for drugs to permeate intercellularly, unlike the more straightforward transcellular route.

[ii] The intercellular area consists of alternating structured bilayers, meaning a drug must go through repeated cycles of partitioning and diffusing between both aqueous and lipid domains.

This route is generally regarded as the most common for small, uncharged molecules to penetrate the skin [48].

5.3.3. Trans appendageal Route

Also known as the "shunt pathway," this route allows drug molecules to pass through hair follicles, travel along the sebaceous pathways of the pilosebaceous apparatus, or use the aqueous pathways of the eccrine sweat glands. However, this transappendageal pathway is considered less significant due to its small surface area, which constitutes less than 0.1% of the overall skin surface [49].

Kinetics of Transdermal Permeation

A thorough understanding of transdermal dynamics is essential for the effective development of transdermal devices. This understanding encompasses several critical components:

- "Horny Layer Absorption": This term refers to the uptake of drugs through the stratum corneum, which is the outermost skin layer [50].
- "Drug Absorption Across Skin Layers": This involves the process of drug molecules passing through various skin layers, such as the epidermis and dermis, to enter the bloodstream [50].
- "Absorption in the Epidermal-Dermal Papillae": This focuses on how drugs are absorbed within structures called epidermal-dermal papillae, found within the epidermis where it interfaces with the dermis [50].

Each of these elements plays a vital role in the overall process of transdermal drug delivery.

5.3.1 Factor affecting transdermal permeability.

Physicochemical Factors

- Partition coefficient [51]

For effective transdermal permeability, a lipid/water partition coefficient of 1 or higher is generally required. This coefficient indicates how a drug partitions between lipid (fat) and water, with values above 1 suggesting a greater affinity for lipid environments, which is crucial for absorption through the skin.

It is important to recognize that chemical modifications can sometimes change this partition coefficient without substantially impacting the drug's pharmacological activity. This approach can be an advantageous strategy in drug development to improve transdermal delivery while preserving the drug's therapeutic efficacy.

- Skin Hydration

The permeability of the skin rises considerably upon exposure to water. Hydration plays a vital role in enhancing this permeability. As a result, humectants are frequently utilized in transdermal delivery [52]. These

substances aid in moisture retention and keep the skin hydrated, which can improve the absorption of drugs and other compounds through the skin.

- **Temperature and pH**

Temperature significantly influences the permeability of drugs through the skin. When temperatures increase, drug permeability can rise sharply, sometimes by tenfold or more. On the other hand, a decrease in temperature leads to a reduced diffusion coefficient for drugs within the skin, which can impact the rate at which drugs are absorbed through the skin.[52]

- **Penetrant concentration**

In transport involving membranes, it is commonly noted that a rise in the concentration of a dissolved drug results in a corresponding increase in flux, which refers to the rate of drug movement across the membrane. Furthermore, when the concentration of the drug exceeds its solubility threshold, any surplus solid drug can serve as a reservoir. This reservoir effect aids in maintaining a stable drug concentration at the membrane interface over a prolonged period, facilitating sustained release of the drug. [53]

- **Molecular Weight**

The process of percutaneous absorption, where substances move through the skin, typically shows an inverse relationship with the drug's molecular weight. Smaller molecules are usually absorbed more easily. In a passive diffusion system for transdermal drug delivery, drugs with a molecular weight of less than 500 Daltons are generally preferred. Nonetheless, the permeation rate can be improved by utilizing different penetration enhancers that assist larger molecules or those with less ideal characteristics in traversing the skin. [54]

.3. *Biological factors [55]*

5.4.1. Skin condition

The skin functions as a natural defense against numerous substances; however, certain agents, including acids and alkalis, can infiltrate the skin, especially if they are corrosive or can damage skin tissue. Solvents like methanol and chloroform are recognized for their ability to strip away the skin's lipid layer, leading to the formation of tiny openings that may facilitate the absorption of other substances. These interactions underscore the necessity of comprehending how different agents affect the skin's barrier properties, particularly in situations involving chemical exposure or transdermal drug delivery.

5.4.2. Skin age

The sensitivity of skin to different substances can indeed differ between individuals and age groups. Typically, the skin of young children and adults tends to be more reactive or vulnerable to certain agents compared to that of older adults. This variation can be attributed to differences in skin thickness, composition, and the effectiveness of natural protective barriers.

Certain substances, such as specific acids, steroids, boric acid, and hexachlorophene, may cause particular side effects or adverse reactions when applied to children's skin. Children's skin is generally more sensitive and can absorb and respond to substances in a way that differs from adult or elderly skin. Consequently, it is crucial to exercise caution and adhere to appropriate guidelines when using these substances on children, especially in medical or healthcare situations.

