Insight into Control Architecture of Skin Pathology and Skin Penetration by Mathematical Modeling: an Introduction for Non-mathematicians

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ABSTRACT---- ***Mathematical modeling involves construction of a set of equations or description of a stochastic process closely mimicking a real phenomenon of practical significance and biological or physiological relevance. This paper reviews some specific pathological conditions of the skin and permeation of drugs across the skin during topical administration and transdermal route of delivery in the light of mathematical modeling. It aims at providing an insight into different variables governing any pathological situation of the skin involving a complex architecture of chemical mediators. The factors controlling skin permeability of a drug molecule have also been studied. The final outcome of the paper is to equip non-mathematicians with simple mathematical tools to conduct real experiments in a more satisfactory manner and explain the physiological phenomena in a robust fashion.***

Keywords--- Mathematical modeling, Atopic dermatitis, psoriasis;,transdermal drug delivery.

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1. INTRODUCTION

Mathematical modelingg can strengthen our knowledge about the pathogenesis of skin conditions, challenges and strategies to overcome them successfully. Collection of real-time data from patients and their analysis is a prerequisite for modeling studies which will ultimately help in advancement of research in the field. The output from this research will be an useful tool for the biologists to delve deep into the hidden mechanisms underlying any alteration in normal skin functions and to test conditions that are difficult to be realized in practice with experimental set up. A highly beneficial aspect of mathematical modeling is to categorise different skin diseases possessing same etiology and expand the concept to any related condition exhibiting similar phenotypic manifestations [1], [2]. (Kirschner, DiRita, & Flynn, 2005; Squires & Tappenden, 2011).

Dynamic events are an integral part of skin with continuous replenishment of epidermal cells and immune cells. Development of a pathophysiological condition of skin is governed by an array of chemical mediators or cytokines secreted by the resident skin cells and complex interplay among different regulatory mechanisms operated by these molecules. These regulatory interactions occur across various spatial and temporal scales, varying from the order of minutes to days. Initiation of any inflammatory condition of skin is marked by disruption of its barrier function and subsequent malfunction of the regulatory framework. The epithelial layer is the first line of defense against harmful external stimuli in the form of disease-causing pathogens or foreign chemicals like drugs, environmental pollutants. Cells primarily involved in imparting the barrier function to the skin are the keratinocytes by virtue of their ability to undergo cornification. During invasion by any agent, cyclic and continuous process of cell trafficking from one compartment to another in the skin and subsequent cytokine release are affected. After antigen presentation to the dendritic cells in the skin, they migrate to the lymph nodes and activate the T cells to undergo proliferation. The T cells then migrate back to the skin, induce release of cytokines which result in onset/persistence of inflammation. Alterations in the barrier permeability are manifested as imbalances in the epithelial homeostasis and disturbances in the highly ordered sequence of growth, differentiation or cornification, proliferation, migration and programmed cell death mediated by cytokines and other effector molecules. The cytokine profile of the diseased skin varies significantly from that of normal human skin. A common feature of any inflammation-associated disease phenotype is the chronic increase in cytokine levels in the affected area over extended periods of time [3].

Mathematical model of any disease can be assumed to be a defined sequence of processes like definition of the problem and hypothesis to be checked. Initial steps of modeling approach requires a strong interdisciplinary link between the biologists and mathematicians, both having deep understanding of their respective fields. Next step is the identification of system outputs and inputs. Usually, the inputs are the internal and external stimuli acting as triggers for the disease and different types of clinical outcomes, i.e. symptoms and manifestations of varying degrees, alterations in histological and biochemical parameters are regarded as the outputs. Mechanistic model structure and establishment of physical interactions between the key components of the disease constitutes the next step which utilizes experience from in vivo experiments. For the purpose, different mathematical tools, such as, differential equations, agent-based models are used. Experimental results from patients are translated into mathematical equations to find parameters. The value ranges for the parameters were derived from literature. Conditions for steady state are determined by employing analytical methods like bifurcation analysis, time course analysis and parameter sensitivity analysis. Ultimate objective of modeling study is to avoid unrealistic number of variables to prevent complexity, facilitate easy analysis and interpretation but still able to encompass the salient features of the pathological state of the skin [4].

A differential equation model was developed to study the initial stages of chronic inflammatory process and it provided quantitative data on the levels of dendritic cells in the lymph node and in the skin, antigen concentration and number of effector T cells. Certain assumptions were made during generation of the model. The concentration of dendritic cells in the blood is maintained at a constant level throughout the simulation study. Accumulation of antigen occurs in the skin linearly over time until it attains a maximum value. Suboptimal concentration of antigen below the threshold value fails to induce migration of dendritic cells to the lymph node in sufficient quantity. High levels of antigen can only stimulate increased flow of the cells from blood to skin and then from skin to the lymph node. Monocytes from the blood are recruited as dendritic cells during development of an inflammatory response and they do not proliferate in the skin. Dendritic cells that pick up antigen reach the lymph node and participate in activation of T cells. For the T cells to proliferate, the concentration of dendritic cells should exceed a threshold value. In this simple but quite useful model, the role of cytokines in the process of chronic inflammation was overlooked [3], [5].

