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NOVEL APPROACHES IN TRANSDERMAL DRUG DELIVERY SYSTEM

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Abstract

ransdermal patches are designed to deliver a therapeutically effective amount of drug across the skin membrane. In order to deliver therapeutic agents through the skin for systemic effects, the great physicochemical, morphological and biological properties of the skin are taken into consideration. Transdermal drug delivery system offers controlled release of drug substance into patient's skin; it enables a mild blood level profile, resulting in reduced systemic side effects over the other dosage forms. Transdermal delivery is more convenient and painless technique for administration of drugs. It is likewise significant because of its interesting benefit such as less absorption, more uniform plasma levels, improved bioavailability, decrease side effect, efficacy and quality of the product. Transdermal dose structures may give clinicians a chance to offer more therapeutic alternatives to their patients to upgrade their consideration. The basic goal of TDDS is to administer medications at a predefined pace into systemic circulation through the skin with little inter- and interpatient variance. The basic goal of TDDS is to administer medications at a predefined pace into systemic circulation through the skin with little inter- and interpatient variance.

Keywords: Transdermal drug delivery system (TDDS), Transport mechanism, Permeation mechanism, Iontophoresis, Microneedles.

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INTRODUCTION

Transdermal drug delivery system is defined as the topically administered medications, which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate". Drugs are administered by various routes such as oral, parenteral, nasal, transdermal, rectal, intravaginal, ocular etc. Among all of them, oral route is most common and popular but this route of administration has some drawbacks like first pass metabolism, drug degradation in gastrointestinal tract due to pH, enzyme etc. Now a day many drugs are administered orally, but they are observed not more effective as desired so to upgrade such character TDDS was created. Drug delivery administered by the skin and attain a systemic effect of drug is called as transdermal drug delivery system. The transdermal drug delivery system, also known as patches is a painless way of systemically administering therapeutically active medications by placing a drug formulation on intact and healthy skin. The oral route is a more liked route of drug delivery, but it has a few disadvantages, including first-pass metabolism, drug degradation in the gastrointestinal tract due to enzymes and pH of the stomach, GI irritation, low bioavailability, etc. Now a day many drugs are administered orally, but they are observed not more effective as desired so to upgrade such character TDDS was created. Drug delivery administered by the skin and attain a systemic effect of drug is called as transdermal drug delivery system. The first transdermal system, Transdermal SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Most transdermal patches are designed to release the active ingredient at a zero-order rate for a period of several hours to days following application to the skin.

ANATOMY AND PHYSIOLOGY OF SKIN

Skin is the most extensive organ of the body covering an area of about 2m2 on in an average human adult. This multi-layered organ receives approximately one third of all blood circulating through the body. With thickness of only a millimeter, the skin separates the underlying blood circulation network from outside environment.

Human skin comprises of three distinct but mutually dependent tissues:

- The stratified, vascular, cellular called as "epidermis"

- Underlying dermis of connective tissues
- Hypodermis [1].

Route of Drug Permeation Though Skin:

In the process of percutaneous permeation, a drug molecule may pass through the epidermis itself or may get diffuse through shunt pathway, mainly hair follicles, sebaceous glands and the sweat ducts. Therefore, there are two major routes of drug permeation [2].

- Epidermis
- Dermis
- Hypodermis

. In simpler terms, our skin serves as a large canvas that interacts with a significant portion of our blood supply, facilitating important functions and maintaining the well-being of our body as a whole [1].

Epidermis

It is the peripheral hard and thin surface of the skin, as shown in Figure No.2. Mainly, the cells present in the epidermis are Keratinocytes; these cells form cells in the inner layer of skin, known as basal layer. It is a barrier like– structure, and they are composed of dead cells, which are the outermost part of the epidermis. This layer acts as obstacle; many drugs are not able to penetrated through the stratum corneumbut lipotropic drugs can easily penetrate as compared to hydrophilic drugs [3].

