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Recent trends in microfluidics-based skin-on-a-chip models and applications

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ABSTRACT

Skin in the human body plays a major role being a dermal barrier, maintains homeostasis, and is a vital route for administration of cosmetics and pharmaceutical formulations. Currently, skin diseases are also posing a threat globally, being ranked fourth among the non-fatal diseases. Preclinical studies of drugs and therapeutics are required to be performed at a faster rate and ensure that the results obtained are accurate. Using conventional methods of animal testing, is leading to high failure rates and expensive drug development process. To circumvent these limitations, miniaturized microfluidic devices are gaining immense popularity with respect to diagnostics, biomedical research, and drug testing. Skin-on-Chip is one of the micro-engineered biomimetic platforms that can used as an alternative to animal testing in preclinical studies. This review gives a brief overview of the limitations in conventional drug development process. It gives clear insights into general designing of skin-on-chip device and collates recent developments that skin-on-chip models are subjected to, with an overview of the side effects testing of sorafenib using skin-on-chip model. Integration of microsensors are also summarized in this review. The use of iPSCs and Skin-on-Chip in a combination resulting in better in vitro skin models is also highlighted. Further, this review gives information about the utilizations of Skin-on-a-Chip models in diffusion studies, wound healing, and progress in precision medicine tailored to the person. Finally, the potential challenges that have to be overcome for its widespread utilization are elucidated.

Keywords— *Animal testing, microfluidic devices, Skin-on-chip, sorafenib, microsensors, iPSC, wound healing, precision medicine*

1. INTRODUCTION

The body's most important protective barrier is the skin, which is made up of a variety of cell types in several layers. Skin, a part of the innate immune system, is the human body's first line of protection against several pathogens, radiations, chemicals etc. It can be subjected to various diseases like inflammations and cancers. It is responsible for carrying out physiological functions like thermoregulation, fluid homeostasis, defense of the immune system which are essential for the survival of an individual. The large surface area of skin and its easily accessible nature, is considered to be an essential route for cosmetic products application and drug administration to test for irritancy and toxicity. These products are necessary to be tested for their therapeutic efficacy, dosage, their mode of action, adverse reactions and environmental risks when applied on skin [1]. Around 1.9 billion people are being affected by skin and subcutaneous disorders, which accounts for almost one-third of the world population [2,3]. Therefore, alternative techniques and platforms are to employed for testing various therapeutics within limited time period and account for their effects in the human body, for which, biomimetic and microfluidic devices offer a great promise for the future for pharmaceutical and cosmetic applications.

1.1. Limitations of conventional drug development process

The first important problem in drug discovery and distribution to clinics is the immense time gap in timelines, which takes around 10-12 years in order for each drug to be accessible commercially after regulatory agencies approve formulations [4,5]. There are few diseases like cancer which progresses rapidly with time and is a major cause of death in millions of people in a year. As a result, it is critical to produce formulations as quickly as possible with the necessary scrutiny, maintaining a balance between safety and effectiveness in their application. Drug production is also costly, with the cost of producing one novel drug projected to

be around $2.6 billion USD. Alarmingly, the efficacy level of drugs which make it from pre-clinical trials to clinical trials has indeed been recorded as low as 12% [6].

At present, animal models and cell lines are widely being utilized for testing of drugs yet they are normally deficient with regards to availability, profoundly tedious and expensive, time-consuming, and also includes various ethical concerns. They might not address the immune system, physiology and metabolic reactions taking place in the human skin accurately, bringing about a restricted capacity to extrapolate to the human conditions. Due to the differences in the genomes of both animals, there is uncertainty about the safe initial dosage and a clear affirmation of PK parameters. As a result, various drugs are also proven to be toxic to humans, even after they have been tested in animal models [1]. Notably, the sluggish drug discovery phase that has animals' dependency for pre-clinical studies restricts their efficacy in the progress of manufacturing a vaccine for pandemic diseases like COVID-19 [7].

In 2D cell cultures, which is used as a traditional method in medicinal or clinical trials, cells are mounted haphazardly on a relatively uniform culture plate in a homogeneous growth medium. Only one side of the solid substrate is aligned with cells in 2D cultures, resulting in irregular morphology and polarization. Furthermore, all cells have access to oxygen, nutrients, and molecules added to the medium. The complex and diverse network of tissues and organs vary widely from these conditions.

