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A COMPREHENSIVE REVIEW OF TRANSDERMAL PATCHES

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ABSTRACT

To address the challenges associated with drug delivery, particularly oral routes, transdermal drug delivery systems were introduced. Transdermal patches are medicinal adhesive patches that are put to the skin to deliver a predetermined dosage via the skin and into the circulatory system. It encourages the body's wounded areas to mend. Transdermal drug delivery systems have beneficial action over other forms of administration, like oral, intravenous, topical i.m, and others. in that, the patient can administer medication in a controlled manner through the patch. Typically, it's accomplished by either melting thin layers of medicine incorporated in the adhesive with body heat or by covering a reservoir of medication with a porous membrane. So, this review has been focused on the challenges associated with transdermal drug delivery system & and their specifications with brief insights into transdermal patches to deliver the drug at their targeted site.

KEYWORDS:- Transdermal drug delivery system, World Health Organization, Controlled rate, Transdermal patches, Reactions, Mechanism.

INTRODUCTION OF TRANSDERMAL DRUG DELIVERY SYSTEM

Over two decades have passed since the introduction of the transdermal medication delivery technology. This is a self-contained, desiccating dosage form that, when applied to undamaged skin, delivers the medication to the blood circulation at a regulated rate. Transdermal delivery, or the administration of medications through the skin for a systemic impact, was initially utilized in 1981 when Ciba-Geigy introduced Transdermal V, which is

now sold as Transdermal Scopes to stop the motion sickness-related sickness and vomit. Up until 2003, the FDA had permitted more than 13 molecules' worth of transdermal patch products. In 2001, the transdermal market in the US was approximately 1.2 billion dollars. Eleven drug molecules served as its basis: fentanyl, nitroglycerine, estradiol, and ethylestradiol.[01-03]

Transdermal medication delivery allows for the regulated release of medicines into the patient. It allows for a stable level in the blood profile, which can occasionally lead to increased efficacy over other dose forms and a decrease in systemic negative reactions. Transdermal drug delivery systems' primary goal is to administer medications into the circulatory system over the skin at a set pace with the least amount of individual and inter-patient fluctuation.[04-06]

Technological innovation is advancing at a steady pace, creating a clean atmosphere for investigations and development of products in the epidermal route, transdermal patches are used to deliver drugs into the systemic circulation. it may be control release or immediate release The transdermal drug delivery has an active and passive design which provides an alternative route of administrative medicinal effect. It only delivers a small number of medicinal products.[07-09]

A short summary of skin structure

The skin is the broadest and easiest organ in the body to reach, occupying 1.7 m^2. An average person's skin makes up about 16% of their total body mass.[16,17,18] Providing a layer of defense against germs, UV radiation, toxins, allergies, and most forms of water, the skin's primary role is to shield the body from the outside world.[19]

The three primary sections of skin are the stratum corneum is found in the outermost portion of the skin, called the epidermis; the dermis is found in the middle layer; and the hypodermis is found in the innermost layer.[5,20,21]

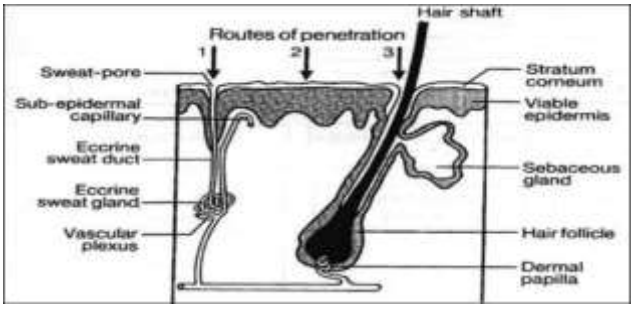


Figure 1: Structure of skin.

