

# Development Considerations with Maximum Effect Formulations

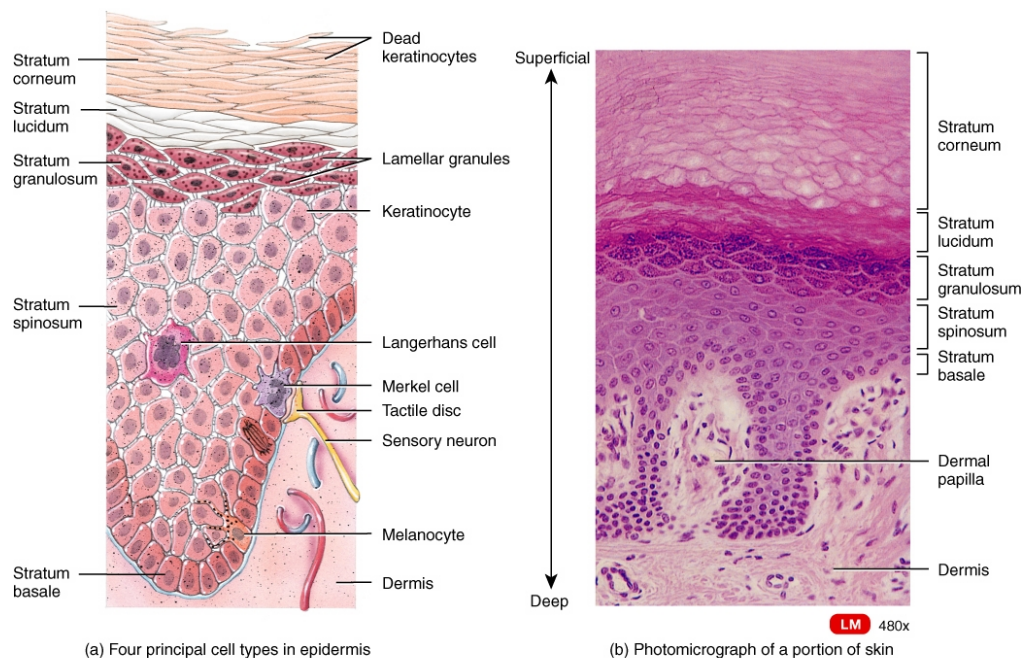
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This presentation will outline the basic problems in getting an active ingredient (or drug) to enter the skin via topical absorption through the Epidermis. I will discuss the physical problems preventing this associated with the skin's natural barrier system, the rate of absorption and how we can modify this process to enhance absorption for skin rejuvenation or reduce absorption in the case of sunscreens. The product parameters discussed will be the emulsifier, the emollients, the formulation type, the drug itself and the additives that can affect skin penetration. Particular examples used will be to explain the effects of skin lighteners.

The skin has a defined structure although the various layers may vary in thickness from area to area.

## The Epidermis



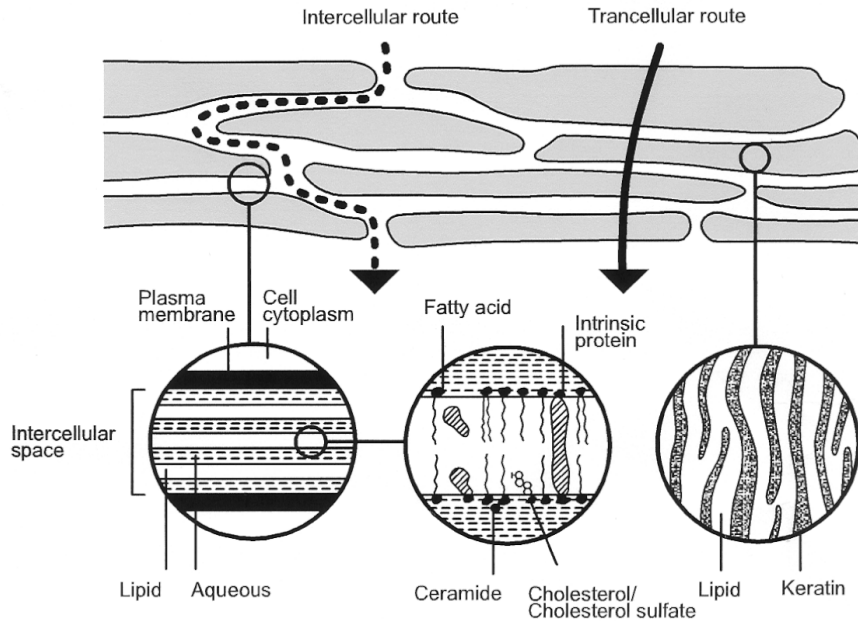
(a) Four principal cell types in epidermis

(b) Photomicrograph of a portion of skin

Is the superficial protective layer at the surface. It varies in thickness from 0.007 mm to 0.12 mm and is composed of stratified squamous epithelium. The process of Keratinisation occurs in the Epidermis where the Keratinocytes (cells that produce Keratin), are found. As new cells are formed, they move further away from the sources of nutrients (ie. blood vessels) and eventually degenerate and die. The remains are almost pure keratin which, because of the overlapping matrix layers and the fact that keratin is a hard, waterproofing protein, act as the outer physical barrier.

The Stratum corneum is the outermost layer, and consists of approximately 25 layers of dead, flat cells composed of Keratin, with protein deposits. These cells act as the primary physical protective layer and compose the layer that any drug, applied to the surface, must penetrate to have any chance of being absorbed into the body. The outermost cells are continuously lost but are also continually replaced with cells from lower layers (desquamation). It can take from 40 to 55 days from cells to move from the Stratum basale to the surface (ie. across the Epidermis) although this rate will change with age (becomes slower) or illness (eg. in eczema, psoriasis or skin cancers it becomes quicker). I had mentioned earlier that two billion cells which make up the skin are in constant renewal, three hundred million of them being replaced on a daily basis. This desquamation acts to mechanically remove pathogens and other contaminants that are trapped in the outer layer of the Epidermis, but obviously remove beneficial drugs applied to the skins surface as well.

The intercellular channels between the layers in the Stratum Corneum are composed of a lamellar structure of lipid layers (nearest the cells) and water layers between. The water layer is lined with surface active agents that have a polar nature. It is this polar nature that restricts polar chemicals (eg. water soluble vitamins, amino acids and almost all water soluble drugs) from penetrating.



