# An Overview on Nanoparticle-Enabled Wound Dressing Patch

Nisha Thakre
*Research Scholar, Madhayanchal Professional University, Bhopal (M.P) India*

***Abstract*** **- The word "nanoscale" refers to particle sizes ranging from 1 to 100 nanometers; however nanoparticles in the range of 50 to 500 nanometers are suitable for medication delivery depending on the route of administration. The way a medication is administered can have a big impact on its effectiveness. When topical, regional, or systemic effects are required, the skin has long been a popular route for drug administration. Because of electrostatic interactions, nanoparticles have a strong affinity for biological membranes. Some studies have discovered that surface charge has an impact on membrane permeability, for example, the polymer charge density of dendrimers has been found to have a substantial impact on membrane permeability. Nanoparticles (NPs), which have the potential to improve medication penetration over the skin, have been used in recent developments in TDDS. NPs can also offer controlled release, administer both hydrophilic and hydrophobic medicines, and decrease adverse effects, and they are non-invasive when employed in a TDDS manner. Skin patches with microneedles are another emerging technique for TDDS. New studies have focused on incorporating two TDDS techniques to overcome the limitations of traditional drug delivery systems. Loaded nanoparticles are used to create the structures, which may also be used to make patches and wound healing materials. The goal of this review paper is to show how such patches and wound dressings may be processed in new ways.**

***Index Terms*** **- Nanoparticles, TDDS, Microneedles, Transdermal patches, Wound healing patch.**

## INTRODUCTION

Topically administered medicaments in the form of patches or semisolids (gels) that release medicines for systemic effects at a predefined and regulated rate are known as transdermal drug delivery system (TDDS) [1]. Because of its flexibility and ease in contrast to other routes of delivery, the transdermal route has garnered increasing attention in drug delivery [2]. It is one of the most appropriate, practical, safe, and cost-effective ways to administer drugs.

The advantages of a transdermal drug delivery system over traditional modalities of drug administration include a regulated rate of drug release, avoidance of hepatic metabolism, simplicity of termination, and a long duration of effect. A medication is administered to the inside of a patch that is worn on the skin for an extended period of time in a reasonably high dosage. The medication enters the circulation immediately via the skin through a diffusion mechanism. Because the patch has a high concentration and the blood has a low concentration, the medication will continue to diffuse into the blood for a long time, keeping a steady drug concentration in the blood flow [3].

Wound healing is the process of repairing the skin and other soft tissues after an injury. An inflammatory reaction happens after an injury, and cells below the dermis (deepest skin layer) begin to produce more collagen (connective tissue). The epithelial tissue (outer skin) regenerates later. Wound healing is divided into three stages: inflammation, proliferation, and remodelling. Angiogenesis, collagen deposition, granulation tissue development, epithelialization, and wound contraction are all characteristics of the proliferative phase. Angiogenesis is the formation of new blood vessels by endothelial cells. Fibroblasts expel collagen and fibronectin to build a new, temporary extracellular matrix during fibroplasia and granulation tissue development. Myofibroblasts grab the wound margins and constrict using a process similar to that of smooth muscle cells [4]. Epithelial cells then crawl over the wound bed to cover it, and the wound is then closed by epithelial cells.

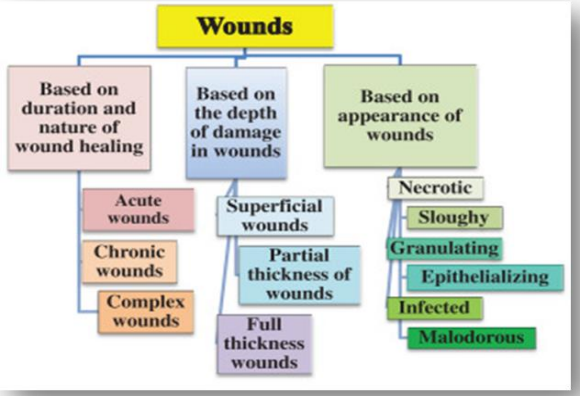


Fig. 1 Wounds Types

Transdermal drug delivery systems (TDDS) or patches are controlled-release devices that contain a medication for targeted treatment of tissues under the skin or systemic therapy following topical administration to the skin surface [5]. Although the formulation matrix of various delivery systems varies, TDDS are available for a variety of medicines. The following are some of the ways they differ from traditional topical formulations:

They feature an impermeable occlusive backing film that protects the skin beneath the patch from losing a lot of water;

- The patch's formulation matrix preserves the drug concentration gradient inside the device after application, ensuring that drug delivery at the patch-to-skin interface is maintained; and
- An adhesive layer keeps TDDS in place on the skin's surface, guaranteeing drug contact and continuous drug administration.

