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RECENT ADVANCES IN TRANS-DERMAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. First-generation transdermal delivery systems have continued their steady increase in clinical use for delivery of small, lipophilic, low-dose drugs. Second-generation delivery systems using chemical enhancers, non-cavitational ultrasound and iontophoresis have also resulted in clinical products. Third-generation delivery systems target their effects to skin's barrier layer of stratum corneum using microneedles, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound. Microneedles and thermal ablation are currently progressing through clinical trials for delivery of macromolecules and vaccines, such as insulin, parathyroid hormone and influenza vaccine. Using these novel second and third-generation enhancement strategies, transdermal delivery is poised to significantly increase impact on medicine. The advantages of TDDS include improved patient compliance, reduced risk of infection, and enhanced therapeutic efficacy.

KEYWORDS: Trans dermal drug delivery, Micro needles, Thermal ablation, Macro molecules.

INTRODUCTION

Transdermal drug delivery systems (TDDS) have revolutionized the way drugs are administered, offering a non-invasive, pain-free, and convenient alternative to traditional oral

and parenteral routes. By bypassing first-pass metabolism and providing a steady, controlled release of drugs, TDDS have improved patient compliance, reduced side effects, and enhanced therapeutic outcomes. Over the past decade, significant advances have been made in TDDS, driven by innovations in materials science, nanotechnology, and pharmaceutical formulation. Microneedles and thermal ablation are currently progressing through clinical trials for delivery of macromolecules and vaccines, such as insulin, parathyroid hormone and influenza vaccine. This review aims to provide an overview of the recent advances in TDDS, highlighting the key technologies, techniques, and applications that are transforming the field of transdermal drug delivery.[1]

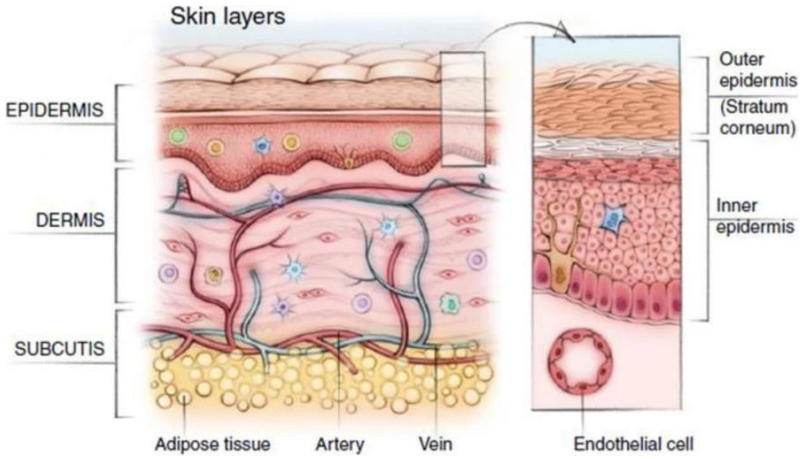

Figure 1: Anatomical Structure of Human Skin: Key Barrier for Transdermal Drug Delivery.

Different generation Transdermal Drug Delivery

Water-soluble drugs cannot get through the stratum corneum because it is so densely packed, but lipid-soluble drugs can get through the corneocytes and spread across the lipid layer. illustrates the classification of TDDSs into four generations, each with unique advantages and limitations. The second generation focuses on improving the delivery of small molecules through the skin by altering the skin structure or boosting the drug's effectiveness.[2]

The third generation incorporates innovative technologies like microneedles and iontophoresis, which help to overcome limitations and enable the delivery of macromolecules and peptides. The fourth generation, currently under development, seeks to enhance drug delivery through the skin by utilizing nanotechnology and targeted delivery systems for precise drug delivery. This will allow for real-time monitoring and personalized treatment.[3]