The second layer of the Epidermis is the Stratum lucidum. This layer is more prominent in pressure sensitive areas such as the palms of the hand and soles of the feet. This acts as an extra barrier to physical attack from large sharp objects. The layer consists of rows of clear, flat, dead cells. They contain Eleidin, the precursor to keratin production.

The third layer is the Stratum granulosum. This layer (three or four rows of flattened cells) is where the cells begin to die and because of this have a granular appearance, hence its name. Site of formation of keratin complex and lipid synthesis - these lipids form the intracellular cement.

The fourth layer is the Stratum spinosum which contains several stratified layers of living cells, although no new cells are being produced in this layer. This is the site of active protein synthesis generating tonofibrils of keratin that migrate to the granular layer. The cells are not flat but have an irregular shape with sharp edges, giving them a spiny appearance. This layer contains Langerhans cells (nonpigmented granular dendrocytes that are associated with the internal protection of the skin) and activation of these cells is believed to improve the skins protective ability against chemical attack.

The inner (fifth) layer of the Epidermis is the Stratum basale. This is a single layer of cells consisting of keratinocytes, melanocytes and tactile cells. Basal keratinocytes divide and migrate to other layers. Melanocytes contain the pigment forming protein, Melanin, which is activated by UV light and gives the skin its ethnic coloured characteristic, a tanned appearance in lighter skin types or such non-uniform features such as freckles and sunspots. To affect skin colour this is the layer we must find a pathway to.

Sometimes scientists refer to the Stratum spinosum and Stratum basale together, referred to as the Stratum germinativum or the germative layer as here the skin cells, we see, are produced.

## The Dermis

The dermis is the connective layer of the skin (connecting the subcutaneous layer and the Epidermis) comprising collagen and elastin. Because of this the Dermis gives the skin its strength, extensibility, elasticity and "tone". It is also thick in the palms of the hand and soles of the feet while very thin in areas that require extra sensitivity (eyelids, mucous membranes and sexual areas). This is the layer that contains the hair roots, sweat glands, sebaceous glands (sebum production), nerve endings (pain and touch), Meissner's Corpuscles, Paccinian Corpuscles and other corpuscles (pressure and touch), Krause's End Bulbs (cold) and

Ruffini's Endings (warmth). Smaller blood vessels also proliferate in the Dermis. The Dermis consists of cellular, fibrous and ground substance components in two layers: Papillary dermis and reticular dermis.

## Conclusion

It is apparent that any drug has a treacherous path to the site of action particularly if this involves blood transport. The chances of materials passing through the skin are slim and many do not pass through the skin at all. The outer most layer is a layer of dead skin and it must pass through the intercellular channels between cells in this layer. The next layers are a series of Lipid layers hence lipophilic ingredients have some chance whereas Lipophobic (or hydrophilic) ingredients have great difficulty.

## Factors affecting the rate and extent of absorption are;

Structure of skin – hair density, skin thickness and physical health of skin have an effect.

Increased hair density will assist absorption as the drug may lodge itself in hair follicles (and outlets from sweat glands) and be “available” longer particularly at a moist surface, which is an ideal condition for absorption.

Thicker or tougher skin will have a reduced rate of absorption due to the longer pathway the drug has to navigate.

Biochemistry of skin – lipid composition (from diet), moisture content (from external humidity) and the general energy levels (fitness) of the subject have an effect. One must also consider the rate of exfoliation, of skin, as any drug that remains on the surface of the skin would be lost when the outer layer (Stratum corneum) is lost through abrasion (clothes, towelling, etc.) or normal desquamation.

Sex – male skin tends to be a greater barrier than female skin

Age – the older you get the less penetration occurs due to the loss of general structure of skin

Heredity – some may have enhanced ability because of heredity factors such as thin skin.

Disease – dermatological (eg exposure of lower layers of skin increasing absorption) and systemic (hardening of the blood vessels slowing down transfer to the circulatory system).

Physical damage to the skin - scarring will prevent absorption while abrasion or cuts will increase absorption.

Environment – increasing temperature and increasing humidity will increase absorption

Diet – Nutrition will affect absorption, as healthy skin will behave normally

Drugs – drugs will affect absorption, as some drugs will alter skin physiology and either aid or decrease skin absorption.

Both diet and drugs can affect blood flow and glandular function which in turn affect absorption.

## Modes of transfer are;

### Diffusion

The passage or movement of an active ingredient (or drug) across a membrane (usually skin or cell membrane in this field). It usually involves diffusion against a concentration gradient where the active ingredient (or drug) diffuses across the membrane from an area of high concentration to one of low concentration, ie. passive diffusion along a concentration gradient. The result is an equal concentration on both sides of the membrane, unless there are other factors which may affect the result. Water transfer into and out of skin cells or in the kidneys to excrete excess water are classic cases of diffusion.

### Adsorption

where an active ingredient (or drug) is adsorbed or attached to the surface of a carrier which is then transported across the skin membrane where the active ingredient (or drug) can work. It is a means of protecting the active ingredient (or drug) from chemical change during transport. It can also mean the technique of attaching the active ingredient (or drug) onto the surface of the skin cell where it will slowly diffuse into the cell.

## Absorption

where an active ingredient (or drug) directly passes unaided across the skin or cell membrane where it begins to work. This is the basic technology for Percutaneous Absorption, and probably the major pathway that is used by Cosmetic Chemists.

## FORMULATION

The basic structure of an emulsion is well known but the selection of emulsifiers and lately the selection of the emollient are undergoing much closer scrutiny.

### Emulsifiers

Originally Soap was the first emulsifier used. Sodium Stearate however has some major drawbacks. It is somewhat insoluble actually causing the product to gel at levels above 5% (Note; 8% is used to solidify products such as deodorant sticks), it has low oil carrying capacity and it is only effective in alkaline conditions (otherwise it hydrolyses back to the fatty acid).

Later Triethanolamine Stearate was used proving to be more soluble and hence higher levels could be used (also increasing the oil carrying capacity). The pH was also lower but still in the mild alkaline region for best stability.

