ActiVLayr Working Mechanism

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ActiVLayr, is the marine collagen nanofibre matrix, incorporated with bioactives designed to offer a natural, quick and efficient method of delivering actives directly deep into the skin. The technology that proves to instantly deliver bio-actives within 1 min to 1.5 mm deep uses active chemical and bio-chemical strategy to permeate the skin layer to diffuse the carried bioactives/drugs for effective delivery.

1 Background

In the skin chemistry a general perception about the molecule diffusion theory is: A high molecular weight compound does not permeate through the skin; so when such molecules administrated to the skin, it remains on the skin surface and functions as a moisturizer. This is the widely accepted theory as the molecule's diffusing capacity through the skin barrier is superficially related to its molecular weight, especially for protein and polysaccharides bioactives such as collagen and hyaluronic acid (HA). The concept is quickly adopted by cosmetic, or drug formulators mainly because the low-molecular-weight alternatives for collagen and HA has the size to its advantage and seen as accessible and low-cost. Although the "diffusion theory" is true for some molecules, e.g., macromolecules and globularmolecules that have low solubility parameters and branched structures, it is not universally pertinent. Moreover, it is now evident that the diffusion of a molecule through the skin is correlated to given molecular features of the compound than the compound's molecular weight [1]. To truly understand and design an active molecule to deliver it through the skin, it is highly essential to gain knowledge on the (a) structure of the skin barrier (figure 1) and the (b) permeating capacity of any active molecules through the skin barrier.

The skin's extraordinary barrier properties are due in large part to the stratum corneum, which is a structurally organized composite material made of proteins and lipids. The stratum corneum comprised of corneocytes limits the transdermal delivery of drugs through the layers. However, the existence of pores extracellular matrix (ECM), not only adds complexity to the extracellular pathway but also provides additional opportunities for novel drug delivery strategies. This particular pathway advocates a meandering, polar pathway for water transport through lamellar boundaries with the lipid bilayers. Furthermore, the theory advocates the lacunar domains embedded within this lipid bilayers undergoes swelling and creates "pore pathway" upon occlusion or prolonged hydration.

As aforementioned, understanding the permeating behavior of a compound is equally essential to understanding the structure of skin barriers and different routes of drug penetrations. Generally, the permeating behavior of a molecule and a compound is not universal and differs with the molecule's features like size, shape dimensions, and topography.

$$J = KpCv \tag{1}$$

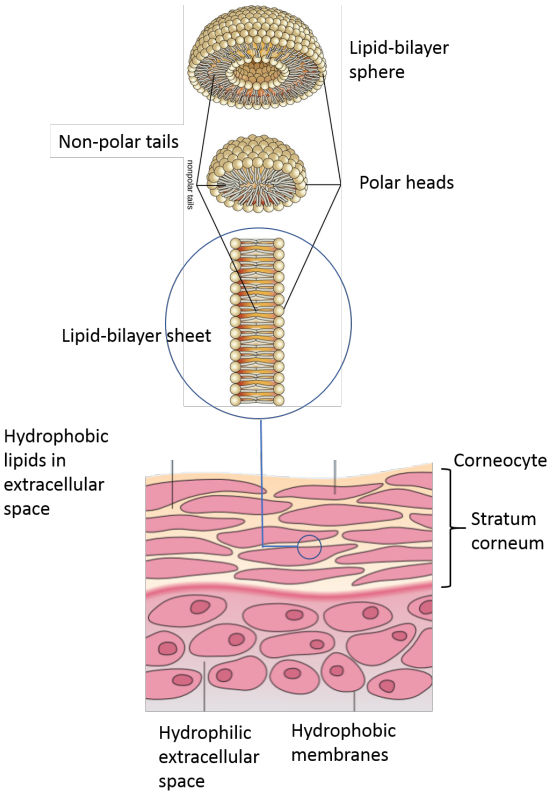

Figure 1: *The structure of Stratum Corneaum*

$$J = Cv\left[\frac{DKm}{L}\right] \tag{2}$$

Other than the molecular features of a compound, the permeability of an active compound is governed by four additional factors, (a) permeability coefficient K_{p} of both the compound and the barrier. The K_{p} is proportionately related to the concentration of the compound in the vehicle C_{v}, (b) partition coefficient K_{m}, (c) diffusion coefficient D, and inversely related to the length of the diffusion pathway L [2]. According to Fick's law, the rate of absorption or flux (j) of any substance across a barrier is proportional to its concentration difference across that barrier [3]. For topically applied formulas, the percutaneous molecule absorption can be explained by following equation 2 .