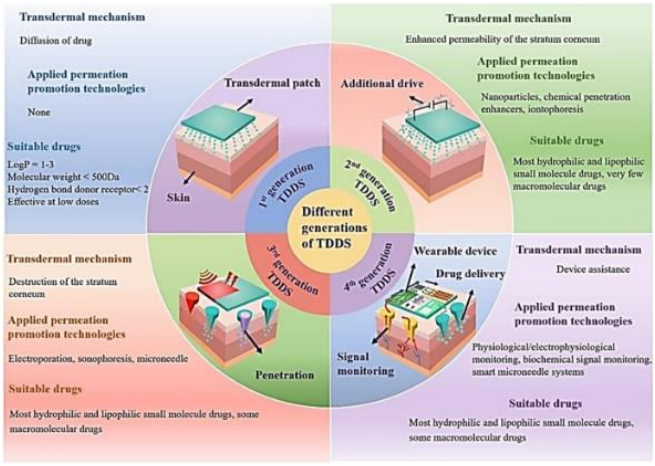

Figure 2: Classification of Transdermal Drug Delivery Systems (TDDS) by Generation and Mechanism.

FIRST-GENERATION TRANSDERMAL DRUG DELIVERY

Transdermal drug delivery systems were first developed from herbal plants and progressed to the current patch technology. The formulations in this generation, which include ointments, creams, sprays, gels, or patches, must be sufficiently low molecular weight, lipophilic, and effective at low doses. Owing to these factors, there is a limited number of drugs that can be delivered through the skin. For example, lipophilic drugs can cross the stratum corneum and reaching the capillary bed at a slow rate.[4]

SECOND-GENERATION TRANSDERMAL DRUG DELIVERY

The purpose of the second generation of transdermal drug delivery is to increase skin permeability by temporarily disrupting the function of the stratum corneum to allow drugs to cross it. This generation involves the use of different enhancements that do not damage the dermis. Conventional chemical enhancement, iontophoresis, and non cavitational ultrasound are three approaches associated with this generation.

Iontophoresis involves the application of a constant low-voltage electric current on the skin that increases the delivery rate of ionized molecules or drugs; the principle of charge repulsion is the basis of this approach. For example, if there is interest in delivering a positively charged drug, then the positively charged drug needs to be dissolved in the electrolyte with the same polarity.

The other member of the second generation of transdermal drug delivery is non cavitational ultrasound showed that ultrasound was able to facilitate the movement of hydrocortisone

ointment across an avascular membrane in 1950. An ultrasound device was approved by the United States Food and Drug Administration in 2004 for local dermal anaesthesia with lidocaine.

THIRD-GENERATION TRANSDERMAL DRUG DELIVERY

This generation of transdermal drug delivery aims to deliver vaccines, proteins, and macromolecules across the stratum corneum layer. This strategy involves enhancing the rate of drug delivery while protecting the deeper layers of the skin from injury. Technologies associated with this generation include electroporation, microdermabrasion, thermal ablation, cavitational ultrasound, and microneedle-based delivery.

Electroporation is also considered a third-generation transdermal drug delivery approach. Electroporation uses high voltage pulses in a short period of time to disrupt the skin lipid bilayer. This disruption process makes pathways for small-molecule drugs, vaccines, peptides, and DNA to be delivered.[5]

Microneedles

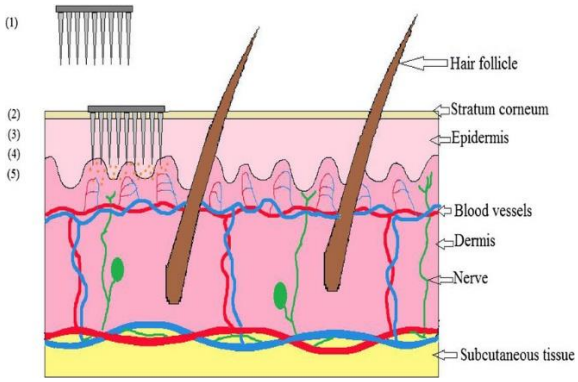

Figure 3: Mechanism of Transdermal Drug Delivery Using Microneedles.

