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ADVANCEMENTS IN SKIN DELIVERY: A TRANSDERMAL SCIENCE

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ABSTRACT: Transdermal drug delivery system (TDDS) provides an alternate safe way of drug delivery compared to other invasive techniques. Documented advancement in transdermal science provides sustainable delivery of drug molecules, improved bioavailability, the better therapeutic efficacy of embedded drug's and ability to deliver the drug at a constant rate and also reduces the adverse effects associated with oral delivery of drugs. Skin provides a formidable barrier for topical delivery of drugs to overcome its various agents have been used. TDDS have received more attention recently due to their unique features such as improve bioavailability, controlled release of medication and better patient compliance. Transdermal patches, which consist of the drug along with other ingredients provide an effective way to overcome this barrier. The present review mainly focuses on the various advancement of transdermal drug delivery, the various available method for preparation of transdermal patches, characterization and assessment tools for transdermal patch preparation, patents filled, clinical trial performed on transdermal compounds along with drug approved and future applications of transdermal drug delivery system.

INTRODUCTION: Transdermal drug delivery system (TDDS) is a method to administer drugs through the skin for the systemic as well as for local distributions [1]. TDDS *via* the skin to the systemic circulation gives as a suitable route of administration for a variety of clinical applications [2]. Transdermal drug delivery has various advantages compared to the oral route. In particular, the first-pass effect that is responsible for the pre-systemic metabolism of drugs can be avoided.

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Besides, it has certain other benefits such as drugs that can be transdermal drug delivery under suitable rate control could minimize the pulse entry into the bloodstream and undesirable side effects particularly seen with peak plasma levels can also be avoided [3]. Depending upon their design, transdermal patches used today are broadly classified into two main categories: reservoir-type and matrix-type patches detailed below in this manuscript. The number of a drug candidate that can be delivered by transdermal patches is still low in spite of recent success.

In order for a drug to be delivered across the skin, it must have three basic characteristics: small molecular mass (<500 Da), high lipophilicity and small dose (up to milligrams). The smallest drug planned in a patch is nicotine (162 Da) and the largest is oxybutynin (359 Da). The transdermal

drug delivery is the delivery of large hydrophilic drugs across the skin is still a major challenge [4].

Important Breakthrough in Transdermal Drug Delivery: Various advancements took place in the last century **Fig. 1** describes the development which took place over the period of the last 100 years in the transdermal drug delivery system.

