IJPSR (2022), Volume 13, Issue 5 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 17 July 2021; received in revised form, 04 September 2021 accepted, 06 September 2021; published 01 May 2022

AN UPDATED REVIEW ON GLOBAL PHARMACEUTICAL FORMULATION DEVELOPMENTS AND FUTURE POTENTIAL OF NON-INVASIVE TRANSDERMAL DRUG DELIVERY SYSTEM

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Keywords:

Iontophoresis, Electroporation, Phonophoresis, Microneedles, Jet-injectors

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ABSTRACT: Background: Over the last several years, there has been much research into the development and modification of new pharmaceutical substances. We have also been able to attain the newest in transdermal drug delivery system treatment with existing pharmaceuticals. We have successfully implemented numerous drug regimens with transdermal delivery systems as one of the most significant developments, offering numerous advantages. **Main Body:** The distribution of drugs takes place in a detached dose form from the skin-adhesive devices or patches by diffusing throughout the layer of skin to reach out systemic circulation. The worldwide market for transdermal drug delivery systems was reached United States Dollar 4,200.3 Million in 2016 with a predictable increase of compound annual growth rate at 7.5% over the estimated time (2017-2024). The factors like growth and increasing geriatric population in the chronic disease across the globe are promoting the development of the transdermal drug delivery market. **Conclusion:** We will examine the essential influence of pharmaceutical breakthroughs and the future prospects of non-invasive transdermal drug delivery systems in this review paper, as well as strategies that are being researched to overcome limitations and problems.

INTRODUCTION:

Background: The global market for Transdermal Drug Delivery systems was estimated to be around USD 31.6 billion in 2015. When the number of chronic diseases rise and oral medications have a low therapeutic efficacy due to hepatic first-pass metabolism, the transdermal drug delivery industry has a substantial impact. The transdermal administration of pharmaceuticals is a precise, prestigious and fascinating research applied to the skin for therapeutic purposes. To transport the medicine into the circulation, the average skin surface area is $2m^2$.

However, because the skin acts as a barrier, it's important to understand skin anatomy, the implications of medication selection and the mechanism for delivering the treatment to the skin. Drugs used in the TDDS (Transdermal Drug Delivery System) should be very potent, lipophilic

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(5).1896-07

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(5).1896-07

and have a molecular mass of less than 600 Da (Dalton) [2, 3]. The stratum corneum, dermis, epidermis and hypodermis are the four tissue layers that makeup skin. The outermost layer stratum corneum is composed of 6-16% (percent sign) lipids (phospholipids, glycosphingolipids and cholesterol sulphate) and 74-84 percent proteins (keratin), with a length of 35-43 m (micrometer) [4]. The viable epidermis is a skin layer (55-105m broad) made up of nautical fibrils and 90% water [5]. The dermis layer (2000 m to 3000 m) lies beneath the epidermis layer, with a fibrous proteins matrix embedded in the bottom matter [6]. Unattached connective white fibrous tissue, lymph vessels, blood vessels, and sweat glands are coated on subcutaneous connective tissue [7].

Main Text: The Product Development Approach is quality-driven, with medication physiochemical qualities, devices, and formulation ingredient features all taken into account when designing for skin locations. In the early stages of development, indirect methods were utilized to improve drug influx, pass the skin barrier and design permeability. Sustained drug gradient, membrane permeability, diffusivity, drug micro-reservoir for preserving release kinetics uniformity, and adhesion qualities with their involvement in drug release are only a few of the aspects [8].

Permeation Pathways: Passive diffusion of the substance is included in percutaneousdermal immersion. Two diffusional courses of action are included in a little identifiable unit of a medication [9]. The sebaceous glands, hair follicles, and sweat glands make up the appendageal route, which is also known as the shunting route and bypass route because it passes through the stratum corneum. This method is designed to have a minimal total skin surface area [10]. The epidermal pathway is an intact horney layer with transcellular and intracellular micro paths for entry and exit [11]. Trans cellular pathway route possesses epithelial membrane drug passage by the mechanism of the active passage of polar and ionic compound, passive transport of small particle size drugs, and transcytosis and endocytosis of large particle size drugs [12]. Para cellular pathways involve the transport of drug molecules in the middle of skin cells or all over [13]. The passage of drug particles mainly involves mainly by partition coefficients (log K) through compact junctions [14]. A drug of hydrophilic nature is conversely into intracellular junctions, whereas to the greatest extent, permeants disperse through the stratum corneum by both intercellular and intracellular pathways. Although the intercellular pathway is extensively examined as a principle route, it is a significant obstacle to permeate most drugs [15].

