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OPTIMIZATION TECHNIQUES IN TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal drug technology specialists are continuing to search for new methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with the oral route. Transdermal Drug Delivery System (TDDS) is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Skin is an effective medium from which absorption of the drug takes place and enters in to circulatory system. Various types of transdermal patches are used to incorporate the active ingredients into the circulatory system via skin. The patches have been proved effective because of its large advantages over other controlled drug delivery systems. This review article covers a brief outline of various components of transdermal patch, applications of transdermal patch, their advantages, disadvantages, when the transdermal patch are used and when their use should be avoided, types of transdermal patch, recent techniques for enhancing TDDS.

INTRODUCTION: Acute and chronic diseases are treated by delivery of drugs to patients using various pharmaceutical dosage forms. These dosage forms provide a burst release of drug. But recently, several sophisticated technical approaches have been generated for drug delivery and these techniques are helpful, controlling the rate of drug release. The term-controlled release has a meaning that goes beyond scope of sustained release.

The classification of controlled drug release –

1. Rate-pre-programmed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Out of these classes first class (Rate-preprogrammed drug delivery system) contains new drug delivery systems as transdermal delivery of drug [1].

Transdermal Drug Delivery System adheres to the body surface and delivers the drug, across the skin at controlled rate in to the blood stream. Transdermal drug delivery system is self contained, discrete dosage form [2]. Transdermal drug delivery system is also known as a transdermal patch or skin patch which deliver a specific dose of medication to the systemic circulation. It is a medicated adhesive patch. Morphological, biophysical and physicochemical properties of the skin are to be considered when therapeutic agents are delivered through the human skin for systemic effects[3].

Transdermal patch of scopolamine is the first transdermal patch which is approved by FDA in 1981. Transdermal delivery systems of scopolamine is used for the prevention of motion sickness (TransdermScop, ALZA Corp.) and nitro-glycerine for the prevention of

angina pectoris associated with coronary artery disease (Transderm-Nitro). Transdermal drug delivery products give therapeutic benefit to patients. Approximately 16 active ingredients and more than 35 Transdermal drug delivery products have been approved for use globally and for sale in the US respectively. In the year 2005 market of $ 12.7 billion is found by statistics analysis that is expected to increase to $ 21.5 billion in the year 2011 and $31.5 billion in the year 2015 [4].

Transdermal drug delivery system is a Novel drug delivery system and its aim to achieve a programmed delivery of the therapeutic products when applied on the skin for the optimal beneficial effects while avoiding the side effect of drugs. Novel drug delivery system solves the multiple drug delivery problem of therapeutic agent such as:

1. Delivery of Proteins and Peptides
2. Pulmonary and Nasal drug Delivery
3. Oral Drug Delivery Systems and Materials
4. Parenteral and Implant Drug Delivery Systems
5. Transmucosal Drug Delivery
6. Transdermal and Topical Drug Delivery
7. Drug Delivery Pipelines

Nicotine is the smallest drug molecule which is formulated in a patch (162Da) and the oxybutinin is the largest drug molecule (359 Da) [5].

Advantages of Transdermal Drug Delivery System (TDDS) [2, 3, 6]

The advantages of transdermal delivery over other traditional delivery modalities are as follows:

1. Hepatic first pass metabolism, salivary metabolism and intestinal metabolism are bypassed thus increasing bioavailability and efficacy of drugs.
2. Self-administration is possible.
3. In case of an emergency, termination of the patch by removal of the application from the surface of the skin at any point of time during therapy can instantly stop active ingredient input.
4. Minimal inter and intra patient variation because the composition of skin structurally and biologically is the same in almost all the humans.
5. Avoidance of gastrointestinal incompatibility.
6. Avoidance of hazards and discomfort associated with parenteral therapy and improves patient compliance, as it is easy to apply.
7. Steady and optimum blood concentration time profile achieved which reduce adverse effects.
8. Release of drug for prolonged time with single application which extend the duration of activity.
9. Drugs entity with short biological half lives and narrow therapeutic window are utilized.
10. Avoiding the fluctuation in plasma level of drug.
11. Plasma concentration of potent drugs is maintained.
12. Termination of therapy is easy at any point of time.
13. Elimination of typical multiple dosing profile an enhancement of patient compliance.
14. When oral route is unsuitable as with vomiting and diarrhoea then transdermal route is used as alternate for deliver the drug candidate.