Interactions between the immune cell populations mediated by specific, dose-dependent production of cytokines have been included in another model for better representation of the underlying mechanisms for development of an inflammatory reaction. Changes in the rates of production of cytokines result in modified feedback loops by causing the switch-like immune system effect inducing bistable behavior which are expressed as different disease phenotypes. Parameter values of the equations in the model were altered without producing any change in the system of equations. This ensured that the same cell population are handled mathematically which are responsible for creation of immune response in normal situation. The combinations of parameter values are linked to the implementation of the model on actual cytokines. In experimental studies, it is very difficult to ascertain real cytokines because usually static comparisons between experimental groups are carried out without any consideration of dose-dependent curves or dynamic information. Variation in parameter values was done to simulate the effect of internal and environmental stimuli on the resident cell population of the skin. The most important outcome of the model was its ability to provide idea about the individual characteristics of immune cell populations and define homeostasis as particular cytokine level estimated by the intersection of the immune cell population cytokine dose-response curves. Under normal situations, temporal increase in cytokine levels may occur leading to imbalances in homeostatic process but the equilibrium is restored within very short time. Disease condition occurs only when deviation in the cytokine profile produces a disturbance in the homeostasis which cannot be restored quickly. The systems biology model could successfully distinguish between normal inflammatory reaction and pathological inflammation. Information thus obtained from the model may prove beneficial in guiding search for most effective therapeutic opportunities. The proposed drug should either eliminate the second possible level of stable or unstable homeostasis or diminish the prevalent cytokine level. This approach thus forms the stepping stone in elucidation of different complex interactions between more than two cell populations in development of chronic inflammatory condition [3], [6].

The goal of the present paper is to establish a framework of mathematical principles employed in modeling of some representative inflammatory skin disorders like atopic dermatitis, psoriasis, Erythema gyratum repens, wound healing disorders like hypertrophic scar and keloid, UV radiation-induced skin pigmentation. The second aspect of the paper is to review the mathematical explanation of drug penetration across the skin in topical and transdermal drug delivery. Although numerous studies have been done to generate mathematical models for each of the pathological conditions mentioned as also to describe the process of drug permeation, none of these has attempted to approach the topic in a very simplistic manner for the non-mathematicians. Good knowledge about the concept of modeling may prove to be valuable for biologists in performing successful realistic experiments.

1.1 Mathematical Modeling of Skin Pathological Conditions

1.1.1 Atopic Dermatitis

There are internal stimuli like genetic polymorphisms, reduced expression of filaggrin(protein functioning in maintenance of intercellular cohesion in the epidermal layer) and external stimuli like exposure to environmental elements (allergens and pollutants) which are known to precipitate this specific pathological state. The hallmark features of the disease include loss in barrier function of the skin and exacerbated inflammatory response to the external stimuli as evident by the formation of pruritic, eczematous erythematous plaques. It has been observed that the levels of IL-17, IL-20, IL-21, IL-22, IL-24, IL-31 and IL-21 receptor increases significantly in patients with the disease. Elevation in the levels of IL-21 and IL-31 leads to activation of different subpopulations of T cells and migration of dendritic cells to the sites of inflammation. This is accompanied by severe itching and increased sensitivity to the environmental stimuli. Over-expression of other cytokines is manifested as hyperproliferation of keratinocytes thereby inducing acanthosis/hyperplasia and excessive thickening of the epidermal cell layers. Expression of the interferon, IFN-γ is also increased [3], [6]-[9].

The salient features of the study in paper included development of a structure of dual control or bi-directional interplay at cellular and tissue levels, differential effects of individual risk factors on the structure manifested as dermatitis of different degrees of severity. In the extreme situation, complete breakdown of the epidermal homeostasis may occur in the presence of more than one risk factor at a time increasing the susceptibility of an individual to the disease. The proposed model could identify certain terms and parameters of significant biological relevance and they correlated well with the known risk factors. The mathematical model stated in the investigation was developed on the basis of cellular-level regulatory mechanisms controlled by proteolytic enzymes, the kallikreins(KLKs). Ordinary differential equation (ODE) model has been put forward to describe the intertwined regulatory events occurring at two different scales-slow disruption (duration span in the order of hours) of epithelial integrity occurring at the tissue level and fast immune reactions (length of reaction being in the order of minutes) initiated by the enymes taking place at cellular level. In a clinical setting, the tissue level events are observed as markers of disease as also as end-points for determination of therapeutic modalities. However, such long term dynamics are closely linked with the rapid protein-protein interactions(PPI) at the cellular level. For the construction of the model, it has been assumed that (a) balance exists between excitation and inhibition of the kallikreins and (b) another balance operates between stimulus intensity at the tissue level and dual (positive-negative) feedbacks by signaling pathways leading to inflammation [8].

Physical integrity of the epithelium is maintained by the balance between the differentiation of keratinocytes in the granular layer to corneocytes against desquamation (elimination of corneocytes at the skin surface) and also by the lipid profile of the skin. Activation of kallikreins (KLK) causes premature breakdown of corneodesmosomes, corneocyte desquamation, degrades the intercellular junctions, activates protease-activated receptor 2(PAR2), inhibits the release and transport of lamellar body lipid into the epithelium, triggers the PPI network and ultimately reduces the integrity of the barrier thereby creating a portal for influx of exogenous stimulus. The activation of PAR2 is the most important event in the entire sequence of inflammatory responses following the initiation of atopic dermatitis. The final event is responsible for elimination of stimulus from the system as also inflammatory responses observed visually in the patients. The above sequence of events constitutes a positive feedback loop originating from activated KLK and PAR2. The chronic condition persists and inflammation may even aggravate in absence of the stimulus. There are several factors which may affect the activation of kallikreins such as pH, basal expression rate of lymphoepithelial Kazal-type-related inhibitor(LEKTI), a KLK inhibitor with strong effect on the feedback loop. Variation in the degree of immune responses by the cellular elements induces changes in the negative feedback from activated PAR2 to the level of the stimulus. Different parameters that have been described to construct the model are concentration of exogenous stimulus, skin permeability, strength of stimulus eradication by activated PAR2 mediated cellular immune responses, immune reactions independent of activated PAR2, concentration of skin barrier precursors, strength of lipid release inhibition by activated PAR2, skin barrier integrity and rate of desquamation by activated kallikreins [8].

