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A FACET UPSHOT ON TRANSDERMAL THERAPEUTIC SYSTEMS: IN MIDDLE OF UPDATED PERSPECTIVE

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ABSTRACT

Transdermal drug delivery (TDD) is a non-invasive route of drug administration, although its applications are limited by low skin permeability. Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver the drug through the skin in order to achieve both local and systemic effect of drug at a predetermined rate over a prolonged period of time. Its main advantages includes with minimum side effects, improved bioavailability, bypass first pass metabolism and many more. The main challenge is in the design of a polymer matrix, followed by optimization of the drug loaded matrix not only in terms of release properties, but also with respect to its adhesion–cohesion balance, physicochemical properties, and compatibility and stability with other components of the system as well as with skin. The low permeability of the skin relative to other biological tissues is well known and keeps the skin as a minor port of entry for drugs. The skin is a very effective barrier for the permeation of most xenobiotics. It is rare that the industry produces a new chemical entity specific for dermal or transdermal use and often, therefore, its inherent physicochemical properties are not ideally suited to uptake into and through the skin. This means that considerable effort has to be expended on the appropriate design of a formulation or a device to deliver enough of the medicine such that there is sufficient present at its site.

KEY WORDS: Transdermal patch, xenobiotics, bioavailability, controlled release.

INTRODUCTION

Transdermal drug delivery systems are devices containing drug of defined surface area that delivers a pre-determined amount of drug to the surface of intact skin at a pre-predefined rate.

The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time-released dose of medication systemically for treating illnesses. The discovery of transdermal drug delivery systems (TDDS) is a breakthrough in the field of controlled drug delivery systems. The ability of TDDS to deliver drugs for systemic effect through intact skin while bypassing first pass metabolism has accelerated transdermal drug delivery research in the field of pharmaceutics. Over a decade of such extensive research activities, many transdermal patches have been developed and successfully commercialized.[1, 2]

The components of transdermal devices include

1. Backing laminate
2. Drug containing reservoir

a. Polymer matrix

b. Drug

c. Permeation enhancers

d. Plasticizers

e. Other excipients

3. Membrane/Release control layer
4. Pressure sensitive adhesive
5. Release liner
6. Packet Guard

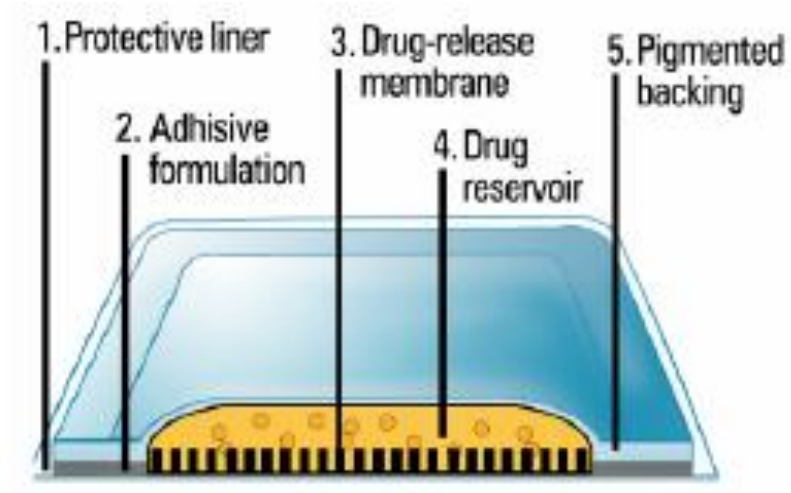

Fig. 1 Schematic view of transdermal therapeutic system

1. Backing Laminate

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an `overemphasis on the chemical resistance may lead to stiffness and high occlusivity to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. An ideal backing laminate is flexible and provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is usually impermeable to water vapours and protects the product during use on the skin. A low moisture vapour transmission rate is essential to retain skin moisture and hydrating the area where by increases drug penetration. e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc.[3]

2. Drug Containing Reservoir

a. Polymer matrix

The polymers play a major role in transdermal drug delivery systems of drugs. The development of transdermal systems requires judicious selection of a polymeric material or a series of polymers whose diffusive characteristic will be such that a desirable permeation rate of a specific drug or other bio-active agent can be obtained. The release of drug to the skin is controlled by drug free film known as rate controlling membrane.[3, 4] Polymers are also used in the matrix devices in which the drug is embedded in polymer matrix, which control the duration of release of drugs. The polymers should fulfill the following requirements:

1. Molecular weight, Glass transition temperature, and chemical functionality of the polymer must allow the diffusion of the drug substances at desirable rate.
2. The polymer should be chemically non-toxic, non reactive or it should be an inert drug carrier.
3. The polymer must be easy to manufacture and fabricate into the desired product.
4. It should allow incorporation of large amount of active agent.
5. The polymer and its decomposed product should be nontoxic.
6. The cost of the polymer should not be excessively high. Some of the polymers used for transdermal devices are as follows

Natural polymers

Cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.

