Review Article

Transdermal Drug Delivery System for Controlled Drug Administration - A Review

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ABSTRACT

Transdermal drug delivery system (TDDS), is one of the most approaching and convenient methods for drug administration. The transdermal patch aims to deliver an appropriate concentration of drug into systemic circulation in a controlled fashion. The TDDS has proved to be an advantageous method over the conventional delivery system by overcoming the drawbacks of the later which include first-pass metabolism, low bioavailability, and drug degeneration. Skin being a protective membrane affects the ingression of the drug to the peripheral circulation. TDDS enhances the performance of the drug considering the safety and efficacy of the drug and thus, making it penetrate the skin easily and reach the systemic circulation. TDDS is a painless user-friendly device that provides regulated, uniform administration and continuous supply of drugs on the targeted site to treat numerous diseases like neurological disorders, cardiovascular diseases, and skin diseases. This article highlights various applications of the transdermal patch such as Nicotine patches, Estrogen patches, Nitroglycerine patches, and microneedles in the healthcare sector. TDDS being a new approach to delivering drug overcomes the current drug delivery approaches thus providing a promising future for the administration of a variety of newer drugs by improving the performance of the drug as well as the method of drug administration.

Keywords: Transdermal Drug Delivery System, Transdermal Patch, Drug Administration, microneedle.

INTRODUCTION

Transdermal drug delivery system (TDDS) is a medicated-adhesive patch designed in a dosage form which focuses on delivering an appropriate proportion of drug via the skin into the systemic circulation.[1] Although the oral drug delivery system (ODD) has an advantage of easy administration, it also has some significant drawbacks which include first-pass metabolism, drug degeneration, and poor bioavailability of the drug. Nowadays, TDDS is one of the most imminent methods used for drug administration,[2] it has several advantages over other traditional administration methods such as (i) reducing first-pass effect and drug degradation, (ii) reduction in frequency of the dosage, (iii) improving bio-accessibility, (iv) easy and non-invasive drug delivery, (v) supplying a controlled release of the medication, (vi) reduced side effects, (vii) reduction in fluctuation of circulating drugs and (viii) more uniform effect of the drug.[3,4]

Over recent years, the development of a controlled drug delivery system has become extremely important in the pharmaceutical industry. TDDS has enhanced the performance of drugs in case of safety and efficacy and to amend the complication of conventional drug delivery systems namely oral, intravenous and intramuscular.[5] Human skin acts as a barrier to the ingress of materials and allows only a small proportion of drug penetration and absorption across the dermis layer. To administer the drug across the skin, the transdermal system requires to overcome this barrier which can be accomplished by two technologies namely Passive and Active.[6] The passive technologies include use of systems like microemulsions[7] such as oleic acid (oil phase),[8] plurol isostearique (surfactants)[9] and water/buffer (aqueous phase),[10] electrospun nanofiber produced by electrospinning of various polymers such as cellulose acetate, gelatine and polyvinyl chloride (PVC),[11,12] liposomal formulations such as hydroxypropyl methylcellulose,[13] poloxamers[14], and carbopol gels,[15] and vaccines or nanoparticles such as solid-lipid nanoparticles,[16] inorganic nanoparticles(gold, silica),[17] and polymeric micelles.[18] On the other hand, active technologies make utilization of electroporation,[19,20] microneedles such as solid,[21] hollow,[22] coated[23] and dissolving microneedles,[24] iontophoresis[25-27] or magnetospheres.[28] In comparison, the conventional drug delivery method involves the accumulation of the drug across a biological membrane whereas in TDDS the drug is discharged in a dosage form. This system helps in maintaining the essential drug levels in the body consequently preventing any damage to the healthy tissue.[29]

The patch is integrated with a porous membrane that serves as a coating for the drug reservoir which is further embedded in the adhesive. After the patch is applied to the skin, the drug is released at a controlled rate from the reservoir into the blood circulation through the diffusion process. The application of the transdermal patch onto the skin surface is illustrated in **figure 1**. Transdermal drug delivery technologies include the use of microneedles, suitable formulations, penetration enhancers, nanoparticles, and carriers further has improvised the drug administration performance, hence they are used for

treating skin disorders, cardiovascular diseases, and neurological disorders-Parkinson's disease.[31,30,32]

