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Review Article

Microneedles: A Novel Approach on Transdermal Drug Delivery

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ABSTRACT

Transdermal drug delivery via microneedles is emerging as a more effective alternative to traditional oral medication routes. Oral delivery often faces challenges such as exposure to stomach acid and digestive enzymes, leading to drug denaturation and poor effectiveness. Microneedle technology addresses these issues by delivering drugs through the skin, bypassing the gastrointestinal tract. This method also helps patients who experience discomfort from injections, improving overall compliance. There are five main types of microneedles: solid, coated, dissolving, hollow, and hydrogel forming. Each type offers unique advantages depending on the materials used in their production. Microneedle arrays, in particular provide a minimally invasive way to administer medications by only piercing the outer layer of the skin, known as the stratum corneum. This study explores various therapeutic drugs, focusing on protein pharmaceuticals, vaccines, and small molecule drugs used in regenerative medicine. The significance of microneedles lies in their ability to enhance drug delivery, offering a promising approach for improving patient outcomes in various medical treatments.

INTRODUCTION

The skin, which occupies an area of 1.8 m2 and accounts for over one-fifth of the average person's total body mass, is the largest and outermost organ in the human body. Transdermal drug delivery (TDD) is a technique used to administer therapeutic medications through the skin layer. Numerous issues with oral medication distribution, include low patient compliance, hepatic first-pass metabolism clearance, and gastrointestinal discomfort. Although they were discovered some time ago, microneedles (MNs) were not properly produced and used until the 1990s [1]. Transdermal drug delivery systems are primarily used to transfer medications through the skin to the systemic circulation. It improves patient compliance and reduces negative pharmacological adverse effects brought on by transient overdosage. In addition to enabling continuous, regulated drug administration, transdermal distribution also permits continuous, short

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biological half-lives [2]. currently, oral medication distribution is the most used method. A novel drug delivery method must be created in order to get over these obstacles [3]. With over 35 products approved for sale in the US and over 16 active components approved for usage as TDDS globally, the market value of TDDS products is growing at a rapid pace. Transdermal drug delivery systems are topically applied medications in the form of patches that distribute medications at a predefined, regulated rate for systemic effects [4]. he pace at which a liquid medication in the reservoir of the skin patch can permeate the epidermis and enter the bloodstream is regulated by a unique membrane [5]. Active cosmetic molecules can be delivered directly to the skin using microneedles, lowering the risk of infection for skin injuries and enhancing the safety and efficacy of cosmeceutical products. these distinctive marketing features give rise to the promise that cosmeceutical treatments will penetrate the skin more deeply and speed up the healing process [6]. The skin has many functions, and its ability to act as a barrier protects the underlying organs from environmental threats such as chemicals, physical strains, and microbes. It is a desirable approach to provide treatments, such as medications, vaccines, biomolecules, and tiny molecules that are challenging to distribute, through the skin. Many research institutes and businesses have expressed interest in the microneedle-mediated delivery method, which is defined as the non-invasive delivery of drugs through the skin's surface. It has been demonstrated that the microneedle delivery system can enter the skin's viable epidermis. The device comprises of a series of sub milli meter-sized needles (up to 1500 µm in length) coupled to a base support. The technology has shown to be an effective method for delivering medicinal molecules with different polarity and larger masses (above 500 Da). Small molecules, biomacromolecules (proteins, hormones, peptides), COVID-19, MERS, and SARS vaccines, and DNA are among the medicinal constituents. However, it is important to address the drawbacks of the Microneedle technology early on in the product development process [7]. The emergence of side effects associated with treatment compromises the long-term management of Parkinson's disease and can significantly reduce levodopa's efficacy. It has taken a while to produce a transdermal medication preparation for Parkinson's disease that is successful [8]. The integument of humans, or human skin, has several purposes. The kind of permeant that can pass through the barrier is physio-chemically limited by the protective role of human skin. A drug's molecular weight must be less than 50 Da and it must have sufficient lipophilicity in order to be passively distributed via the skin. The quantity of products that are commercially accessible that use transdermal or dermal distribution has been restricted by these limitations [9].

