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A Review on Transdermal Patches to Deliver a Constant and Controlled Dosage over Extended Periods for Systemic Therapy

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ABSTRACT

Transdermal patches have emerged as a promising drug delivery system, offering a non-invasive, patient-friendly method for administering medications over extended periods. This review provides a comprehensive overview of the design, development, and therapeutic applications of transdermal patches aimed at achieving constant and controlled drug release for systemic therapy. The article highlights the fundamental principles underlying transdermal delivery, including drug permeability, formulation techniques, and the role of excipients in enhancing bioavailability.

Advances in patch technology, such as microneedle-assisted systems, iontophoresis, and nanocarrier-based designs, are explored in detail, demonstrating their potential to overcome conventional barriers like low skin permeability and limited drug loading capacity. Furthermore, the review examines the clinical applications of transdermal patches in managing chronic diseases such as hypertension, diabetes, and pain, emphasizing their advantages over oral and injectable routes.

Challenges such as skin irritation, adhesive quality, and scalability in manufacturing are also discussed, along with potential strategies for addressing these limitations. The article concludes by outlining future perspectives, focusing on the integration of wearable technologies and personalized medicine to enhance the efficiency and patient compliance of transdermal drug delivery systems.

Keywords: Transdermal patches, systemic therapy, controlled drug delivery, microneedles, bioavailability, wearable technology

1 INTRODUCTION

Drugs can be delivered across the skin to have an effect on the tissue adjacent to the site application (topical delivery) or to have an effect after distribution through the circulatory system (systemic delivery)[1]. The drug has been applied to the skin to treat superficial disorders, for the transdermal administration of therapeutics to maintain systemic alignment and as cosmetics, dating back to the oldest existing medical record of man. The skin is the latest organ in the human body by mass, with an area of between 1.5 and 2.0 m^2 in adults. This review being with the earliest therapies and traces topical delivery to the present–day transdermal patches, describing along the way initial trials, devices and drug delivery system that underpin current.[2] Transdermal patches products were first approved in 1981 by FDA.The Main objective of transdermal drug delivery system is to deliver drug into systemic circulation into the skin through skin at predetermined rate at with minimal inter and intra patient variation [3]. Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation [1]. The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs.[4]

2 SKIN

The skin is a largest organ in a body, covering its entire external surface the skin has three layer.

- Epidermis
- Dermis
- Hypodermis

EPIDERMIS

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum and theremainder of the epidermis, also called viable epidermis, cover a major area of skin [1].

DERMIS

Dermis is a 3 to 5 mm thick layer and is composed of a matrix of connective tissue which contains blood vessels, lymph vessels, and nerves. The continuous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation [4].

HYPODERMIS

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area, This layer helps to regulate temperature, provides nutritional support and mechanic protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery, only penetration through stratum corneum is essential and then retention of drug in skin layers is desired[5].

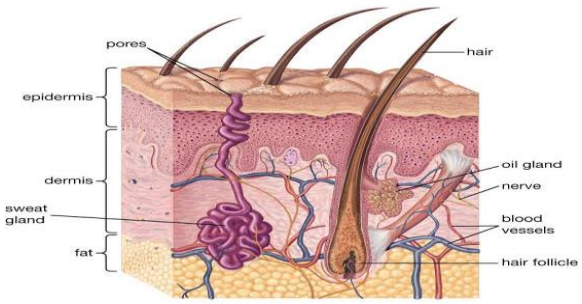

Fig.1 Human Skin

TRANSDERMAL PATCHES USED IN SKIN

Transdermal & skin patches are medicated adhesive patches intended to deliver a specific dose of any therapeutic compound at a regulated/controlled rate through the skin non-invasively.[6]

➢ **Factors effecting transdermal patches:-**

- Biological factor
- Skin conditions
- Skin age

- Body weight
- Blood supply
- Skin metabolized

➢ **Physiological chemical factor:-**

a) Skin hydration

b) Temperature

c) pH

d) Molecular size

e) Molecular shape

➢ **Environmental factors:-**

a) Sunlight

b) Cold season

c) Air pollution

3 Treatment options

For treating mild VMS, lifestyle changes, either alone or in conjunction with non-prescription remedies, are generally recognized as first-line treatment options. Lifestyle modifications include maintaining air temperature as cool as possible to help keep the core body temperature cool and behavioral changes such as exercising regularly, maintaining healthy body weight, avoiding hot drinks and foods that may trigger hot fl ashes, and using a variety of relaxation techniques.

