Does skin permeation kinetics influence efficacy of topical dermal drug delivery system?: Assessment, prediction, utilization, and integration of chitosan biomacromolecule for augmenting topical dermal drug delivery in skin

Akshaya Iyer,
Vaskuri G. S. Sainaga Jyothi,
Aashruti Agrawal,
Dharmendra Kumar Khatri[1],
Saurabh Srivastava,
Shashi Bala Singh[1],
Jitender Madan

Departments of Pharmaceutics and [1]Biological Science, National Institute of Pharmaceutical Education and Research, Hyderabad, Telangana, India

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Abstract

Skin permeation is an integral part of penetration of topical therapeutics. Zero order in addition to Higuchi permeation kinetic is usually preferred in topical drug delivery cargo. Penetration of therapeutic entities through epidermal barrier is a major challenge for scientific fraternity. Furthermore, penetration of therapeutic entities determines the transportation and ultimately therapeutic efficacy of topical dermal dosage forms. Apart from experimentation models, mathematical equations, *in silico* docking, molecular dynamics (MDs), and artificial neural network (Neural) techniques are being used to assess free energies and prediction of electrostatic attractions in order to predict the permeation phenomena of therapeutic entities. Therefore, in the present review, we have summarized the significance of kinetic equations, *in silico* docking, MDs, and ANN in assessing and predicting the penetration behavior of topical therapeutics through dermal dosage form. In addition, the role of chitosan biomacromolecule in modulating permeation of topical therapeutics in skin has also been illustrated using computational techniques.

Key words: Artificial neural network, chitosan biomacromolecule, *in silico* docking, permeation, skin, topical delivery

INTRODUCTION

Skin is the largest organ in human body accounting for approximately 15% of total body weight with a surface area of 1–2 m^2. A plethora of skin disorders such as blisters, acne, hives, rosacea, actinic keratosis, carbuncle, psoriasis, eczema, cellulitis, in addition to basal and squamous cell carcinoma, melanoma, lupus, ringworm, vitiligo, and melasma have been documented in the literature [Figure 1].[1]

Impetigo, a bacterial skin disorder, is superficial, crusting epidermal skin infection, further categorized as bullous and nonbullous impetigo.[2] On the other hand, fungal diseases are broadly classified into three categories,

Address for correspondence:
Dr. Jitender Madan,
Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Hyderabad, Telangana, India.
E-mail: jitenderpharmacy@gmail.com

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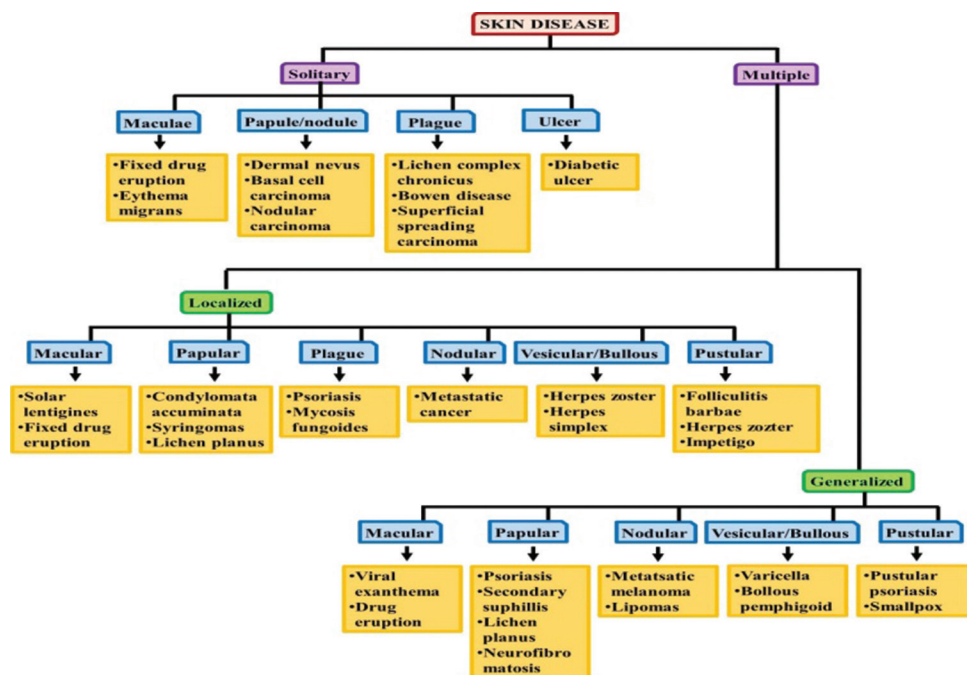
Figure 1: Schematic representation of classification of skin disorders

namely superficial, deep, and systemic infections based on depth of affected area. Causative agents for superficial infections include molds, yeasts, dermatophytes, and nondermatophytes.[3] Correspondingly, viral infection such as genital warts followed by chronic infection is caused by human papillomavirus that is intricate to treat.[4] Allergic skin infections such as atopic dermatitis, contact dermatitis, and pruritus have also been reported.[5] Dermatological diseases which are bound within primary category of illness need customized treatment modalities such as antimicrobials and vaccines [Figure 1].