With the advent of synthetic surfactants in the 1950s Sodium Lauryl Sulfate was used (Aqueous Cream BP) although the use of Sodium Lauryl Sulfate provides such stable emulsions that they do not absorb into the skin readily. They are best used for cleansers or sunscreens that you do want to absorb into skin. pH was also lower with an ideal range of 5.5 to 8, lower than 5.5 hydrolysis occurs with loss of emulsification power.

Cationics have been used to a minor extent particularly where the additional benefits of antiseptic efficacy is desired. These have not had widespread acceptance due to their poor stability profile, cationic surfactants being poor emulsifiers. The BP lists Cetrimide Cream BP. Still they are substantive to skin and may assist in holding the drug on the skin to aid absorption.

Later the use of Cetomacrogol 1000 (or now called Cetareth-20) or ICI's extensive development of ethoxylated fatty alcohols and Sorbitan derivatives allowed nonionic emulsions to be formed having a wide range of pH values, excellent penetration characteristics and a vast range of applications (from Water-in-Oil emulsions to Wetting Agents to Oil-in-Water emulsions to Solubilised Oil Phases depending on the Hydrophilic-Lipophilic Balance (HLB) chosen). The BP contains formulations for Cetomacrogol Cream BP and Sorbolene Cream BP.

The use of a correct emulsifier for skin lightening products depends both on the active drug used for skin lightening and on the type and quantity of emollients used. The only time the selection of a correct emulsifier is of major concern is when there is a compatibility concern. For example, when using Ascorbic Acid or Kojic Acid a low pH is required for maximum chemical stability of the drug. At low pH's there are certain emulsifiers, such as Sodium Lauryl Sulfate, that are not stable. In these cases an acid stable emulsifier should be selected.

### Emollients

Again early emulsions, reported in such august publications as the British Pharmacopoeia, used an emollient phase based on Paraffin Liquid (or Mineral Oil), Petrolatum and Paraffin Wax. These are extremely stable (being predominantly alkanes) but the penetration is very poor, because they are these large stable molecules. Vegetable oils became popular, particularly during the 70s with the push towards so-called "Natural" materials. Note; I have begun calling Mineral Oil, Petrolatum and Paraffin Wax "Putrefied Wood Extracts" to reflect their true origin.

Still the vegetable oils, although offering a slight improvement in absorption (probably because they were more compatible with the triglycerides found in the skin lipids), were still quite slow to absorb.

The 60s and 70s saw the expansion of synthetic esters (condensation products made from short chain fatty acids with short chain fatty alcohols, a typical example would be Decyl Oleate). The widespread use of Isopropyl Myristate and Isopropyl Palmitate in the 70s was halted recently with the discovery that they implicated in the formation of adult acne (ie are comedogenic materials). Still, it must be said that not all synthetic esters are comedogenic, but it can also be said that they offer the cosmetic chemists a vast array of options to affect the percutaneous absorption of cosmetic products. For those who wish to pursue this area I will refer you to an award winning paper by Dr Johann Weichers (of Uniqema Holland) titled "Formulating for Efficacy" where he outlines a procedure for selection of water phase and oil phase in relationship to drug type, for best efficacy.

Other common materials used are Cetyl Alcohol, Stearic Acid and Glyceryl Monostearate that do little for absorption only used for their consistency contributing factor.

We have also had to endure the change in perception from consumers that have seen oils such as whale oil or mink oil discouraged, fortunately we have found more than adequate replacements with vegetable Squalane, Jojoba Oil and other more exotic emollients.

It is known that short chain emollients and straight chain emollients have better absorption characteristics than long chain or branched chain emollients. Emollients that are polyunsaturated also seem to have better penetration characteristics than saturated emollients. If they have better penetration characteristics they also seem to assist with drug delivery.

An interesting oil, finding its way into some formulations, is Emu Oil. Due to Emu Oil's lack of phospholipids it appears to be an excellent oil for skin penetration, and as an anti-inflammatory commonly used in preparations for arthritis.

When you have selected a drug for the desired effect, such as for skin lightening, the emollient system is chosen so as to provide solubility, if it is an oil soluble drug such as Ascorbyl Tetraisopalmitate, or to provide sensory attributes, if it is a water soluble drug such as Ascorbic Acid or the newer peptides. I will also refer you to "Formulating for Efficacy" which is outlined in a later section of this paper. If the drug is poorly soluble in water or oil (eg. Sabiwhite from Sabinsa) then the emollient phase also has the requirement to aid in suspension of the drug to keep it, firstly, to keep it suspended in a stable product, and secondly, to prevent agglomeration.

### Emulsion Type

While this seems to be of minor importance some specific conditions exist.

It has been found that for hydrophilic drugs increased absorption is achieved from very stable water-in-oil emulsions, provided the internal phase has very small micellar structure. This is probably due to the ionic nature of the drug being shielded from the ionic character of the surfactants in the intercellular channel thereby reducing the tendency for the drug to be trapped in the stratum corneum. It also assists when the drug must pass through the lipid layers deeper in the skin.

For lipophilic drugs very stable water-in-oil emulsions seem to be better for sunscreens in that they stay on the surface and do not penetrate readily. More unstable water-in-oil emulsions are better in aiding penetration.

For oil-in-water emulsions the stability (as mentioned earlier) plays a more major part with unstable oil-in-water emulsions being better penetrators, particularly where lipophilic drugs are used.

It is unfortunate that most water-in-oil emulsions are not aesthetically pleasing being more a "greasy" feel. To overcome this multiple emulsions are used. Water-in-oil-in-water emulsions have the dual benefit of containing a very small micellar structure of a water-in-oil emulsion with the more aesthetically pleasing feel of an aqueous phase as the external phase.

Multiple emulsions are also used where two hydrophilic drugs are required which may be incompatible with each other eg where one is acidic and the other basic or different pH's are required for stability of each. Here one is dissolved in the internal water phase and the other dissolved in the external water phase with the interlaying oil phase protecting one from the other. Nonionic emulsifiers must be used and one generally makes the internal water-in-oil phase very stable with the oil-in-water combination being somewhat less stable.

Nanotechnology is described by the US National Nanotechnology Initiative as the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications. Essentially, nanotechnology is a branch of science devoted to the design and production of extremely small matter. Due to the small size and special properties of nanotechnology materials, they have great potential for use in a vast array of therapeutic products.