Physiology and cell-ECM interactions can be mimicked in 3D-cultures made from hydrogel scaffolds assembled into more complex structures. These models, however, are still unable to replicate the tissues and organs hierarchical structure, spatiotemporal microscale gradients, as well as mechanical or electrical induction. Oxygen and nutrient supply are challenging, removal of waste and carbon dioxide, study of cells is problematic due to the increase in complexity, cell viability challenges and sampling are its other limitations [8].

1.2. Organ-on-a-chip platform

Organ-on-a-chip (OOC) is a type of artificial organ that is a multi-channel 3-D microfluidic cell culture chip that imitates the behaviour, dynamics, and physiological response of entire organs and organ systems. The microenvironment of the chip mimics that of the organ in regards to interfaces with the tissue and mechanical stimulation, more accurately than cell-based models, thanks to a connection of cell biology, chemistry, and technology of biomaterials. This represents the structural and functional features of human tissues and can be used to project how people will respond to a variety of stimuli, as well as impacts of drug and its environmental effects. In precision medicine and biological protection, OOAC has a variety of uses. [9]. Further to that, these systems have a lot of promise in terms of advancing tissue engineering research, simulating organ physiology, and examining stable and diseased tissues and their etiologies, among other things [10].

1.3. Skin-on-a-chip

All things considered, studying the physiology of skin diseases and infection, checking topical medications and cosmetics, and testing for the existence of pathogens or antibodies that may indicate the existence of a pathogen are all examples of skin-on-a-chip (SoC) applications. Skin-centered organ-on-a-chip applications have been implemented, with the goal of allowing a biologically engineered skin equivalent to be continually perfused via a microvascular network [11].

Moreover, in the chip cultures, tissue disintegration was also reduced. The ability of the organ-on-a-chip skin counterpart widely used for wound-healing studies has already been demonstrated. It is to replicate the native skin's three-layered design on one organ-on-a-chip, complete with appendages, sensory organs, such as hair follicles as well as sweat and sebaceous glands, and a complete vascularized network. If developed, this can be inserted onto multi-organ chips to simulate an organism's natural environment, allowing for more effective treatment screening methods. In addition, incorporating multiple in situ biosensors into skin-on-a-chip systems has several advantages. It is a non-invasive method of obtaining real-time reports on the role of skin tissue as well as input on drug action.

Latest biomimetic designs that can imitate the reaction of human organs or tissues to a drug are being created are needed for efficient drug production. Accelerated evaluation of these repositories against target proteins using high-throughput screening (HTS) technologies recognizes products with therapeutic benefits. Despite this, the quantity of novel drugs accepted per billion dollars spent on research and development is decreasing year after year. Cell cultures and animal models are the widely and usually used drug screening systems. The former studies the reaction of human cells to some medications, but since they are limited to one cell type, they are not able to replicate the systemic response; the latter, on the contrary, provides a systemic response, yet the findings are mostly not equivalent to those in humans due to differences in physiology and immunity at the skin level. As a result, the majority of medications struggle during clinical trials when existing models fail to anticipate the human body's systemic response to a drug. Organ-on-a-chip platforms utilize microfluidic cell culture systems to mimic complex tissue and organ anatomy and physiology, along with tissue- and organ-level dynamics, with the objective of replicating the human body's diverse or heterogeneous existence. Under physiological fluid flow conditions, microfluidic devices and microfabrication techniques allow for detailed monitoring of cell patterning, tissue-tissue interfaces, and chemical and physical gradients, despite the fact that these technologies are still in their infancy [11].

2. DESIGN OF SKIN-ON-CHIP (SoC) DEVICE

The device is made up of three important layers: a lowermost layer with the microvascular tube, a porous membrane stacked at the middle, and an uppermost layer with the culture vessel or chamber and two lateral pneumatic networks. For mechanical stimulation, two pneumatic channels are built on both the sides of the central culture vessel [12].

