A COMPREHENSIVE REVIEW ON PATENTS OF TRANSDERMAL DRUG TECHNOLOGY

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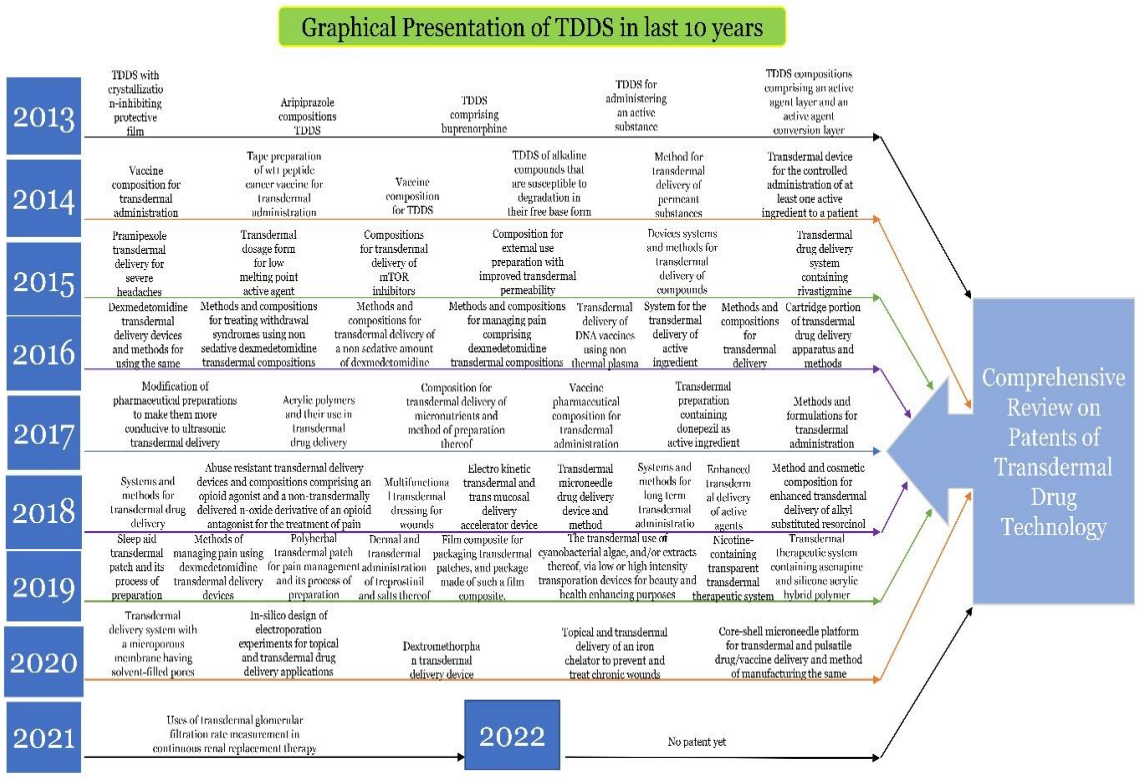
Abstract

In this article we have compiled the various patents which have been granted in the transdermal drug delivery system in the past ten years along with the recent innovations that have come up. A rigorous review of the 54 patents during the past 10 years was done and presented here in chronological order to show the journey of the dosage form in the last decade. Patents have been granted for various drugs like aripiprazole composition, buprenorphine, dexmedetomidine, pramipexole, diclofenac, rivastigmine and opioid antagonist. Some patents were also granted for some vaccines, controlled drug delivery, penetration enhancers and mTOR inhibitors. A brief introduction of the dosage form including history, types and methods/ technology used for the formulation of transdermal drug delivery system has also been provided. An overview of recent invention and future aspects of the TDDS has been included.

Keywords: Transdermal Drug Delivery System 2; Patent 3; TDDS 4; Patch 5; Treatment

Graphical Abstract



INTRODUCTION

In recent years, treating illnesses has involved giving drugs to the body through a variety of methods, including oral, sublingual, rectal, parental, etc. [1]. In that the oral route is the most typical and well-liked method of drug delivery.

However, there are several substantial disadvantages to this mode of administration, such as the first passes of metabolism and drug breakdown in the gastrointestinal system due to enzymes, pH, etc. By boosting patient compliance and eliminating first pass metabolism, transdermal administration offers a competitive advantage against injectables and oral methods [2].

The TDDS is typically utilized when other drug delivery methods fall short or when a local skin illness, such as a fungal infection, is present. The application of a medication-containing product formulation for the human skin to treat cutaneous disorders directly is known as topical drug delivery [1]. The TDDS method works well for medications with low bioavailability and first-pass metabolism [3].

The 1970s saw the beginning of the development of TDDS, and the United States Food and Drug Administration (FDA) approved the first transdermal patch of scopolamine in 1979 for the relief of motion sickness and nausea. Later, nitroglycerin patch therapy for angina pectoris was commercialized [4].

Scopolamine was given by a three-day patch. Since the approval of nitroglycerin patches in 1981, other patches for other medications—including clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, estradiol, etc.—have been created and are in use [2].

As is generally known, the skin serves as both the primary target and obstacle for topical and transdermal medication delivery. In regard to accessibility and simplicity of use, it also serves as the optimal method for drug administration [5].

In order to accomplish systemic absorption of the medicine at a predetermined pace over a protracted period of time, a transdermal patch is a sticky patch that is medicated and applied to the skin [2].