Because the skin functions as a natural and protective barrier, topical or transdermal medication administration is difficult. TDDS were first launched to the US market in the late 1970s,but transdermal drug administration had been used for many years. There have been earlier instances of mustard plasters being used to relieve chest congestion and belladonna plasters being used as analgesics. When topical, regional, or systemic effects are required, the skin has long been a popular route for drug administration. Nonetheless, because few medicines have the properties necessary to penetrate across the stratum corneum in sufficient quantities to reach a therapeutic concentration in the blood, skin serves as an effective barrier and provides challenges for transdermal administration of therapeutic agents. Different techniques have been studied, developed, and patented in attempt to improve medication transdermal absorption. Transdermal medication administration has regained popularity thanks to advancements in physical permeation-enhancement technology. Iontophoresis, electroporation, ultrasound, microneedles to open up the skin, and, more recently, the use of transdermal nanocarriers are some of these innovative advanced transdermal permeation-enhancement technologies [6-7].

Various techniques have been studied, developed, and patented in attempt to increase medication transdermal absorption. Transdermal medication delivery has regained popularity due to advancements in physical permeation-enhancement technology. Iontophoresis, electroporation, ultrasound, microneedles to open up the skin, and, more recently, the use of transdermal nanocarriers are only a few of these innovative advanced transdermal permeation-enhancement technologies.

## THE SKIN OF A HUMAN

For decades, scientists have recognized the possibility of exploiting undamaged skin as a route for medication delivery to the human body. The skin, on the other hand, is a highly tough barrier to the entrance of materials, enabling only minute amounts of a medication to pass through over time. To develop a medication delivery system, one must first understand skin anatomy and how it affects the drug of choice and delivery mechanism.

With a surface area of 1.8-2.0 $m^2$, the human skin is the biggest organ in our body. The epidermis, dermis, and hypodermis (subcutaneous layer) are the three major layers (Fig. 1). The skin is a highly energetic organ that protects the body from external influences while also regulating heat and water loss.

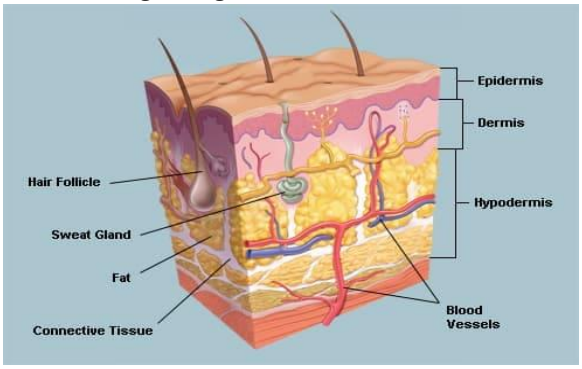


Fig. 2 The Human Skin

## ROUTES OF DRUG PENETRATION THROUGH THE SKIN

Diffusion of medicines via the intact epidermis and skin appendages is required for drug penetration into the skin (hair follicles and sweat glands). These skin appendages, which account for barely 0.1 percent of total human skin, provide shunt routes across the intact epidermis. The stratum corneum is recognised to provide a barrier to drug penetration through the skin. There are three primary penetration pathways that have been identified.

## THE INTERCELLULAR LIPID ROUTE

The stratum corneum's interlamellar areas, particularly linker regions, have less organised lipids and more flexible hydrophobic chains. The nonplanar gaps between crystalline lipid lamellae and their neighbouring cells' outer membrane are due to this. Fluid lipids in the skin barrier are critical for lipidic and amphiphilic molecules' transepidermal diffusion, occupying those gaps for their insertion and migration via intercellular lipid layers. Hydrophilic molecules diffuse mostly “laterally” along surfaces of less abundant water-filled interlamellar gaps or across such volumes; polar molecules can exploit the empty space between a lamella and a corneocyte outer membrane to achieve the same goal.

## THE TRANSCELLULAR ROUTE

Keratin is abundant in the stratum corneum's intracellular macromolecular matrix, which does not contribute directly to the skin diffusive barrier but does promote mechanical stability and hence stratum corneum integrity [8]. For transdermal drug delivery, transcellular diffusion is virtually irrelevant. Confocal laser scanning microscopy was used to detect the limited aqueous transepidermal channels. Regions of poor cellular and intercellular lipid packing correspond with wrinkles on the skin surface and are also the areas of lowest skin barrier to hydrophilic entity transfer. This channel of least resistance connects clusters of corneocytes at points where such cellular groupings have no lateral overlap. Pathway broadening or multiplication, such as that induced by exposing the stratum corneum to a strong electrical (electroporation/iontophoresis), mechanical (sonoporation/sonophoresis), or heat stimulation, or appropriate skin penetrants, can enhance the contribution to transdermal drug transport.