Dermis

Dermis is 3 - 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerve tissue. The cutaneous blood supply plays a vital role in the regulation of body temperature. Additionally, it also provides nutrients and oxygen to the skin, eliminating toxins and waste products. The capillaries reach up to0.2m of skin surface and provide sink conditions for most of the molecules penetrating through the skin barrier.

Hypodermis

The hypodermis or subcutaneous fat tissue holds up the dermis and epidermis. It is described as a fat storage area. This layer helps to regulate temperature, provides nutritional support, and spontaneous protection. It carries the principal blood vessels and nerves to the skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate all the three layers and arriving in systemic circulation [3].

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal drug delivery system avoids gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and other orally administration of drug

- Avoidance of first pass metabolism
- Minimizing undesirable side effect
- In a transdermal medication, there is the possibility of self-administration.
- Topical patches have a constant drug release in the bloodstream.
- Avoids GIT incompatibility of drugs.
- Dose and therapeutic effects are advanced.
- TDDS is a durable treatment.
- Better patient's compliance.
- Avoiding frequent dose administration.
- Side effect gets reduced.
- Drug duration of action is extendable.
- Number of dosage frequency reduced.
- Easier to remember and used [4,5].

DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM;

- Transdermal drug delivery system does not suitable for delivery of ionic drugs.
- No use of ionic drugs.
- May cause allergic reactions.
- A molecular weight of drug molecules less than 500daltons is essential.
- Transdermal therapy is suitable for certain potent drugs only.
- Transdermal therapy is not carried out for ionic drugs [6-8]

ROUTE OF DRUG PERMEATION THROUGH SKIN

In the process of percutaneous permeation, a drug molecule may pass through the epidermis itself or may get diffuse through shunt pathway, mainly hair follicles, sebaceous glands and the sweat ducts. Therefore, there are two major routes of drug permeation. The skin, which has several layers and is the body's outermost organ, serves to shield us from external dangers including chemicals, heat, and toxins. The dermis, which contains blood vessels and produces skin cells, and the epidermis, which serves as protection, are the two layers that make up this skin. There are chemicals in each layer that prevent transdermal distribution. Moving through intercellular spaces enables the diffusion of non-polar or lipophilic solutes within the continuous lipid matrix. Molecules travelling through the transappendegeal route cross across hair follicles and sweat glands [1, 9, 10].

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEMS

Single-layer drug- in–adhesive

The adhesive layer in this type of system also contains the drug. In this system of patches, the adhesive layer not only serves to adhere the number of layers together, along with the whole system, to the skin but is also responsible for the release of the drug. The adhesive layer is bounded by a temporary liner and a backing membrane [13].

Multi-layer drug in adhesive:

The multi-layer drug in adhesive is analogous to the single-layer system in that both adhesive layers are also responsible for the release of the drug. But it is different however in that it adds another layer of drug-in-adhesive, generally separated by a membrane. This patch also has a short-term liner of drug-layer and enduring backing [13].

Drug reservoir-in-adhesive:

This transdermal system contains a distinct drug layer. The drug layer is a liquid compartment adhering to a drug solution or suspension, separated by backing layer. In this reservoir system, the rate of release is zero order [13].

Drug matrix-in-adhesive

This matrix system has a drug layer of semisolid matrix containing a drug solution or suspension [13].

METHODS FOR CHARACTERIZING TDDS

The evaluation of delivery efficiency and effectiveness is a very important process in TDDS. There are various methods used for this, depending on the type and purpose of the drug to be delivered.