Extensive pharmaceutical research has shown that the delivery vehicle is a vital link between an active/drug potency and therapeutic effectiveness and can profoundly influence the rate and extent of absorption and its bioavailability [4]. On a nutshell, with a perfect strategy and appropriate knowledge on skin chemistry, the transdermal delivery of molecules can be enhanced, and the permeation of drugs can be regulated using a delivery vehicle.

1.1 Permeation Strategy

Lately, significant efforts have been expended on developing new strategies to enhance transdermal drug delivery through chemical, biochemical, and physical approaches [5]. Quite often, the **physical approach** is invasive and involves mechanically disrupting the lamellar bi-layers of the epidermal region, which on sensitive skins can leave scars and bruises: example, ion-electrophoresis (iontophoresis), micro needling, injections, and light therapies.

The **chemical approach** involves chemical enhancers being employed to increase the permeability of compounds that can already cross the skin reasonably well, but unable to reach deeper the skin layers due to macromolecular structures. The most common chemical enhancer is water with high permeability constant 5.5 x 10-6 cm/hr. Water prefers "pore pathway" through occlusion or hydration. In brief, hydrating skin with water leads to swelling of corneocytes and distention of intercellular space leading to dilation of the lacunar network. This distention of lacunae creates "pores" in the stratum corneum interstices through which polar and non-polar substances pass through readily [6](the lacunar "pore pathway" model shown in figure 2). Solvents like water can affect the partition coefficient (K_{m}) positively, i.e., create effective partitioning into the skin and thereby increase the rate of diffusion (D).

The **biochemical approach** involves increasing the permeability of the stratum corneum lipid matrix by swelling as well as by affecting the lipid metabolism [7, 8]. These approaches are easily applicable to any topical formulations where drugs/bioactives carried in cream, gel, or solution form. Factors such as molecular weight and molecular branching affect the effective partitioning into the living layers of the epidermis or diffusion into the skin in the conventional cream form. In most cases, the diffusion behavior of a molecule is taken into account when formulating a drug carrier and therefore, low molecular weight molecules are preferred. However, for carriers with unconventional molecular features, the dimensions, the charge, and the kinetics of diffusion behavior of the molecule becomes important, more than its molecular weight.

Researchers are bringing a new dimension to the drug delivery and cosmetic technology by designing topical formula/carriers that differ from a conventional liquid form like gel, cream, and sprays to incorporate the benefits of high molecular weight compounds. One such topical formula that has been extensively researched recently is nanofibre. Nanofibre generated significant interest in the drug delivery due to its 2D solid dry form which has low bacterial risk, target delivery design, and high-shelf life. Moreover, factors such as molecular weight and molecular branching become less important in the 2D nanofibre form as the nanofiber is in the dis-entangled form of its bulk. Meaning, high molecular weight macromolecules can effectively be delivered into the stratum corneum in a nanofibre form as similar to its low molecular weight counterparts in liquid form, but deeper. Particularly, nanofibre that is highly polar, hydrophilic, and water-