Skin disorders are generally treated via systemic or topical route of administration. Systemic route has its own pros and cons such as desirable high bioavailability, nonselective biodistribution, and consequently deposition of subtherapeutic amount of drug entity at the site of target. Nevertheless, topical dermal drug delivery (TDDD) demonstrated upper-hand *vis-à-vis* systemic route for handling skin disorders.

Skin is prone to several physical and environmental stresses.[6] Topical formulation (ointments, gels, creams, lotions, solutions, suspensions, and shampoos) delivers drugs conveniently to the affected area.[7] However, only the active agent in the molecular state penetrates the skin. Generally, penetration and biodistribution depends on the barriers such as stratum corneum and the pathophysiological state. For instance, medicated ointment retains transepidermal water and facilitates drug transport by hydrating skin layers.[8] Thus, the thermodynamic activity and concentration gradient drives the transport of drug across the skin in a saturated vehicle than that from a dosage form with subsaturation.[9] Hence, topical dermal products designed for thermodynamics, chemical gradient, physical barrier, and pathophysiological state offer distinct release and permeation patterns.

Furthermore, advancements regarding permeation pattern were assessed by computational programs for predicting the drug permeation from TDDD systems. Moreover, mechanistic pathways and utility of chitosan biomacromolecule in augmenting TDDD were illuminated using computational techniques.

TOPICAL DERMAL DRUG DELIVERY: WHAT WE SHOULD KNOW?

Skin: Organ of exposure and primary shield

Skin is the primary shield protecting all the vital organs from the external environment. It is a physical barrier that blocks the microorganism, pathogen, and allergen entry. It also offers metabolic, immunologic, and protection from ultraviolet rays. The physiological milieu in the skin is slightly acidic in nature owing to pH range of 4.7–5.7. Human skin comprises three main layers, specifically epidermis (50–150 μm thick), an outermost layer of skin without blood vessels, followed by 250-μm thick inner dermis layer below which resides a subcutaneous fat tissue [Figure 2]. Hence, nutrients have to circulate through epidermal-dermal intersection to preserve the vigor of the outermost layer.

Epidermis layer is divided into five layers, the outermost of which is stratum corneum, stratum lucidum, stratum
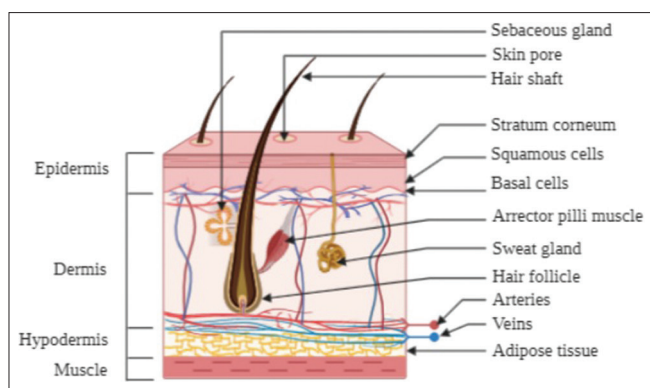
Figure 2: Schematic representation of different layers of skin. Stratum corneum (15—20-μm) acts as the main barrier of the skin

granulosum, stratum spinosum, and stratum germinativum being the deepest epidermal layer. Stratum corneum acts as a key barrier with a thickness of 15–20 μm and is composed of corneocytes which are implanted within a lamellar arrangement of rigid intercellular lipids. In this way, stratum corneum offers a strict barrier to molecules that are >500 Da.[10]

Skin contains two types of glands, namely eccrine and apocrine having 30–40 μm and 80–100 μm of average pore size, respectively. Moreover, epidermis also comprises melanocytes (production of melanin), keratinocytes, Langerhans cells (immunological response), and merkel cells (sensory perception). Including cellular components, pilosebaceous unit encompasses hair follicles which are associated with sebaceous glands. To preserve its optimal protective properties, renewal of the stratum corneum takes place depending on the anatomical site and age.[11] Skin houses enzymes such as alcohol dehydrogenase, flavin-dependent aldehyde dehydrogenase, monooxygenase, cytochrome P450, and carboxylesterase that participate in biotransformation of topically applied drugs and thereby determine the duration of action.[12]

Conventional topical dermal dosage forms: Limitations and applications
Topical dermal drug delivery systems (TDDDSs) have been used since ages for the treatment of skin diseases. Majority of conventional TDDDSs are designed for local action. Ointments, creams, gels, lotions, liniments, and oils are varying in their mode of application, physicochemical properties, compositions, and purpose of treatment. Ointment bases are majorly composed of petrolatum, mineral oil, waxes, fatty alcohols, or combination of these. The greasy nature owes to decreased patient compliance. Cream is an emulsion with the least stability due to high thermodynamic free energy resulting in cracking or phase separation. On the other hand, gels are comparatively more stable and nongreasy with high patient compliance. Upon application of TDDDS, a concentration gradient is established across the layers of skin, due to which rapid absorption occurs.[13]