1. Diffusion cell method.
2. Tape stripping.
3. Mechnism of transdermal permeation

Transdermal permeation of a drug delivery system based on the

1. Permeation of drug by feasible epidermis
2. Sorption through stratum corneum
3. Take up of the drug moiety through the capillary system in the dermal papillary layer the rate of transdermal drug permeation, dQ/dt, through several layers of skin tissues which can be expressed as

dQ/dt =Ps (Cd - Cr) ……. (1) Where

dQ/dt = Rate of skin permeation

Cd and Cr = the concentrations of skin penetrate in the donor phase (stratum corneum) and the receptor phase (systemic circulation)

Ps = overall permeability coefficient of the skin

Ps is defined as by L john PS = KSDSS/HS (2)

Where,

Ks = Partition coefficient of the penetrant

Dss = Apparent diffusivity of penetrant

Hs = Thickness of skin

At constant rate of drug permeation is achieved when

Cd>Cr Then equation (1) becomes dQ/dt = PS.CD

(dQ/dt) becomes as constant when Cd value remains genuinely constant done the span of skin permeation. To retain the Cd at a constant value, it is simple to make the drug to be released at a rate (Rr) which is regularly more prominent than the rate of skin take-up (Ra) therefore Rr>>Ra.

Thusly, the drug concentration on the skin surface (Cd) is kept up at a level which is constantly more prominent than the equilibrium (or saturation) solubility of the drug in the stratum corneum (Ce), i.e., Cd>>Ce ; and a most extreme rate of skin permeation (dQ/dt)m, as written by equation.

(dQ/dt)m = PSCeS

Where (dQ/dt)m=Magnitude of Rate of skin permeation PS = the skin permeability coefficient of drug CeS-equilibrium solubility in the stratum corneum14,15].

Factors Affecting Transdermal Permeation

The factors that affect the permeability of the skin are classified into following three categories:

A. Physicochemical properties of the penetrant molecule
B. Physicochemical properties of the delivery system
C. Molecular size and shape
D. Partition co-efficient
E. Ph condition
F. Ionization
G. Drug concentration

Physicochemical properties of the drug delivery system

H. The affinity of the vehicle for the drug molecules
I. Composition of drug delivery system
J. Enhancement of transdermal permeation Physiological and Pathological condition of the skin:
K. Skin age
L. Lipid film
M. Skin hydration
N. Skin temperature
O. Cutaneous drug metabolism
P. Species differences
Q. Pathological injury to the skin
R. Blood flow
S. Skin metabolism [16, 17].

FACTORS AFFECTING ON TRANSDERMAL BIOAVAILABILITY

Physicochemical factors

Skin hydration: When exposed to water, the skin's permeability greatly increases. Adequate hydration plays a crucial role in enhancing skin permeation. Consequently, humectants are employed in transdermal delivery.

Temperature and pH: The drug permeability experiences a ten-fold increase due to temperature fluctuations. As the temperature decreases, the diffusion coefficient decreases as well. Weak acids and weak bases dissociate based on the pH and pKa values.

Diffusion coefficient:

The ability of a drug to permeate tissues is influenced by the diffusion coefficient of the drug. When the temperature remains constant, the diffusion coefficient is determined by various factors, such as the characteristics of the drug itself, the properties of the surrounding medium through which it diffuses, and the potential interactions occurring between the drug and the medium.

Drug concentration

The flow rate is directly related to the difference in concentration between the two sides of the barrier, and this difference will be greater if there is a higher concentration of the drug across the barrier. Molecular size and shape: Drug absorption is inversely proportional to molecular weight; small molecules penetrate faster than large ones [18].

EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

Evaluation studies are more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage form and can be classified into following types:

A) Physicochemical evaluation

A. In vitro evaluation
B. In vivo evaluation

A. Physicochemical Evaluation:

- Thickness of the patch
- Uniformity of weight
- Drug content
- Content uniformity
- Determination of surface pH

a) Shear adhesion test
b) Peel adhesion test

B. In vitro release studies

- Paddle over disc apparatus (USP apparatus 5)
- Cylinder apparatus (USP apparatus 6)
- The reciprocating disc (USP apparatus 7)

In vitro permeation studies

In vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Westar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using an electric clipper; the dermal side of the skin is thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater.