Microneedles

A needle is used in the microneedle drug delivery system, a revolutionary drug delivery method, to administer medication to the circulatory system. This approach includes puncturing the skin's superficial layer with needles the size of microns, which diffuses the medicine throughout the epidermal layer. Metal or polymer microneedles are made by laser-mediated fabrication processes. This process primarily involves creating an inverse mold based on the microneedle structure in order to produce silicon or dissolving/hydrogel microneedles photoresist etching [10]. Drug delivery through the SC layer and into the deeper layers is accomplished by microneedle (MN) technology. Microneedles ranging in length from a few micro meters to up to 2000 µm are used in

these delivery systems. The SC can be punctured without harming the nerves in the skin's deeper layers because of the MN's short length. MNs are preferred over conventional drug delivery methods because of their simple, painless, and minimally invasive delivery mechanism, which combines the convenience of transdermal application with the effectiveness of invasive needles and syringes. since MNs are meant to be self-administered by patients [11]. The goal of MN technology is to replace traditional syringe injections with an active transdermal drug delivery method. With a minimally invasive technique, the MN array is used to pierce the stratum corneum and administer the medication [12]. External factors such skin physiology, physiochemical characteristics, and environmental circumstances can affect the MN drug delivery route [13]. These include the surrounding temperature and relative humidity (v) in the application area [14]. Because they avoid digestion and first-pass metabolism, microneedle patches require less medication than oral consumption to provide the same therapeutic effects [15]. When compared to the oral route, the pharmacokinetics of microneedles demonstrate rapid absorption in the bloodstream, which can be helpful for treating localized illnesses with substantially lower drug loading. [16].

Types Of Microneedles

To create solid, coated, hollow, or dissolveable microneedles, a range of materials have been employed, including silicon, polymers, sugar and stainless steel. Every variety of microneedle has distinct qualities and a different kind of substance. There are five types of microneedles: solid, hollow, coated, dissolving, and hydrogel-forming [17].

1) Solid Microneedle

The purpose of this kind of microneedle shape is to promote drug administration to the dermis, hence increasing the drug's bioavailability and kinetic transport across the skin by penetrating the stratum corneum [18]. Compared to hollow microneedles, solid microneedles are easier to make, have better mechanical qualities, and have sharper points [19]. Solid microneedles can be made from a variety of materials, including polymers, metals, and silicon [20].

2) Hollow Microneedle

The hollow microneedle is made up of a hollow, empty core or chamber that can be used to inject or store medication [21]. For high molecular weight substances, a hollow microneedle can also transfer the medication into the viable dermis or epidermis [22]. Because hollow microneedles are comparatively weaker than solid microneedles are require special attention in terms of needle design polymers 2021, 13,2815 of 34 and insertion method [23]. They have received less attention than solid microneedle.

3) Coated Microneedles

The solid-type MN coated with a medication solution is the coated microneedle (Figure 8). Generally, the medicine is carried in a reduced quantity based on the coating layer's thickness [24]. A coated MN has the benefit of quickly delivering the medication to the skin; but, any remaining medication at the needle's tip could potentially infect further patients [25]. Similar outcomes were obtained when administering the vaccine by coated MN as opposed to intradermal and intramuscular methods [26].