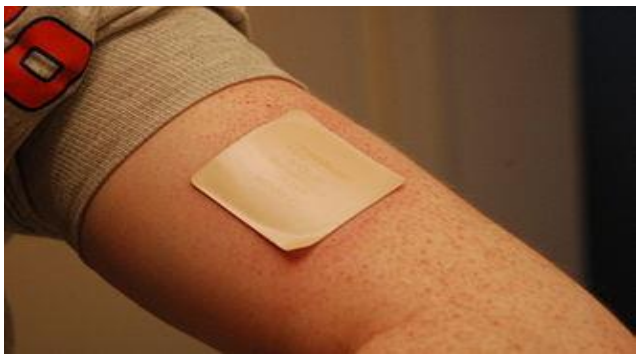

Figure 1: Representation of transdermal patch applied onto the skin[4]

ANATOMY OF THE SKIN

Skin is referred to as the largest and heaviest body organs with a surface area of 1-2 m^2 and 16 percent of total body weight. It plays an important immunity role in protecting the body against environmental factors such as toxic substances, microorganisms, UV radiation and prevents loss of water and nutrients. Skin is divided into three layers: Epidermis, the outermost layer, Dermis, the middle layer, Hypodermis, the innermost layer as shown in **figure 2**.[33]

The epidermis is the skin's outermost layer with a thickness of approximately about 0.2 mm and is composed of keratinocytes (95% of cells), melanocytes, Langerhans, and Merkel cells.[32] This layer is further sub-divided into 5 layers i.e. stratum basal, stratum spinosum, stratum granulosum, stratum corneum, and stratum lucidum.[34] Stratum basal also called stratum germinativum, is the innermost layer that acts as a junction between the epidermis and the dermis layer. This layer consists of keratinocytes that get differentiated and propagated within the basal layer, once developed are then migrated to the surface and this takes about 15-30 days of duration. It also contains melanocytes. The next layer is the stratum spinosum, also called as prickle cell layer (8-10 cell layers) comprises of irregular, polyhedral cells sometimes called spines due to spiny appearance which are outstretched and get in touch with the neighbouring cells by desmosomes. The keratinocytes start producing cytokeratin within this layer. Stratum granulosum (3-5 cell layers), is referred to as the layer between the stratum spinosum and the corneum layer. It comprises keratohyalin granules which facilitate the formation of filaggrin from its precursor protein that ultimately aggregates into complex granule structures. Lipid containing lamellar granules is secreted to the surface which serves as a permeability barrier of the epidermal layer. This layer, stratum lucidum (2-3 cell layers), is considered as the subdivision of the stratum corneum. Mainly present in the areas of thick skin and are found in palms and soles, thin clear layer containing eleidin (transformation product of keratohyalin). Stratum corneum (20-30 cell layers), the outmost epidermal layer, often referred to as "brick and mortar", consist of corneocytes (horny cells) and lipids produced by keratinocytes, act as a barrier to the epidermal layer. It helps in regulating the exchange of oxygen and moisture, prevent water loss and invasion foreign substances into the body.

The dermis layer is composed of two connective tissue layers- (a) Papillary layer- Upper sublayer, consisting of loosely connected tissue, a large number of nerve fibres, capillaries, water and cells (b) Reticular layer- lower sublayer with dense and thicker networks of connective tissue. Whereas hypodermis is the innermost layer beneath the dermis, also known as a subcutaneous layer, comprising of fat cells along with the blood vessels, hair follicles, and sensory neurons. It helps in providing mechanical protection as well as nutritional support and also regulating temperature.[35-40]

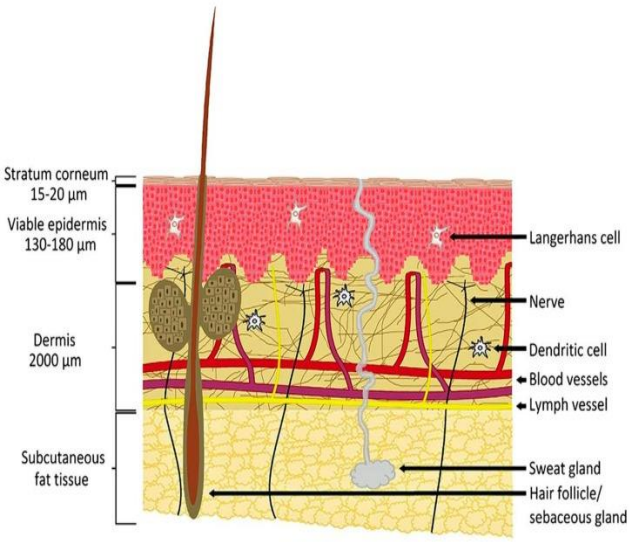

Figure 2: Illustration of the anatomy of human skin structure i.e. Epidermis, Dermis and Hypodermis[33]

