A Review: Transdermal Drug Delivery System: Future Direction

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Abstract- *A Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. The transdermal drug delivery system is one of the novel drug delivery systems which overcome arise from the conventional dosage. Transdermal patches are pharmaceutical preparation of varying sizes, containing one or more active ingredients to the systemic circulations. The review gives valuable information about the transdermal patch like its advantage, disadvantage, mechanism of action, types of transdermal patch, factors basic components, methods and evaluation, application of a transdermal patch. A wide variety of pharmaceuticals are now available in transdermal patch form. Transdermal drug delivery systems (TDDS) are dosage forms that involve drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. However, the skin, in particular the stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. During the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. It is intended to improve the therapeutic efficacy and safety, maintain the steady state plasma level of drugs and overcome the significant drawbacks of the conventional oral dosage forms and parenteral preparations. It is ideally suited for the diseases that demand chronic treatment with frequent dosing. This review deals with a brief insight on the introduction, the formulation aspects, the physical and chemical enhancers explored or being explored to enhance the transdermal delivery of drugs across the stratum corneum, the evaluation parameters(physicochemical, in vitro, in vivo studies) and therapeutic applications of TDDS.*

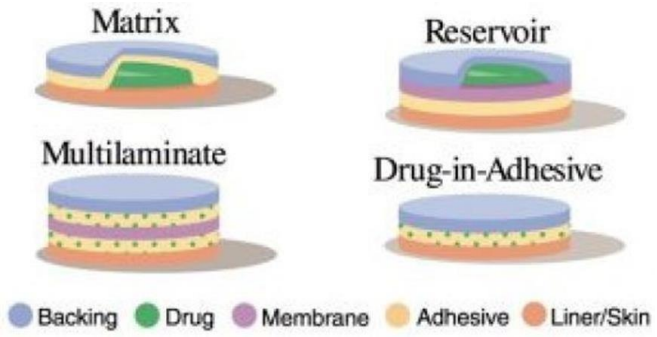
Keywords- Transdermal drug delivery system; Hydrin Rubber; Silicon Rubber; Polyvinylalcohol; Transdermal pat

I. INTRODUCTION

The transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic sideeffects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation[1]. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Moreover, it overcomes various side effects like painful delivery of the drugs and the firstpass metabolism of the drug occurred by other means of drug delivery systems. Many drugs which can be injected directly into the bloodstream via skin have been formulated.. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first-pass metabolism espectively1. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into the systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery systems such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems, etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first-pass metabolism, enhancement of therapeutic efficiency, and maintenance of steady plasma level of the drug. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with ravel, particularly by sea. With the introduction of the first transdermal patch of scopolamine in 1979, the transdermal drug delivery has made an important contribution to the medical practice in the past three decades but is yet to be recognized as a major alternative to the oral delivery and hypodermic injections (Langer, 2004; Prausnitz et al., 2008). The major obstacle for the topical drug delivery is the low diffusion rate of drugs across the relatively impermeable, outermost skin layer, the stratum corneum

(Bouwstra et al., 2002). Besides, the intercellular lipid region, the major pathway for lipophilic drugs, has a diffusion path length of about 500mm which is much longer than the thickness of stratum corneum (20 mm) (Gaur et al., 2009; Phillips et al., 1995). Tablets and injections have been the traditional way to take medications; new options are becoming increasingly popular.

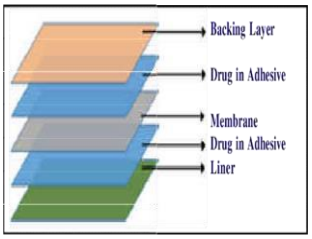
TYPES OF TRANSDERMAL PATCHES



SINGLE-LAYER DRUG IN ADHESIVE:

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

Multi-layer drug in adhesive: This type is also similar to the single-layer but it contains an immediate drug-release-layer and the other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the release of the drug. This patch also has a temporary liner layer and a permanent backing.



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Vapour patch: The patch containing the adhesive layer not only serves to adhere the various surfaces together but also serves to release the vapor. The vapor patches are new to the market, commonly used for releasing the essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduce cigarette smoking conditions.

Reservoir system: In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane.

The drug releases only through the ratecontrolling membrane, which can be microporous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel, or dispersed in a solid polymer matrix. The hypoallergenic adhesive polymer can be applied as an outer surface polymeric membrane that is compatible with the drug.

Matrix system:

A)Drug-in-adhesive system: This type of patch is formulated by mixing the drug with adhesive polymer to form a drug reservoir. It is then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-inadhesive. The system is considered to be compatible with a wide variety of drugs. Moreover, the system is competent to deliver more than one drug in a single patch. It offers advantages in reduced size and thickness and improved conformability to the application site, helping drive patient preference provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeant very low and the resulting concentration difference across the epidermis provides the essential concentration gradient for transdermal permeation.

Matrix-dispersion system: The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with a definite shape and thickness. This drug-containing polymer disk is fixed onto an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of the adhesive rim.

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Micro reservoir system: The system consists of microscopic spheres of drug reservoirs that release drugs at a zero-order rate for maintaining constant drug levels. A micro reservoir system is a combination of the reservoir and matrixdispersionsystem. The aqueous solution of the water-soluble polymer is mixed with the drug to form a reservoir. It

is then followed by dispersing the solution homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross-linking agents are added to stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer[8]

Components OfTrandermal Drug Delivery System

- Polymer matrix
- Drug
- Permeation enhancers
- Pressure sensitive adhesive
- Backing laminate

Penetration enhancers –

Permeation enhancers are defined as substances that are capable of promoting penetration of drugs into skin and transdermal therapeutic systems offers a more reliable mean of administering drug through the skin.

