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Application of Transdermal Drug Delivery System in Major Depressive Disorders

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ABSTRACT

Adherence to medications and dose optimization can be affected by several physiological and psychological factors such as undesirable side effects, dosing regimen, route of administration, nature of the illness, belief systems and personal attributes. Innovations in transdermal delivery systems (TDS) have made important contributions to medical practice by providing advances in the delivery of treatment with existing and novel drugs. TDS have significant advantages over other routes of administration, such as providing prolonged and steadier drug levels, the ability to interrupt treatment by removing the patch and less frequent dosing. Drug delivery through skin means avoidance of gastrointestinal incompatibility and hepatic first-pass metabolism, without the unpleasant and painful experiences with injections or rectal applications.

INTRODUCTION

Transdermal formulations for pain relief, smoking cessation and hormone replacement, but the use of psychotropics as transdermal patches is less studied and under-investigated. Advances in enhancing transdermal drug delivery have led to treatment options for various psychiatric and neuropsychiatric conditions. Conditions such as depression, attention deficit hyperactivity disorder (ADHD), Parkinson's disease and dementia benefit from long-acting formulations due to the nature of the symptom relief required and this can be achieved through constant plasma levels of medication against episodic peaks. TDS may be of particular use in patients who are unable or unwilling to take oral or intramuscular medicines. Offering patients another formulation also facilitates control and choice over their treatment. An appropriately administered patch which is visible and potentially easy to monitor offers clinicians reassurance in patients who are noncompliant that medicine is administered without the need for invasive and often injurious intramuscular injections when given under restraint.

Time of increasing financial constraints, the demand to implement a more efficient approach to the delivery of community-based healthcare is increasing. In patients receiving antidementia therapies for longer periods at adequate doses, there is a greater chance of slowing or delaying the progression of cognitive decline, leading to fewer admissions to nursing homes and reduced healthcare costs. However, misunderstanding complex titration schedules can result in people with dementia receiving subtherapeutic. Medications featuring less frequent dosing schemes, such as extended-wear transdermal patches, are capturing the interest of providers and healthcare purchasers.

Advantages

- Patient and carer satisfaction because of ease of use and tolerability.
- Limiting hepatic first-pass metabolism, hence a lower dose of medication can obtain the desired plasma level compared with oral formulations.
- Reduced frequency of dosing.
- Constant drug serum level versus episodic peaks.

- Reduced side effects are secondary to gastrointestinal intolerance and fluctuations of drug levels Avoidance of unpleasant and inconvenient parental administration.

- Easier to titrate to achieve optimal therapeutic doses.

- Potentially reduces the risk of a drug overdose.

- Removal of the patch stops drug delivery.

Transdermal Drug Delivery[2, 3]

The most common routes of drug delivery are the oral and parenteral routes with the majority of small-molecule drugs conventionally delivered orally. The oral route has the advantage of pre-determined doses, portability, and patient self-administration. For these reasons, the oral route remains the most convenient means of delivering medications. However, most therapeutic peptides or proteins are not delivered by the oral route, due to rapid degradation in the stomach and size-limited transport across the epithelium. The primary mode of administering macromolecules is therefore via injection which is not without limitations, such as the invasive nature of injections eliciting pain and lower acceptance/compliance by patients, in addition to the requirement for administration by a trained administrator. Rationally, the conventional routes of medication delivery have many inherent limitations which could potentially be overcome by advanced drug delivery methodologies such as transdermal drug delivery (TDD).

TDD is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When the drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation. TDD has many advantages over other conventional routes of drug delivery. It can provide a non-invasive alternative to parenteral routes, thus circumventing issues such as needle phobia. A large surface area of skin and ease of access allows many placement options on the skin for transdermal absorption. Furthermore, the pharmacokinetic profiles of drugs are more uniform with fewer peaks, thus minimizing the risk of toxic side effects. It can improve patient compliance due to the reduction of dosing frequencies and is also suitable for patients who are unconscious or vomiting, or those who rely on self-administration. TDD avoids pre-systemic metabolism,

thus improving bioavailability. Concerning the use of the skin as a novel site for vaccination strategies, this organ is known to be replete with dendritic cells in both the epidermal and dermal layers which play a central role in immune responses making TDD an attractive vaccination route for therapeutic proteins and peptides. The requirement for an inexpensive and non-invasive means of vaccination, especially in the developing world, has given rise to substantial research focused on the development of simple, needle-free systems such as TDD for vaccination purposes.

