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TRANSDERMAL PATCHES AND 'SKIN-ON-A-CHIP' MODEL: A REVIEW ON THEIR APPLICATIONS

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Highlights:

- Skin-on-a-chip model is more successful for drug testing compared to traditional 2D culture and animal models.
- There are two significant drawbacks to animal research. There are moral and legal concerns, and secondly, there is a significant difference between mouse and human skin, namely in terms of thickness, hair density, and appendages. So, skin-on-a-chip model is developed.
- Skin-on-a-chip can be used in many applications like diffusion studies, toxicity studies, and efficacy testing.
- Full-thickness skin equivalents are more commonly used in studies of drug interactions with the skin.

ABSTRACT: The efficacy of orally administered medications gets affected by multiple pharmacokinetic parameters. So, the technology involving transdermal delivery of medication was developed to enhance the pharmacokinetic qualities and overcome some of the disadvantages related to the oral route of administration. In this article, we have included the history of the transdermal drug delivery system, factors affecting drug permeation through the skin, advantages, limitations, and use in pediatrics and elderly patients. This review article compiles the different models of skin-on-a-chip for drug testing (human skin equivalent models and full-thickness skin equivalent models). The human skin equivalent model utilizes the technique of incorporating a biopsy of the skin. The in-situ skin-on-a-chip is about making the skin model directly in the chip. The most recent scientific research on the applications of skin-on-a-chip technology in drug diffusion studies has been discussed.

Keywords: Transdermal drug delivery, skin on-a-chip model, drug analysis, Full-thickness skin equivalents, drug diffusion.

1. Introduction:

Transdermal therapy systems have been created to allow continuous, controlled drug delivery to the body's nervous and circulatory systems through the skin. The skin can be employed as a regulated systemic drug distribution method because it is impervious to drug molecules.

Four techniques make it possible to effectively ingest medications through the skin and deliver them to the body in a controlled way. The medication is suspended in a saturated state in a water-miscible solvent in the drug reservoir of the partition-controlled delivery system known as the micro-sealed system. The matrix-diffusion-controlled system is second. The membrane-permeation-controlled system is the third and most used transdermal medicine delivery method. The gradient-charged system is the fourth newly revealed technology (Parivesh S et al.,2010).

A transdermal patch is used to transdermally administer a prescribed dosage of medication to the bloodstream. Transdermal administration devices containing hydrocortisone, fentanyl, and nicotine are already available for use in pain management and smoking cessation. TDDS has some advantages over traditional injection and oral techniques, including it lessens the strain on the liver and gastrointestinal system, improves patient compliance, and reduces adverse side effects from transient overdoses (Dhiman S et al.,2011). The USFDA approved the first transdermal system containing scopolamine in 1979, and nicotine patches in 1984. Transdermal patches were FDA-approved and marketed ten years later for the treatment of pain, analgesic activity, contraception, and hormone replacement therapy (Al Hanbali OA et al.,2019).

Over the past few years, transdermal medication administration has become increasingly significant. The sector is expanding quickly since it can offer sustained-release therapies and is simple to use and administer. Transdermal delivery product sales peaked at $12.7 billion in 2005; by 2010, they're projected to reach $21.5 billion, and by 2015, $32 billion.

Transdermal patches operate quite simply in theory. The inside of a patch, which is worn on the skin for a prolonged period, receives a relatively high dosage of medicine. The medication diffuses through the skin and reaches the bloodstream immediately.

The medicine will continue to diffuse into the blood for a considerable amount of time since it has a large concentration on the patch and a small concentration in the blood, maintaining a consistent concentration of the drug in the blood flow (Hanumanaik M et al., 2012).

The medication is painless, and the regulated drug release is one of the system's key benefits. A transdermal patch that clings to the skin is primarily used to administer the medication to the skin (Alam MI et al., 2013).

1.1. The advantages of transdermal drug delivery system:

This form of drug delivery has various benefits over conventional ones. The patch enables continuous dosing as an alternative to the oral method, preventing medicine levels from fluctuating as they do when taken orally over several days using a single application (Hanumanaik M et al., 2012).