As we know, the drug must pass through different skin layers to reach out to the bloodstream for therapeutic use. In the first step, drug patches are applied to the skin's upper layer. Then, by the mean of diffusion, it is absorbed into the stratum corneum, transferred to the viable epidermis, and transported to the inner dermal layer. Drug uptake occurs through the dermal papillary layer through capillaries and blood vessels [16]. Drug moiety's transdermal permeation includes the subsequent steps as describe in **Fig. 1.** Permeation involves penetration across skin layers, passing throughout the SC (stratum corneum) to epidermis, followed by upper dermis diffusion and penetration from downward layers to reach out systemic absorption. In the TDDS, either drug is presented as a liquid/gel-dissolved substance or stored in solid form. The release of the drug takes place as the concentration gradient exists with flux expressed as µg (microgram)/cm (centimeter) 2 h (hour) in the skin.

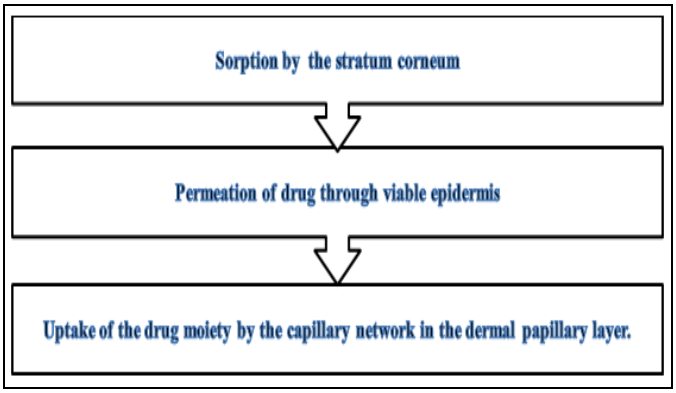

FIG. 1: MECHANISM OF TRANSDERMAL PERMEATION

The drug usually follows steady-release kinetics with an initial lag time, small or more. As the different drugscapability to go through the skin barrier differs, there is a requirement of thermodynamic thrust for passive diffusion in the skin. In the TDDS, drug load has to go through some challenges like being strongly promising in

pharamacological activities and related to the transdermal delivery with approved physiochemical properties. Various drugs have moderate flux, due to which they can penetrate less through the skin. On the other hand, drugs having low permeability because of the skin barrier can be enhanced by the ways of physical-chemical-physiochemical-acoustics- radioactive-based techniques to increase the delivery output. In addition, many pharmacokinetic factors that influenced the trans-dermal drug delivery consist of the distribution of drug, therapeutic amount in plasma, drug's half life, whole body clearance, and bioavailability [17]. A permeation enhancer is a substance that increases the permeability of skin and thus increases the drug's absorption power through the skin [18].

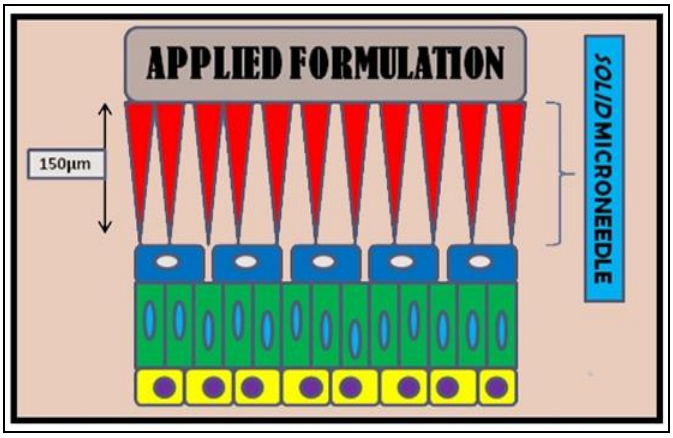

FIG. 2: TRANSDERMAL PERMEATION ENHANCEMENT TECHNIQUE BY MICRONEEDLE ARRAY

Ionizable drugs such as timolol maleate and impermeable drugs such as heparin can be delivered through the skin to maintain plasma concentration into the blood [19]. The molecular weight substance such as hormones and peptides and less potentially active drugs, e.g. (exempli - gratia) oxymorphone delivery, can be possible by using permeation enhancer [20].