Microneedles are micron sized ranging from 25-2000μm in height made of difference varieties and shapes. These can be fabricated within a patch for transdermal drug delivery patches containing microneedles can be evaluated in the delivery of drugs biopharmaceutical, vaccines, etc microneedle are thin short do not penetrate the dermis layer with its nerves hence painless possible Gerstel and Place invented microneedle technology in the year 1971. Microneedle are more capable of enhancing the transport of drug across skin as compared to other transdermal drug delivery methods.[6]

Thermal ablation

Thermal ablation, also known as thermophoresis, is a promising technique for selectively disrupting the stratum corneum structure by localized heat which provides enhanced drug delivery through microchannels created in the skin. To ablate the stratum corneum by thermal ablation, a high temperature above 100 °C is required and this leads to heating and vaporization of keratin. Additionally, the degree of alteration of the stratum corneum structure is proportional to the locally elevated temperature, indicating that it is an ideal technique for precise control of drug delivery. The thermal exposure should be short within microseconds to create a high enough temperature gradient across the skin for selective ablation of the stratum corneum without damaging the viable epidermis.

Techniques of thermal ablation

1. Radiofrequency Ablation: Uses high-frequency electrical energy to create heat and disrupt the skin barrier.
2. Laser Ablation: Uses high-intensity laser light to create heat and disrupt the skin barrier.
3. Cryoablation: Uses extremely low temperatures to create ice crystals and disrupt the skin barrier.

Microdermabrasion

Microdermabrasion involves the degradation of the stratum corneum and other skin layers in effort to increase skin permeability. Previous studies demonstrate that micrometre-scale abrasion results in higher rates of drug delivery. The microdermabrasion method can remove layers of the epidermis beyond the stratum corneum to enhance the drug delivery rate. Insulin, lidocaine, and 5-fluorouracil have been delivered by microdermabrasion of the skin. A vaccine delivery can also be facilitated by microdermabrasion.[7]

Electroporation

This method uses the application of high voltage electric pulses ranging from 5 to 500 V for short exposure times (~ms) to the skin, which leads to the formation of small pores in the SC that improve permeability and aid drug diffusion. For safe and painless drug administration, electric pulses are introduced using closely positioned electrodes. This is a very safe and painless procedure involving permeabilization of the skin and has been used to demonstrate the successful delivery of not only low MW drugs, such as doxorubicin, mannitol, or calcein, but also high MW ones such as antiangiogenic peptides, oligonucleotides, and the negatively charged anticoagulant heparin. However, this method has the disadvantages of small delivery

loads, massive cellular perturbation sometimes including cell death, heating-induced drug damage, and denaturation of protein and other bio macromolecular therapeutics.[8]

Polymeric nanoparticles

Nanoparticles (NPs) are nanocarriers with sizes ranging between 1 and 1000 nm and can be classified into several types according to their composition. Drug administration in the form of NPs leads to targeted and controlled release behaviour, changes in in vivo dynamics of the drug, and extends the drug residence time in the blood, which further lead to improved drug bioavailability and reduced toxicity and side effects. NPs are conventionally generated by polymerization and crosslinking, and biodegradable polymeric materials such as gelatin and polylactic acid (PLA) are often used. In the field of TDDS, polymeric NPs are gaining increased attention because they can overcome the limitations of other lipid-based systems, such as by conferring protection to unstable drugs against degradation and denaturation and achieving continuous drug release to reduce side effects. Increase in the concentration gradient improves transdermal penetration of the drug. Depending on the manufacturing method and structure, polymeric NPs can be classified as nanospheres, nanocapsules, and polymer micelles. Widely used polymers include polylactic acid, poly (D, L-lactide-co-glycolide) (PLGA), polycaprolactone, polyacrylic acid, and natural poly esters (including chitosan, gelatin, and alginate). These polymer chains can be synthesized by covalent linkage of two or more single polymeric units under specific conditions, such as the presence of a synthetic membrane that mimics the cellular lipid bilayer membrane. Although these polymers can form a complex structure, the polymer membrane is highly structured owing to the high MW polymer chains; for this reason, polymeric NPs, characterized by high mechanical strength and non-deformability cannot pass through pores with dimensions smaller or equal to their size. However, these NPs can be difficult to break down, which means drugs can be stored for a substantially long period, followed by its release from the NPs and diffusion into deeper layers of the skin.[9]