Route of drug penetration through the skin

To reach the systemic circulation, the drug must penetrate all three layers of skin. The drug can be penetrated mainly through two routes namely, transepidermal route, and transappendageal route.[41] Schematic representation of the drug penetration through the skin is shown in **figure 3**.

In the Transepidermal route, the drug passes across the corneum layer of the skin via two pathways: (a) Transcellular pathway: transport of drugs through differentiated keratinocytes, called corneocytes, as well as the phospholipid membranes. Firstly, the drug has to penetrate through each cell in the lipophilic layer followed through the inactive keratinocytes. (b) Intercellular pathway: Involves the administration of drugs through the small gaps between the skin cells thus, making the route more complex.[42-44]

The transappendageal route, also known as the shunting route, primarily involves the dissemination of drugs via the hair follicle and sweat gland and it has been reported as an

efficient pathway for transmission of large and water-soluble drugs. [45,46] In recent times, the Transfollicular route has been taken into consideration for the administration of drugs via nanocarriers and can penetrate through the hair follicle openings to reach the tissue depth of the skin.[46-48]

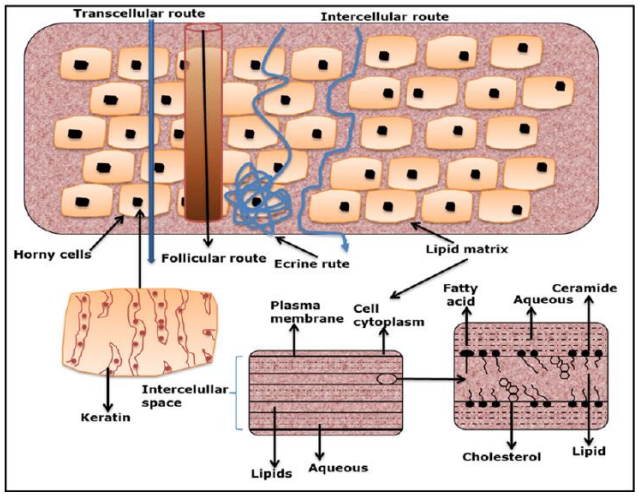

Figure 3: Schematic representation of routes of drug penetration across the corneum layer of the skin [47]

The basic principle of transdermal permeation

The main principle for transdermal permeation lies in the passive diffusion of drugs. The mechanism involves drug dissemination through the transepidermal layer and assimilation through the transappendageal layer and finally, it gets into the corneum layer.

Steps involved in the transportation of the drug from the skin to the systemic circulation: [5,49,50]

- Transmission of the drug from the patch to the rate-controlling membrane.
- The disintegration of the drug within the formulation and release from it.
- Dissemination of drugs via a lipidic intercellular pathway in the stratum corneum.
- Penetration of drug through the viable epidermis layer and in the papillary dermis layer.

FACTORS AFFECTING TRANSDERMAL PERMEATION

Biological factors and physiological factors are the prime factors that affect the administration of drugs via the transdermal drug delivery system. The overview is shown in **figure 4(a)**.

A. Biological Factors

The biological factors include skin condition, skin age, the supply of the blood, skin metabolism and also anatomy of the skin.[51] In terms of skin condition, many agents such as acids and alkali, solvents like chloroform, methanol disrupt the skin cells and penetrate through them. The intact skin act as a protective barrier against these chemicals which affects the penetration by forming artificial shunts in the skin allowing the drug molecules to pass easily. The young skin appears to be more permeable than mature old skin and thus percutaneous absorption of toxins such as steroids, boric acid, and hexachlorophene occurs in children at a faster rate than that in adults.[52-54] Similarly, in the case of blood supply, the transdermal permeation is affected by the changes occurring in the peripheral circulation.[55] In terms of skin metabolism, the extent to which these molecules (Hormones, steroids, chemical carcinogens, and other drugs) are metabolised by the skin helps to determine the efficacy of drug permeation through the skin.[56] It is also seen that the anatomy of the skin of different species plays an effective role in the transdermal permeation as different species have different skin thickness, nature of corneum layer, appendage density, and skin keratinization. Hence, each factor has its importance in skin permeation.[57]