6. Classification and application of Nano-formulations.

6.1 Vesicular carriers

Vesicular carriers are colloidal particles filled with water, and their outer structure consists of amphiphilic molecules arranged in a bilayer formation. In environments with excess water, these molecules organize into either single-layered (unilamellar) or multiple-layered (multilamellar) vesicles[66]. These vesicles can encapsulate both water-soluble and lipophilic drugs, enhancing their ability to penetrate the skin for transdermal delivery. When used topically, vesicles can serve as carriers for drugs, allowing for controlled, sustained release. In the context of transdermal drug delivery systems (TDDS), the multilayer design of these vesicles can help regulate the rate at which drugs are absorbed[67].

6.1.1 Liposomes

Liposomes are spherical soft-matter structures made up of one or more lipid bilayers that enclose an aqueous solution. The primary building blocks of liposomes are typically phospholipids, which may also contain cholesterol. Phospholipids consist of a polar head group and two hydrophobic hydrocarbon tails. Liposomes form naturally when dry lipid films are rehydrated in an aqueous solution[68]. This distinct structure enables liposomes to possess both hydrophilic and hydrophobic properties, allowing them to encapsulate substances that are either water-soluble or lipid-soluble[69].

6.1.2 Transfersomes

The term “Transfersomes®” was introduced by Cevc et al. and refers to a type of deformable or elastic liposomes, also known as ultra-flexible liposomes. The key characteristic of these vesicles is their elasticity, which results from the inclusion of a single-chain surfactant, often referred to as an “edge activator.” Examples of such surfactants include sodium cholate, Tween®, Span®, polysorbic acid, and dipotassium glycyrrhizinate. These surfactants weaken the phospholipid bilayer, giving the vesicles enhanced deformability, which led to the development of the first generation of Transfersomes®.[70]

6.1.3 Ethosomes

Ethosomes were first introduced by Touitou in 1996 and later reported in 2000. These carriers are made up of phospholipids, alcohol, and water. Unlike liposomes, ethosomes contain a higher concentration of alcohol. The alcohol enhances the ability of ethosomes to penetrate the skin, with the phospholipid also playing a role in this process. The alcohol replaces the water molecules near the lipid bilayer’s head group, increasing the flexibility and fluidity of the ethosomal structure. Ethosomes are known for their small particle size, stability, and high drug entrapment efficiency, which allows for controlled release[71]. As a result, ethosomes can deliver drugs deeper into the skin or even directly into the bloodstream, significantly improving transdermal drug delivery compared to conventional liposomes[72].

6.1.4 Niosomes

Niosomes, also known as non-ionic surfactant-based elastic vesicles, are molecular aggregates formed by the self-assembly of non-ionic surfactants in an aqueous environment, often with the addition of cholesterol or its derivatives [73]. These vesicles are considered second-generation elastic vesicles and can be classified into three types based on their size: small unilamellar vesicles (SUV) (10–100 nm), large unilamellar vesicles (LUV) (100–3000 nm), and multilamellar vesicles (MLV), which contain multiple bilayers[74]. Niosomes can enhance the duration of drug retention in the stratum corneum (SC) and epidermis, while also reducing the systemic absorption of the drug. The permeation of niosomes primarily occurs due to the action of non-ionic surfactants. Their transdermal characteristics are similar to those of liposomes [75]. When niosomes come into close contact with the skin’s SC, they adsorb and fuse with the skin’s surface. This interaction increases the thermodynamic activity gradient of the drug at the skin interface, thereby promoting the permeation of lipophilic drugs[76].

6.1.5 Invasomes

Invasomes, developed by the Verma and Fahr research teams [77], are vesicles made from phosphatidylcholine (such as soy-phosphatidylcholine), lysophosphatidylcholine, ethanol, and a blend of terpenes. The phosphatidylcholine forms the core bilayer structure of the invasomes, while lysophosphatidylcholine acts as an edge activator, enhancing the flexibility of the bilayer. Both ethanol and terpenes function as penetration enhancers, increasing the permeability of the vesicles and adding fluidity to the phospholipid layers [78]. Invasomes have been demonstrated to be effective drug delivery systems for both hydrophilic and lipophilic compounds[77,79].