Epidermis:- The thickness of the epidermis, the skin's outermost layer, differs; on the hand surfaces of hands and soles of feet, it spans around 0.8 mm.[19] The epidermal layers underneath the stratum corneum are sometimes referred to as the viable epidermis. It is made up of areas with many layers of cells called epithelial cells.[8-19] Melanocytes, Langerhans cells, and Merkel cells make up the remaining cells in the epidermal layers, accounting for approximately 95% of the total number of cells present in the epidermis.[14] The stratum corneum is the epidermis topmost layer.[19,23,24]

The skin's exterior layer is about Keratinocytes makeup approximately ninety-five percent of the cells in the epidermis; melanocytes, Langerhans cells, and Merkel cells make up the remaining cells in the epidermal layers. Collagenous (70%) and elastin fibers make up the majority of the 2-3 mm wide epidermal layers, which are responsible for the skin's power and suppleness.[17] The blood veins in the dermis provide sustenance to both the epidermis and dermis. Nerves, macrophages, and lymphatic veins are also present in the dermis layer.[23]

The hypodermis, sometimes referred to as the subcutaneous layer, is the lowest layer of skin and is composed of an interconnected system of fat cells.[17] It acts as the layer of contact that exists between the skin and the tissues that lie underneath, such as the bones and muscles of the body. Therefore, heat insulation, shielding against mechanical shock, and support and conductance of the skin's vascular and nerve impulses are the main functions of the hypodermis.[27] The hypodermis contains fat cells which collectively make up around half of the body's fat; the two primary cell types found there are fibroblasts and macrophages.[28]

Drug penetration route

There are two routes via which the penetration passes through The trans epidermal pathway involves a chemical pass through both the multicellular barrier and the stratum corneum, intracellular pathway via corneocytes, and keratinocytes undergo terminal differentiation. permits the movement of polar or lipophilic solutes.

Transport via the intercellular gaps enables the migration of lipophilic or non-polar solutes through the persistent lipid matrix. Molecular transport through the transappendegeal route occurs in sweat glands along with hair follicles.[5-30]

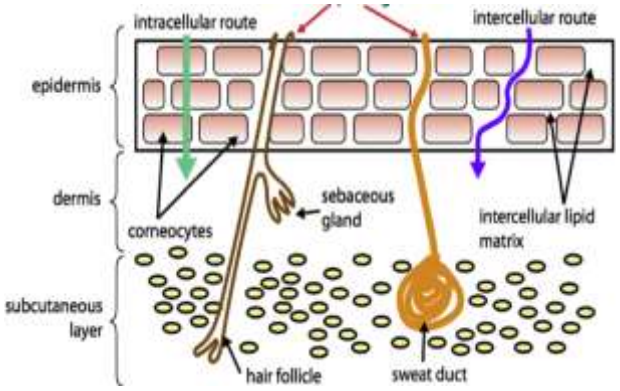


Figure 2: Structure of skin penetration route.

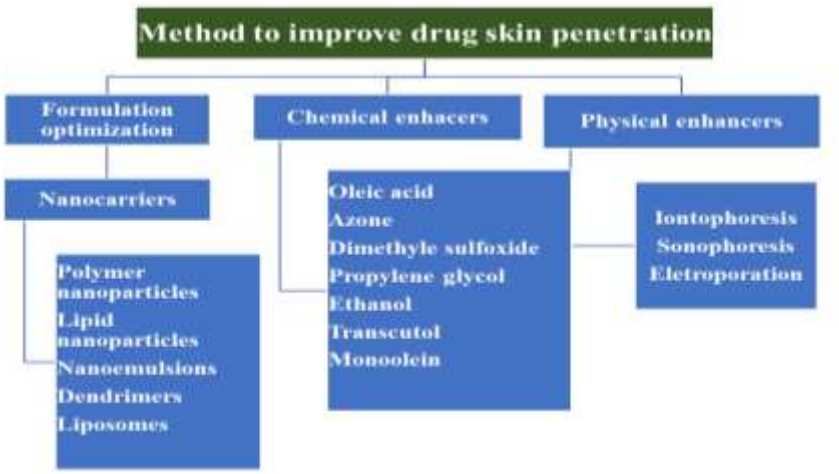
Characteristics of TDDS

- Must have a tiny molecular count.
- A preference for hydrophilic and lipophilic phases.
- Its melting point needs to be modest.
- Its half-life needs to be brief.
- Must not be irritating or poisonous

Techniques for enhancement of skin permeabilization

Technologies that alter the stratum corneum's barrier characteristics fall into two categories: active/physical and passive/chemical. To alter the stratum corneum structure, passive approaches include optimizing the formulation and changing the interactions between the medication and the carrier.[29,41,42] Adding passive techniques to transdermal patches, including chemical boosters and emulsions, is not too difficult.[43] The primary disadvantage of passive approaches, however, would be the apparent adverse effect on medications with rapid onset, such as insulin, due to drug release.