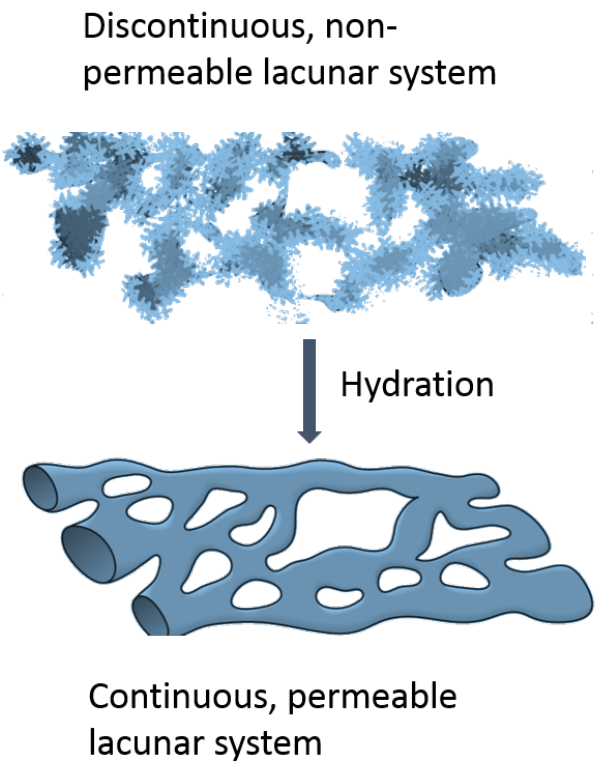

Figure 2: *Lacunae "pore pathway" model*

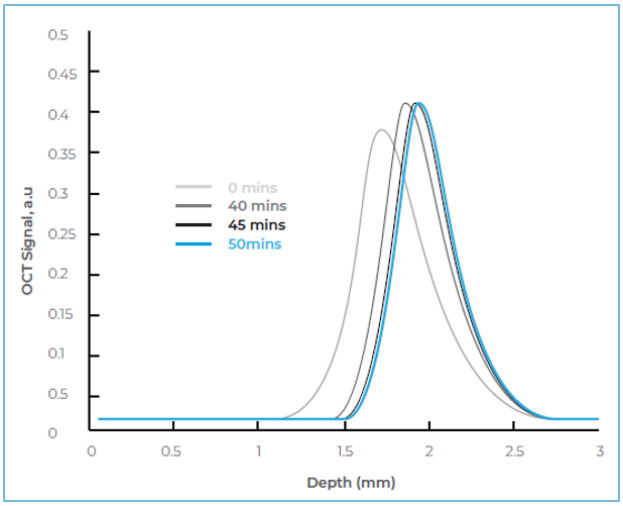

Figure 3: *Optical Coherence Tomogrpahy (OCT) signal showing the penetration of activlayr formula into the skin with time*

soluble is preferentially studied due to the rapid dissolving property, that overpowers the molecular weight factor. Such format has proven to be an intelligent delivery system for macromolecules to permeate deep into the skin layers. actiVLayr™ technology is one such intelligent, and revolutionary delivery system made of marine collagen nanofibres used for transdermal applications. The nanofibre is applied on wet skin to permeate the skin layers. This technology has taken a chemical and biochemical approach as an effective strategy to enhance the transdermal delivery of actives, along with its favorable kinetics characteristics.

2 actiVLayr™ technology

actiVLayr™ is composed of nanofibre matrix made of marine collagen sourced from New Zealand Hoki fish (Macruronus novaezelandiae),Hylauronic acid (HA) and bioactives or drugs of choice. For skin applications, the nanofibre is applied on wet skin to permeate the skin layers. This technology has taken a chemical and biochemical approach as an effective strategy to enhance the transdermal delivery of actives, along with its favorable kinetics characteristics. The chemical enhancer here is the water that dissolves the actiVLayr™ nanofibre before penetrating the stratum corneum. That is, due to the high polarity and solubility of the marine collagen nanofibre, the difference between the kinetics of nanofibre dissolution (K_n) in water (related to intermolecular forces), and the kinetics water permeability (K_m) (related to partition coefficient K_p) through the skin becomes negligible. Conversely, in case of bulk macromolecules, the intermolecular forces will overseed the kinetics of water permeability. Therefore, during the application, the water would permeate the skin before the bulk macromolecule could dissolve in the water. i.e., K_n would be less than K_m leading to inefficient delivery. Whereas in actiVLayr™ as aforementioned the $K_n > K_m$ or $K_n = K_m$, and the nanofibre dissolves in water before the water permeates the skin. Consequently, the liquid that enters the skin layer is dissolved nanofibre. Besides, the low concentration of nanofibre dissolved in water does not change the concentration of the molecule in the vehicle (water) C_v or density of the vehicle drastically. Therefore the nanofibre dissolved water becomes the vehicle itself. This newly constructed vehicle's steady-state diffusion can be explained through Fick's law (see equation 3), where j, is the diffusion flux or the mass transported per unit time per unit area. The actiVLayr™ technology due to its rapid dissolving property with diffusion flux (j) similar to water, takes a chemical approach to permeate the skin through the dilation of the lacunar system (see Figure 2).

The rapid permeation of the vehicle takes an active delivery route before the lacunar system relaxes back to its original discontinuous filaments. The actiVLayr™ formula also contains HA for prolonged hydration process which is required for effective lacunae dilation. This strategy has proven to produce superior results in permeating deep inside the skin layers within a min (up to 1.5 mm dermal layer) and continuous penetration up to 2 mm dermal layer in 50 min through optical coherence tomography (OCT)(see Figure 3) and proven to be effective on all types of skins [9].

In addition, the collagen proteins present in the backbone of the nanofibre involves in biochemical alteration

of the extracellular matrix (ECM) due to natural affinity to the collagen molecules making the ECM, this to an extent can enhance the permeation of active molecules.

3 References

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