Alternative treatment options

Nonprescription remedies such as dietary isoflavones, black cohosh, and vitamin E have been suggested as possible alternatives to HT. When studied in randomized, placebo-controlled studies, these remedies have not demonstrated a clinically relevant reduction in VMS. However, a recent study found significant reductions in severity and frequency of hot flashes with a soy isoflavone extract compared to placebo in post-menopausal women experiencing five or more hot fl ashes per day at baseline after 10 months of treatment[7,8].

4 NOVEL DRUG DELIVERY SYSTEM

During the past few years, interest in development of novel delivery system for existing drug molecules has been renewed. Development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves. Patient compliance and overall therapeutic benefit to a significant extent. When properly designed and developed for a particular drug, the novel delivery system can overcome specific hurdles associated with conventional methods of delivery e.g., drugs undergo partial or complete degradation before reaching the site of action could be effectively delivered with improved bioavailability by using a novel concept of time or pulsatile release, or gastro-resistant delivery.[10]

EFFECT OF DRUG CHARACTERISTICS

The properties of a drug that enable good penetration through the SC can be deduced from the equation for steady-state flux therapeutically attainable plasma concentration defined by the rate of delivery from the patch through the skin. This can ultimately be controlled by the patch size, application at the appropriate skin site, and incorporation of adjuvant or skin penetration enhancer. The controlled release that avoids fluctuating blood levels (seen with oral dosing) and the convenience offered by patches, makes TDP an ideal candidate for drugs with short elimination half-lives [11].

5 DESIGN AND CURRENT APPROACHES TO PAINLESS DRUG DELIVERY

The development of a safe and efficient drug delivery system is the aim of every pharmaceutical researcher and industry. The transdermal route of drug delivery can achieve local and systemic therapeutic effects. Transdermal drug delivery is an attractive substitute for oral drug administration as it bypasses first-pass metabolism and gastrointestinal effects and it can overcome the poor patient compliance associated with other drug delivery routes.

Safety of transdermal drug delivery systems Transdermal drug delivery systems have an improved safety profile as this delivery system can be absorbed adequately in patients who do not have a functional gastrointestinal tract. In addition, transdermal formulations typically have a favorable drug concentration profile as the factors that limit gastrointestinal absorption (e.g., changes in pH, rate and extent of gastric emptying, transit times, presence/interaction with food, intestinal motilities) are avoided. Delayed absorption prevents peaks and valleys associated with variations in drug concentrations. Lack of venous access, reduction in infection risk, improved compliance, and potential for use in patients who are unable to swallow are also indicative of an improved safety profile associated with these delivery systems. Drug deactivation typically occurs with oral administration drugs via first-pass metabolism and interaction with liver and digestive enzymes. TDDS avoids first-pass metabolism, the process by which the liver metabolizes drug products before it passes into systemic circulation. In this context, TDDS may reduce drug-drug interactions associated with concomitant medications that are metabolized in the liver [12].

CLINICAL EFFECTS WITH TRANSDERMAL DOSING

One of the major obstacles to the effective treatment of AD with oral cholinesterase inhibitors has been tolerability, which can prevent many patients from reaching efficacious therapeutic doses in clinical practice. Until recently, all cholinesterase inhibitors were administered orally, but the newly developed rivastigmine patch appears to overcome this tolerability obstacle by employing a different dosing route and may offer a substantial clinical advantage. Modeling analyses adjusting for baseline demographic factors demonstrated that the 9.5 mg⁄24 h patch (10 cm2) provides comparable exposure, and therefore potentially similar efficacy, to the highest doses of rivastigmine capsules (12 mg⁄day). The pharmacokinetic profile, with a reduced Cmax and prolonged tmax, also predicts an improved tolerability profile vs. Conventional rivastigmine capsule administration. These hypotheses are supported by results from the landmark Investigation of transdermal Exelon in Alzheimer's disease trial (IDEAL). This was a randomized, double-blind, double-dummy, placebo-controlled trial to investigate the efficacy and tolerability of the rivastigmine patch (4.6–17.4 mg⁄24 h) vs. Capsules (3–12 mg⁄day) in 1195 AD patients. Patients randomized to patch treatment were started on the 4.6 mg⁄24 h patch and titrated in a single step to the recommended 9.5 mg⁄24 h patch. During the 24-hour application period, patients were able to pursue all normal activities, including washing and bathing. The trial was also conducted in countries with varying climates, including some hot and humid regions (e.g. Guatemala, and Venezuela). The 9.5 mg⁄24 h patch provided similar efficacy to the highest doses of capsules (12 mg⁄day) on various outcome measures, with three times fewer reports of nausea and vomiting. This supports the rationale for the patch that a smoother pharmacokinetic profile would yield fewer cholinergically mediated while maintaining therapeutic concentrations. Similar efficacy between the 9.5 mg⁄24 h patch and 12 mg⁄day capsule groups, despite the patch providing slightly less drug, demonstrates the advantage with transdermal delivery of the avoidance of first pass metabolism by peripheral cholinesterases in the gut.[14]

