WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Transdermal drug delivery systems (TDDS) offers controlled or sustainable release of the drug into the patient, it enables a constant or steady blood level profile, Resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The administration of Drugs by transdermal route offers mainly the advantage of being relatively painless. The appeal of using the skin as a portal of drug Entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks And the non invasive nature of drug delivery. The main objective of transdermal patches system is to deliver drugs into Systemic circulation through skin at predetermined rate with minimal inter and intra patient variation also .

Keywords: *Transdermal drug delivery, Transdermal patches, Controlled release*

1. INTRODUCTION [1, 2 ,3,4]

Transdermal drug delivery systems is a Novel drug delivery systems that is (TDDS), also known as patches are applied on the skin , are dosage forms designed to deliver a therapeutically amount of drug across a patient's skin. TDD is a painless or invasive method of delivering drug systemically by applying a drug formulation onto inact and patient skin .The drug initially penetrates through the stratum corneum and then pass through the deeper epidermis layer and dermis layer without drug accumulation in dermal layer . When drug reaches the dermal layer , it becomes available systemic absorption via dermal microcirculation .

Fig 1 : General representation of Transdermal patch

Transdermal drug delivery systems (TDDS) is a delivery provides a leading edge over injectable and oral route by increasing patient compliance and it avoiding the first pass metabolism respectively . Transdermal drug delivery systems not only provide controlled , constant administration of the drug, but also allows continuous input of drugs with short biological half lives and eliminate pulsed entry in the blood or systemic circulation, which often causes undesirable side effects.

Which are used for the preparation of TDDS are as follows.

Drug or medicine containg: - Drug is in direct contact with release liner.

Innovation in the area of drug delivery is taking place at a much faster pace compared with the last two decades. Improved patients compliance and effectiveness are inextricable aspects of new drug delivery systems. optimum therapeutic outcomes not only developing controlled drug delivery has

become increasingly important in the pharmaceutical industry .The pharmacological response, both the desired therapeutic effect and the undesirable side and adverse effect ,of drug is dependent on the concentration of the drug at the site of action .

Tablet , capsule , liquid orals and injection have been the traditional way to take medication .The news options are becoming increasingly have been the traditional way to take the medication and new options are becoming increasingly popular .one highly successful alternative delivery method is the trandermal .Skin of an average adult body covers a surface of approximately **2 m^2** and and receive about one third of the blood circulating through the body . To deliver a drug into the body through transdermal layer of skin , it is necessary to understand about the skin . Transdermal drug delivery systems (TDDS) is the one of the system lying under the category of controlled drug delivery systems, of an in which the aim is to delivery the drug through the skin in a predetermined and controlled rate .

Transdermal patch generally refers to topical application. Delivers agents to healthy intact skin either for localized Treatment of the tissues underlying the skin or for systemic Therapy. Transdermal Patch offers many advantages over the Conventional dosage forms or controlled release . Transdermal patch provides constant drug releaase maintain therapeutically range concentration levels. The application of transdermal delivery to a wide range of drugs is limited due to the significant barrier to penetration across the skin . which is allied primarily with the outermost stratum corneum layer of the epidermis. Formulation on skin can be classified into two categories that according to the target site of the action. One has systemic action after drug uptake from the cutaneous micro vascular network and other exhibits local effects in the skin. Transdermal drug delivery can closely mimics the slow intravenous infusion without its potential hazards and also offer another most important advantage in allowing the patient to terminate the drug therapy by simply removing the patch at desired time if toxicity develops.

NSAID (Non-steroidal anti-inflammatory drugs) are Mostly used for the preparation of transdermal patches for the treatment of inflammation or pain to the 8patient. The NSAID patches are safer and convenient than its oral form. Patient with rheumatism received different NSAID tablets. The side effects like stomach bleeding, increased acidity, ulcers are avoided by using transdermal patches of NSAID.

In Targeted drug delivery system can produces both type of Effect local as well as systemic effect. It is important to Prevent the, GI toxicity, Gastric irritation and GI Mucosal Damages. Transdermal drug delivery system is important To maintain the health of skin and prevent the infection of Skin or mucus membrane, It can includes in Transdermal Medicament contain such as Ointment, creams, gels, Micro Emulsions, Transdermal patches is important to prevent the Infection of skin and maintain the appropriate health of Skin. Transdermal patches were introduced in the late 1970's, starting with a 3 day patch to treat motion sickness. Since then, the market for drug administration through patches has been steadily increasing. However transdermal delivery is severely limited by the in ability of the majority of drugs to cross skin at therapeutic rates due to the barrier imposed by the skin's outer stratum corneum layer .

Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivering drug molecules to the systemic circulation by this route.

Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. The development of transdermal drug delivery systems is a multidisciplinary activity that encompasses fundamental feasibility studies from the selection of a drug molecule to the demonstration of sufficient drug flux in an ex vivo and/or in vivo model the fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical and Stability factors), the patient (comfort and cosmetic appeal), the (scale-up andmanufacturability), and most , the economy. This review article provides an overview of TDDS, its advantages over conventional dosage forms, drug routes across human skin, penetration enhancers, various components of Transdermal patches, types of Transdermal patches.

Advantages:

1) Avoid the first pass metabolism.
2) Transdermal medication delivers a steady infusion of a drug over an extended period of time an equivalent therapeutic effect.
3) Self adminstration is possible .
4) Reduce the dose rangeing or number of dose get reduce .
5) For sutained and prolonged time drug realse action .
6) Improve bioavailability.
7) Increase the patient compliance by non invasive in pediatrics and geriatric patient.
8) They are easily and rapidly identified in emergencies (e.g.unconscious or comatose patient) ,Because of their physical presence, features and identifying the marking .
9) Transdermal drug delivery systems are enables the avoidance of gastrointestinal absorption with its associated pitfalls of enzymatic and pH associate the deactivation .

10) Transdermal drug delivery systems is novel approach and it can be invassive for patients .

11) TDDS can be used as an alternative delivery systems for patients who can not tolerate oral dosage forms

12) They can be used for drugs with narrow therapeutic Window.

Disadvantages:

1) Molecular size is restrictions <500 Dalton .

2) Possibility of local irritation at site of application.

3) May cause allergic reaction .

4) Transdermal drug delivery systems cannot deliver ionic drug.

5) It cannot develop if drug or formulation causes irritation to skin.

6) It cannot achieve high drug level in blood .

7) Not suitable for the high dose of the drug .

8) TDD not deliver ionic drugs.

9) High cost .

10) Variations in barrier function i.e age ,site etc

2] History of Transdermal drug delivery systems [2,13,15]

1) The first Transdermal patch approved in 1981 to prevent nausea and omitting associated with motion sickness .

2) The FDA has approved, till 2003 more than Transdermal product spinning 13 molecules .

3) The US Transdermal market approach $1.2 billion dollars in 2001 years It was based on 11 drug molecules , fentanyl , Nitroglycerin , estradiol, ethynielestradiol , ethindronacetate ,testesteron , cholidine, scopolamine, lidocaine , prilocaine. Etc.

4) Two new recently, approved Transdermal patches product containg contraceptive ethinyl estradiol and nor – elgestromin And a patch to treat overactive bladder containg oxybutynin.

   In 1980, a US patent disclosed a transdermal patch for hypertension treatment therapy. The system contained a gelled mineral oil–polyisobutene–clonidine reservoir and contact adhesive layer with a microporous membrane in-between that controlled the drug release rate (Chandrasekaran et al., 1980)effect.

3] Brief review of the skin structure:

Skin is the most accessible and largest organ of the body. with a surface area of 1.7 m2, 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) Epidermis :- The outermost layer, the epidermis, which contain the stratum corneum;

2) the middle layer, the dermis and The inner most layer, the hypodermis.