B. Physiochemical Factors

Physiochemical factors include hydration of skin, temperature, and pH of the skin, diffusion coefficient of the drug, concentration of the drug, partition coefficient, molecular size and absorption.[51] When the physiochemical are considered hydration of the skin plays a very important role in enhancing the permeability of the drug through the skin. A study has also shown that the penetration rate is increased for water-soluble esters than that for other esters. Also, it is seen that the temperature and pH greatly affect the permeation rate, an increase in temperature increases the permeation rate of the skin and hence it is said that the rate of permeation of skin is directly proportional to the skin temperature. Vasodilation of blood vessels may be increased with an increase in skin temperature which in turn leads to increases percutaneous absorption.

Furthermore, pH also affects the absorption of acidic or basic drugs while unionized drugs have the excellent penetrating capacity.[58-62] Similarly, drug penetration depends on the diffusion coefficient of the drug. This diffusion coefficient decreases as the temperature fall and at a constant temperature, the diffusion coefficient of drugs depends upon the properties of diffusion medium, drug, and interaction between them. Other factors include the concentration of the drug which directly affects the passive diffusion process that is taking place during the transdermal permeation process. Also, it is seen that transdermal permeation is linearly proportional to the partition coefficient. An optimal partition coefficient(K) is an essential requisite for good action. Drugs with low K value will not be able to permeate through the skin while that with a higher value of K does not leave the lipid portion of the skin. Molecule size and absorption also have a key role in drug permeation, smaller molecules tend to penetrate faster than the larger ones and hence it can be remarked drug absorption is inversely correlated to the drug's molecular weight.[63,64]

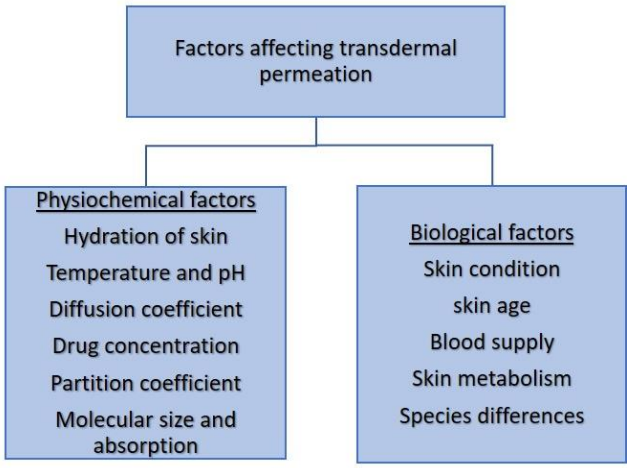

Figure 4(a): Shows the two different types of factors namely physiochemical and biological factors

Ideal properties of TDDS

The ideal properties of transdermal drug delivery system are shown in **figure 4(b)**:[65]

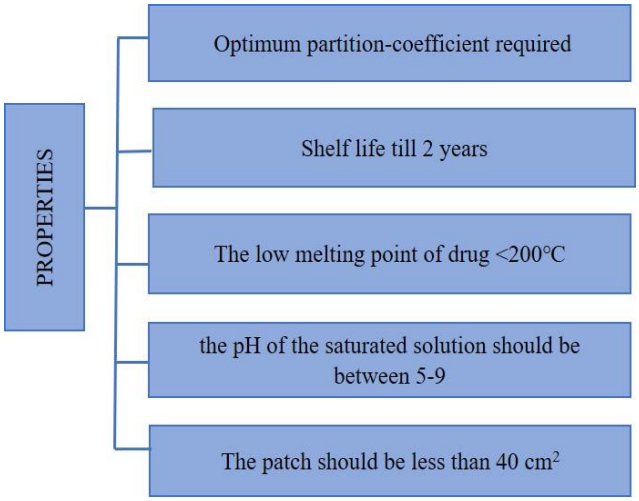

Figure 4(b): Represents ideal properties of TDDS[65]

COMPONENTS OF TDDS

Polymer matrix/drug reservoir

Table 1: Shows the classification of polymers

Natural polymers	Synthetic Elastomers	Synthetic Polymers
Cellulose and its derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums, natural rubbers, starch, etc.	Nitrile Acrylonitrile, Butyl rubber, Neoprene, Hydrin rubber, silicone rubber, polysiloxanes, etc.	polyacrylate, polypropylene, polyurea, polyvinyl alcohol, polyvinyl chloride, polyethylene, etc.