Despite desirable features, still topical dermal dosage forms are associated with certain limitations.[14] Common drawback of TDDDS over other routes is that it requires a high therapeutic concentration of drug to maintain steady-state level at the site of action. Consequently, higher concentration promotes toxic reactions in dermal cells. Physical hitches include uncontrolled loss of active moiety due to evaporation or skin surface contacts along with unpleasant odor. Patient routine activities and hygiene of the skin also impact the dermal delivery of drug.

Penetration is the major challenge and penetration enhancers are utilized to increase the transportation of drugs in dermal layers by increasing the transfer rate through the epidermal layer and augment skin retention of active ingredient.[15,16] Therefore, it is mandatory to optimize the application of penetration enhancers to maintain the therapeutic concentration of drug at the target area by integrating several assessment techniques such as permeation kinetic, *in silico* docking, molecular simulation techniques, artificial neural network (ANN), and nanoscaled TDDDS.

ASSESSMENT OF SKIN PERMEATION: EXPERIMENTAL MODELS AND SKIN PERMEATION MATHEMATICS

### Experimental models used to measure skin permeation and retention
Drug transportation from TDDDS to the layers of skin initially depends on partitioning of drug between dosage form and stratum corneum. Subsequently, the diffusion of drug molecules across stratum corneum happens with the help of intercellular lipids. Following saturation of stratum corneum, drug transports from stratum corneum to dermis layer by crossing the viable epidermis cells. Subsequently, since dermis layer is perfused, diffused drug then enters systemic circulation via blood capillaries [Figure 3]. Therapeutic entity from topical dermal delivery cargo is usually absorbed via two pathways, namely transepidermal and transappendageal routes. Transepidermal is further subdivided into transfollicular and intercellular, whereas drug via transappendageal route diffuses either through intracellular space comprising hair follicles and sebaceous glands or through eccrine glands. However, all the transportation pathways destine in the dermis layer of skin.[17] A summary of vertical diffusion cell [Figure 4] and modified holding cell [Figure 4] in addition to other reported cells to assess skin permeation is presented in Table 1.

Skin permeation: Mathematical model to predict skin concentration
Skin permeation is majorly determined by Fick's law, which states that flux (J) or absorption rate of any substance across a barrier is related to its diffusion which in turn is directly proportional to the concentration gradient.[24-26] For drugs
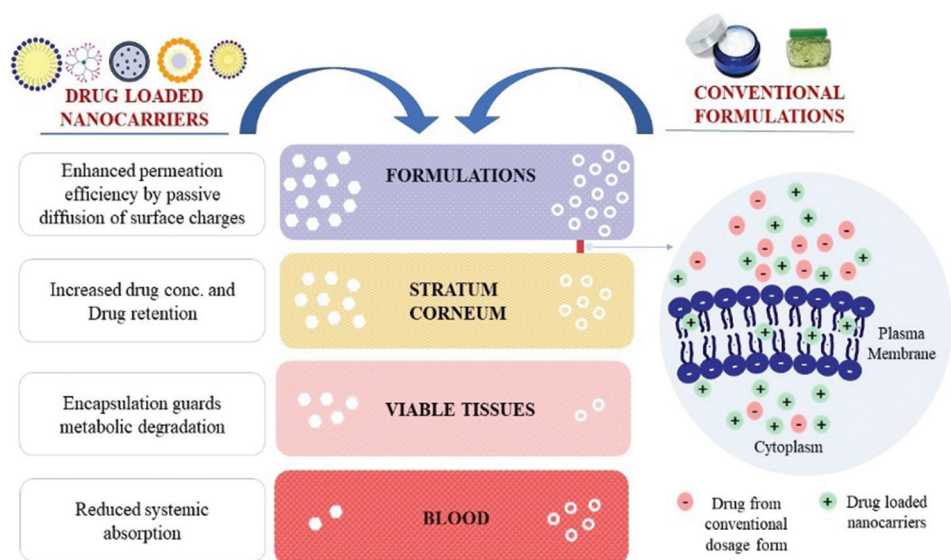
Figure 3: Mechanisms of permeation of drug from skin through conventional and drug-loaded topical nanocarriers
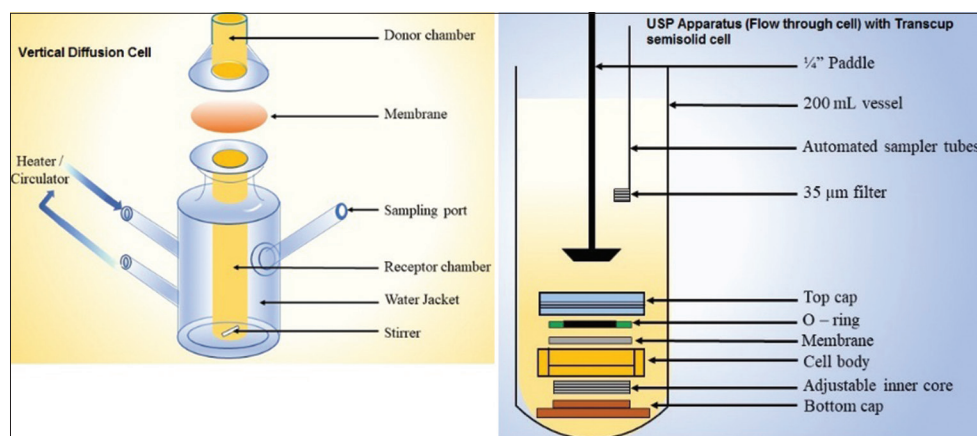
Figure 4: Schematic representation of diffusion cells employed to estimate release kinetics from topical dermal drug delivery systems

