

# SPECIAL DELIVERY

## ELLIOT ISAACS ON THE TECHNOLOGY OF COSMECEUTICAL DELIVERY SYSTEMS

As the Medik8 adage goes, "there is no point having a magic bullet, if there's no gun to fire it". Both standard actives and the latest expensive peptide ingredients are only as good as the delivery system used to introduce them to the deeper skin layers. More often than not, these hi-tech substrates merely sit on the epithelial surface with only a fraction reaching the target area in the lower epidermal, dermal and hypodermal layers.

As with pharmaceuticals, the two pillars of good cosmeceutical design are preparation and bioavailability – that is the efficacy of the active itself – and the amount delivered to the target areas.

Research into transcutaneous administration (transport across the skin) is led by drug companies seeking to develop techniques to circumvent the negatives of other administration methods such as the oral and intravenous routes. However, some cosmeceutical companies are now harnessing these technology spin-offs for anti-ageing skincare. When evaluating a product, have this schematic equation in mind:

**(quality ingredients x high percentages) + efficient delivery = cosmeceutical results**

A pharmacologist is tasked not just with designing novel ingredient structures but also with ensuring their bioavailability or delivery across the skin to the target areas. This is why pharmacological development of medical skin products is essential to ensure that the latest peptide and traditional antioxidant actives are transported to the site of action.

Physiologists are experts in normal human function and therefore understand how the skin is mechanically structured and how that structure changes with age. Close collaboration between physiology and pharmacology experts ensures the delivery of actives to the target areas.

### BACKGROUND ON THE STRATUM CORNEUM

The stratum corneum (the horny layer) is the outermost layer of the epidermis. The primary function of the stratum corneum is to retard evaporative water loss from the aqueous interior.

The stratum corneum also protects against mechanical insults and the ingress of foreign chemicals and micro-organisms. It provides the first defence against ultraviolet light, screening out

more than 80% of incident ultraviolet B irradiation. It is composed mainly of dead cells that lack nuclei. As these dead cells slough off, new cells from the stratum germinativum (basal layer) continuously replace them in a 28-30 day cycle, replacing the entire epidermis. In the human forearm, for example, about 1,300 cells/cm<sup>2</sup>/hr are shed and commonly accumulate as house dust. Cells of the stratum corneum contain keratin, a protein that helps keep the skin hydrated by preventing water evaporation.

The thickness of the stratum corneum varies according to the amount of protection and/or grip required by a region of the body. For example, the hands are typically used to grasp objects, requiring the palms to be covered with a thick stratum corneum. Similarly, the sole of the foot is prone to injury, and so it is protected with a thick stratum corneum layer. In general, the stratum corneum contains 15 to 20 layers of dead cells. Although the average layer thickness is just about 0.01mm it is very resistant to the intrusion of foreign substances, cosmetics and pharmaceutical active substances. Therefore it also is called the epidermal barrier. The challenge to serious skincare providers is to provide the best ingredients in an application that can traverse this barrier.

### THE SKIN AS A BARRIER

Looking at a schematic diagram of the skin's surface, it is helpful to distinguish between three main routes of primary penetration: the sweat pore, regular skin surface and the hair shaft (Fig 1).