## FOLLICULAR PENETRATION

Because medication targeting to the hair follicle is of significant relevance in the treatment of skin disorders, follicular penetration has recently been a prominent topic of study. Follicular orifices, on the other hand, account for barely 0.1 percent of the total skin surface area. As a result, it was thought to be a minor route for drug entry. Hair follicles, on the other hand, have been demonstrated in a number of studies to be a viable alternative for medication penetration through the skin [9]. Topical delivery of polystyrene nanoparticles has also been advocated through follicular routes. They were studied in both porcine and human skin (ex vivo) (in vivo). Polystyrene nanoparticles aggregated preferentially in the follicular openings, according to surface pictures. The follicular localization was promoted by the lower particle size, which enhanced the dispersion in a time-dependent way. The study also found that the penetration of both membranes is identical (porcine and human skin). Differential stripping has been used in various studies to demonstrate the impact of microparticle size on skin penetration. Nanoparticles can be used as medication transporters via the follicle or as follicle blockers to prevent topically administered drugs from penetrating.

## MAIN FACTORS FOR NANO-BASED DELIVERY SYSTEM

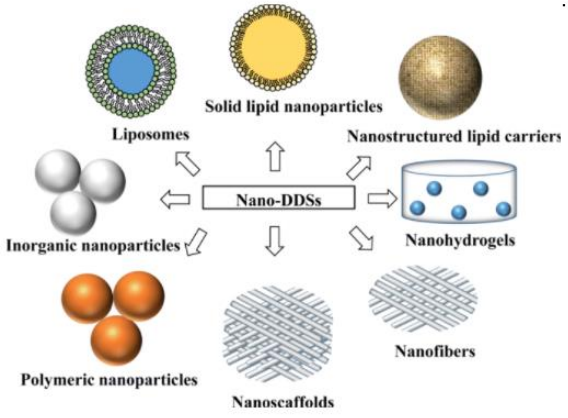


Fig. 3 Nano drug delivery systems

*Particle size, size distribution and zeta potential*

Drug release, physical stability, and cellular absorption of nanoparticulate materials are all affected by particle size and shape. Certain in-process activities and circumstances, such as stirring rate, temperature, type and quantity of dispersion agent, as well as the viscosity of the organic and aqueous phases, impact each system's yield and size distribution [10, 11]. Dispersion's zeta potential is required for dispersion stability [12].

*Surface properties*

The surface charge of nanoparticles has an impact on their ability to adhere to cell membranes. In vitro and in vivo, changing the particle surface charge might regulate tissue binding and guide nanoparticles to certain cellular compartments. Negatively charged sulphated proteoglycan molecules dominate cellular surfaces and perform critical roles in cellular proliferation, migration, and motility [13].

Cell surface ocalize atio are made up of a membrane-anchored core protein and one or more glycosaminoglycan side chains (heparan, dermatan, keratan, or chondrotine sulphates) that form a structure that extends away from the cell surface.

Because of electrostatic interactions, nanoparticles have a strong affinity for biological membranes [14]. Cell membranes are known to feature extensive negatively charged domains that resist negatively charged nanoparticles. The non-specific process of nanoparticle adsorption on the cell membrane and the creation of nanoparticle clusters are linked to the high cellular absorption of negatively charged nanoparticles [15]. The electrostatic interaction between negatively charged particles and positively charged sites might result in ocalize ocalize ation and subsequent membrane bending, favouring endocytosis for cellular uptake [16]. As a result, the surface characteristics of nanoparticles can impact their cellular absorption and intracellular distribution, and surface charge can be used to ocalize nanoparticles to particular intracellular destinations (lysosomes, mitochondria, cytoplasm, etc.) [17].

Some studies have discovered that surface charge has an impact on membrane permeability, for example, the polymer charge density of dendrimers has been found to have a substantial impact on membrane permeability. The most densely charged polymer aids dye molecule transport through the membrane [18]. In another study, lipid coating of ionically charged nanoparticles increased endothelial cell layer crossing by 3 or 4 times compared to uncoated particles, whereas nanoparticles coating of neutral particles had no effect on their permeation characteristics across the endothelial cell monolayer [19].

Transdermal drug delivery methods had previously been restricted to a small number of medicines with varying molecular weights and lipophilicity, as well as charge preferences. Because the skin has a negative surface charge owing to phosphatidylcholine [20], and carbohydrates present in human cells include negatively charged groups, cationic substances have a beneficial impact on skin penetration. As a result, transdermal permeability would be aided by nanoparticles with a significant positive charge.

## DERMATOPHARMACOKINETICS

The pharmacokinetics of topically administered medicines in the stratum corneum with pharmacodynamic effects is referred to as dermatopharmacokinetics. In dermatopharmacokinetic approach, clever methods (tape stripping and microdialysis) are used to evaluate the cutaneous drug concentration at the application site. Dermatopharmacokinetics has been demonstrated in several studies to be a valid and repeatable approach for assessing bioequivalence, and it is relevant to all topical dermatological medication formulations.