Due to features including regulated release, reduced dose frequency, enhanced patient compliance, minimal variations in plasma drug concentration, and maximal drug use, the transdermal route is excellent and can therefore provide hypertensive patients with additional therapeutic benefits [6].

Because it is simple to use and prevents medication degradation in the GI tract, TDDS is a popular method for administering medicinal medicines. However, because of the stratum cornea is the principal barrier to medication penetration, the chemicals that can be administered via transdermal methods are restricted to tiny (500 Da) and mildly hydrophobic molecules [7].

Since then, a few additional medications have been successfully incorporated into TDD systems, including nicotine, fentanyl, estrogen, and testosterone. The current research focus is on using technology to improve transdermal medication delivery systems and to find novel ways to enable skin permeation of bigger, hydrophilic medicines that were previously believed to be skin impermeable [8].

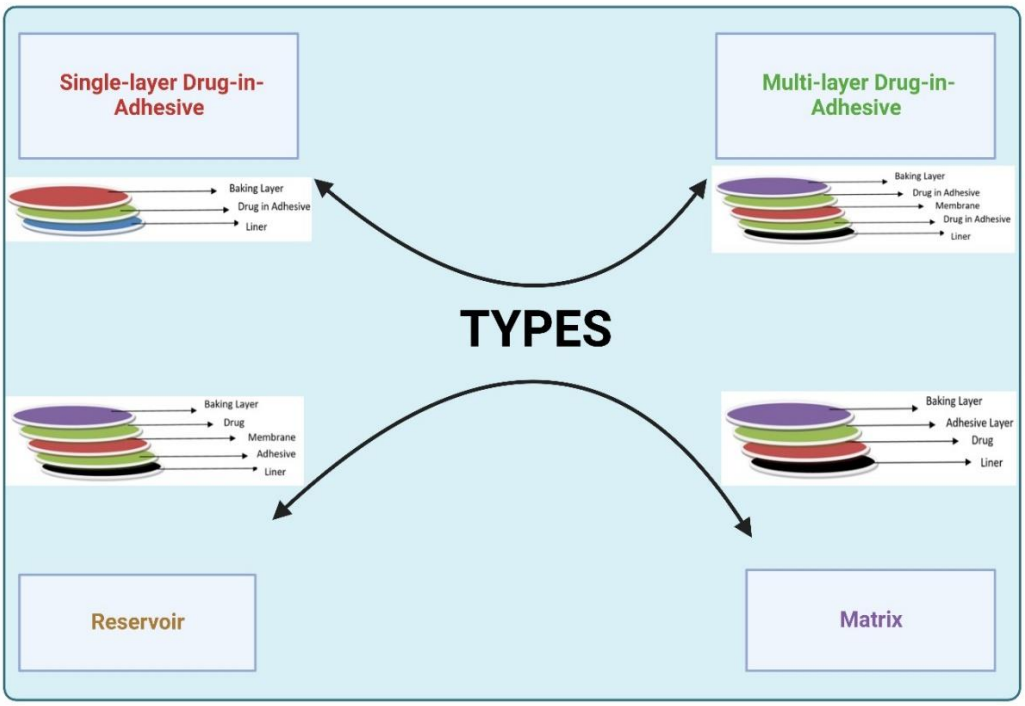


Figure 1: Types of Transdermal Drug Delivery System

Physical disruption (heat, magnetic, pressure, laser, or mechanical modulation, moisture, electroporation, phonophoresis, microneedles, skin abrasion, and piercing), chemical disruption (cellular uptake or penetration enhancers, prodrug design, and combinations of these approaches), and chemical disruption (permeation enhancers alone and in combination with other approaches) are just a few of the techniques that have been used to disturb the skin barrier and improve drug transdermal penetration [9].

Chemical permeation enhancers specifically increase drug absorption via the skin by doing the following

1) Modification of stratum corneum structure and fluid;
2) Improvement of the skin's solubility properties for drug delivery
3) Disordering of the SC lipids' alkyl chains;
4) Localizing division of lipid domains to produce hydrophilic pores and/or a drug reservoir in the stratum corneum.

The creation of structured skin carriers such as liposomes, nanoparticles, transferosomes, microemulsions, as well as solid nanoparticles of lipids is another current trend towards improvisation [9].

