REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM

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KEYWORDS:

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. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method. A wide variety of pharmaceuticals are now available in transdermal patch form.
INTRODUCTION:
During the last two decades, significant advances have been made in the controlled release drug delivery of therapeutic agents. In the early stages of research on controlled release drug delivery, major emphasis was focused on the development of zero order release devices. Current technology has improved to such a level that delivery of some drugs at a constant rate for certain period of time ranging from days to years is not a major issue anymore. Transdermal patches deliver drugs at a constant rate for 24 hours or longer and the Norplant system releases progestin levonorgestrel from silicon rubber tubular capsules for several years [1].
The premise of zero order release is to maintain a constant drug concentration in blood for an extended period of time. The zero order release of a drug, however, does not necessarily result in a constant drug concentration in blood. The absorption of the drug by the body usually does not follow the zero order kinetics, except when the drug is directly delivered into the blood stream by an infusion pump. The nonzero order drug absorption is still effective in most cases as long as the drug concentration is maintained between the minimum effective and maximum safe concentrations. The drug delivery needs to be feedback controlled depending on the drug concentration in blood pharmacologic effect. In many situations, drug needs to be released only when the body requires it. For example, insulin is required only when the glucose concentration in the blood is increased. Once the glucose level is decreased, no further insulin is required [2].
The term controlled release has a meaning that goes beyond the scope of sustained drug action. It implies a predictability and reproducibility in the drug release kinetics, which means that the release of drug ingredients from a controlled release drug delivery system proceeds at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another.
Treatment of illness through medication has entered an era of rapid growth. History reveals that topical application of drugs has been an ancient practice as evidenced by application of ointments on various parts of the body for various purposes. Now a days also a range of topical preparations like ointments, creams etc are used. Theoretically drugs can be applied topically as powders, sprays or solutions. The topical preparations generally carry drugs for local action on the tissues near the site application.
However, recently the skin has been increasingly employed for sustained delivery systems, easy to apply and afford precise modulation of the rate of drug entry into the systemic circulation. Through such drug delivery excessive dumping of the drug into the blood, otherwise associated with other dosage forms, can be minimized. Poor patient compliance is a frequent problem in daily clinical practice with other dosage forms i.e. oral dosage forms or IV or IM dosage forms etc [3].
The unfavorable pharmacokinetic of the drug, the inconvenience of the standard form of such drug application and the side effects due to the administration route often are the reasons of poor patient compliance.

Delivery via the transdermal route is an interesting option in this respect because transdermal route is convenient and safe. This offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of action, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and Pharmacological response, avoiding the fluctuation in drug levels, inter and intra-patient variations and most importantly, it provides patient compliance as the drug delivery is painless. Transdermal therapeutic systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation.

Transdermal drug delivery systems can also be programmed to deliver a drug from 1 to 7 days.

1) Scopolamine releasing transdermal therapeutic systems - scopolamine patch for motion sickness is applied backside of the ear and Transderm-Nitro is applied on the chest. When a pharmacologically active material has to be presented to the skin, an occlusive or allergic response is significant, limits have to be determined for the acceptability of the undesired effect [4].

2) Nitroglycerin Transdermal patches - Diffusion of nitroglycerin from drug delivery patches through micro-fibre filters using Fourier transform infrared photoacoustic spectrometry. A spectrum was obtained from the sticky face of the Nitro-Dur patch, so that the absorption peaks of nitroglycerin could be located [5].

3) Isosorbide dinitrate releasing Transdermal therapeutic system for treatment of Angina pectoris. The skin has the ability to metabolize isosorbide dinitrate in porcine skin, it is limited and easily saturated compared to the ability of the liver to metabolize drugs presented it via the portal vein [5].

The various classes of drugs that can be given by Transdermal therapeutic systems are Antihypertensive, Antihistamine, Anti-inflammatory, Analgesic, Anti-arthritis, Steroidal and Contraceptive drugs.
Skin as a site for drug infusion

Fig. 2.1 Structure of human skin

The skin of an average adult body covers around 2m² of the surface area and receives 1/3rd of all blood circulating through the body. It has a thickness of only a fraction of mm, the skin separates underlying blood circulation network from the outside environment.

- An average human skin surface is known to contain, on the average, 40 to 70 hair follicles and 200 to 250 sweat ducts on each square cm of skin area.
- Presently there is an increasing recognition that skin can also serve as the part of administration for systemically active drugs.
- In this case, the drug applied topically will be absorbed first into blood circulation and then be transported to target tissues, which would be rather remote from the site of drug application to achieve its therapeutic doses.

The skin is a multi layer organ composed of many histological layers. It is generally described in terms of three major tissue organs.