Dermatopharmacokinetics is the study of topical actives' concentration-time curves in the stratum corneum. This is similar to plasma/urine concentration-time curves for systemically or orally administered medications. Although this process is invasive, it is a method with tremendous promise for providing information of high value and relevance, and the idea is obviously applicable to microdialysis, where drug is determined in the skin compartment in which the microdialysis fibre is positioned. A chamber within the skin might be used for sampling. It's a unique situation. However, it is a technically hard technique that necessitates a high level of experimental dexterity.

Tape-stripping of the stratum corneum is a minimally invasive approach for measuring drug levels in the human stratum corneum in vivo. It entails applying adhesive tapes repeatedly to a location that has been treated with a topical preparation and measuring drug

levels in stratum corneum samples collected on tape strips.

Topical drug products, when applied to diseased skin, cause one or more therapeutic responses, the onset, duration, and magnitude of which are determined by the relative efficiency of three sequential processes, namely:

- the drug's release from the dose form
- drug penetration through the skin barrier, as well as the production of the required pharmacological impact

Because topical products deliver the drug directly to or near the intended site of action, dermatopharmacokinetics can be used to compare the bioequivalence of two topical drug products by measuring drug uptake into and drug elimination from the stratum corneum [21-22]. Two formulations that yield similar stratum corneum concentration-time curves are likely to be considered bioequivalent, just as two oral formulations are.

Dermatopharmacokinetics can be used to compare the bioequivalence of two topical drug products by measuring drug uptake into and drug elimination from the stratum corneum [23,24]. Because topical products deliver the drug directly to or near the intended site of action, dermatopharmacokinetics can be used to compare the bioequivalence of two topical drug products by measuring drug uptake into and drug elimination from the stratum corneum. Two formulations that produce similar stratum corneum concentration-time curves, just like two oral formulations, are likely to be considered bioequivalent. Dermatopharmacokinetics can be used to compare the bioequivalence of two topical drug products by measuring drug uptake into and drug elimination from the stratum corneum [25, 26]. Because topical products deliver the drug directly to or near the intended site of action, dermatopharmacokinetics can be used to compare the bioequivalence of two topical drug products by measuring drug uptake into and drug elimination from the stratum corneum[27].

The stratum corneum itself is the location of action in some cases. Fungi live in the stratum corneum in fungal diseases of the skin; hence dermatopharmacokinetic assessment of an antifungal medication in the stratum corneum is a direct measurement of drug concentration at the site of action [28]. In cases when the stratum corneum has been disturbed or injured, in vitro drug release can help with the bioequivalent evaluation [29-31]. Because studies show a favourable connection between stratum corneum and follicular concentrations, the dermatopharmacokinetic method is still predicted to be useful in these conditions. Although the exact mechanism of action for some dermatological drugs is unknown, the dermatopharmacokinetic approach may still be useful as a measure of bioequivalence because it has been shown that the stratum corneum acts as a reservoir and that stratum corneum concentration is a predictor of drug absorption [32].

Dermatopharmacokinetic principles should be applied to all topical dermatological medication products, including antifungal, antiviral, antiacne, antibiotic, corticosteroid, and vaginally administered drug products, for the reasons stated above. As a result, the dermatopharmacokinetic method may be used to document bioavailability and bioequivalence. Because skin with illness shows considerable variability and changes over time, bioequivalence evaluations utilizing dermatopharmacokinetic studies are often done in healthy people. Healthy participants were used in bioequivalence tests for oral medication items, which is consistent with previous research.

A dermatopharmacokinetic approach is not appropriate in the following situations:

- The stratum corneum is damaged by a single application of the dermatological preparation.
- For otic preparations, unless the product is intended for otic skin irritation; and
- For ophthalmic preparations, because the cornea and stratum corneum are physically distinct.

## WOUND DRESSING PATCH

Wearable patches have received a lot of attention in recent years because of their unique benefits such as flexibility, real-time monitoring, noninvasive, disposable, high integration, high sensitivity, and high stability. With the growing demand for medical big data and personalised medical care, there is also a growing demand for wearable patches, and intelligent wearable patches have a lot of potential in the next generation of wound management. The biosensing patches, for example, are based on biochemical and physiological sensing of potential hydrogen (pH), glucose, and temperature [33]. Several reviews have been published to date, focusing on self-healing

materials, antibacterial ability, drug release, flexible electron and artificial skin of wound healing, and wearable patches. A comprehensive review that focuses on various-aspect monitoring and smart drug release of wound dressings, on the other hand, has yet to be presented [34-37].

Fig 4. Wound Dressing Patch

## IDEAL DRUGS FOR DERMAL AND TRANSDERMAL DELIVERY

Only a restricted number of medicines can be administered systemically at therapeutically relevant rates because to the selective nature of the epidermal barrier [38]. Only a few medicines make up the whole transdermal drug industry. Aside from potency, moderate lipophilicity and low molecular weight are two physicochemical drug properties that are frequently recalled as favourable for percutaneous administration [39]. A substantial number of pharmaceutical compounds, however, do not meet these requirements. This is especially true for macromolecules like insulin, human growth hormone, or cyclosporine, which are notoriously difficult to transport. The following are the physicochemical characteristics of an optimal medication for transdermal delivery:

- Molecular weight less than approximately 1000 Daltons.
- Affinity for both lipophilic and hydrophilic phases.
- Low melting point.
- Should be potent, with short half life and be non-irritating.