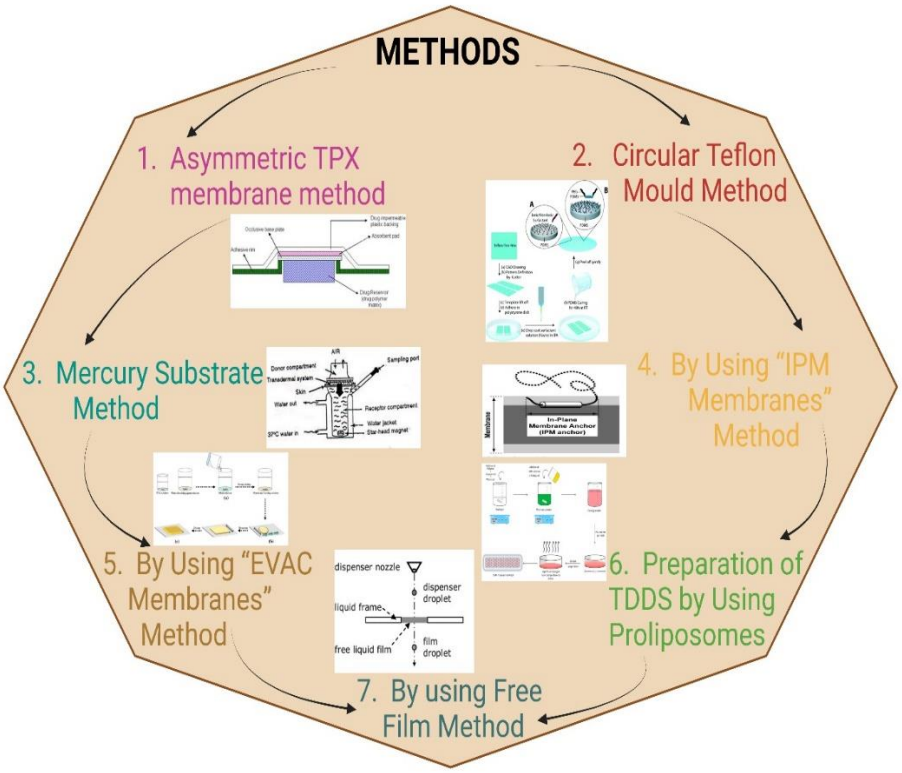


Figure 2: Methods of Transdermal Drug Delivery System

TDD systems are regarded as patient-friendly since they are non-invasive, do not require professional administration, reduce gastrointestinal (GI) side effects, and boost patient adherence.

Additionally, because they avoid the metabolic reactions brought on by oral route, bioavailability, effectiveness, and translocation are enhanced. Three categories of transdermal patches (TDP) can be distinguished: matrix, reservoir, and drug-in-adhesive. Whereas in drug-in-adhesive (DIA) formulations, the drug is actively consolidated into the adhesive layer, the matrix patch keeps the medication in the polymer matrix, which regulates the release of the medication.

The medicine is kept in the reservoir patch under a leak-proof rate-limiting layer in a liquid reservoir. Reservoir formulations are frequently utilized when a drug is unsuitable for or poorly dissolved in the transdermal device, while the DIA patch is typically employed when a drug is able to rapidly permeate the dermis and matrix [10].

Patents filed in last 9 years

Figure 3: Journey of transdermal patents from 2013 to present

2013

The year 2013 saw the patenting of many transdermal drug delivery systems starting with Bracht S et al. transdermal therapeutic systems with crystallization-inhibiting protective film (release liner). In this TDDS the side facing patch from the skin that includes the sequence baking layer, adhesive layer, release layer and an active

ingredient containing matrix of single or double layer and the pressure sensitive adhesive surface that is covered with a removal protective film that is release liner [11].

Plakogiannis FM et al patented transdermal delivery for aripiprazole in which the transdermal patch distribution of aripiprazole is accomplished with the help of the compositions of the current invention, which are liquid and gel formulations [12].

Fleschhut J et al described transdermal patch that contains TDDS, a type of buprenorphine patch that is converted from intravenous infusion. Transdermal administration systems prevent hepatic metabolism of the therapeutically active agent, which is frequently seen upon other routes of an active pharmaceutical agent, which is one of the reasons for this invention. The invention typically consists of a multi-layered system with at least one sticky layer carrying a medicament. The transdermal drug delivery composition with buprenorphine or a buprenorphine analogue as the active component is included in the drug-containing adhesive layer. The transdermal drug-delivery formulation also includes a penetration enhancer made of a keto acid, as well as an adhesive component made of both crosslinked and non-crosslinked acrylic polymers. The invention is described in the patent as a TDDS for delivering an active substance through the skin, said system being useful for an application duration of at least 3 days, comprising the layers set up in a manner similar to a cover layer, an active ingredient layer consisting of a polymer matrix containing active substance, and an adhesive layer consisting of a contact adhesive, which is made up of a contact adhesive and a contact adhesive [13].

Hamlin R et al. patented a weak base and, preferably, a carboxylate ingredient which is included in the conversion layer of the transdermal formulations that also include an active agent layer. Kits including the transdermal formulations as well as instructions for using them are also given [14].

2014

In 2014 many transdermal drug delivery systems are got patented in which Shishido T et al. was described the composition of vaccine for transdermal system in which an antigen-containing vaccine formulation for transdermal delivery is used to establish cellular immunity; the composition's recipient model animal's cell ratio must be 10% or higher [15].

Maeda Y et al. patented the cancer vaccine of wt1 peptide via a transdermal administration. In order to induce cellular immunity, the invention offers a cancer vaccine film preparation that consists of assistance, an adhesive layer with an adhesive positioned on one side of the help, and an adhesive layer that contains a WT1 peptide or an altered WT1 peptide along with a first cellular immunity initiation promoter. The tape preparation offers excellent effectiveness [16].

Scasso AF et al. was patented an apparatus for transdermal administration of alkaline chemicals that are prone to base breakdown in their free form. The invention is more specifically a tool for the transdermal delivery of an alkaline pharmaceutically active ingredient that is susceptible to degradation in its free base form (for example, rivastigmine), which consists of an adhesive matrix layer, a backing layer, and a release or protective film, wherein the adhesive matrix sheet contains pharmaceutically active compound, triethyl-citrate, and hydrochloric acid. The invention also has something to do with how such devices are made [17].