In addition, these small materials often have physical or chemical properties that are different than those of their larger counterparts. Differences include altered magnetic properties, altered electrical or optical activity, increased structural integrity, and enhanced chemical and biological properties. These differences have the potential to lead to scientific advances. For example, this technology could be used to create new drug formulations and routes of delivery to previously inaccessible sites in the body.

## “Formulation for Efficacy”

At this point I would refer you to the late Dr Johann Wiechers paper titled “Formulating for Efficacy” where he explained how the thermodynamic activity of an active ingredient could be optimized in a cosmetic formulation by the choice of a primary and secondary emollient. The essence of this theory is the fundamental difference between dermal and transdermal delivery and is dependent on the parameter that you need to change to get the desired effect. In transdermal drug delivery, pharmaceutical formulators use skin penetration enhancers that enhance the diffusivity of a chemical through the skin. The result is more drug going in faster. Therefore there is less drug in the skin but more drug through the skin. This is, in fact, exactly the opposite of what one would like to achieve in dermal delivery. There, you would like more active ingredient to go into the skin but then to stay there. The way to do this is by increasing the partition coefficient and not the diffusion coefficient.

How does one enhance the partition coefficient of an active ingredient? How does one change the ratio of its concentrations in the stratum corneum and the formulation? A partition coefficient is the ratio of the solubilities of an active ingredient between the stratum corneum and the formulation. Therefore, the partition coefficient can be increased by increasing the solubility of the active ingredient in the stratum corneum (while keeping the concentration in the formulation the same) or by reducing its concentration in the formulation (while keeping the concentration in the stratum corneum the same).

Therefore, one needs to know the solubility of the active ingredient in both formulation and the stratum corneum. Measuring these values is not as easy as it sounds. But the solubilities can be estimated via the Hansen Solubility Parameters.

A few cautions with this theory is that;

1. It applies only to oil soluble drugs in oil-in-water emulsions.  
Water soluble drugs, in a oil-in-water emulsion, are readily absorbed from the external phase of the emulsion and no or little assistance is generally required.
2. The solubility parameters are not available for a majority of drugs used in cosmetics.

## The Drug

The original chemical applied to the skin may not be the active intended (eg when Vitamin B5 is applied to the skin it is not actually vitamin B5 (Pantothenic Acid) but a precursor to vitamin B5 (D-panthenol) and will only be converted into vitamin B5 when it enters the skin and it reacts with the skins acids, Vitamin A is similar where, because of stability reasons, we add an ester analogue of Retinoic Acid, Retinyl Palmitate. Once in the skin there is a metabolic pathway that converts Retinyl Palmitate into true Vitamin A (Retinol).

Micronisation of the active drug is also increasing in importance. Again the work being done with sunscreens is a useful tool in this quest, the data so far indicating that (using Zinc Oxide as the “active drug”) a particle size of 150 nm and above does not penetrate skin but remains on the surface as a white precipitate. Reducing the particle size reduces the white appearance on skin but also reduces the Zinc Oxide’s effectiveness as a sunscreen. Current theory is that a particle size of 80-120 nm is the best balance. Regulatory authorities are currently concerned with one manufacturer’s claims to have an effective Zinc Oxide sunscreen with a particle size of approximately 20-50nm, particularly when you need around 20% to give an SPF of 30+. The reason for both the loss of efficacy and the FDA’s concern is probably due to increased concern re absorption of the Zinc Oxide into the dermis (and probably the bloodstream) with the smaller particle sizes.

In a paper “Nanotechnology and Skin Delivery - Infinitely Small or Infinite Possibilities” by Dr. Johann Wiechers, where he quotes world experts, including Professor Michael Roberts of Queensland University’s Therapeutic Research Unit, the author presents available evidence that shows nanoparticles in the range 3-10 nm tend to accumulate in the hair follicles and sweat glands, but do not penetrate further into the Dermis. Professor Roberts also shows that there are polar hindrances to particles of Zinc Oxide and Titanium Dioxide penetrating through the Epidermis. From this paper and others any evidence presented by those that say nano-size Zinc Oxide penetrates skin base their evidence on finding Zinc ions in the Dermis. This is shown to be flawed hypothesis as the Zinc ions have come from Zinc Oxide or Zinc Carbonate dissolving in the skin’s fatty acids or in the formulation and therefore being more bioavailable. In any case evidence shows that the level of Zinc found in the Dermis is less than background Zinc levels, indicating that the amount absorbed is insignificant. Another question Professor Roberts asks is with the low levels of Zinc detected is that harmful. At levels less than background concentrations one would think not.

In essence this work showing Zinc Oxide or Titanium Dioxide do not penetrate skin has given us a hypothesis that you need to have a particle size of less than 3 nm or to have a soluble particle for any of it to be absorbed through the Epidermis and into the Dermis.

I have said above that “The chances of materials passing through the skin are slim and many do not pass through the skin at all. The outer most layer is a layer of dead skin and it must pass through the intercellular channels between cells in this layer. The next layers are a series of Lipid layers hence lipophilic ingredients have some chance whereas Lipophobic (or hydrophilic) ingredients have great difficulty.” and “The intercellular channels between the layers are composed of a lamellar structure of oil layers (nearest the cells) and water layers between. The water layer is lined with surface active agents that have a polar nature. It is this polar nature that restricts polar chemicals (eg. water soluble vitamins, amino acids and almost all water soluble drugs) from penetrating.”

Two factors stand out

1. smaller molecules penetrate better than large molecules.
2. non-polar molecules (and lipophilic molecules) penetrate better than polar hydrophilic molecules.

Obviously polar hydrophilic molecules will try to get down the intercellular channels via the aqueous channel and with the polar ends of “emulsifiers” lining the surface of these channels the flow will be retarded, sometimes halted depending on the affinity of the drug for the “emulsifier”. This theory is akin to the technology on which the Gas Chromatograph is based.

Reducing the polarity of the drug seems to work. Research being done by a French company indicates that condensation of small peptide chains (3 to 5 amino acids) with Palmitic Acid (C16) will allow these polar peptides to not only be absorbed readily through the stratum Corneum but also easily penetrate living cells. The purpose of doing this is to use fragments of DNA to “trick” the cell into thinking it has damaged DNA hence activate the cells skin repair mechanism.