Ideal characteristics should be associated with the drug; should not indicate any adverse effect on the body; must be biocompatible and should no cause irritation, allergy, and toxicity; should not have any odor, color and taste; should not cause leakage of fluid from the body; after removing these materials skin should restore its original property [21]. No permeation enhancer passages are all reliable properties as mention. A major task is to reduce the allergic responses of the skin [22].

In the approaching year, the transdermal market is predicted to be profitable with growth opportunities because of the use of technology and innovations in trans dermal, such as microneedles arrays and mechanical arrays. The innovations involve alterations in penetration enhancers, transdermal patch designs, and internalization of pressure-sensitive adhesives, which increases the capacity of the reservoir to hold a large quantity of drugs and improved drug diffusion. Furthermore, advancement contains highly developed transdermal patches, advanced reservoir type, and miniaturization that distribute accurate medication dosage. During the estimated period, the fastest-growing relevances were identified in Mechanical arrays. There is a prediction that the mechanical arrays sector will grow at a productive evaluation of 12.5% in an estimated period. Elevation of the sector's growth potential can be represented by an increase in the number of manufactured goods started by well-known industry players. There are many transdermal products in the late phase of clinical trials, such as a mechanical array or microneedle.

In TDDM (Transdermal Drug Delivery System Marketplace), cardiovascular is considered the fastest-developed application. This type of development can result in increasing consumption of TDDS for the cure of congestive heart failure, angina pectoris, and hypertension. For example, in treating hypertension, use of clonidine nitroglycerin and is sorbide dinitrate transdermal have extreme efficacy. North America in 2015 represents a significant share of more than 50.0% and is considered as largest region in the transdermal drug delivery marketplace. This boost in the area is due to patent expirations resulting in the entry of other companies into the marketplace. Some of the factors controlling the substantial share seizing in the region include repositioning of failed drugs, reformulation of existing drug compounds, and enlarged investments.

Due to the high growth intensity and research study, there is a positive development in the marketplace of Asia Pacific (Countries such as India and China) as likely to show exponential CAGR (Compound Annual Growth Rate) of over 12.0 %, which results in developing health care infrastructure and increasing healthcare

expenditure. The most leading market player is Mylan Pharmaceuticals Inc. (Incorporated), in the TTDS market. There are certain companies that dominate the market are Watson Pharmaceuticals, Transdermal Technologies, Inc., Biogel Technology, Inc., Johnson & Johnson, Noven Pharmaceuticals, Inc., Johnson & Johnson, Transdermal Corporation, 4P Therapeutics, Novartis AG, Echo Therapeutics, Inc., Boehringer Ingelheim GmbH, 3M Company, LLC and Skyepharma, Inc. The growth in the industry is based upon the decisions taken by industry players which can be product launches, geographical expansions, acquisitions, mergers in order to acquire larger shares. For the cure of Alzheimer's disease a transdermal patch was launched by Novartis AG in September 2015. This launch was a big achievement to acquire a large share of Alzheimer's disease patients. There are mostly three ways for penetration enhancements: Chemical approach, Biochemical approach, and Physical approach [23].

Chemical Approach: Some of the mainly used ones are illustrated as alcohol, which acts by various mechanisms to increase skin properties which are swelling of stratum corneum to enhances the permeation of the drug into the skin, lipid and protein extraction, ethanol flux linearly related to flux across the skin [24].

Long-chain alcohols increase in permeation is level of unsaturation increase from one to two double bonds with three double bond level of permeation decrease. Saturated fatty alcohols are Myristyl alcohols, tridecanol, lauryl alcohol, undecanol, decanol, octanol, *etc*.

Unsaturated fatty alcohols are Linolenyl alcohol, Oleyl alcohol, *etc.* Propylene glycol increases the flux of verapamil hydrochloride, heparin sodium hydrochloride, ketoprofen, methotrexate, azone, and cyclosporine A. PG (Propylene Glycol) provides hydrogen bonding on sites to solvates stratum carenum keratin. PG in preparation of azone acts as increased intercellular drug diffusion to release a large amount of glycol. More the length of carbon chain in n-alcohol more will be drug flux [25]. Short Chain Glyceride has a remarkable hydrophobic system that increases absorption and permeation of furin and papaverine [26].