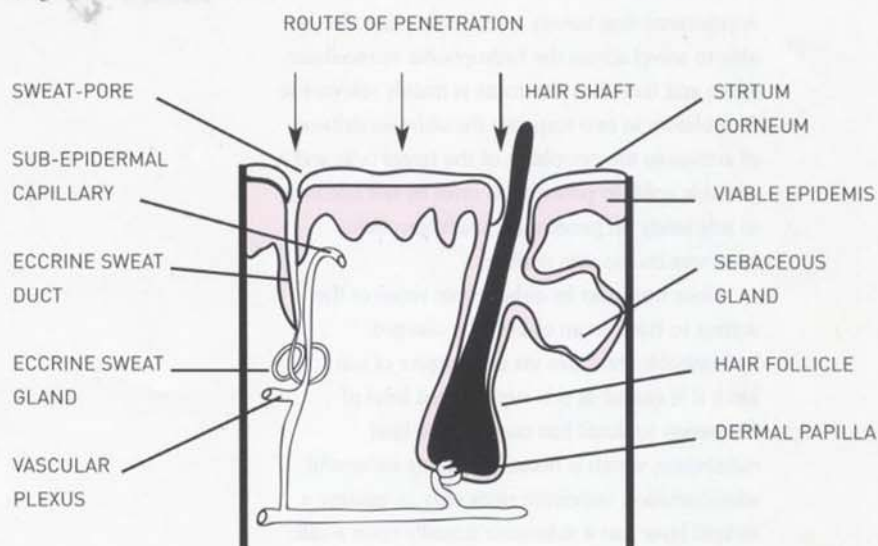
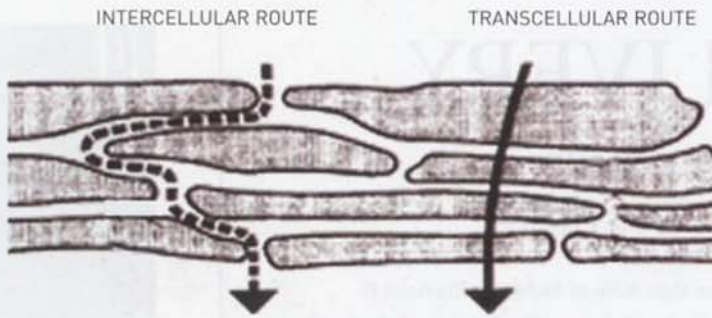


FIGURE 1



### Elliot Isaacs

graduated from Leeds University in physiology and pharmacology. He is now CEO and medical director of dermaceutical specialists Pangaea Laboratories, creators of the Medik8 range. From pharmaceutical stock, he grew up around empirical evidence and wanted to emulate that value system in skincare along with other leaders in the field. He pioneered the cocktail-theory approach to cosmeceutical skincare taking his lead from pharmaceutical prescribing. As such, he insists that each Medik8 product contains multiple vector actives and up to triple clinical trial dosing



All three routes of penetration involve crossing the stratum corneum as this lines the inside walls of the sweat pore and hair shaft, just like it covers the skin surface proper. Two routes exist to cross this barrier namely the intercellular route (between the cells) or transcellular route (across the cells) (Fig 2).

FIGURE 2

The stratum corneum is composed of vertically-stacked, polyhedral corneocytes surrounded by a matrix of lipid-enriched membranes. Thus, it is a two-compartment system which can be likened to a brick wall, composed of anucleated cells (the 'bricks' with no nuclei) and intercellular lamellar membranes (the 'mortar'). The corneocytes are devoid of lipids or organelles, but are filled with structural proteins (keratin filaments) and osmotically active small molecules. The matrix between corneocytes is composed of hydrophobic lipids arranged in multiple lamellar sheets.

**THE INTERCELLULAR ROUTE**

It would seem straight-forward to traverse the stratum corneum between the cells as shown by the dotted line in Fig 2. The area between the cells however is filled with hydrophobic lipids and so any water based skincare products cannot pass thorough unless they are enclosed in a lipophylic membrane. Equally, any oil-based products that are not repelled must have the ability to penetrate the aperture dependant on size, molecular weight and electrical charge.

**THE TRANSCELLULAR ROUTE**

A substance that travels across cells must also be able to travel across the hydrophobic intracellular space and therefore this route is mainly relevant to formulators in two respects: the ultimate delivery of actives to the cytoplasm of the target cells and a possible uplift in penetration rates by not needing to rely solely on penetrating the intercellular apertures on the skin surface.

Since transport by either route requires the actives to traverse an electrically charged hydrophobic structure via an aperture of some kind; it is easiest at this summarised level of discussion to detail just crossing the lipid membrane, which is necessary in any successful administration technique since only by passing a bi-lipid layer can a substance actually enter a cell.

