

Available online on 15.04.2024 at <http://ajprd.com>

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

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Review Article

New Insights in Topical Drug Delivery for Skin Disorders: A Review

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ABSTRACT

Drug delivery systems are methods which are used to ensure that drugs get into the body and reach the area where they are needed. These systems must take a number of needs into account, ranging from ease of delivery to effectiveness of the drugs. The paper reviews an overview of a conventional and novel approach in the topical drug delivery system. Drug delivery via the skin is becoming progressively popular due to its convenience and affordability. The skin is the most important mechanical barrier to the penetration of many drug substances and acts as an ideal site to deliver the drug both locally and systemically. The topical route has been a favored route of drug administration over the last decades. Despite conventional topical drug delivery systems limits in poor retention and low bioavailability. To address some of the limitations posed by conventional dermatotherapy, nano-based technologies have been developed and have demonstrated a significant improvement in dermatotherapy. Their distinct physicochemical properties demonstrate their overall superior therapeutic efficacy in providing sustained and effective targeted drug release, as well as improved solubility of hydrophobic actives with optimized drug formulations. These nanocarriers are commonly classified as polymeric, lipid-based, metallic, and vesicular nanocarriers, including nanoemulsions, nanofibers, and microneedles.

Key words: Topical Drug Delivery Systems, Skin Patches, Skin Penetration, Conventional and novel techniques**ARTICLE INFO:** Received 23 Nov 2023; Review Complete 10 Jan 2024 ; Accepted 15 Mar 2024 ; Available online, 15 April. 2024

Cite this article as:

Saini M, Garg S, Sharma P, Bhatt S, New Insights in Topical Drug Delivery for Skin Disorders: A Review, Asian Journal of Pharmaceutical Research and Development. 2024; 12(2):107-114 DOI: <http://dx.doi.org/10.22270/ajprd.v12i2.1323>

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INTRODUCTION

However, the transappendageal route covers only 0.1% of the total skin surface. Consequently, it does not contribute significantly to the penetration of large molecules and nanoparticles into deeper layers of the skin where the disease is primarily localized. The applications of such novel nanovehicle systems can deliver potent drugs to the preferred site in an exact manner. The skin reservoirs created from designed nanosystems effectively control therapeutic agent release to the damaged area at the skin site with a localized effect. Moreover, the site-specific dermal targeting was facilitated by nanosized particles, and their narrow size distribution may increase medication retention. Novel approaches to skin delivery of bioactive substances may be based on the entrapment of therapeutically active agents in nanocarriers, which are progressively used in skin targeting and topical delivery.

Such delivery vehicles aid release in a sustained manner, leading to prolonged activity or improved absorption and perhaps a reduction in deleterious effects. The prime goal of this current review is to assess the various innovative nanocarrier-based delivery systems employed to enhance therapeutic moiety uptake through the skin and their potential for treating disorders associated with the skin. Patents on topical delivery are mentioned with a brief overview of marketed topical products.¹

Topical Drug Delivery

Topical drug delivery systems are localized drug delivery system for local delivery of therapeutic agents via skin to treat the cutaneous disorder. These systems are generally used for local skin infection. The formulations are available in different forms, like from solid through semisolid to liquid. If the drug substance in the solution has a favorable lipid/water partition coefficient and if it is a non-electrolyte,

then drug absorption is enhanced via the skin. Dermatological products have various formulation and range in consistency though the most popular derma products are semisolid dosage forms

Topical Drug Classification System (TCS)

Based on qualitative & quantitative composition, TCS provides a framework for classifying topical drug products. Topical drug products are classified into 4 classes

Rationale for topical preparation

With the purpose to formulate an efficient and effective topical preparation, considerations are mainly concerned with the site of action of the drugs and its effect. Topical preparations may be used produce:²

Advantages of topical drug delivery systems

- Avoidance of primary pass metabolism.
- Convenient to use and easy to apply.
- Easily to terminate the medications.
- Drug delivered selectively to a specific site.
- The gastro-intestinal incompatibility will be avoided.
- Provides drugs utilization with short biological half-life and narrow therapeutic window.
- Better patient compliance.
- Self-medication.
- It provides effectiveness in low doses and by continuous drug input.
- Avoids fluctuation in drug levels and risks.
- A large area of application compared to other route.
- Drug delivery at a specific site

