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

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
namely superficial, deep, and systemic infections based on depth of affected area. Causative agents for superficial infections include molds, yeasts, dermatophytes, and nondermatophytes.\cite{3} Correspondingly, viral infection such as genital warts followed by chronic infection is caused by human papillomavirus that is intricate to treat.\cite{4} Allergic skin infections such as atopic dermatitis, contact dermatitis, and pruritus have also been reported.\cite{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.\cite{6} Topical formulation (ointments, gels, creams, lotions, solutions, suspensions, and shampoos) delivers drugs conveniently to the affected area.\cite{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 transdermal water and facilitates drug transport by hydrating skin layers.\cite{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.\cite{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
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. For drugs
administered topically, the concentration gradient depends on the difference observed between concentration of drug in the vehicle ($C_v$) and layer of skin (Eq. 1).

\[ J = K_p C_v \]  

(1)

Subsequently, the proportionality constant relating flux can be correlated as the permeability coefficient ($K_p$). Physicochemical properties of drugs, barriers, and interaction between drug and skin lipids affect the permeability coefficient. In other terms, partition coefficient ($K_{ow}$), 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).\(^{[26]}\)

$$J = \frac{D K_m C_v}{L}$$

(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 acquire 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.\(^{[31]}\)

The zero-order release kinetic looks like a constant release of the drug over the entire time period. Zero-order release

| Mathematical model | Theory | Equation | Equation terms | Description | Reference |
|--------------------|--------|----------|----------------|-------------|-----------|
| Zero-order kinetic model | Concentration is independent of time | $C_t = C_0 + k t$ | $C_t$: 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 | $\frac{dC}{dt} = k(C_0 - C_t)$ | $\frac{dC}{dt}$: 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 | $Q_{1/3}^{1/3} - Q_{1/3}^{1/3} = k t$ | $Q_t$: Amount released at time $t$, $k$: 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 | $Q_t = k t^{1/2}$ | $Q_t$: 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 polymeric system | $M_t/M_\infty = k^{n}$ | $M_t/M_\infty$: 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 $K_p$ was established. A comparative evaluation was carried out between prediction and experimental results to obtain the relationship between Abraham descriptors and log $K_p$. 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 $K_p$. 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
Colloidal drug delivery systems (CDDSs) are continuously exploring for TDDDS. Further, CDDSs containing therapeutic modalities 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.

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. The permeability augmenting effects of chitosan and its derivatives have been studied in recent years [Table 4] which...
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, hydrophilic, Log P = −4.46, M.W = 418.566 Da | 108 ± 1 nm and 17.0 ± 0.6 mV | Fickian diffusion-type mechanism | [71] |
| Chitosan hydrogel | 6-phosphogluconic triosidic 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, M.W = 401.431 Da | 285.8 ± 5.2 nm and −19 to −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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