Advantages –

1. Hepatic first-pass metabolism, salivary metabolism, and intestinal metabolism are avoided.
2. The ease of usage makes it possible for patients to self-administer these systems.
3. In case of an emergency, removing the patch at any point of time during therapy can instantly stop drug input.
4. Since the composition of skin structurally and biologically is the same in almost all humans, it is minimal inter and intrapatient variation.
5. Drugs showing gastrointestinal irritation and absorption can be suitably administered through the skin.

- There is the possibility of skin irritation due to one or many of the formulation components.
- Binding of the drug to the skin may result in dose dumping.
- It can be used only for chronic conditions where drug therapy is desired for a long period of time including hypertension, angina, and diabetes.
- Lag time is variable and can vary from several hours to days for different drug candidates.
- Cutaneous metabolism will affect the therapeutic performance of the system[2].

Polymer used in transdermal drug delivery system –.

Rservoir system –

The drug reservoir is placed between an impermeable backing layer and a rate-controlling membrane in this system. The drug can be released through a rate-controlling membrane that is either microporous or nonporous. The drug can be in the form of a solution, suspension, gel, or dispersed in a solid polymer matrix in the drug reservoir compartment.

II. FACTORS AFFECTING TRANSDERMAL PERMEATION

1)Biological factor

Skin conditions: The intact skin itself acts as a barrier but many agents like acids, alkali cross the barrier cells and penetrates through the skin, many solvents open the complex dense structure of horny layer Solvents like methanol, chloroform remove lipid fraction, forming artificial shunts through which drug molecules can pass easily.

Skin age: It is seen that the skin of adults and young ones are more permeable than the older ones but there is no dramatic difference. Children show toxic effects because of the greater surface area per unit body weight. Thus, potent steroids, boric acid, hexachlorophene have produced severe side effects.

Blood Supply: Changes in peripheral circulation can affect transdermal absorption. Skin metabolism: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So, skin metabolism determines the efficacy of drug permeated through the skin. Species differences: The skin thickness, density of appendages, and keratinization of skin vary from species to

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

Temperature and pH: The permeation of the drug increases ten folds with temperature variation. The diffusion coefficient decreases as the temperature falls

III. APPLICATION OF TDDS

- The antihypertensive drug like clonidine and ketoprofen, the non-steroidal antiinflammatory drug are also available in the form of transdermal patches.
- Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as postmenopausal osteoporosis.
- Other transdermal patches for hormone delivery include the contraceptive patch.

- Transdermal delivery agent for Attention Deficit Hyperactivity Disorder (ADHD).
- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl and Buprenorphine.

Future of Transdermal Drug Delivery System

Future aspects in Drug delivery system include liposomes, Niosomes and micro emulsion. Aim of this development is to improve delivery of drug that has low inherent solubility in most of classical formulation excipients. A wide range of potential drugs for delivery like steroids, antifungal, antibacterial, interferon, methotrexate, local anesthetics are formulated. The market for transdermal patches has been estimated to increase in future and has recently experienced annual growth of at rate of 25%. This figure will increase in future as novel devices emerge and list of marketed transdermal drug increases. Transdermal delivery of analgesics is likely to continue to increase in popularity as there are further improvements in design. Research is being performed to increase safety and efficacy. To improve practical matters such as the experience for the wearer of the patch, and also to provide more precise drug delivery associated with increased duration of action. Other potential improvements include improved transdermal technology that utilizes mechanical energy to increase drug flux across the skin either by altering the skin barrier or increasing the energy of the drug molecules. After the successful design of patches using iontophoresis, various modes of 'active' transdermal technologies are being investigated for different drugs. These include electroporation (short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (uses heat to make the skin more permeable and to increase the energy of drug molecules). Magnetic energy, magnetophoresis, has been investigated as a means to increase drug flux across the skin. The transdermal patch may be an underutilized tool for management of acute and chronic pain. With improved delivery and a wider range of analgesics, we expect the popularity and applicability of this modality to deliver drugs to increase. In current scenario, transdermal route of drug delivery system in comparison with oral treatment as the most successful innovative research area in new drug delivery system, with around 40% of the drug delivery candidate products under clinical trails related to transdermal or dermal system. The transdermal drug delivery systems (TDDS) have been designed as an alternative, safest and easy route for systemic drug delivery. The systemic drug administration though skin holds several advantages such as maintenance constant drug level in blood plasma, less number of side effects, and improvement of bio availability by circumvention of hepatic first pass metabolism and increase patient compliance with respect to drug regime used for treatment. In recent times, skin considered as a safest port for drug administration, to provide continuous drug release into systemic circulation [17].

IV. CONCLUSION

TDDS has gained realistic potential as the next generation drug delivery system for the prolonged, controlled release of both hydrophobic and hydrophilic drugs, efficiently addressing the low oral bioavailability and inconvenience of injections. Future research will be aimed at better transdermal device design with greater understanding of the different mechanisms of biological interactions with permeation enhancers and improving the flux for a wide variety of molecules especially macromolecules and vaccines using cost effective, novel physical enhancement techniques along with the existing chemical enhancers. Less absorption, more uniform plasma levels, improved bioavailability, decreased adverse effects, efficacy, and product quality are all advantages of using a transdermal drug delivery system for therapeutic therapy. When it comes to providing medication to small children and the elderly, transdermal distribution enhances and simplifies patient compliance. Penetration enhancers are used to increase the drug availability through intact skin. This article discusses the nature of the skin and its barrier, as well as penetration enhancers, formulation, and evaluation of transdermal patches. The transdermal medication delivery system has the potential to become one of the greatest innovative drug delivery systems in the future. 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.

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