Therapy can be stopped at any time with ease. This ensures self-administration appropriateness. Scraping off the application from the skin's surface will rapidly end a drug treatment (Tanwar H, Sachdeva R 2016). This prevents the hassle of parenteral therapy because they are non-invasive. Patients who are dizzy or unconscious benefit greatly from it, and transdermal patches are reasonably priced (Yadav V 2012).

Transdermal administration can prevent problems with gastrointestinal drug absorption brought on by gut pH, enzymatic activity, and drug interaction with food, drink, and other drugs administered orally. It can prevent first-pass metabolism. Transdermal drug administration is a great option for medications that need relatively constant plasma levels. Transdermal administration is an excellent option for medications that induce gastrointestinal discomfort since it prevents direct effects on the stomach and intestine (Dhiman S et al.,2011).

1.2. Disadvantages of transdermal drug delivery system:

The transdermal path is inappropriate when the medication dosage is high, the drug's molecular weight is substantial (which makes absorption challenging; it should ideally be below 800-1000 Daltons), the medication causes sensitization and itching, the medication is metabolized in the skin, the medication experiences protein binding, the medication is highly lipophilic or hydrophilic (should be moderately solubilized in both oil and water), and the drug is highly hydrophilic (Mali AD 2015).

1.3. TDDS limitations

For the medicine to penetrate the stratum corneum, it must have some favourable physicochemical qualities. If a medication dose greater than 10 mg/day is needed for therapeutic efficacy, transdermal distribution will be extremely challenging, if not impossible. Another restriction is that the medicine, excipients, and enhancers of the drug used to boost percutaneous absorption may cause skin irritability or contact dermatitis. Before deciding to develop a transdermal product, it is important to thoroughly consider clinical need as another aspect. The skin's ability to act as a barrier varies from one spot to another on an individual, from person to person, and with age (SHINGADE GM 2012).

1.4. A brief history of transdermal products

A Greek physician, Galen created the first cold cream using an emulsion of vegetable oil, beeswax, and water (Lin TJ 2010), for topical application. Because they believed the cold cream had antibacterial properties, they used it for skin injuries, burns, and joint discomfort (Fratini F et al.,2016). Later, the ancient Chinese tribes developed bandages and plasters to apply herbal mixtures (Pastore MN et al., 2015). For localized treatment, they combined herbal components with the natural rubber gums and affixed the plaster to the skin. Unguentum Hydrargyri, a mercury-containing ointment formulation for the treatment of syphilis, was one of the first transdermal products discovered in the 15th century (Cole HN et al., 1930). A pharmacist from Germany named Paul Carl Beiersdorf created a plaster-based remedy called "gutta-percha plaster gauze" in 1880 to treat skin conditions (Krylova OV et al.,2018). Emplastrum belladonna, a plaster prepared from the leaves of the Atropa belladonna plant, was one of the most well-known plasters used to treat tumors and

tuberculosis (Pastore MN et al., 2015). However, it wasn't always accepted as fact that medications could be injected into the bloodstream.

Then, in the 20th century, certain cases of unintentional intoxication were noted, such as poisoning caused by phenol spills on the skin (Brown AM et al., 1960). Significant new information about topical and transdermal drug delivery methods was provided by this event. Because of this, Nitrol®, the first transdermal ointment to treat angina pectoris, was introduced in the 1950s (2 percent nitroglycerin ointment) (Pastore MN et al., 2015). However, this product had restrictions regarding the frequency of administration and the application (greasy and unreproducible) (several times a day). Therefore, to lessen the frequency of administration, researchers were encouraged to create transdermal "measured-dose" application methods for various medications (Watkinson AC et al., 2016).