In the model, three different dynamic signatures have been identified as responses to environmental challenges of the stimuli for integrity of the epithelial barrier : homeostasis (a characteristic feature of healthy epidermis), oscillation (observed in patients with moderate degree of atopic dermatitis) and persistent damage (permanent loss of the ability to restore homeostasis). These processes are the outcomes of intertwined feedback regulatory mechanisms functional at cellular and tissue levels at different time scales. From such studies, it is evident that each individual risk factor contributes differently to the course of disease, its constituent elements and can be characterized by its unique dynamic behavior. Assessment of influence of risk factors facilitate design of personalised treatment regimen for each patient thereby improving the success rate and reducing the cost of therapy.

A novel mathematical model (two variants) investigating the feedback regulation of KLK activity in the skin has been developed on the basis of the core mechanisms of KLK induction: KLK self-activation, KLK inhibition by LEKTI, PAR2

activation by KLK and lastly, activated PAR2 mediated feedback regulation of KLK and LEKTI. The system parameters that have been defined in the model are the association rate and dissociation rate of LEKTI-activated KLK5, activation rates of KLK5 and PAR2, degradation rates of KLK5, activated KLK5, PAR2, activated PAR2, LEKTI and LEKTI-activated KLK5, production capability of LEKTI, half-saturation of KLK5 activation and PAR2 activation, basal production rates for KLK5, PAR2 and LEKTI, rate of production of KLK5 and LEKTI by stimulus, feedback strength from activated PAR2 to KLK5 and finally, feedback strength from activated PAR2 to LEKTI. Bifurcation analysis of the model showed reversible and irreversible bi-stability which indicates outbreak of inflammation by exogenous stimuli. One of the models assumed positive feedback from activated PAR2 to KLK5 and the second assumed negative feedback from activated PAR2 to LEKTI. The two feedback loops thus observed can be coupled to describe the system behavior in a much better way [4], [10].

The developed model can be validated by giving the clinically observed data as inputs to the system and verifying the responses with the actual responses. Validation of the model with experimental data will facilitate identification of the actual risk factor contributing to the disease and prediction of the disease severity with exposure to any of the risk factors studied. The mathematical model described provides a platform for characterizing multi-scale regulatory interactions, a common feature in most of the physiological situations.

Atopic dermatitis is associated with itching whose severity depends highly on the degree of pruritus. Uncontrolled and persistent itching may worsen the inflammatory skin condition and may hamper the patient's sleep pattern. Duration of the scratching time increases with the gravity of the disease and it has been measured as an index (TST in percentage) which is described as the ratio of total scratching time (TST) to total measurement time during sleep. Therefore, monitoring of scratching motion and its precise measurement specially when the patient is asleep, may serve as an important parameter in diagnosis of skin diseases. In this context, the investigators developed a mathematical model based on unconstrained bed sensing method by piezoceramics where it was not required to wear sensors on the body of the patient. The TST % was estimated from the output signals measured by ceramic sensor devices. The different variables and constants that have been included in the study are force part of the piezoelectric device, mass of bed including patient in supine position on it, stiffness constant of the metallic plate, damping coefficient of the stainless steel plate, capacitance between the piezoceramic, input resistance of the processor, time, resultant displacement of the metal plate, force generated by the device, electric charge generated by external strain or bend to the ceramics, displacement of the device plate, output voltage, different lengths from the centre of gravity to different sides of the bed, displacement of the centre of gravity of the bed and sinking angle of the bed [11].

1.1.2 Psoriasis

It is a multifactorial chronic skin disease, triggered by external and systemic stimuli and shares some of the manifestations of atopic dermatitis. Skin lesions exhibit hyperproliferation and aberrant differentiation of the keratinocytes, marked infiltrates of T cells and neutrophils and a significantly higher rate of epidermal turnover. Detailed investigation of pathogenesis of psoriasis reveals that the disease is a result of systemic inflammatory process driven by a number of chemical moieties and its root linked to disturbances in the homeostasis of the human immune system. Data from clinical studies and experimental models suggest it to be a T-cell mediated skin disease where all the subclasses of T cells play a significant role. The cytokine network comprises of actions and interactions of numerous cytokines, chemokines, growth factors and their receptors secreted by different cell types. The levels of cytokines IL-2, IL-17, IL-22, IL-23 IFN-γ and tumor necrosis factor (TNF-α) are elevated in psoriatic lesion. Keratinocytes have been identified as the primary downstream targets for a defined set of cytokines. Any alteration in the cytokine level or profile induces secretion of chemokines and antimicrobial peptides. Moreover, changes are also observed in the differentiation states and migration capacities [3], [6].