Table 1: Method to improve skin penetration.



Transdermal patches

Introduction:- Transdermal patches are medicinal adhesive patches with API that are applied to the skin to release medication into the body's circulation system. They are causing a relaxation of control. With an adult skin area of 1.5-2.0 m^3, When it comes to bulk, the skin is the biggest organ in the body. Subsurface illnesses have been treated with drugs put topically on the skin. Since the earliest known medical records of mankind, the transdermal delivers medication for the treatment of circulatory illnesses as well as cosmetics. For example, the use of plants, animal or mineral extract in lotions, ointments, potions, and even patches was typical in the Babylonian medicine of ancient Egypt (C.3000 BC).[60-67]

History:- Regarding their preparation for dermatology and cosmetology (ointments, lotions, pomades, rouges, powders, and paints for the eyes and nails), the ancient Egyptians employed oil (such as castor oil, olive, and sesame), fats (mostly animal), scents (such as bitter almond, peppermint and rose marry) and other components (Forbes, 1955). The mineral ores galena (dark gray) and malachite (green) were used to make kohl, a paste that was used to paint the eyes. According to Lucas and Harris (1962), Red ochre was used as a cheek or paint for the face, and a lotion that was a blend of oil and the powdery line was used for washing. Religious beliefs state that ancient lead-based objects were utilized for both aesthetic and preventive purposes against eye diseases (Tapsoba et al, 2010). However, considering how recently, these effects could have been real.[59-65]

Table of dose, Indication, Site of Application and Design of figure 3

Types of transdermal patches

One-layer drug adhesive:- The adhesive layer of this system also contains the drug. The patch's sticky layer in this type of patch releases the medication in addition to holding the system's components to the skin and holding the different layers together. There is a backer and a temporary liner all around the adhesive layer. It is distinguished by the drug's direct incorporation into the skin-contacting glue that is applied to the epidermis**.**[41-43]

Multi-Layer adhesive:- A multi-layer attachment patch includes another layer of drug-in-adhesive, which is frequently separated by a membrane, in a manner akin to a single-layer technique. The medication is released from the reservoir in two stages: one layer releases the medication immediately, while the second layer releases it gradually. This patch also features

a permanent backing and a transient liner layer. The permeability of the membrane and the drug molecules' diffusion determine the drug release from this.[44-46]

Reservoir:-There is a distinct medication layer in the reservoir transdermal system. The medication layer is a fluid chamber that is divided by adhesive and contains a drug mixture or concentration. The medication reservoir is completely contained in a small chamber made of a drug-resistant metallic plastic lamination. A compound resembling vinyl acetate makes up the rate-controlling layer on one side of the chamber.[48-50]

Matrix:- The framework of the system's drug layer is a partially solid matrix that contains a drug mixture or slurry. This patch surrounds the drug coating with adhesive, covering it slightly. The physical characteristics of the matrix dictate the release rate. Also called a monolithic apparatus**.**[47-48]

Vapor patch:- This patch's sticky layer not only holds the several layers together but also emits vapor. Vapor patches emit fragrances for up to six hours and primarily serve for elimination.

Microneedle patch:- The spacing of 100–1000 μm tips in a tiny needles patch allows for the passage of biomolecules up to 20 μm in size via the patch's 20 μm thickness. There are two types of needles used: water-insoluble needles made of metal, ceramic, or polymer, and dissolved in water syringes made of soluble polysaccharides or sugars.