2. Use of transdermal drug delivery system in the elderly:

Several medications used by older individuals are currently being explored as transdermal formulations. Reviewing how age-related skin changes affect the dispersion of medications through the skin of old patients is interesting since aging effects are so obvious in the appearance of the skin. Multiple skin changes brought on by aging affect how medications are absorbed via the skin. The cutaneous structures are altered by extrinsic or sun-exposed and intrinsic or chronological skin aging. A significant majority of the documented aging skin changes appear to be caused by sun exposure (Kaestli LZ et al.,2008). The elasticity of the skin itself is related to the water content and age; older people generally tend to have drier and less elastic skin (Venkatraman S, Gale R 1998).

Table 2.1: Main transdermal drugs available on the market for an elderly patient

Molecule	**Indication**
Estrogens	Postmenopausal therapy
Selegiline	Major depressive disorder
Fentanyl	Chronic pain
Buprenorphine	Chronic pain
Rotigotine	Parkinson’s disease
Progesterone	Postmenopausal therapy
Glyceryl trinitrate (nitroglycerin)	Angina pectoris left ventricular heart failure

3. Transdermal medication administration used in kids:

The use of transdermal delivery for pediatric medicine delivery offers a non-invasive and practical solution. Although older children and term newborns have a competent skin barrier function that prevents the percutaneous input and loss of water of substances, including medications, children's lesser dose requirements make it simpler to reach therapeutic concentrations. Fentanyl, buprenorphine, clonidine, scopolamine, methylphenidate, estrogens, nicotine, and tulobuterol are among the drugs transdermally applied to children. While some patches are used without a license, others have pediatric labeling that is supported by clinical research. Two iontophoretic devices were licensed for use in children, and novel drug

delivery techniques like sonophoresis and microneedles are being studied for their efficacy and safety. Growth hormone is often administered using needleless injectors. On the other hand, premature infants' underdeveloped and quickly changing skin barrier function poses a considerable formulation difficulty (Delgado-Charro MB, Guy RH 2014).

4. Impact of human biology on the performance of TDS

The reliability and barrier qualities of the skin are influenced by several variables, including age, gender, ethnicity, skin moisture, and metabolism, which cause changes in the amount of medicine absorbed. Male and female skin differ mostly in pH and sweat and sebaceous gland pore size (men have larger skin pores) (pH of male skin is significantly lesser than that of female skin) (Kaestli LZ et al.,2008).

5. Factors affecting drug permeation through the skin

pH: The inside environment of the body typically has a pH between 7-9, while the skin typically has an acidic pH range of 4-6. In the past, it was believed that an acidic skin surface served as a physiological defense against invading pathogens. More recently, it has been shown that pH has a significant impact on several important enzymes involved in the manufacture and maintenance of a competent skin barrier.

Table 5.1: Skin pH is influenced by a variety of endogenous and exogenous substances (Bird D, Ravindra NM 2020).

Endogenous factors	Exogenous factors
Age	Soaps, detergents, cosmetics
Anatomic site	Occlusive dressings
Skin moisture	Skin irritants
Sebum	Topical antibacterial
Sweat	
Genetic predisposition	
Ethnic differences	

The skin's pH maintains the stratum corneum's integrity and cohesiveness and controls the permeability barrier. The amount of unionized medicine that is available for absorption might be affected by the pH of the skin in terms of percutaneous penetration. The pH-partition hypothesis states that only the drug's unionized form can significantly cross the lipid barrier. Skin deterioration could result from a formulation with a very low or extremely high pH value (Ali SM, Yosipovitch G 2013).

Temperature:

When it is warmer, the skin is more permeable. The kinetic energy of the drug molecule and the proteins, lipids, and carbohydrates in the cell membrane are found to rise with heat. This will speed up medication distribution to the dermis

while slowing down local delivery (Clarys P et al.,1998). The experiments have demonstrated that changes in the permeability of the cell membrane require a temperature shift of about 5°C (Brown MB et al.,2008).

Molecular weight: The drug's molecular weight has an inverse relationship with the percutaneous absorption. It might have an impact on the drug's specific diffusion coefficient. Although less than 500 Dalton is the desired molecular weight for transdermal drug delivery systems using passive diffusion, the rate of permeation may be accelerated by using a variety of penetration enhancers (Shabbir M et al., 2014).