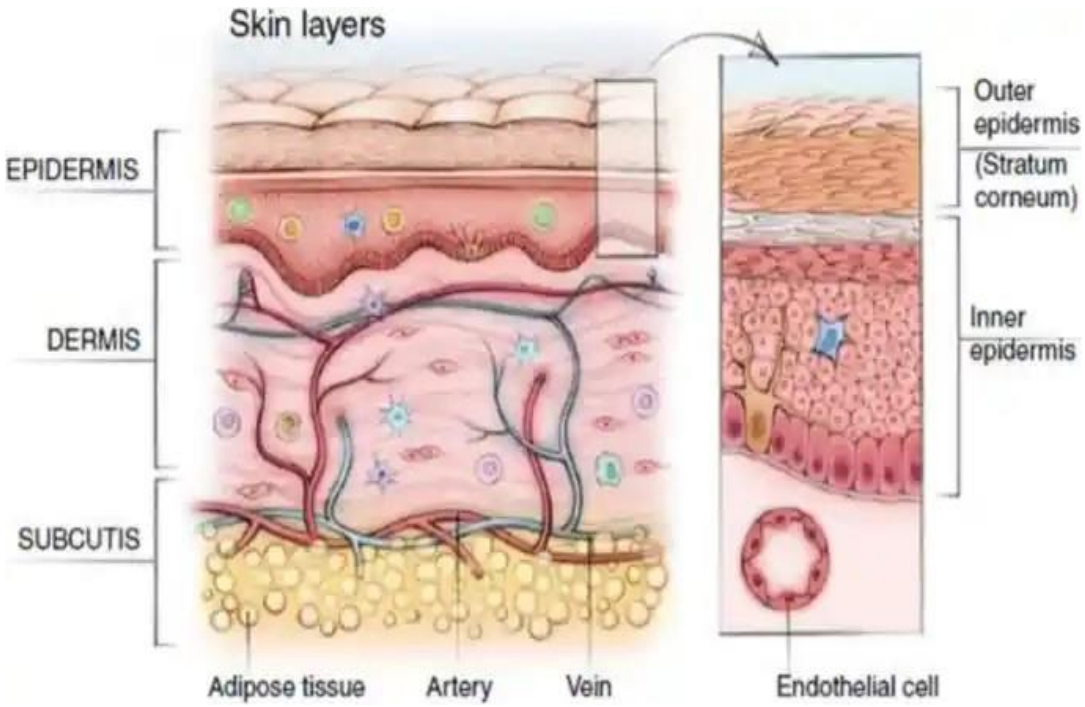


Fig 2. Structure of skin

A] Epidermis

The multi-layered epidermis varies in thickness , depending on the cell size and number of cell layer of epidermis , ranging from 0.08 mm on palms and soles to 0.06 mm on the eyelids. Stratum corneum ,this is the outer most layer of skin also called as horny layer . It is approximately 10 mm thick when dry but swell to several times this thickness when fully hydrated . It contain 10 to 25 layers of dead , kertainized cells called corneocytes . It flexible but relatively impermeable .

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 .

In Epidermis layer containg five sub layer i.e as following:-

a) Stratum corneum
b) Stratum lucidum
c) Stratum granulosum
d) Stratum spinosum
e) Stratum basal.

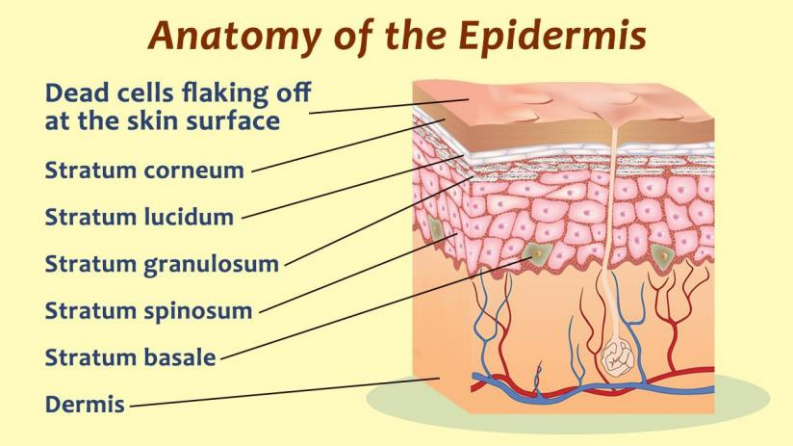


Fig 3. Basic Structure of epidermis layer

B] Dermis:

Dermis is 3 to 5 mm thick layer and is composed of a matrix of connective tissue which contains blood vessels , nerves and lymph vessels . The cutaneous blood supply has essential functions in regulation of body temperature .it also provides a nutrients and oxygen to the skin . While removing toxin waste product . Capillaries reach to within 0.02 mm of skin surface and provide sink condition for the most molecules penetrating the skin barrier . The skin blood supply thus keeps dermal concentration of permeates vary low and resulting concentration difference across the epidermis provides essential concentration gradient for transdermal permeation.

Dermis can be divided into two anatomical region

A) Papillary dermis

B) Reticular dermis

Papillary is the thinner outermost portion of the dermis .collagen and elastin fibers are mostly vertically oriented in the papillary region and connected with the dermal epidermal junction .