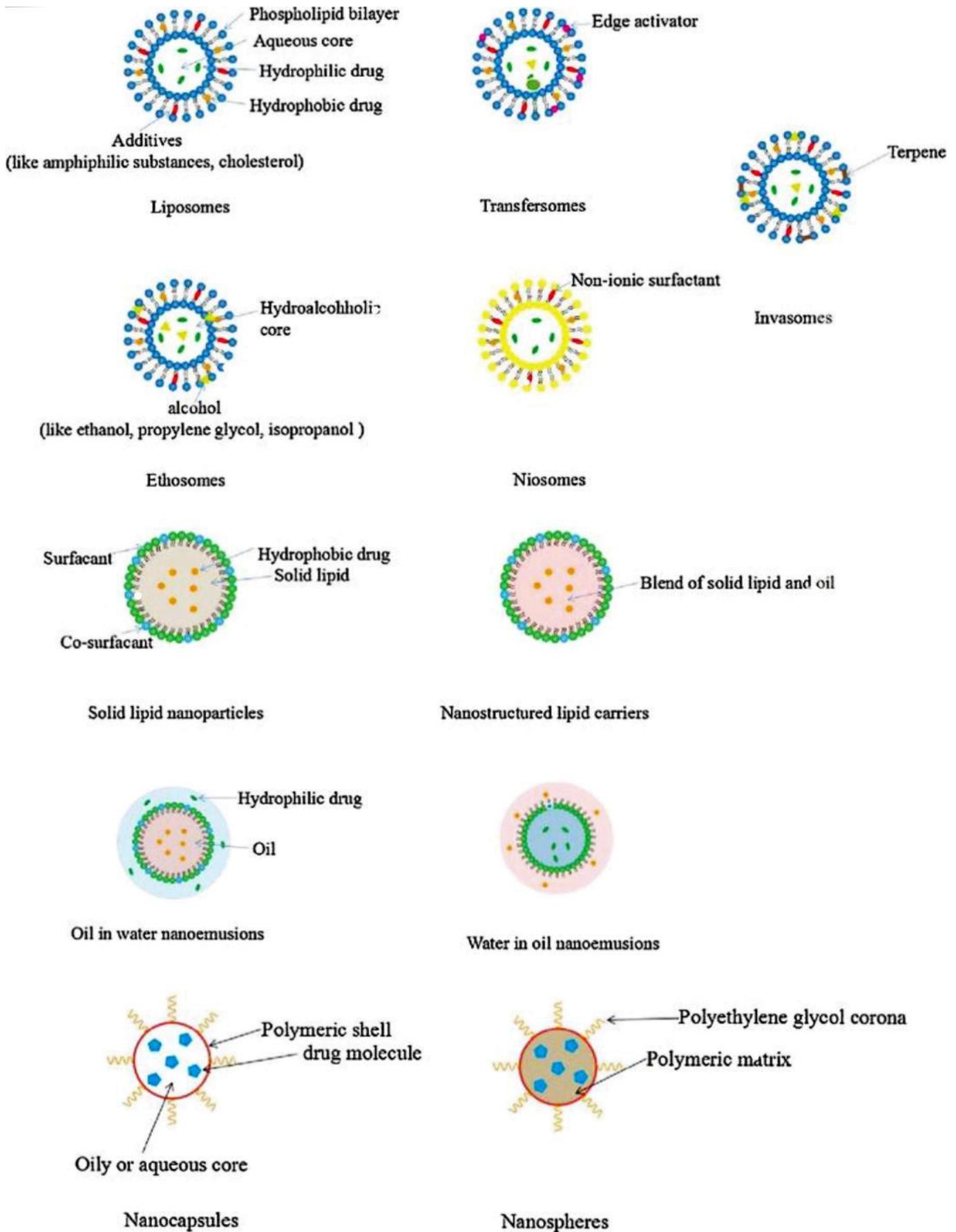
6.2 Nanoparticles

The terms “nanomaterials” or “nanoscale” refer to structures with dimensions between 1 and 100 nm[80]. However, particles sized from 1 to 1000 nm have been accepted as nano carriers[81]. In this review, we’ll use the term “nanoparticles” to describe particles within the 1–1000 nm range for transdermal drug delivery systems (TDDS). Drugs can be encapsulated, dissolved within these nanoparticles, or attached to their surface[82]. When drugs are delivered as nanoparticles, this approach allows for targeted and controlled release, modifies drug behavior within the body, extends their presence in the bloodstream, enhances bioavailability, reduces toxic effects, and ultimately improves therapeutic effectiveness[83].