Design of transdermal delivery system

Any transdermal delivery system's fundamental parts are the medication absorbed or distributed within an inactive matrix of polymers that serves as a vehicle and scaffold for the dissolution of the medication. Features of drug release and patch activity are determined by two fundamental designs of the patch system.

1) **Monolithic or matrix:-** The drug attaches itself to the inactive polymer matrix, controlling the way it escapes from the device.

2) **Reservoir or membrane:-** The polymer matrix does not control the release of pharmaceuticals. A rate-controlling membrane, situated between the sticky layer and the medication matrix, now serves as the restricting barrier for releasing the medication from the device.[80]

Innovations in transdermal drug delivery system development

Several innovations that regulate the rate at which medications are released and penetrate the skin have been created effectively. These technologies can be divided into four fundamental categories.[71-81]

Permeation of polymer membranes controlling TDD systems:- The drug reservoir in this device is sandwiched between an alloyed plastic laminate that is impermeable to drugs and a rate-controlling polymeric membrane. The drug molecules can only be released through the rate-controlling polymeric membrane. The membrane that controls the flow rate can be made of microporous or nonporous polymeric materials, including ethylene-vinyl acetate copolymers.

Diffusion-Controlled Polymer Matrix TDD Systems:- By using this technique, drug storage is created by evenly dispersing the drug particles in an aqueous or hydrophobic matrix of the polymer. Afterward, medicinal platters with a predefined thickness and surface area are formed from the resultant medicated polymer.

Dissolution-Controlled Micro-reservoir TDD Systems;- The polymer matrix drug dispersion-type TDD system can be adjusted to vary the drug loading level incrementally, creating a gradient of drug reservoir along the diffusional path across the multilaminate adhesive layer and overcoming the non-zero-order drug release profiles.

MATERIAL AND METHOD

Method of preparation of TDP

Following the addition of varying concentrations of permeation enhancer and chilling, vigorous shaking was used to ensure that all of the components were thoroughly mixed. filled molds and stored A drug transdermal patch was created using the solvent evaporation technique.

First, ethyl cellulose and medication were added to ethanol to create solution A. Water and weighed amounts of Poly Vinyl Alcohol were combined to create Solution B, which was then melted at a temperature between 60 and 80°C. Solution A was melted and then poured into B, allowing it to dry at room temperature.

An inverted funnel was placed on top of it to stop the solvent from evaporating quickly and preserve the smooth, wrinkle-free patch.

Films were removed from the mold once they had dried and covered with the help of aluminum paper for additional research.

This polymeric film is made up of solvents, drugs, and polymers.[51-59]

The formula for a transdermal patch with permeation enhancers[64-66]

Table 2: Formula of patches.

FN*	(EC: PVA)	PEG -400 (mg)	EO (mg)	PLG (mg)	T- 80 (mg)	PEG- 400 +PLG (mg)	EO + PLG - 400 (mg)	PG+ EU (mg)	PLG- 400+ T- 80 (mg)	Blank (mg)	Drug (mg)	Ethanol (ml)	Water (ml)
MF1	1:4	5	-	-	-	-	-	-	-	-	20	5	e.a
MF2	1:4	-	5	-	-	-	-	-	-	-	20	5	e.a
MF3	1:4	-	-	5	-	-	-	-	-	-	20	5	e.a
MF4	1:4	-	-	-	5	-	-	-	-	-	20	5	e.a
MF5	1:4	-	-	-	-	1:1	-	-	-	-	20	5	e.a
MF6	1:4	-	-	-	-	-	1:1	-	-	-	20	5	e.a
MF7	1:4	-	-	-	-	-	-	1:1	-	-	20	5	e.a
MF8	1:4	-	-	-	-	-	-	-	1:1	-	20	5	e.a
MF9	1:4	-	-	-	-	-	-	-	-	-	20	5	e.a

Where,

EC= ethyl cellulose, FN= Formulation number, T-80= Tween 80, EO= Eucalyptus oil, PLG= propylene glycol, E.A = enough amount.