In vivo studies:

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using animal models and human volunteers.

a) Animal model
b) Human models [19, 20, 21].

EVALUATION OR CHARACTERIZATION OF TDD

Physical Appearance

All the formulated patches were visually audited for color, clarity, opacity, translucency, flexibility and smoothness.

Thickness of Patch

To determine the thickness of the formulated patches, various points on each patch were measured using digital micrometers, micrometer screw gauges, travelling microscopes, or vernier calipers. The measurements were taken at different points on each patch.

Water Vapor Permeability Evaluation [WVP]

It is determined by natural air circulation. It can be estimated by using following formulae:

$$WVP=W/A$$

WVP is expressed in g/m2per 24 hours.

Where W = amount of vapor permeated through the patch (gm/24 hour) A = surface area of exposure samples (m2) .

Skin Irritation Test;

Skin permeation and sensitization testing involves the use of healthy rabbits.

The formulated patches are carefully applied on the skin of rabbits, specifically on the dorsal surface. Prior to attaching the patch, the hair is removed from the rabbits' skin. After duration of 24 hours, the skin is meticulously observed and examined for any potential signs of irritation or adverse reactions.

Weight Uniformity;

Prior to conducting the weight uniformity test, the formulated patches were subjected to a drying process at a temperature of 60C for duration of 4 hours Drug Content Analysis;

The formulated patches are carefully weighed and added to a solvent that can dissolve the drug effectively. This mixture is then subjected to continuous shaking for duration of 24 hours using a shaker incubator. Subsequently, the solution undergoes sonication to ensure proper mixing, followed by filtration to remove any impurities [20]

APPLICATION OF TDDS

- Transdermal patch containing nicotine, which releases nicotine in controlled manner to help with cessation of tobacco smoking.
- Nitroglycerine patches are used in the treatment of angina pectoris.
- Transdermal agent for the attention deficit hyperactivity disorder (ADHD).
- Transdermal patch of the selegiline (MAO inhibitor) became the first transdermal delivery agent for major depressive disorder.
- Some transdermal patches for hormone delivery include the contraceptive patch.

1. The nicotine patch is highest-selling transdermal patch for the cessation of tobacco smoking. It was approved in 2007 as a vapor patch to reduce smoking.
2. Hormonal application:
   - Oestrogenpatches are used to treat menopausal symptoms.
   - Ortho Evra or Evra as a contraceptive patch.
3. Scopolamine patches are used for motion sickness.
4. For treatment of angina nitroglycerine patch is used.
5. Cynocobalaminepatch.
6. Caffeine patches are designed to deliver caffeine to the body through the skin

CONCLUSION AND FUTURE PERSPECTIVES

This article provides valuable information regarding the transdermal drug delivery systems and the details of evaluation process of TDDS is more useful reference for the research scientist. The study of transdermal drug delivery shows that it has great potentials, being able to

use it for both hydrophilic and hydrophobic active substance into promising deliverable drugs. The development of TDDS technology is widely recognized as the development of a mass delivery methodology, which makes it the preferred drug injection modality for transdermal delivery across skin types, while preventing first-pass metabolism and other sensitivities associated with various alternative drug administration routes. In various devices and TDDSs, drugs can be delivered through the skin to the systemic circulations TDDS technology has been a breakthrough in mass delivery, avoiding first-pass metabolism and other perceptivity associated with drug delivery routes Over the years, significant advancements have been made in the transdermal route of drug delivery, starting from its inception in 1981 up until the recent developments in 2022. TDDS used for the used for drug therapy for a less absorption, more uniform plasma levels, improved bioavailability, decrease side effect, efficacy and quality of the product. A patch has some simple components, which perform a vital role in the release of drug through the skin. Future prospective of TDDS would be focused on the controlled therapeutic use.

AUTHOR CONTRIBUTIONS

All authors are contributed equally

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The Authors have no Conflicts of Interest to Declare.

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