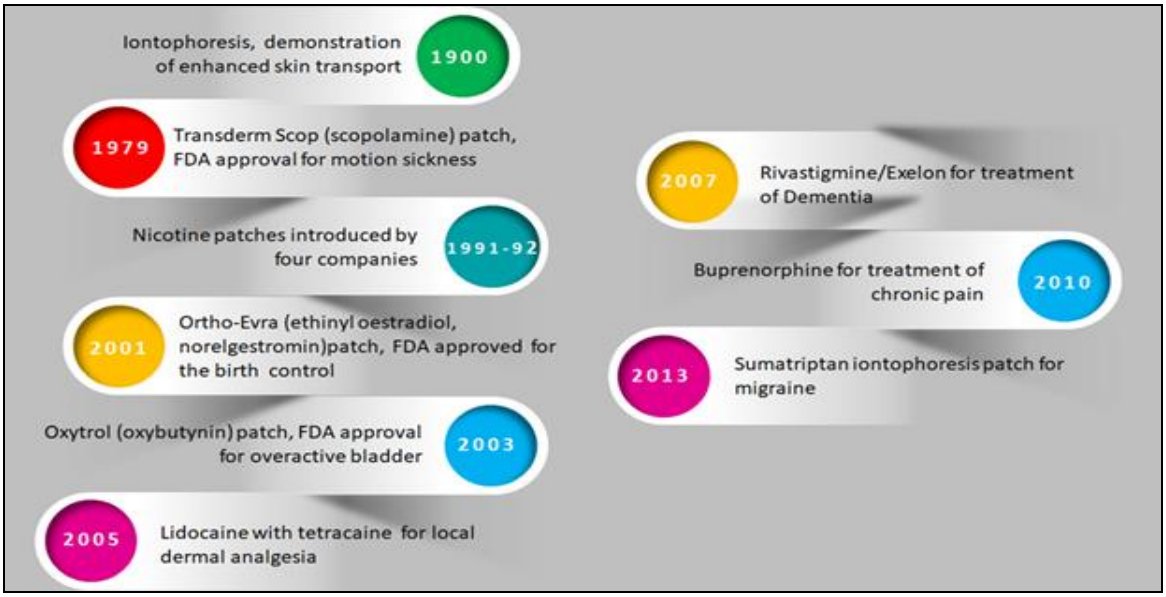

FIG. 1: IMPORTANT BREAKTHROUGH IN THE TRANSDERMAL DRUG DELIVERY SYSTEM

2. Routes and Barriers for Drug Transport through Human Skin: Skin is the largest organ of the human body; skin provides a trouble-free and acquiescent interface for systemic drug administration. Human skin is an operative, selective barrier to chemical permeation, the epidermis precisely, the stratum corneum) provides the major barrier-most small hydrophilic, non-electrolyte diffuses thousand times rapidly when the horny layer is not present.

The special structure of the lipid-rich matrix in which corneocytes are fixed in the upper strata of the skin- the stratum corneum is mainly responsible for this barrier. The corneocytes which are made up of cross-linked keratin fibers are about 0.2-0.4 μm thick and about 40 μm wide.

The corneode-smosomes hold the corneocytes together, which is responsible for structural stability to the stratum corneum [5]. The stratum corneum is composed of cholesterol, ceramides and fatty acids that are assembled into multi-lamellar bilayers. This unusual extracellular matrix of lipid bilayers acts as the primary barrier function of the stratum corneum. The stratum corneum is continuously shaded off by the skin and is renewed every two to four weeks. It is continuously repaired by cellular secretion of lamellar bodies after the breakage of its barrier due to environmental insults. Stratum corneum lipid bilayer controls the transport of solutes.

Transportation of solute in stratum corneum lipid bilayer is very anisotropic size-dependent. Specifically, lipid bilayers show tough structural heterogeneity those results in spatial variations in the solute partition and diffusion coefficients.

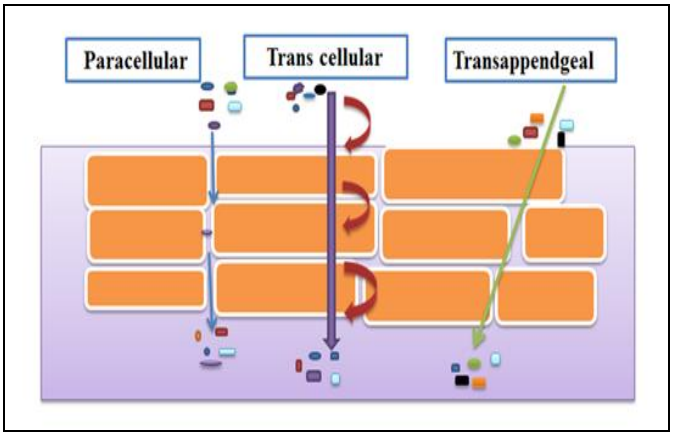

FIG. 2: ROUTES DRUG TRANSPORT THROUGH HUMAN SKIN

Because of that molecules are thought to diffuse across the skin following a difficult pathway within either the tail group (for hydrophobic molecules) or

head-group (for hydrophilic molecules) regions, in which transport between bilayers can occur at bilayer-bilayer interfaces or other sites of structural disorganization [6]. The mechanism of transportation of drugs across the skin is given in **Fig. 2**.

Factors Affecting Transdermal Permeation: There are numerous biological, formulation and physiological factors listed in **Table 1** which alter the permeation of drugs from the transdermal route [7, 8].

TABLE 1: FACTORS INFLUENCING TRANSDERMAL PERMEATION

Biological factors	Formulation factors	Physiological factors
Condition of skin	Type of vehicle used	Skin hydration
Anatomical site of application on skin	Method of application	Temperature and pH
Race and ethnicity	Use of penetration enhancers	Diffusion coefficient
Skin age	Type of membrane used	Drug concentration
Skin sensitization		Partition coefficient
Blood flow to theskin		Molecular size and shape

3. Methods to Improve Drug Delivery through the Skin: It is necessary to increase the transdermal delivery so that the drug can easily reach the systemic circulation and exerts its action [8, 9]. The following are the ways used to improve the permeation of drug through the skin in **Fig. 3**.