Polymer matrix performs like a backbone for TDDS since it controls the release of the drug from the system. The matrix is prepared by dispersing the drug in a solid or liquid state polymer. The polymer must be biocompatible as well as non-reactive with the drug and other components of the tool and also provides an effective release of the drug. The degrading polymer products must be non-toxic and non-antigenic to the host.[66-69] Classification of polymers are shown in **Table 1**.

Drug

The transdermal patch offers benefits to drugs that cause the first-pass effect and to drugs with a short half-life that disrupts drug delivery to the targeted site resulting in unstable gastrointestinal (GI) conditions. Some examples of suitable drugs are clonidine, captopril, indapamide, propranolol hydrochloride, etc. The properties of a drug that should be taken into consideration for transdermal delivery are shown in **figure 5**.[64,70,71]

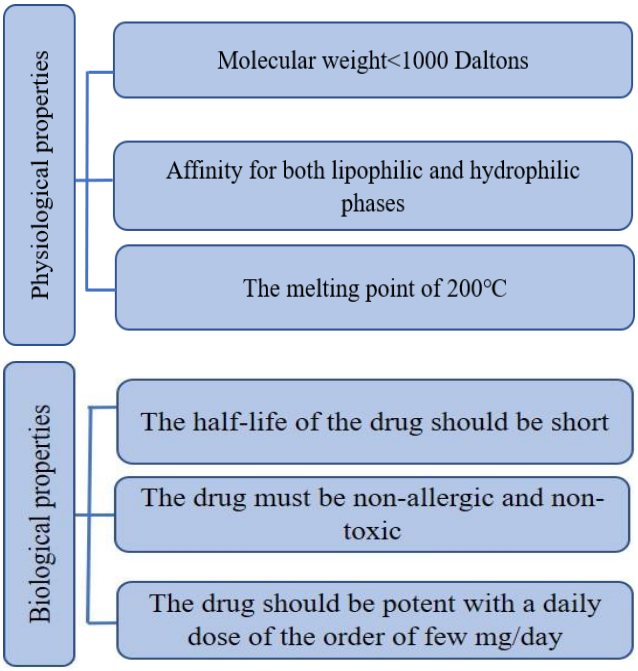

Figure 5: Schematic representation of physiological and biological properties of drug[64]

Permeation enhancer

These compounds are also called a penetration enhancer, which promotes the permeability of the stratum corneum by altering the proteins and lipid layer. This can be classified as solvents, surfactants, and chemicals. The solvents involve swallowing of the protein and lipid layer which in turn increases permeability. Examples: alcohols like methanol and ethanol, alkyl methyl sulfoxides like dimethyl sulfoxide, pyrrolidone like 2 pyrrolidones, and alkyl homologs like methyl sulfoxide dimethylacetamide. Surfactants are compounds that enhance polar pathways. Examples: Non-ionic- Pluronic F68, Pluronic F127, Anionic surfactants- sodium lauryl sulphate, dioctyl sulphosuccinate, etc. Chemicals are the compounds that disrupt the intercellular lipid bilayers of stratum corneum, hence allowing better permeation of drugs. Includes urea, N, N-dimethyl-m-toluamide, calcium thioglycolate, etc.[72-74]

Pressure-sensitive Adhesives

These are the materials that are non-reactive and forms a bond with the substrate when pressure is applied and when removed leaves no residue. It helps to maintain contact between the transdermal patch and the surface of the skin. The selection of adhesives depends on factors like drug formulation and patch design. The most widely used adhesives in TDDS are polysiloxanes, polyacrylate, polyisobutylene-based adhesives, etc. The PSAs should be compatible with drugs, enhancers, and excipients of the device. It should not sensitize the skin and also not leave any unwashable residue during the removal process, should adhere to the skin aggressively, dispersion of drug into the skin should not be affected.[75-77]