Nano-emulsions

Nano emulsions are a mixture characterized by low viscosity and isotropic, thermodynamic, and dynamic stability. The mixture consists of transparent or translucent oil globules dispersed in an aqueous phase stabilized by an interfacial membrane formed by surfactant or co-surfactant molecules of extremely small droplet size. The particle size of commonly used nano emulsions ranges from 100 to 1000 nm, although an upper limit to the particle size has

been proposed on account of its nanoscale dimensions. Nano emulsions are different from microemulsions; although nano emulsions have almost the same droplet size range, composition, and appearance as microemulsions, they differ greatly in terms of structural aspects and long-term thermodynamic stability. The small particle size, large specific surface area, and low surface tension of nano emulsions provide excellent wettability that ensures close contact with the skin. In addition, nano emulsions offer many other benefits such as high solubilization capacity and physical stability, improved bioavailability, ease of preparation, production with less energy input, and long shelf life. Nano emulsions exhibit a shorter transdermal time and better transdermal absorption than commonly used topical skin preparations. Depending on the composition, nano emulsions can include oil-in-water (O/W: oil phase dispersed in a continuous aqueous phase), water-in-oil (W/O: aqueous phase dispersed in a continuous oil phase), and bicontinuous/multiphasic emulsion. Several studies have reported the increased use of O/W nano emulsions as a delivery system for encapsulating lipophilic components in pharmaceuticals, highlighting the immense potential of nano emulsions in contributing to novel TDDS-based advances in pharmaceutical applications.[10]

Electricity-stimulated Patch

Wearable patches incorporating electronics offer precise control over drug delivery through electrical signalling and microprogrammed control units (MCUs). The hydrogel patch moves electricity around and acts like a tissue, keeping the electrolytes stable for iontophoresis and electrochemical sensing. Wearable technology commonly uses magnetic nanoparticles to enhance drug permeation through the skin. Triboelectric nanogenerators (TENG) convert biomechanical energy from body movements into electrical energy, enabling self-powering mechanisms for wearable devices.[11]

Passive delivery

Various factors, including the formulation, dose of the active ingredient, and skin conditions. Because of its strong binding to proteins, catalytic chitosan releases slowly. On the other hand, hyaluronic acid breaks down faster than polyesters or silk fibroin. Skin factors such as thickness, pH, temperature, and surface microbes also have an impact on TDDS degradation. Furthermore, the size and shape of drug reservoirs can affect the rate of transdermal drug delivery degradation, with smaller reservoirs diffusing more quickly and

larger reservoirs taking longer to degrade. Pre-existing skin damage or inflammation can affect how drugs break down by altering how easily they can pass through the skin barrier.

Fick's law, a cornerstone principle of passive drug delivery, offers crucial insights into the movement of molecules through diffusion within substances, enabling the optimization of their transportation. This law posits that the concentration gradient, skin characteristics, thickness, and interface area determine the drug diffusion rate. Furthermore, other factors, like skin surface temperature, pH, and molecular weight, also exert specific influences. For example, an increase in skin surface temperature can enhance drug diffusion by stimulating blood flow and vasodilation, whereas a decrease in pH can alter the drug's ionization state and permeability. Additionally, the molecular weight of a drug can affect its ability to penetrate the skin, with smaller molecules typically diffusing more easily than larger molecules. They used Eudragit to prepare a rate-limiting membrane for diclofenac sodium, ensuring a sustained release rate for a considerable time. The patch consistently released the drug for 12 hours in living organisms, demonstrating a value of 0.9753 for zero-order kinetics and 0.949 for non-Fickian diffusion. These results suggest that a polyvinyl alcohol patch could gradually release diclofenac sodium over an extended period, making it a potential option for long-term drug administration. Moreover, the use of Eudragit RS100 as a rate-limiting membrane highlights its effectiveness in maintaining a consistent release rate over an extended period.[12]