A Brief Review of Skin Structure

- Skin is the most accessible and largest organ of the body with a surface area of 1.7 m^2, compromising 16% of the total body mass of an average person.

- The main function of the skin is to provide a protective barrier between the body and the external environment against microorganisms, the permeation of ultraviolet (UV) radiation, chemicals, allergens and the loss of water.

- Skin can be divided into three main regions:

(1) The outermost layer, the epidermis, which contains the stratum corneum;

(2) The middle layer, the dermis and

(3) The innermost layer, the hypodermis.

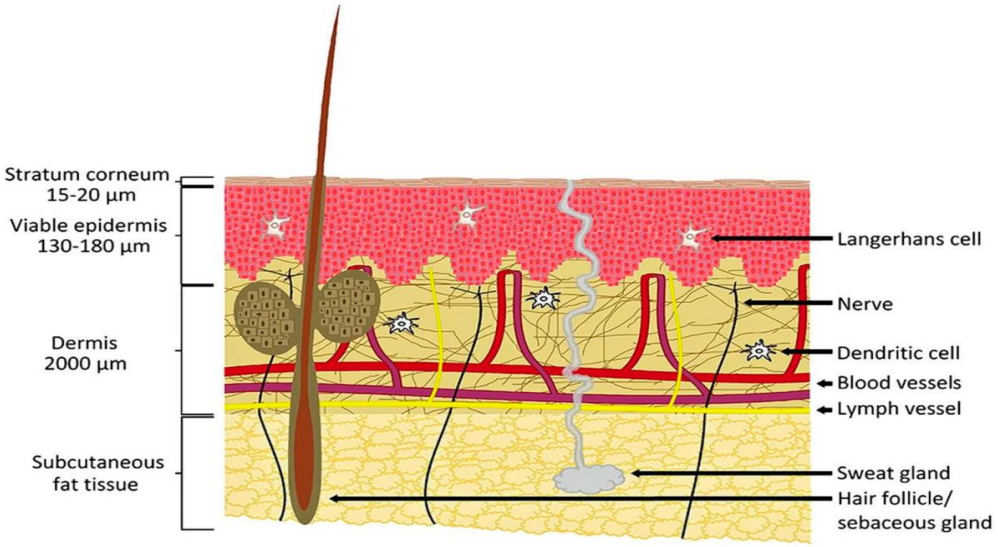

Figure No. 1: Anatomy of skin

1) Epidermis.

The epidermis is the outermost layer of the skin and varies in thickness with approximately 0.8 mm on the palms of the hands and soles of the feet. It consists of multi-layered regions of epithelial cells and the viable epidermis is often referred to as the epidermal layers below the stratum corneum. The cellular content of the epidermis consists predominantly of keratinocytes (approximately 95% of cells), with other cells of the epidermal layers including melanocytes, Langerhans cells, and Merkel cells.

The stratum corneum is the most superficial layer of the epidermis. It is in direct contact with the external environment and its barrier properties may be partly related to its very high density (1.4 g/cm3 in the dry state) and its low hydration of 15%–20%. The cells of the stratum corneum are composed mainly of insoluble keratins (70%) and lipid (20%). Water in the stratum corneum is associated with keratin in the corneocytes.

2) Dermis.

The dermis is approximately 2–3 mm thick and consists of collagenous (70%) and elastin fibers which give strength and elasticity to the skin. Blood vessels found in the dermis provide nutrients for both the dermis and epidermis. Nerves, macrophages and lymphatic vessels are also present in the dermis layer.

3) Hypodermis

The hypodermis or subcutaneous layer is the deepest layer of the skin and consists of a network of fat cells. It is the contact layer between the skin and the underlying tissues of the body, such as muscles and bone. Therefore, the major functions of the hypodermis are protection against physical shock, heat insulation and support and conductance of the vascular and neural signals of the skin. Hypodermis-resident fat cells account for approximately 50% of the body's fat with the other predominant cells of the hypodermis consisting of fibroblasts and macrophages.