It is proposed that keratinocyte hyperproliferation in psoriasis is triggered by cutaneous lymphocyte infiltration, activation and differentiation of T cells, macrophages and dendritic cells. Localised cytokine environment is created which helps in maintenance and reinforcement of the pathogenic cascade leading to disease maturation and fully developed skin lesions [12]-[14].

A set of differential equations has been formulated to model the effect of negative feedback control on the growth of keratinocytes. This effect is comparable to that of drug administration. A time delay has also been incorporated to account for the time taken for activation of T cells and dendritic cells to epidermal keratinocytes. It has been observed that population density of keratinocytes can be normalized by regulation of their cytokine-mediated activation by T cells [15].

Systemic sequencing of data from clinical and cell-biological studies helped in depicting an advanced density-type model for immunopathogenesis of psoriasis. Contribution of cytokines and other chemical molecules in disease progression and maturation cannot be overlooked. In the model development, three model variables have been recognized : leucocytes, keratinocytes and proteins. There are several cell-biological processes controlled by either of the three subtypes of cells.

These processes have been identified as upstream influx of T cells, dendritic cells and other leucocytes to the affected part of the epidermis, secretion of various proteins by leucocytes, contribution of keratinocytes to circulating protein concentration, stimulation of keratinocytes by leucocytes to proliferate, degradation of active keratinocytes by nitric oxide produced through i-NOS pathway. It has been proved that psoriasis can be terminated by reducing the influx of leucocytes below a threshold value [16].

Since, more than one cytokine is actively involved in progression of both atopic dermatitis and psoriasis, targeting of cytokine to stall the development of disease seems more logical intervention than to target the keratinocytes. This strategy could lower the potential risks associated with over-production of a cytokine in the system which tries to complete the vicious circle involving it. New drugs can be successfully screened by using this inflammatory cytokine network [6].

Response of psoriatic plaques to UVB irradiation has been aptly modeled by suitable mathematical tools. It is proposed that UVB exerts a direct effect on keratinocytes and cell cycle arrest occurs as a response to UV radiation. It has been observed that for a specific erythemal response, number of exposures required for remission of symptoms is not dependent on the frequency with which the patients arrive for treatment. Furthermore, it has been suggested that rapid clearance occurs at higher exposure dose per treatment [17].

1.1.3 Erythema gyratum repens(EGR)

This rare, inflammatory condition of the skin with unknown etiology is characterized by unique morphological nature of the eruptions and patterns thereof exhibiting circinate and gyrate bands of erythematous and scaly skin. It shares some characteristics common with Belusov-Zhabotinski (BZ) reaction like ordered spatio-temporal oscillating concentration profiles of immunoregulatory mediators. Pattern formation can be described with the help of a simple non-linear reaction-diffusion model. The model could explain the dynamic and morphological features of the pathological condition from biochemical aspect and could enable quantitative analysis. During model formulation, it has been assumed that bands of inflammation propagate at definite velocities exhibiting wave-train like phenomena and also thermodynamic changes occur as evident by reduction in Shannon entropy of the system. Immune responses and skin eruption possess a dissipative structure which depend on non-linear feedback between production, autocatalysis and inhibition of immunoregulatory molecules and the relative concentrations of agonist and antagonist. In the study, the researchers investigated about the role of pro-inflammatory cytokine, Interleukin 1, in the development of rashes associated with EGR. However, there are still lacunae left in modeling of the disease encompassing its every feature in a physiologically and biochemically relevant way [18].

1.1.4 Wound Healing Disorders

Dermal wound healing is a natural process which may assume an abnormal proportion due to fibro-proliferative disorders like keloid and hypertrophic scar. These pathological conditions may cause physical pain and mental trauma to the affected person. Alterations in profiles of fibroblastic cells and inflammatory growth factor mediators secreted thereof occur. An attempt has been made by the scientists to gather knowledge about the important clinical problems associated with fibroplasias and wound contraction in adult mammalian dermis with the help of deterministic mathematical model. These disorders are characterized by distinct stages of initiation, fibroblastic cell migration, proliferation, cessation and regression /wound contraction accompanied by diffusion of growth factors, production by cells and removal or decay of the damaged cells. The processes of cessation and regression are controlled by spatiotemporally different forms of the cellular production rate of the chemical. All these phenomena have been embodied in the model which will thus be beneficial in qualitative and quantitative prediction of the course of progression, stability, therapeutic intervention and expected outcomes of a suitable control measure [19].

Three continuous, overlapping temporal stages of inflammation, proliferation and remodeling are present in any normal healing response to a full-thickness dermal excisional wound. Regulatory network of cellular events control the architecture of fibroblasts, their proliferation, differentiation into myofibroblasts under the influence of growth factors and extracellular matrix proteins. Several aspects of secretion, transport, metabolism and inactivation of the chemicals can be assumed to follow simple linear decay process and can be appropriately described with Michaelis-Menten dynamics. For mathematical representation of the abnormal contraction of fibroplasias and wound contraction after a linear(slash) wound, non-dimensional model equations have been derived where several parameters have been considered. They involve fibroblast density, myofibroblast density, concentration of growth factor and mediator and collagen concentration. The model variables are independent of wound depth. However, variations in some of the model parameters may occur during healing of burn wounds which is characterized by excessive infiltration of inflammatory cells [20].