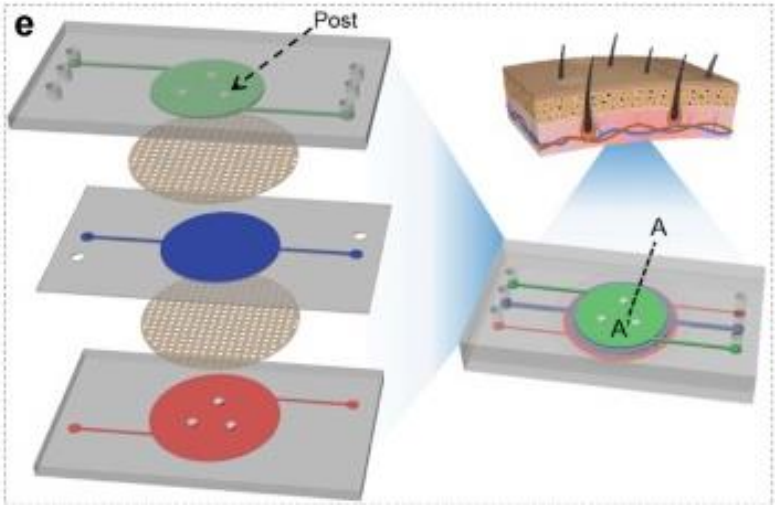

Figure 1: Diagrammatic representation of skin-on-a-chip model comprising of 3 layers with top green epidermal layer, a blue colored dermal layer, and a bottom red endothelial layer with porous membrane stacked in between the layers [12].

A matrix that is hydrogel-based is implanted with fibroblasts that mimic the dermal layer may be used to create an organotypic skin culture. When human plasma fibrin (fibrinogen) reacts with thrombin, it forms a hydrogel that can be remodeled with the help of fibroblasts, ultimately using collagen instead of fibrin, initiating the coagulation cascade. Furthermore, when keratinocytes and HaCaT cells are deposited upon those matrices and exposed to air, they experience suprabasal differentiation, allowing for the spontaneous development of the epidermis. The skin counterpart created by these techniques is entirely made of human materials, making for a more accurate representation of human biochemistry [13]. As a result, a central chamber or vessel that can handle a 3D skin culture is an essential component of architecture. A microvascular channel was introduced into the model based on skin vascularization concepts. This channel connects to the culture cavity through a porous membrane that divides the device's bottom and top layers. Furthermore, the membrane's vascular side provides mechanical assistance for creating a monolayer of endothelium.

The endothelial layer, known to form the walls of the capillaries in vivo, controls transport through them and has a vital function in hemostasis as well as reactions of inflammation, making it necessary to summarize the exchange of capillaries. Lastly, two pneumatic channels for mechanical stimulation were built on both the sides of the central culture vessel. A compact, computer-controlled vacuum pump can be used to collapse the pneumatic channels inwards and deform the chamber walls outwards to stretch the tissue [14].