Disadvantage of Transdermal Drug Delivery System (TDDS) [6, 7]:

1. Only potent drugs are suitable candidates for transdermal delivery
2. Skin irritation may occur in some patient at the site of application
3. The delivery system is not suitable for drugs needs high blood levels

4. This system is uneconomic
5. Dose dumping may occur due to Binding of drug to skin
6. It can be used only for chronic conditions not for acute condition because chronic condition require drug therapy for a long period of time e.g., hypertension, angina and diabetes etc.
7. Therapeutic performance of the system Affected by Cutaneous metabolism
8. Ionic drugs is not suitable candidate for Transdermal therapy

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Therapeutic agent	Marketed name (Company)
Clonidine	Catapres-TTS (Boehringer Ingelheim)
Estradiol	Vivelle (Novartis)
Fentanyl	Duragesic (Janssen)
Nicotine	Prosstep (Lederie)
Testosterone	Testoderm (Alza)
Nicotine	Habitrol (Novartis Consumer)
Nitro-glycerine	Transderm-Nitro (Novartis)
Nicotine	Nicoderm CQ (Smithkline consumer)
Scopolamine	Transderm-Scop(Novartis Consumer)

Drug Selection Criteria for Transdermal Patch [4, 8, 9]:

1. The dose of drug should be low i.e.<20mg/day.
2. The drug should have short half life (which causes non-compliance due to frequent dosing).
3. The drug should have Molecular weight <400 Daltons (high molecular weight fail to penetrate the *stratum corneum*).
4. The drug should have partition coefficient (octanol-water) between 1.0 and 4 (logP).
5. Drug should be non-irritating and non-sensitizing to the skin.
6. The drug should have low Oral bioavailability.
7. The drug should have low therapeutic index.
8. The drug should have affinity for both – lipophilic and hydrophilic phases. The drug should have low melting point(less than 200°C).

Factors influencing Transdermal Drug Delivery [10]: The effective transdermal drug delivery can be formulated by considering three factors as Drug, Skin, and the vehicles. So the factors affecting can be divided in to classes as biological factors and physicochemical factors.

A. Biological factors:

1. **Skin condition:** Acids and alkalis, many solvents like chloroform methanol damage the skin cells and promote penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.
2. **Skin age:** The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDS.
3. **Blood supply:** Changes in peripheral circulation can affect transdermal absorption.
4. **Regional skin site:** Thickness of skin, nature of *stratum corneum*, and density of appendages vary site to site. These factors affect significantly penetration.
5. **Skin metabolism:** Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.
6. **Species differences:** The skin thickness, density of appendages, and keratinization of skin vary species to species, so affects the penetration.

B. Physicochemical factors:

1. **Skin hydration:** In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectants is done in transdermal delivery.

2. **Temperature and pH:** The permeation of drug increase ten fold with temperature variation. The

diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and p*K*a or p*K*b values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

3. **Diffusion coefficient:** Penetration of drug depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

4. **Drug concentration:** The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

5. **Partition coefficient:** The optimal *K*, partition coefficient is required for good action. Drugs with high *K* are not ready to leave the lipid portion of skin. Also, drugs with low *K* will not be permeated.

6. **Molecular size and shape:** Drug absorption is inversely related to molecular weight; small molecules penetrate faster than large ones. Because of partition coefficient domination, the effect of molecular size is not known.