## Whitening Agents

### Hydroquinone

In medical literature, hydroquinone is considered the primary topical ingredient for inhibiting melanin production. Its components have potent antioxidant abilities. Topical hydroquinone comes in 2% (available in cosmetics) to 4% (or more) concentrations (available from a physician or by prescription), alone or in combination with tretinoin 0.05% to 0.1%. Research has shown hydroquinone and tretinoin to prevent sun- or hormone-induced melasma.

Hydroquinone is a strong inhibitor of melanin production, meaning that it prevents skin from making the substance responsible for skin color. Hydroquinone does not bleach the skin but lightens it, and can only disrupt the synthesis and production of melanin hyperpigmentation. It has been banned in some countries (e.g. France) because of fears of a cancer risk and is restricted, at levels exceeding 2 percent in other countries such as the United States and Australia, where it can only be sold as an over-the-counter drug.

Some concerns about hydroquinone's safety on skin have been expressed, but the research when it comes to topical application indicates negative reactions are minor or a result of using extremely high concentrations or from other skin-lightening agents such as glucocorticoids or mercury iodine. Any perceived risk is most likely applicable for African women. Hydroquinone has been shown to cause leukemia in mice and other animals. The European Union banned it from cosmetics in 2001, but it shows up in bootleg creams in the developing world.

Because of hydroquinone's action on the skin, it can be irritant, particularly in higher concentrations of 4% or greater and predictably when combined with tretinoin. Some medications have been created that combine 4% hydroquinone with tretinoin and a form of cortisone. The cortisone is included as an anti-inflammatory. The negative side effect of repeated application of cortisone is countered by the positive effect of the tretinoin so that it does not cause thinning of skin and damage to collagen. Safer alternatives are more expensive but are available.

## **Arbutin**

Natural Double Action Whitening Agent

A new type of skin de-pigmentation and whitening agents, an extract of Bearberry plant which produced by a solid /liquid extraction, an environmentally friendly process.

Cosmetic uses of Arbutin:

Arbutin protect the skin against damage caused by free radicals, Arbutin is a skin whitening agent which is very popular in Japan and Asian countries for skin de-pigmentation, Arbutin inhibits the formation of melanin pigment by inhibiting Tyrosinase activity.

Arbutin in medical use:

Back in the 18th century Arbutin was first used in medical areas as an anti-inflammatory and antibacterial agent. It was used particularly for cystitis, urethritis and pyelitis. These uses still until today where natural medicine uses only natural ingredients to treat any disease.

It may be used to repress the virulence of bacterial pathogens and to prevent contaminating bacteria, it is also used for treating allergic inflammation of the skin . More recently, Arbutin has been used to prevent pigmentation and to whiten the skin beautifully. It can be used to whiten the skin, to prevent liver spots and freckles, to treat sunburn marks and to regulate melanogenesis.

The encapsulation of Arbutin constitute a delivery system to potentialize the effect in time. It is a way to incorporate the hydrophilic Arbutin in lipophilic media. Arbutin give three main properties; Whitening effects, anti- age effect and UVB/ UVC filter.

Regulatory: Arbutin is a relatively safe skin agent for external use which does not have toxicity, stimulation, unpleasant odour or side effect such as Hydroquinone. However, a it is a derivative of Hydroquinone, Arbutin is also restricted in use in Australia, due to the potential to breakdown to Hydroquinone, or have impurities of Hydroquinone, from manufacture or storage.

Lightening gels and emulsions. Recommended use level: 1 to 2%

## **Arctostaphylos uva-ursi ( Bearberry ) :**

This plant from the botanical family of the ericaceae grows in many areas of the world, in Europe, in Northern Temperate Asia and north America. The bush is green of 15-20 centimetres high with leaves dark green on the upper surface, paler beneath, leathery, obovate, spatulate, about 2 cm long and 0.5-1 cm broad, margins entire, slightly revolute.

The scarlet red fruits (drupes), commonly named bear berries. The part of the plant traditionally used for extraction are the leaves. It has an astringent taste and slight odor.

## **Vitamin C (L- Ascorbic Acid)**

There is an increasing awareness that Vitamin C has a wide variety of role in human health. New therapeutic uses are being investigated daily, among recent discoveries is that Vitamin C can play important role in the health and beauty of your skin.

Vitamin C as Ascorbyl form has been tested extensively and reported in journal of American Academy of Dermatology to inhibit the production of the melanin ( Melanin is the pigment which give the skin it's dark color ), when Vitamin C inhibit the production of the melanin, a lighter and brighter skin will reveal in just few weeks.

Vitamin -C does more than that also, Vitamin -C is required for collagen synthesis, which declines markedly in aging skin. As we grow older, we suffer diminished micro capillary circulation within our skin, which deprives our skin cells of the supply of Vitamin -C it needs for youthful collagen synthesis. The topical application of Vitamin -C in a skin-penetrating medium can dramatically enhance the availability of Vitamin -C for collagen production.

Vitamin -C regenerates vitamin E in the skin. An antioxidant like vitamin E can only suppress a limited number of free radicals before it runs out of electrons to donate. Vitamin -C regenerates vitamin E and enables vitamin E to provide sustained antioxidant protection in the skin's elastin fibers.

Vitamin -C plays a vital role in skin repair. When your skin is injured, its Vitamin -C content is used up rapidly in the scavenging of free radicals, and in synthesizing collagen to speed healing.

## **Licorice**

Glycyrrhetic acid, isolated from Glycyrrhiza glabra (licorice) is widely used in cosmetic industry. Licorice inhibit tyrosinase activity of melanocytes without any cytotoxicity, it also showed that UV-B–induced pigmentation and erythema can be inhibited by topical application of 0.5% Licorice The anti-inflammatory properties of Licorice were attributed to inhibition of superoxide anion production and cyclooxygenase activity.



### **Kojic acid**

A fungal metabolic product, kojic acid inhibits the catecholase activity of tyrosinase, which is the rate-limiting, essential enzyme in the biosynthesis of the skin pigment melanin. Kojic acid also is consumed widely in the Japanese diet with the belief that it is of benefit to health. Indeed, it has been shown to significantly enhance neutrophil phagocytosis and lymphocyte proliferation stimulated by phytohemagglutinin. Melanocytes treated with kojic acid become nondendritic with a decreased melanin content. Additionally, it scavenges reactive oxygen species that are excessively released from cells or generated in tissue or blood. Unfortunately Kojic Acid is banned from use in Australia due to its potential irritant effects.