6.3 Nanoemulsions

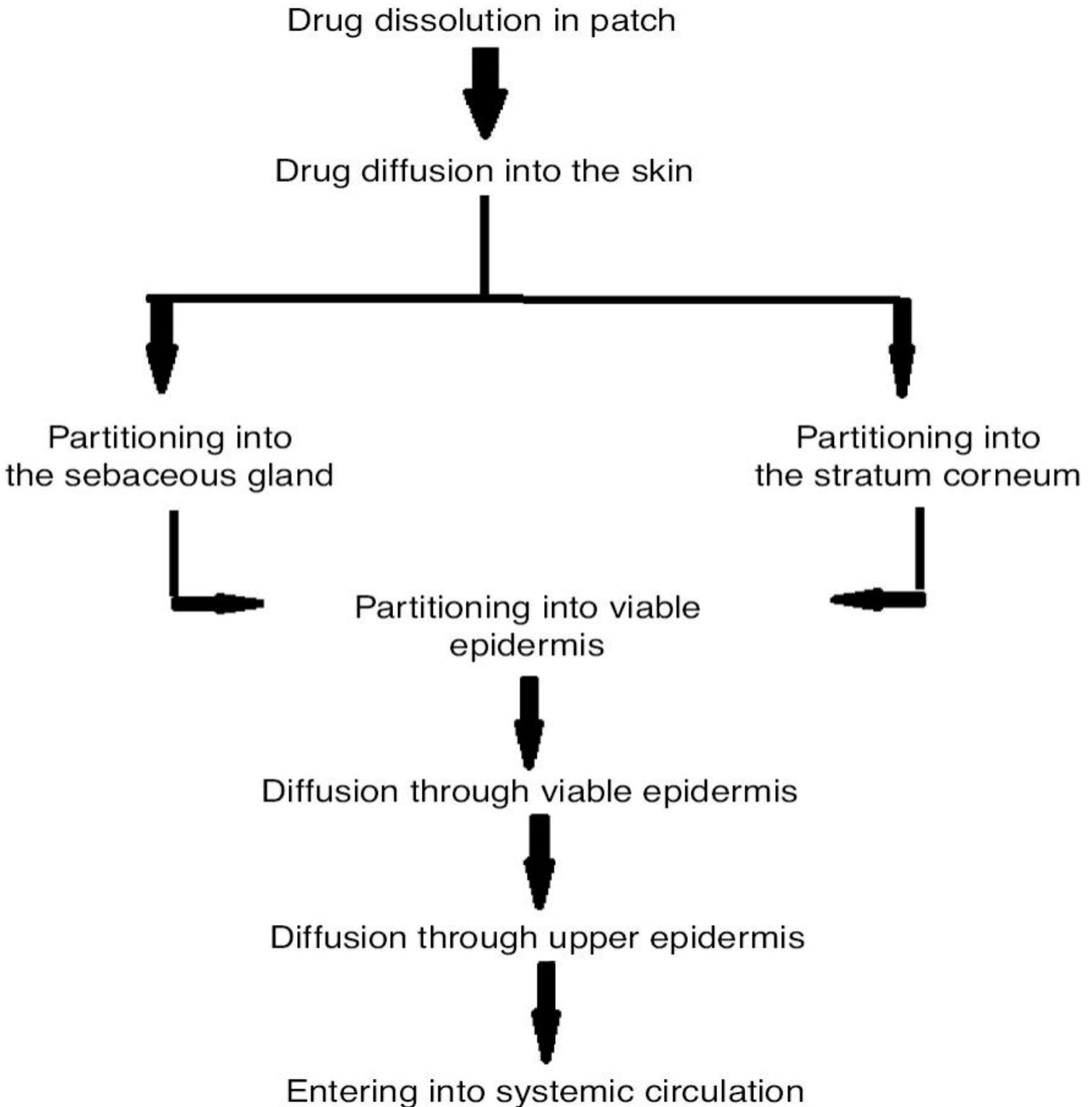
Nanoemulsions (NE) are low-viscosity, isotropic mixtures known for their thermodynamic and kinetic stability, showing no significant flocculation or coalescence even with extended storage. These mixtures contain transparent or translucent oil droplets dispersed in a water phase, stabilized by a layer of surfactant or co-surfactant molecules, resulting in very

small droplets typically averaging less than 500 nm in diameter. There is some debate regarding the particle size range for NE, with proposed upper size limits of 1000 nm, 500 nm, 200 nm, and 100 nm[84,85]



Transdermal mechanism of Nano formulations

Due to their small particle size and high specific surface area, nano-formulations can closely interact with the skin, enhancing drug absorption through it. However, various nano-formulations engage with the skin in different ways to achieve this effect.



CONCLUSION

This review provides a systematic summary of the components, properties, and transdermal delivery mechanisms of various nanoformulations, including liposomes, transfersomes, ethosomes, niosomes, invasomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, and nanoemulsions in transdermal drug delivery systems (TDDS). By presenting a comprehensive overview of TDDS, this review aims to enhance understanding of nanoformulations in TDDS, support future research, and encourage the clinical use of these advanced delivery systems.

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