Backing membrane

These are flexible and impermeable membrane that protects the product from the outer environment. Chemical resistance of the material and excipient compatibility should be taken into consideration while designing a backing laminate. A backing laminate having properties such as good oxygen transmission, high flexibility, high moisture vapor transmission rate, and low modulus are considered to be the best. Examples of backing membranes include plastic baking with an absorbent pad, metallic plastic laminate, adhesive foam pad with occlusive base plate, etc.[78,79]

Liner

The liner protects the product during storage which is removed before use. The drug solution is in direct contact with the liner. Therefore, it is considered as the primary packing material rather than a part of the dosage form of the drug for the delivery process. Composition of the liner: a coating layer made of silicon or Teflon and a base layer that may be occlusive or non-occlusive.[80]

TYPES OF TDDS

Single-layer Drug-in-Adhesive

This type of system involves the inclusion of drugs within the adhesive layer. The adhesive layer is responsible for the release of the drug and also serves as a base to adhere to the system as well as to the skin. The layer is surrounded by a liner and a backing membrane. The releasing-rate of the drug depends on the dissemination of the drug across the skin. Illustration of the system is shown in **figure 6(a)**.[81,82]

Multi-layer Drug-in-Adhesive

It is similar to the Single-layer Drug-in-Adhesive system, wherein two layers of the required drug solution is taken, i.e. controlled and immediate drug release layer in addition to the adhesive layer which is responsible for the discharge of the drug. It also includes a permanent backing membrane and a temporary liner layer. Illustration of the system is shown in **figure 6(b)**.[83,84]

Drug Reservoir-in-Adhesive

This system involves enclosing the drug reservoir between the backing layer and the rate-controlling membrane. The drug in the reservoir may either be a solution, suspension gel or dispersed in a solid bio-compatible polymer matrix. This is then discharged through the porous rate-controlling membrane. Illustration of the system is shown in **figure 6(c)**.[85,86]

Drug Matrix-in-Adhesive

The system is represented by the incorporation of a semisolid matrix consisting of a drug solution or gel suspension which in-turn is in contact with the rate-controlling release liner. The skin adhesion component is integrated as a laminate and a concentric configuration is formed around the semisolid matrix. Illustration of the system is shown in **figure 6(d)**.[87,88]

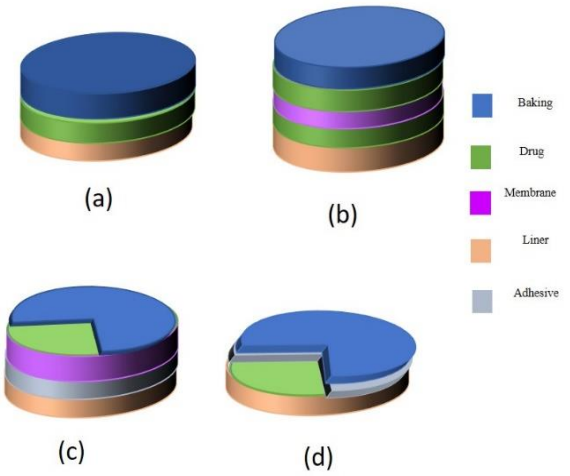

Figure 6: Represents an illustration of different types of TDDS **(a)** Single-layer Drug-in-Adhesive system, **(b)** Multi-layer Drug-in-Adhesive, **(c)** Drug Reservoir-in-Adhesive and **(d)** drug-matrix-in-adhesive system.[4]

The transdermal drug delivery system has become a recent trend for incorporating the drug into the body via skin without rupturing the skin membrane and transdermal route. The drug showing hepatic first-pass metabolism and unstable GI conditions are a suitable candidate for TDDS. This system is becoming the most widely preferred route for the administration of a drug and many researchers are working in present to incorporate new drugs with the help of this system.[4,88]