4) Dissolving Microneedles

Based on its features, the dissolvable MN, which debuted in 2005, is a technology that shows

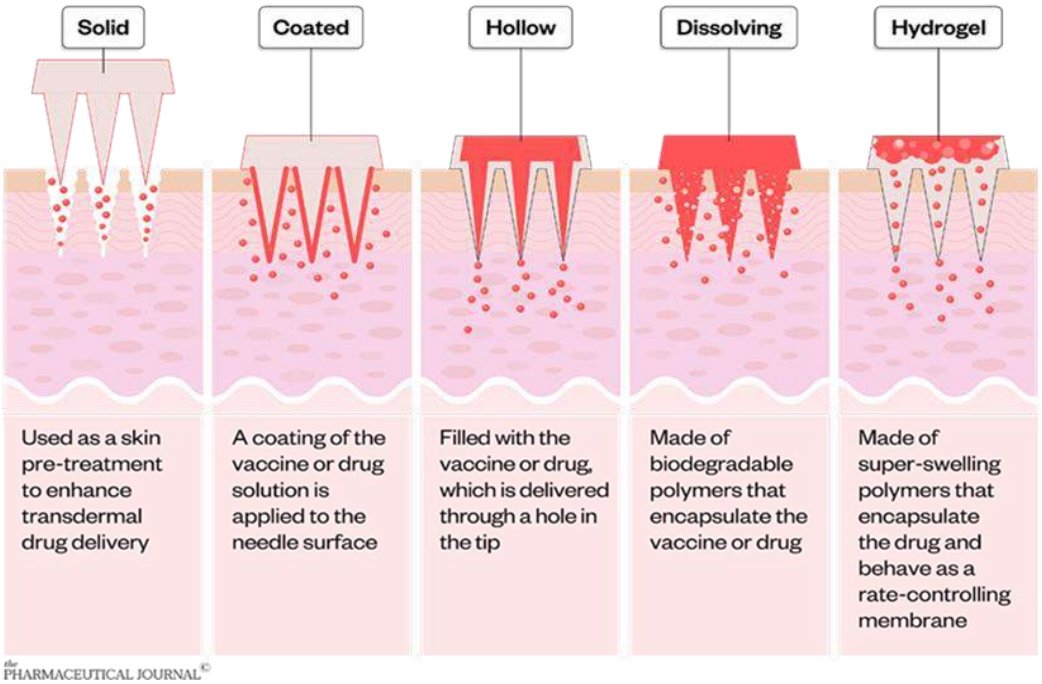
promise. One of these features is that it makes macromolecule release happen more quickly [27]. The best materials to use for making a dissolvable microneedle are those that dissolve in water [28]. This kind of MN has a delayed dissolving period and necessitates full insertion, both of which might be challenging to achieve [29]. The most appropriate fabrication technique for the dissolvable Microneedle is the Micro-mold method [30].

5) Hydrogel Microneedles

Every part of the hydrogel microneedle tip, base substrate, and patch backing contains the medication, which is gradually released when the patch is placed to the skin [31]. A sizable portion of the medication in the hydrogel can reach the skin thanks to diffusion. Due to the fact that the drug may be applied evenly across the microneedle patch, this technology is suitable for large-dose distribution; however, because the drug is supplied slowly, it is necessary for the patch to remain on the skin for a prolonged amount of time [32].

Drug Delivery System

Medications have been administered in a number of methods to enhance health and prolong life. Chewing medicinal leaves has given way to capsules, tablets, injectables, and implantable devices, which represent significant advancements in drug delivery systems [33]. Targeting the specific area of illness while minimizing a drug's harmful effects on healthy cells has been shown to increase a treatment's therapeutic efficacy [34]. The human body can receive drugs through a variety of methods, such as oral, parenteral, inhalation, transdermal, etc.