C] Hypodermis:

Subcutaneous, or Hypodermis in histology , is the third layer beneath the dermis. Subcutaneous is an elastic layer and includes a large amount of fat cells that work as a shock absorber for blood vessel and nerve ending .The thickness of this layer is 4 to 9 mm on body average . however , the actual thickness differ from person to person and it depends on the body region . When a molecule reaches intact skin , it contact with the cellular debris , nirmal flora of microorganisms , sebum other materials.

- **Skin pathway for drug delivery systems**

TDD is a painless method of delivering drugs systemically by 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.

The main route of transport for water soluble molecules is transcellular . It involves the passage through the cytoplasm of an corneocytes and lipid arrangements of the stratum corneum. The pathways of transport for lips soluble molecules is intercellular , it implicates the passage apparently through the the endogenous lipid with in the stratum corneum . The transcellular and intercellular route is should be collectively known as trans epidermal route as shown in below.

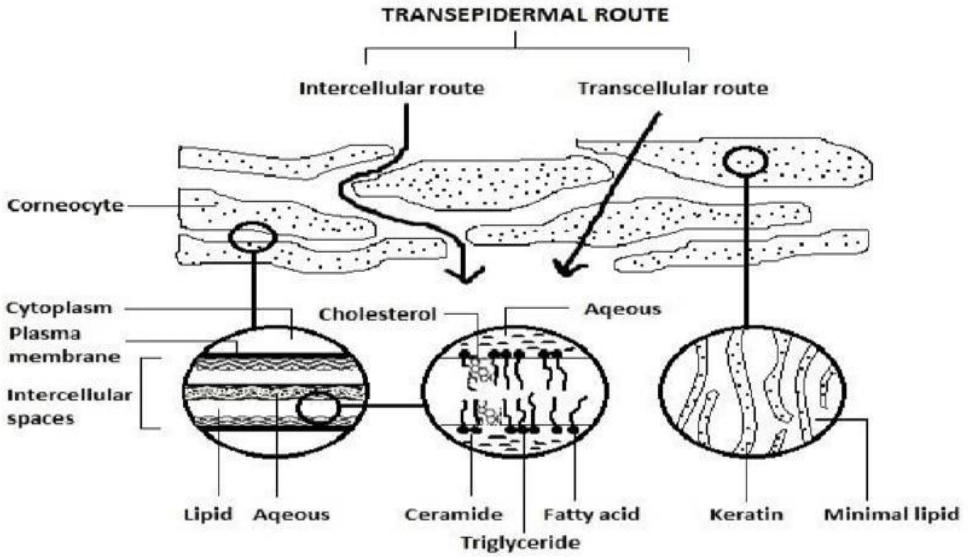


Fig 4. Skin pathway of drug delivery system

Solute molecules may penetrates the skin through the hair follicles, sweat duct or through the sebaceous glands. These passage are collectively known as shunt or appendageal route.It is generally accepted the skin appendages comprises for approximately 0.1%of fractional area for drug permeation. Thus the main focus is to develop permeation strategies through the stratum corneum rather than through the appendages.

The main barrier to absorption are the dead cells of SC, restricting the inward and outward movement of drug substance having the electrical resistance. The SC is heterogeneous tissue, composed of flatted keratinized cells

- **Percutaneous Absorption**

It is a step wise prices of penetration of substance into various layer of skin and permeation acrosss the skin into the systemic circulation and can be divided into as follows:

a) **Penetration:** the entry of a substance into the particular layer .

b) **Permeation:** the penetration from one layer into another , and is different both functionally and structurally from the first layer .

c) **Absorption:** the uptake of a substance into Systemic circulation.

3] BASIC COMPONENETS OF TRANSDERMAL DRUG DELIVERY SYSTEMS: [4- 12]

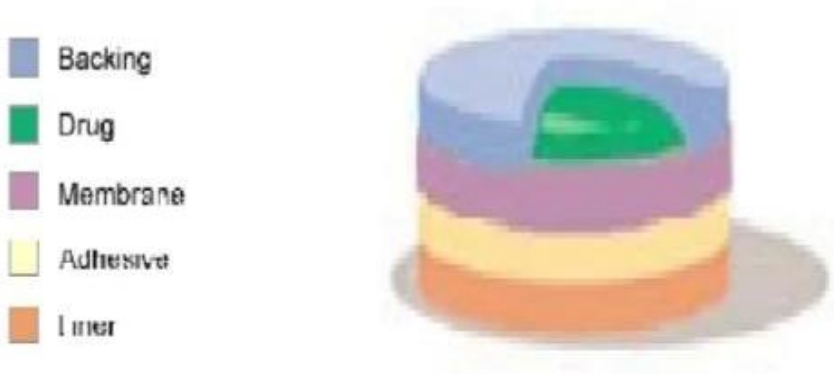


Fig 5. Component TDDS

The components of Transdermal device include

- Polymer matrix
- Drug
- Membrane
- Backing laminates
- Adhesive layer
- Permeation enhancers
- Other excipients