APPLICATIONS OF TDDS

Nicotine patches

Nicotine is an addictive substance found in tobacco which can cause dependence. To reduce the tendency of an individual to consume tobacco, patches incorporated with nicotine are used. On the application of this patch onto the skin, nicotine is discharged and soaked by the skin. When the discharged nicotine binds to the nicotine receptors in the body, the cravings for nicotine get reduced which in turn reduces withdrawal symptoms like anxiety,

depression, anger, irritability, etc, consequently leading to quitting smoking. These patches are available in a variety of dosages. Higher dependent smokers should use strong patches while lower dependent smokers must use low dosage patches.[89-92]

Ortho Evra (Estrogen patches)

To treat symptoms of menopause as well as post-menopause, patches incorporated with estrogen are used. The patch has three layers: the inner release liner- must be removed before applying, a layer consisting of hormones, and an outer protective layer. On applying the patch on the required area of skin, hormones are released and absorbed to provide a continuous flow during menstrual cycles.[93,94]

Nitroglycerine patches

These patches are used by people who have coronary artery disease (narrowing of the blood vessels) to forbid episodes of angina (chest pain). Nitroglycerine corresponds to a class of drugs known as nitrates. When the heart muscle does not receive enough blood, angina occurs. When the patch is applied to the skin, nitroglycerine releases are absorbed by the body. This drug works by relaxing and widening the blood vessels allowing the blood to flow easily to the heart.[95,96]

Microneedles

Administration of drugs or vaccines via skin can be accomplished by the application of micro-scale needles, called microneedles. The formulation of microneedles can be achieved through several methods such as micro-molding or photolithography. When a patient uses this patch, drugs are circulated to the target site. Microneedles are mainly divided into four categories: dissolving microneedles, solid microneedles, drug-coated microneedles, and hollow microneedles, as shown in **figure 7**.[97,98]

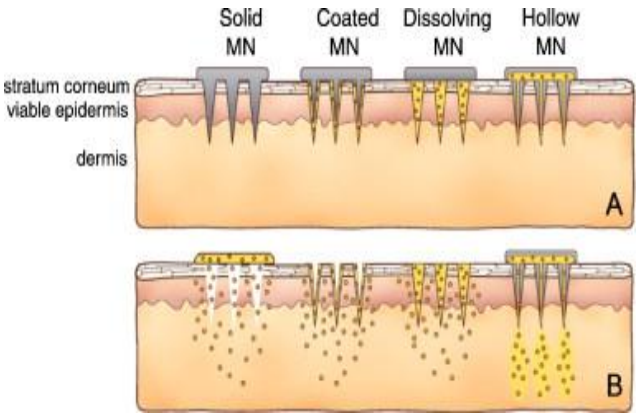

Figure 7: illustration of 4 types of microneedles namely solid, coated, dissolving and hollow and their mechanism.[97]

(a) Dissolving microneedles encloses the drug in a water-soluble or biodegradable polymer which dissolves entirely after it is applied into the skin and thus releases the drug to the target site.[99,100]

(b) Solid microneedles are used to form pores on the skin surface through which the drug circulates into the body after the drug is applied on the skin externally.[101]

(c) Drug-coated microneedles are coated with a drug-using water-soluble formulation. When the patch containing these microneedles is applied on the skin, the drug coating is dissolved into the body, after which microneedles are released.[102]

(d) Hollow microneedles are used for the administration of liquid drugs into the body via skin.[12,103]

CONCLUSION

Transdermal drug delivery system serves to be an efficient way for drug administration to the target site in a very controlled manner. Recent advances in technology have proved transdermal drug delivery as one the most approaching route for administration of the drug on the targeted site without damaging the membrane of the skin. The system provides various advantages over other traditional methods by addressing the pain and inconvenience of injections, degeneration of drugs, poor bioavailability, first-pass metabolism, etc. The transdermal system has the potential to deliver the drug safely and efficiently on the target site to treat numerous diseases like neurological disorders, cardiovascular diseases, and skin diseases. A transdermal patch is a point of care device that allows the drugs to be delivered in a dosage form. Such easy-to-use devices are painless and non-invasive making it a safe and effective drug delivery device that can offer instant relief to the patients and increase their survival rate. Several new and emerging technologies have been introduced such as iontophoresis, electroporation, electrospun nanofiber, microemulsions, and microneedles. Recently researchers are focussing on the incorporation of new drugs through this system into systemic circulation by improvising the drug as well as the administration techniques. Therefore, we suggest that the transdermal drug delivery system could be used for most biological applications as the drug could be administered easily.

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