Care taken while applying Transdermal patch [10]:

1. The part of the skin where the patch is to be applied should be properly cleaned.
2. Patch should not be cut because cutting the patch destroys the drug delivery system.
3. Before applying a new patch it should be made sure that the old patch is removed from the site.
4. Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch.
5. The patch should be applied accurately to the site of administration.

Conditions in which Transdermal patches are used[10]

Transdermal patch is used when:

1. 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.
2. 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.
3. It can be used in combination with other enhancement strategies to produce synergistic effects.

Conditions in which Transdermal patches are not used [10]:

The use of transdermal patch is not suitable when:

1. Cure for acute pain is required.
2. Where rapid dose titration is required.
3. Where requirement of dose is equal to or less then 30 mg/24 hrs.

Principles of Transdermal Permeation [4, 11]: *Stratum corneum* which is outer layer of skin act as an impermeable protective barrier, skin also acts as a route for systemic administration for drug. The various steps involved in transport of drug from patch to systemic circulation are as follows:

1. Drug diffuses from drug reservoir to the rate controlling membrane.
2. Drug diffuses from rate limiting membrane to *stratum corneum*.
3. Sorption of drug by *stratum corneum* and penetration of drug through viable epidermis.
4. Uptake of drug in the dermal papillary layer by capillary network.
5. Effect on target organ

Pathway of Transdermal Permeation [12, 13, 14]

Permeation can occur by diffusion via:

1. Transdermal permeation, through the *stratum corneum.*

2. Intercellular permeation, through the *stratum corneum.*

3. Trans-appendaged permeation, via the hair follicle, sebaceous and sweat glands.

Basic Components of TDDS [15]:

1. **Polymer matrix / Drug reservoir:** Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and pressure sensitive adhesive.

2. **Drug:** The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery. Drug is in direct contact with release liner.

3. **Permeation enhancers:** These are compounds, which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant.

4. **Pressure sensitive adhesive (PSA):** The pressure-sensitive adhesive (PSA) affixes the Transdermal drug delivery system firmly to the skin. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue.

5. **Backing laminates:** The primary function of the backing laminate is to provide support. They should be able to prevent drug from leaving the dosage form through top. They must be impermeable to drugs and permeation enhancers

6. **Release liner:** During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug.

7. **Rate controlling membrane:** Rate controlling membranes in transdermal devices govern drug release from the dosage form. Membranes made from natural polymeric material such as chitosan show great promise for use as rate controlling membranes. It should be flexible enough not to split or crack on bending or stretching. Some of rate-controlling membranes are polyethylene sheets, ethylene vinyl acetate co-polymer, and cellulose acetate. . Recently composite poly-2-hydroxyethyl methacrylate (PHEMA) membranes have been evaluated as rate controlling barriers for transdermal application.

8. **Other excipients-**Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethyleneglycol and propylene glycol are added to provide plasticity to the transdermal patch.

Types of Transdermal Patches [2, 7]:

a) **Single layer drug in adhesive-**In this transdermal system design, the drug is enclosed with in the adhesive which is attached to skin. Various layers of polymer are adhering together on adhesive layer and drug release occurs from adhesive layer to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

b) **Multi-layer drug in adhesive:** This type of transdermal system is similar to the single layer drug in adhesive system except that this system has more than one layer of drug in adhesive which is separated by a membrane. Drug release is depending upon adhesive layer. This patch also has a temporary liner-layer and a permanent backing

c) **Vapor patch:** In this system, the adhesive layer helpful in releasing the vapour of drug and serves to adhere the various layers together along with the skin. This type of patches commonly used for releasing the essential oils in decongestion. To improve the quality of sleep and reduces the

cigarette smoking conditions other kind of vapour patches are used.

d) Reservoir: Liquid like solution or suspension of drugs are present in compartment of drug reservoir which is separated from the liner by a membrane (semipermeable) and adhesive.