In another study regarding mathematical modeling of wound healing in experimental animal, rabbit has been extensively studied. It involved calculation of three indices based on the measurement of well-defined and quantifiable parameters like length of the re-epithelialisation zone, distance between the borders of the wound along the straight line of epidermis, depth of the wound from the epidermis to the first layer of the connective tissue at the deepest point of the wound, thickness of the new tissue at the centre of the wound and thickness of the natural dermis on both sides of the wound. The indices that were estimated from the model were Superficial Contraction Index(SCI), Deep Contraction Index(DCI) and Wound Severity Index(WSI), with their values lying in the range of 0 and 1. The DCI is governed by the external nature of the wound. The above mentioned three indices can be combined into a single parameter, Global Healing Index(GHI). It enables precise monitoring of the healing process and scope for scoring for comparative assessment. Additionally, Remodeling Index was also obtained in the rabbit model where migration of hair roots to the tissue is closely related with wound contraction. Global Remodeling Index (GRI) was calculated from Hair Remodeling Index(HRI) and Matrix Remodeling Index(MRI). Evaluation of the five indices helped in scoring of the histo-pathological data obtained from clinical studies and subsequent comparison of the effects of different treatment options, biopolymers or pharmacological preparations on healing and remodeling of soft tissues [21].

In an entirely different approach to mathematical modeling of the final stage of wound contraction in the process of wound healing, the complex interplay between two cell types(fibroblasts and macrophages), two cytokines (tissue plasminogen activator [tPA] and transforming growth factor-β [TGF-β]), growth factors and anisotropic orientation of fiber species in the extracellular matrix has been envisaged. During contraction, wound area starts receding which accelerates the healing process. The cells have been represented as discrete entities and all other variables have been defined on a triangular mesh. Production of tPA has been modeled as a hyperbolic tangent depending on the distance to the wound edges and that of growth factor has been expressed using Dirac delta functions. The variables which were considered for the model were minimum and maximum diffusion rates of tPA and TGF-β, minimum and maximum collagen synthesis, influence of fibrin and collagen density on cell movement, factor of fibrin decay, maximum velocities for fibroblasts and macrophages, factors of directional persistence of fibroblasts and macrophages, directional sensitivity to chemo-attractant for both the cell types and finally standard deviation in the random walk. The receptors for TGF-β have been considered since cellular response usually follows binding to the receptor. To account for bigger time steps in real cases, contact forces between cells pushing each other need to be incorporated. Moreover, involvement of another cytokine may be required in order to describe the migration of macrophages to the wound space. Furthermore, it seems more logical to consider a large wound from above rather than the cross-section. The corresponding partial differential equations have been solved by employing finite element method. Modifications in the finite element method after incorporation of the above conditions and comparison of the outputs with those of the analytical technique involving Green's functions will be the next essential step in mathematical modeling of wound healing in practical cases [19].

A morphoelastic model and a fibrocontractive model have been formulated to provide a realistic simulation of tissue mechanics underlying the process of dermal wound healing. It has been observed that factors responsible for hypertrophic scar and contracture development are different from those for keloid invasion. Myofibroblasts are activated and their apoptosis inhibited during scar formation. However, activation and spread of TGF-β is the key feature for induction of keloid growth. From time to time, various modifications have been performed on the mechano-chemical models involving migration of both fibroblasts and myofibroblasts through the extracellular matrix. Linear viscoelasticity and linear stress-strain relationship have been assumed and the magnitude of strain is high in wounds healing with sufficient contraction. In one study, transformation of fibroblasts to myofibroblasts has been proposed to occur in response to environmental cues, when minor changes in their mechanical environment are observed [22].

1.1.5 UV-radiation-induced Skin Pigmentation

The pigment, melanin, present in skin melanocytes protects it from the harmful effects of UV radiation. Moreover, UV radiation, in controlled doses, can actually help in remission of psoriatic symptoms and forms the basis of phototherapy. In-depth knowledge about the optical properties of the skin is necessary to ascertain the fraction of incident UV radiation on different layers. Epidermis was initially regarded as a homogeneous layer having the capacity to absorb radiation which is accentuated by the presence of melanin. However further advancements have found that epidermis is composed of sub-layers and scattering of radiation occurs. Moreover, melanin distribution is non-uniform. The Monte Carlo method was used to describe the scattering by epidermis. Scattering of photons was studied as they travel through a medium till they are absorbed by a chromophore, reflected from or transmitted through the medium. Different variables included in the study were tissue thickness, refractive index, absorption coefficient, scattering coefficient and anisotropy factor. The outputs that were estimated were reflectance, transmittance and photon absorption energy density [23].

UVA_1 induces skin pigmentation and this may affect its ability to induce collagenase which shows great promise in phototherapy of skin diseases involving thickened skin due to disorders in collagen deposition like scleroderma. To determine an optimal phototherapy regimen with UVA_1, in treatment of fibrosis, differential equations have been developed. Dose and frequency of radiation and reduced collagenase response to skin darkening have been considered in the formulation of mathematical model [24].