It is assumed that it is easier for the same substance that can pass into a cell to be able to pass between the cells.

Epithelial corneocytes, or skin cells, have a lipid bilayer membrane encircling the cell contents, called the cytoplasm. The membrane, as illustrated below, comprises two layers of identical sub-components arranged side by side. Each sub-unit has a head and two tails. The head is hydrophobic (likes oil) and the tails are hydrophilic (like water). The second layer is flipped over making a sandwich with the tails in the centre (Fig 3).

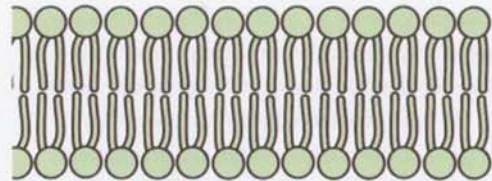


FIGURE 3

As explained above, either between cells or within the membrane itself are gaps or pores. It is through these pores that formulators attempt to pass actives. Within a cell membrane, this pore is called a protein channel. For ease of reference, both these apertures will be called 'pores' (Fig 4).

Honed over millions of years of evolution, this barrier, even with pores, is very difficult to

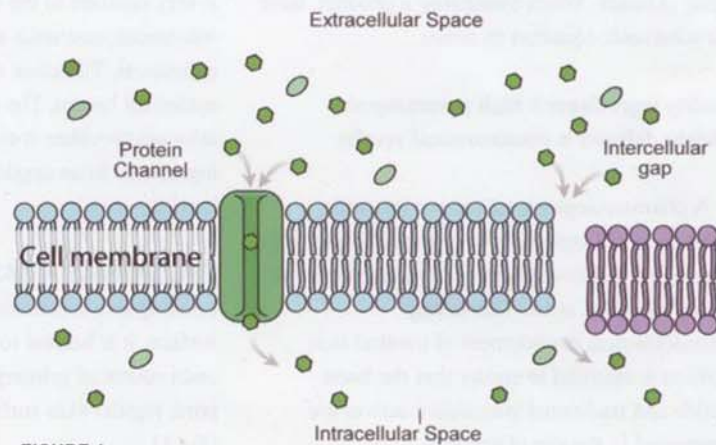


FIGURE 4

penetrate but certain physical and chemical techniques have been utilised and shown to work. Many of them are practical and relevant to the field of skincare active bioavailability – others are not. Some methods work more effectively than others and are safe to be used over the long term. Many can be used in conjunction with each other. Before looking at the methods used by formulators to improve bioavailability – it is helpful to remind yourself that the three prevalent factors are:

- (1) Pore Size (of inter/intra membranes)
- (2) Electrical Charge (of active/membrane)
- (3) Molecular Weight (of active)

“PHYSICAL PROCEDURES ALONE WILL NOT TEND TO RESULT IN DEEPER PENETRATION BUT WILL HELP SIGNIFICANTLY IN AMPLIFYING THE AMOUNT OF ACTIVE INGREDIENT TRAVERSING DEEPER INTO THE SKIN”

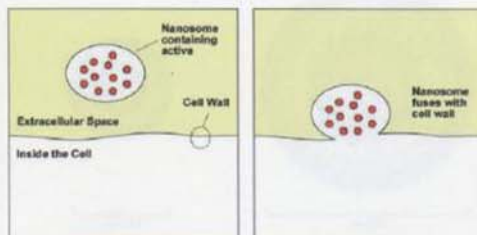


FIGURE 8

TO DELIVER MOLECULES TO SITES OF ACTION, THE VESICLE LIPID BILAYER CAN FUSE WITH THE CELL MEMBRANE BILAYER DELIVERING THE LIPOSOME CONTENTS.

miniscule particles and further, do not require traditional liposomal casings (phospholipids bilayer) and are thus much more easily absorbed.