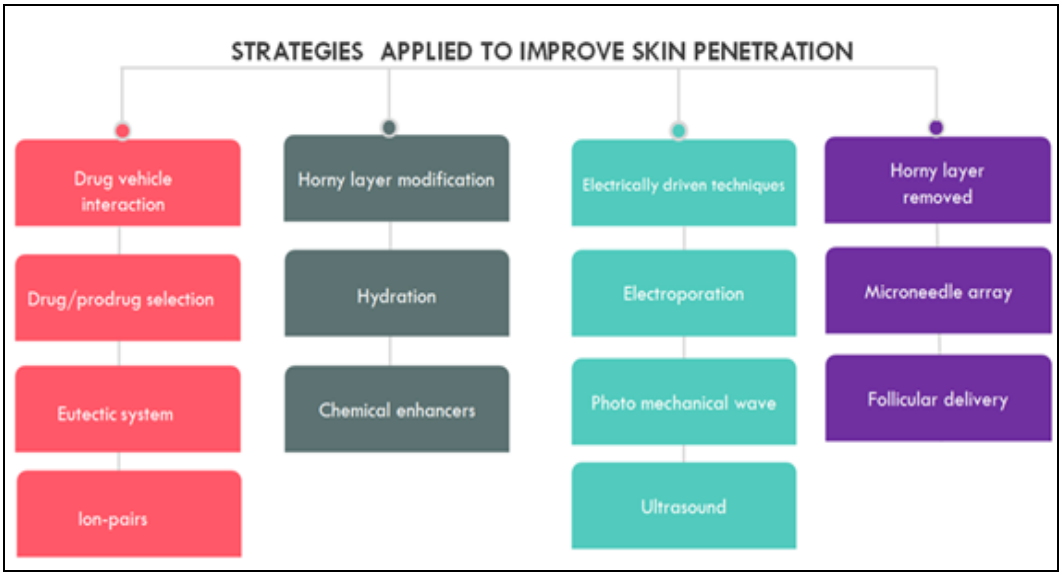

FIG. 3: METHODS TO IMPROVE PERMEATION THROUGH HUMAN SKIN

Prodrug/Drug: The use of prodrug has been recommended to escalate the transdermal delivery of a drug with a poor partition coefficient. The design of prodrugs involved the attachment of pro-moiety to enhance the partition coefficient and solubility of the original compound in the stratum corneum.

One such example of enhancing solubility and penetration involves esterification of beta-methasone to the 17-valerate analog, which increases its topical potency by 450 folds [9].

Iontophoresis: The iontophoresis involves the use of a tiny electrical current (usually, 500 microamperes cm ^{2}) to accelerate the passage of transfer of the drugs across the skin. The electrical potential across the membrane causes the charged species to repel into and through the skin. The effectiveness of this process depends upon the valency, polarity, current profile, *etc*. [9]

Eutectic System: A eutectic system is a blend of chemical compounds or elements that has a single chemical composition that becomes solid at a lesser temperature compare to other composition. Such changes result in better skin permeability because of their thermodynamic activity in vehicle [10].

Electroporation: Electroporation requires the use of short, high voltage electrical pulses to the skin. This has been suggested to produce transient pore formation. High voltage (1000 v) and a short period (milliseconds) are most commonly used.

This method is used to enhance the skin penetration of molecules with lipophilicity and molecular weight more than 7 kilos Dalton [10].

Ultrasound: The ultrasound requires the use of sound frequency greater than kHz to compromise the skin barrier. The frequency varying from 20 kHz to 10 MHz with intensities of up to 3W cm^2 have been used in order to increase transdermal drug delivery [10].

Chemical Enhancement: The most thoroughly investigated enhancement tactics encompass the use of chemicals which can reversibly alter the skin's barrier function and thus allow the passage of molecules into the membrane and through to the systemic circulation. Some of the substances which can be used for this purpose include amines, alcohol, fatty acids, esters, surfactants and phospholipids [10].

4. Transdermal Patch:

- A transdermal patch is a medicated adhesive patch which when placed on skin deliveries a particular dose of medicine *via* skin in the systemic circulation. The important parts of the transdermal patch are:
- Liner-It safeguards the patch during storage; it should be removed before application.
- Drug-it is at direct contact with release liner.
- Adhesive-it holds all the components of the patch together with keeping the patch to the skin.
- Membrane-the release of the drug from the reservoir and multi-layer patches is controlled by the membrane.
- Backing-it protects the patch from environmental damage [11].