6 ORAL VS TRANSDERMAL PHARMACOKINETIC DIFFERENCES

While both oral and transdermal have been proven effective for the relief of menopausal symptoms, several differences exist between these routes that may influence safety and patient acceptance of the regimen. Oral administration of estrogen is associated with extensive gut and first-pass liver metabolism as well as significant hepatic stimulation [15]. To overcome these metabolism processes, oral estrogens must be administered in relatively high doses to provide blood levels adequate to reduce menopausal symptoms. Extensive metabolism of oral estrogens results in the conversion of a large portion of the dose to estrone and its conjugates, which have less estrogenic activity than estradiol. Significant metabolic conversion of oral estrogens to estrone results in a higher ratio of estrone to estradiol in the bloodstream, which is the opposite of the physiological levels in premenopausal women [16]. In addition, some metabolites of conjugated estrogens formed during first-pass metabolism appear to have antiestrogenic or unrecognized pharmacologic activity in the human body [17]. Conversely, transdermal dosage forms deliver estradiol directly to the systemic circulation through the skin, bypassing gut and first-pass hepatic metabolism [18]. Avoidance of gut and liver metabolism via transdermal administration helps maintain an estradiol-oestrone ratio similar to that found in premenopausal women [19]. However, the clinical relevance of the estradiol-to-estrone ratio is currently unknown. Significant variations in the metabolism of oral estrogens result in wide fluctuations in estrogen blood levels throughout the day, potentially resulting in inconsistent control of VMS [20]. Transdermal administration provides more consistent blood levels by avoiding the peaks and troughs inherent to oral estrogens.[15]

TRANSMUCOSAL DRUG ABSORPTION

A thorough description of the oral mucosa and its function is available elsewhere [17]. We have only included those details relevant to the oral mucosal delivery of drugs. The oral cavity comprises the lips, cheek (buccal), tongue, hard palate, soft palate, and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa and includes the buccal, sublingual, gingival, palatal, and labial mucosa. The mucosal tissues in the cheeks (buccal), the floor of the mouth (sublingual), and the ventral surface of the tongue account for about 60% of the oral mucosal surface area. The buccal and sublingual tissues are the primary focus for drug delivery via the oral mucosa because they are more permeable than the tissues in other regions of the mouth. The surface area of the oral mucosa (200 cm^2)[18] is relatively small compared with the gastrointestinal tract (350000 cm^2) and skin (20000 cm^2)[19]. However, the oral mucosa is highly vascularized, and therefore any drug diffusing into the oral mucosa membranes has direct access to the systemic circulation via capillaries and venous drainage. Thus, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver. The rate of blood flow through the oral mucosa is substantial and is generally not considered to be the rate-limiting factor in the absorption of drugs by this route [20]. The oral mucosa is made up of closely compacted epithelial cells, which comprise the quartertone-third of the epithelium [21-23]. The primary function of the oral epithelium is to protect the underlying tissue against potentially harmful agents in the oral environment and from fluid loss [24]. In order for a drug to pass through the oral mucosa, it must first diffuse through the lipophilic cell membrane, and then pass through the hydrophilic interior of the cells of the oral epithelium. Thus, the oral mucosa provides both hydrophilic and hydrophobic barriers that must be overcome for efficient mucosal delivery. An enzymatic barrier also exists at the mucosa, which causes rapid degradation of peptides and proteins, limiting their transport across the oral mucosa. Although these layers provide a unique challenge for drug delivery via the oral mucosa, several different approaches in the design and formulation of suitable delivery systems have been developed to circumvent these barriers [25].