1. The Epidermis
2. The Dermis
3. The hypodermis.
2.1.1. The Epidermis

Epidermis is the most superficial layer and is composed of stratified squamous type of epithelium. From outside inward stratified epithelium may be divided into 5 layers, they are,

- a. Stratum Corneum
- b. Stratum Lucidum
- c. Stratum Granulosum
- d. Stratum Spinosum
- e. Stratum Germinatum

**a. Stratum Corneum**

The Stratum Corneum is most superficially placed and consists of many layers of compacted, flattened, dehydrated, and keratinized cells. They are dead cells converted into proteins and are continuously shed. The cell outlines are indistinct and the nuclei are absent. The stratum Corneum has a water content of only ~20% as compared to normal 70% in physiologically active Stratum Germinatum. This layer is thickest at the sole and the palm and thinnest at the lip. Hairs, loops, nails, feathers, scales, etc., are special outgrowths of this layer.

**b. Stratum Lucidum**

This is a thin more or less transparent layer 3 to 5 cells deep placed below the stratum corneum. The cell outlines are indistinct and the nuclei are absent. The cells contain droplets of “eleidin” which is the precursor of keratin.

**c. Stratum Granulosum**

Stratum Granulosum is situated below the stratum Lucidum and consists of 3 to 5 layers of flattened polyhedral cells filled with keratohyalin granules which takes a deep stain with haematoxylin.

**d. Stratum Spinosum**

This is a broad layer of variable thickness and is made up of polyhedral cells is apparently covered with minute spines, which interdigitate with similar spines of adjacent cells. There are consequently known as “prickle cells”. As the microscopic studies indicate that the prickle cells are in fact cytoplasmic protrusions and the branches from two cells actually do not have cytoplasmic continuity, but attached by well developed cytoplasmic nodes called as desmosomes.

**e. Stratum Germinatum**

This is a growing layer is composed of a single layer of columnar epithelium which has got transverse, thin, short cytoplasmic processes on its basal lamina by means of which they anchor the epithelium to the underlying dermis. These cuboidal to columnar cells with oblong nuclei, placed perpendicularly on the basement membrane, produce new cells to replace those of the above layers by the process of mitosis.
2.1.2. The Dermis

The true skin is made up of connective tissue and lies below the epidermal layer which it supports and binds to the underlying tissues. It is made up chiefly of collagenous and elastic fibres which provide it with a tensile strength equal to that of a thin steel wire. This layer is utilized for the production of leather after chemical processing. From the structural point of view the superficial part of the dermis is compact and forms the papillary layer because it sends innumerable finger-like projections into the prickle cell layer of epidermis. The deeper part of the dermis is composed of rather loose connective tissue and is infiltrated with fat. The reticular layer of the dermis merges imperceptibly into the subcutaneous layer of fat.

2.2. Functions of skin

Protection
Stratum Corneum which is the outermost layer is horny and formed by the keratinized stratified epithelial cells resist the action of external agencies. It protects the internal individual injury and bacterial invasion. The nails are also defensive appendages of the skin.

Regulation of body temperature
Cutaneous vasoconstriction diverts the blood to the interior of the body and so diminishes heat loss. This is an important mechanism of protection against cold environment. Vasodilatation of the skin helps in elimination of heat from the body.

General sensation
The skin serves as the medium for receiving the general sensation. Tough, pain, temperature, etc., are subserved by the respective nerve endings present in the skin. The hair roots are richly supplied with nerves. Consequently, slight movement of the hair, such as by a blast of wind arouses. In this way hairs help the sensory functions of the skin.

Gaseous exchange
Absorption of oxygen and excretion of CO₂ may go on to a considerable extent through the skin in those animals whose skin is thin and moist, e.g. frogs. It is said that it can be carried to such an extent that these animals may live even after the extirpation of the lungs or in the hibernating period when the lungs do not function.

Absorption
Waxy layer hinders water absorption though the skin. But the skin is not completely waterproof and on prolonged exposure to water, there is water absorption causing swelling of the Stratum corneum. Lipids are easily permeable through the skin. Lipid-soluble substances like vitamins are easily absorbed through the skin [6].
2.3. Transdermal permeation of drugs

The drug molecules can diffuse not only through skin layers but also through the openings of the hair follicles and the sweat gland regions. The Stratum Corneum is a complex layer and is capable of binding some drug molecules. The steady state Transdermal flux of drugs through the skin can be mathematically represented by following equation

\[ Ps = \frac{Ds}{Cs} \]

Where,
- \( Ps \) = permeability coefficient
- \( Ds \) = Transdermal flux
- \( Cs \) = Concentration difference across the skin barrier.

One of the major problems faced in Transdermal permeation of the drugs is the low penetration rate. The Stratum Corneum is the rate-determining barrier.

Incorporation of drug into elastic vesicles of dilauryl phosphotidyl choline and hepatoxyethylene lauryl ether leads to enhancement of penetration. Freeze-Fracture Electron Microscopy confirmed this fact. These elastic vesicles induce large changes in structure of Stratum Corneum thus enabling greater penetration of drugs.