Overcoming poor skin permeability to xenobiotics can be accomplished in a number of ways, and it is a current study topic. Depending on the physicochemical nature of the molecule, its effectiveness and applicability will differ from drug to drug. New drug development is still a difficult process that necessitates a significant amount of time and money. Because the active compounds used in the formulation have already been approved, formulation change technologies provide a relatively simple approach to creating new pharmaceuticals compared to new drug discovery [40-41]. They also provide a relatively simple approach to creating new pharmaceuticals compared to new drug discovery because the active compounds used in the formulation have already been approved.

## ADVANTAGES OF DERMAL AND TRANSDERMAL DRUG DELIVERY

Transdermal distribution allows patients to self-administer medications in a convenient and pain-free manner. It avoids frequent dosing and the peaks and troughs in plasma levels associated with oral dosage and injections, allowing for consistent drug concentrations and the delivery of a medication with a short half-life. All of this increases patient compliance, which is especially important when long-term treatment is necessary, such as in chronic pain treatment and smoking cessation therapy [7,42,43].

- Another benefit of transdermal administration is that it avoids hepatic first-pass metabolism and the gastrointestinal (GI) tract for poorly bioavailable medicines. The elimination of the firstpass effect enables for a smaller dose of medication to be delivered, making it safer in hepatocompromised patients and reducing side effects.
- When compared to other medicines on a monthly basis, transdermal systems are typically less expensive, as patches are designed to administer medications for 1 to 7 days.
- Another advantage of transdermal delivery is that with today's programmable systems, multiple dosing, on-demand, or variablerate drug administration is feasible, adding to the benefits of traditional patch dosage forms.
- The transdermal route allows the use of a reasonably powerful medication with less danger of system toxicity, as seen by the growing market for transdermal products.

- In the event of toxicity, the patient can quickly remove the transdermal patch [44,45].

## DISADVANTAGES OF DERMAL AND TRANSDERMAL DELIVERY SYSTEMS

Although dermal and transdermal delivery methods offer several advantages over traditional topical formulations, they nevertheless have a number of drawbacks. According to Ranade and Cannon [46], cutaneous and transdermal delivery methods have the following drawbacks:

- Not all medicines are appropriate for transdermal administration.
- It is not possible to deliver drugs that need high blood levels.
- The glue used may not be suitable for all skin types.
- Drugs or medication formulations may induce sensitivity or irritation, and this must be considered early in the development process.
- Wearing the patches may or may not be pleasant.
- Because the formulation needs specialist technology, it is more expensive to produce than normal dosage forms, making it unaffordable for most patients.

## CHARACTERIZATION OF DERMAL AND TRANSDERMAL DELIVERY SYSTEMS

Different techniques are used to describe dermal and transdermal delivery systems.

*Drug solubility determination*

Early in the formulation process, determining the drug's solubility in the transdermal/dermal matrix might help to avoid the problem of crystallisation, which is one of the instabilities in transdermal drug delivery systems (TDDS). The formulation becomes metastable as a result of the instability in the matrix, which might be related to supersaturation, and changes in the liberation/release rate of the drug from the formulation during storage.

Micromeritic measurements

*Particle-size, shape and zeta potential analysis*

Light scattering is a common method for determining the characteristics of colloidal and macromolecular dispersions, and it might be useful in determining the parameters of particulate TDDS, such as ethosomes. Wet laser diffraction sizing, also known as dynamic light scattering (DLS), is used to determine particle size and size distribution [47]. Dynamic light scattering may also be used to determine the size of a formulation (e.g. using a Zetasizer). This is required in order to determine the impact of size on drug release and penetration through barriers in transdermal and dermal administration, as well as to track stability over time. A formulation's zeta potential is extremely significant. It is determined using Zetsizer or other methods and provides information on the charge of the particles as well as their inclination to aggregate or remain discrete in a formulation.

*Visualization by transmission electron microscopy*

To observe skin structures and specific disturbances in the skin, a combination of transmission electron microscopy (TEM) and freeze fracturing, also known as freeze fracture electron microscopy (FFEM), might be employed. A micrograph picture is created by passing an electron beam through a material that has been prepared to improve the visibility of skin structure features. The TEM's high resolution allows it to see both structures and transition processes in the epidermis. Epidermal granules [48], Langerhans cells [49], and lipids in the stratum corneum and epidermis [50], among other things, have been identified using various methods.