Amines and Amides: They are cyclic urea permeation enhancer contains a long chain of alkyl ester group and polar parent moiety. Because of the presence of hydrophilic groups and lipid disruption, they promote hydration of stratum carenum also increase the penetration of trans dermal patches. They are biodegradable and non-toxic [27]. Cyclodextrin is a higher concentration form complex with lipophilic drugs that reduce the flux. It enhances the drug's solubility in aqueous solutions and is also reported as biocompatible. Pyrrolidones such as N-methyl pyrrolidone act as transcutaneous absorption enhancers [28].

Unsaturated Fatty Acids: These enhance more absorption than saturated fatty acids. The best permeation enhancer is Palmitic acid. It increases absorption 640 times on hairless mouse skin. PG (Propylene Glycol) increases intracellular transport, whereas azone increases intercellular transport. PG and azone together combine great permeation enhancements through stratum corneum in both lipophilic lines and hydrophilic routes. PG gives hydrophilic components to the protein region whereas azone facilitates the flow of drugs through the lipid bilayer. The flux of piroxicam and methotrexate increase when the Azons and PG combination was used [29]. Dimethyl sulfoxide (DMSO) acts as an aprotic solvent because it absorbs the bonding of intracellular hydrogen. It can dissolve anything and act as a universal solvent it does not exhibit any kind of odor and colour. DMSO denatures the skin protein and acts as a penetration enhancer [30].

Surface Active Agents: Anionic surfactant changes the barrier properties of SC by removing water-soluble agents and is then increase the permeation, e.g., Sodium lauryl sulphate. Cationic surfactant absorbs at the skin surface and then increases skin permeation. They are greater penetrant as compare to anionic surfactants, the reason they can damage skin too. Non-ionic surfactants emulsify the sebum and increase the permeation by changing partitioning properties [31]. Terpenes and terpenoids are made from repeating isoprene (C5H8) units. They are ingredients of essential oils. They are a tremendous percutaneous permeation enhancer, e.g., L-Menthol (L- Livo) form a eutectic mixture with drug and drop their initial melting point.

This makes the drug more soluble and increases absorption through the skin. Menthol also alters the skin property and increases the permeation of stratum corneum [32].

Biochemical Approach:

Pro Drug: It converts into active form covered by enzyme after absorption and diffusion into viable tissue. So prodrug helps maintain a proper partition coefficient for crossing skin barrier, e.g., N-acyl derivatives increase the permeability of 5-Fluorouracil to 25 times, 6-Mercaptopurine permeation increased by 240 times S6-acetoxymethyl and 9-dialkyl aminomethyl. Prodrug also increases the permeability of nalbuphine, buprenorphine, and beta-blocker [33].

Skin Metabolism Inhibitor Co-Administration: These as skin permeation also can be increased by altering one or all processes of lamellar homeostasis. This process includes synthesis, assembly, secretion, processing, activation. Synthesis of ceramide, cholesterol and fatty materials block temporarily by synthesis inhibitor. Fluvastatin increase water/octanol partition coefficient of Lidocain Hydrochloride by 50 times [34].

Physical Approach:

Micro Needle Array: `It works as both transdermal patch and hypodermic needles. Microneedles help to deliver the drug from the drug pool to the stratum corneum without reaching nerve-ending **Fig. 2.** Needles Specification (200-750 microns) Length, (150 - 650 microneedles) Array/cm^2, Interfacial Area (490 µm2), Diameter of tip - 25 µm, Insertion force (0.058 N{Newton}), Material - Silicon, Sugar, metal and plastic. Several types of needles are poke with patch.

Applying patch locally and excruciating into the epidermal layer, coat and poke needles placed into the drug. Drug release occurs by the biodegradable microneedles containing drug placed into an eco-friendly polymeric microneedle, resolution and the epidermal surface punctured by hollow micro needle with hollow bore [35]. Marketed products are Macro Flux (A), an enhanced hydrophilic peptide released such as hexapeptide, tetrapeptide-3, and oxytocin with microneedle array pre-treatment with porcine ear skin.

Microdermabrasion: It selectively removes the stratum corneum to increase skin permeability. Large molecular weight drugs can be delivered through this technique, e.g., Peptides, vaccines, and insulin [36].