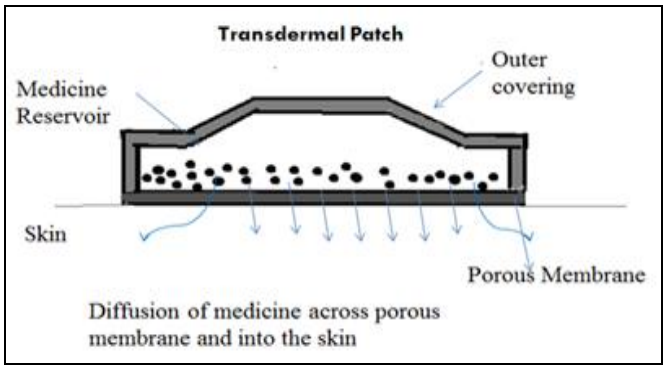

FIG. 4: BASIC COMPONENTS OF TRANSDERMAL PATCH

Types of Transdermal Patches:

Single-Layer Drug-in-Adhesive: In the single-layer drug-in-adhesive system drug is in direct contact with the skin-contacting adhesive.

The adhesive not only acts to keep the system to the skin but also works as the foundation for a formulation that contains the drug and other all the excipients under a single backing film [12].

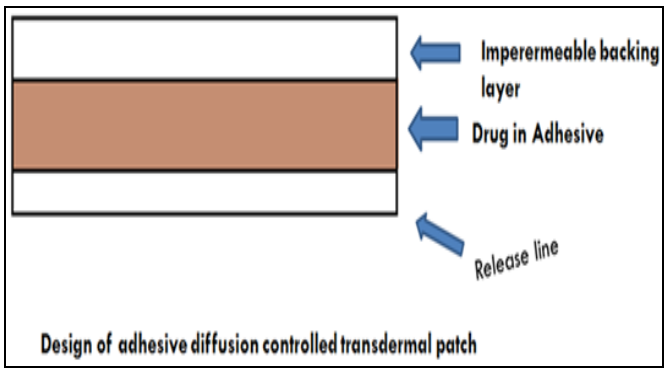

FIG. 5: SINGLE-LAYER DRUG-IN-ADHESIVE

Multi-Layer Drug-in-Adhesive: It is similar to the Single-layer Drug-in-Adhesive in that the drug is added directly into the adhesive. But the multi-layer encloses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film [12].

Reservoir: This system has a separate layer of the drug. The layer of a drug is a liquid chamber that contains the drug solution or suspension segregated by an adhesive layer. The backing layer is also present to provide support to the patch. This patch provides a zero-order drug release [13].

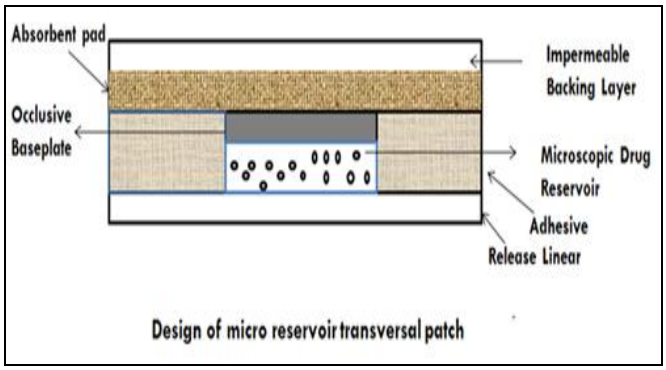

FIG. 6: RESERVOIR TYPE TRANSDERMAL PATCH

Matrix Type: The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it [13].

5. Characterization and Assessment Tools for Transdermal Patch Preparation:

Drug-Polymer Interaction Studies: Interactions between drugs and polymers in a lipid matrix can be determined using a number of thermal and physico-analytical techniques (82-84), such as differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FTIR), X-ray powder diffractometry (XRPD), nuclear magnetic resonance (NMR) spectroscopy, and infrared (IR) radiation. The identification of components in an eutectic drug-polymer mixture is possible because each chemical has a unique peak in DSC, IR and NMR spectra. To observe interactions between cell surface and polymer, a fluorescence agent is attached to the polymer, the complex is incubated with cells, and the polymer-cell complex is visualized under a confocal microscope. NMR can be used to clarify the effect of the polymer on lipid membrane fluidization/ stabilization [14].

Patch Thickness: Patch thickness is calculated by taking readings at three to five places on the patch with a digital micrometer screw gauge. Mean thickness and standard de*via*tion of such multiple readings are determined to make sure that patch thickness is appropriate [14].

Weight Uniformity: Weight uniformity is determined by weighing 10 individuals, randomly selected patches, and calculating the average weight and standard de*via*tion. Individual patch weight must not vary to a large extent from the average weight [14].

Folding Endurance: When a particular part of the patch is sliced evenly and repeatedly folded at an identical point until it breaks, folding endurance is the number of times the film is folded without breaking [14].