In FFTEM, samples are frozen and then longitudinally fracturing is performed under high vacuum, almost parallel to the original skin surface [51]. The sample might be subjected to further treatment before being examined under high voltage. This type of imaging can reveal information about the interaction of the nanoparticle composition with the skin. FFEM micrographs of treated stratum corneum frequently show the lipid coated surfaces of corneocytes or the lipid lamellae since the fracture will always travel along the plane of least resistance.

*Stability*

Carriers' physical and chemical instability frequently restrict their usage in medical applications [49]. Hydrolysis or oxidation of the phospholipid molecules causes instabilities in ethosomes and other nanocarrier formulations, which manifest as leakage of the encapsulated medication and changes in vesicle size

owing to fusion and aggregation [52-53].Changes in size and size distribution, entrapment efficiency, and vesicle aggregation are all important indicators of stability. These characteristics may be measured using EM or DLS over time and under various storage circumstances.

Small unilamellar ethosome vesicles showed a high tendency to form aggregates due to increased surface area exposed to the medium, despite the fact that multilamellar and large unilamellar benzocaine-loaded ethosome vesicles remained substantially stable with time in terms of drug entrapment yield and particle dimensions [54]. This type of vesicle aggregation implies a state of instability. Furthermore, changes in storage conditions resulted in a significant reduction in particle dimensions and drugentrapping yield, as well as less regular morphology, for frozen-and-thawed multilamellar ethosome dispersions, whereas untreated multilamellar and unilamellar vesicular dispersions remained homogeneous and stable in terms of those parameters assessed over time [55]. In analysing the stability of ethosomes, optical properties, viscosity, and physical changes such as cracking or creaming are also essential. Because ethosomes are colloidal dispersion systems, they may fracture and cream during storage, just like water-in-oil emulsions. It has been suggested that a novel optical analyzer, Turbiscan Lab® Expert, be used to investigate the impact of optical properties on the long-term stability of vesicular colloidal delivery systems [56, 57].

## CONCLUSION

To avoid a major infection that necessitates costly treatment, the wound must be properly managed. It is critical to have a method to improve wound healing in order to have effective wound therapy. Transdermal patches containing Nanoparticles are a type of wound therapy technology that is non-invasive, easy to use, and allows for consistent medication dosing. In this review, the transdermal patch shows tremendous promise as a medication delivery device for delivering the active ingredient to the intended treatment region, particularly the skin, because it can provide consistent drug release and patient compliance due to its non-invasive nature.

## REFERENCES


[1] Gaur PK, Mishra S, Purohit S, Dave K. Transdermal drug delivery system: a review. Asian J Pharm Clin Res 2009;2(1):14-20.

[2] Singhal P, Singhal R, Kumar V, Goel KK, Jangra AK, Yadav R. Transdermal drug delivery system; A novel technique to enhance therapeutic efficacy and safety of drugs. Am J Pharmtech Res 2012;2(1):105-25.

[3] Fox LT, Gerber M, Plessis JD, Hamman JH. Transdermal drug delivery enhancement by compounds of natural origin. Molecules 2011;16:10507-40.

[4] Raina R, Prawez S, Verma PK, Pankaj NK. Medicinal plants and their role in wound healing. Vet Scand 2008;3:1-7.

[5] Hatto P.ISO concensus definitions relevant to nanomaterials and nanotechnologies. 4th Annual Nano Safety for Success Dialogue. ISO TC 229and BSI NTI/1 Nanotechnologies Standardization Committees. 29th and 30th March 2011. Brussels.

[6] Devi VK, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev. Ind. Pharm. 2003;29:495-503.

[7] Valenta C, Auner BG .The use of polymers for dermal and transdermal deliv- ery. Eur. J. Pharm. Biopharm. 2004;58: 279–289.

[8] Block HL. Biopharmaceutics and drug delivery systems In: Comprehensive Pharmacy Review. Eds. Leon Shargel, Alan H Mutnick, Paul F Souney, Larry N Swanson, Lippincott Williams and Wilkins, USA. 2010;83-96.

[9] Prausnitz MR, Langer R. Transdermal drug delivery. Nat. Biotech. 2008;26(11):1261– 1268.

[10] Escobar-Chávez JJ, Díaz-Torres R, Rodríguez-Cruz IM, Domínguez-Delgado CL, Mo- rales RS, Ángeles-Anguiano E, Melgoza-Contreras LM . Nanocarriers for trans- dermal drug delivery. Research and Reports in Transdermal Drug Deliv. 2012;1: 3–17.

[11] Geinoz S, Guy RH, Testa B, Carrupt PA.Quantitative structure–permeation re-lationships (QSPeRs) to predict skin permeation: a critical evaluation. Pharm Res.2004; 21:83–92.

[12] Cevc G, Vier IU. Nanotechnology and the transdermal route. A state of the art review and

critical appraisal. J. Control. Rel.2010;141:277–299.