Partition coefficient: For a drug to perform its biological activity, the distribution of the drug within an organism must be determined using the partition coefficient, or log P. Due to limited partitioning through the lipid matrix of the stratum corneum, hydrophilic medications are poorly absorbed when administered topically (Morgan CJ et al., 2003).

Hydration: Hydration of the stratum corneum increases the penetration rate of most medicines. By breaking up the stratum corneum's horny layer's compacted structure, it increases the drug's bioavailability (Barry BW 2001). Impermeable films reduce the diffusional path length by preventing surface water loss from the skin, which hydrates the stratum corneum (Shabbir M et al., 2014).

Age: It is observed that older people's skin is less porous than that of adults and children (Rastogi V, Yadav P 2012). According to the investigations, the stratum corneum's cell layers statistically only slightly increase, mostly in males (Ya-Xian Z 1999), whereas the thickness and cell count of the cellular epidermis decrease (Lock-Andersen J et al.,1998). Age-related variations in skin surface pH have also been reported (Luebberding S et al., 2014).

Gender: According to the studies, there is no statistically significant difference between the stratum corneum's thickness or number of cell layers. Despite research showing that men's cellular epidermis is thicker than women's (Sandby-Moller J et al., 2003).

Body site: The investigations indicated that the smallest number of cells in the stratum corneum was found to be in genital areas and the largest number of cells was in the heels (Ya-Xian Z 1999).

Sun exposure: When compared to the stratum corneum on the sun-protected area, which is thinner, the stratum corneum on the area exposed to the sun is thicker (Huzaira M et al.,2001).

Skin condition: The stratum corneum is less able to bind water in atopic dermatitis, leaving patients with dry, stretchy skin. The alteration of intercellular lipid composition with higher cholesterol and lower ceramide levels severely reduces barrier function. Additionally, the pH of the skin is higher than it is for healthy skin (Knor T et al.,2011).

6. Skin on a chip model for transdermal drug evaluation:

The complex human body's organ known as the skin performs a variety of vital physiological tasks for human existence, including fluid balance, temperature control, immunological protection, and sensory perception. It creates a strong physical obstacle that shields it from UV radiation, harmful chemicals, mechanical stress, and environmental infections (Ponec M 2002). Skin is regarded as an accessible and important route for medicine administration and cosmetic product application

due to its sizeable surface contact area (Abaci HE et al.,2017). Thus, it is necessary to test these compounds on human skin to determine their dosage and treatment effectiveness, to detect any possible unfavorable skin reactions and their mechanism of action, and to assess the hazards to human health and the environment (Van Gele M et al.,2011). For this goal, millions of animal tests have been conducted worldwide, mostly on mice (Serpell J 1996). However, there are two significant drawbacks to animal research. Firstly, there are moral and legal concerns, and secondly, there is a significant difference between mouse and human skin, namely in terms of thickness, hair density, and appendages (Schmook FP et al.,2001).

Animal models are currently widely employed for such drug testing and needs animal ethics committee approval. They are typically expensive, time-consuming, do not accurately reflect the physiology, immunology, and human skin metabolism, limiting their applicability to human settings (Flaten GE et al.,2015). To research the molecular origins of cellular reactions in skin physiology and disease, human skin equivalents (HSEs) for drug testing employing created intracellular skin models are regarded as helpful tools (Mathes SH et al.,2014).

6.1. Limitations of 2D and 3D culture models:

Traditional two-dimensional (2D) culture models on microtiter plates or Petri dishes have used keratinocyte cultures or co-cultures of keratinocytes with immune cells and dermal fibroblasts (Ponec M 2002). These models are widely used and easy to use, but they do not accurately simulate the complicated three-dimensional (3D) cell-cell and cell-matrix interactions that take place in the body, which restricts their ability to predict the complex effects of drug breakdown on the actual skin.