Microdermabrasion (Histological Imaging): It is used for removing wrinkles and scars; this technique is applied, e.g., Aluminium oxide crystals (30-35 K), Sodiumbiocarbonate, Magnesium oxide, Alminium oxide diamond [37]. Dye penetration is used for the removal of a tattoo or permanent makeup. "Food and Drug Cosmetic Act" must approve the dye [38]. Skin electrical resistance is used for removal of stratum corneum whose resistance range must be (1750 ± 1340 k cm^2 [39]. Follicular delivery of drug can be through sweat glands (86 ± 37 µm) and hair follicles (172 ± 70 µm). This technique is best for transdermal drug delivery as they are hydrophilic with high molecular weight moiety can store for up to 10 days [40].

Electrically Driven Technique:

Ultrasound (Phonophoresis or Sonphoresis): In this technique, the ultrasonic wave increases the permeation of the skin. Mechanism of Sonphoresis includes the frequency of an ultrasonic wave is greater than 20 kHz applied on skin which increases skin fluidity of lipid and via a transcellular pathway. They form bubbles that create holes. The holes give passage to large molecular weight drug penetration into the skin. Examples are Dexamethasone, Lidocaine, Ketoprofen. The limitation is these ultrasound waves transform into heat energy which causes the formation of attenuation [42].

Iontophoresis: Voltaic cell or galvanic cell generates an electrical impulse of 0.5 A/cm. which permeate ionized drug through the skin. The mechanism is based on Faraday's law, according to which the current applied is directly proportional to the drug permeation. Skin pH is a key factor more the skin pH, more will be skin penetration**.** Faraday's law is expressed in the following formula D= IT/(IZI)F where F = Faraday's Constant (Coloumb/Mol.), I = Current (Ampere), D = Drug Permeated, IZI = Valance [43]. Types of Iontophoresis are Direct Iontophoresis in this anions are passively diffuse through the skin.

Reverse Iontophoresis involves the movement of negative ions into the anode and positive ions into cathode. Apomorphine for the treatment of idiopathic Parkinson's disease is distributed in this way. In the future drug-like vasopressin, insulin, inulin, calcitonin, the parathyroid hormone can be delivered by this mechanism [44].

Magnetophoresis: Permeability of skin increased by applying a magnetic field around the solute used to penetrate into skin [45]. Examples are Benzoic acid has diamagnetic nature when we applied magnetic field its diffusion properties increase. Limitations are stratum corneum properties can be altering [46].

Electroporation: It involves the application of an electrical pulse of DC voltage of more than 100 voltages (milliseconds) that causes the formation of pore in the lipid bilayer (corneocytes). By this technique, a small charged molecule can't penetrate through the skin. By giving high voltage can cause aqueous pores into the epidermis [47]. This helps to penetrate through the five or six lipid membranes. It helps in the delivery of oligonucleotide, heparin, insulin, proteins, vitamin C, and dextran. In biotechnology and medicines by increase permeation and cell survival. In the food industry and sterilization by electric pulse lead to cell death (necrosis) [48].

Photochemical Wave: These are laser-based generated stress pressure waves by the incision of polystyrene. Epidermis's lacunar system is changed by it. This technique is used in rejuvenation, acne scar's healing, and delivering macromolecules [49, 50].

High-Velocity Particles: Powder jet instrument with the help of Helium gas (600-900 m/s speed) it propulsive drug into the skin. This technique does not involve any pain and is non-invasive. In reversible nature, this technique causes rupture of epidermis layer [51]. Examples are delivery of testosterone, calcitonin and lidocaine hydrochloride made possible.

Needle-Free Injection: Inject used to Deliver the drug (0.1 to 1 ml) without a needle. Imlajet is a fine needle used to open channels of the skin by pushing and permeating the Intrajet used. The liquid drug can propel by nitrogen gas force into small pores of the skin. Miniject is a polycarbonate syringe inject the drug subcutaneous as well as intramuscularly. Jet - syringe is a short therapy technique capable of injecting (0.5 ml of drug) into the skin. Cross-ject are polycarbonate gas nozzle propelled drug subcutaneous [54].