Table 1: Experimental models to assess skin permeation and experimentation requirements

Experimental models	Experimentation requirements	Reference
Vertical diffusion cell	Franz diffusion cell with a synthetic inert membrane and dissolution medium of pH 5.6	[18]
MHC	USP apparatus II type is used, assisted with a mini paddle	[19]
USP apparatus-4	Flow-through cell along with transcap semisolid cell	[20]
Extraction cell	USP apparatus type II assembly with a motionless extraction cell placed underneath the dissolution vessel	[21]
Ex vivo skin parallel artificial membrane permeability assay model	Cell-free permeability model with lipid-infused artificial membrane	[22]
Tape-stripping model	Stratum corneum applied with the pieces of adhesive tape mounted with topical dermal dosage form	[23]

MHC: Modified holding cell

administered topically, the concentration gradient depends on the difference observed between concentration of drug in the vehicle (C_v) and layer of skin[27] (Eq. 1).

$$J = K_p C_v \qquad (1)$$

Subsequently, the proportionality constant relating flux can be correlated as the permeability coefficient (Kp). Physicochemical properties of drugs, barriers, and interaction between drug and skin lipids affect the permeability coefficient. In other terms, partition coefficient (K_m), diffusion coefficient (D), and length of the

diffusion pathway (L) influence the penetration of the drug in skin. Hence, four factors control the skin permeation; however, C_v and K_m are highly dependent on the vehicle which is of great practical importance (Eq. 2).[28]

$$J = \frac{D\,K_m C_v}{L} \qquad (2)$$

ASSESSMENT OF SKIN PERMEATION KINETICS: MATHEMATICAL OUTLOOK

TDDDSs are designed in order to effectively deliver a therapeutic modality at the site of action; however, formulations offer distinct drug release and permeation patterns depending on the composition and/or cross-linking network. For instance, ointments due to the presence of lipid-soluble bases acquiesce lipidic nature and thus favor delivery of lipophilic molecules. In contrast, aqueous nature of gels promotes encapsulation of hydrophilic molecules. Hence, mechanism of drug release and permeation of molecules from the matrices are usually different owing to dissimilar compositions. This consequently displays diverse therapeutic behaviors of different semisolid dosage forms.

Hence, permeation kinetic should be monitored carefully to predict the therapeutic efficacy of customized TDDDs.

To understand the concept behind the release kinetics and structuring the method of data analysis and interpretation, integration of drug delivery science and mathematical functions is performed to yield equations that can accurately predict the release kinetic and ultimately the therapeutic efficacy. Zero-order, first-order, Higuchi, Hixson-Crowell, Peppas, and Korsmeyer-Peppas [Figure 5 and Table 2] equations are being employed to calculate the release kinetic of drug permeated from topical dermal dosage forms.[29]

Considering the mathematical release kinetic equations, we noticed that zero-order release kinetic is superior to first order, Higuchi, Hixson-Crowell cube root law, and Korsmeyer-and Peppas model with regard to the continuous release of the drug at its action site. Further, subtypes of semisolid dosage forms such as ointment, cream, gel, and lotions could not be investigated under identical release kinetic equations due to distinct pharmaceutical features.[37] The zero-order release kinetic looks like a constant release of the drug over the entire time period. Zero-order release

Table 2: Mathematical models to assess skin permeation and experimentation requirements

