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RECENT ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal Drug Delivery System (TDDS) are topically administered medicaments that deliver drugs for systemic effects at predetermined and controlled rate. Polymer matrix, drug permeation enhances are the main components of TDDS. TDDS are of many types varying from single layer drug in adhesive to the multi-layer drug in adhesive and other are reservoir and matrix systems. TDDS is a recent technology which promises great future it has potential to limit the use of needles for administering wide variety of drugs. Transdermal patches are helpful to deliver specific dose of the drug. The main objective of TDDS is to deliver drugs into systemic circulation through skin with minimal inter and intra patient variations. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. This review on TDDS highlights various recent advancement, fabrication methods and improved efficacy of transdermal drug delivery system.

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INTRODUCTION

TDDS is defined as a system, where the medicament leaves the formulation and travels into the skin to provide its pharmacological action when applied topically. Transdermal Drug Delivery System are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A Transdermal Drug Delivery device, which may be of active or passive design is device which provides an alternative route of administering medication.

These devices allow for pharmaceutical to be delivered across skin barrier:-

A. First Generation Transdermal Drug Delivery system have continued their steady increase in clinical use for delivery of small, lipophillic, low dose drugs.
B. Second Generation delivery systems using chemical enhances non- cavitational ultrasound and inotophoresis.
C. Third Generation delivery systems target the effects to skin's barrier ,layers of stratum, corneum using microneedles , thermal ablation, microdermabrasion, electroporation and cavitational ultrasound. [1, 2].

Transdermal drug delivery manifests the progression in the arena of research and development, by increasing the efficacy of the product through delivery of innovative solutions. To overcome certain drawbacks associated with the traditional products, application of nanotechnology is escalating in the area of TDDS. Transdermal devices and patches are regarded as the fastest growing segment of the pharmaceutical industry and the use has risen drastically over the years. TDDS used for delivering the medication through skin, for local and systemic effects and have come into widespread use because of advancement in drug delivery techniques.

Advantages:-

Transdermal drug delivery System has various advantages:

- It helps to substitute for oral administration of medication when route is unsuitable in some conditions like vomiting, diarrhea and unconsciousness.
- Transdermal medication provides safe, convenient and pain free self-administration for patients.
- Helps to avoid first pass metabolism and also helps to avoid gastrointestinal drug absorption difficulties.
- Drug therapy may be terminated rapidly by removal of application from the surface of the skin.
- Transdermal Delivery may be useful in those patients who are polymedicated.
- Transdermal drug delivery provides a constant rate of release of medicine to maintain concentration level of drug for a longer period of time as to avoid peak and drop associated with oral dosing and parenteral administration.
- Transdermal patches improved therapeutic effects of various drugs by avoiding specific problems associated with drugs such as presystemic metabolism, formation of toxic metabolites, low absorption, gastrointestinal irritation etc. useful in drugs possesses short half-life as to avoid frequent dosing administration.[1,3,4]

Disadvantages:-

- The drug moiety must possess some physicochemical properties for penetration through skin and if dose of drug is large i.e. more than 10-25mg/day transdermal delivery is very difficult. Daily dose of drug preferred less than 5 mg /day.
- Only potent drugs are suitable for transdermal patch because of natural limits of drug entry imposed by skin's impermeability.
- Local irritation at the site of administration such as itching, erythema and local edema may be caused by drug or the excipients used in the formulations.
- Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
- Some patient develop contact dermatitis at the site of application due to components.
- Long time adhere is difficult.
- The barrier function of the skin changes from one site to another from person to person and with age. [1, 3, 4].

Anatomy of skin:

Skin Layers: -

Skin is multi-layered organ. It is the largest organ of the human body which cover a surface are of approximately 2 sq. m and receives about one third of the blood circulation through the body. It serves as permeability barrier against the transdermal absorption of various chemical and biological agents. Skin has three layers –Histological layers.

a. Epidermis: -Epidermis is outermost layer of skin, provides waterproof barrier and creates our skin tone.

b. Dermis: - Dermis present below the epidermis, contains through connective tissue, hair follicles and sweat glands.