In the same year, Smith A et al. patented the methods for permanent transdermal delivery of substance in which forming at least one delivery aperture in the skin tissue with a total opening size of between approximately 40 and about 90 microns is a step in a method for trans-dermally delivering permeant substances into an animal's membrane [18].

Faupel M et al. got patented the controlled administering of a transdermal device with at least a single substrate positioned to be applied to the mucous membrane or the skin surface. A control mechanism is organized to start generating light pulses of a predefined wavelength that are intended to break the covalent bonds in between active substance or the receptor to remove the active component from the substrate. One active component is at least inserted to the substrate from at least a photolabile ligand. The substrate consists of a porous matrix that defines at least three-dimensional tank. The matrix is made of a polymer between chitosan and chitin and has a three-dimensional structure with numerous pits arranged in a sponge-like pattern. The ligand grafts and confines the active component [19].

2015

In 2015 many transdermal drug delivery systems are got patented in which Rossi DT et al. got patented the transdermal delivery of pramipexole drug, which is used for treating and preventing cluster migraines and headaches described in the invention involving application of pramipexole trans-dermally [20].

Sivaraman A et al. patented the low melting point transdermal dosage for active agent in which a patch that contains a medication enables transdermal drug delivery. The patch has a hydrophobic reservoir with a primary and secondary surface that holds the medication. The primary surface of the reservoir is covered with a drug-impermeable backing. The secondary surface of a reservoir may have a release sheet on top of it. The hydrophobic reservoir comprises of a hydrophobic filler (to effectively adsorb the medicine), a solution of mineral oil and polyisobutylene, and a hydrophobic matrix. As a hydrophobic filler, hydrophobic colloidal silica may be present in the hydrophobic matrix. The hydrophobic reservoir film might function as an adhesive layer that touches the skin. As an alternative, the skin-contacting adhesive film could be replaced with a release-controlling layer. The hydrophobic colloidal silica and a compound of polyisobutylene and mineral oil may be present in the release-controlling adhesive layer [21].

Kaspar RL et al. got patented the mTOR inhibitors composition for transdermal drug delivery in which the compositions for the transdermal distribution of rapamycin or other associated compounds are the focus of the invention. An mTOR inhibitor, such as rapamycin, water, a polymer with surfactant properties, a polymer with thickening properties, a liquid solution for solubilizing the mTOR inhibitor, a glycol, a C10–C20 fatty acid; and a base are specifically included in one embodiment of a preparation for trans-dermally delivering rapamycin [22].

In the same year Lee DI et al patented the composition to improve the transdermal drug permeation for external use. In this invention, a skin topical composition that contains tranexamic acid or even a salt of it as well as skin penetration booster is offered, demonstrating noticeably better sense of use, reduced storage stability and skin irritation [23].

Stephen I. patented the devices and methods for the delivery of transdermal compounds. A transdermal sensor that can detect a specific indicator, such as the active ingredient itself or a biomarker that is impacted by the active substance, is included in a device for monitoring and measurement of a subject concurrently with transmucosal or transdermal delivering of an active ingredient at the contact site with the patient's skin. A formulation containing the therapeutic agent is also included for active or passive transdermal drug delivery [24].

Ryoo JP et al. got a patent containing drug rivastigmine used in transdermal patch and its pharmaceutically acceptable derivative delivered trans-dermally, along with a process for producing it [25].

2016

In 2016 many transdermal drug delivery systems are got patented in which Pongpeerapat A et al. patented methods for the treatment of dexmedetomidine delivery trans-dermally in which a transdermal delivery system for giving a subject dexmedetomidine. These systems contain a single film matrix of dexmedetomidine composition. Dexmedetomidine and a pressure-sensitive adhesive that is offered in a single layer formulation are two components of transdermal delivery devices, according to some implementations. Furthermore, kits comprising the transdermal drug delivery devices as well as instructions for using them to provide dexmedetomidine to a patient are provided [26].

Pongpeerapat A et al. got another patent on the above mentioned composition for curing withdrawal syndromes by the help of non-sedative composition of dexmedetomidine. The invention also includes methods of treating it by placing a transdermal delivery system having a dexmedetomidine compound formulated to deliver a non-sedative amount of dexmedetomidine. A transdermal delivery system with a dexmedetomidine formulation is applied to a subject during the practice of certain embodiments, and it stays connected with the subject long enough to give a non-sedative quantity of dexmedetomidine to cure symptoms of withdrawal in the subject. Additionally offered are kits that contain the transdermal delivery systems and transdermal delivery devices that are designed to give a non-sedative dose of dexmedetomidine necessary for practicing the subject procedures [27].

Pongpeerapat A et al. patented the non-sedative composition for the transdermal drug delivery of dexmedetomidine and their methods in that the application of a transdermal delivery system to a patient is covered by the invention. This device is designed to administer a non-sedating dose of a dexmedetomidine formulation. A non-sedative quantity of a dexmedetomidine formulation is trans-dermally administered to a subject in procedures according to some embodiments and applied for a sufficient period of time to supply a non-sedative quantity of dexmedetomidine to the subject. In addition, kits including the transdermal delivery systems and dexmedetomidine in non-sedative amounts suitable for practicing the subject procedures are offered [28].