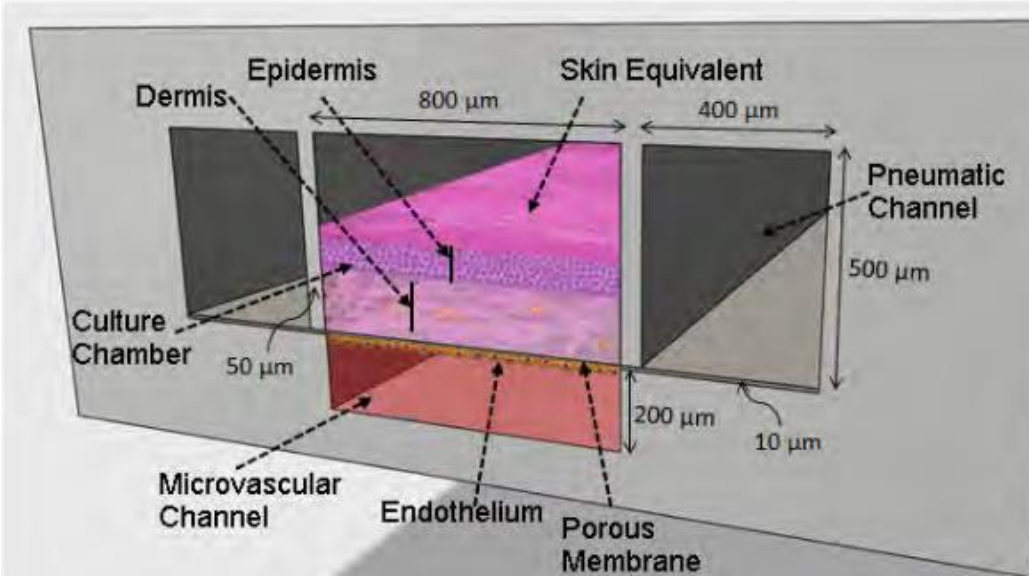

Figure 2: The culture compartment with an entirely formed skin counterpart, the microvascular pathway, the pneumatic outlets and the porous membranes are shown in this cross-sectional view of the skin-on-a-chip unit [14]

Various complex cell cultures of the epidermis, including such keratinocytes, are used to illustrate skin-on-a-chip platforms because of their effectiveness in maintaining skin homeostasis in vivo. Furthermore, such devices make it easier to study drugs' wound-healing abilities. In addition to this, a discovery of a close link between wound-healing and skin's electric potential, implies that the modification of the skin's trans-epithelial potential initiates the healing process. In order to fix this issue, the development of a microfluidic wound-healing chip platform which is associated to an electric field helps to gain better knowledge in cell migration and differentiation that happens during the process of recovery and healing [8].

3.SKIN-ON-CHIP MODELS

Fabrication method of chip	Skin model layers	Ingredients in the model	Time period (days)	Stimuli	Achievements
Laser cutting	Epidermis + immune cells	PDMS PMMA PET membrane	17	Allergen testing & UV radiation	Parallel experiments, TEER sensors integrated.
3D printing	Epidermis & dermis + blood vessels	Silicon rubber Collagen ECM	4	Cyclic stretch	Blood vessels were used to perfuse the media.
Lithography	Epidermis	PDMS	3	Keratinocytes seeded on collagen patch	Suitable for high-throughput toxicity screening
	Epidermis and dermis	PDMS collagen ECM	7	Uniaxial cyclic stretch	Mimicking skin wrinkling
	Epidermis and dermis with blood vessels	PDMS PET membrane fibronectin ECM	21	TNF-α to simulate inflammation, and dexamethasone to treat inflammation	Modeled edema and inflammation

Figure 3: Figure depicts a table presenting few Skin-on-chip platforms evolved with their important achievements [15-20].

4. TESTING THE SIDE EFFECTS OF SORAFENIB USING MICROFLUIDIC SKIN-ON-CHIP

Sorafenib is a therapeutic drug prescribed for hepatocellular carcinoma, which is known to decrease the growth rate of cancer/tumor tissue via multi-kinase inhibitors which can target angiogenesis. Patients administered with this drug reported various side effects which include weight loss, diarrhea, adverse reactions on skin particularly, hands and feet with sesory abnormalities, burns and pains on palms and foot, etc, The level of hyperkeratosis was investigated in patients administered with sorafenib using skin-on-chip model by immunohistochemical staining, staining technique using Haemotoxylin and Eosin(H&E), and quantitative analysis using real-time PCR [21].

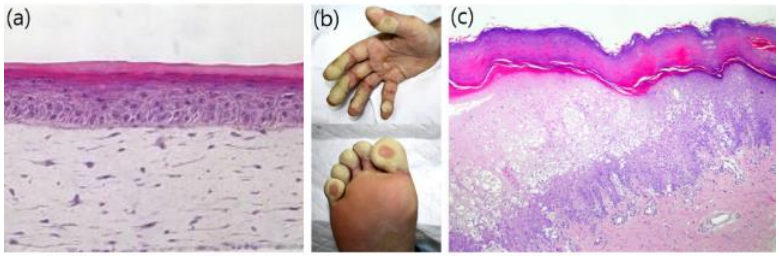

Figure 4: (a)H&E staining of normal human skin, (b) image depicting hyperkeratosis, (c) H&E staining of hyperkeratosis tissue [22].