1) Polymer Matrix: The polymer controls the release of the drug from the Device. The following criteria should be satisfied for a Polymer to be used in a Transdermal system. Possible Useful polymers for Transdermal devices are;

Natural polymer	**Synthetic elastomer's**	**Synthetic polymers**
Cellulose derivatives, Zein, Gelatin, Waxes, Proteins, Gums, Natural rubber, Starch.	Polybutadiene, Hydrin rubber, polysiloxane, silicone rubber, Nitrile, Acrylonitrile, Butylrubber, Styrenebutadiene, Neoprene etc.	Polypropylene, Polyacrylate , Polyamide, Polyvinylpyrrolidone, Polymetyl methacrylate,Epoxy, Polyurea, etc.

2) Memebrane:-mem-membrane be sealed to the backing form a pocket to enclose the drug containg matrix or use a single llayer in the patch construction . The diffusion properties of the membrane are used to control availability of the drug and excipients to the skin .

For example ethylene vinyl acetate , silicone rubber ,polyurethane are used as a rate controlling membrane.

- **Liners**: Protects the patch during storage.

  Ex: polyester film.

- **Adhesive**: Serves to adhere the patch to the skin for systemic delivery of Drug.

  Ex: Acroliths, Polyisobutylene, Silicones etc .

3) Drug :-

For successfully developing a Transdermal drug delivery System, the drug should be chosen with great care.

Ex: containing API Of drug like , Nicotine, Methotrexate and Estrogen.

4) Backing laminates

The primary function of the backing laminate is to Provide support. They should be able to prevent Drug from leaving the dosage form through top. They must be impermeable to drugs and Permeation enhancers. They should a low Moisture vapor transmission rate. They must have Optimal elasticity, flexibility, and tensile strength. They must be chemically compatible with the Drug, enhancer, adhesive and other excipients. They must be relatively inexpensive and must Allow printing and adhesive lamination.

5) Adhesive layer The fasting of all transdermal devices to the skin Using a pressure sensitive adhesive that can be Positioned on the face or in the back of device is Necessary. It should not cause irritation, Sensitization or imbalance in the normal skin flora During its contact with the skin. It should adhere .To the skin aggressively.

6) Permeation enhancers: Controls the Release of the drug.

Ex: Trepans, Threnodies, Pyrrolidones. Solvents like alcohol, Ethanol, Methanol. Surfactants like Sodium Laurel sulfate.

Properties of TDDS:-The Following are some of the desirable properties of a drug for

Transdermal delivery as .

A] Physicochemical Properties:

- The drug should have a molecular weight less than approximately 1000 Daltons.
- The drug should have affinity for both- lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
- The drug should have a low melting point.

2] Biological Properties:

- The drug should be potent with a daily dose of the Order of a few mg/day.
- The half life (t1/2) of the drug should be short.
- Drugs, which degrade in the GI tract or are inactivated By hepatic first-pass effect, are suitable candidates for Transdermal delivery.
- Tolerance to the drug must not develop under the near Zero-order release profile of Transdermal delivery.
- The drug must not induce a cutaneous irritation or Allergic response
- Drugs, which have to be administered for a long

Period of time or which cause adverse effects to non-Target tissues can also, be formulated for Transdermal Delivery.

5) Permeation Enhancers:

Permeation enhancers or promoters are agents that have no Therapeutic properties of their own but can transport the Sorption of drugs from drug delivery systems onto the Skin. The flux, of drugs across the skin can be written as:

J = D Xdc/dx

Where,

D: is the diffusion coefficient and is a function of Size, shape and flexibility of the diffusing molecule as well As the membrane resistance;

C: is the concentration of the Diffusing species;

X: is the spatial coordinate.