Pongpeerapat A et al. further patented the pain management by the help of dexmedetomidine composition and methods of transdermal drug delivery. The application of a transdermal delivery system having a dexmedetomidine formulation formulated to deliver an effective quantity of dexmedetomidine to a person suffering from pain is one method of controlling pain according to the invention. A transdermal drug delivery system having a dexmedetomidine formation is applied to a patient during the practice of methods in accordance with certain embodiments, and the device stays

connected with the patient long enough to deliver an adequate dose of dexmedetomidine to the subject to manage pain. Additionally offered are kits that contain the transdermal delivery systems as well as transdermal delivery devices that are designed to administer an amount sufficient enough of dexmedetomidine to practice the subject procedures [29].

Kalghatgi S et al. was patented the DNA vaccine by the help of non-thermal plasma in transdermal delivery. The invention includes the illustrative delivery systems and procedures for DNA vaccines. Delivering a plasma producer for administering plasma to a treated area for long enough to open a single or more pores is part of an exemplary technique of administering DNA vaccines. The process includes administering a transdermal vaccine for DNA to the affected area and wait for DNA vaccine to pass through the affected area's one or more pores. The illustrative process also involves injecting plasma into the treated area at a concentration that will induce the DNA vaccine to be taken up by cells [30].

Sameti M et al. got patented the active compounds for delivery trans-dermally where a transdermal therapeutic device (TTS) for administering pharmacological active substances is the subject of the invention. The TTS consists of a protective film and at least one carrier substance that contains active ingredients. The active ingredient-containing carrier material is fixed to the cover layer by at least one retention element, which is situated between the active ingredient-containing carrier agent and the cover layer. The method of attaching a carrier material containing active ingredients to a TTS cover layer in the existence of hook-and-loop strip sections is another aspect of the invention, as is the application of hook-and-loop strips to the transdermal or iontophoretic management of medicinal or therapeutic active compounds to subjects [31].

Matsushita K et al. got a patent to reduce the penetration of skin by the composition of transdermal patch. The invention offers a composition that accelerates skin penetration without requiring a drug to be formed it into particle structure and significantly enhances a drug's skin penetration capabilities without damaging the skin's tissue. Additionally, it offers a patch preparation and a preparation for transdermal delivery that contain the skin penetration-accelerating formulation. A skin penetration-accelerating formulation for drugs that contains a flavonoid component, and a surfactant is offered by the current invention [32].

Benjamin M. Yu et al. patented the composition and methods for the transdermal drug delivery. Vitamin E, Alpha-lipoic acid, vitamin D, glutathione, astaxanthin, beta carotene, resveratrol, vitamin A, vitamin C, vitamin B6, vitamin B12, folic acid, and taurine are a few examples of AI compounds. Another factor of the discovery relates to AI-helper compositions, which include an AI compound and one or more helper esters. The AI chemical can be effectively delivered to a subject by transdermal distribution using the AI-helper formulations described. The preparation and application of the AI-helper formulations is another part of the invention [33].

Baker AT et al. got a patent for the portion of cartridge of the apparatus or methods in transdermal drug delivery system where a cartridge that can be used as a component of a transdermal delivery system. It may have a body that at least partially defines an interior that will hold fluid that will be administered by the system. The body may also specify first and second apertures to its interior, with the primary and secondary openings located near the body's first and second opposing ends, respectively. The

cartridge may also have a self-sealing component that at least partially closes the first opening and a movable component that at least partially closes the second hole, at least a piece of which is designed to be pushed into the body's interior to raise pressure there [34].

Baker AT et al. got another patent in the same year for the methods and apparatus controlled portion in transdermal delivery. A pushing method mounted to move comparative towards the housing, a force supplier placed between it housing and its moving system to move the pushing method similar to a housing and a latching system to selectively restrict and allow relative motion between the housing and moving system are all components of a controller that may be applied in a transdermal medication delivery apparatus. The pushing mechanism might be set up to press against the transdermal delivery system's reservoir. The pushing mechanism may be set so that the arms release when the opposite ends are forced toward one another. The latching system also includes movable arms stretching between the opposite sides of the latching mechanism [35].

2017

In 2017 many transdermal drug delivery systems are got patented. Redding BK et al. patented the modification in ultrasonic transdermal drug delivery to make its preparation more conductive. It involved a technique for enhancing the ultra - sonic transdermal application of a drug by altering the excipient solution. An active ingredient is mixed with in a pharmaceutical formulation, whereby the selection of excipient solution is altered to one that will be more ultrasound-friendly and propagate the drug product at a higher speed of delivery through to the skin under ultra - sonic excitation. Converting a formulation that typically contains dibasic sodium phosphate to one that uses very less sodium and less preservative components is an example of changing the excipient. Formulation of sodium diphosphate, which has been reduced in response, in sonification of the same, steps such as reducing the quantity of dibasic sodium phosphate in the composition to produce a decreased dibasic sodium phosphate formulation, as well as producing a compound in accordance with the decreased dibasic sodium phosphate formulation [36].

Silverberg EN et al. got a patent for the acrylic polymers used in the transdermal delivery. The random acrylic co-polymers that can be used for transdermal applications are the focus of the patent. The described co-polymers' creation and application processes are also explained [37].

Singh R et al. patented the methods of micronutrients preparation. The procedure of making lipid vesicles loaded with micronutrients is provided by the current invention. The micronutrient packed lipid vesicles, which are preferably phospholipid vesicles, are made up of edge activators, lipid, and micronutrients. The current invention furthermore includes preparation methods for lipid vesicle-containing compositions. Transdermal formulations such as peel-off gel, film-forming gel, lotions, face cream compositions, clear transparent gel, patches etc. are among the compositions. The makeup of the micronutrient-loaded vesicles and how quickly and effectively micronutrients can pass through skin and into the circulation [38].