4.1. Skin-on-chip fabrication

Polydimethyl siloxane (PDMS) was used to fabricate a skin-on-chip model. The model contains PDMS layers at the upper and lower layer of a porous membrane (0.4µm) between them. A skin equivalent is kept on it. A culture solution is supplied to the skin equivalent through the semi-permeabiity of the porous membrane. To supply the culture solution, a microfluidic channel was constructed on either side of the culture chamber as shown in fig 4. A gravity fluid system was set up to make sure that the direction of flow of culture solution in the micro channel is in the direction of gravity [22].

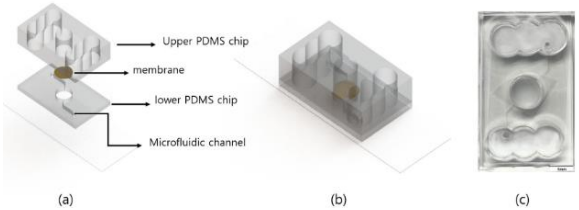

Figure 5: (a & b) perspective view of microfluidic based skin-on-chip that is pupmless, (c) image of the fabricated skin-on-chip [22]

The human fibroblasts, keratinocytes were cultured and an epidermis layer was formed to develop a skin-equivalent. Cell differentiation is induced by air exposure, following which the drug was administered. Air exposure was performed for 3, 5, and 7 days with three concentrations of sorafenib (0µM, 1µM, and 10µM) by dissolving in DMSO.

4.2. Tests and Results

4.2.1. Histochemistry staining (H&E staining)- the skin equivalent was embedded in paraffin following a sequence of steps and H & E staining was done for the tissue, which was affirmed with light microscopy. With treatment of the drug, thickness of the horny layer changed showing that similar reactions are taking place. 1µM and 10 µM concentrations of sorafenib showed increased thickness of basal and spinous layer and the horny layer. In case of high concentration of, horny layer was keratinized. These results proved that drug concentration and count of fibroblasts are inversely proportional. These changes prove the adverse reactions in the patient with hyperkeratosis.

4.2.2. Immunohistochemical staining- the slide from H & E process is undergoes automatic immunostaining after which it is treated with primary antibody and scanned for results. The levels of expression of FN at the layer of dermis, as well as K-10, filaggrin, and involucrinin the layer of epidermis, are all verified. A reduction in FN is caused by a decrease in epidermal layer activity. Filaggrin, involucrin, and K-10 expression levels have been shown to be elevated, exhibiting similarity to hyperkeratosis, one of the adverse conditions observed among unhealthy patients taking Sorafenib.

4.2.3. Analysis using Real time quantitative Polymerase Chain Reaction: the mRNA was obtained by employing the usage of TRIzol reagent and was checked for quantification using Nanodrop. cDNA synthesis was performed followed by quantitative analysis using real-time. Studies on gene expression levels of proteins are performed. Filaggrin, Laminin α5 and K-10 levels increased with the increase in the concentration of the drug showing damage to the skin due to high levels of Laminin α5, hyperkeratosis due to increased levels of K-10 and Filaggrin. The level of expression of P53 which destroys the cancer cells or brings about cell death by mechanical stress, is shown to decrease when the concentration of the drug rises on 5th and 7th day of exposure rather than 3rd day. This result is depicted owing to Sorafenib's chemotherapeutic effect.

The clinically observed side effects was replicated by drug toxicity studies with 3D human skin equivalents using pumpless skin-on-a-chip. These findings suggest that the skin-on-a-chip can be used in clinical settings. It can not only replace clinical animal experiments, but it can also greatly reduce the time it takes to develop new medicines [22].

5. CELL SOURCES FOR IN-VITRO SKIN MODELS

5.1. Primary cells

Normal and unhealthy skin models have been created from Primary cells for a long time now. A Skin-on-chip model with primary cells, Epiderm FT™ (FT,NH KCs & Fbs), with and without ex vivo subcutaneous tissue, has achieved 7 day maintenance of tissue through dynamic perfusion. It uses biopsies and Skin Equivalents, adipose tissue but lack the flow of endothelial barrier, flow's mechanical effects and the media change takes place very frequently [23]. One of the most significant drawbacks of primary skin cells being used in skin-on-chip devices is that the population doublings are finite, and eventually die [24].