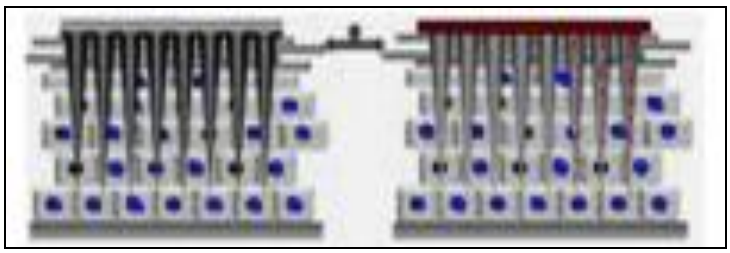
e) Matrix: This type of transdermal system contain a medicament layer of drug in the form of solution or suspension, which behave like semisolid matrix, this is in direct contact with the liner. The adhesive layer in this device surrounds the drug layer partially overlaying it.

f) Micro reservoir system: In this system, the suspension of drug which is formed by dissolving the drug in an aqueous solution of water soluble polymer is disperse in the solution of a lipophilic polymer to form microscopic spheres of drug.

Recent Techniques for Enhancing TDDS/optimization Techniques

A. Structure-Based Enhancement Techniques [7, 9, 12, 16]:

1. **Micro fabricated Microneedles-** Microneedles are recently used techniques for transdermal drug delivery designed to form a physical pathway through the upper epidermis to enhance skin permeability. Micro-fabricated microneedles are devices which are hybrids of the hypodermic needle and transdermal patch in this technology needles of micron dimension are inserted in to skin surface. It damages or produces pores only in SC portion so one does not feel any pain since nerve fibers are located into deeper region of the skin. Moreover distance to be travelled by drug will decrease.



(A) HOLLOW MICRONEEDLES (B) SOLID MICRONEEDLES

FIGURE 1: DESIGN OF MICRONEEDLE DELIVERY DEVICES (A) HOLLOW MICRONEEDLES (B) SOLID MICRONEEDLES

Microneedles are tiny and very sleek devices that are manufactured by the silicon etching technology and micro-mechanical system manufacturing (MEMS) technique. There are number of delivery approaches that have been employed to use the microneedles for TDDS. These include;

- **Poke with patch approach:** Involves piercing into the skin followed by application of the drug patch at the site of treatment.
- **Coat and poke approach:** Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.
- **Biodegradable microneedles:** Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.
- **Hollow microneedles:** Involves injecting the drug through the needle with a hollow bore.

2. **Macroflux-**This system incorporates a titanium microprojection array that creates superficial pathway through the skin barrier layer .The main component of the microprojection patch is a titanium disk affixed to a polymeric adhesive back. The titanium disk is $8cm^2$ and consists of an array of microscopic, titanium, tooth-like microprojections that are coated with medicinal substances. There are as many as 300 microprojections per cm with the length of individual micro projection less than 200µm. They penetrate just the 10µm to 25µm-thin layer of dead cells of the *stratum corneum*, in which they create 'holes' – microchannels – large enough to permit the transport of large molecules to the physiologically active deeper layers of the epidermis. The titanium microprojections are too small to cause pain. This technology offers a needle-free and painless transdermal drug delivery of large-molecular-weight compounds such as insulin, several peptidic hormones, and vaccines. With this new system; patients can receive drugs for 12 weeks.

Three types of Macroflux have been designed. They include,

1. Dry-Coated Macro flux system-this is used for short period delivery that consists microprojection array coated with medicament that adhered to a elastic polymer adhesive backing.

2. D-TRANS Macro flux system-this is also for short duration administration that consists of a microprojection array combined with reservoir of drug.

3. E-TRANS Macro flux system-this is for on demand delivery that involves a microprojection array combined with an electrotransport system.