### **Mulberry**

This tyrosinase inhibitor was isolated from a plant herbal extract. The plant roots from which paper mulberry was isolated were collected in Korea. The tyrosinase inhibition of paper mulberry was compared to kojic acid and HQ. The IC50, the concentration causing 50% inhibition of the activity of tyrosinase, was reported to be 0.396% compared to 5.5% for hydroquinone and 10.0% for kojic acid.

### **Retinol**

The most important natural form of vitamin A Vitamin A is the first vitamin to be used topically for the treatment of damaged human skin. Today, the term vitamin A is applied to retinol (Vitamin A alcohol), retinal (Vitamin A aldehyde) and tretinoin (Vitamin A acid). Vitamin A stimulates mitotic activity and the production of collagen - the stuff skin is made of. It is now known that the clinical effect obtained with high doses of vitamin A is necessary for normal differentiate and maintenance of epithelial tissues. Especially, retinol is held out as the new great hope for reduction of photo aging skin. Retinol or Vitamin A helps to renew and exfoliate the skin, giving a new lighter, beautiful skin .

### **Azelaic acid**

Azelaic acid is a component of grains, such as wheat, rye, and barley. It is applied topically in a cream formulation at a 20% concentration. Azelaic acid is used to treat acne, but there also is research showing it to be effective for skin discolorations. Other research also indicates azelaic acid may be an option for inhibiting melanin production.

## **COMMERCIAL INGREDIENTS**

### **O.D.A.white (INCI: Octadecendioic Acid)**

Sederma launched a skin brightening ingredient with a new mechanism of action from the heart of the melanocyte. O.D.A.white (INCI: Octadecendioic Acid) was designed to treat skin pigmentation disorders such as freckles, melasma, hyperpigmentation and general dark color of ethnic skin.

The enzyme tyrosinase is the target for this interference, as it is the limiting factor of the rate of melanogenesis. While many skin lightening ingredients inhibit tyrosinase, O.D.A.white reportedly decreases melanin synthesis via another, further upstream mechanism.

The skin lightening ingredient does not mediate melanin synthesis reduction by a direct inhibition of tyrosinase, but can inhibit the whole melanin synthesis pathway from the melanocyte nucleus by targeting the tyrosinase gene via the PPAR $\gamma$  complex. Testing conducted by the company showed a 50% decrease in mRNA tyrosinase and tyrosinase quantities, a decrease of the pigmentation by 44 and a 28% increase in skin clarity. According to the company, the ingredient also brightens the skin.

### **Lumiskin**

**Function and Characteristics:** LUMISKIN is a solution of diaecetyl-boldine (DAB) in C8C10 triglycerides that inhibits the activity of tyrosinase, enzyme responsible for melanin synthesis.

**Cosmetic interest (properties):** LUMISKIN stabilizes the tyrosinase in its inactive form via the  $\alpha_2$ -adrenergic antagonist receptors and calcium flow regulation.

**Applications:** Skin lightening products. Recommended use level: 4%

### **Melaclear 2**

**Function and Characteristics:** MELACLEAR 2, a multi-component hydroglycolic solution, contains a keratolytic enzyme that eliminates the strongly pigmented epidermal cells in the first place. MELACLEAR 2 also contains several other components, the aim of which is to regulate tyrosinase activity, thus to diminish progressively the pigmentation located on the skin's surface:

- $\beta$ -carotene: by binding in a competitive way on cell receptors of vitamin A - which is well-known for stimulating the melanocyte activity - it acts by temporarily "freezing" melanogenesis.
- Dithiooctanediol: OH-CH<sub>2</sub>-CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>2</sub>-OH

This molecule contributes to the activity of MELACLEAR 2 by its inhibiting effect on tyrosinase glycosylation.

- Gluconic acid: HOOC-CHO-CHOH-CHOH-CHOH-CH<sub>2</sub>OH

This molecule possesses chelating properties for metals, including copper. It helps inhibit tyrosinase activity.

Cosmetic interest (properties):

MELACLEAR 2 contributes to complexion brightening and skin lightening:

- by accelerating cell renewal and elimination of strongly pigmented cells of the stratum corneum, through the keratolytic action of the protease;

- by slowing down the rhythm of melanogenesis by interfering with the activation and inherent activity of tyrosinase.

Furthermore, thanks to its exfoliating action, the regular use of a cream containing MELACLEAR 2 provides a smoother cutaneous surface, leading to a rejuvenated skin appearance.

Applications: Lightening gels and emulsions. Recommended use level: 2 to 8 %

### **Etiloine**

Function and Characteristics:

ETIOLINE is a concentrated, purified and standardized extract obtained from a rare African plant: *Mitracarpe*, of Spermaceae genus.

In Benin, the most original property attributed to *Mitracarpe* leaves lies in the treatment of dark spots and in skin fading. In order to obtain a marked synergic effect, we associated *Mitracarpe* with Bearberry (*Arctostaphylos uva ursi*) extract.

Cosmetic interest (properties): ETIOLINE is an active ingredient designed for the treatment of pigmentary spots and cutaneous discolouration problems. Its activity based on African ethnobotanical experience is confirmed by a strong tyrosinase inhibitory activity in vitro and ex vivo.

Applications: Whitening lotions and creams. Recommended use level: 2 to 5 %

### **Sabiwhite**

SabiWhite™\* (INCI: Tetrahydrodiferuloyl-methane) is a color-free natural extract derived from *Curcuma longa* (Turmeric) roots. Laboratory studies revealed that SabiWhite™ is an effective skin lightening agent with multifunctional topical benefits. The extract is safe for topical use with no irritant or sensitization side effects.

SabiWhite™ is chemically Tetrahydrocurcumin, which is a major metabolite of curcumin, (the yellow pigment of turmeric), in the body.

Antioxidant action: SabiWhite™ offers effective topical antioxidant protection. Its antioxidant action is of a comprehensive "bioprotectant" nature, efficiently preventing the formation of free radicals, while quenching pre-formed ones as well. This dual action protects the skin cells from damage by UV radiation and the resultant inflammation and injury with far reaching beneficial effects on overall health and well being. The free radical scavenging activity of SabiWhite™ was found to be superior to that of the synthetic vitamin E analog, Trolox.