Transdermal Drug Delivery System

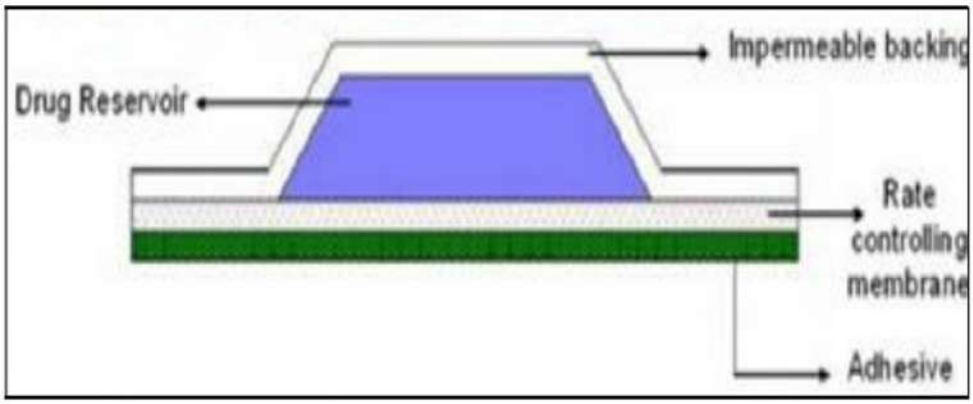
The first step in transdermal drug delivery is to apply the medication directly to the skin. The medication passes through the dermis and epidermis before penetrating the stratum corneum [36]. By regulating the rate of skin diffusion, this technique seeks to transfer the medication

molecules into the bloodstream [37]. Compared to other drug delivery techniques, transdermal drug delivery (TDD) offers a number of benefits. TDD can continuously and carefully administer the prescribed dosage of the medication to the blood in a controlled manner [38]. By keeping medications from entering vital organs like the liver and kidneys, the transdermal route further reduces the likelihood of adverse drug reactions [39]. Transdermal drug delivery systems can help with the limited bioavailability of several oral medications [40]. After comparing oral and transdermal distribution, Michal Goodman came to the conclusion that transdermal delivery has a better safety profile across a range of domains [41]. For medications that require significant dosages, passive transdermal drug administration is not appropriate [42]. The main obstacle for TDD is that it is currently restricted to around 22 strong medications that have perfect physicochemical qualities but are not commercially viable. These include substances that can passively diffuse and intercellularly penetrate through skin barriers to reach therapeutic concentrations, such as nicotine, nitro glycerine, and Estradiol [43]. Transdermal drug administration begins with the application of medication directly onto the skin. The medication enters the stratum corneum and then travels through the epidermis and dermis [44]. Four generations can be distinguished in transdermal medication administration. The first generation focused on administering a modest amount using patch-based technology that leveraged natural diffusion. The focus of the second generation was on using chemical precursors to activate medication delivery. The third generation include techniques including thermal ablation, electroporation, and microneedling that can precisely target the medication upon penetrating the stratum corneum. Drug delivery microneedles and sensing modalities are combined in the fourth generation to precisely control the release of medicinal compounds [45]. The paracellular, intracellular, and trans follicular pathways are examples of transdermal pathways. medicines that enter the dermis through the gaps between corneocytes are referred to as entering through paracellular transport, and this process is typically linked to small molecule heterophilic medicines. The phrase "intracellular transport" describes how a drug moves within the SC's cells; most pharmaceuticals do not go down this route since it requires many partitioning of the hydrophilic and heterophilic environments and is demanding of the drug's qualities [46]. Trans follicular transport, sometimes referred to as the trans adnexal route, is the process by which medications are absorbed by sebaceous glands, hair follicles, or sweat glands. Compared to the first two methods, this one avoids the stratum corneum and has a higher rate of medication absorption. However, this approach is not the main mode of transdermal drug absorption since the total area of the skin appendages is too tiny, limiting the total amount of drug absorption

Methods of preparation of TDDS

1) Polymer membrane permeation control TDDs [47][48]