Disadvantages of topical drug delivery systems

- Possibility of local skin irritation at the site of application.
- Contact dermatitis due to some drug may occur.
- Some drugs with poor permeability are difficult to penetrate via the skin.
- Drugs with larger particle sizes are difficult to penetrate.
- Possibility of allergenic reactions.
- Drugs with a very small plasma concentration can be used for action

Transdermal drug products:

The world's first transdermal system for the systemic administration of drugs was a three-day scopolamine patch for treating motion sickness, approved in the United States in 1979. Just a generation later, the first blockbuster transdermal product, the nicotine patch, significantly increased the perceived value of transdermal delivery among the healthcare community and the general population. Nowadays, there are numerous transdermal delivery systems for drugs like oestradiol, fentanyl, and testosterone. Additionally, there are combination patches containing multiple drugs for contraception and hormone replacement.³

This is a list of Drug Products in some transdermal patches available on the current market:

Anatomy of skin:

The structure of human skin can be categorized into three main layers and represented in (Fig.1)

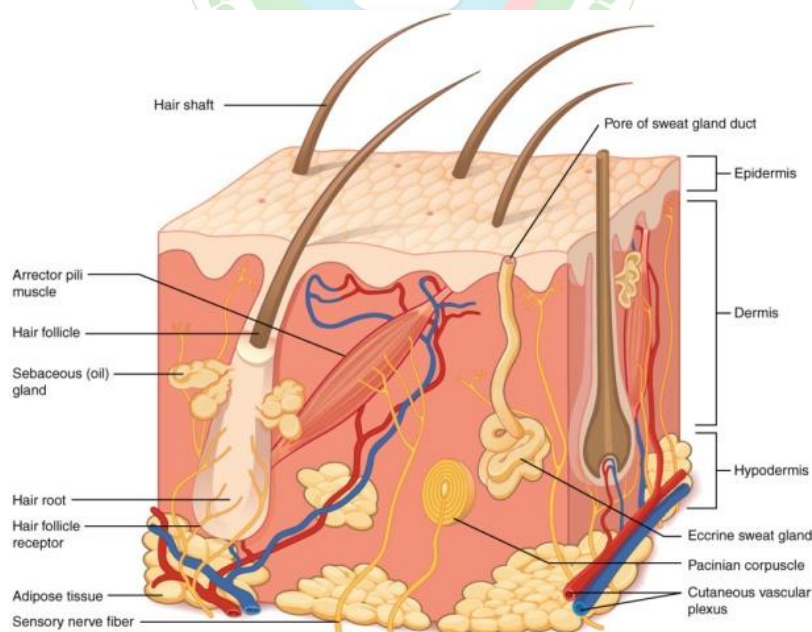


Figure 1: Structure of skin

Epidermis:

Is a continually self-renewing, stratified squamous epithelium covering the entire outer surface of the body and primarily composed of two parts which is represented in (Fig.2). The living cells of the malpighian layer (viable

epidermis) and the dead cells of the stratum corneum (non-viable epidermis), commonly referred to as the horny layer. Viable epidermis is further classified into four distinct layers.⁴

- Stratum lucidum
- Stratum granulose

- Stratum spinose
- Stratum basale

Stratum corneum:

This is the outermost layer of skin also called as horny layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. The stratum corneum is the principal barrier for penetration of drug. In this model, the keratinized cells function as protein “bricks” embedded in lipid “mortar.” Viable epidermis is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal.⁵⁻⁶

Dermis:

Is the layer of skin just beneath the epidermis which is 3 to 5 mm thick layer and is composed of a matrix of connective

tissues, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. In terms of transdermal drug delivery, this layer is often viewed as essentially gelled water, and thus provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules.