Although the solution for

J:- with various boundary Conditions and membrane heterogeneities can be very Complex, the basic concepts regarding flux enhancement Can be found in above equation. The concentration Gradient is thermodynamic in origin, and the diffusion Coefficient is related to the size and shape of penetrate and The energy required to make a hole for diffusion.

Chemical Enhancer

Chemical that promote the penetration of topically applied drug are commonly referred to as accelerants , absorption promoters or penetration enhancers. Some of the most widely studied penetration enhancers are sulphoxide (DMSO) , fatty acid (oleic acid) , alcohol , glycol (propylene glycol) and surfactant (anionic surfactant)

Chemical Enhancer act by :

- Increasing the thermodynamic activity of the drug when functioning as cosolvents .
- Increasing the partition coefficient of the drug to promote it's release from the vehicle into the skin .
- Condition of Stratum corneum to promote drug diffusion .
- Promoting penetration and establishing drug reservoir the stratum corneum.

(2)Physical Enhancers

Iontophoresis and ultrasound techniques are examples of he physical means of enhancement that have been used for enhancing percutaneous penetration of various therapeutic agent .

1) Iontophoresis is the method of transferring substance across the Skin by applying the electrical potential difference . It promotes the transfers of charged ionic drug and possibly high molecular weight substance such as peptide . Electric current is applied through two electrodes placed in the patient skin .

2) Ultrasound techniques: The ultrasonic energy distrubs the lipid packing in stratum corneum by cavitation . Sonicatores operating at frequencies in the range of 20 kHZ to 3 kHz are available commercially and can be used for frequencies.

Ideal properties of penetration enhancers [7]

- The should be non toxic , non irritating and non allergic .
- They should ideally work rapidly , and the activity the duration of the effect should be both predictable and reproducible.
- They should no pharmacological activity with in the body , i.e should not bind to receptor site
- The penetration enhancers should be work unidirectional
- When the removed from skin barrier properties should return both rapidly and fully .
- They should be cosmetically acceptable with an appropriate skin feel.

Surfactants: These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the head group and the hydrocarbon chain length. These compounds are skin irritants, therefore, a balance between penetration enhancement and irritation have to be consider.

Examples of commonly used surfactants are

Anionic Surfactants: Dioctyl sulphosuccinate, Sodium Lauryl sulphate, Decodecylmethyl sulphoxide etc.

Nonionic Surfactants: Pluronic F127, Pluronic F68, etc.

Bile Salts : Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

4] Types of transdermal patches [4,5,]

1. Single-layer drug -in-Adhesive

The adhesive layer of this system also contains wood. Ku this type of pool adhesive layer does Not just work with adhesive various layers together, and the whole system in skin, but also Responsible for the release of the drug. The adhesive layer is surrounded by a temporary liner And a support.

2. Multi-layer Drug-in-Adhesive

The multi-layer drug-in adhesive patch is similar to a single layer system in that both adhesive Layers are also responsible drug extraction. Multi-horizontal system different however is that it Adds another layer of wood -adhesive, usually separated by a membrane (but not at all charges). This clip also has a temporary liner layer and permanent support.

3. Reservoir

Unlike Single-layer and Multi-layer Drug-inadhesive systems reservoir transdermal system has A different drug layer. The drug layer is a fluid that contains a drug solution or suspension Separated by a coating layer. This clip is also supported by a supporting layer. In this type of System release rate is zero order.

4. Matrix

The Matrix system consists of a drug matrix of semisolid matrix containing a drug solution or Suspension. Paste layer in between this clip wraps around a thin layer of wood.