C. Hypodermis: - Deeper hypodermis is made of fat and connective tissue. Fig 1 shows different layers of skin.

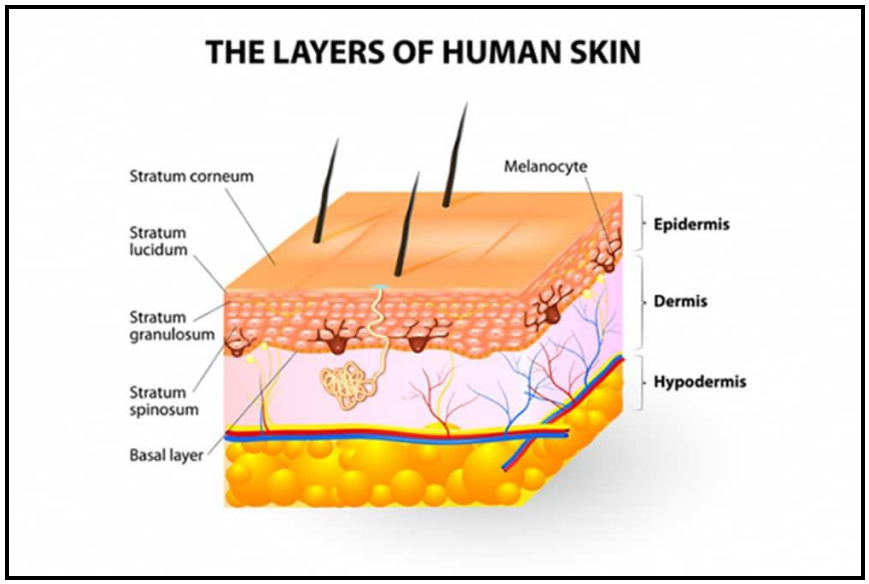

Fig 1: The layers of skin.

Drug Delivery across skin:
When molecule reaches intact skin, it contacts with cellular debris, sebum and other materials, these molecules can penetrate by
a. Sweat ducts.
b. Hair follicles.
c. Sebaceous glands.
d.
The release of therapeutic agents from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process are shown in fig 2.

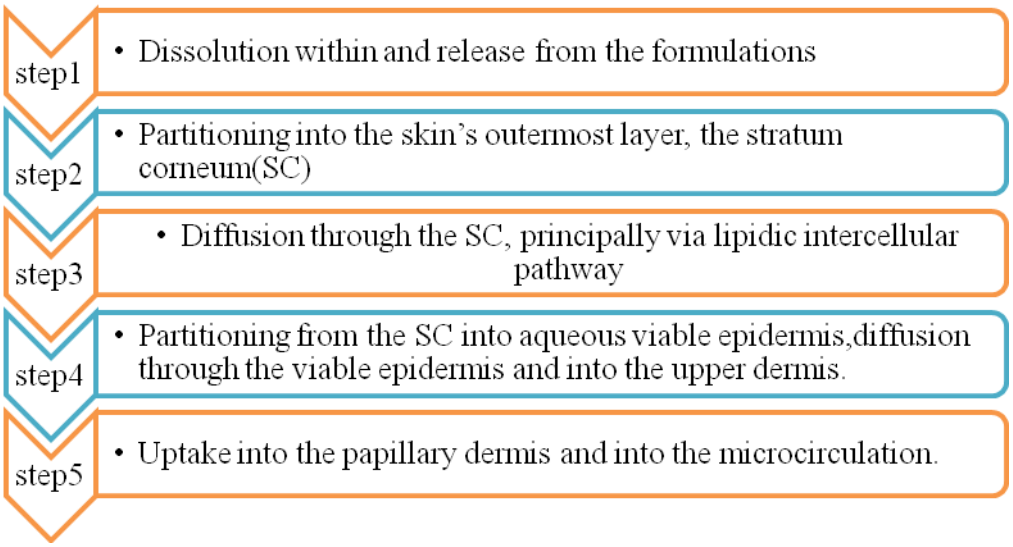

Fig 2: Release of therapeutic agents from TDDS.

Routes of Drug penetration through skin:

In the process of permeation, a drug molecule may pass through epidermis or may get diffuse through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands.
Drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium and sebaceous glands.

Properties that influence transdermal delivery:

I. Release of the medicament from the vehicle.
II. Penetration through skin barrier.
III. Activation of the pharmacological response. [4, 5].

Factors Affecting Transdermal drug Delivery system:-

Biological factors-

Skin Condition :->

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

Skin age :->

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

Blood supply :->

Changes in peripheral circulation can affect transdermal absorption

Skin metabolism :->

Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

Physicochemical factors-

Skin Hydration :->

Generally when water saturates the skin, it swells the tissues, soften wrinkles on the skin and its permeability increases for the drug molecules that penetrate through the skin.