Shishido T et al. patented the composition of vaccine for transdermal drug administration. The invention offers a pharmaceutical vaccine composition for transdermal delivery that is safe, effective at generating a systemic immune response, and suitable for use as a preventative or medicinal treatment for cancer or viral

infections. It can be applied to either human or animal skin, and the vaccine's pharmaceutical composition contains: a lipopolysaccharide or its salt, obtained of at least one gram-negative bacterium, like as Lelercia, Serratia, Rahnella, Acidi-philium, Acidic-aldus, Acidisphaera, Acidocella, Acidomonas, Asaia, Belnapia, Gluconacetobacter, Glucon etc. as an immunostimulant; and at least one antigen, with a mass ratio of 0.002 to 500 between the immunostimulant as well as the antigen, or the total weight of the immunostimulant in the vaccine pharmaceutical composition [39].

Choi YK et al. got a patent for the active component of donepezil pertaining to a transdermal formulation that contains donepezil as an active substance and contains: (1) a backing layer; (2) a drug having matrix layer containing, based on the total weight of the drug-containing matrix layer, (B-1) 15–55 weight percent of donepezil and a pharmaceutical formulations acceptable salt thereof, (B-2) 25–70 weight percent of such an EVA-based adhesive, (B-3) 5–20 weight percent of at least one selected from the group made up of a pyrrolidone derivative as well as a C8–18 aliphatic derivative [40].

Sand BJ et al patented the formulation and method for the transdermal drug administration for mproved topical therapy. Formulations are revealed that guarantee at least localized transdermal or systemic administration of an active participant through skin, nails, or hair follicles [41].

2018

In 2018 many transdermal drug delivery systems are also got patented in which Roy S et al. patented methods and systems for the transdermal drug delivery. The backing film that is substantially impermeable to isopropyl alcohol, (s)-ketorolac, isopropyl myristate, butylated hydroxytoluene, oleic acid, hydroxypropyl cellulose, triethanolamine, and water is one component of a liquid-reservoir Structure (LRS) for topical application of (s)-ketorolac. Additionally, it may have a (s)-ketorolac one to fifteen percent by weight (s)-ketorolac or a salt of it, one or even more drug solubilizing vehicles, one or more permeability enhancers, an antioxidant, a thickening agent, purified water, and a buffering agent are all possible additions to the liquid-reservoir gel formulation. Providing an LRS, withdrawing a release liner film by peeling it away, putting the LRS on a patient's skin with the backing layer facing outward, and adding pressure to the backing film to non-permanently attach the LRS to the sample surface are all steps in a transdermal drug delivery system [42].

Whitelock S et al. got a patent about the devices and mixtures for treating pain that are abuse-resistant. Transdermal administration of an opioid agonist or a non-trans-dermally administered n-oxide derivatives of such an opioid antagonist in which the invention offers a transdermal delivery system for a pharmaceutical composition that contains an opioid agonist and salt thereof and an opioid antagonist in the form of an N-oxide derivative [43].

Rangan KK et al. patented the transdermal delivery a multipurpose clay product devoid of polymers that contains clay, zwitterion, a silver component, and an analgesic for wounds healing and dressing. The multipurpose clay product without polymers has antibacterial and pain-relieving qualities to treat burns. Multifunctional polymer-free clay goods that can be made using the technique includes clay, zwitterion, a silver component, and an analgesic [44].

Henley J et al. got a patent for trans mucosal delivery of accelerator device and the electro kinetic transdermal delivery in which a reservoir for holding the medication, and oscillation driver electrically connected to a vibrational element, and a current driver electrically connected to an electrode are all components of a medical device for dispensing medication. The electrode creates a number of fluid channels that connect to the reservoir. Also offered is a way to administer a medication [45].

Kulkarni G et al patented the methods and delivery of microneedles. In this a transdermal delivery device consists of a reservoir for storing a drug, at least one microneedle in liquid communication with the reservoir, and a transdermal delivery device that is hidden from view while the device is in use [46].

Lee ES et al. got a patent describing the methods for long term use of transdermal patch. Devices, systems, formulations, and procedures are offered for sustained or long-term transdermal deliveries of an active ingredient are described [47].

In the same year Sand BJ et al. got a patent describing the enhancement of active agent of transdermal delivery in that the efficient transdermal transportation of active compounds is made possible by enhanced preparations that mix chemical absorption enhancers with additional ingredients such that the formulations concurrently penetrate both fat and cellular matrices [48].

Damodaran A et al. patented the delivery of the alkyl substituted of resorcinol composition and method. In this a cosmetic composition is disclosed that includes: I at least 1 pyridine chemical of Formula I or II; wherein, in Formula I and Formula II, X is S or O; R1, R, R2, or R3 are either —SH, —H, —OH or a CMS saturated or linear, unsaturated, branched, and cyclic hydrocarbon group; and Y is —SH, —H or CMS saturated and unsaturated, linear, branched, or It is also disclosed how to create a cosmetic composition with improved TDD of such an alkyl substitution resorcinol using a pyridine derivative of Formula I or II [49].