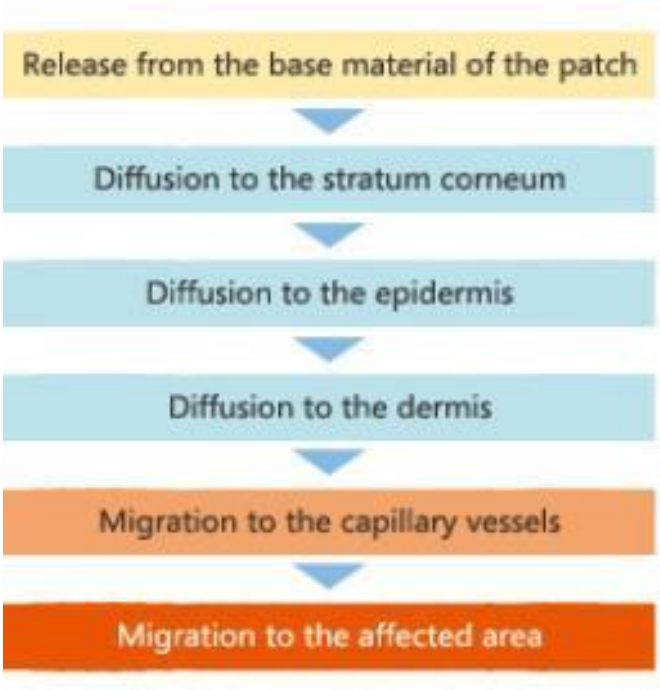
5. Vapor Patch

In this type of patch the adhesive layer is not only functional sticking different layers together But also releasing vapor. Vapor patches are new to the market and are releasing essential oils For up to 6 hours. Vapors patches are released essential oils and are used in congestion Conditions in particular .

Some steam sheets on the market are steam controller pamphlets Improve sleep quality. The vapor closes that reduce the amount of cigarettes a person smokes Per month are also available in the market.

5] Mechanism action of Transdermal patches [6,7,8]

The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer.



Flowchart 1.mechanism action of transdermal patch

6] Approaches [7,9]

I. Membrane moderate system

Various technologies have been developed to provide quality control the release and transdermal permeation of the drug.They are referred to as Membrane moderate system: Solid drug dissolves in a solid polymer matrix or in a viscous liquid again coveredin a shallow area associated with the drug Stainless steel plastic laminate and quality control polymeric membrane .Drug molecules enter just to release polymeric membrane control level rate limit . membrane can be microporous or non porous polymeric membrane with known anti-drug properties. To access to close links to the drug delivery system with skin, a thin layer of hypoallergenic drug adhesive polymer can be used. Drug withdrawal rate from the transdermal drug delivery system can be maintained by changing the composition of the polymer, consistency efficiency or thickening of the reducing membrane once adhesive. Internal level of drug release in this type of the drug delivery system is provided as

$$\frac{dQ}{dt} + \frac{\mathrm{CR}/1}{Pm} + \frac{1}{Pa}$$

There,

CR = Drug overflow in water storage.

Pa = Collaborative work of the strength of the attachment layer.

Pm = Co-operation to measure the level of membrane control.

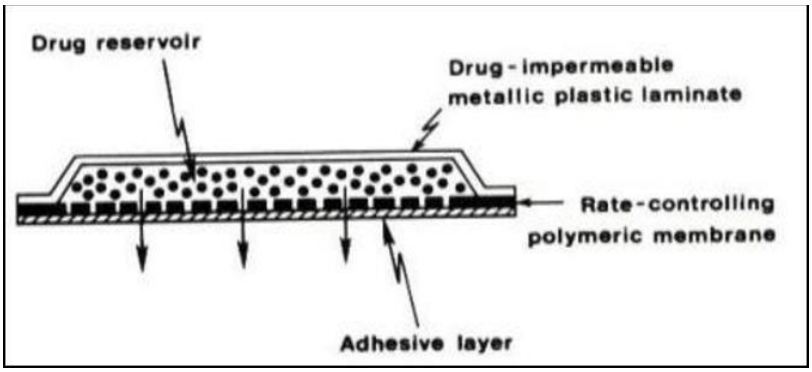


Fig 6. Membrane moderated TDDS

II. Adhesive dispersion type System

In this program the drug directly disperses the drug to adhesive polymer and spread the Adhesive glue in the reservoir layer form a reservoir. In this non-layer medicated dose Controlled polymer adhesive of regular thickness is used .The drug release rate of this type of System is defined as

$$\frac{dQ}{dt} = \frac{\frac{\text{Ka}}{\text{r}}.\text{Da}}{ha} . CR$$

There,

Ka / r = Partition co-efficient separation by face Drugs form a reservoir layer to the adhesive layer.

Da = Diffusion co-operation in the attachment layer.

ha = The strength of the adhesive layer.

CR = Drug overflow in water storage.