2.4. Advantages of Transdermal patches

- Provide relatively steady and sustained drug concentration in plasma in contrast to conventional systems where peaks and troughs are a common feature.
- Variability due to factors such as pH, intestinal motility, food intake, etc, which make vast difference in the bioavailability of the drugs given through oral route, are not existent.
- The hepatic first pass metabolism is avoided.
- A constant rate of absorption is possible in a vast variety of adverse patient population.
- Ease of administration and patient convenience.
- Drug input terminable by mere removal of the Transdermal patches.
- Drugs that cause gastrointestinal upset can be good candidates for Transdermal delivery because this method avoids direct effects on stomach and intestine.
- Increased therapeutic value due to avoidance of hepatic first pass effect, gastrointestinal irritation and low absorption problem.
- Drugs that are having short biological half-life can be given by this therapeutic systems and it also reduces dosing frequency.
- Transdermal patches are used for cessation of tobacco smoking.
2.5. Disadvantages of Transdermal patches

- Can be used only for drugs, which require very small plasma concentrations for action.
- Local irritation and arrhythmia are possible. Enzymes in epidermis or derived from microorganisms present on the skin may denature the drugs.
- Another significant disadvantage of Transdermal drug delivery is that skin is less permeable because it serves as protective barrier for the entry of foreign particles.
- In order to maintain constant release states, transdermal patches must contain surplus of active drug.

2.6. Types of Transdermal patches

The various Transdermal technologies can be classified into four approaches as follows:

1. Membrane modulated systems
2. Matrix diffusion control systems
3. Micro reservoir systems
4. Adhesive diffusion controlled systems.

1. Membrane modulated systems

![Fig. 1.2 The cross section of Membrane modulated systems](image)

In this system the drug reservoir is covered on all sides but one, which consists of the rate controlling polymeric membrane. Rate release variations are possible by changing in the composition and thickness of the polymer membrane. The dose quantum can be altered by varying the surface area of the patches. The basic design of such systems is figuratively illustrated above.

2. Matrix diffusion control systems

![Fig. 1.3 The cross-section view of Matrix diffusion control systems](image)
3. **Micro reservoir systems**

![Image of Micro reservoir systems](image_url)

Fig. 1.4 The cross-section view of Micro reservoir systems

This can be considered a combination of the reservoir and matrix diffusion type drug delivery systems. Here the drug reservoir is formed by first suspending the drug solids in an aqueous solution of water soluble liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer. eg. Silicon elastomers by high energy dispersion technique to form several discrete, unleachable microscopic spheres of drug reservoirs. The quick stabilization of this thermodynamically unstable dispersion is accomplished by immediately cross-linking the polymer chains insitu. This produces a medicated polymer disc with a constant surface area and a fixed thickness.

4. **Adhesion diffusion controlled systems**

![Image of Adhesion diffusion controlled system](image_url)

Fig. 1.5 The cross-section view of adhesive diffusion controlled system

This type of drug delivery system is a simplified version of the membrane modulated drug delivery system. Instead of completely encapsulating the drug reservoir in the compartment fabricated from a drug impermeable metallic plastic backing, in this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymers and then spreading the medicated adhesive, by solvent casting, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer [8].
Inflammation may be defined as the series of changes that occur in living tissues following injury. The injury which is responsible for inflammation may be brought about by a variety of conditions such as physical agents like mechanical trauma, ultra-violet or ionizing radiation, chemical agents like organic and inorganic compounds.

Almost three decades ago, steroids namely: prednisolone, dexamethasone, betamethasone and hydrocortisone were considered to be the drug of choice as anti-inflammatory agents. Owing to the several adverse effects caused by either short term or long term steroid therapy, these have been more or less replaced by much safer and better tolerated non-steroidal anti-inflammatory drugs. The seriousness and enormous after effects of steroid therapy necessitated an accelerated research towards the development of non-steroidal anti-inflammatory drugs since the past three decades. A good number of these agents have been put in to clinical usage widely and confidently thereby exhibiting positive therapeutic efficacy accompanied with fewer untoward reactions.

The mechanism of action principally responsible for most of the NSAID’s seems to be inhibition of prostaglandin synthesis by causing almost complete blockade of the activity of the precursor or enzyme, cyclogenase. In fact, there are two isozymes that have been duly recognized for the cyclo-oxygenase enzyme (COX 1 and COX 2). However, both isozymes practically perform the same reactions, but COX-1 is the isozyme that is found to be active under normal healthy conditions. Importantly, in rheumatoid arthritis, COX-2 which is usually found to be quite dormant, gets duly activated and yields a substantial quantum of inflammatory prostaglandins. Based on these critical facts and observations a vigorous concerted effort is being geared up to develop such newer drug substances that are specifically selective for the COX -2 isozyme, with a view to arrest particularly the production of the inflammatory prostaglandins.

In general, there exists virtually very little difference between the therapeutic efficacy of different NSAID’s, ascertain patients would respond to one “drug” better than another. In reality, it is almost difficult to predict the best suitable drug for a patient; thus, it invariably necessitates to arrive at the best-fit-drug via trial and error only [9].

CONCLUSION:
Transdermal drug delivery systems have been used as safe and effective drug delivery devices since 1981. A lot of progress has been done in the field of Transdermal Patches. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers. Many new researches are going on in the present day to incorporate newer drugs via this system. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care.
In recent years the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity.

3. REFERENCES