2019

In 2019 many transdermal drug delivery systems got patented in which Male SR et al. described the preparation and process of a patch for sleep aid. This invention pertains to a transdermal patch for sleep aids that contains an active substance derived from a natural herb, as well as additives that work together and excipients that are authorized for use in pharmaceutical products. The current invention relates to a transdermal patch formulation for treating insomnia that includes valerian as a natural herbal ingredient, licorice, skullcap, and passionflower as synergistic additives, as well as pharmaceutically approved excipients. The process described in the present invention—which includes melting, mixing, coating, laminating, and cutting—is effective for creating transdermal for use as a sleep aid [50].

Gonsalves RM et al. got a patent on the drug dexmedetomidine for the management of pain by the help of transdermal drug delivery devices. For application of an epidermal delivery device having a dexmedetomidine formulation formulated to administer a pain-relieving appropriate quantity of dexmedetomidine to such a person is one way of treating pain in a subject according to the invention. When using some embodiments of techniques, a transdermal drug delivery device with a dexmedetomidine formulation is placed to a person and stayed connected with the subject long enough to give an adequate dose of dexmedetomidine to manage the subject's pain. Some implementations of the procedures involve hydrating the subject,

maybe by giving them a fluid composition that contains hydration. Co-administering an opioid to a patient is another step in certain embodiments' methods. A transdermal delivery system that can deliver enough dexmedetomidine to practice the subject approaches is also offered, as are kits that contain the transdermal delivery system [51].

Male SR et al. got a patent for the pain management by the help of polyherbal patch. Its preparation and processing in this invention pertains to the formulation of polyherbal transdermal patches that combine pharmaceutically acceptable excipients with natural herbal extracts as active components. The current invention relates to the formulation of polyherbal transdermal patches that contain a mixture of natural herbal extracts, including cat's claw, devil's claw, ginger, licorice, evening primrose oil, and blackcurrant seed oil. The current innovation also relates to the formulation of a polyherbal transdermal patch for the diagnosis of pain that contains Boswellia extract, blackcurrant seed oil, evening primrose oil, ginger, licorice, cats claw, and devil's claw as natural and herbal components. The process of making polyherbal transdermal patches utilizing the hot-melt coating method, which includes the stages of melting, laminating, mixing, coating, cutting, pouching, and labelling, is also a part of the present invention [52].

Zhang X et al. patented the transdermal drug delivery of Treprostinil drug for the dermal and transdermal delivery of Treprostinil or its salts, as well as an additional therapeutic agent. The present disclosure offers techniques, formulations, apparatus, and systems. Any medical disease sensitive to therapy with Treprostinil, including pulmonary hypertension, like pulmonary arterial hypertension, may be treated with Treprostinil and its salts by dermal or transdermal administration [53].

Herb M et al. got a patent describing the packaging and compassion of film in that a film composite for making planar ships of pharmaceutical active substances, such as transdermal patches, comprising, from the film composite's outer side it toward inner side: an acrylic-acid-containing joining layer; a metal layer; and a COC film made of cycloolefin copolymer, with the side of the COC layer that faces away from the metal layer serving as an exposed surface of the film composite [54].

Scoglio S et al. got a patent describing the application of cyanobacterial algae and/or their extracts trans-dermally using low- or high-intensity transportation devices to improve one's appearance and health. In this the term "invention" refers to the transportation of cyanobacterial algae or their extracts through sono-poration (sound), electro-poration, radio-poration (radio frequency), photoporation (light), and by any other transport method for improving the topical penetration of cyanobacterial particles via the transfer of some strength, be it powered, or generated by sound, light, and/or radio frequencies. The present invention relates to the application of entire cyanobacterial algae or their extracts having varying degrees of transdermal penetration, such as light intensity transit, which can be used for deep skin regeneration and aesthetic purposes as well as dermatological issues, and high impact transportation, that can be used for metabolic, muscular, and osteopathic problems. After a thorough explanation of the innovation, we reveal incredibly important findings in various fields of beauty and health [55].

Hille T et al. patented the transdermal devise for the transparent patch of nicotine. This invention is applicable to clear therapeutic systems (TTS) that include nicotine as the active ingredient and at least 1 acid amide group like a lateral substituent. Transparent

and covert TTS are both possible. The invention also pertains to techniques for making these TTS, which are made utilizing techniques that use the forementioned polymers and are then printed with active ingredients [56].

Mohr P et al. got a patent describing the silicone acrylic mixed polymer and asenapine containing transdermal drug delivery system in which the therapeutic transdermal system contains a silicone acrylic combination polymer. The invention relates to therapeutic transdermal systems for the topical application of asenapine that include an asenapine-containing layers, said asenapine-containing film structure comprising 1) a backing layer and; 2) an asenapine-containing layer [57].

2020

In 2020 many transdermal drug delivery systems got patented in which Lee ES et al. patented the transdermal drug delivery mechanism having solvent filling pores in microporous membrane in that a transdermal delivery mechanism with a drug reservoir film that contains an active ingredient and a tissue adhesive layer is described. Between the medicine reservoir film and the tissue sticky film is a micro - porous membrane that has been prepared with a membranes treatment compound before the tissue is included in the system [58].