Partition Coefficient :->

The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of the skin. Also, drugs with low K will not be permeated.

Molecular size and shape :->

Drug absorption is inversely related to molecular weight, small molecules penetrate faster faster than large ones.

Temperature and PH of the skin :->

The penetration rate varies of if the temperature varies and the diffusion coefficient decreases as the temperature falls; however adequate clothing on the body prevents wide fluctuations in temperature and penetration rates. According to PH, only unionized molecules pass readily across the lipid membrane, and week acids and bases dissociate to different degrees according to their pH and pKa or pKb values. Thus the concentration of unionized drug in applied phase will determine the effective membrane gradient, which is directly related to its pH.

Environmental factors-

Sunlight :->

Because of sunlight the walls of blood vessels become thinner leading to bruising with only minor trauma in sun exposed areas.

Air pollution :->

Dust can clog pores and increase bacteria on the face and surface of skin, both of which lead to acne or spots. This affects drug delivery through the skin. Invisible chemical pollutants in the air can interfere with skin's natural protection systems, breaking down the natural skin's oils that normally trap moisture in skin and keep it supple. [1, 4, 6, 7].

Components of TDDS:-

- Polymer matrix.
- Permeation enhances.
- Pressure sensitive adhesive.
- Other excipients.

Polymer matrix:-These control the release rate of the drug from the device and are hence considered as the backbone of the system. These are generally prepared by dispersing the drug in liquid or solid state synthetic polymeric base.

Permeation enhancers:-The chemical compounds that increase permeability of stratum corneum i.e. proteins or lipids and alter the protein and lipid packaging of stratum corneum and modifying chemically the barrier functions which increases permeability. **(5, 7, 8)**.

Evaluation of transdermal patches:-

Development of controlled release transdermal dosage form is a complex process involving extensive research transdermal patches have been develop to improve clinical efficiency of the drug & to enhance patient compliance by delivering smaller amount of drug at the predetermine rate.

This makes evaluation studies even more important in order to ensure their desired performance & reproducibility under the specified environmental condition.

Evaluation parameters are classified into following type

1. Physicochemical evaluation
2. In vitro evaluation
3. In vivo evaluation

Physicochemical evaluation [9, 10]

a. Thickness:-The thickness of transdermal film is determined by travelling microscope, dial gauge .Screw gauge or micrometer at different point of the film.
b. Uniformity of drug:-Weight variation is studied by individually weighting to randomly selected patches calculating the average weight. The individual weight should not deviate significantly from the average weight.
c. Dug content determination:-Accurately weighed portion of the film is dissolved in suitable solvent in which drug is soluble and evaluated spectrophotometrically
d. Content uniformity test:-10 patches are selected and content in between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115% then the transdermal patches pass the test.
e. Moisture content: - The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 hr.

Formula:

Percent moisture content: - $\frac{\text{Initial weight - Final weight X 100}}{\text{Final weight}}$

f. Moisture uptake:-Weighed films are kept in desiccators at room temperature for 24 hours. Percent moisture uptake is calculated as given below.

Formula:

Percent moisture uptake: - $\frac{\text{Final weight –Initial weight X100}}{\text{Initial weight}}$

g. Flatness:-A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study.
h. Folding Endurance:- Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding.

The number of times the films could be folded at the same place without breaking is folding endurance value.

Adhesive studies:-

I. Shear adhesion test:-This test is applied to determine the cohesive strength of the adhesive polymer. The adhesive coated patch is applied over a smooth surface and a specified weight is hung to patch parallel to the surface. The time it takes to pull off the patch from the surface gives its shear adhesion property.
II. Peel adhesion test: - The force required to remove the patch from a surface is calculated in this test. The patch is applied on the surface of a steel plate and is pulled away at 180^0 angle from the surface. The force required to pull off the patch is measured.
III. Tack properties: - It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymers.

Test for tack include:-

I. Thumb tack test: - This is subjective test in which evaluation is done by pressing the thumb in to the adhesive.

II. Rolling ball test: - This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive, the less tacky the adhesive, the further the ball will travel. Apparatus is shown in fig 3.