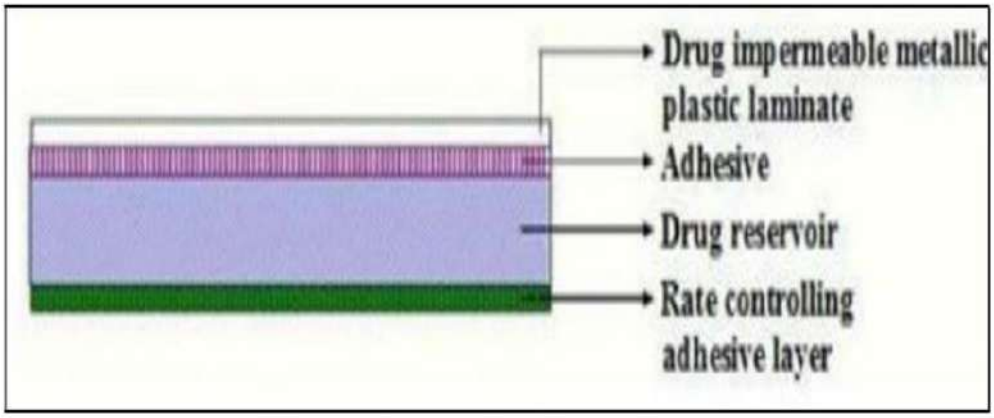
A rate-controlling membrane is placed between an impermeable backing layer and the drug reservoir. Only the rate-regulating membrane which may or may not be microporous allows the medication to release. Changes in the polymer composition, permeability coefficient, and membrane thickness of this kind of transdermal drug delivery system allow for customization of the drug release rate.



Membrane permeation controlled system.

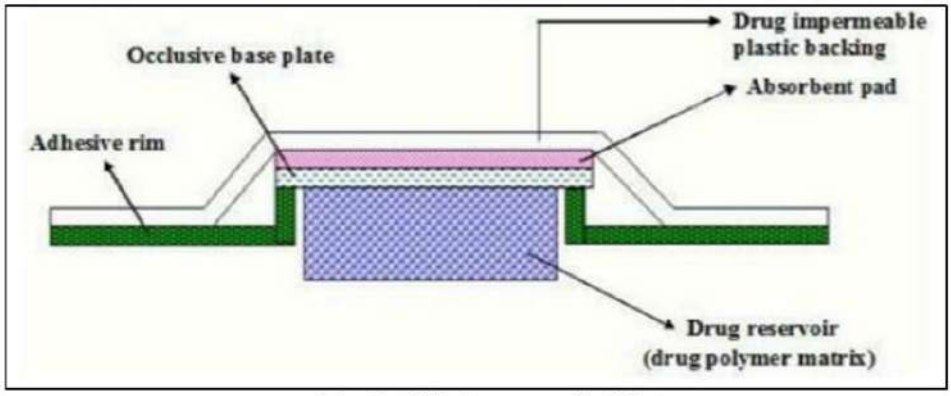
2) Adhesive diffusion controlled TDDs

The medication reservoir is created by dispersing the medication in an adhesive polymer, which is subsequently applied to an impermeable backing layer by solvent casting the medicated polymer adhesive or, in the case of hot-melt adhesives, melting the adhesive. After that, a non-medicated, constant-thickness adhesive polymer is applied over the drug reservoir layer to create an adhesive diffusion-controlled drug delivery system.