Generating 3D skin models using cells cultivated in extracellular matrix-like materials (such as hydrogels) is quickly attracting substantial interest as a solution to these limitations since they can more accurately mimic the complexity in structure and chemistry of live tissues (Bhatia SN, Ingber DE 2014). Typically, a 3D HSE should have 3 separate layers: subcutaneous fat tissue, the dermis, and the epidermis (Yildirimer L et al.,2017). Additionally, cells developed in 3D skin models should produce a lot of tight and gap junctions. These minute cellular details can sustain skin tissue integrity and function, improve cell-to-cell communication, and simplify in vitro drug testing. Models of drug use in 3D culture must disperse over numerous cellular layers to arrive at their intended targets, particularly in terms of drug dispersion. Similar to the skin's protective functions in humans, In 3D models, designed stratum corneum structures lower the medication absorption rate and considerably lower the rate of absorption of the medication. However, because these delicate structures could not be preserved on hard culture dishes, Under the conditions of the 2D culture environment, this barrier function is absent (Polini A et al., 2014). However, the majority of existing 3D skin models still suffer from fundamental flaws like poor barrier functions, and a lack of skin extensions like follicles of hair and sweat glands, and are therefore unable to accurately represent the tissue's multicellular complexity in human skin (Van den Broek LJ et al.,2017). These 3D skin models could potentially pose certain technical difficulties, such as sampling luminal contents for drug absorption, distribution, metabolism, elimination, and toxicity (ADMET) analyses and harvesting cellular components in precise

locations for in-depth biological analyses. Additionally, these 3D skin models are unable to offer precise control over ambient physical factors and spatiotemporal chemical gradients (such as temperature, gas, and mechanical forces) (Van Duinen V et al.,2015). Thus, new physiologically accurate drug testing on functional skin models is urgently needed.

6.2. Skin-on-a-chip Model:

A special skin model known as a "skin-on-a-chip" or "on-chip skin model" has achieved important advancements in the field of engineering skin cells. It offers the opportunity to address all of the above-mentioned restrictions by bridging the distance between conventional 2-Dimensional culture and the *in-vivo* environment. The culture of skin tissues in a microfluidic system known as "skin on a chip" allows for precise control of several physical and biological factors, such as chemical gradients, fluxes, and stresses (Zhang Q et al.,2018). Since there are significant differences between all skin-on-a-chip methods in key areas like fabrication methods and materials or tissue preservation, it is difficult to categorize them. In this perspective, we have categorized the gadgets based on how the chip creates the skin. To create microfluidic chips for modeling skin, two main strategies have been developed: the first one, known as "transferred skin-on-a-chips," involves the direct development of a skin piece obtained from a biopsy or a chip with HSE, and the second, known as "in-situ generation of the tissue directly on the chip" (in situ skin-on-a-chip).

A. Transferred skin on a chip: The methods that directly introduce tissue within the device have been the most popular for creating skin-on-a-chip models. These transplanted tissue fragments come from either an *in-vivo* produced HSE or a skin biopsy taken from a volunteer. One of the models utilizing HSEs for the chips, skin microfluidic chips has been created utilizing both commercially available and lab-created counterparts.

B. **In situ skin-on-a-chip:** The creation of the skin model directly on the chip is the main objective of the second strategy (Valencia L et al.,2021). In this method, the organ is constructed inside the apparatus, with the channels serving as compartments for tissue storage and delivery of nutrients. The systems implement several functionalities to create a reliable skin model (Varga-Medveczky Z et al.,2021).

6.3. Skin-on-chip models for applications in drug analysis:

An overview of recent research for skin-on-a-chip models, their layouts, and their physiological characteristics relevant to drug analysis are described in the section that follows. We particularly emphasize FTSEs models (Zhang Q et al.,2018).

6.3.1. Full-thickness skin equivalents (FTSEs): FTSEs made up of dermal and epidermal are substantially more resemble *in-vivo* skin in terms of transport properties than reconstructed single human epidermal equivalents. As a result, they are more commonly used in studies of drug interactions with the skin (Mathes SH et al.,2014).