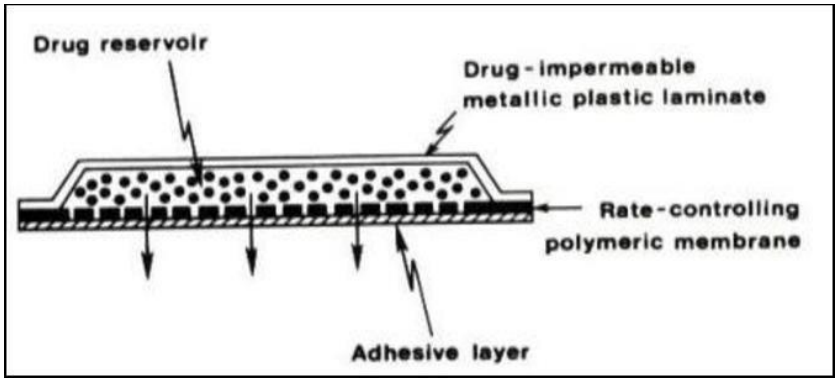


Fig 7Adhesive dispersion TDDS

III. Polymer Matrix diffusion controlled system:

In this project, the reservoir was formed by disbanding the similar drugs in polymer Hydrophilic or lipophilic matrix and then converted into a medical disc with precise location And controlled stiffness. The disc is attached to the top of the occlusive base plate in a Commissioned area from a non-slip plastic base. Glue the polymer is distributed circularly to Form an adhesive edge next to a disc with trees The rate of drug release in this matrix Distribution system is defined as

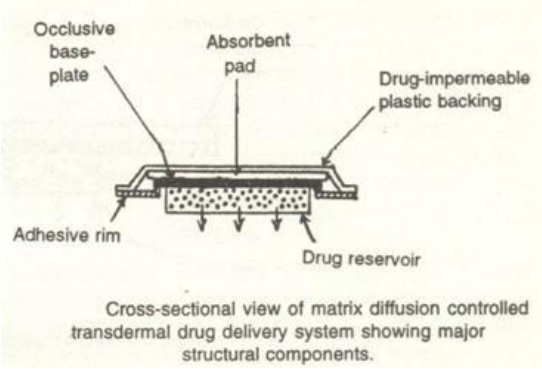


Fig 8.Matrix diffusion controlled system

$$\frac{dQ}{dt} = \left[\frac{ACp\ Dp}{2t}\right]\ 1/4$$

A = The initial load of the drug is dispersed in the polymer matrix

Cp = is a solubility of the Drug

Dp = is the diffusivity of the drug

IV. Microreservoir system

In this program the drug store is created first suspension of the drug (solid form) in aqueous Solution of a polymer dissolved in water and then dispersed evenly drug suspension in Lipophilic polymer with high shear mechanical force. Linking a polymer chain, in this case a Composite polymer disc of a permanent and defined surface thickening quickly strengthens this Dispersion.

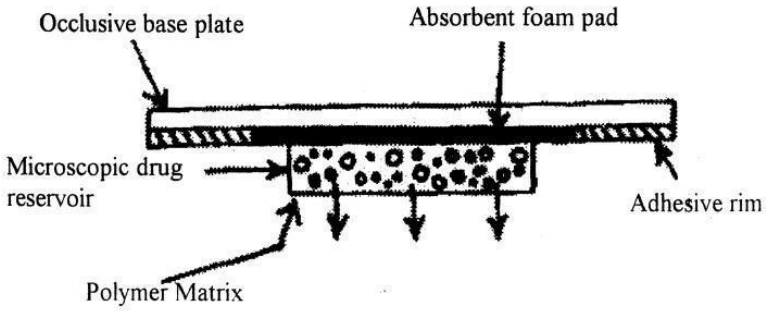


Fig 9. Micro reservoir controlled system

7] Evolution parameters of Transdermal patches [13,15,16]

- Weight uniformity
- Interaction studies
- Percentage moisture content
- Percentage moisture uptakes
- Drug content
- Water vapour permeability evaluation
- In-vitro drug release studies
- In vitro skin Permeation studies
- Skin irritation test

- Stability studies

2. CONCLUSION

This review provides knowledge about "Transdermal Drug Delivery" related to drug by discussing briefly the anatomy and physiology of skin penetration pathways, physicochemical property of drug molecules. Advancement in TDD Will lead to enhanced disease prevention, diagnosis and control, with concomitant improvement in Health-related quality of life for patients worldwide .To this end, this review has charted the development Of numerous novel TDD methodologies, highlighting the advantages and disadvantages of each Approach.After preparation of transdermal Patches, they are evaluated for physicochemical studies, in Vitro permeation studies, skin irritation studies, animal Studies, human studies and stability studies. Future Developments of TDDSs will likely focus on the increased Control of therapeutic regimens and the continuing Expansion of drugs available for use.

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