Hypodermis:

Is the subcutaneous fat tissue that supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanically protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to penetrate through all three layers and reach in systemic circulation.⁷⁻⁹

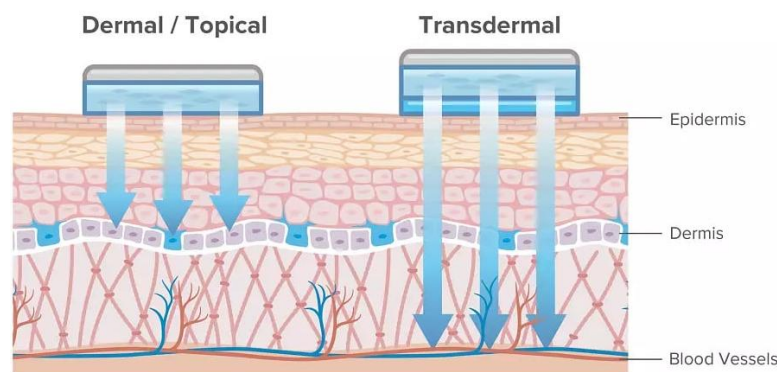


Figure 2: Parts of Skin

Components of TDDS:¹⁰⁻¹¹

Various components of a TDDS are

Polymers:

The polymer controls the release of the drug from the device. Polymers are the backbone of transdermal drug delivery system. a drug polymer matrix is sandwiched between two polymeric layers, an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive, or rate-controlled membrane.

Ideal properties of a polymer to be used in TDDS:¹²⁻¹⁴

Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.

- Should be stable.
- Should be nontoxic
- Should be easily of manufactured
- Should be inexpensive
- The polymer and its degradation products must be non-toxic or non-antagonistic to the host.
- Large amounts of the active agents are to be incorporated into

Table: 1 Various polymers used in TDDS

Type	Example
Natural polymers	Cellulose derivatives, gelatin, waxes, proteins, gums, shellac, natural rubber, starch.
Synthetic elastomers	Hydrin rubber, silicone rubber, nitrile, acrylonitrile, neoprene.
Synthetic polymers	Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamide,

Drug:¹⁵⁻¹⁷

For successfully developing a TDDS, the drug should be chosen with great care. Drug solution in direct contact with release liner

Physiochemical properties of drug:

- The drug should have a molecular weight less than 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases.
- The drug should have a low melting point.

Biological properties of drug substance:

- The drug should be potent with a daily dose of the order of a few mg/day.
- The half-life ($t_{1/2}$) of the drug should be short.
- The drug must not produce allergic response.
- Tolerance to the drug must not develop under the near zero-order release profile of transdermal

Penetration enhancers:

These are compounds which promote the skin permeability by altering the skin as barrier to the flux of a desired penetrate.

Ideal properties of penetration enhancers:

- should not cause loss of body fluids, electrolytes or other endogenous materials
- Nontoxic, nonallergic, non-irritating
- Pharmacological inertness
- Ability to act specifically for predictable duration
- Odourless, colourless, economical and cosmetically acceptable.

Other excipients:

Solvents: Such as chloroform, methanol, acetone, isopropanol, and dichloromethane, are used to prepare drug reservoir.

Plasticizers:

Such as dibutylphthalate, propylene glycol are added to provide plasticity to the transdermal patch.

Adhesives:

Such as polyacrylamates, polyacrylates, polyisobutylene, silicone-based adhesives.

Ideal properties of Adhesives:

- The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device.
- It should not be irritant
- It should be easily removed
- It should not leave an un washable residue on the skin
- It should have excellent contact with the skin.
- Physical & chemical compatibility with the drug
- Permeation of drug should not affect.

Linear:

During storage release linear prevents the loss of drug that has migrated into the adhesive layer and contamination. However, as the linear is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water.¹⁸⁻¹⁹

Desirable features for TDDS:

- Composition relatively invariant in use.
- System size reasonable.
- Defined site for application.
- Application technique highly reproducible.
- Delivery is zero order.
- Delivery is efficient.

Conditions in which transdermal patches are to be used:

- When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.
- Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.
- It can be used in combination with other enhancement strategies to produce synergistic effects.