For instance, following complete differentiation, stratification, and cornification, FTSEs consisting of dermal and epidermal divisions outside the chip were created by Abaci *et al*., who subsequently mounted them on a pumpless

microfluidics platform (Abaci HE et al.,2015). The stability of the air-liquid interface and the physiological blood residence time in human skin tissues were carefully considered in the design of this chip. Due to this architecture, FTSEs were able to mature, differentiate, and maintain their barrier function for three weeks (Zhang Q et al.,2018).

According to a recent study by Alberti et al., circular sections of FTSEs were inserted into a specially made microfluidic chip to thoroughly evaluate their absorption over the static Franz diffusion cell, a conventional in vitro skin permeation assessment method (Alberti M et al.,2017). This skin-on-a-chip model may be able to reduce the impact of the unstirred water layers that could accumulate in the static Franz diffusion cell and affect the drug transport procedure, according to caffeine diffusion research. The dynamic culture could not benefit from FTSEs since they were not directly created in the microfluidic device. Therefore, despite suggesting that these simple chips could be useful as in vitro platforms for skin drug evaluation, these experiments were not entirely successful.

More recently, Wufuer *et al*., created a microfluidic system that allows for direct co-culture of keratinocytes (epidermal layer), fibroblasts (dermal layer), and vein endothelial cells (endothelial layer) on an in-vitro human skin on a chip device made of three polydimethylsiloxanes (PDMS) layers and two porous membranes (Wufuer M et al.,2016). The three PDMS layers' diverse microfluidic channel systems allowed several types of culture media to be perfused at differing flow rates. Tumor necrosis factor-alpha (TNF-alpha) was then infused via the microfluidic channels to create the sick vascularized skin model, which was then utilized to evaluate the effectiveness of the therapeutic medicine (dexamethasone) in lowering TNF-induced inflammation and edema (Zhang Q et al.,2018).

6.4. Applications of Skin-On-A-Chip Systems:

In addition to other things, artificial membranes may be utilized to reproduce the skin surface of humans, make it *in-vivo*, or create *ex-vivo* skin models. Furthermore, we outline the main applications for these skin-on-a-chip devices in the areas of basic cutaneous research and applied toxicological or pharmaceutical research studies (Lukács B et al.,2019).

6.4.1. Diffusion Studies

The systemic and topical effects that the main components of cosmetic and pharmaceutical formulations exhibit are strongly influenced by the drug's ability to cross the skin barrier. Knowledge of the process involved in the absorption of topical chemicals is essential for determining their pharmacokinetics, pharmacological, and toxicological characteristics. Various *in-vitro* and *ex-vivo* systems can be used to study skin penetration. The testing on skin-on-a-chip technology is the main subject of this review. According to Lukacs and colleagues, cutaneous diffusion testing was used to validate a Microfluidic skin on chip technology using preparations made from excised animal skin and caffeinated cream (Bajza, Á et al.,2020). Bajza and colleagues extended their experiment by using skin-chip technology to investigate how skin's efflux transporter works. Erythromycin and quinidine, two P-glycoprotein prototype substrates, were examined in gel and cream forms in the outer layer of the skin on a chip system. This study demonstrates that it is also feasible to accomplish the parallelization of the device (Cong Y et al.,2020).

6.4.2. Toxicology Studies:

It was shown in the review by Chong and colleagues that the models for microfluidic chips are employed to identify the harmful effects of medication. Organ-on-a-chip technology was used to identify several toxicity indicators (Wufuer M et al.,2016).

6.4.3. Efficacy Testing:

When the skin experiences reactions like inflammation, irritation, allergies, or cancer, the skin's capacity to provide protection is diminished. Human skin disorders can be modeled using skin-on-a-chip technologies. The applied skin model was shown to successfully simulate skin inflammation and edema in the study by Wufuer *et al*., The model can be used in drug testing to assess how well a treatment (such as dexamethasone) reduces inflammation and edema brought on by tumor necrosis factor-alpha (TNF-alpha) (Suhail S et al.,2019).