Synthetic elastomers

Polybutadiene, polysiloxane, acrylonitrile, butyl rubber, Neoprene, polyisoprene, ethylene-propylene-dieneterpolymer etc.

Synthetic polymers

Polyvinyl alcohol, polyvinyl chloride, polyethylene, polystyrene polyester, polyacrylate, polymethylmethacrylate, polypropylene etc. The polymers like cross linked polyethylene glycol,eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for TDDS. Other polymers like ethylene vinyl acetate, silicon rubber and polyurethane are used as rate controlling membrane.[1,5,6]

b. Drug

Judicious choice of drug is critical in the successful development of a transdermal product. The important drug properties that affect its diffusion from device as well as across the skin include molecular weight, solubility, physical properties and melting point. The structure of the drug also affects the skin penetration. Diffusion of the drug in adequate amount to produce a satisfactory therapeutic effect is of prime importance. Other parameters such as skin irritation and clinical need should be considered before a drug is chosen.[7, 8]

Selection of Drug

Drug should be chosen with great care, various parameters to be considered for the selection of drug includes

1) Physicochemical properties of drug

1. Should have molecular weight less than 1000 daltons.
2. Should have affinity for both lipophilic and hydrophilic phase.
3. Should have low melting point.

2) Biological properties of drug

1. Should be potent with daily dose of few mg.
2. Should have short half life.
3. Drug must not induce cutaneous irritation or allergic response.

4. Drug which degrade in GIT or are inactivated by hepatic first pass effect are suitable candidates.
5. Tolerance to drug must be developed under near zero order release profile of transdermal delivery.
6. Drugs which have to be administered for long period of time or which causes adverse effectto non target tissues can also be formulated.[9-11]

Table 1. List of Currently Available Drugs for Transdermal Delivery[11, 12]

Drug	Trade name	Type of transdermal Patch	Manufacturer	Indication
Fentanyl	Duragesic	Reservoir	Alza / Janssen Pharmaceutica	Moderate/ Severe Pain
Nitroglycerine	Deponit Minitran Nitrodisc Nitrodur TransdermNitro	Drug in adhesive Drug in adhesive Micro reservoir Matrix Reservoir	Schwarz Pharma 3M Pharmaceuticals Searle, USA Key Pharmaceuticals Alza/Novartis	Angina Pectoris
Nicotine	Prostep Nicotrol Habitraol	Reservoir Drug in adhesive Drug in adhesive	ElanCorp/Lederie Labs Cygnus Inc. /McNeil Consumer Products Ltd. Novartis	Smoking Cessation
Testosterone	Androderm Testoderm TTS	Reservoir	Thera Tech/ GlaxoSmithKline Alza	Hypogonadism in Males
Clonidine	Catapres-TTS	Membrane matrix hybrid type	Alza/Boehinger Ingelheim	Hypertension
Lidocaine	Lidoderm	Drug in adhesive	Cerner Multum, Inc.	Anesthetic
Scopolamine	Transderm Scop	Membrane matrix hybrid Type	Alza/Novartis	Motion sickness
Estradiol	Climara	Drug in adhesive	3M Pharmaceuticals/ Berlex Labs	Postmenstrual Syndrome
Ethinyl Estradiol	Vivelle Estraderm Esclim Ortho Evra	Drug in adhesive Reservoir Drug in adhesive Drug in adhesive	Noven Pharma/Novartis Alza/Novartis Women First Healthcare, Inc. Johnson & Johnson	Postmenstrual Syndrome

C. Permeation Enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. The flux, J, of drugs across the skin can be written as:

$J = D. dc/dx$ Where D is the diffusion coefficient and is a function of the size, shape and flexibility of the diffusing molecule as well as the membrane resistance; C is the concentration of the diffusing species; X is the spatial coordinate. Permeation enhancers are hypothesized to affect one or more of these layers to achieve skin penetration enhancement. A large number of compounds have been investigated for their ability to enhance stratum

corneum permeability.[13-18] These may be conveniently be classified under the following main headings

1. Solvents

These compounds increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. Eg.,water alcohols-methanol and ethanol ; alkyl methyl sulfoxides-dimethyl sulfoxide, dimethyl acetamide and dimethyl formamide,miscellaneous solvents-propylene glycol, glycerol, isopropyl palmitate.[17]

2. Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. Anionic surfactants can penetrate and interact strongly with the skin. Cationic surfactants are reportedly more irritant than the anionic surfactants and they have not been widely studied as skin permeation enhancers. Of the 3 major classes of surfactants, then Non-ionics have long been recognised as those with the least potential for irritation and have been widely studied.[17]

Anionic surfactants

Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.

Nonionic surfactants

Pluronic F127, Pluronic F68, etc.