Mathematical model	Theory	Equation	Equation terms	Description	Reference
Zero-order kinetic model	Concentration is independent of time	$C_t = C_0 + kt$	C_t: Concentration at time t C_0: Initial concentration k: Rate constant	Drug level at the site of action remains constant throughout the period of drug delivery once administered	[30-32]
First-order kinetic model	Rate of change of drug concentration depends on the concentration gradient	$dc/dt = k(C_0 - C_t)$	dc/dt: Rate of change of drug C_t: Concentration at time t C_0: Initial concentration k: Rate constant	Drug release is predicted to be the consequence of dissolution of active ingredient followed by diffusion of the molecules through semi-permeable membrane. Where dissolution is given by Noyes and Whitney equation	[33-36]
Hixson-Crowell cube root law	This law is considered for the systems that do not remain constant in terms of diameter and surface area of the particles throughout the release period	$Q_0^{1/3} - Q_t^{1/3} = kt$	Q_t: Amount released at time t Q_0: Total amount of drug k: Rate constant	Systems that have suspended particles such as suspension/lotions or even ointments display this kind of release pattern. Moreover, to derive an equation for a system containing uniformly sized particles is possible using Hixson-Crowell cube root law	[33, 37]
Higuchi model	The dimension regarding thickness is mathematically considered to be negligible	$Q_t = kt^{1/2}$	Q_t: Amount released at time t k: Rate constant	Topical dermal dosage form upon application onto the skin forms a film, where the surface is much larger in comparison to its thickness and calculation of drug release was carried out on the basis of one-dimension with the consideration that the film or ointment base has no ability to swell or dissolve in the dissolution medium	[33, 38]
Korsmeyer-Peppas Model	Drug release from polymetric system	$M_t/M_\infty = kt^n$	M_t/M_∞: Fraction of drug released at time t k: Rate constant n: Release or diffusion exponent	Zero-order release for $n = 0.89$, the release is best elucidated by Fickian diffusion for $n = 0.45$, the release is through anomalous diffusion or non-Fickian diffusion (cylindrical and swellable matrix) for $0.45 < n < 0.89$	[39]

is modified into a first-order kinetic model. In order to surmount various physicochemical, biopharmaceutical, and physiological barriers, there is a need to modulate the release kinetic of therapeutic entity from semisolid dosage form for continuous supply at the target site.
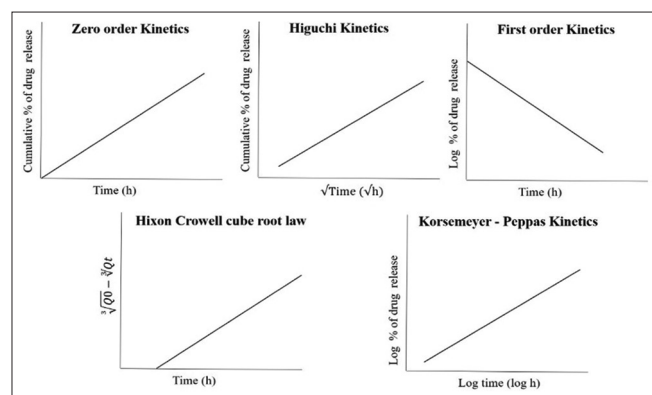
MEASUREMENT OF DRUG PERMEATION AND RETENTION FROM TOPICAL DERMAL DOSAGE FORMS USING COMPUTATIONAL TECHNIQUES

Prediction of permeability using *in silico* docking techniques

Developing and assessing TDDDS entails the investment of time and money, thus, it is crucial to reinstate a few parameters, namely skin permeability of various topical therapeutic modalities, which are empirical such as porous pathway theories,[40] quantitative structure permeability relationships,[41] and setting up of rigorous structure-based models.[42] Decoding of stratum corneum structure allowed the development of a fitting virtual model[43] to precisely imitate its barrier properties. Therefore, a variety of computational techniques and their findings regarding drug permeation is summarized in Table 3 and illustrated in Figure 6, respectively.

In vitro permeation analysis using artificial neural network

Artificial neural network (ANN)[58] was developed to forecast the release kinetic profile of drug in TDDDS. Polymer concentration, time, and carrageenan amount were the permeation governing factors and consequently cumulative amount of drug released and cumulative permeation of drug per unit surface area with respect to time were determined. Data were compared with Franz diffusion cells (FDC) mounted with excised rat skin. ANN accurately predicted the release kinetic profile of diclofenac sodium with variation in the range of 0.00–3.65 for cumulative drug release and 0.00–0.08 for the cumulative drug permeation. Moreover, ANN simultaneously demonstrated that release and diffusion mechanisms are influenced by the formulation parameters.[58] In another experiment, a predicting model for skin permeability represented as log Kp was established. A comparative evaluation was carried out between prediction and experimental results to obtain the relationship between Abraham descriptors and log Kp. Multiple linear regression model was computed that demonstrated $n = 215$ with determination coefficient and $R^2 = 0.699$. In addition, the mean square error (MSE) was 0.243 along with F value of 493.556. Further, ANN model calculated $n = 215$ with MSE = 0.136 and $R^2 = 0.832$ in addition to $F = 1050.653$. Comparative analysis suggested that ANN model displays a nonlinear relationship between Abraham descriptors and log Kp. Henceforth, Abraham descriptors are possibly employed to envisage skin permeability, but ANN model is profitable as it tenders advanced skin permeability calculations.[59]