As detailed earlier, the molecular weight (the weight of the molecule – measured in the unit of Daltons), can affect how easily it transports across a cell membrane. Molecular weight can play a role in choosing which delivery method to employ. An aqueous active will have a lower Dalton value than an oily one and formulators can use that factor to their advantage. Equally, electrical charge is a primary factor to contend with when formulating. Cell membranes carry an electrical charge which when ‘standing still’ is at  $-90\text{mV}$ . As you would expect, positively charged molecules are therefore attracted to the inside of the cell and therefore are more easily transported across the membranes. In order to make products charge compatible, different delivery systems should be used depending on the active concerned. Bilipid and monolipid vesicles have different charge levels (Fig 8).

Human skin experiences extensive alterations when exposed to a strong electric field. In high voltage electric shocks, tissues in the current path undergo large-scale changes; the stratum corneum loses its barrier function against ionic transport.

The primary mechanism of electric field

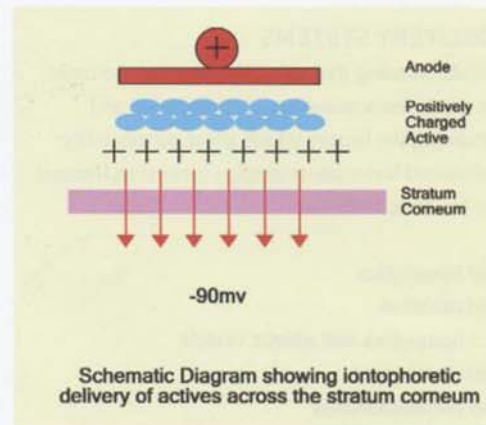



FIGURE 9

interaction with the skin is the creation of aqueous pathways, which increase the permeability of the skin to ions and macromolecules. It may seem a bit drastic to electrocute yourself to increase skin permeability however very lower voltage systems which can barely be detected by the patient have been successfully used by therapists as treatments and there is good evidence that permeability increases temporarily – long enough to introduce ingredients placed under the probe creating the electric field and in contact with the skin. Effective for professional use, it has not taken off as a home-based regime.

These electric field procedures are called iontophoresis (Fig 9) and electroporation. These and other techniques such as the use of high frequency sound waves, ultrasonics (works by creating bursts of sonic pressure) all share the same goal – to disrupt stratum corneum structure in order to create ‘holes’ big enough for molecules to pass through. Another method of physically increasing permeability sets about actually creating physical holes in the stratum corneum by the use of so-called micro-needles which pierce the stratum corneum but not the hypodermis.

No article on delivery systems can exclude the role of exfoliation which reduces the amount of barrier to pass through by sloughing off a layer of stratum corneum cells.

These physical procedures employed to increase permeability of the stratum corneum can all be used to ameliorate the effects of chemical-based penetration enhancers, that is delivery systems, as described throughout. Physical procedures alone will not tend to result in deeper penetration but will help significantly in amplifying the amount of active ingredient traversing deeper into the skin. 

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## DELIVERY SYSTEMS

Understanding that using the pores as the main route of transcutaneous administration and knowing the factors which affect permeability, advanced formulators employ various techniques to facilitate transport.

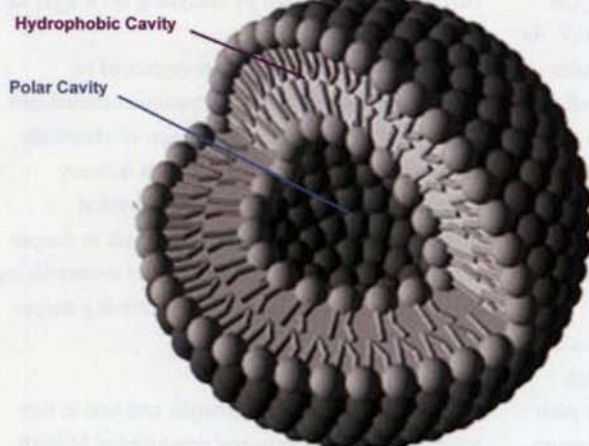
- (a) lipophylics
- (b) micelles
- (c) liposomes and elastic vesicle
- (d) nanosomes
- (e) nanoemulsions
- (f) physical pore expanders – iontophoresis etc

Lipophylics are just oil-based formulae that rely on the cohesive forces between oily substances to allow absorption. Micelles are tiny droplets of oil suspended in a water base. Using either will result in very limited absorption.