Gajula K et al. got a patent for the transdermal or topical delivery of the electroporation preparation of in- silico design. In this the limitations of conventional systems and methodologies prevent them from understanding electroporation beyond the scope of the simpler stratum corneum (SC) concept and estimated parameters. Additionally, these methods are restricted to one type of phenomena, whether it be molecular or macroscopic level permeation. Furthermore, flux and cumulatively dissolution profile could not be derived using molecular models according to these models' constraints in terms of time and length scales. The design of electroporation experimental techniques, which call for the selection of various pulse parameters, also falls short of conventional simulation research. System and method for in-silico creation of tissue electroporation parameters are provided by embodiments of the current disclosure. Skin lipids membrane simulation is used to calculate physical attributes such as diffusion coefficient. Additionally, during electroporation, macroscopic diffusion is modelled, and the flux and cumulative free profiles of actives are determined. As a design tool, the system of the current disclosure can be used to choose an appropriate electroporation procedure from factorial simulations [59].

Borsadia S et al. got a patent describing the device for transdermal delivery of dextromethorphan in which devices for transdermal dextromethorphan delivery are offered. The transdermal drug delivery device can be distinguished by its novel design, which could include having an adhesive film and a reservoir sheet, an adhesive layer made up of a combination of two adhesives, and/or a skin permeation enhancer that can significantly increase the flux of dextromethorphan. The transdermal delivery system may also be distinguished by the desirable pharmacokinetic profile it can produce in vivo and in vitro. Using the topical delivery system described here, additional treatment options for the diseases and disorders mentioned here are also available [60].

Gurtner GC et al. got a patent for the treatment of chronic wounds by the iron chelator. It is used for the cure of Sickle Cell Ulcers, a transdermal patch is offered as the delivery system. An iron chelator like DFO can be delivered more easily with the help of the patch. To increase absorption by the dermis and penetration into it, the DFO

may also be encapsulated inside a reversible micelle. The patch can be utilized to hasten healing and lessen the discomfort brought on by Sickle Cell Ulcers [61].

Nguyen TD et al. patented the core-shell microneedle platform and manufacturing process for topical and pulsatile for drug/vaccine delivery. In this a pulsatile drug delivery device that is designed to release medications or vaccines at predetermined periods utilizing biodegradable polymers although with adjustable dosages is provided by a core-shell microneedle mechanism and a method of producing the microneedle system. Like several bolus injections, this microneedle technology can be fully implanted into skin and thereafter deliver medications or vaccinations in quick, sharp bursts [62].

2021

In 2021 Goldstein SL et al. got patented the transdermal delivery for the therapy of renal replacement for constant rate measurement of glomerular filtration. A procedure for choosing a medication's dosage prescription for a subject undergoing CRRT is disclosed in this article. The procedure typically entails injecting medication into the patient's bloodstream a fluorescent agents; giving the customer at least single dose of the medication; giving the patient CRRT following the administration of the fluorescent agent; revealing the fluorescent operator to infrared or visible light; tracking transcutaneously a transition in the fluorescent agent's spectral energy over time; pertaining a shift in the intensity of the fluorescent agent's spectral energy to a change in the fluorescent agent's clearance rate from the patient's bloodstream; and calculating the patient's clearance charge of the medication; calculating the amount of the medication in the patient's blood as a function of the time; and modifying the patient's dosage instructions [63].

Future aspects

Transdermal System for Drug Delivery in the Future Liposomes, niosomes, and micro emulsion are upcoming developments in drug delivery systems. The purpose of this invention is to enhance the distribution of drugs with limited intrinsic solubility in the majority excipients used in traditional formulations. Steroids, antibacterial, antifungal, interferon, methotrexate, and local anesthetics are just a few examples of the many potential medications that could be delivered. Transdermal patch sales are predicted to grow in the future and have lately grown at a rate of 25% annually. As new devices are developed and the number of transdermal drugs that are marketed grows, this number will rise in the future. As there are more advancements in design, transdermal distribution of analgesics is probably going to gain prominence. Research is being done to improve effectiveness and safety [8]. To enable more precise medication distribution with an extended duration of action, as well as to improve practical aspects like the patch wearer's experience. Improved transdermal technology, which either modifies the skin barrier or boosts the activity of the drug molecules, can improve drug flux across the skin by using mechanical energy. Following the development of iontophoresis-based patches, multiple 'active' transdermal technology modes are being researched for various medications. These include sonophoresis (which employs lower frequencies vibrations to disturb the stratum corneum), thermal energy, and electroporation (which uses brief electric signals of high frequency to form transitory aqueous holes in the skin) [3]. The use of magnetic energy, or magnetophoresis, to boost medication flux over the skin has been studied. An underappreciated technique for managing both chronic and acute pain may be the

transdermal patch. We anticipate that this method of drug delivery will become more widespread and applicable with enhanced administration and a wider selection of analgesics. With over 40% of the delivery of drugs candidate items currently in clinical trials connected to transdermal and dermal system, route of administration of drug delivery is currently the most successful novel field of research in new drug delivery drug delivery system system when compared to oral treatment. The alternative, safest, and most convenient method for systemic delivery is the transdermal delivery method (TDDS). The administration of drugs systemically through the skin has several benefits, including the maintenance of a continuous drug rate in blood plasma, a reduction in side effects, an increase in bioavailability due to the bypassing of hepatic 1st pass metabolism, and an increase in patient compliance with regard to the drug regimen. For continuous medication release into the systemic circulation, skin is now thought to be the safest route for drug administration [64 - 68].

CONCLUSION

In this article it is well described about the transdermal drug delivery system in this article includes the history of the transdermal drug technology and the types of the transdermal delivery it is also describes the preparation and evaluation methods of the transdermal drugs in this article also includes the patents filed in last 10 years in the field of transdermal technology and the future aspects of the same.

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