4. **Metered-Dose Transdermal Spray (MDTS)**-It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution . The use of MDTS reaches the sustained level and better permeation of the drug via skin. The MDTS has the following potential advantages:

   a) It improves delivery potential without skin irritation due to its non-occlusive nature.

   b) Increased acceptability.

   c) Dose flexibility

   d) Simple manufacture

B. Electrically-Based Enhancement Techniques [7, 8, 9, 12, 16, 18]:

1. **Iontophoresis:** In iontophoretic delivery devices, Drug is placed on the skin under the active electrode, and a current (< 0.5mA) passed between the two electrodes effectively repelling drug away from the active electrode and into the skin. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anaesthesia.

2. **Ultrasound:** The application of ultrasound of a suitable frequency significantly enhances the transdermal transport of drugs by means of skin system not larger than wrist watch-a phenomenon referred to as phonophoresis or sonophoresis. It is a combination of ultrasound therapy with topical drug therapy to achieve therapeutic drug concentrations at selected sites in the skin. In this technique, the drug is mixed with a coupling agent usually a gel but sometimes a cream or ointment is used which transfers ultrasonic energy from the device to the skin through this coupling agent. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier. It employs ultrasound waves ranging from 20 kHzto 10 MHz with intensities of up to $3Wcm^{-2}$ have been applied to mitigate the stratum corneum barrier property.

3. **Photomechanical Waves:** The mechanism of photochemical wave was found to act by producing changes in the lacunar system which results in the formation of transient channels through the *stratum corneum* by permeabilization mechanism.

4. **Electroporation-**In this method, aqueous pores are generated in the lipid bilayers by the application of short electrical pulses of approx 100-1000 volt/cm. It may combine with Iontophoresis to enhance the permeation of peptide.

5. **Electro-Osmosis:** If a charged porous membrane is subjected to a voltage difference, a bulk fluid or volume flow, called electro osmosis.

Velocity Based Enhancement Techniques [2, 9, 16]:

1. **Needle-Free Injections**

   a) Intraject

   b) Implaject

   c) Jet Syringe

   d) Iject

   e) Mini-ject

   f) Cross jet

   g) Jet Syringe

2. **Powderject Device:** The powderject system fires solid particles (20-100 mm) through *stratum corneum* into lower skin layers, using a supersonic shock wave of helium gas.

Other Enhancement Techniques [7, 8, 9, 12, 19]:

1. **Liposomes-**Liposomes are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. They are lipid vesicles that fully enclose an aqueous volume. Liposomes acts by penetrating the epidermis, carrying the drug into skin.

2. **Transferosomes:** Transferosomes are modified liposomes i.e. they are liposomes with edge activators (sodium cholate). Transferosomes by passes the cutaneous capillary bed because they are too large to enter the blood vessels locally and reach subcutaneous tissue. Transferosome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug.

3. **Skin Abrasion:** The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. In general, one approach is adopted to create micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules are generally known as Microscissuining.

4. **Medicated Tattoos:** Med-Tats is a modification of temporary tattoo which contains an active drug substance for transdermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

5. **Laser Radiation:** This method involves direct and controlled exposure of a laser beam to the skin which results in the ablation of the *stratum corneum* without significantly damaging the underlying epidermis. Removal of the *stratum corneum* using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs.

6. **Super saturation:** Thermodynamic activity of drug can be increased by employing supersaturated systems. In this method, when saturated formulation is used, the thermodynamic activity of the drug in the vehicle is increased above unity, thus enhancing the permeability of topically applied formulations. Skin permeation was directly related to the degree of saturation and was independent of the absolute concentration of the drug.

7. **Magnetophoresis:** The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength.

CONCLUSION: This review suggests that, the recent optimization techniques of transdermal patches are enhances the transdermal delivery of drug through the skin. The various criteria of drug which are include in transdermal patches such as the dose of drug should be <20mg/day and molecular weight <400 Daltons. In the TDDS the drug should have short half-life (3-5hr) and also low oral bioavailability. In this system, the drug bypass hepatic metabolism, salivary metabolism and intestinal metabolism due to that bioavailability and efficacy of drugs are increased.

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