Drug Penetration Routes

There are two possible routes of drug penetration across the intact skin, namely the transepidermal and trans appendageal pathways, which have been diagrammatically presented in Figure. The transepidermal pathway involves the passage of molecules through

the stratum corneum, an architecturally diverse, multi-layered and multi-cellular barrier. Transepidermal penetration can be termed intra- or inter-cellular. The intra-cellular route through corneocytes, terminally differentiated keratinocytes, allows the transport of hydrophilic or polar solutes. Transport via inter-cellular spaces allows diffusion of lipophilic or non-polar solutes through the continuous lipid matrix. The trans appendageal route involves the passage of molecules through sweat glands and across the hair follicles.

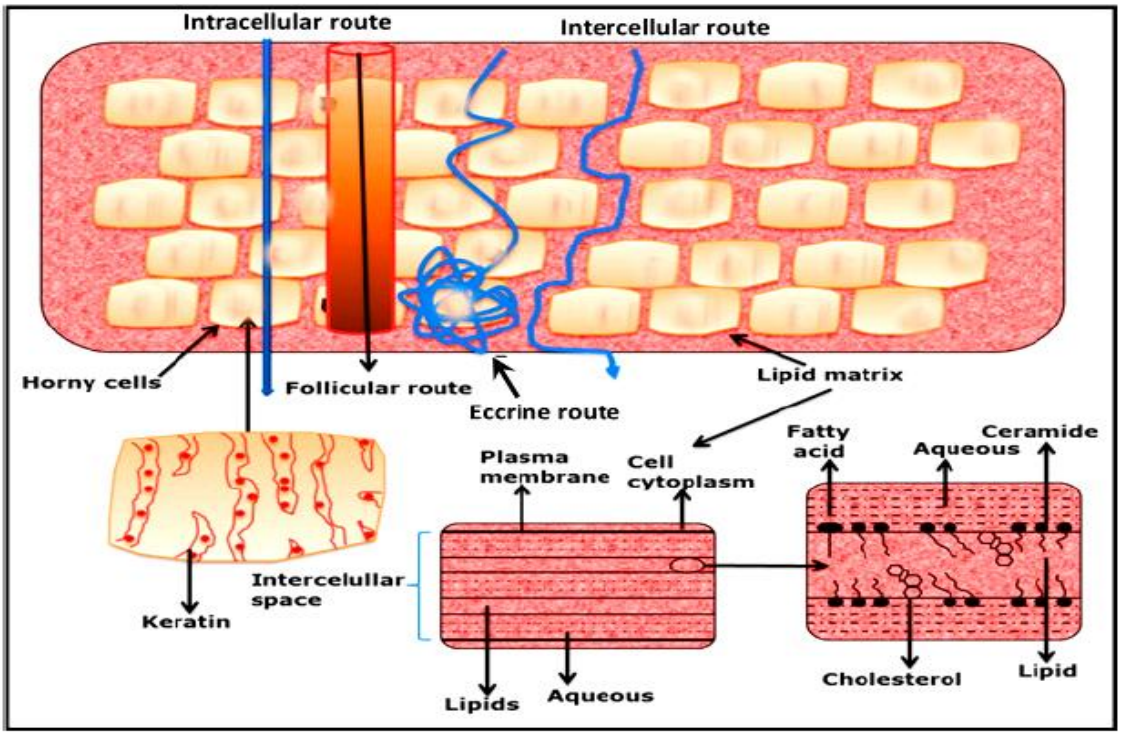

Figure No. 2: Possible drug penetration routes across human skin.

Percutaneous absorption

It is the penetration of substances into various layers of skin and permeation across the skin into the systemic circulation. Percutaneous absorption of molecules is a stepwise process involving:

i. Penetration: The entry of a substance into a particular layer of the skin.

ii. Partitioning from the stratum corneum into the aqueous viable epidermis.

iii. Diffusion through the viable epidermis and into the upper dermis.

iv. Permeation: The penetration of molecules from one layer into another, which is different both functionally and structurally from the first layer.

v. Absorption: The uptake of a substance into the systemic circulation.

Components of a transdermal patch

The main components to a transdermal patch are as follows.