Curcuminoids are reported to protect normal human keratinocytes from hypoxanthine/xanthine oxidase injury in in-vitro studies. This study suggests that curcuminoids and therefore SabiWhite™ offer protection to the skin and could be included in as functional antioxidants in topical preparations<sup>5</sup>.

Luminosity Booster and Powerful Tyrosinase Inhibitor

Preliminary in vitro studies indicate that SabiWhite™ efficiently inhibits tyrosinase, the rate limiting enzyme in the synthesis of melanin. Its efficacy is superior to that of commonly used natural skin lightening agents such as kojic acid, and of related compounds (Table 1).

Anti-inflammatory and UV protectant effects

Laboratory studies revealed that SabiWhite™ offers topical protection against UVB induced inflammation and the resultant damage to the skin. These properties are particularly useful in antiaging, skin lightening, sun care and after sun care formulations.

Cosmeceutical applications: The culinary spice, turmeric, has a rich tradition of topical use in South Asia. However, its brilliant yellow color, effected by the curcuminoids, does not blend well with currently manufactured cosmetics. SabiWhite™ (Tetrahydrocurcumin, THC) does not pose this problem as it is color free, and can be conveniently dispersed into cosmetic formulations.

The powerful tyrosinase inhibitory activity of SabiWhite™ could also slow down melanogenesis, thereby lightening the skin tone. Use levels range from 0.1 to 2% w/w; typically 0.25%.

### **Melfade J**

MELFADE®-J is a purified aqueous extract derived from bearberry leaves (*Arctostaphylos uva-ursi*) combined with magnesium ascorbyl phosphate.

Properties: MELFADE®-J combines the topical activity of bearberry leaf extract with that of magnesium ascorbyl phosphate, for a powerful and longer lasting skin lightening.

MELFADE®-J is a very effective inhibitor of tyrosinase activity demonstrated in in-vitro studies, and is very popular in Asian countries as an effective means to depigment the skin.

Function: MELFADE®-J reacts on the melanocytes to inhibit the tyrosinase activity by reducing melanin biosynthesis.

Cosmetic application: MELFADE®-J is appropriate for use in all types of skin lightening formulations.

Suggested concentration: 1.0% when combined with an exfoliant, otherwise up to 8%.

INCI Name: Water, *Arctostaphylos Uva-Ursi* Leaf Extract, Glycerin, Magnesium Ascorbyl Phosphate

### **Symwhite 377**

This compound (INCI: phenylethyl resorcinol) can be used in a wide variety of cosmetics applications, such as lightening skin tone, treating for and generally reducing light-induced pigmentation of the skin and hair.

SymWhite® 377 is an excellent antioxidant that is also highly effective in influencing the formation of pigmentation. The efficacy of SymWhite® 377 has been demonstrated in many studies (both in vitro and in vivo), in which researchers also observed that the compound is well tolerated.

SymWhite® 377 thus succeeds where other skin-bleaching agents fail by eliminating the side-effects and disadvantages – such as skin irritation and poor performance – associated with these preparations. In a direct comparison with  $\beta$ -arbutin, for instance, SymWhite® 377 was shown to be over one hundred times as effective at lightening hair, and when tested in vivo on skin that had not been exposed to light, 0.5% SymWhite® 377 proved to be more effective than 1.0% kojic acid. A concentration of between 0.1 and 0.5% is recommended.

SymWhite® 377 has been approved for use worldwide and a patent application has already been submitted. Symrise can now offer the international cosmetics industry an innovative, well-tolerated and highly efficient lightening agent for use on the skin.

### **Melanostatin-5**

INCI; Water & Dextran & Nonapeptide-1

MELANOSTATINE®5 is a biomimetic peptide antagonist specific of the  $\alpha$ -MSH ( $\alpha$ -Melanocyte-Stimulating Hormone). As an antagonist, MELANOSTATINE®5 competes against the natural ligand ( $\alpha$ -MSH) on its specific receptor (MC1-R) by preventing any further activation of the tyrosinase, and thus blocking melanin synthesis.

Tyrosinase inhibition reduces the formation of unwanted pigmentation allowing for the control over skin tone and brown spots.

### **$\beta$ -White**

INCI: Water & Butylene Glycol & Hydrogenated lecithin & Sodium Oleate & Oligopeptide-68 & Disodium EDTA

$\beta$ -White™ inhibits tyrosinase activity and melanin synthesis.  $\beta$ -White™ decreases proteins involved in the pigmentation process such as MITF, TRP-1, TRP-2 & tyrosinase. Inspired by TGF- $\beta$  and MITF role in skin pigmentation,  $\beta$ -White™ is a TGF- $\beta$  biomimetic peptide encapsulated in a liposome vehicle. It differentiates itself from other traditional whitening agents with its unique inhibitory action on the MITF cellular pathway to decrease constitutive and facultative pigmentation allowing optimal whitening and lightening effect with an excellent safety profile.  $\beta$ -White™ decreases melanin synthesis with higher activity than Arbutin and Vitamin C, 2 well-known skin whitening agents.

### **Percutaneous Absorption Enhancers**

Common percutaneous absorption enhancers are the lower Organic Alcohols (Ethanol), Humectants (such as Propylene Glycol) and specialties such as Dimethyl Sulfoxide.

Organic Alcohols (Ethanol) are common (and low cost) penetration enhancers, also offering the added preservative (or even antiseptic) action. There are concerns using ethanol in that some believe it may remove the oils from skin. Well it will if wiped off but when used as a penetration enhancer it is left on the skin, the excess simply evaporating, without taking the precious oils with it.

Propylene Glycol has been recommended for many years, however recent evidence suggests that while adding small amounts of Propylene Glycol (and Glycerine or Sorbitol) does increase absorption, high levels may in fact decrease absorption. The optimum level must be determined for each drug/carrier combinations.

Essential oils (particularly those high in Terpenes) have also been shown to aid in the penetration of drugs. As an example Piperine has been shown to be effective in this area.