[13] Pinto Reis C, Nuefeld RJ, Ribeiro AJ, et al., Nanoencapsulation 1. Methods for preparation of drug-loaded polymeric nanoparticles. Nanomedicine. 2006;2: 8-21.

[14] Maestrelli F, Capasso G, Gonzalez-Rodriguez ML, et al., Effect of preparation technique on the properties and in vivo efficacy of benzocaine-loaded ethosomes. J Liposome Res 2009; 19(4): 253-60.

[15] Attama AA, Schicke BC, Paepenmüller T, Müller-Goymann CC. Solid lipid nanodispersions containing mixed lipid core and a polar heterolipid: Characteriza- tion. Eur. J. Pharm. Biopharm. 2007;67: 48-57.

[16] Bernfild M, Gotte M, Park PW, Reizes O, Fitzgerald ML, Lincecum J, Zako M (1999) Functions of cell surface heparan sulphate proteoglycans. Annu. Rev. Biochem. 1999;68: 729-777.

[17] Honary S and Zahir F (2013) Effect of Zeta Potential on the Properties of Nano-Drug Delivery Systems - A Review (Part 1).Trop. J. Pharm Res.2013; 12 (2): 255-264

[18] Win KY, Feng SS. Effects of particle size and surface coating on cellular uptake of polymeric nanoparticles for oral delivery of anticancer drugs. Biomaterials 2005;26: 2713–2722. 224 Application of Nanotechnology in Drug Delivery

[19] Patila S, Sandberg A, Heckert E, Self W, Sea S. Protein adsorption and cellular uptake of cerium oxide nanoparticles as a function of zeta potential. Biomaterials 2007;28: 4600–4607.

[20] Wolinsky JB, Grinstaff MW. Therapeutic and diagnostic applications of den- drimers for cancer treatment. Adv. Drug Deliv. Rev.2008; 60: 1037–1055.

[21] Chang JH, Cho MA, Son HH, Lee CK, Yoon MS, Cho HH, Seo DS, Kim KJ. Characterization and formation of phospholipid nanoemulsion coatings on Mgmodified sericite surface. J. Ind. Eng. Chem, 12: 635-638. 2006.

[22] FDA Guidance for Industry: topical dermatological drug product NDAs and ANDAs-in vivo bioavailability, bioequivalence, in vitro release and associated studies (Draft). 1998.

[23] Shah, V. P. and H. I. Maibach (eds.). Topical Drug Bioavailability, Bioequiva- lence and Penetration, Plenum Press. 1993.

[24] Shah VP, Flynn GL, Yacobi A, et al., "Bioequivalence of topical dermatological dosage forms - Methdods of evaluation of bioequivalence," Pharm. Res. 1998;15: 167-171.

[25] Schaefer, H. and T. E. Redelmeir (eds.). Skin Barrier, Principles of Percutaneous Absorption, Eds, Karger Publishers. 1996.

[26] Pershing LK, Lambert L, Wright ED, et al., ."Topical 0.05% betamethasone di- propionate: Pharmacokinetic and pharmacodynamic dose-response studies in hu- mans," Arch Dermatol, 1994;130:740-747.

[27] Allec A, Chatelus A, Wagner N . "Skin distribution and pharmaceutical aspects of adapalene gel," J. Am. Acad. Dermatol.1997; 36: S119-125.

[28] Hueber F, Schaefer H, Wepierre J. Role of transepidermal and transfollicular routes in percutaneous absorption of steroids: in vitro studies on human skin, Skin Pharmacology, 1994;7: 237-244.

[29] Illel B, Schaefer H, Wepierre J, Doucet O. Follicles play an important role in percutaneous absorption, J. Pharm. Sci. 1991;80: 424-427.

[30] Rougier A, Rallis M, Kiren P, Lotte C ."In vivo percutaneous absorption: A key role for stratum corneum/vehicle partitioning," Arch Dermatol Res. 1990:282: 498-505.

[31] Kalpana SP, Mikolaj M, Courtney LS, Nicole KB, Priyanka G, Audra LS Chal- lenges and opportunities in dermal/transdermal delivery. Ther. Deliv.2010; 1(1): 109–131.

[32] Bos JD, Meinardi MMHM . The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Ex. Dermatol. 2000;9(3): 165–169.