Pharmaceutical Transdermal Formulation Developments: Various drugs are being developed and marketed as transdermal products because of friendly attributes and better compliance with treatment regimens. A team of experts with good knowledge of pharmaceutics, biology, material science, and engineering is required for the development of an optimal transdermal system. The steps are to find out technical compatibility of the drug with excipient and prediction of skin permeability to get an initial read on trans dermal feasibility. The property of drug target patient group and desired delivery profile is the key element [51].

Transdermal System Design: For the scale development, we require the batch size of 1- 1000, scale for the technical development is 1-1000 and scale for the commercial product is 100- 3000. Liquid and the adhesive matrix is applied on to the release liner in such manner that dame concentration of active substance evenly distributed on every point. Then matrix is dried and fixed to the release liner. The patch form is formed, the baking film is applied on the dried matrix (1.5 m across and 300m length), then laminates having release liner, baking film, and adhesive layer is cut down to various sizes. The machine can punch any kind of shape, which can be round, oval, and square comfortable to the patient. Finished patches are then separated from one another and heated sealed into pouches [52]. In reservoir type design drug is in the form of a solution stored in a liquid reservoir type compartment; a semi-permeable membrane separates adhesive and releases liner.

Therapeutic drugs present in the adhesive system delivers the drug directly to the skin through adhesive. Various kinds of multi-laminated drugs in the adhesive are available in the market with distinct layers under single baking, which are preferable to the patient [53]. Well, design transdermal drug delivery formulations include various elements like factors of delivery, skin tolerability, a combination of components with drug and drug product yield, and adhesive use. The

selection of adhesive is most important because it affects the adhesion of the patch to the skin and drug delivery The patch can be worn within 7 days, so good adhesion throughout the period is required and is also a significant challenge. Body moments apply stress to the patch in many directions, so customization of adhesive is the key challenge for transdermal drug delivery formulation [54].

Transdermal Drug Delivery Market Overview: The worldwide market for transdermal drug delivery systems was reached USD 4,200.3 Million in 2016, with a predictable increase of CAGR at 7.5% over the estimated time (2017-2024). The factors like growth and increasing geriatric population in the chronic disease across the globe are promoting the development of the transdermal drug delivery market. The universal TDDM is fragmented into Latin America, North America, middle East & Africa regions, and Europe. Among the above regions in the TDDM, a major allocation of 35.1% in terms of profits by 2024 is set for North America [55]. The development in this region is promoted by more spending on healthcare.

In the North American region, advancements in technologies are considered for spreading out of the TDD market. The well-known market in this area is U.S. [56]. Besides North America, the healthy development over the predicted period was admitted by Asia Pacific, which displayed considerable growth at a CAGR of 8.2% over the estimated period (2017-2024). In the estimated time, the European transdermal drug delivery market also considered showing increased CAGR. In European countries, growing health expenses is likely to grow in the market in forthcoming years. In 2016, about 12.2% of the market share was attained from the European market by the U.K. transdermal drug delivery market. Additionally, the cardiovascular transdermal sector also contributed to 23.5% shares of the marketplace in 2016 and maintained this optimistic development for the estimated time [57].

Market Segmentation: The study has divided the worldwide transdermal drug delivery marketplace into the following sections [58]:

On the basis of Application[59]:

- Pain Management
- Cardiovascular
- CNS
- Dermatology
- Others

Based on Technology [60]:

- Electric current
- Thermal Ablation
- Mechanical arrays
- Chemical Enhancers
- Others

Based on Region: Universally Transdermal Drug Delivery marketplace is divided on the basis of regions as:

- Europe (France, U.K., Italy, Germany, Hungary, Spain, NORDIC (Finland, Norway, Sweden, Denmark), BENELUX (Netherlands, Belgium, Luxembourg), Russia, Poland, Rest of Europe), opportunity analysis, Market size, growth and future forecast.
- Latin America, Market size, opportunity analysis, future forecast and growth.
- North America (Canada, United States), - growth Market size, future forecast and opportunity analysis, market size, - growth.
- Africa (GCC (Saudi Arabia, UAE, Kuwai, Bahrain, Oman, Qatar) Israel) and the middle east.
- South Africa, the Rest of the Middle East and Africa, North Africa growth, market size, future forecast, and opportunity analysis.
- Asia-Pacific (India, Japan, China, South Korea, Indonesia, Hong Kong, Malaysia, Taiwan, Rest of Asia-Pacific, Australia, New Zealand), growth, Market size, future forecast and opportunity analysis [61].