7 SAFETY OF TRANSDERMAL DRUG DELIVERY SYSTEMS

Transdermal drug delivery systems have an improved safety profile as this delivery system can be absorbed adequately in patients who do not have a functional gastrointestinal tract. In addition, transdermal formulations typically have a favorable drug concentration profile as the factors that limit gastrointestinal absorption (e.g., changes in ph, rate and extent of gastric emptying, transit times, presence/interaction with food, intestinal motilities) are avoided [26]. Drug deactivation typically occurs with orally administration drugs via first-pass metabolism and interaction with liver and digestive enzymes. TDDS avoid first-pass metabolism, the process by which the liver metabolizes drug products before it passes into systemic circulation [1,14]. In this context, TDDS may reduce drug-drug interactions associated with concomitant medications that are metabolized in the liver [27].

Some TDDS products may predispose patients to burns when receiving MRI scans. A transdermal system formulated with an aluminum backing could injure a patient if worn during MRI procedures. Use of these patches during MRI procedures may cause a concentration of electrical currents to be directed at the application site thereby resulting in excessive heating and tissue damage [28]. The FDA has released several reports warning of the increased risk of excessive heating and burns associated with the use of MRIs in patients wearing patches and has included an updated list of prescription and OTC drugs that should be avoided during MRI procedures (e.g., clonidine, lidocaine/ epinephrine; lidocaine/tetracaine; scopolamine; nicotine; testosterone; fentanyl; and methyl salicylate/menthol)[29].

8 PATCH ADHESION

Another limitation common to transdermal delivery systems is the efficacy of patch adhesion. Absorption of the medicine can be compromised if a patch does not remain in contact with the skin. One study examined patch adhesion over 12 hours of wear time (during a summer day, including swimming and engaging in other physical activities) for children with ADHD. In this study of the MPH transdermal system, among 36 participants over 8 days, 18 patches fell off and another 18 required additional taping.[30]

9 THE USE OF TRANSDERMAL THERAPEUTIC SYSTEMS IN PSYCHIATRIC CARE

A study of nonsmoking teenagers with ADHD demonstrated improvement in multiple cognitive domains with the administration of nicotine [31]. Finally, nicotine may also have a role as adjunctive therapy in the treatment of depression, as studies on rats demonstrate improvement in depressive characteristics with nicotinic agonists. Open-label studies with nonsmoking human subjects diagnosed with major depression have shown improvement in mood with the administration of nicotine [32].

➢ **Physicochemical factors**

- **Skin hydration**

In contact with water, the permeability of the skin increases significantly. Hydration is the most important factor in improving the permeation of skin. So use of humectant is done in transdermal delivery.

- **Temperature and pH**

The permeation of the drug increases tenfold with temperature variation. The diffusion coefficient decreases as the temperature falls. Weak acids and weak bases dissociate depending on the pH and pka or pkb values. The proportion of unionized drugs determines the drug concentration in the skin. Thus, temperature and pH are important factors affecting drug penetration.

- **Diffusion coefficient**

Penetration of a drug depends on the diffusion coefficient of the drug. At a constant temperature, the diffusion coefficient of the drug depends on the properties of the drug, the diffusion medium, and the interaction between them.

- **Drug concentration**

The flux is proportional to the concentration gradient across the barrier and the concentration gradient will be higher if the drug concentration is more across the barrier.

- **Partition coefficient**

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

- **Molecular size and shape**

Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones. [33]

- **Evaluation of transdermal patches**

The transdermal patches can be characterized in terms of the following parameters:

- Physicochemical evaluation
- In vitro evaluation
- In vivo evaluation

➢ **Physiochemical evaluation**

- Thickness
- Uniformity of weight
- Drug content determination
- Content uniformity test
- Moisture test
- Moisture uptake
- Folding endurance

- Tack properties
- Thumb tack test
- Quick stick test

- **Thickness**

The thickness of the transdermal film is determined by traveling microscope, dial gauge, screw gauge, or micrometer at different points of the film [34].

- **Uniformity of weight**

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight [35].