6.4.4. Wound Healing:

The purpose of skin is to protect cells from physical, chemical, and microbial injury by acting as physical blocks. Reconstructed human epidermis (RHE) models and other first in vitro skin model cell cultures were two-dimensional. Cell cultures in three dimensions were later developed (Jeon B et al., 2020). It is possible to analyze permeability and absorption using RHE models, although these models do not include endothelial cells and gauge discomfort to the skin depending upon the survival of individual cells (CV) (Biglari S et al.,2019). Angiogenesis, which transports nutrients and oxygen to the developing cells and eliminates anabolic sludge, is crucial to wound healing. Angiogenesis aids in the healing of tissues in post-burn wounds in this way. Therefore, the skin containing blood vessels will be utilized to enhance the repair of injuries to simulate wound pathology and evaluate treatments.

The microenvironment and physiological reactions are important in acute and chronic wounds. Cell proliferation, homeostasis, and inflammation are the three most crucial stages of the intricate wound-healing process. For researching cell movement throughout the injury repair process and the impact of therapeutic interventions, the alternative to *in-vivo* systems the Skin on a Chip model can be also used in vitro. Biglari and colleagues developed a microfluidic wound-on-chip model to recreate the inflammatory phase and provide more information on the behaviour of different cell types associated with injury repair (Kim J et al.,2020).

6.4.5. Repair:

Skin serves as the outermost barrier of the human body and is crucial in separating it from its surroundings. When the skin is injured, it triggers the expression of cytokines, resulting in inflammation and defense against possible pathogen intruders. Angiogenesis and the substances that promote angiogenesis through promoting endothelial cell proliferation, migration, and tube formation, PDGF (platelet-derived growth factor), VEGF (vascular endothelial growth factor), and TGF- may aid in the regeneration of the tissue (Giacomoni PU et al.,2004). Inflammation, enhanced cell migration, and proliferation are examples of skin defensive reactions and mending mechanisms that are excessive UV exposure and an epidermal layer of skin damage are comparable, according to studies (Liu ZY et al.,2009).

6.4.6. Inflammation:

Animal research on topical medications and cosmetics that cause irritation and inflammation is particularly contentious. Testing shouldn't be abandoned because these compounds carry a potential danger of toxicity and allergic reactions on human skin. However, using non-animal alternatives can take the place of animal use. Skin-on-a-chip techniques are one of these possibilities (Wang Y et al.,2005).

6.4.7. Aging

Senescent skin cells do not protect the skin from harmful environmental hazards that speed up aging. To explore the process of skin aging, several organ-on-a-chip techniques were created. A pump-less skin-on-a-chip device has been utilized as a skin model in the articles by Kim *et al*., to examine coenzyme Q10 and curcumin's anti-aging effects (Giacomoni PU et al.,2004).

Conclusion: One of the innovative drug delivery methods that is advancing the fastest is transdermal drug delivery. The transdermal method of drug administration is becoming increasingly recognized as a result of recent technological developments and the capacity to administer medicine systemically without rupturing the skin barrier. This review article concludes that the skin-on-chip approach is more successful for drug testing in comparison to the traditional 2D culture and animal models. Accordingly, Skin on Chip models have proven to be superior to animal models for pre-clinical research in terms of accuracy, throughput, and cost. These Skin on Chip models can be used in cutaneous toxicity research, transdermal and topical formulation creation, and mimicking the 3D microenvironment of natural human skin.

Abbreviations: TDDS, transdermal drug delivery system; USFDA, United States Food and Drug Administration; FDA, food and drug administration; HSEs, human skin equivalents; SOC, Skin-on-a-chip; 2D, two dimensional; 3D, three dimensional; FTSEs, Full-thickness skin equivalents; TNF-alpha, Tumor necrosis factor-alpha; RHE, Reconstructed human epidermis; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor;

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