Conditions in which transdermal patches are not to be used:

- Cure for acute pain is required.
- Where rapid dose titration is required.
- Where requirement of dose is equal to or less than 30 mg /24 h.²⁰⁻²³

Types of TDDS:**Single-layer drug-in-adhesive:**

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adheres the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

Multi-layer drug-in-adhesive:

The multi-layer drug inadhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-inadhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

Reservoir:

Unlike the single-layer and multi-layer drug-inadhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer.

This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

Matrix:

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

Vapour patch:

In this type of patch the adhesive layer not only serves to adheres the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller

vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

Treatment Approaches for Various Disorders Using Topical Drug Delivery

The skin controls the entry and exit of many chemicals, preventing moisture loss and controlling body temperature to preserve balance as homeostasis within the body. Topical medication delivery systems obviously depend on the drug being able to transmit into the skin's barrier and reach its intended delivery site. Various skin disorders treated by the topical delivery approach are mentioned below.²⁴⁻²⁸

Table 2: Topical Drug Delivery Intended for Several Skin Diseases

Disease	Therapeutic agent	Animal model	Route
Acne	Adapalene	Rabbit auricle	Topical
Acne vulgaris	Retinyl palmitate	Female Wistar rats	Topical
Acne	Azelaic acid, tea tree oil	Female Wistar rats, testosterone-induced skin acne male Swiss albino mice	Topical
Acne	Dapsone	Male BALB/c mouse	Topical
Acne	Isotretinoin, clindamycin phosphate	Testosterone-induced skin acne male laca mice	Topical
Skin fungal infections	Ketoconazole	Albino rabbits, Wistar rats	Topical
Skin infections and disorders	Rhein	Male Wistar rats	Topical
Skin infection	Garvicin KS, micrococin P1	BALB/cJRj mice	Topical
Skin fungal infections	Miconazole	Albino rats	Topical
Skin fungal infections	Luliconazole	<i>Candida albicans</i> induced skin fungal infection Albino rats	Topical
Psoriasis	Gemcitabine HCL, tacrolimus, methotrexate sodium, triamcinolone, betamethasone 17-valerate	12-O-Tetradecanoylphorbol 13-acetate-induced skin hyperplasia and inflammation male Swiss mice	Topical
Face skin cancer	Small interfering RAN	Mouse xenograft model	Topical
Inflammatory skin disorders	Pioglitazone	Arachidonic-induced inflammatory skin BALB/c male mice	Topical
Psoriatic skin lesions	Imiquimod, curcumin	Psoriasis-induced mice, skin of male Albino rats	Topical
Cutaneous leishmaniasis	Amphotericin B		

DISEASE CURED/TREAT VIA TRANSDERMAL ROUTE²⁸⁻²⁹

Herpes simplex

Herpes labialis and vaginal herpes are the most prevalent varieties of herpes simplex, which is brought on by the herpes simplex virus. The type 1 and type 2 herpes simplex viruses are what cause cold sores, also known as herpes labialis, although genital herpes more frequently affects the vaginal region than HSV-1.

Varicella and herpes zoster

Varicella and herpes zoster are brought on by primary VZV infection, and they are both caused by VZV. Patients with impaired immune systems are more likely to experience

consequences such hepatitis, myelitis, cranial nerve palsies, meningitis, pneumonia, and widespread infection.

Warts

Warts or verrucas are cutaneous viral infections brought on by the human papillomavirus [HPV]. They manifest as papules or plaques, which can vary in size and frequently have an abrasive, scaly surface. Skin lesions that have spread locally are rather common. Common warts [verruca vulgaris], fat warts [verruca plana], plantar and palmar warts [condyloma acuminatum], and anogenital warts [verruca vulgaris] are the four main classifications of warts based on their anatomical locations or morphologies. Treatment for warts often involves the physical destruction of infected epithelial cells or the use of immune-mediated methods.