Basic components of TDDP

The following are the parts of the transdermal device[68–70]

1. One polymer matrix
2. Medicine
3. Enhancers of penetration
4. An additional excipient

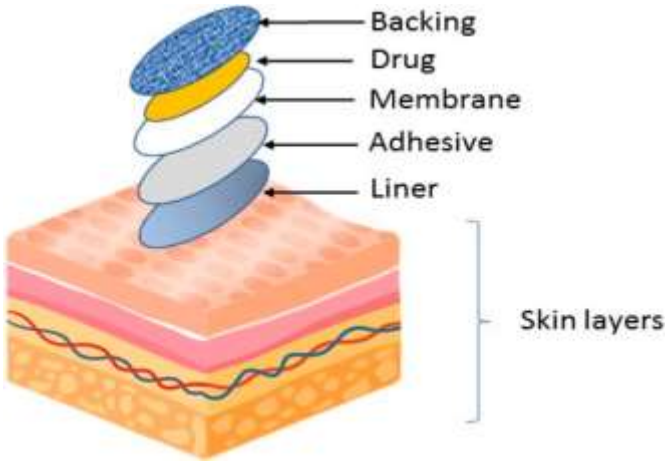


Figure 4: Layers of skin structure.

Release mechanism of formulation

To release the drug sample's mechanism from the transdermal patch that has been developed for the formulations. The % cumulative drug release findings were analyzed using kinetic models like these:

Zero-Order Model (Chien, 1992):- Zero-order kinetics refers to dose formulations that deliver the drug at a regulated, expected, and more leisurely pace than usual.

$Q = k_0t$.

where Q is the drug release quantity in t time

First-order model:- This dissolving mechanism's most common dose types are these. This kind of dissolving pattern is followed by some customized delivery preparations, notably delayed release formulas.

$Log = K_1t$.

where K_1 = delivery rate constant and Q = the percentage of medication delivered.

Higuchi model (Chien, 1992):- Several modified release dosage forms in this approach have some kind of matrix structure in them. This matrix dissolves the medication. The water penetration rate determines the drug's dissolution pattern, hence the following relationship holds:

$Q = K_2t_{1/2}$.

where K2 =diffusion rate constant, Q = proportion of drug release at time t. Plotting the cumulative percentage of drugs delivered against the squared base of time in the Higuchi model is linear.

Hixon-Crowell Model (Chien, 1992):- Many uniformly sized and shaped medication particles that dissolve smoothly are present in some specialized dosage forms. The dissolving process in such cases is shown by the squared base law. The following relationship is true if the real distribution of medicinal molecules determines the drug's dissolution pattern:

$(100 - Q)^{1/3} = 100^{1/3} – K_3t$

where k is the Hixon Crowell Constant, Q = drug deliver quantity in t time. The cumulative % of drug maintained vs time in this presentation has a linear cube root.

Pappas and Korsmeyer's Model (Chien, 1992):- The release is zero-order if n = 1; if n = 0.5, then Fickining diffusion provides the best explanation for the release; and if 0.5 < n < 1, then The emission can be explained by either case II dispersion or anomalous dispersion.

$Q = Kt_n$.

where n = diffusional exponent, K = diffusion rate constant, Q = fraction of drug release at time t. A log percent medication emission vs log time plot in this model is linear.

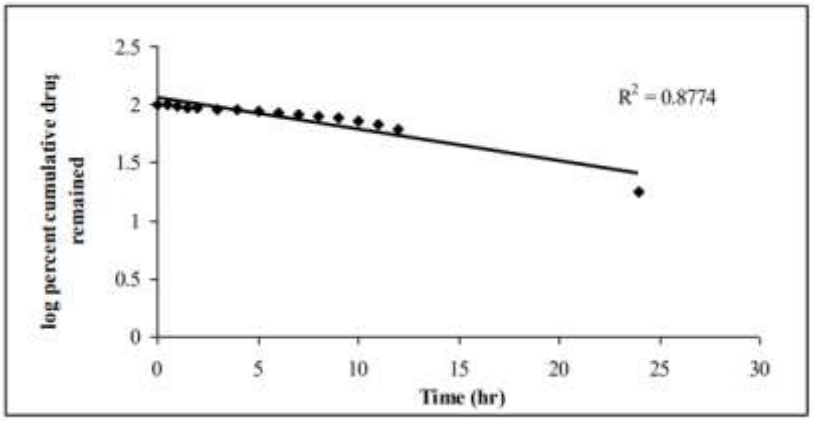


Figure 4: First order drug release model of optimized formulation

Figure 5: First-order reaction.