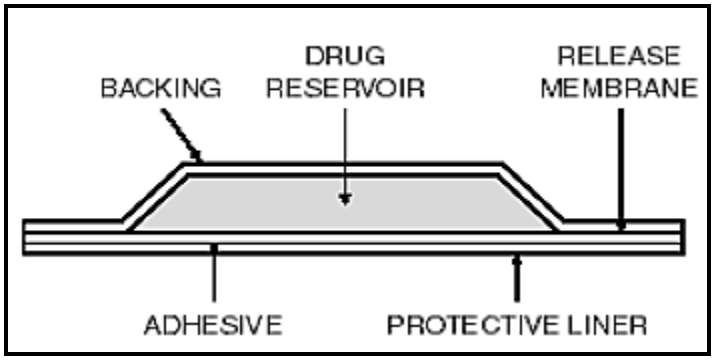

Figure No. 3: The main components to a transdermal patch

1. **Polymer matrix**– the backbone of TDDS, which control the release of the drug. The polymer should be chemically non-reactive, should not decompose on storage, should be non-toxic, cost should not be high. E.g.- cellulose derivatives, zein, gelatin, shellac, waxes, gums, Polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, Polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate.

2. **Drug**- The transdermal route is an extremely attractive option for drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first-pass metabolism, drugs with narrow therapeutic window, or drugs with a short half-life. eg fentanyl, nitroglycerine, etc.

3. **Permeation enhancers**- increase the permeability of stratum corneum to attain higher therapeutic levels of the drug. These are of three types-lipophilic solvents, surface active agents and two-component systems. E.g. DMSO.

4. **Adhesive**- increase the permeability of stratum corneum to attain higher therapeutic levels of the drug that increase the permeability of stratum corneum to attain higher therapeutic levels of the drug.

5. **Backing laminates**- should have low modulus or high flexibility. Eg-vinyl, polyethylene.

6. **Release liner**- Protects the patch during storage. The liner is removed before use.

7. **Other** excipients like plasticizers and solvents.

Types of Transdermal Patches

A. Single-layer Drug-in-Adhesive.

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

B. The multi-layer drug-in-adhesive.

It is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. One of the layers is for the immediate release of the drug and another layer is for control release of drug from the reservoir. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane Multi-layer Drug-in-Adhesive (but not in all cases). This patch also has a temporary liner-layer and a permanent backing. Unlike the Single-layer and Multi-layer Drug-in-adhesive systems, the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system, the rate of release is zero order.

C. Reservoir.

Unlike the Single-layer and Multi-layer Drug-in-adhesive systems, the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system, the rate of release is zero order.

D. Matrix

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

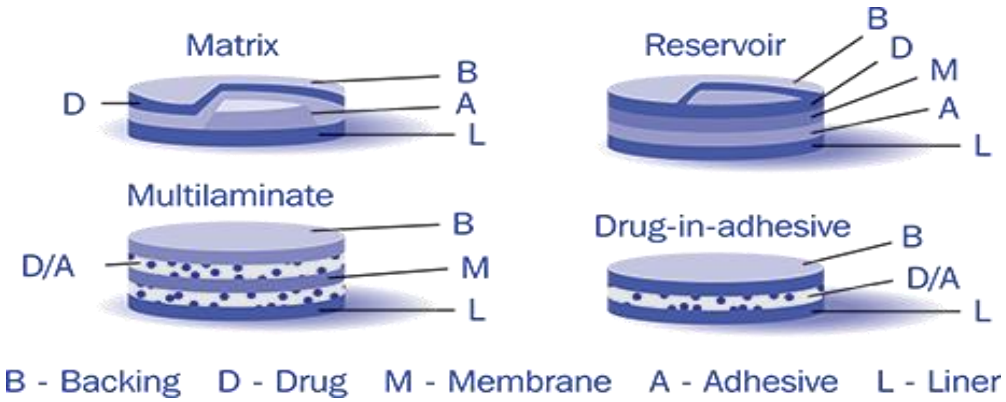

Figure No. 4: Types of Transdermal Patches

Evaluation Parameters for transdermal patch

1. The thickness of the patch	10. Water vapor transmission studies
2. Weight uniformity	11. Rolling ball tack test
3. Folding endurance	12. Quick Stick (peel-tack) test
4. Percentage of Moisture content	13. Probe Tack test
5. Content uniformity test	14. In vitro drug release studies
6. Moisture Uptake	15. In vitro skin permeation studies
7. Drug content	16. Skin Irritation study
8. Shear Adhesion test	17. Stability studies
9. Peel Adhesion test	

Techniques for Enhancement of Skin Permeabilisation

Technologies used to modify the barrier properties of the stratum corneum can be divided into passive/chemical or active/physical methodologies. Passive methods include the influencing of drug and vehicle interactions and optimization of formulation, to modify the stratum corneum structure. Passive methods are relatively easy to incorporate into transdermal patches such as chemical enhancers and emulsions. However, the main drawback

of passive methods may be a lag time in drug release incurred with obvious negative influence on rapid onset drugs, such as insulin.

