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INHERENT PROPERTIES OF THE MEYERZALL DELIVERY SYSTEM

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1. INTRODUCTION

The essential polyunsaturated fattyacids (EFAs), Linolenic acid and Linoleic acid (excluding arachidonic acid), are inherent components of the MeyerZall delivery system and hence primary constituents in the formation of the Emzaloid™.

In the epidermis of the skin, the metabolism of EFAs is highly active. The most abundant polyunsaturated fatty acid (EFA) in humanskin is the 18-carbon-n-6 fatty acid, Linoleic acid (LA). Dietary deficiency of Linoleicacid in normal epidermis,results in a characteristic scaly skin disorder and excessiveepidermal water loss.

During active processes in the epidermis, the EFAs are transformed into (mainly) monohydroxyfattyacids, which have been shown to exhibit**anti-inflammatoryproperties** (*in vitro*). Thus the supplementation of topical actives with the appropriatepurified essential fatty acids may generate localcutaneous anti-inflammatory and anti-proliferative metabolites. Thisin turn could result in a lessening of inflammation and excessive cell division, and therefore be of use in the treatmentof inflammatory skin disorders such as psoriasis and eczema.

Because of the inability of normal skinepidermis to desaturate LA to linolenic acid, LA is transformedby the epidermal enzyme 15-lipoxygenase to mainly 13-hydroxyoctadecadienoicacid (13-HODE), which functionally exerts antiproliferative propertiesin the tissue. As hyper-proliferation is one of the major clinical symptoms, this process helps to normalise cell proliferation and reduce scaling.

2. THE CELLULAR LEVEL

LA and its metabolites play an important role in the **water barrier system** and membrane fluidity of the skin.

EFAs are crucial in the maintenance of **cell membrane fluidity** – the higher the degree of unsaturation of the EFA's in the membrane, the lower the membrane viscosity, and the higher the membrane pliability. This means that several cellular processes are influenced by the fluidity of cellular membranes, one of which is the epidermal water barrier function

A substantial body of evidenceindicates that LA is involvedin the maintenance of the epidermal water barrier [(5);] and disruptionof this barrier is one of the major abnormalities that is observed in skin diseases such as psoriasis, eczema and cutaneousEFA deficiency. LA will help reduce scaling and thinning of the skin, especially in cases where patients have been treated with corticosteroids for prolonged periods. [(6, 7,8,9, 10)]

3. THE MOLECULAR LEVEL

The role of linoleic acid on hyper-proliferation:

In vitro studies with LA and the epidermal FA enzyme15-lipoxygenase (EC 1.13.11.33), preparedfrom skin epidermis, showed that skin epidermis is uniquein that it preferentially metabolises LA to hydroxyoctadecadienoic acid (13-HODE).

Ziboh et al determined that the 13-HODE–metabolite has a selective effect on total epidermal protein kinase C (PKC) activity and the expression of two epidermal protein kinase C (PKC) isozymes, PKC-ßand PKC-α. They observed marked inhibition of totalPKC activity with substantial selectivity for inhibition ofPKC-ß but a negligible effect on PKC-α[(10).] These results suggest that the amount of LA present in the epidermis can, as precursor of the 13-HODE, modulate epidermalPKC activity and expression, which are purportedly associatedwith epidermal hyper-proliferation. It was found that in animalsdeficient in essential fatty acids (EFAs), a reduction in 13-HODEparalleledboth epidermal hyper proliferation (scaly lesions) and elevatedexpression and activities of PKC- and -ß when compared with control animals. The deficiency is reversible and resulted in the selectiveregulation of PKC-ß expression as well as suppressionof epidermal hyper-proliferation. This is part of the regulatory mechanism of cells to external stimuli and can be visualised as follows:

[LA]↑→ 13HODE→ [PKC]↓ → CELL PROLIFERATION ↓

These results suggest thatthe epidermal concentration of 13-HODE, which is normally obtained fromdietary LA, plays a role in vivo in modulation of cutaneous hyper-proliferation. They also suggest that the supplementation of a topical preparation with LA may have the same beneficial effect in the treatment of skin diseases such as psoriasis where excessive cell proliferation needs to be normalised

4. CELLULAR UPTAKE OF ESSENTIAL FATTY ACIDS

The mechanism by which fatty acids are taken up in the cell is a controversial subject. The relative importance of diffusional (passive) versus protein-mediated (active) mechanisms has yet to be determined. It is however clear that when presented at high concentrations, free fatty acids (FFAs) can diffuse across biological membranes at rates sufficient to support metabolism. However, that would not explain firstly, the very fast rate of transport of MeyerZall-formula associated drugs across the cell membrane or secondly, the high amounts of drugs delivered by MeyerZall formulations. It is suggested that the Emzaloids are transported by protein-mediated transfer i.e. an active rather than a passive process. This is one of the features that determine the fatty acid composition of the MeyerZall formulations with regard to tissue specific targeting of drugs.

Various researchers have recently identified proteins that efficiently mediate trans-bilayer movement of fatty acids. These intracellular fatty acid-binding proteins (FABPs) are members of a multigene family of more than 9 members, which bind ligands in a reversible manner.Different members of the family show unique tissue-specific expression patterns for each member of the family

Analyses of their *in vivo* function by molecular and genetic techniques reveal specific function(s) that fatty acid-binding proteins (FABP) perform with respect to fatty acid uptake, oxidation and overall metabolic homeostasis.

Proposed functions of this family include:

- Facilitating the rapid transport of fatty acids across the plasma membrane (PM)
- Transport of the fatty acids within the cell, to where the drug is to be delivered
- Facilitation of solubilisation of the fatty acids in an aqueous environment, to release the drug from the Emzaloid™
- Modulation of activity of enzymes involved in fatty acid metabolism
- Protection of enzymes and membranes from detergent-like effects of fatty acids, which means that which means that excessive cell proliferation and consequent scaling, is reduced.

5. SUMMARY

The composition of fatty acids in membranes has a significant effect on membrane fluidity and functions such as transport and signal transduction. Fatty acids are also precursors for various lipid-signalling molecules produced via the cyclo-oxygenase, lipoxygenase and epoxygenase pathways. The resultant lipid second messengers exert their effect through both cell-surface and intracellular receptors.

Essential fatty acids contained in the Emzaloid™ delivery system play a dual role in effecting their functions:

- Firstly, the fatty acids are the primary component of the delivery system Being essential fatty acids, they are natural body components, that the immune system recognises as self and therefore there are no safety implications.
- Secondly, the presence of the selected fatty acids contribute in the normalization of the physiological micro-environment, resulting in the following functional contributions to treatment:

  - ❑ Added anti-inflammatory action by the EFAs
  - ❑ Suppression of epidermal hyper-proliferation
  - ❑ Normalizing the water barrier of the skin
  - ❑ Fast and efficient delivery due to binding to the FABPs localized in the membranes of the cells.

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* Written whilst in the employ of MeyerZall Laboratories