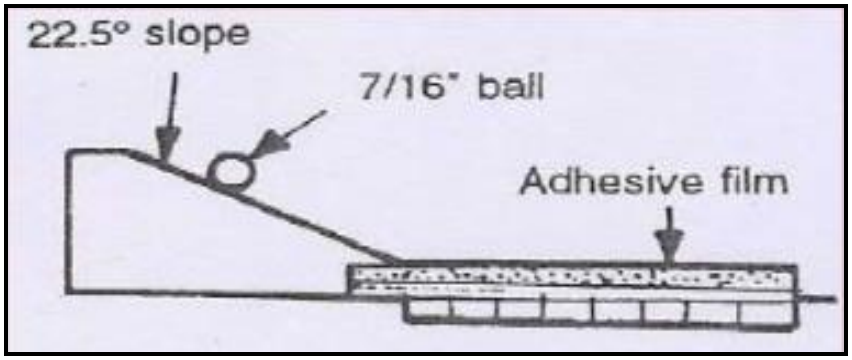

Fig-3: Rolling ball tack test for adhesive evaluation.

III. Peel tack test:-The peel tack test required breaking the bond between and adhesive and substrate is measured by pulling the tape away from the substrate at 90 at the 12 inch/min.Apparatus utilized for the test is shown in fig 4.

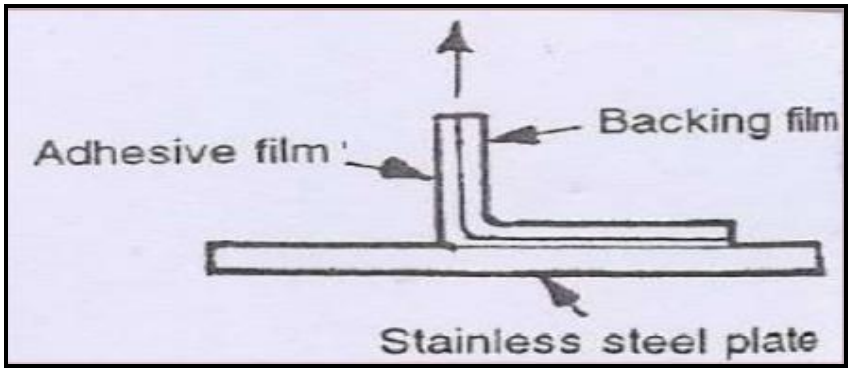

Fig-4: Quick stick test for adhesive evaluation.

In vitro evaluation:-Drug release mechanism and kinetics are two characteristic of the dosage forms which may play in important role in describing the drug dissolution profile from a controlled release dosage forms and hence there in vivo performance.

In vitro dissolution test can be performed by the following type:-

a. The paddle over disc:- This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32+ 5^0C.

b. The cylinder modified USP basket:-This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32+ 5^0C.

c. Permeation of skin for permeation study:- An in vitro permeation study can be carried out by using diffusion cell. These can be use when the drug has lower solubility in the receptor compartment. These cell can be fully automated and connected directly to HPLC. Usually permeation study are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in a vertical diffusion cell such as Franz diffusion cell or Keshary-chin diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophilic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature and continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted approximately and absorbance is determine spectrophotometrically. Then the amount of drug permeated per centimeter square at each time interval is calculated. Franz diffusion cell is shown in fig 4 which is used for permeation test.

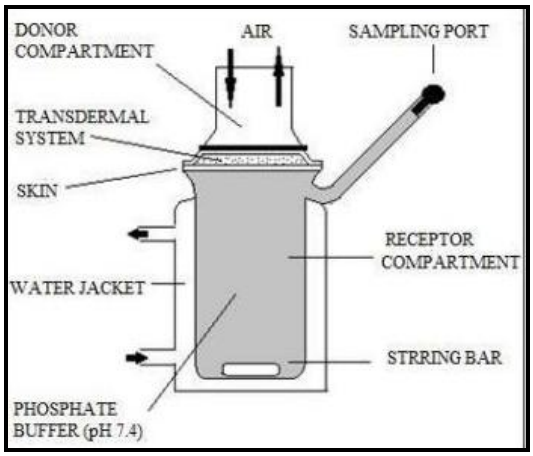

Fig 5: Franz diffusion cell.

In Vivo evaluation:- In vivo evaluation 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:

a. Animal models
b. Human volunteers

I. Animal models:-Most preferably in vivo study is conducted on animal models as compared to human models because of easy availability of animals.Varies species of mouse, rat, dog, monkey, gunia pig, cat, rabbit and squirrel are preferred over hairy animals for transdermal formulation evaluation.