Adhesive Dispersion – Type Systems

3) Matrix diffusion controlled TDDS

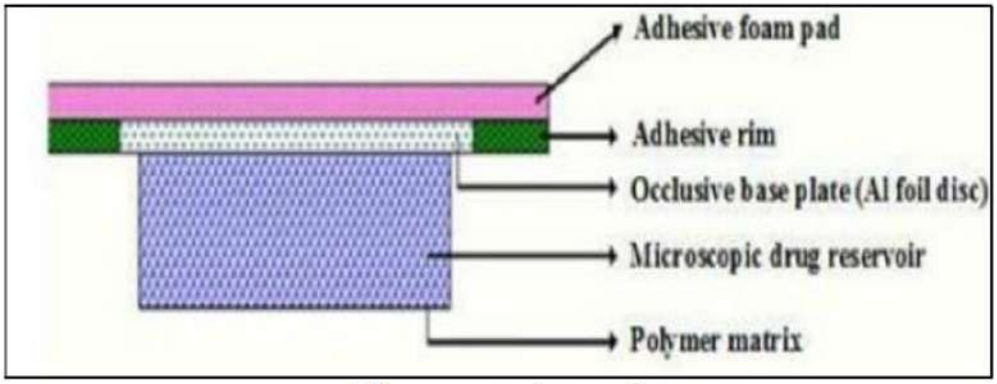


Matrix diffusion controlled Systems

The medication is uniformly distributed within a hydrophilic or lipophilic polymer matrix. After that, the drug-containing polymer disk is affixed to an occlusive base plate within a compartment made of a backing layer impermeable to drugs. Rather than covering the entire surface of the medication reservoir, the adhesive is applied all the way around to create an adhesive rim strip.

4) Micro reservoir controlled TDDS

This drug delivery device combines matrix-dispersion and reservoir technologies. To create thousands of impenetrable, microscopic spheres of drug reservoirs, the drug is first suspended in an aqueous solution of a water-soluble polymer and then uniformly dispersed in a lipophilic polymer. The polymer is crosslinked in situ right away, stabilizing the thermodynamically unstable dispersion. A medicated disc with an adhesive ring surrounding it is at the centre of a transdermal system, therapeutic system.



Micro reservoir type Systems

Basic components of TDDS

Polymer Matrix: - The most crucial and essential part of the transdermal drug delivery system is polymer. Various polymeric material classes have been employed to accomplish rate-controlled transdermal administration. The physicochemical characteristics of the drug and the polymer used to make the device determine the drug release mechanism.

The subsequent standards for a polymer utilized in TDDS;

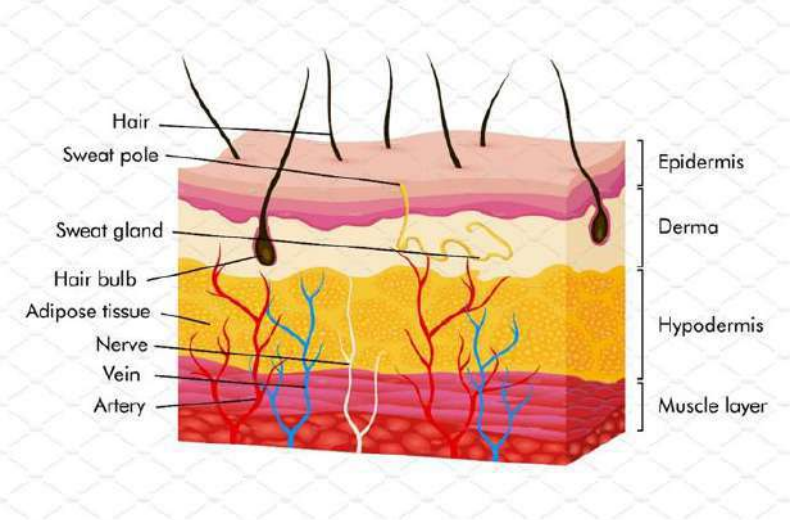
The chemical functionality of the polymer, its molecular weight, and its glass transition temperature must all permit the release and dispersion of a particular medication. • A significant proportion of the medication should be able to be incorporated into the polymer. • The medicine and polymer shouldn't interact chemically or physically. • Polymers and the products that result from their decomposition must not be harmful. • The polymer should be affordable, easily maintained, and fashioned into the desired product. No one material may possess all of these qualities; characteristics can be changed by adding specific excipients. To improve the drug's solubility, cosolvents including ethanol, propylene glycol, and PEG 4000 could be used. Table: Effective polymer for transdermal administration.