Passive approaches

One of the most widely used passive approaches is the use of chemical penetration enhancers which facilitate drug permeation across the skin by increasing drug partitioning into the barrier domain of the stratum corneum, without long-term damage to the skin. Penetration enhancers have several mechanisms of action such as: increasing the fluidity of the stratum corneum lipid bilayers, interaction with intercellular proteins, disruption or extraction of intercellular lipids, increase of the drug's thermodynamic activity and increase in stratum corneum hydration. Several types of penetration enhancers are known and they can be divided into several groups based on their chemical structure, rather than their mechanism of action. Most of these have mixed modes of action so it is difficult to classify them according to this characteristic. Examples of commonly investigated.

Penetration enhancers are alcohols, sulphoxides, azone, pyrrolidones, essential oil, terpenes and terpenoids, fatty acids, water, and urea, However, the major limitation for penetration enhancers is that their efficacy is often closely correlated with the occurrence of skin irritation. Gels have been used in TDD and recent developments in the technology have introduced new variations of semisolid vehicles such as proteasomes and microemulsion gels into the field of penetration enhancers. Proniosomes are non-ionic based surfactant vesicles, they are known as ''dry niosomes'' because they may require hydration before drug release and permeation through the skin. Proniosomal gels have been used in TDD because they act as penetration enhancers that enhance the drug permeation from the skin barrier. Upon hydration proniosomesare converted into niosomes which are capable of diffusing across the stratum corneum and then adhere to the cell surface which causes a high thermodynamic activity gradient of the drug at the vesicle/stratum corneum surface, thus acting as the driving force for the penetration of lipophilic drugs across the skin.

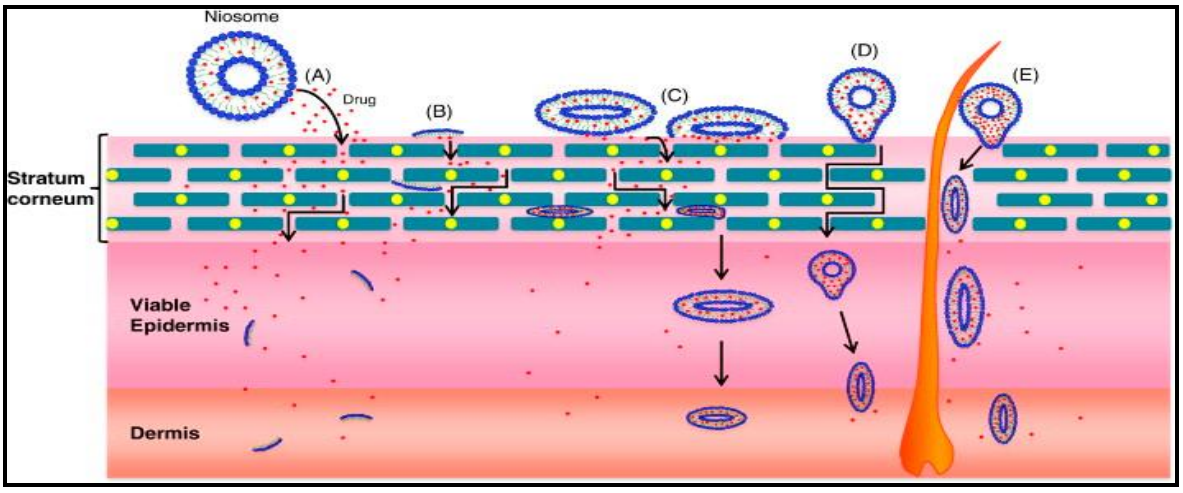

Figure No. 5: Passive approaches

Possible mechanisms of action of surfactant vesicles for dermal and transdermal applications

(**A**) Drug molecules are released by niosomes;

(**B**) Niosome constituents act as a penetration enhancer;

(**C**) Niosome adsorption and/or fusion with stratum corneum;

(**D**) Intact niosome penetration through the intact skin;

(**E**) Niosome penetration through hair follicles and/or pilosebaceous units.