- **Drug content determination**

An accurately weighed portion of the film (about 100 mg) is dissolved in 100 ml of suitable solvent in which the drug is soluble and then the solution is shaken continuously for 24 h in a shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, the drug in solution is estimated spectrophotometrically by appropriate dilution [36].

- **Content uniformity test**

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then an additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test [37].

- **Moisture content**

The prepared films are weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using the following formula [38].

$$\%moisture\ uptake = Final\ weigjht - Initial\ weight \times 100$$

- **Folding Endurance**

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it breaks. The number of times the films could be folded at the same place without breaking is the folding endurance value.[39]

- **Tack properties**

The polymer can adhere to the substrate with little contact pressure. Tack is dependent on the molecular weight and composition of the polymer as well as on the use of resins in the polymer [40,41].

- **Quick stick (Peel tack) test**

The peel force required to break the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90 at the speed of 12 inches/min [42]

- **In vivo Studies**

Transdermal patches can be in vivo evaluated in terms of In vivo evaluations are the true depiction of the drug performance. The variables that cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo, evaluation of TDDS can be carried out using animal models and human volunteers.

- **Animal models:**

Considerable time and resources are required to carry out human studies, so animal studies are preferred on a small scale. The most common species used for evaluating transdermal drug delivery systems are mouse, hairless rats, hairless dogs, hairless rhesus monkeys, rabbits, guinea pigs, etc. Various experiments conducted led to the conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. The Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man.

- **Human model**

The final stage of the development of a transdermal device involves the collection of pharmacokinetic and pharmacodynamic data following the application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance, etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short-term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in a large number of patient populations and phase IV trials at post-marketing surveillance are done for marketed patches to detect adverse drug reactions. Human studies require considerable resources to assess the performance of the drug.[38]

- **Unwanted skin absorption and potential for toxicity**

Concerns about the undesirable systemic absorption of actives and excipients have focused primarily on antiseptics and other topical treatments routinely applied to newborns and, more particularly, preterm infants. The risk of systemic exposure has to be carefully balanced against the need for effective skin disinfection, which is essential to reduce the incidence of infections in newborns, especially in premature infants who are often subjected to multiple invasive procedures. The potential for undesirable chemical skin absorption in neonates is historically illustrated by hexachlorophene, an antibacterial that was later withdrawn due to safety concerns [43]. Similarly, topical iodine-based disinfectants have also been withdrawn [44]. For example, their use was associated with hypothyroidism in 4 infants (average 37week GA) with spina bifida, a side-effect attributed to excessive iodine absorption from antiseptic dressings (povidone-iodine 10%) [45]; another study in 30 (26-30week GA) infants found increased levels of urinary iodine and some effects on thyroid function [46,74]. A concluded that topical exposure of preterm infants to iodine (< 32-week GA) leads to thyroid dysfunction. Similarly, the use of alcohol-based products in pre-term infants can cause serious harm as illustrated by the case of a 27-week GA whose skin was cleaned with methylated spirits (95% ethanol; 5% wood which contains a minimum of 60% methanol); post-mortem blood samples (18 h after exposure) revealed concentrations of ethanol and methanol of 2.59 mg.ml-1 and 0.26 mg.ml-1, respectively [47,73].