Cryotherapy, which employs liquid nitrogen to freeze and kill wart lesions, is currently the most often used method. But because cryotherapy is so painful, some patients might not be able to put up with additional treatments.³⁰⁻³³

Influenza

Influenza is a contagious respiratory disease caused by influenza viruses. The intensity of flu symptoms can range from mild ones like fever, headaches, sore throats, and runny nose to more serious ones like pneumonia that can lead to hospitalisation or even death. Immunosuppressed or elderly patients are far more likely to develop serious problems and die as a result. The influenza vaccine is the most effective way to prevent influenza and its population spread.

Measles

The measles is a highly contagious illness that spreads through the respiratory system when aerosols or droplets are inhaled. It is still a leading cause of illness and mortality in children worldwide, despite having a safe and effective

vaccine.

COVID-19

COVID-19 is a deadly global pandemic caused by SARS-CoV-2, a new virus of the Coronavirus family. It is the seventh known Coronavirus and belongs to the genus "Beta-Coronavirus" and family "Coronaviridae". As of 15 August 2020, in India, 25, 89,208 cases, 6, 77,959 active cases, 18, 60,672 recovered cases and 50,085 deaths have been reported.

Parkinson's disease

The neurochemical foundation of Parkinson's disease [PD] is the gradual degradation of the nigrostriatal neuron and the resulting decrease in striatal dopamine. The first evidence of a striatal dopamine deficiency in the post-mortem brains of PD patients was found in 1960, and this finding served as the impetus for the development of dopamine replacement therapy.³⁴

Table 3: Diseases cured by TDDS and Role of TDDS in the or Management

S.NO.	DISEASE	TYPE OF TDDS	ROLE OF TDDS
1.	Herpes Simple	- Buccal mucoadhesive patches - Moisture-activated patches - Dissolving polymeric microneedles	Drug Delivery of Acyclovir
2.	Varicella and Herpes Zoster	- Transdermal patches - Coated microneedles with recombinant gE of VZV	Drug delivery of lidocaine for post-herpetic neuralgia VZV Vaccine
3.	Warts	- Transdermal karaya gum patches - Solid microneedles - Microneedle patches - Microneedle arrays with HPV pseudovirusencapsidated Plasmids	Drug delivery of salicylic acid Facilitated penetration of topical bleomycin and 5-FU Drug delivery of bleomycin HPV vaccine
4.	Influenza	- Coated microneedles with inactivated influenza virus - Coated microneedles with VLPs - Microneedles with trimeric Influenza Hemagglutinin protein - Tip-coated [selective antigen] Microneedles - Surface-modified microneedle Arrays	1. Influenza Vaccine 2. Capture circulating influenza antigen-specific IgG
5.	Measles	- Coated microneedles with live attenuated measles virus - Polymeric microneedles with standard measles vaccine - Dissolving microneedle patches	Measles Virus
6.	COVID-19	- Microneedle based oropharyngeal swabs with integrated virus-specific Antibody - Dissolving microneedles containing embedded SARS- CoV-2-S1 subunits	Reduce False negative result of COVID-19 Testing COVID-19 Vaccines
7.	Parkinson's Disease	Subcutaneous patch	Delivery of ND0611 carbidopa

CURRENT TRANSDERMAL DRUG FOR MEDICAL USE US MARKET LISTED

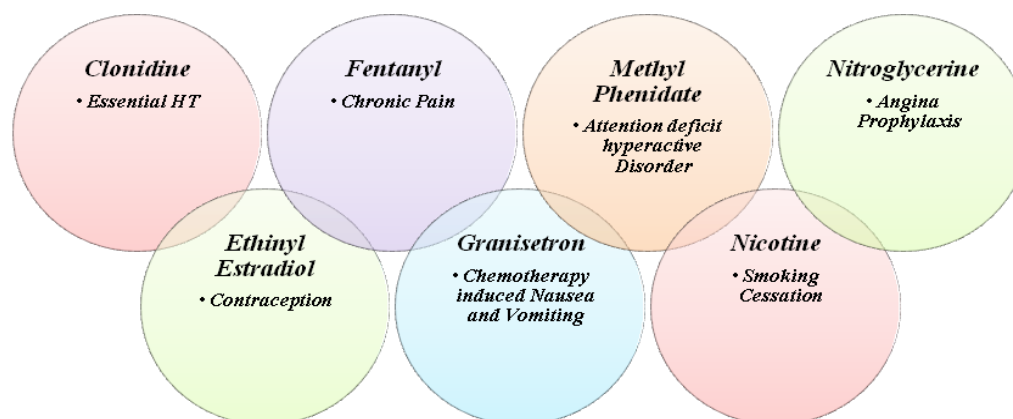


Figure 2: Current TDDS and their Medicinal uses

CONCLUSION:

The fore going shows that TDDS have great potential being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. TDDS is a realistic practical application as the next generation of drug delivery system. This article provides a valuable information regarding the TDDS and their evaluation process details, as a ready reference for the research scientists who want updated information regarding TDDS.

REFERENCES:

- Wang M, Luo Y, Wang T, Wan C, Pan L, Pan S, et al. Artificial skin perception. *Adv Mater*. 2020; 33:e2003014.
- Hutton AR, McCrudden MT, Larrañeta E, Donnelly RF. Influence of molecular weight on transdermal delivery of model macromolecules using hydrogel-forming microneedles: potential to enhance the administration of novel lowmolecular weight biotherapeutics. *J Mater Chem B*. 2020;8(19):4202–9. <https://doi.org/10.1039/D0TB00021C>.
- Andrews SM, Jeong EH, Prausnitz MR. Transdermal delivery of molecules is limited by full epidermis, Not Just Stratum Corneum. *Pharm Res*. 2013; 30(4):1099–109.
- Chaulagain B, Jain A, Tiwari A, Verma A, Jain SK. Passive delivery of protein drugs through transdermal route. *Artif Cells Nanomed Biotechnol*. 2018; 46(1):472–87. <https://doi.org/10.1080/21691401.2018.1430695>.
- Schuetz, Y.B.; Naik, A.; Guy, R.H.; Kalia, Y.N. Emerging Strategies for the Transdermal Delivery of Peptide and Protein Drugs. *Expert Opin. Drug Deliv*. 2005, 2, 533–548.
- Schoellhammer, C.M.; Blankschtein, D.; Langer, R. Skin Permeabilization for Transdermal Drug Delivery: Recent Advances and Future Prospects. *Expert Opin. Drug Deliv*. 2014, 11, 393–407.
- Shahzad, Y.; Louw, R.; Gerber, M.; du Plessis, J. Breaching the Skin Barrier through Temperature Modulations. *J. Control. Release* 2015, 202, 1–13.
- Hopp SM. Developing Custom Adhesive Systems for Transdermal Drug Delivery Products. *Pharmaceutical Technology* 2002, 30-36.
- Misra AN. Transdermal Drug Delivery. In Jain NK, Editor. *Controlled and Novel Drug Delivery*. New Delhi: CBS Publishers and Distributors, 2002; 101-107.
- Prausnitz MR, Langer R. Transdermal drug delivery. *Nat Biotechnol*. 2008; 26(11):1261–8.
- Kalia YN, Merino V, Guy RH. Transdermal drug delivery: clinical aspects. *Dermatol Clin*. 1998; 16(2):289–99.
- Kornick CA, Santiago-Palma J, Moryl N, Payne R, Obbens EA. Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. *Drug Saf*. 2003;26(13):951–73.
- Ita K. Transdermal delivery of drugs with microneedles—potential and challenges. *Pharmaceutics*. 2015;7(3):90–105.
- Varvel J, Shafer S, Hwang S, Coen P, Stanski D. Absorption characteristics of transdermally administered fentanyl. *The Journal of the American Society of Anesthesiologists*. 1989;70(6):928–34.
- Rouphael NG, Paine M, Mosley R, Henry S, McAllister DV, Kalluri H, et al. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch [TIV-MNP 2015]: a randomised, partly blinded, placebo-controlled, phase 1 trial. *Lancet*. 2017; 390(10095):649–[https://doi.org/10.1016/s0140-6736\(17\)30575-5](https://doi.org/10.1016/s0140-6736(17)30575-5).