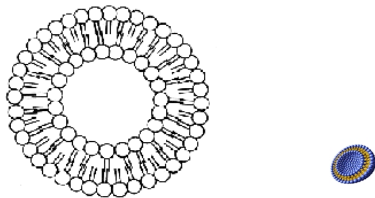
Another means is by patches or “plastic wraps” where the ingredient is kept (in a very humid environment) for a longer time than usual thereby increasing the chance of absorption. For those that doubt its relevance to the topic it is a “cosmetic approach” to see customers, in beauty salons, sitting there swathed in “Glad-Wrap”.

In a more “refined” form of this treatment Film forming agents are used, such as the Carbomers, PVP and some Polyquaterniums that assist penetration by trapping the drug into the film matrix and holding it onto the skin, thereby increasing the time a drug is in contact with the skin, thereby enhancing its penetration.

Liposomes and other percutaneous absorption enhancers assist with this transfer, some having more luck than others. Liposomes act by dissolving the active ingredient within its unique structure then, because of its lipophilic nature will pass into the skin where the active is released.

Other ways ingredients can penetrate is through the skin is through the hair follicles, sebaceous (oil) glands or eccrine (sweat) glands, where the ingredient once in the follicle or gland has passed the horny layer and can be more easily absorbed – still the assistance from the above aids will apply. I will leave this discussion to the experts and will refer anyone interested to the work done by Professor Michael Roberts and Dr Sheree Cross at the University of Queensland.

Liposomes are unique forms of Triglycerides and PhosphoLipids in that they form a special structure in solutions. If this structure becomes large (and this can be created by special formulations then Liposomes are formed. A typical structure appears as



Where the Triglycerides and PhosphoLipids form a spherical structure of a bi-layer of Triglycerides and PhosphoLipids molecules. Each side of the bi-layer has the ionic part of the molecule point outwards from the bi-layer and the hydrophobic “tails” point inwards each other.

This forms a very stable structure with unique properties.

- Water soluble components that are susceptible to degradation by other required additives can be formulated inside the Liposome and hence be made more “stable”. Eg Vitamin C
- Oil soluble components that are susceptible to degradation by other required additives can be formulated inside the Liposome shell (between the bi-layers) and hence be made more “stable”. Eg Vitamin A
- Water soluble components that are not susceptible to degradation by other required additives or those in large abundance can be formulated outside the Liposome.

When the Liposome is applied to the skin three possible mechanisms allow the actives to be delivered from the Liposome;

- the Liposome is broken by the action of rubbing and the actives released to the skin surface.
- the Liposome does not break up and the actives slowly diffuse through the bi-layer onto the skin.
- the Liposome is absorbed into the skin and the actives slowly diffuse through the intercellular channel into the skin.

Liposomes act to alter the molecules “external” polarity. The benefits of Liposomes are that their outer surface has essentially low polarity with the polar drug encapsulated. Hence the Liposomes can pass through the intercellular channels, releasing the drug in lower layers of the skin where it is more easily absorbed.

New technology now available utilizes an active drug, completely encased in a capsule usually comprised of an Agar-Chitin film. This film is insoluble in the water phase of an emulsion but biodegradable, and when applied to the skin is either broken by the mechanical action of spreading over the skin or broken down by the skin’s microflora releasing the active onto the skin. This technology while not strictly a Liposome is used to protect drugs that have known instability in cosmetic formulations such as retinol. The bioavailability of Retinol in this case would be increased from a typical value of about 15% to a minimum of 85%, mainly due to the increased shelf life or stability in the formulation before use.

An extension of the use of film formers is used in sunscreens and wear resistant lipsticks, where the film former is chosen from a group that have very high water resistance, and these are combined with emollients that are also water resistant, or have low penetration ability, the combination forming a matrix with the drug actives preventing them from entering the skin. This is particularly important in sunscreens, as you do not want the sunscreen active to penetrate skin, but to reside on the surface to protect the skin. These film formers also have the ability to form a uniform topical layer which gives a consistent uniform layer of sunscreen that will also provide better protection. This is a case where the target of drug delivery is not in the skin but on the skin.

## Product Stability

A new theory on another factor that may affect the rate of drug penetration is that relating to the emulsion stability.

That is, when a water based solution or an oil based solution is applied to skin the drug (and solvent) seems to penetrate fairly rapidly. However, when a cream is applied to the skin it requires the emulsion to break down (the less stable emulsions breaking down quicker) into the original component parts, of water phase and oil phase. The rate of this breakdown determines the rate of absorption.

When the emulsion does not break down readily into its oil and water phases it is prevented from absorption. This is because the emulsion particles are usually spherical in nature while the interfacial layers, between skin cells, are separate lamellar phases of oil and water (see the earlier description of these layers). It requires energy to convert the spherical particles into lamellar particles for absorption and this is only achieved by persistent rubbing.

When there are these discreet phases of oil and water on the skin, because the emulsion has broken down readily, absorption appears to be enhanced. That is, if the emulsion readily splits into the component phases this energy required to allow oil and water components to enter the skin's lamellar interfacial phases, is not required and the product seems to absorb readily.

An example of this is a cream, when rubbed onto skin, appears to form a creamy/milky layer that is hard to absorb. This occurs because the emulsion has not broken down and hence does not absorb.

Two things achieve absorption in this case;

1. Continual rubbing, applying energy to the system, will cause absorption. That is, it requires energy to convert the spherical particles into lamellar particles for absorption and this is only achieved by persistent rubbing.
2. If you allow the creamy/milky layer to sit for a few seconds then rub again it seems to absorb more readily. This occurs when the waiting period allows some solvent (usually water) to evaporate and the emulsion, having changed its oil:water ratio, will become less stable. When it is less stable the emulsion breaks more readily, into its basic components, and the cream seems to absorb more rapidly.

The theory why nonionic creams are better penetration enhancers than anionic creams is that the nonionic creams are generally less stable.

I am not saying that we should produce unstable emulsions as we still need a certain shelf life for commercial viability. However we should be producing emulsions that have the ability to break down readily, and by producing a slightly less stable emulsion than one with complete physical stability, this assists in the rate of skin penetration.

As I said earlier we are still learning more about this area of absorption every day and despite major advances still have a long way to go before total understanding, however from these thoughts we can formulate for any degree of stability on application hence regulate percutaneous absorption.