5.2. Cell lines

Immortalized cell lines of skin can be utilized to solve the disadvantages of using primary cells. Many ways have been devised to resolve cell death and achieve immortality, including immortalization that happens spontaneously, telomerase overexpression or telomerase reverse transcriptase, and telomerase reverse transcriptase overexpression (TERT). The quality of the skin constructs in terms of stratification, differentiation of the epithelium, and functions of the barrier varies depending on the immortalization as well as culture methods used. An example of cell line-based skin-on-chip model is HaCaT KC CL which is a multi-monolayer skin inflammation or edema model, mimicking interaction between Keratinocytes-Fibroblast and also between Fb-EC. Cell lines have a general drawback of failing to reflect patient heterogeneity within a disease, making them unsuitable for population-based research.

5.3. iPSC

iPSCs are obtained from adult somatic cells by reprogramming and reverting the cells to their pluripotent state. Differentiation of iPSC yields various types of cells like keratinocytes, melanocytes, fibroblasts, endothelial cells and smooth muscle cells, so that they can be potentially used in skin models to mimic healthy and diseased skin. In a study, endothelial cells derived from iPSC were introduced into a microfluidic skin model, which exhibited a network of blood vessels and capillaries with improved barrier function of the endothelium, as well as skin barrier, proving an increased capacity of skin models using iPSC. Since haemetopoietic stem cells and their progeny can be acquired from iPSCs differentiation, further it is required to introduce the cells of immune system along with appendages derived from iPSC into the skin models. However, hair follicles and sebaceous glands generation using iPSC is still under research. Apart from making healthy human skin models, diseased skin models can be generated from iPSC that is derived from mutated somatic cells. Gene repair of the possible genetic anomalies in individual based diseased iPSCs, e.g. through homologous recombination or Zinc Finger nucleases, will eventually provide an unrestricted supply of immunologically compatible cells to continue treatment medically for genetic disorders that lack appropriate care. Reprogramming of iPSC and verification of their pluripotency is labor intensive, time consuming, restricting throughput time, size and reproducibility claiming its disadvantage. On the whole, iPSC-derived skin cells have an infinite supply of cells which could be used to create normal and unhealthy skin models in vitro.

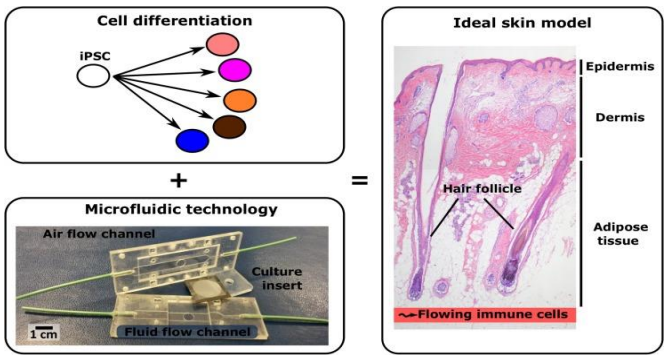

Figure 6: The next generation skin models are built on the foundation of a microfluidic system and iPSCs. An alternative to animal research will be an immunologically capable skin model similar to in-vivo models consisting of 3 skin layers (epidermis, the dermis, and adipose tissue) along with appendages in the field of drug testing and toxicology [24].

5.4. Skin-on-chip models

Many organ-on-chip versions are in the development pipeline, like skin-on-chip, with the goal of achieving more physiologically meaningful immune cell exchange, a regulated environment, and improved barrier function. A two layered keratinocytes with fibroblasts and endothelial cells with fibroblasts was stacked in between three microchannels, Wufuer and colleagues present a simple structure for material diffusion through skin [20]. The first skin-on-chip model consisting of an immune component was designed by Ramadan and his colleagues which explains the connection amongst the U937 cell lines and HaCaT KC- cell lines in a bi-channel device. Authors use LPS and UV stimulation to show its utility in drug testing. Both Trans-epithelial electrical resistance (TEER) calculation along with magnetic bead immune assay, incorporated into the system, are used to evaluate the results [15].