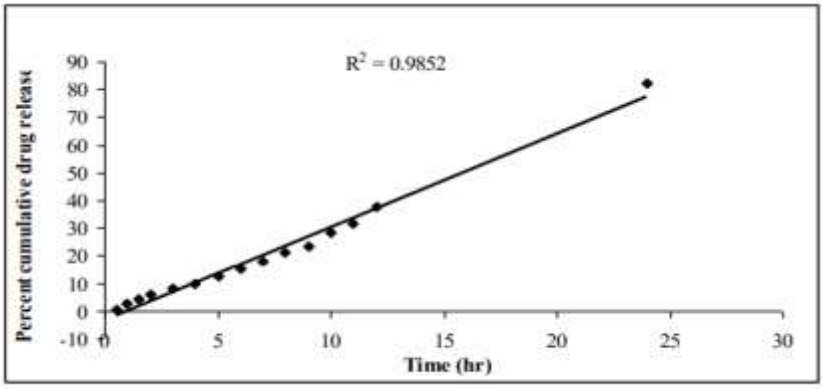


Figure 3: Zero-order drug release of optimized formulation

Figure 6: Zero-order reaction.

Table 3.

Factors effecting TDP Things Affecting Transdermal Patches: Several things can influence how well transdermal patches function. Those are listed further:[82]	
a. Physical-Chemical Characteristics	**b. Physiological & Pathological Conditions of Skin**
1) Partition coefficient 2) Molecule size 3) Melting point and solubility 4) Ionization	1) The horny layer's reservoir effect, temperature of the skin, fat layer, skin moisture, geographical variations, pathogenic skin disorders, cutaneous self-metabolism, cutaneous barrier qualities in neonates and early infants 2) The qualities of the skin barrier in older skin. 3) Site of the body 4) Utilized penetration enhancers

Conditions transdermal patches will used

If a patient requests an alternate drug delivery mechanism due to unpleasant side effects or is unable to take oral medication, a transdermal patch is employed.

Where effective administration could potentially improve pain control. This may be useful for patients who are impaired in thinking or who, for whatever reason, are unable to take care of themselves with their analgesics.[83-84]

Conditions transdermal patches will not used

Transdermal patches should not be used in the following situations:

(1) Acute pain treatment is necessary.

(2) When a quick dose titration is necessary.

(3) When the dosage requirement is 30 mg or less per 24 hours or less.[83-84]

Advantages

1. Diminished Adverse Reactions
2. Absence of Needles
3. Quicker Outcomes
4. Steady and Managed Delivery
5. Enhanced Obedience
6. Increased Bioavailability of Therapeutics
7. Less Occupying
8. Simple to Use

9. Not Gulping or Biting
10. Reduced Chance of Abuse, Addiction, or Unintentional Overdose

Limitations

1. This method cannot be used to provide any kind of medication.
2. The medication needs to possess certain favorable physicochemical qualities.
3. Unsuitable for medications requiring elevated plasma levels.
4. Unsuitable for medications with a large molecular weight.
5. Unsuitable for medications that are metabolized as they travel through the skin.

CONCLUSION

Dermal forms of delivery have been used as cosmetics and to treat a wide range of ailments since the beginning of humanity. with the definition of appropriate potential drugs for transdermal administration and the accompanying advancement of either active or passive technology, better distribution, more precise drug dose, and greater satisfaction of individual demands have been made possible throughout time. Developing pharmaceuticals for transdermal patches and comparable methods of distribution with adequate potency that can permeate the skin using appropriate transdermal techniques remains a priority. A significant difficulty is providing therapeutic and cosmetic demands that won't be appropriately and reasonably fulfilled through conventional delivery systems.

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