Percent Moisture Content: The films which are prepared and weighed are put in a desiccator where fused calcium chloride is already kept at the room. After 24 h films are reweighed, and moisture content is determined by the given formula [15].

Percentage moisture content = [Initial weight - Final weight / Final weight] × 100

Percentage Moisture Uptake: The films which are prepared and weighed are kept at desiccator for 24 h at room temperature. It also contains a saturated solution of potassium chloride for maintaining 84% relative humidity. After 24 h the wright of films is taken again and percentage moisture content is determined by given formula [15].

Percentage moisture uptake = [Final weight - Initial weight / initial weight] × 100

Drug Content: A particular part of the patch is dissolved in an appropriate solvent in explicit volume. Then the solution is passed from a filter medium for and drug content is analyzed by a method that is best suited (UV or HPLC technique). Each value is representative of a mean of three samples [15].

Uniformity of Dosage Unit Test: The required portion of the patch is cut into tiny pieces and shifted to a volumetric flask of a particular volume. It is dissolved in a specific solvent and sonicated to totally extract the drug from the patch. The solution which results is kept for settlement for an hour, and the supernatant was diluted to the required concentration with the solvent. The filtration of a solution is done *via* 0.2 µm membrane filter and analysis is performed by UV or HPLC and drug content in each piece is calculated [15].

Polariscope Examination: This test is used to determine the drug crystals from the patch by polariscope. A particular surface area is placed on the object slide, and the observation of drugs crystals is made to distinguish the presence of either crystalline or amorphous form of the drug in the patch [15].

Shear Adhesion Test: This test is carried to determine the cohesive strength of an adhesive polymer. The tape which is coated with adhesive is applied onto the stainless-steel plate hang from the tape, to carry it pulling in a direction parallel to the plate. The time taken to pull off the tape indicates the shear adhesion strength. Shear strength is the directly proportional time taken for removal of the tape [11].

Peel Adhesion Test: In this test, the power required to expel an adhesive covering structure a test substrate is called peel adhesion. The molecular weight of adhesive polymer, amount and type of additives are variables to measure peel adhesion

test. A solitary tape is connected to a tempered steel plate or backing membrane and afterward, the tape is drag from the substrate at a 180° edge and the power required for tape expelled is estimated [11].

Thumb Tack Test: This test is used to determine the tack property of adhesive. The pressing of the thumb is done on the adhesive and the relative tack property is checked [11].

Flatness Test: Each strip is cut into three longitudinal strips at the various parts one is cut from inside one from the left side and another one from the exact side.

The length of each strip was estimated and the changes in length as a due to non-consistency in flatness were estimated by deciding percent constriction with 0% constriction is equal to 100% flatness [11].

Percentage Elongation Break Test: Percentage Elongation break can be evaluated by observing the length before breakpoint, it can be calculated by using formula.

$$\text{Elongation percentage} = L_1\text{-}L_2/\ L_2 \times 100$$

Where L_1 is the final length of each strip, and L_2 is the initial length of each strip [11].

Quick Stick (Peel-tack) Test: In a quick stick test, the tape is expelled away from the substrate at 90 ºC at a speed of 12 inches/min. The strip power needed to break the bond among adhesive and substrate is estimated and tack value, which is communicated in ounces [15].

Probe Tack Test: In this test, the tip of a pure probe with a well-known surface is brought in connection with the adhesive a bond is framed among test and adhesive.

The simultaneous removal of probe breaks it mechanically and the power needed to pull the test away from adhesive at a fixed rate is measured as a track and it is communicated in grams [15].

***In-vitro* Drug Release Studies:** Mechanism of drug release and kinetics are two attributes of the measurements of a dosage form which plays a significant job in depicting the drug dissolution profile from a controlled release dosage form. There are different techniques accessible for measurement of the drug release rate of TDDS [16].

A) The Paddle over Disc: This method is just like the USP paddle dissolution apparatus, with the exception that in the TDS system is affix to disc or cell resting at bottom of the vessel in which medium present at 32 ± 5 ℃ [16].

B) The Cylinder Modified USP Basket: This methodology is similar to the USP type dissolution apparatus, except the actual framework is appended to the surface of a hollow cylinder which is submerged in a medium at 32 ± 5 ℃. The amount of drug which is ready for absorption and reaching the systemic circulation is controlled by the polymeric film [16].