II. Human Volunteers: - In final stage of formulation development human volunteers are studied to determine the pharmacokinetic and pharmacodynamic profile of the drug including safety and efficacy of the formulations. Clinical trials are conducted in IV phase.

Phase-I trials are conducted on small groups of volunteer to determine the safety and toxicity profile.
Phase-II trials are conducted on a small group of patient for safety and toxicity for short term.
Phase-III study is conducted on a large group of patients.
Phase-IV is the post marketing survey. [1,6,7,8,9,].

Available Market Products for TDDS: - [10, 11].

The market for Transdermal products has been in a significant upward trend that is likely to continue for the future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. The table gives detail information of the different drugs which are administered by this route and the common names by which they are marketed. It also gives the conditions for which the individual system is used. Table 1 enlists different available transdermal products.

Table 1: Different transdermal marketed products.

Product Name	Drug	Manufacturer	Indication
Alora	Estradiol	TheraTech/Proctol Gamble	Postmenstrual Syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism in Males
Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Postmenstrual Syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
Combipatch	Estradiol/Nore thindrone	Noven , Inc/Aventis	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-pharma	Angina pectoris
Duragesic	Fentanyl	Alza/janssen pharmaceutical	Moderate/severe pain
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome
Fematrix	Estrogen	Ethical Holdings/solvay Healthcare Ltd.	Postmenstrual syndrome
Fempatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Habitraol	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nicotrol	Nicotine	Cygnus Inc /McNeil Consumer Products, Ltd	Smoking Cessation

Recent advances in the field of transdermal patches:-
There are many technologies which are available in this field.

Patch Technology for protein delivery:-
-Transdermal delivery of large proteins is novel and exciting delivery method.
There is no commercial technology currently available for that.
Transpharma uses its unique printed patch technology, such patches contains accurate doses of proteins in dry state.
It is postulated that highly H2O soluble proteins are dissolved by interstitial fluid i.e. secreted from skin through RF-micro channels, into the viable tissues of the skin, diffusing across steep concentration gradient.

Pain-free diabetic monitoring using transdermal patches:-
-It becomes utilizing micro-heating elements integrated into the structural layer of the patch closest to the skin surface, high temperature heat pulse can be applied locally, breaching stratum corneum.
-During this process, the skin surface experiences temperature of 1300C for 30 minutes.
-The temperature diminishes rapidly from the skin surface and neither living tissue nor the nerve endings are affected.
-This is painless and bloodless process, the size of hair follicle, allowing the interstitial fluid to interact with the patch's electrode sites.

Testeron transdermal patch system in young women with spontaneous premature ovarian failure :-
-In premenopausal women, daily testosterone production is approximately 300mg of which approximately half is derived from the ovarian failure may have lower androgen levels, compared with normal ovulatory women.
-Testosterone transdermal patch (TPP) was designed to deliver the normal ovarian production rate of testosterone.

Molecular absorption enhancement technology:-
-Considerable research has been done on absorption enhancers, compounds that promote the passage of drugs through the stratum corneum.
-Terpene derivatives as well as certain phenols to improve transdermal absorption.
eg. Linalool, alpha-terpineol and carvacol.

Future technologies and approaches:-
-Thermal portions is the formation of aqueous pathways across stratum corneum by the application of pulsed heat, this approach has been used to deliver conventional drug and to extract intestinal fluid glucose from human body.
-Jet injectors are receiving increased attention now days, which is opening doors for improved device design for controlled, needle free injection of drug solutions across skin and into deeper tissue.
-Small needle is inserted few mm into skin and drug solution is flowed through the needle into the skin at controlled rates using micro-infusion pump i.e. contained morphine has been delivered to humans using this approach.
-Trans Pharma is focused on products for which our technology will provide clear benefits over existing therapies.
-The via derm system may be applied to the delivery of local medications for topical applications in the fields of dermatology and cosmetics. [3, 4].

Some recent research's in TDDS are highlighted in table 2.

Table 2: Recent Research Reports of TDDS [12].