The development of safe and unhealthy models of skin for progression of the disease or recovery modelling, as well as repetitive dosage toxicity monitoring, are planned in the future. Controlling air movement and gas distribution in the cavity exposed to air will help boost differentiation, homeostasis, and stratification by simulating the skin's natural environment. Controlling the pressure on the tissue will also help researchers better understand the role of mechanics in wound healing.

To conclude, it can be said that various types of cells that are immunologically matched can be obtained by the differentiation of iPSC, and accurate skin models with a regulated environment, possibility of immune cell exchange and an improved barrier function, can be obtained with this skin-on-chip technology. As a result, skin-on-chip paired with iPSC might result in superior skin models in the lab, both healthy as well as infected [24].

6. REAL-TIME SKIN HEALTH MONITORING WITH MICROSENSORS

Integration of electrochemical, biochemical sensors with the culture systems provides high throughput, constant, automated testing of cell health, by reducing cell destruction may enhance experimental results [25]. The electrical resistance of the monolayers of epithelium and endothelium is commonly measured with transepithelial electric resistance (TEER) sensors, that could be derived to provide details regarding integrity of tight junction formation [26]. Additionally, to track the extracellular acidification rate, pH measurements were done regularly [27].

Ramadan and Ting, on the other hand, demonstrated an integrated TEER sensor within a bi-channel chip made immune-competent for studying keratinocyte-monocyte interactions. During the culture process, electrodes of Ag/AgCl were inserted at the upper and lower side of the skin model, with recordings of regularly measured cell layer integrity and confluence. Temperature, composition of the medium, current density which is not uniform, and the cell number all had an impact on the TEER sensor readings, meaning that caution must be exercised when conducting tests and reviewing the findings [26].

A comprehensive understanding of cell activity could be accomplished by combining several sensors on the same platform. Micro-fluidic instruments have easy sensor positioning, both inside the tissue or downline, to detect substance growth in the cell culture medium, thanks to their perfusable networks and allow for versatile sensor placement techniques [25].

7. APPLICATIONS

7.1. Diffusion studies

Perforation of drugs via the barrier of dermal layer is a key determinant in the systemic effects as well as topical effects of bioactive components in formulations of pharmaceuticals and cosmetics. To evaluate pharmacokinetics, pharmacological, and toxicological profiles, it is important to understand the absorption mechanism of topical formulations [28]. A study conducted by Lukacs proved that skin-on-chip systems are the best possible solutions for analysis of skin penetration and reactions related to drugs at the barrier of the dermal layer by using caffeine cream in the microfluidic devices [29].

7.2. Toxicology studies

Skin irritation, corrosion, sensitization and skin phototoxic effects can be tested using skin-on-chip models. The chemical agent moves into the skin and induces excessive endothelium penetrability, edema, and vasodilationin chemically induced skin irritation. Tight junctions (TJ) could be seen and assessed mostly in the dermis' microvascular components to determine physiological responses to drugs/chemicals [28].

7.3. Efficacy testing

Wufuer et al. showed that the implemented model of skin effectively emulated skin inflammatory reactions in skin and edema in their research. The model could be utilized for drug research to determine whether a therapeutic drug i.e., dexamethasone is effective in decreasing TNF-α induced edema and inflammatory responses. Microfluidics based Skin-on-chip models are proved to be important to find out the main causes of disorders related to skin as well as screening of drugs for effective treatment [20].

7.4. Wound healing

Skin being a protector of tissues from various microbial, physical and chemical agents [30]. Angiogenesis is a process that transports oxygen and nutrients to developing tissues while also removing catabolic wastes. Angiogenesis aids the healing of post-burn wound tissues in this way. Hemostasis, inflammation, and cell proliferation are the most important processes in the complicated wound healing process. For researching cell proliferation in the healing process in case of wounds and the impact of medicinal treatments, the Skin-on-a-chip platform could be used as an in vitro substitute for in-vivo systems. A research led by Bilgari, created a wound-on-chip microfluidic device to simulate the process of inflammation as well as learn much more regarding the actions of various types of cells associated with wound healing. It was further used for anti-inflammatory compound screening [31].