C) Preparation of Skin for Permeation Studies: An *in-vitro* penetration study can be performed by utilizing a diffusion cell. Full-thickness stomach skin of male Westar rat which is weighing around 200 to 250 g is used. Hair from the stomach area is to be evacuated cautiously by utilizing an electric scissors; the dermis layer of the skin is washed and clean thoroughly with water to remove the adhering tissue or blood vessels, kept in PBS 7.4 for an h before start-up of the experiment it is kept on a magnetic stirrer with a small magnetic needle for equal dispersion of diffusant. The temperature of the cell is kept up at 32 ± 0.5 ℃ utilizing a thermostatically controlled heater. The mounting of isolated rat skin is done between the compartments of the diffusion cell, the epidermis is kept in such a way that it is facing up towards the donor compartment. A specific amount of sample is removed from the receptor compartment periodically and it is replaced by the same volume of fresh medium. Samples are filtered and analyzed by spectrophotometry or by HPLC [16].

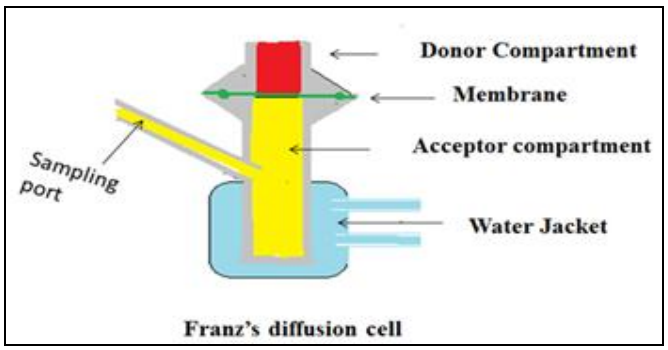

FIG. 7: FRANZ'S DIFFUSION CELL

6. USFDA Approved Transdermal Products: Since the approval of the first transdermal patch of scopolamine in 1979, various transdermal patches have been approved by USFDA.

Table 1 describes the name of the drug product along with the clinical condition for which it has been approved along with the name of the company.

TABLE 2: TRANSDERMAL DRUGS APPROVED BY THE USFDA

Approval year	Drug/product name	Indication	Marketing company
1990	Fentanyl /duragesic	Fentanyl /duragesic	Janssen Pharmaceutica (Titusville, NJ, USA)
1998	Estradiol with norethidrone/combipatch	Menopausal symptoms	Novartis
1999	Lidocaine/lidoderm	Post-herpetic neuralgia pain	Endo pharmaceuticals (Chadds Ford, PA, USA)
2001	Ethinyl estradiol with norelgestromin /ortho evra	Contraception	Ortho-McNeil Pharmaceutical (Raritan, NJ, USA)
2003	Oxybutynin /oxytrol	Overactive bladder	Watson Pharma (USA)
2004	Lidocaine (Ultrasound) / sonoprep	Local dermal anesthesia	Echo Therapeutics (franklin, MA, USA)
2005	Lidocainewith tetracaine /synera	Local dermal analgesia	Endo Pharmaceuticals
2006	Fentanyl HCl (Iontophoresis) / ionsys	Acute postoperative pain	Alza
2007	Rivastigmine /exelon	Dementia	Novartis
2010	Buprenorphine	For chronic pain	Purdue Pharma L.P.
2013	Sumatriptan	Iontophoresis patch for migraine	NuPathe Inc.

Table 2 includes transdermal patches and delivery systems approved by the US food and drug administration. Only the first approved product for a given drug or drug combination administered by a given delivery method is shown. Topical creams, ointments, *etc*. are not included.

7. Patents Granted on Transdermal Drug Delivery System: Various patents have been granted to researchers in the TDDS based upon there clinical utility, some of the important patents are listed below in **Table 3**.