1.2 Modeling of Drug Penetration across Skin

Skin is an important site not only for application of cosmetics but also for drug administration either for local or systemic action. When it is applied on the skin in the form of lotions, suspensions, gels, ointments or creams, for treatment of localized infections, inflammation or wound healing, it is known as topical route of administration from which systemic absorption is not required. However, in cases of fungal infections on the skin, psoriaisis, eczema, local as well as systemic action are desirable and percutaneous absorption of the drug is very crucial to achieve maximum therapeutic efficacy. In case of transdermal drug delivery, a patch is applied on the skin from which drug is released slowly and should penetrate the epithelial barrier and reach the blood circulation to elicit pharmacological action. This type of dosage form is highly suitable for sustained release of action for extended period of time and is a favorite for treatment of migraine, motion sickness, nicotine withdrawal syndrome, angina pectoris etc. In order to predict skin permeability of different molecules, various empirical approaches have been employed with varying degree of success like quantitative structure-permeability relationships, porous pathway theories, structure-based models. To exploit the benefits of any of these approaches to its fullest, the primary step is the quantification of the key parameters involved in the process [25].

Highly effective barrier function of skin is attributed to its outermost layer, stratum corneum, constituted by corneocytes embedded in continuous, crystalline lipid bilayer. Drug is transported across the skin by either of the two mechanisms: simple penetration or co-transport. In order to enhance the rate of drug permeation, the most common strategy is to use penetration enhancers in the form of water-miscible co-solvents like propylene glycol as vehicle, which is transported along with the drug molecule leading to co-transport. Rate of permeation by this process essentially depends on drug solubility in the vehicle and also the proportion of propylene glycol in the vehicle. Simple penetration, on the other hand, involves transport along the concentration gradient of the permeant. For compartment modeling of drug penetration, lipophilic dodecanol membranes were used as the acceptor and time-dependent changes in concentration in different compartments were determined from model equations. Influence of drug dissolution in the vehicle on its transport via any mechanism is quite significant which has been assessed by an appropriate mathematical model. For the sake of simplicity, it is assumed during modeling of co-transport phenomenon that co-solvent velocity is the co-transport velocity. Moreover, the concentration gradients of both the permeant and the co-solvent drive the process of penetration across the synthetic membrane [26].

Drug transport through rat skin can be assumed to occur via diffusion through either full-thickness skin consisting of stratum corneum, epidermis and dermis or one-layer skin formed by epidermis and dermis. Diffusion through one-layer has been alternatively termed as one-layered diffusion model. Through a homogeneous single layer of the membrane, drug diffusion is assumed to occur following Fick's second law of diffusion. At sink condition in the receiver compartment, a set of initial and boundary conditions are observed which depend on the magnitudes of the partition coefficient of the permeant from the vehicle to the membrane and drug concentration in the vehicle. In case of full-skin model or two-layered diffusion model, concentration of drug in the stratum corneum and additionally, that in the viable epidermis and dermis of the skin are governed by same Fick's law. Initial and boundary conditions are obtained similarly. Since, physical process of diffusion is the common underlying transport mechanism for both the models, mathematical tools can be employed to replace membrane concentration in the two-layered model with that in the single-layer diffusion model. To elucidate the actual mechanism of drug penetration, several factors should be considered. Firstly, in Franz diffusion cell or the in vitro permeation apparatus, there always remains undissolved drug in the donor compartment to maintain the drug concentration at the saturation level. Secondly, a stagnant layer of medium is always associated with the membrane on the receiver side of the diffusion cell. Therefore, simultaneous estimation of drug dissolution constant in the donor compartment, thickness of the stagnant layer and drug diffusion coefficient is necessary to increase the accuracy of prediction. There is a threshold value for permeability/dissolution constant ratio beyond which the dissolution flux fails to achieve equilibrium with permeation flux. Formulation of the model requires measurement of drug solubility and partition coefficient in the full-skin and in the dermis-epidermis. However, drug diffusion coefficient in the dermis-epidermis layer can be determined experimentally. The results are fitted to the model on drug permeation data of full skin to derive the diffusion coefficient in the stratum corneum. Therefore, most of the physical parameters relevant to drug permeation are determined from actual experiments and only one such quantity is obtained from the model by data fitting. It has been concluded that in the full-skin model, the drug dissolution flux value is greater than the permeation flux which maintains a constant concentration of drug in the donor compartment throughout the duration of the study. The reverse situation is observed in the one-layer model. Simple method

based on pseudo steady state approximation may provide misleading values for membrane resistance to drug permeation when full-skin is considered [25], [27].

Compartment modeling serves as a good measure of the pharmacokinetic parameters for the drug penetrating across the skin and provides a good understanding about the fate of the drug in the body. In this approach, skin and the body is regarded as a single or multiple compartments where the drug is distributed, stored, absorbed or metabolized. The rate of transfer from one compartment to the other or the rate of influx and efflux to and from a compartment can be described by simple first-order kinetic equations. For example, in analysis of drug transport in one-compartment skin layer, the following variables are of utmost importance : position-averaged drug concentration in the skin layer, volume of skin layer and the rate constants for drug transfer between vehicle, skin and blood compartments. These models are very effective in risk assessment in prediction of change in output with variations in the parameters of the system like change in blood flow to the skin during a particular pathological condition. One-compartment monolayer diffusion model has been proposed to describe the pharmacokinetics of a high molecular weight drug diffusing from an array of microneedles in the viable skin tissue to the dermal microcirculation. A software has been utilized to solve the partial differential equations by finite difference method. The computer program generated blood concentration profile of the drug from inputs of different parameters and permeability of drug could also be calculated. Various factors affecting transdermal drug delivery have been studied by scaling analysis using Buckingham's π theorem. It has been observed that drug concentration in the blood is governed by a number of variables related to microneedle system such as, length of the microneedles, duration of application and surface area of the array system [28].