Natural polymers	Synthetic Elastomer	Synthetic polymers
Cellulose derivatives	Polybutadiene	Polyvinyl alcohol
Zein	Hydrin Rubber	Polyethylene

Geatin	Polysiloxane	PVC
Proteins	Acrylonitrile	Polyacrylates
Shellac	Neoprene	Polyamide
Arabino Galecti/n	Chloroprene	Acetal copolymer

Anatomy of skin

Three separate layers make up human skin, which are discussed below:



Epidermis

The stratified, squamous, keratinizing epidermis is made up of epidermal cells. The epidermis's complex layer differs in depending on the thickness, size, and quantity of epidermal cell layers, which range from 0.8 mm on the palms and soles to 0.06 mm on the eyelids. Eight percent of epidermal cells are melanocytes, while about 90% of epidermal cells are keratinocytes, or chest rated in five layers and producing keratin protein. They produce black, yellow, or melanin-colour melanin, which contributes to skin darkening and absorbs harmful UV rays. From red bone marrow, a Langerhans cell proliferates and migrates to the epidermis, where it makes up a small fraction of epidermis cells. The smallest subset of epidermal cells are called markel cells [48].

Dermis

The layer known as the dermis is 3 to 5 mm thick and is composed of a lattice of connective tissue that houses nerves, lymph arteries, and veins. The cutaneous blood supply can regulate body temperature on a fundamental level. In addition, it replenishes the skin with nutrients and oxygen while eliminating waste products and pollutants. The majority of atoms entering the skin barrier are given sink conditions via vessels, which extend to within 0.2 mm of the skin's surface. In this way, the blood supply prevents a substance from being too centralized on the skin, and the fixation contrast that follows across the epidermis provides a fundamental focus and tendency toward transdermal penetration [49].

Hypodermis

The dermis and epidermis are supported by the hypodermis, or subcutaneous fat tissue. It acts as a storage space for fat. This layer provides

mechanical security, healthy assistance, and temperature control. It may have palpable weight organs and transmits primary veins and nerves to the skin. In order for transdermal medication delivery to occur, sedate must penetrate all three of these layers and enter the foundational flow. In contrast, if topical medication delivery is to occur, only the stratum corneum must be entered, and then the medication must be maintained in the layers of the skin [50].

Advantages of TDDs

1. To avoiding the metabolism of first pass.
2. A steady and regulated blood pressure.
3. Equivalent properties to intravenous infusions.
4. Simplicity of stopping the medication's effect, if needed.
5. Extended activity times (from a few hours to a week).
6. No disruption of the intestinal and stomach fluids [51].

Disadvantages of TDDS

1.The dosage of the drug is high.
2. The drug's higher molecular size hinders absorption; ideally, it should be less than 800-1000 Dalton.
3. The medication irritates and sensitizes.
4. The skin metabolizes the drug.
5. The drug binds to proteins in the skin.
6. The medication is hydrophilic or highly lipophilic, meaning it should dissolve somewhat In oil and water [51].

Physicochemical factor [52]

1) **Hydration of the skin:** Skin becomes much more permeable when it comes into contact with water. The most crucial element in boosting skin penetration is hydration. Humectants are therefore used in transdermal delivery.
2) **Temperature and pH:** Changes in temperature cause the medication to permeate ten times more deeply. With a drop in temperature, the diffusion coefficient falls. pKa or pKb levels and pH determine the dissociation of weak bases and weak acids.
3) **Diffusion coefficient:** A drug's ability to penetrate a certain area is dependent on its diffusion coefficient. The drug's diffusion coefficient at a given temperature is determined by the drug's characteristics, the diffusion medium, and their interactions.
4) **Drug concentration:** If there is a greater concentration of the drug across the barrier, the concentration gradient will be higher and the flow will be proportionate to it.
5) **Partition coefficient:** A good course of action necessitates the optimal partition coefficient (K). Medication with a high K content isn't ready to leave the skin's lipid layer. Furthermore, medications with low K won't permeate.
6) **Molecular size and shape:** Smaller molecules enter more quickly than larger ones, and drug absorption is negatively correlated with molecular weight.

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