7.5. Inflammation

In animal science, itching and inflammation studies for topical drugs and cosmetics are a hot subject. These substances should cause toxicity and allergic reactions in humans if they are not tested; therefore, testing should not be cancelled. Alternative techniques like skin-on-chip, can be used instead of animals [20,32]. The side effects of fucoxanthin application such as topical inflammation can be investigated with an Organ-on-chip device developed by Tavares et al. using the culture of reconstructed human skin, which showed its antioxidant and cytoprotective functions [33].

7.6. Aging

When the skin develops cellular senescence, it is exposed to adverse environmental risks that accelerate aging which is studied using skin-on-chip models [28]. A study led by Kim investigated the effects of curcumin and coenzyme Q10 on aging [34].

7.7. Shear stress effects

Shear stress affects the structure, equilibrium, development, and high density of skin cells in microfluidic device owing to its poor, reciprocating, as well as increased shear stress. It explains how shear stress affects skin cells in a few different applications [28].

7.8. Clinical trials for different populations

Usually the participants in clinical trials are middle aged adults, children are hardly involved in clinical testing owing to risks and adverse effects. Nonetheless, every day, children are given drugs, but the safety data obtained from adults is the only evidence available. Since, Children do not resemble adults with regards to their physiology, immunity etc, their reactions can differ from those of adults. Other factors, such as population genetic variations can increase the risk of adverse drug reactions, but with this technology we can build communities on a chip, which could revolutionize clinical testing.

8. FUTURE SCOPE

The significant challenges that must be addressed include standardization and validation of manufacture of in vitro skin equivalents, packaging and storage of the skin equivalents, design and development of SoC device must be optimized, a culture medium common for multicellular skin equivalents must be developed [35].

Other obstacles to overcome include: (1) Simulating the systemic dynamics of active human skin, such as vascularization, defense, appendages, pigmentation, subcutis, and innervation, is one of the most difficult tasks. (2) Controlling the microenvironment of the skin, tracking, and studying medical conditions in a user-friendly manner, that could be achieved by proper microfluidic device design and manufacturing; (3integrating equipment with novel investigative techniques like sensor integration, mass-fabrication of optimised designs, easy handling for consumers, and controlling flow with bubble-free technique are all technological advancements that might significantly assist in disease modelling as well as personalized medication [24].

At present, the genetic makeup of the patients is generalized and diversity in different populations is ignored such as gender, age, race etc. When iPSCs acquired from affected individuals are paired with Skin-on-Chips, they have the potential to become a valuable tool in personalized medicine for performing patient-specific testing, like testing for allergies, ensuring that the person is not harmed [23]. This skin-on-chip system will speed up the production of personalized medicine and personalized cosmetics, and with the stem cell sector advances, more number of donor-matched autologous transplants can be generated [36].

9. CONCLUSION

Recent advancements in microfluidic technology suggest that a sophisticated and skin-on-a-chip paradigm that mimics in vivo for drug research has a lot of promise. These organ-on-chip systems serve a link between the synthesis of molecule and clinical trials, allowing researchers to reliably predict preclinical toxicity and efficacy. On the whole, the advancement of microfluidic based skin-on-a-chip systems brings us near to experimenting of actual, human skin and helps to eliminate the use of animal models. Parallel skin-on-chip platforms can be designed and are likely to be attached to networks operated by robots, allowing for medium-throughput screening or drug testing in the cosmetics and pharmaceutical industries. Their collaboration on developing, constructing, optimizing, and evaluating a skin-on-a-chip platform would cut down on animal testing and speed up drug development.

This paper gives an overview the different skin-on-chip models used currently for diagnostics and drug testing and their achievements. A general design of Skin-on-Chip device is explained. It gives insights into the utilizations of skin-on-chip models, more technological advancements like integration of biosensors and modeling of diseases. Sorafenib, an anticancer therapeutic's side effects verified using a skin-on-chip model is highlighted. The merits of iPSC in combination with skin-on-chip models which help in developing personalized medicine are elucidated. The potential future scope and limitations of the present developed models are discussed.

Recently, there has been an increased demand in the commercialization of Organ-on-chip platforms, with funding provided from a wide range of private and public sector organizations. Such significant efforts for the industrialization of these systems would significantly improve the drug production procedure and accelerate the advancement in precision medicine can result in the identification of novel therapeutic drug targets.

10. ACKNOWLEDGEMENT

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