A slight modification in the compartment modeling approach has introduced the concept of effective diffusion coefficient instead of simple diffusion coefficient. It is based on the fact of binding of drug molecules to the stratum corneum prior to penetration and the formation of drug reservoir at the site. Binding is assumed to be instantaneous and the rate of equilibriation between the free and bound drug is faster compared to the rate of diffusion. So, in the modified approach, binding and dissociation rate constants have been taken into consideration. The resultant differential equations of the advanced model have been solved by taking Laplace transform.

During assessment of key parameters associated with percutaneous absorption following topical and transdermal drug delivery, new ideas have been brought to describe the complexity of the stratum corneum and to explain it in a more realistic fashion. The organisation of the lipids and the effect of the packing on drug partitioning has been studied extensively by several researchers. For example, a two-dimensional brick-and-mortar geometry for the stratum corneum has been proposed with scope for permeable corneocyte phase. In this new composite model, three microscopic drug transfer coefficients in the stratum corneum have been described : lateral lipid diffusivity, transverse mass transfer coefficient and an isotropic corneocyte phase diffusivity [29].

In the finite element method for numerical solution to both linear and non-linear partial differential equations, the skin or domain with complex geometries and boundaries is assumed to be divided into a discrete set of connected sub-domains. The dermis is discretised into three layers and the concentration of the drug is assumed to vary linearly in each layer. A mesh of triangles or polygons is created with varying densities depending on the significance of the areas of interest. Such model has been developed for characterization of drug permeation parameters for a transdermal patch. In this approach, metabolic reactions occurring in the skin are neglected since, transdermal route of administration bypasses first-pass hepatic metabolism [30].

For iontophoretic drug delivery across skin, a one-layer two-pathway mathematical model and a three-layer two-pathway model have been formulated. In the first case, drug delivery through the stratal corneal is only considered whereas, in the latter case, delivery from iontophoretic unit to the stratal corneal and then from stratum corneum to the capillaries via the viable epidermis are included in the model [31].

A good mathematical model describing drug penetration across the skin is the one which can be extended to structurally-related compounds as also drugs belonging to different chemical classes, easy to comprehend and any parameter can be accurately predicted from the model with prior knowledge of other parameters of the system. Furthermore, any reasonable modification in the model should yield statistically significant results in comparison to the models already in use.

2. CONCLUSION

Unraveling the mystery of mathematical modeling for the biologists, clinicians and non-mathematicians widens the scope of experimental studies in a much better way. Validation of an established model with experimentally determined data enables prediction of effect of alteration of any one variable on the whole system. Information collected in the present study are indispensable for any scientist working in the area of dermal pathology and drug delivery across the skin for local and /or systemic effects. Knowledge about the parameters affecting a process helps in creating a robust experimental space with little or no ambiguity of the data.

3. REFERENCES

[1] D. Kirschner, V. DiRita, and J. A. Flynn, "Overcoming math anxiety: Malthus meets Koch," *ASM News* vol. 71, pp. 357-362, 2005.

[2] H. Squires, and P. Tappenden,"Mathematical modeling and its application to social care," *Meth. Rev*. vol. 7, pp. 1-22, 2011.

[3] N. V. Valeyev, C. Hundhausen, Y. Umezawa, N. V. Kotov, G. Williams, A. Clop, C. Ainali, C. Ouzounis, S. Tsoka, and F. O. Nestle,"A systems model for immune cell interactions unravels the mechanism of inflammation in human skin," *PLoS Comput. Biol*., vol. 6, no. 12, e1001024, 2010.

[4] R. J. Tanaka, and M. Ono,"Skin disease modeling from a mathematical perspective," *J. Invest. Dermatol*. vol. 133, pp. 1472–1478, 2013.

[5] L. Erikson, A. Wise, S. Fleming, M. Baird, and Z. Lateef, "A preliminary mathematical model of skin dendritic cell trafficking and induction of T cell immunity," *Discr. Cont. Dyn. Syst., Series B*, vol. 12, no. 2, pp. 323-336, 2009.

[6] K. H. Hänel, C. Cornelissen, B. Lüscher, and J. M. Baron,"Cytokines and the skin barrier," *Int. J. Mol. Sci*. vol. 14, pp. 6720-6745, 2013.

[7] E. Domı´nguez-Hu¨ttinger, M. Ono, M. Barahona, and R. Tanaka,"Risk factor-dependent dynamics of atopic dermatitis: modelling multi-scale regulation of epithelium homeostasis," *Interface Focus*, vol. 3, 20120090, 2013.

[8] R. J. Tanaka, M. Ono, and H. A. Harrington,"Skin barrier homeostasis in atopic dermatitis: feedback regulation of kallikrein activity," *PLoSONE*, vol. 6, no. 5, e19895, 2011.

[9] J. Witt, S. Barisic, E. Schumann, F. Allgo¨wer, O. Sawodny, T. Sauter, and D. Kulms, "Mechanism of PP2Amediated IKK beta dephosphorylation: a systems biological approach," *BMC Syst. Biol*., vol. 3, 71, 2009.

[10] E. A. O'Toole,"Molecular biology," in *Rook'sTextbook of Dermatology,* T. Burns, S. Breathnach, N. Cox, et al. Eds. UK: Wiley-Blackwell, Oxford, 2010 , pp. 1–22.