A. Ultrasound Devices.

Ultrasound is an oscillating sound pressure wave that has long been used for many research areas including physics, chemistry, biology, engineering, and others in a wide range of frequencies. Ultrasound, sonophoresis, or phonophoresis can be defined as the transport of drugs across the skin by application of ultrasound perturbation at frequencies of 20 kHz–16 MHz which has a sufficient intensity to reduce the resistance of the skin. The use of ultrasound has resulted in the effective delivery of various categories and classes of drugs, regardless of their electrical characteristics, by increasing skin permeability. These drugs have included hydrophilic and large molecular weight drugs. However, the mechanism of action is still not clearly understood or characterized. The proposed mechanisms by which ultrasound affects tissues and cells include thermal effects and cavitation effects caused by

the collapse and acoustic streaming which can be explained as an oscillation of cavitation bubbles in the ultrasound field. Ultrasound can increase the temperature of the insulating medium (the skin) by the absorption of the sound waves with a frequency greater than the upper limit of the human hearing range. The higher the medium's absorption coefficient, the higher the increase in temperature and thus the greater the thermal effect. All recent studies point out that cavitation is believed to be the predominant mechanism in the enhancement of TDD via ultrasound treatment.

The concept of ultrasound for use in TDD was initially reported by Fellinger and Schmidt in 1950 for the successful treatment of polyarthritis using hydrocortisone ointment combined with sonophoresis. However, the first ultrasound device for the transdermal application was approved in 2004 by the FDA for the delivery of local dermal anesthesia by the Sontra Medical, SonoPrep ®. Since that time, ultrasound has been widely used as a TDD system in the treatment of many other diseases including bone joint diseases and bursitis. Many challenges must be overcome before such devices gain commercial acceptance, however. Some of these challenges include the availability of easy-to-use devices the determination of the duration of treatment required; gaining a full understanding of how the technology functions; broadening of the range of drugs that can be delivered and evaluation of the safety profiles of the devices. Examples of undesirable side effects of ultrasound approaches were observed by Singer *et al.* (1998) when it was shown that low-intensity ultrasound caused minor skin reactions in dogs while high-intensity ultrasound was capable of inducing second-degree burns. Limitations such as this must be overcome before these innovations can garner full acceptance.

B. Electroporation.

The two major means of electrically-facilitated TDD are iontophoresis and electroporation.

In electroporation, cells are temporarily exposed to high intensities of electric pulses that lead to the formation of aqueous pores in the lipid bilayers of the stratum corneum, thus allowing the diffusion of drugs across the skin. The technique was first described by Neumann *et al.* in 1982. Usage of high voltage pulses (50–500 V) for short times of only one second has been shown to increase transport across the skin for different molecular weight drugs ranging from small e.g., fentanyl, timolol, or calcein, to high molecular weight drugs such as LHRH, calcitonin, heparin or FITC–dextran with molecular weights up to 40 kDa. However, the

main drawbacks are the lack of quantitative delivery, cell death with high fields and potential damage to labile drugs, e.g., those of protein origin.

C. Iontophoresis.

Iontophoresis involves the application of physiologically acceptable electrical currents (0.1–1.0 mA/cm2) to drive charged permeants into the skin through electrostatic effects and make ionic drugs pass through the skin into the body by its potential gradient.