TABLE 3: LIST OF PATENT INVENTION ON TRANSDERMAL DRUG DELIVERY SYSTEM

Summary of Invention	Patent No.	Inventor
In this research, inventor formulated the system and techniques for synchronizing the administration of compounds with the human body's natural circadian rhythms and addiction rhythms to balance symptoms when they are probably at their worst by utilizing an automated and pre-programmable transdermal or other drug administration system	US 9,555,227 B2	Dipierro *et al.* [17]
The present invention relates to an active TDDS performing transdermal drug delivery consisting of a patch having the ability to attachable on the skin of the Subject.	US 9,327,105 B2	Ramdas *et al.* [18]
The present invention demonstrates a solid dispersion TDDS consisting of a therapeutic agent in a stable amorphous form and a combination polymeric stabilizing and dispersing agent having a hydrogen bond-forming functional group and a procedure of formulation of these systems is given	US 9.226,902 B2	*Tang et al.* [19]
This invention discussed an abuse-deterrent and Misuse deterrent transdermal patch consisting of aversive agents added in the backing layer of the patch.	US 2017/0007550 A1	Enscore *et al.* [20]
This invention Described TDDS for the transdermal administration of testosterone, comprising a polymer matrix and testosterone. Methods of producing and utilizing such systems also explained	US 9,320,742 B2	Mantelle *et al.* [21]
This invention highlights a drug delivery device that delivers pharmacologically active substances transdermal utilizing microneedles arranged on a belt-mounted rotatably about a plurality of rollers	US 9,649.483 B2	Chowdhury *et al* [22]
Present discovery discusses an embeddable micro-needle patch for TDD and the method of producing the same is explained	US 9,675,789 B2	Chen *et al.* [23]
This patent described is transdermal drug delivery systems for the transdermal administration of levonorgestrel and ethinyl estradiol, comprising an acrylic polymer matrix. Methods of making and using such systems also are described.	US 9,314,470 B2	Patel *et al.* [24]
The invention concerns a transdermal delivery system for controlled dispensing of an active substance to and through a porous surface	US 2017/0100572 A1	Zumbrunn *et al.* [25]
This invention described is transdermal drug delivery systems for the transdermal administration of levonorgestrel and ethinyl estradiol, comprising an acrylic polymer matrix. methods of making and using such systems also are described	US 2017/0000745 A1	Kulakofsky *et al.* [26]

8. Clinical Trial Performed on Transdermal Compounds: Many compounds have been found effective in clinical trials and hence been introduced recently in marked. **Table 3** shows a list of such compounds [27].

TABLE 4: CLINICAL TRIAL PERFORMED ON TRANSDERMAL COMPOUNDS

Compound	Delivery System	Stage of Development	Company
Alprostadil	Gel-alprox-TD	Launched in china	Nexmed
Buprenorphine	Patch-transtec	Launched in europe	Grunethal
Dihydrotestosterone	Gel-andractim	Launched in france and the netherlands	Unimed/solvay
Ethinylestradiol and norelgestromin	Patch-ortho evra	Launched in the USA	J and J
Lidocaine	Patch-lidoderm	Launched in the USA	Endo

9. Future Aspects of Transdermal Drug Delivery: The transdermal drug delivery systems are a novel, convenient and easy way to deliver the drug molecules in the systemic circulation. The recent studies indicate skin is among the safest getaways to deliver the drug into the bloodstream. The delivery of the drug *via* skin has numerous advantages such as maintenance of an optimum level of drug in blood plasma, reduce side effects, avoidance of the first-pass effect and improve patient compliance.

Further, research is going on to increase safety and improve the effectiveness of transdermal delivery of drugs. Other improvements include better transdermal technology that uses various mechanical devices to improve drug permeability by changing skin barrier function. The TDDS is a novel way to deliver the drug molecules it has practical application as the next generation of drug delivery systems [28].

CONCLUSION: Transdermal drug delivery systems are a very useful innovation for the delivery of drug particularly in case patients who find it difficult to swallow their medications. Topical delivery of drugs offers numerous advantages compared to oral and parenteral of drug delivery such as avoidance of pre-systemic metabolism because of the first-pass effect, maintenance of constant plasma level of the drug. This article provides useful information related to the basic feature of the transdermal drug delivery system, various advancements and various approved transdermal products along with patents which are filled on a TDS system. It is a very useful way to deliver the drug especially for elderly people and children who are unable to swallow their medicaments. Compared to oral and parenteral delivery of drug transdermal delivery provides wide advantages, including reduction in side effects, improved effectiveness of drug molecules, prevention of pre systemic metabolism of drugs. This article highlights the basic information regarding the common feature of the transdermal system, various advancements, and various approved transdermal products along with patents that are filled on a transdermal drug delivery system.

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REFERENCES:

1. Kitaoka M, Wakabayashi R, Kamiya N and Goto M: Solid-in-oil nanodispersions for transdermal drug delivery systems. Bio J 2016; 11(11): 1375-85.
2. Malvey S, Rao JV and Arumugam KM: Transdermal drug delivery system. A Mini-Review 2019; 8(1): 181-19.
3. Jain AK and Kumar F: Transfersomes: ultra deformable vesicles for transdermal drug delivery. Asian J Biomater Res 2017; 3: 1-3.
4. Arunachalam A, Karthikeyan M, Kumar DV, Prathap M, Sethuraman S, Ashutoshkumar S and Manidipa S: Transdermal drug delivery system: a review. Current Pharma Research 2010; 1(1): 70.
5. Barry BW: Novel mechanisms and devices to enable successful transdermal drug delivery. European Journal of Pharma Sci 2001; 14(2): 101-14.
6. Prausnitz MR, Mitragotri S and Langer R: Current status and future potential of transdermal drug delivery. Nature Reviews Drug Discovery 2004; 3(2): 115-24.
7. Jawale N, Bhangale C, Chaudhari M and Deshmukh TA: Physical approach to transdermal drug delivery: a review. Journal of Drug Delivery and Therapeutics 2017; 7(3): 28-35.
8. Marwah H, Garg T, Goyal AK and Rath G: Permeation enhancer strategies in transdermal drug delivery. Drug delivery 2016; 23(2): 564-78.
9. Tanwar H and Sachdeva R: Transdermal drug delivery system: a review. Int J Pharm Sci Res 2016; 7: 2274-90.

10. Naik A, Kalia YN and Guy RH: Transdermal drug delivery: overcoming the skin's barrier function. Pharmaceutical Science and Technology Today 2000; 3(9): 318-26.
11. Hafeez A, Jain U, Singh J, Maurya A and Rana L: Recent advances in transdermal drug delivery system (TDDS): an overview. J Sci Innov Res 2013; 2(3): 733-44.
12. Bala P, Jathar S, Kale S and Pal K: Transdermal Drug Delivery System (TDDS)-a multifaceted approach for drug delivery. Journal of Pharmacy Research 2014; 8(12): 1805-35.
13. Ghulaxe C and Verma R: A review on transdermal drug delivery system. The Pharma Innovation 2015; 4(1): 37.
14. Al Hanbali OA, Khan HM, Sarfraz M, Arafat M, Ijaz S and Hameed A: Transdermal patches: design and current approaches to painless drug delivery. Acta Pharmaceutica 2019; 69(2): 197-15.
15. Shingade GM: Review on: recent trend on transdermal drug delivery system. Journal of Drug Delivery and Therapeutics 2012; 2(1): 66-75.
16. Mali AD: An updated review on transdermal drug delivery systems skin. International Journal of Advances in Scientific Research 2015; 1(6): 244-54.
17. Pierro DG and Levy AJ: Inventors; chrono therapeutics inc, assignee. optimized bio-synchronous bioactive agent delivery system. United States Patent Application US 16/165,720 2019; 21.
18. Ramdas R, Karri K, Sharma CV: Inventors; itrace biomedical inc, assignee. active transdermal drug delivery system and the method thereof. United States patent US 9,327,105 2016; 3.
19. Tang J: Inventor; mylan technologies inc, assignee. stabilized transdermal drug delivery system. United States Patent US 9,226,902 2016; 5.
20. Enscore DJ, Tagliaferri F, Damon SP, Smith A and Gaulding JC: inventors; 4P therapeutics, assignee. abuse and misuse deterrent transdermal systems. United States Patent Application US 15/113,545. 2017; 12.
21. Mantelle JA: Inventor; noven pharmaceuticals inc, assignee. transdermal testosterone device and delivery. United States Patent US 9,320,742.P 2016; 26.
22. Chowdhury DF: Inventor. microneedle transdermal delivery device. United States Patent US 9,649,483 2017; 16.
23. Chen MC and Huang SF: Inventors; national cheng kung university, assignee. embeddable micro-needle patch for transdermal drug delivery and method of manufacturing the same. United States Patent US 9,675,789 2017; 13.
24. Patel P, Nguyen V ans Liao J: Inventors; noven pharmaceuticals inc, assignee. transdermal drug delivery systems for levonorgestrel and ethinyl estradiol. United States Patent US 9,314,470 2016; 19.
25. Zumbrunn W, Imanidis G, DiPierro G and Venn VDHW: Inventors. transdermal drug delivery method and system. United States Patent Application US 15/385,638 2017; 13.
26. Kulakofsky J and Liao J: Inventors; Noven Pharmaceuticals Inc, Assignee. transdermal drug delivery systems for levonorgestrel and ethinyl estradiol. United States Patent Application US 15/200,397 2017; 5.
27. Samad A, Ullah Z, Alam MI, Wais M and Shams MS: Transdermal drug delivery system: patent reviews. Recent Patents on Drug Delivery and Formulation 2009; 3(2): 143-52.
28. Sudam KR and Suresh RB: A comprehensive review on: transdermal drug delivery systems. International Journal of Biomedical and Advance Research 2016; 7(4): 147-59.

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