- Kim E, Erdos G, Huang S, Kenniston TW, Balmert SC, Carey CD, et al. Microneedle array delivered recombinant coronavirus vaccines: immunogenicity and rapid translational development. *EBioMedicine*. 2020; 55:102743.
- Liu GS, Kong Y, Wang Y, Luo Y, Fan X, Xie X, et al. Microneedles for transdermal diagnostics: recent advances and new horizons. *Biomaterials*. 2020;232:119740.
- Yarmush, M.L.; Golberg, A.; Sersa, G.; Kotnik, T.; Miklavcic, D. Electroporation-based technologies for medicine: Principles, applications, and challenges. *Annu. Rev. Biomed. Eng*. 2014, 16, 295–320.
- Eriksson, F.; Totterman, T.; Maltais, A.-K.; Pisa, P.; Yachnin, J. DNA vaccine coding for the rhesus prostate specific antigen delivered by intradermal electroporation in patients with relapsed prostate cancer. *Vaccine* 2013, 31, 3843–3848.
- Thomson, K.R.; Cheung, W.; Ellis, S.J.; Federman, D.; Kavnoudias, H.; Loader-Oliver, D.; Roberts, S.; Evans, P.; Ball, C.; Haydon, A. Investigation of the Safety of Irreversible Electroporation in Humans. *J. Vasc. Interv. Radiol*. 2011, 22, 611–621.
- Sammata, S.M.; Vaka, S.R.K.; Murthy, S.N. Transcutaneous electroporation mediated delivery of doxepin-HPCD complex: Asustained release approach for treatment of postherpetic neuralgia. *J. Control. Release* 2010, 142, 361–367.
- Singer, A.J.; Homan, C.S.; Church, A.L.; McClain, S.A. Low-frequency Sonophoresis: Pathologic and Thermal Effects in Dogs. *Acad. Emerg. Med*. 1998, 5, 35–40.
- Waghule, T.; Singhvi, G.; Dubey, S.K.; Pandey, M.M.; Gupta, G.; Singh, M.; Dua, K. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. *Biomed. Pharmacotherapy* 2019, 109, 1249–1258.
- Ita, K. Transdermal Delivery of Drugs with Microneedles-Potential and Challenges. *Pharmaceutics* 2015, 7, 90–105.
- Whitley RJ, Roizman B. Herpes simplex virus infections. *The Lancet*. 2001;357(9267):1513–8.
- Saxena A, Tewari G, Saraf SA. Formulation and evaluation of mucoadhesive buccal patch of acyclovir utilizing inclusion phenomenon. *Braz J Pharm Sci*. 2011;47(4):887–97.
- Shojaei AH, Zhuo S, Li X. Transbuccal delivery of acyclovir [II]: feasibility, system design, and in vitro permeation studies. *J Pharm Sci*. 1998; 1(2):66–73.
- Rossi S, Sandri G, Ferrari F, Bonferoni MC, Caramella C. Buccal delivery of acyclovir from films based on chitosan and polyacrylic acid. *Pharm Dev Technol*. 2003; 8(2):199–208.

30. Schoellhammer, C.M.; Blankschtein, D.; Langer, R. Skin Permeabilization for Transdermal Drug Delivery: Recent Advances and Future Prospects. *Expert Opin. Drug Deliv.* 2014, 11, 393–407.
31. Gratieri, T.; Alberti, I.; Lapteva, M.; Kalia, Y.N. Next Generation Intra- and Transdermal
32. Therapeutic Systems: Using Non-and Minimally-Invasive Technologies to Increase Drug Delivery into and Across the Skin. *Eur. J. Pharm. Sci.* 2013, 50, 609–622.
33. Lakshmanan, S.; Gupta, G.K.; Avci, P.; Chandran, R.; Sadasivam, M.; Jorge, A.E.S.; Hamblin, M.R. Physical Energy for Drug Delivery; Poration, Concentration and Activation. *Adv. Drug Deliv. Rev.* 2014, 71, 98–114.
34. Badkar, A.V.; Banga, A.K. Electrically Enhanced Transdermal Delivery of a Macromolecule. *J. Pharm. Pharmacol.* 2002, 54, 907–912.