Growth Drivers & Challenges: Patch, a transdermal drug delivery tool, showed its major function in diabetic patients for insulin delivery.

And the increased diabetic patients across worldwide is possible to elevate the utilization of patch which is expected to show the development of market [62]. In 2017, according to a WHO report, the worldwide number of people who have diabetes was reported to be about 422 million. And according to the American diabetes association, more than 1.5 million Americans are cured of diabetes each year. The growing rate of diabetic patients in different regions showed potential development of TDDM in forthcoming years. In recent years, numerous new drug introductions are observed, which can be delivered by the transdermal way [63]. Such supporting market actions are expected to lead to present and future development prospects of the marketplace. These encouraging market activities are expected to lead to present and upcoming development scenarios of the market.

The pleasant appearance of TDDM takes place in the early year as the government pharmaceutical licensing organizations to provide the authorization of different transdermal patches. On the other side, the increased rate of technologies such as radio-frequency, electroporation, and others are expected to drop off the development of TDDM. Transdermal drug delivery poses a high rate which arises the unwillingness amongst the population [64]. New generation therapeutics and big demand for extreme potent drugs drive TDDS Market.

The effectiveness of these devices can be seen in the high drug distribution capacity beyond the usual drug delivery routes (pulmonary, oral, and intravenous). In addition, a significant contribution to market expansion is the growing popularity of patients and physicians in relation to painless drug delivery, which is expected to meet market demand in the medium term. The above factors are expected to increase the scope of growth during climatic conditions [65]. In addition, the large demand for self-medication of patients requiring long-term treatment, including for diabetic patients, is increasing the force in this market. According to diabetes, insulin should be injected into a patient's body by regular injections. [66]. There is an increase in the risk of transmission of disease, and insulin can causes pain due to continued use of injection. The rapid rate of acceptance of adhesive skin patches increases higher market growth [67].

In addition, the inclusion of TDDS will boost patients' self-reliability by significantly reducing the frequency of hospital visits and the cost of joint treatment [67]. The Leading Players involved in the global Transdermal Patch market are.

Hisamitsu Pharmaceutical: By doing research and development on medical products, Hisamitsu Pharmaceutical helps in achieving human well-being around the globe. The company mainly focuses on the innovation in products according to the drug delivery system (TDDS). Their products can be applicable to a greater extent according to therapeutics activity. (global. Hisamitsu /operations /tdds).

Derma Light Technology: This technology causes minimal pain when applied and assures complete adhesion. Irritation on the skin can be reduced continuously when applied on the same area (global. Hisamitsu /operations/tdds).

Trans Derma Sal Technology: These technologies make water-soluble substances, such as hydrochloride salts and sodium salts commonly taken by injection or orally, that are stored in non-aqueous substances (adhesives for tape preparations). The earlier pharmaceutical compound that can't be converted into TDDS products can now be converted into TDDS which can be applied to the skin with the help of this technology [68]. Trans Derma Sal® technology is used in Fentos® tape. In June 2010, a narcotic tape product, Fentos® tape, was launched for medical use. It is given well once a day and is expected to gradually reduce the pain of cancer [69].

Microneedles: Technological advancement will allow us to deliver the drug directly to the lower parts of the epidermis with microneedles. The benefit of using Microneedles is that it doesn’t depend on the epidermal blockade, allowing us to produce drug extracts from history that could be delivered by injection [74].

Gel-patch Technology: This technology posses a gel containing water content up to 80 percent, which provides extreme adhesive potency. Pain, as well as skin irritation, can be countered by the high water amount present in gel. Facial masks and MOHRUS® PAP XR by the company also uses this advanced technology [75].

Johnson Johnson: Johnson & Johnson invested with $263.5M to Janssen Pharmaceuticals' Evra transdermal contraceptive patch to unite with Gedeon Richter. (info.creditriskmonitor.com/News Story).

Teikoku Pharma: Lidoderm was the first direction hydrogel topical patch for post-herpetic neuralgia (PHN), approved in the United States in 1999. Lidoderm offers analgesia (without anesthesia) straightforwardly to the affected nerves (teikokuusa.com/products/lidoderm).