Active Delivery Systems

Delivery systems that are responsive to stimuli such as electricity, ultrasound, and light enable drugs or therapeutic agents to be delivered through the skin barrier. Electroporation involves the application of brief, high-voltage pulses to create temporary pores in the skin, which increase its permeability, enabling charged particles to pass through. Drug solubility, molecular weight, and pulse parameters such as voltage and duration all have an impact on this method's effectiveness. Ultrasound has advantages because it can penetrate tissues in various directions, allowing molecules or nanoparticles in low-viscosity solutions to move more easily. We create and pop microbubbles to facilitate this movement. Sonoporation, which involves using ultrasound waves to increase cell membrane permeability, helps deliver therapeutic agents into cells by temporarily damaging cell membranes, making it easier for substances to enter. Light-based delivery systems, such as infrared, visible, and ultraviolet light, offer targeted drug delivery to specific tissues. Encapsulating nanomaterials, like gold

nanoparticles, graphene, and quantum dots, enhances light absorption, allowing for more precise and efficient delivery (figure 3). Light stimulation may also reduce the required dose, minimizing potential side effects.[13]

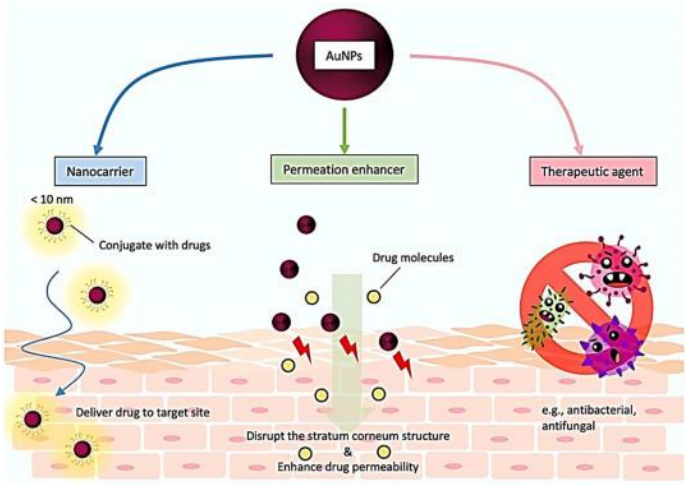

Figure 4: Role of Gold Nanoparticles (AuNPs) in Enhancing Transdermal Drug Delivery.

Technological Advancements

Recent advancements in transdermal drug delivery systems (TDDS) encompass microneedles, iontophoresis, ultrasound-mediated delivery, and nanoparticle-based approaches, which enhance penetration and offer controlled release. These innovative developments demonstrate the progress in TDDS research, indicating improved efficacy and patient adherence. The incorporation of these technological advancements into the review provides readers with a comprehensive understanding of the current state and future possibilities in TDDS research. Moreover, these innovations address key challenges such as skin barrier permeability and drug stability, positioning transdermal drug delivery as a viable alternative to conventional administration routes. The integration of these technologies has the potential to transform drug delivery methods, offering patients more efficacious and convenient treatment options.

Matrix-Based TDDS

The matrix-based drug delivery system (TDDS) is ideal for chronic conditions like hypertension and diabetes that require long-term, steady drug release. By modifying the polymer matrix composition, drug release rates can be adjusted to maintain consistent therapeutic levels over extended periods. This approach improves patient adherence to

medication regimens and treatment outcomes. It also minimizes potential side effects associated with large fluctuations in drug levels. This system offers a reliable and convenient way to manage chronic conditions, providing stable symptom control and fewer adverse reactions. It simplifies the treatment process for individuals with complex regimens and is particularly beneficial for patients who struggle with remembering multiple medications. Overall, matrix-based TDDS streamlines treatment plans and reduces missed doses. By delivering medication consistently over a prolonged period, matrix-based TDDS can also help reduce the risk of drug resistance developing in patients. This innovative system has shown promising results in improving overall health outcomes and quality of life for individuals with chronic conditions.[14]

Nanocarriers

The drug aims to reach the target area and reduce side effects. Using nanocarriers helps you follow your treatment schedule better because it is easier to comply with and reduces the frequency of application. Nanocarriers improve patient adherence by reducing the frequency of applications, allowing you to follow your treatment schedule more easily. Conditions such as skin inflammation and eczema benefit from their effectiveness and efficiency. For instance, by reducing the frequency of applications, this approach minimizes skin irritation and allergic reactions commonly associated with other topical treatments. Consequently, it enhances patient comfort and increases the overall safety profile of the treatment, making it a preferred option for individuals with sensitive skin. These systems can enhance drug delivery by protecting the medication from degradation and facilitating its transport across biological barriers. They offer potential solutions for improving the bioavailability and efficacy of various drugs.[10]