UTILIZATION AND INTEGRATION OF CHITOSAN BIOMACROMOLECULE FOR MODULATING PERMEATION KINETIC FROM TOPICAL DRUG DELIVERY SYSTEMS

Hydrophilic drugs prefer intracellular pathway to permeate drug molecules through water-filled openings. Transappendageal pathway refers to permeation of drug through the hair follicles [Figure 7]. Sebaceous gland and sweat ducts constitute a thrust pathway for infiltration of drug to bypass the stratum corneum. Superior density of hair follicles over the skin makes them a chief donor in this pathway [Figure 7].[60]

Biomaterials play a key role in tailoring the drug delivery vehicles for pharmaceuticals. Biodegradable and biocompatible polymers may be securely applied to the skin and are normally cost-effective. Biomaterials of natural
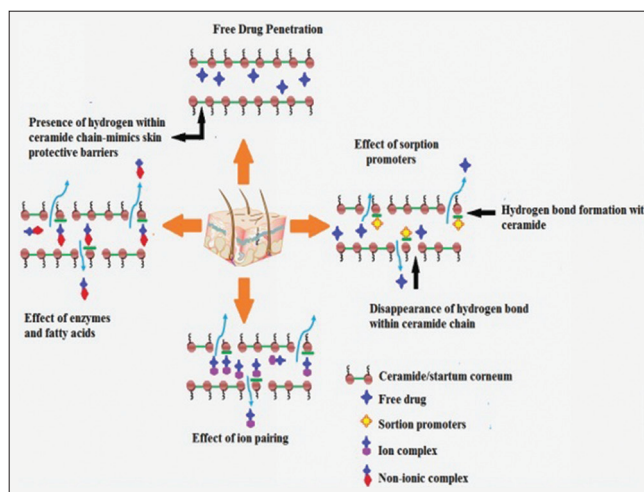

Figure 5: Release kinetic equations zero-order, Higuchi, first-order, Hixson-Crowell cube root law, and Korsmeyer-Peppas are generally employed to calculate skin permeation kinetics

Figure 6: *In silico* analysis of chemical permeation enhancers with skin lipids for optimizing the permeation efficiency

## Table 3: Computation techniques and their findings regarding drug permeation

Techniques	Description	Reference
Computational model for passive permeability profile	Recently, advancements have been made in permeability studies using *in silico* models to calculate the skin permeability based on machine learning algorithms and matrices comprising data of permeability and physicochemical chattels of permeation enhancers. Drug permeability was computed for a variety of therapeutic entities across the lipid bilayer by employing a molecular dynamic computational model. Support vector regression and random forest libraries were formulated to forecast the influence of solvent on skin permeability by testing 421 different drug samples and 31 solvents. These findings elucidated the mechanism of unwinding of intermediate filament organization in response to external stimuli	[44-47]
Establishment of correlation between hydrogen bond formation and skin permeability	Effect of functional groups present in drug structure or permeation enhancer on skin permeation. For example, terpenes as permeation enhancers were investigated by changing the polar functional groups and studies were put forth to analyze their effect on permeation of zidovudine. The variation in heat of formation in hydrogen bonds was correlated accurately with synchronizing increment in permeation intensity. Zidovudine permeation across the rat skin was suggested as intercellular permeability due to its high activation energy (21.4 kcal/mol) and this was well correlated with function of electrical conductivity of human epidermis owing to hydrogen bond formation. In another study to predict methanol effect on the permeability and structural integrity of both single component and ternary mixed bilayers, thus, menthol in high concentration fluidizes the lipids of stratum corneum and enhances the permeability	[48-51]
Effect of complexation on permeability of therapeutic entities	Docking calculations were executed with the program AutoDock 4.2. To comprehend the dissimilarity of ion pairs in diffusion potential. Report indicated that an ion-pair structure of zaltoprofen was formed with all amines and their respective heat of formation was estimated in addition to the nature of charge and resonance assistance. It was noticed that consequent hydrogen bond was superior over exemplary hydrogen bonds and coulombic attraction also contributed to ion-pair stability. These ion pairs experimentally proved to promote the skin permeation of zaltoprofen. It is inferred that stronger affinity of ion pairs to ceramide consequently reduced the energy level and increased the interaction. The affinity of topical drug molecules to keratinase and interaction of the complexes with the skin tissue was evaluated using *in vitro* permeation models and results were correlated with the calculations previously done for hydrogen bond interactions between drug molecule and keratinase. It was concluded that complex formation stabilizes the molecule by reducing its energy, resulting in decline in permeation of drug across skin layers. However, those with less interaction and high energy resulted in amplified permeation across the skin layers	[52-56]
Distinguishing between permeation enhancer and retardant	Molecular docking of penetration enhancers and ceramide molecules aids in predicting skin permeation of drug molecules. Penetration enhancers were brought in propinquity to the molecules of ceramide to calculate the probability of hydrogen bond formation. The maximum distance of not more than 3.5Å was kept to allow the formation of hydrogen bond between donor and acceptor. In this way, enhancers and retardants were defined based on the interactions engrossed between the synthetic molecule and ceramide	[57]