Mylan: Mylan's invested transdermal franchise with complex genric and interchangeable novel transdermal products such AS adhesive patches, Nitroglycerin for angina pectoris and Clonidine for prevention hypertension (investor. mylan. com/news-releases).

Actavis: Approved AS per centralized procedure of Article 10(1) of Directive 2001/83/EC, Rivastigmine Actavis of 4.6 mg/24 h, 9.5 mg/ 24 h. Clonidine transdermal patch of area (4.1 cm^2, 8.2 cm^2 and 12.3 cm^2) is formed using multi layered film. (ema. europa. eu/en/ documents/variation-report/rivastigmine-actavis).

Changzhou Siyao: This company manufacatures trans dermal patches of nicotine, Fentanyl, Buprenorphine *etc.* It is rewarded for National Hi-Tech Enterprise (cphi-online.com).

Watson Prescription Drugs: For the treatment of mild to modrate dementia of Parkinson's or Alzheimer's disease trans dermal system patch are manufactured by Watson (pharmabiz.com).

Noven: Daytrana transdermal patch is the first Noven flagship product for ADHE in children and adolescents. MINIVELLE® was launched by Noven in 2018 for moderate to severe menopause and post-menopausal osteoporosis. For schizophrenia treatment Noven transdermal patches are commercialized by SECUADO®. A various transdermal patches is manufactured by the company are Buprenorphine Transdermal Patch, Fentanyl Transdermal Patch, Clonidine Transdermal Patch, Nicotine Transdermal Patch, Oxybutynin Transdermal patch (noven. com/daytrana). The transdermal patch of Fentanyl for management of moderate to server chronic pain for an extended period of time in opoide tolerant patient is used (access data. fda. gov/drugsatfda_docs).

Summary: The non-invasive and painless technique of drug delivery is the transdermal delivery system. The drug distribution takes place in a detached dose form from the skin-adhesive devices or patches by diffusing throughout the layer of skin to reach out systemic circulation. This showed a remarkable weightage on the amount and diversity of curative agents release, mainly in pain managing, hormonal therapy, central nervous system, and cardio vascular's diseases. With time, advances in the TDDS techniques and delivery devices showed the delivery of hydrophilic, lipophilic and amphiphilic drugs. As advancements in TDDS for delivering hydrophilic, ampophilic drugs with the use of permeation enhancer and physical technique with maximum permeation and minimum soft tissue damage of skin.

The improved delivery performance of the drug is attained by using voltage-gradient iontophoresis for the stable and suitable parameter of drug distribution. Electroporation, microdermabrasion, microneedles, thermal ablation, microporation, micro and radio waves, radiofrequency usage, use of thermal techniques, nano-deliveries, cavitational ultrasound techniques, and electro-mechanical devices showed significant contribution for producing the primary TDDS techniques, which are more eco-friendly, less expansive, viable to choose and competitive in evaluating delivery level.

CONCLUSION: A comprehensive and detailed study of the Global TDDM report illuminates many aspects such as financial position, growth statistics, growth factors, business development strategies to help TDDS vendors and customers understand the global market. The study states that the TDDM has experienced rapid growth over the years and will continue to grow with continuous development in the coming years. In short, this study provides an in-depth overview of the global market that encompasses all key parameters. The study provides important statistical information on the market situation of producers and uses strategies, suggestions, and practical guidance for businesses and beginners interested in the TDDS industry. Research is provided in the context of leading

applications, land studies, including growth, drivers, product types, and segmentation. The TDDM research report highlighted all the key aspects of the economic diversions and market growth discussed as a result of the intense attention received in the coming years.

Ethics Approval and Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

Availability of Data and Material: Not applicable.

Funding: Not applicable.

Authors' Contributions: RP conceptualization, collected data, and bibliography wrote the original draft, reviewed and edited. NP helped with the data collection and interpretations. DNM supervised and helped to revise the article. All the authors read and approved the final manuscript.

ACKNOWLEDGEMENT: Many thanks are addressed to Dr. D. N. Mishra.

CONFLICTS OF INTERESTS: The author has declared no conflict of interest.

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How to cite this article:
Pawar R, Mishra DN and Pawar N: An updated review on global pharmaceutical formulation developments and future potential of non-invasive trans dermal drug delivery system. Int J Pharm Sci & Res 2022; 13(5): 1896-07. doi: 10.13040/IJPSR.0975-8232.13(5).1896-07.