Bile salts

Sodiumtaurocholate, Sodiumdeoxycholate, Sodiumtauroglycocholate

Binary systems

These systems apparently open up the heterogenous multilaminate pathway as well as the continuous pathways. Eg. Propylene glycol-oleic acid and 1,4- butane diol-linoleic acid.[18]

Miscellaneous chemicals

These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein.[13]

Anticholinergic agents

Penetration enhancer should have the following properties[13]

7. The material should be pharmacologically inert.
8. It should be non-toxic, non-irritant, and have a low index of sensitization.
9. They should show a quick onset of action, reduction of barrier function of the skin only in one direction. On removal from skin, the tissues should quickly and fully recover normal barrier function.
10. The enhancer should be chemically and physically compatible with a wide range of drugs and pharmaceutical adjuncts.
11. The material should spread well on the skin.
12. It should be odorless, tasteless, and colorless.

Mechanism of action

Potential mechanisms of action of enhancers are varied, which range from direct effects on the skin to modification of formulation.[13]

1. They act on the stratum corneum i.e. intracellular keratin and denature it or modify its conformation causing swelling and increased hydration.
2. They affect the desmosomes that maintain cohesion between corneocytes.
3. Modify the intracellular lipid domains to reduce the barrier resistance of the bilayer lipids.
4. Alter the solvent nature of the stratum corneum to modify partitioning of the drug or of a co-solvent into the tissue.
5. Modification of thermodynamic activity of the vehicle.

Selection of permeation enhancers

The physicochemical properties of a drug must be considered while selecting the permeation enhancer. If the drug is polar, the enhancing material should interact with the proteins of the stratum corneum to alter the protein conformation. If the drug is lipophillic, the enhancer should fluidize the crystalline lipids. Techniques such as DSC, FTIR and NMR have been used in elucidating the mechanism of action and structure activity relationship ofvarious enhancers. Measurement of transepidermal water loss (TEWL) would a good parameter in evaluating the effect of permeation enhancers. Development of models with the use of solubility parameters to predict drug-vehicle- skin interactions and flux rate may aid in optical selection of enhancer.[14]

d. Plasticizers

These are used to prevent the films from becoming brittle. An ideal plasticizer should possess the following properties[22, 25]

1. Should not show any pharmacological action of its own.
2. Should be chemically and physically stable.
3. Should be compatible with the drug and the formulated components.
4. Should be colourless, odorless and tasteless.
5. Should be non-toxic, non-allergenic & nonirritant.

Plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

e. Other Excipients

A variety of solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir.[23]

3. Membrane/Release Control Layer

This is the rate controlling membrane. It is the important part of Transdermal device. It controls the release of the drug from the reservoir and multi-layer patches and positioned between the drug reservoir and adhesive membrane. The rate controlling membrane can be either a micro porous or a nonporous polymeric membrane with defined drug permeability. The membrane can be constituted with any of the polymers discussed earlier.[25]

4. Pressure Sensitive Adhesive

The adhesion of all transdermal devices to the skin in an essential requirement and it has so far been accomplished using a pressure sensitive polymeric adhesive. The pressure sensitive adhesive can be positioned on the face of the device or on the back of the device and extended peripherally. Both the adhesive systems should fulfill the following criteria[19, 20]

1. Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora during its contact time with the skin.
2. Should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc.
3. Should be easily removed.
4. Should not leave any unwashable residue on the skin.
5. Should provide an excellent contact with the skin at microscopic level.The face adhesive system should fulfill the following criteria.

6. Physical and chemical compatibility with the drug and excipients of the device.
7. Permeation of the drug should not be affected
8. The delivery of simple or intended permeation enhancers should not be affected.

The peripheral adhesive system is less elegant, multilayered and substantially large and is more difficult to manufacture than the face adhesive system. However, there is no need to further package the reservoir layer containing the drug when peripheral adhesive systems are used. The reservoir of the face adhesive system cannot be hermetically contained and therefore has to be packed in an aluminium foil pouch.

Some widely used pressure sensitive adhesives include

Rubber based adhesives

Natural gum (Karaya gum), olylisoprene, polybutene, and polyisobutelene.

Polyacrylic based adhesives

Ethyl acrylate, 2-ethylhexylacrylate, iso-octyl acrylate.

Polysiloxane based adhesives

Polydimethyl siloxane, polysilicate resins, sufloxane blends.

5. Release Liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner 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. Typically, release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates.[21]

6. PACKET GUARD

Packet guard protects the patches against drug loss and contamination on storage. The patches are individually packed in heat sealed foil pouches.[1, 3]

CONCLUSION

The goal of this review is to reflect on the state-of-theart anatomy of transdermal drug delivery systems. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. Transdermal administration has, to-date, solved the non-invasive challenge, thanks to its design, and has successfully delivered drug over relatively long periods of time at primarily sustained and controlled rates. TDDS found to be a realistic practical application as the next generation of drug delivery system.

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