origin (guar gum, *Aloe vera* gel, acacia gum, beeswax, wool fat, chitosan, alginic acid, pectin, phospholipid, cholesterol, etc.),[61] synthetic (polycaprolactone, poly-lactide-co-glycolide, polyvinylpyrrolidone, polyethylene glycol, etc.),[62] and semi-synthetic origin (thiolated chitosan, methyl cellulose, and hydroxypropyl methylcellulose)[63] are being used for customizing TDDDS for modulating release kinetic of therapeutic entities. However, none of them is individually effective to promote the permeation of drug in skin layers. Hence, two or more biomaterials are usually integrated.

Colloidal drug delivery systems (CDDSs) are continuously exploring for TDDDS. Further, CDDSs containing therapeutic modalities subsist in the colloidal shape and consist of small particles in the range of 10–400 nm. CDDSs can be subcategorized into vesicular drug delivery systems [Figure 7] and particulate drug delivery systems [Figure 7] and both can be customized with natural biomacromolecules. Molecular docking study predicted that neutral hydrophobic nanoparticles (2–5 nm) disrupted the lipid bilayer, and within ~ 200 ns, it penetrated into it, whereas the charged nanoparticles adsorbed on the bilayer head group. For neutral hydrophobic nanoparticles, the permeation barrier at the head group of the bilayer was very small which was revealed by the free energy calculation. For charged nanoparticles, minimum free energy was noticed. Permeation of neutral nanoparticles with 2-nm size was maximum and it was minimum for cationic nanoparticles of 3 nm size.[64]

Chitosan or deacetylated chitin, a linear polysaccharide composed of β-(1--4)-linked D-glucosamine and N-acetyl-D-glucosamine, was already approved by the Food and Drug Administration for external applications.[65] The permeability augmenting effects of chitosan and its derivatives have been studied in recent years [Table 4] which
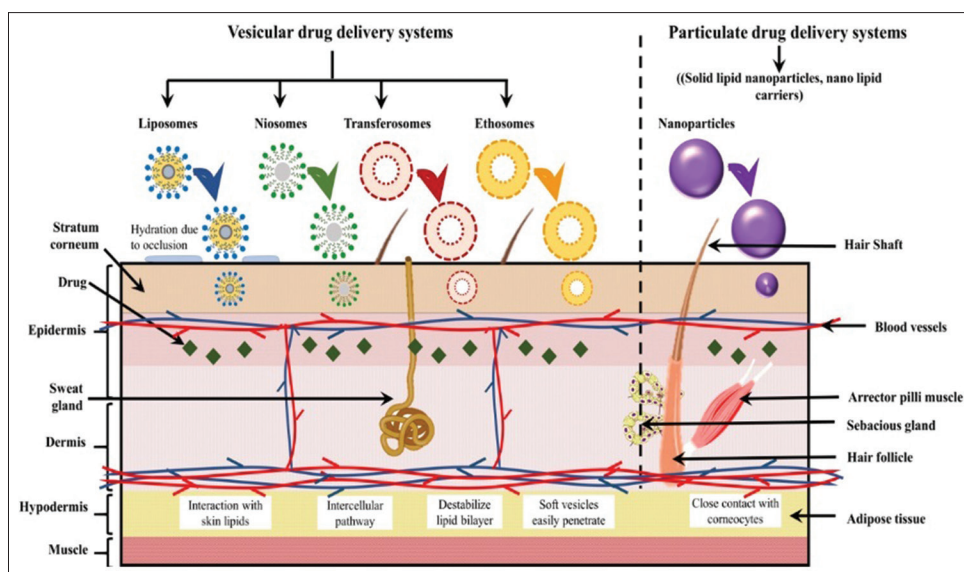
Figure 7: Mechanisms of penetration of vesicular drug delivery systems and particulate drug delivery system

extensively offered desirable Higuchi type release pattern from TDDDS by both bioadhesion and a transient opening phenomena of the tight junction in the cell membrane.