Liposomes are the technological answer to transporting water-based actives. They are often likened to a microscopic soap-bubble with active ingredients inside. Continuing the analogy, their thin and elastic surface allows the 'bubble' to deform and make an oval shape instead of its natural sphere. This is why liposomes are often called 'elastic vesicles', a vesicle being a medical term for a liposome. Pores are sized around 600nm (nanometres) in diameter. Larger liposomes can be up to 1,200nm but due to their elastic membrane, they can deform into an oval and pass through a smaller pore. Normally a liposome will be anything from 600nm upwards. *In vitro* transport studies using three model drugs (pergolide, lidocaine and rotigotine) have shown that elastic vesicles were superior to rigid vesicles, micelles and buffer controls in the enhancement of drug transport across human skin (Fig 5).

Nanosomes are merely small liposomes – they should more accurately be called nano-liposomes.

FIGURE 5

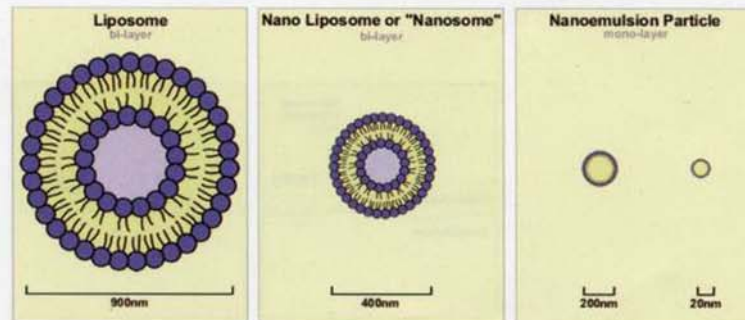


A traditional liposome is sized around 900nm diameter with flexible phospholipid walls

They are constructed in the same way and have the same properties. This means that they do not have to deform to pass through the pore aperture and they can pass more quickly. Very large peptide products simply cannot be made into nanosomes since they themselves are larger than the vesicle, which is why even the most advanced formulators still use liposomes. It is common for professional manufacturers to use the term liposome whatever the size of the vesicle, as this is the correct name for such a structure.

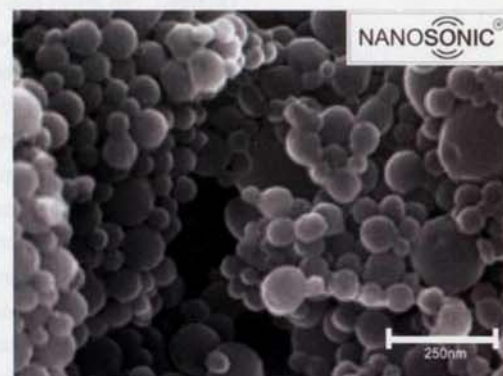
When a manufacturer talks of nanotechnology they must be referring to nanoemulsions if their

FIGURE 6



“LIPOSOMES ARE THE TECHNOLOGICAL ANSWER TO TRANSPORTING WATER-BASED ACTIVES. THEY ARE OFTEN LIKENED TO A MICROSCOPIC SOAP-BUBBLE WITH ACTIVE INGREDIENTS INSIDE”

FIGURE 7



Medix8 electronic micrographs of Nanosonic molecules which vary in size between 20nm and 200nm in size

claim is to be taken seriously. Nanoemulsions are different to liposomes (and nanosomes) – they consist of a mono-layer membrane which not only affects the vesicle elasticity but also terminal vesicle size and electrical charge. Naturally, with smaller particles, molecular weight is smaller too. The latest techniques can produce nanoemulsion particles as small as 20nm and also produce varied size particles (Fig 6-7). Nanoemulsions offer