[11] T. Sumi, S. Nukaya, T. Kaburagi, H. Tanaka, K. Watanabe, and Y. Kurihara, "Development of scratching monitoring system based on mathematical model of unconstrained bed sensing method," *Int. J. Med., Health, Pharm. Biomed. Engg*., vol. 7, no. 12, pp. 554-561, 2013.

[12] R. O. Bak, and J. G. Mikkelsen,"Regulation of cytokines by small RNAs during skin inflammation," *J. Biomed. Sci.*, vol. 17, pp. 53, 2010.

[13] H. Blumberg, H. Dinh, C. Dean, Jr., E. S. Trueblood, K. Bailey, D. Shows, N. Bhagavathula, M. N. Aslam, J. Varani, J. E. Towne, and J. E. Sims, "IL-1RL2 and its ligands contribute to the cytokine network in psoriasis," *J. Immunol.*, vol. 185, pp. 4354–4362, 2010.

[14] W. R. Swindell, X. Xing, P. E. Stuart, C. S. Chen, and A. Aphale et al.,"Heterogeneity of inflammatory and cytokine networks in chronic plaque psoriasis,". *PLoS ONE,* vol. 7, no. 3, e34594, 2012.

[15] P. K. Roy, and A. Datta,"Negative feedback control may regulate cytokines effect during growth of keratinocytes in the chronic plaque of psoriasis: a mathematical study," *Int. J. Appl. Math*, vol. 25, no. 2, pp. 233-254, 2012.

[16] B. Chattopadhyay, and N. Hui, "Immunopathogenesis in psoriasis through a density-type mathematical model,"*WSEAS Trans. Math.* vol. 11, no. 5, pp. 440-450, 2012.

[17] B. L. Diffey, "Towards optimal regimens for the UV-B phototherapy of psoriasis: A mathematical model," *Acta Derm. Venereol.* vol. 84, pp. 259–264, 2004.

[18] S. Gilmore, and K. A. Landman,"Is the skin an excitable medium? Pattern formation wound healing disorders," *J. Theor. Med*., vol. 6, no. 1, pp.57-65, 2005.

[19] W. M. Boon, "Mathematical modeling of wound healing and subsequent scarring," (unpublished Master's degree thesis). Delft University of Technology, 2013. Available : http://repository.tudelft.nl/(URL).

[20] L. Olsen, J. A. Sherratt, P. K. Maini, "A mathematical model for fibro-proliferative wound healing disorders," *Bull. Math. Biol*., vol. 58, no. 4, pp. 787-808, 1996.

[21] N. Lemo, G. Marignac, E. Reyes-Gomes, T. Lilin, O. Crosaz, and D. H. Dohan Ehrenfast, "Cutaneous re-epithelialisation and wound contraction after skin biopsies in rabbits: a mathematical model for healing and remodeling index," *Vet. Archiv*. vol. 80, no. 5, pp.637-652, 2010.

[22] K. Murphy,"Mathematical investigation of the interactions between the inflammatory response and mechanical aspects of dermal wound repair," (*unpublished doctoral dissertation*). Queensland University of Technology, Australia, 2011.

[23] M. M. Stolnitz, A. Y. Peshkova, A. N. Bashkatov, E. A. Genina,"Mathematical modeling of changes in the optical properties of epidermis due to UV-induced melanogenesis," in *Controlling Tissue Optical Properties: Applications in Clinical Study*, V. V. Tuchin, (Ed.), Proceedings of SPIE *4162*, pp. 194-201, 2000.

[24] S. Kang, "Mathematical modeling of collagenase-1 induction *Technology #4053* Inventors

TECHtransfer ," University of Michigan.

[25] H. Todo, T. Oshizaka, W. R. Kadhum, and K. Sugibayashi,"Mathematical model to predict skin concentration after topical application of drugs," *Pharmaceutics*, vol. 5, pp. 634-651, 2013.

[26] S. Huth, L. Boltze, and R. Neubert,"Mathematical assessment of different penetration mechanisms from vehicles with propylene glycol," *J. Contr. Rel*. vol. 49, pp. 141–148, 1997.

[27] N. Coceani, I. Colombo, M. Grassi, "Acyclovir permeation through rat skin: mathematical modelling and in vitro experiments," *Int. J. Pharm.*, vol. 254, pp.197–210, 2003.

[28] B. Al-Qallaf, D. B. Das, D. Mori, and Z. Cui, "Modelling transdermal delivery of high molecular weight drugs from microneedle systems," *Phil. Trans. R. Soc. A*, vol. 365, pp. 2951-2957, 2007.

[29] S. Mitragotri, Y. G. Anissimov, A. L. Bunge, H. F. Frasch, R. H. Guy, J. Hadgraft, G. B. Kasting, M. E. Lane, and M. S. Roberts,"Mathematical models of skin permeability: An overview,"*Int. J. Pharm*., vol. 418, no. 1, pp. 115-129, 2011.

[30] V. Gupta, S. S. Pagey, and V. P. Saxena,"Numerical analysis of drug diffusion in human dermal region with linear shape function," *IOSR J. Math*. vol. 4, no. 2, pp. 31-36, 2012.

[31] A. L. Weltner,"Mathematical modeling of transient state transdermal drug delivery," (*unpublished Master's degree thesis*). Department of Chemical Engineering, Faculty of New Jersey Institute of Technology, 2004.