Positive charge on chitosan interacts with negatively charged tight junction of the dermal cells and opens the pores.[77] Moreover, chitosan expands the lipid monolayers such as fatty acids for instance unsaturated (oleic, linoleic, and R-linolenic acid) and saturated (stearic) acids and cholesterol at pH 4 upon reaching the saturated concentration. The order of expansion was linoleic acid > R-linolenic acid > cholesterol > stearic acid > oleic acid. As a consequence, the solid monolayers of cholesterol and stearic acid were loosened while liquid unsaturated acids were tightened. Hence, chitosan improves permeation through both hydrophobic and electrostatic lipid–chitosan interactions through hydrogen bond formation.[78] In another study, magnetic-adsorbent containing doped spinel ferrite (15%) was encapsulated in glutaraldehyde-cross-linked chitosan matrix. Adsorbent was used to get rid of acid orange 7 dye from aqueous solution. The mean free energy was calculated using Dubinin–Radushkevich isotherm that was in the range of 14.37–16.59 kJ/mol signifying the process of ion exchange. This phenomenon was further elucidated using ANN to compute the factors affecting the adsorption process. Pairing ANN and genetic algorithm presents the most favorable conditions for adsorption and removed 98.01% dye at pH 2.5 with sorbent dosage of 3.88 g/L.[79] Similarly, lysostaphin having positive potential due to Zn_2+ ion interacted with chitosan polymeric gel with a positive binding energy of 10.1 kcal/mol suggested its weak binding affinity. Chitosan gel formed hydrogen bond with amino acid residues; ASN 372, GLY 309, GLY 310, HIS 362, and THR 357 located at the lysostaphin active site.[80] MD simulations were also executed to acquire information regarding the effect of protonation state and degree of N-acetylation on chitosan molecular conformation and its capability to interact with xanthan gum. A considerable restriction in free rotation around the glycosidic bond was observed in protonated chitosan dimers independent to its degree of acetylation. Majorly electrostatic forces contribute toward the formation of complex between chitosan and xanthan gum. The most stable complex was produced when chitosan was at least half-protonated and the degree of N-acetylation was ≤50%. These calculations could be employed to fabricate the chitosan-based controlled release systems. [81] Therefore, several factors such as particle size, surface charge, bioadhesion, hydrogen bond formation, and degree of N-acetylation influence the release and permeation mechanism of drugs encapsulated in chitosan-based TDDDS.

CONCLUSIONS

Dermatological illness is a massive domain that comprises diseases ranging from cuts, burns, and rashes to severe conditions such as psoriasis and impetigo along with oncological conditions such as basal cell carcinoma and melanoma. Drug release and permeation from a TDDDS depends on its physicochemical properties, skin condition, and carrier or dosage form design. Skin permeation kinetics can be evaluated using various methods among which FDC is most widely used. Mathematical models such as zero-order, first-order, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas are used to calculate the drug release kinetics. Moreover, *in silico* docking, molecular modeling, and ANN for predicting skin permeation kinetics are also being used nowadays. Along these lines, key factors affecting release kinetic and permeation of a drug may be identified, assessed, and integrated with chitosan-based TDDDS for augmenting drug delivery to skin disorders.

Table 4: Chitosan-based delivery cargo assisted topical dermal drug delivery for skin disorders

Delivery carrier (nano/micro)	Drug and physicochemical properties	Particle size and zeta-potential	Release kinetic order	Reference
Chitosan nanoparticles	Betamethasone valerate, hydrophilic, Log P~1.138, M.W~476.6 Da	<250±28 nm and+58±8 mV	First order	[66]
Hyaluronic acid-coated chitosan nanoparticles	Betamethasone valerate, hydrophilic, Log P~1.138, M.W~476.6 Da	<300±28 nm and+58±8 mV	Fickian diffusion-types mechanism	[67]
Hydrogel-thickened nanoemulsion	8-methoxypsoralen, hydrophobic, Log P~1.98, M.W~216.9 Da	50-100 nm	Higuchi	[68]
Chitosan-coated Lipid nanoparticles	Clobetasol propionate, hydrophobic, Log P~4.18, M.W~467 Da	257.5±19.9 nm	Higuchi	[69]
Chitosan nanogel	5-fluorouracil, hydrophilic, Log P~-0.85, M.W-130.077 Da	100-180 nm and+43.15 mV	Higuchi	[70]
Chitosan-coated Lipid nanoparticles	Simvastatin, hydrophobic, Log P~4.46, M.W~418.566	108±1 nm and 17.0±0.6 mV	Fickian diffusion-type mechanism	[71]
Chitosan hydrogel	6-phosphogluconic trisodium salt, hydrophilic drug, Log P~ -3.83, M.W~342.08 g/mol	-	First order	[72]
Chitosan gel amalgamated with niosomes	Moxifloxacin hydrochloride, hydrophilic, Log P~0.6, MW~401.431 Da	285.8±5.2 nm and−19-−28 mV	Higuchi and Ritger-Peppas	[73]
Chitosan gel	Croconazole hydrochloride, hydrophilic, M.W~347.2 Da	_	Higuchi	[74]
Chitosan-cellulose hydrogel with ZnO nanoparticles	Quercetin, hydrophobic, Log P~1.82, M.W~302.236 Da	60 nm	Korsmeyer-Peppas	[75]
Thiolated chitosan film	Methotrexate sodium, hydrophilic, Log P~ -0.5, M.W~454.44 Da	_	Korsmeyer-Peppas	[76]

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