DRUG	TYPE OF PATCH AND PREPARATION METHOD	REMARKS
IQP-0410 (HIV Inhibitors)	EC/HPMC based transdermal films and solvent casting technique.	Successful in vitro reduction of HTV-1 activity from the delivered drug over 3 day application suggests potential of IQP-0410 to be administered via transdermal patches.
Donepezil	Matrix type transdermal films.	Alternative delivery approach in alzheimer's Disease treatment.
Buprenorphine	Drug in Adhesive Patch and using Box-Behnken Experimental design.	Chemical preparation enhancers could enhance permeation flux of buprenorphine through the skin.
Zolmitripton	Drug in Adhesive patch and solvent evaporation technique.	Pharmacokinetic parameters were determined via IV and transdermal administrations using animal model of rabbit.
Khordal (Brasicanigra)	Drug in Adhesive Patch and Solvent Evaporation technique.	-Design and Development of an antiemetic transdermal in novel dosage form for a common clinical condition, such as vomiting/emesis. -The patch was found to be stable and should no signs of skin irritation.

Some recent approaches in formulation of TDDS:-

Micro fabricated Micro needles:

-For the sophisticated drug there are need of sophisticated methods for their delivery.

-conventional drug delivery techniques using pills and injections not suitable for transdermal protein based, DNA based and other therapeutic compounds produced by modern biotechnology.

-This approach can avoids degradation in GI tract and first pass effects of the liver.

One technique is Inotophoresis which have an electric field to drive:

- Ionized molecules across skin by the electrophoresis and
- Non-ionized molecules by electro-osmosis.

-In recently, physical methods to increase skin permeability using electroporation and ultrasound is shows effects for delivery of both smalls and micromolecules.

- In novel approach new invention is micro needles. We have used standard microfabrication techniques to etch arrays of micron-size needles into silicon.

-When these needles arrays are inserted into skin, they create medium for transport across stratum corneum, once compound crosses stratum corneum it can diffuse rapidly through deeper tissue and taken up by the capillaries for systemic administrations.

-There are so many products which are newly formulated or advanced products in case of TDDS.[13]

Emulgels:-

-An emulgel is combination of an emulsion and gel.

-Although gels have many advantages, the delivery of hydrophobic drugs has consistently been point of concern. To overcome this limitation, emulgels were introduced and have been used for hydrophobic drug delivery.

-The presence of a gelling agent in the water phase converts a classical emulsion into a emulgel.

-Emulgels have several favorable dermatological properties such as greaselessness, spreadability, emollient, pleasing appearance.

-Emulgels have high patient acceptability because it contains combined effects of emulsion and gels.

Bigels or biphasic gel:-

-Bigels are topical formulations that are obtained by combining on aqueous and lipophilic system.

-These homogenous preparations are prepared by mixing aqueous and lipophilic system at a high shear rate or rpm.

-Since there is no surfactant or emulsifier, bigels differ from creams and emulgel in terms of formulation.

Hydrogels:-

-Gels that consist of an aqueous dispersion medium i.e. gelled with suitable hydrophilic gelling agent are known as hydrogels.

-Hydrogels are three-dimensional hydrophilic polymer networks, which have the ability to absorb large quantities of water.

-Hydrogels can be formed via chemical or physical cross links, which provide networked structure and physical stability.

-Drug release from hydrogels can occur from different mechanisms: diffusion and by chemical stimulation.

i. Diffusion is regulated by movement through the polymer matrix or by balk errosion of the hydrogel.
ii. Chemical stimulated gels swell in response to external cues like PH and temperature or by enzymatic action and effectively open their pores of the entrapped drug. [14, 15].

Examples of TDDS Drug:-
TRANSDERM-NITRO:- Nitroglycerin Once a day medicastion for angina–NOVARTIS.
TRANSDERM-SCOP:- scopolamine for 72 hrs in the treatment of motion sickness-NOVARTIS.
TRANS-VER-SAL:- Salicylic acid for topical keratolytic action-DOAK.
Several for Anti-hypertension, Anti-angina, Anti-histamine, Anti-inflammatory, and steroids.[2]

CONCLUSION

TDDS is newer approach in area of dosage forms for many injected and orally delivered drugs having appropriate physicochemical and pharmacological properties. Successful transdermal drug application requires numerous considerations. Basic functions of the skin are protection and containment, hence it seem exceptionally difficult to target the skin for drug delivery. However, with our greater understanding of the structure and function of the skin, and how to alter these properties, more and more new drug products are being developed for transdermal delivery. This article provide an valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who are involved in TDDS.In this article various recent approaches utilized for fabrication of TDDS are focused which would help in enhancing research related to TDDS.

List of abbreviations:
TDDS - Transdermal drug delivery system.

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Conflicts of interests:
Nil

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