[33] Wu, M.; Chen, J.; Huang, W.; Yan, B.; Peng, Q.; Liu, J.; Chen, L.; Zeng, H. *Biomacromolecules* 2020, *21*, 2409– 2420

[34] Jing, X.; Mi, H.-Y.; Lin, Y.-J.; Enriquez, E.; Peng, X.-F.; Turng, L.-S. *ACS Appl. Mater. Interfaces* **2018**, *10*, 20897– 20909, DOI: 10.1021/acsami.8b06475

[35] Villanueva, M. E.; Diez, A. M. d. R.; González, J. A.; Pérez, C. J.; Orrego, M.; Piehl, L.; Teves, S.; Copello, G. J. *ACS Appl. Mater. Interfaces* 2016, *8*, 16280– 16288

[36] Liu, H.; Zhao, C. *Current Opinion in Electrochemistry* 2020, *23*, 42– 46,
[37] Zhao, X.; Wang, L.-Y.; Tang, C.-Y.; Zha, X.-J.; Liu, Y.; Su, B.-H.; Ke, K.; Bao, R.-Y.; Yang, M.-B.; Yang, W. *ACS Nano* 2020, *14*, 8793– 8805,
[38] Tsutomu I, Tohru M (2010) Techniques for efficient entrapment of pharmaceuticals in biodegradable solid micro/nanoparticle. Expert Opinion Drug Deliv. 2010;7(6): 1-11.
[39] Moghimi SM, Hunter AC, Murray JC. Nanomedicine: current status and figure prospects. FASEB J. 2005;19: 311-330.
[40] Marcato PD and Duran N. New aspects of nanopharmaceutical delivery sys- tems. J Nanosci Nanotechnology.2008: 6: 2216-2229.
[41] Nnamani PO, Kenechukwu FC, Dibua EU, Ogbonna CC, Momoh MA, Ogbonna JDN, Okechukwu DC, Olisemeke AU and Attama AA . Bioactivity of gentami- cin contained in novel transdermal drug delivery systems (TDDS) formulated with biodegradable polyesters; Afr. J. Pharm. Pharmacol. 2013;7(28): 1987-1993
[42] Dnyanesh NT, Vavia PR. Acrylate-based transdermal therapeutic system of ni- trendipine. Drug Dev. Ind. Pharm. 2003;29: 71–78.
[43] Chandak AR, Verma PRP. Development and evaluation of HPMC based matri- ces for transdermal patches of tramadol. Clin. Res. Reg. Affairs. 2008;25: 13–30.
[44] Mundargi RC, Patil SA, Agnihotri SA, Aminabhavi TM. Evaluation and controlled release characteristics of modified xanthan films for transdermal delivery of atenolol. Drug Dev. Ind. Pharm.2007; 33:79–90.
[45] Mutalik S, Udupa N .Glibenclamide transdermal patches: Physicochemical, pharmacodynamic and pharmacokinetic evaluations. J. Pharm. Sci. 2004; 93: 1577–1594.
[46] Chang HI, Perrie Y, Coombes AGA (2006) Delivery of the antibiotic gentamicin sul- phate from precipitation cast matrices of polycaprolactone. J. Control. Rel. 2006; 110:414-421.
[47] Ranade VV, Cannon JB. Drug Delivery Systems, Third Edition, Taylor and Francis, Boca Raton. 2011.
[48] Touitou E, Dayan N, Bergelson L, et al.,. Ethosomes-- novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J. Control. Rel. 2000;65: 403-18.
[49] Martin A, Bustamante P. Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences, 4th edn, Lippincott Williams & Wilkins, Philadelphia, PA, pp. 1993;436–439.
[50] Newman A.W (1995) Micromeritics in Physical Characterization of Pharmaceutical Solids, (ed. H.G. Brittain), Marcel Dekker, New York, NY, Ch. 9, 1995:254–264p.
[51] Chikazawa M, Takei T. Specific Surface Area in Powder Technology Handbook (eds K. Gotoh, H. Masuda & K. Higashitani), 2nd edn, Marcel Dekker, Inc., New York, NY, Ch. III. 8, pp. 1997:337–349.
[52] Ishida-Yamamoto A, Simon M, Kishibe M, Miyauchi Y, Takahashi H, Yoshida S, O'Brien TJ, Serre G, Iizuka H. 'Epidermal lamellar granules transport different cargoes as distinct aggregates'. Journal of Investigative Dermatology 2004;122(5): 1137-1144
[53] Demarchez M, Asselineau D, Regnier M, Czernielewski J .'Migration of Lan- gerhans Cells into the Epidermis of Human Skin Grafted onto Nude-Mice'. Journal of Investigative Dermatology, 1995;99(5): S54-S55.
[54] Holman BP, Spies F, Bodde HE .'An Optimized Freeze-Fracture Replication Procedure for Human Skin'. Journal of Investigative Dermatology 1990:94(3):332-335.
[55] Norlen L, Al-Amoudi A, Dubochet J (2003) 'A cryotransmission electron microscopy study of skin barrier formation'. Journal of Investigative Dermatology. 120(4): 555-560.
[56] Stark B, Pabst G, Prassl R. Long-term stability of sterically stabilized liposomes by freezing and freeze-drying: effects of cryoprotectants on structure. Eur. J. Pharm. Sci.2010; 41: 546-555.
[57] Lopez-Pinto JM, Gonzalez-Rodriguez ML, Rabasco AM. Effect of cholesterol and ethanol on dermal delivery from DPPC liposomes. Int. J. Pharm. 2005:298: 1-12.