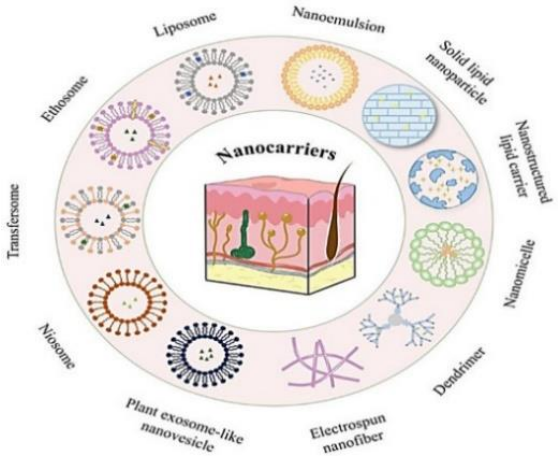

Figure 5: Types of Nanocarriers Used in Transdermal Drug Delivery Systems (TDDS).

CONCLUSION

Transdermal Drug Delivery Systems (TDDS) have revolutionized the way medications are administered, offering a convenient, painless, and controlled release of therapeutic agents. Recent advancements in microneedles, nanoparticles, wearable systems, and 3D printing technology have enhanced the efficiency and precision of TDDS. These systems have shown promise in managing various conditions, including Parkinson's disease, pain, and chronic diseases. As research continues to advance, TDDS is likely to play an increasingly important role in improving patient outcomes and transforming the field of pharmacology.

REFERENCES

1. S. Ganga Sai Pradeepa, K. Uma Maheswari, I. Jashwanth Sai, G. Sowmya Sri, B.Anusha, Dr. Aparna Pisipati. Insulin Delivery by Microneedles-Novel Approach, Journal of Current Science, 2023; 11(1).
2. Z. Liu, J. Nie, B. Miao, et al. Self-Powered intracellular drug delivery by a biomechanical energy-driven triboelectric nanogenerator, Adv Mater, 2019; 31: Article 1807795
3. G. Liu, Y. Zhou, Z. Xu, Z. Bao, L. Zheng, J. WuJanus hydrogel with dual antibacterial and angiogenesis functions for enhanced diabetic wound healing, Chin Chem Lett, 2023; 34: Article 107705.
4. Vargason AM, Anselmo AC, Mitragotri S. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021.
5. Guy RH, Hadgraft J, editors. New York: Marcel Dekker; 2003. Transdermal Drug Delivery. [Google Scholar]
6. Kumar JA, Pullakandam N, Prabu SL, Gopal V. Transdermal drug delivery system: An overview. Int J Pharm Sci Rev Res., 2010; 3(2): 49–54. [Google Scholar]
7. Alkilani AZ, Mccrudden MTC, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics., 2015; **7**(4): 438–470.
8. Charoo NA, Rahman Z, Repka MA, Murthy SN. Electroporation: An avenue for transdermal drug delivery. Curr Drug Deliv., 2010; **7**(2): 125–136.
9. Dhal S, Gavara RR, Pal K, Banerjee I, Mishra M, Giri S. Facile transdermal delivery of upconversion nanoparticle by iontophoresis-responsive magneto-upconversion oleogel. Nano Express., 2020; 1(1).
10. Nanoscale drug delivery systems: from medicine to agriculture. Front Bioeng Biotechnol., 2020; 8: 79.

11. G. Xu, Y. Lu, C. Cheng, X. Li, J. Xu, Z. Liu, et al. Battery-free and wireless smart wound dressing for wound infection monitoring and electrically controlled on-demand drug delivery.
12. K. Rizi, R.J. Green, M.X. Donaldson, A.C. Williams. Using pH abnormalities in diseased skin to trigger and target topical therapy.
13. K. Ita, Perspectives on transdermal electroporation.
14. R. M. Pai, M. S. Desai, A. D. Babtiwale and R. Shrivastava, Adhesive matrix type transdermal drug delivery system for nitroglycerin, Drug Dev. Ind. Pharm., 1994; 20: 1905–1909.