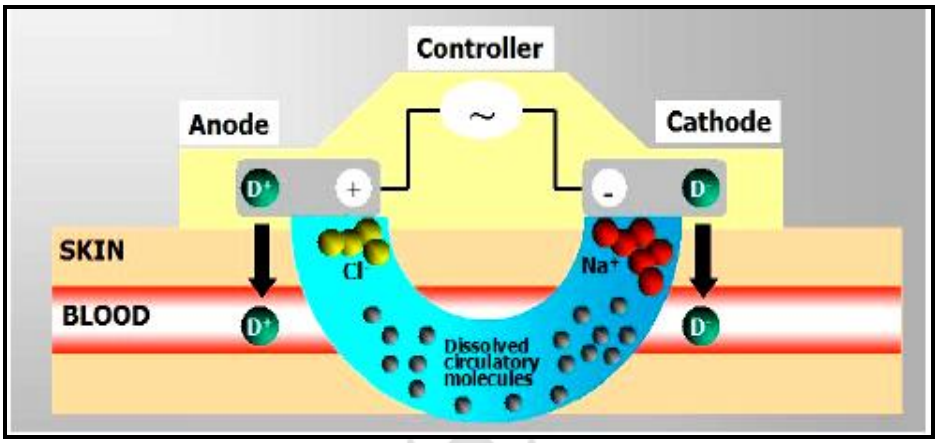

Figure No. 6: Schematic representation of an iontophoresis patch.

Unlike other transdermal enhancement methodologies, it acts mainly by involving a second driving force, the electrical potential gradient as a companion to the concentration gradient across the skin since uncharged species can also be delivered through electro-osmosis.

D. Radiofrequency (RF) Thermal Ablation.

Radiofrequency (RF) thermal ablation involves the placement of a thin, needle-like electrode directly into the skin and application of high-frequency alternating current (~100 kHz) which produces microscopic pathways in the stratum corneum, through which drugs can permeate. Exposure of skin cells to a high frequency (100–500 kHz) causes ionic vibrations within the tissue which attempts to localize the heating to a specific area of the skin and thus ablate the cells in that region, resulting in drug transport across the skin. This technology may enable transdermal delivery of a wide variety of hydrophilic drugs and macromolecules using a low-cost, fully disposable device.

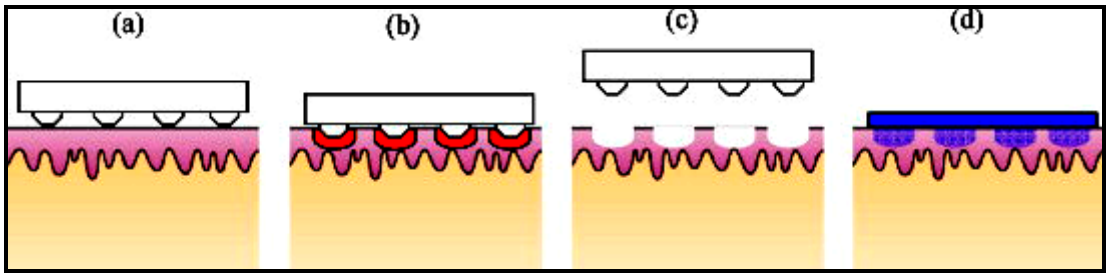

Figure No. 7: Schematic diagrams of drug delivery using thermal ablation

(**a**) Micro-electrodes are pressed against the skin,

(**b**) Skin is ablated via heating due to RF energy or resistive heating in the electrodes,

(**c**) After removing the ablation device,

(**d**) Micropores formed.

Major Depressive Disorders.

Depression is a chronic mental disorder that causes changes in mood, thoughts, behavior and physical health. It's a common but serious disease that can take away a person's ability to enjoy life and cause a decline in capacity to undertake even the simplest daily tasks. Other than its chronic nature, symptoms associated with this mental disorder are often recurring and life-threatening. According to the World Health Organization (WHO), unipolar depression is one of the leading causes of disability-adjusted life year (DALY) and approximately 350million people worldwide are said to suffer from this mental disorder.

CONCLUSION

Successful transdermal drug application requires numerous considerations. Bearing in mind that the basic functions of the skin are protection and containment, it would seem exceptionally difficult to target the skin for drug delivery. However, with our greater understanding of the structure and function of the skin, and how to alter these properties, more and more new drug products are being developed for transdermal delivery. The properties of the drug, the characteristics of the transdermal devices and the status of patient's skin are all important for safe and effective drug delivery. The transdermal drug delivery system could be one day one of the best novel drug delivery system. Understanding how the use of TDS patches may alter the treatment paradigm for patients is important. The effects of

regional blood flow and permeability of the skin, dose titrations, combination treatment with patches and tablets, cumulative effects of long-term TDS use and drug interactions are yet to be fully understood. Can be safely administered without dietary modification to avoid cheese reaction. The pharmaceutical industry should not be shortsighted when developing a novel drug for the treatment of a highly prevalent disorder such as MDD.

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