Chlorhexidine (CHD) was subsequently proposed as a safer alternative for antisepsis in the neonate population as it was less well absorbed through intact human skin [48]. Initial research was conducted in rhesus neonates bathed daily for 13 weeks with a skin cleanser solution containing 8% chlorhexidine gluconate (CHG), twice the concentration routinely used at that time [49]. Blood and tissue levels indicated that little systemic absorption had occurred, with only one blood sample having the minimum detectable concentration (11 ng.ml-1) at the time. Heel prick and venipuncture were then used to assess the potential systemic exposure to CHG in 34 (28-39 week GA) newborn infants [50]. While heel prick measurements were all positive, this was explained by residual chlorhexidine in the skin not removed by an alcohol wipe. Venous samples taken 4h after bathing were 101-460 ng.ml-1 in 3 of 7 infants, but only 5% of the samples taken 12 h after the bath were positive. In this study, Hibiscus (4% CHG in a detergent solution) was used for the daily bath and some of the infants were already a week PNA when the trial began. Further work confirmed the potential absorption of CHD in neonates, particularly in the preterm population, and illustrated the key role of the formulation used [51]. Infants treated with 1% CHD in ethanol had increased plasma levels, whereas the antiseptic was not found in those bathed with 1% CHD and 3% zinc oxide dusting powder. Similarly, when 4% CHG diluted 1:10 was used to bathe full-term infants, no detectable plasma levels (lod=0.1 µg/ml) were found (although, in this case, the head, a significant surface of a neonate, was not bathed) [52]. In contrast, first- and second-degree chemical burns developed in two twins (26 wk GA) treated with 0.5% CHD in methanol despite the immediate washing of the skin with saline [53]. Alcoholic preparations of CHD are not recommended for neonatal care. Elsewhere, it was reported that 10 of 20 neonates (24-31week GA), who were treated with 2% aqueous CHG before catheter insertion, had detectable plasma levels (1.6206 ng.ml-1) of the compound, and the highest concentration was observed at 2-3 days after exposure [54]. Overall, while the evidence suggests that CHG can be absorbed across the skin of preterm and term infants of less than 2 months of age, the clinical significance of the exposure is unknown [48]. Most of the reported adverse effects are local, such as erythema and contact dermatitis. Concerning skin burns, the results from different formulations and the effect of alcohol should be discriminated. Other factors determining accumulation are the area of application considered (whole body bath or umbilical cord application) and the exposure frequency. The safety of CHG in preterm infants has been recently reviewed [56]. And further investigated given that the FDA has now approved a labeling change that allows the cautious use of CHG products in preterm infants [48,54].

Propylene glycol (PG) is an excipient commonly found in topical preparations. High plasma and urinary excretion levels have been reported in premature infants primarily from dressings used to treat burns [55]. PG accumulation may result in toxicity such as serum hyper-osmolarity and lactic acidosis [56-57] and, while the parenteral route is typically associated with a larger exposure [88], there have been cases associated with topical application to compromised skin [86]. The WHO has set an acceptable daily limit of PG intake of 25 mg.kg-1 for adults [58]. Despite the longer elimination half-life in neonates [57,72] that could result in greater accumulation, a median PG exposure of 34.1 mg.kg-1. Day-1 did not affect postnatal renal, metabolic, and hepatic adaptation in 60 neonates who were exposed to PG as an excipient as part of their routine therapy [59]. There is little information about the safety of PG in topical and transdermal formulations applied to intact skin.

The undesired systemic absorption of actives formulated for topical treatments is another concern. While exposure to tacrolimus, when given as an ointment to treat atopic dermatitis, is usually low [60], systemic absorption of the drug has been reported for 3 patients (3, 5, and 14 y old) with Netherton syndrome and erythroderma [61,73]. The systemic absorption of topical steroids used to treat skin diseases has been frequently reported [62-64], and some extreme cases have resulted in depressed adrenal function [65] and development of Cushing syndrome [63,66]. It is well known that hydrocortisone accumulates in the skin upon topical administration and, interestingly, application of a moisturizer containing propylene glycol to the same skin site caused an increase in plasma cortisol levels, presumably due to the mobilization of a drug in the skin 'reservoir' [67, 74].

- **TYPES OF TRANSDERMAL PATCHES**

- **Single Layer Drug -In- Adhesive**

The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film.

- **Multi-Layer Drug in Adhesive**

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension that is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.

- **Drug Reservoir-in-Adhesive**

The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

- **Drug Matrix-in-Adhesive**

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension that is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix [68,69,70].

- **Testosterone transdermal patch system in young women with spontaneous premature ovarian failure**

In premenopausal women, the daily testosterone production is approximately 300 μg, of which approximately half is derived from the ovaries and half from the adrenal glands. Young women with spontaneous premature ovarian failure (sPOF) may have lower androgen levels, compared with normal ovulatory women. Testosterone transdermal patch (TTP) was designed to deliver the normal ovarian production rate of testosterone [71.72].

CONCLUSION

Since the beginning of human history, topical delivery systems have been utilised treating a variety of illnesses and as cosmetics. The identification of appropriate medication candidates for transdermal delivery and the corresponding advancement of passive and active technologies have improved delivery, increased drug dosage accuracy, and improved individual needs satisfaction over time. Finding medications that are strong enough to permeate the skin with the right transdermal technology is still a priority in the ongoing development of transdermal patches and related delivery systems. Meeting therapeutic and cosmetic needs that cannot be suitably and economically satisfied through alternative delivery methods is a major challenge.

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