APPLY TOPICALLY: A Practical Guide to Formulating Topical Applications

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The main objective of Pharmaceuticals and Skin care Development is to create effective products based on the state-of-the-art active ingredients with improved patient compliance and usability. Thus, the vehicle/carrier used to delivery topical active ingredients through the skin layers and mucous membrane, can considerably influence the performance of the *actives'* effectiveness. The carrier can have direct effects on both skin and mucous membrane barrier, as well as it can enhance or retard the delivery of the active agent(s) to the target site of action. In addition it can affect the skin and mucous membranes appearance and the relative sensory properties of the final formulation, often influencing the patient compliance.

Skin and mucous membranes (MB) are, in fact, the first line of the human body' defence and, acting as a biological barrier, offer thermal insulation, prevent water loss, and protect the internal organs from the external environment, foreign toxic substances, and pathogens.

Skin, generally less than 2 mm thick, is composed of several layers, the outermost of which the *stratum corneum* (SC) (10-30um thick) represents the primary barrier. On one hand, SC is composed of corneocytes filled with keratin filaments enclosed by an envelop of cross-linked proteins, and surrounded by a semi continuous matrix of lipids, which create a strong biological barrier. On the other MBs, covered by adhesive gel-like mucus and composed of a densely woven network of natural mucin polymers interspersed with a variety of glycoproteins, create another effective barrier to diffusion across mucosal surfaces. Both the Skin lipids -organized in lamellar fashion and produced/secreted during the maturation of the keratinocytes and mucus, constantly secreted and turned over, represent strong cellular and molecular barriers to penetration of any kind of compounds. Therefore the necessity to overcome these barriers by the use of right vehicles which, able to disturb the lipid structure within the stratum corneum and/or the mucus molecular organization within MB can increase the permeability of the active ingredients through these structures.

The goal of this book, consisting of **VII Sections** and **22 Chapters** is to describe and discuss the key elements necessary to formulate stable and effective cosmetics by different steps.

In **Section I, Chapters 1 to 5**, *The Preliminary Considerations and Selection of Raw Materials* are reported and discussed. Thus the necessity to design and organize a detailed description of the cosmetic to be produced.

First of all concept, goals, and objectives of the project should be stated, reporting the benefits to the

consumer that will be delivered by the product. At the same time, distribution area, potential market, and the related budget have to be determined, describing the desired technologies to use, and defining the desired site of applications and claims. Finally the regulatory rules and the eventual patent restrictions have to be controlled. Once these questions have been considered, a product design flow will begin to form, following the logical tenets of initial formulation and product scale-up.

Emulsions, responsible for delivery the active ingredients into the skin, are the most common forms of vehicles for skin care products. Active ingredients are a mixture of compounds that provide the product with its consistency and effective activity. Recently, the use of nano-emulsions has become a popular approach for formulating more effective and elegant cosmetics. In any way, the emulsions should contain the right concentration of *actives* and bio-based raw materials possibly obtained from renewable resources, having stability features, programmed release kinetics and possibly clinical efficacy, being also skin-friendly, environmentally-friendly and aesthetically pleasing. New innovative cosmetics and services could be brought to the market, for example, by promoting further exploration of marine biodiversity and strengthening marine biotechnology. The unexploited potential of the sea is, in fact, even bigger since more than 90% of marine biodiversity remains unexplored, offering a huge potential for discovery of new species and applications derived from biotechnologies, which is foreseen to generate a 10% annual growth.

A major use in the cosmetic field of raw materials from plant biomass and fishery's by-products should represent a new strategy for an innovative economic growth and development, socially and environmentally sustainable. Transitioning to this *inclusive green economy* is increasingly recognized as an alternative that can deliver low-carbon and climate-resilient development, significantly improving resource efficiency, healthy and more resilient ecosystems, and greater economic opportunities and social justice for disadvantaged groups also. How to formulate skin care products with the right ingredients is the topic reported in section I.

Formulation, Processing and Production Techniques is the topic of **Section II, Chapters 6 to 9**.

Emulsions are complex and versatile systems, which allow the skin care chemist to combine otherwise immiscible ingredients into effective skin care products. This gives the advantage of developing custom-made commercially desirable formulations, designed for various skin types or addressing many skin disorders or conditions. The success of a product depends not only on its effectiveness, but often on its sensorial attributes, in which case the consumer is the best candidate to judge. Thus sensorial and textural properties of the emulsions play a pivotal role in a formulation's acceptance as a final product by the consumer. The Texture Profile Analysis, reported and described in chapter 6 is a promising and novel technique that can help the cosmetic chemist to better verify the final designed formulation. But this formulation has to be stable and effective also, for example, for its moisturizing or healing properties. Moreover it has to be formulated by the use of the right vehicle capable to deliver the active agent(s) to the target site of action in the right time. Finally an effective scale-up to pilot plant manufacturing should occur within good manufacturing practices framework. Scale-up success means designing and implementing an efficient, cost-effective process resulting in a product which consistently meets a comprehensive and appropriate set of pre-determined quality attributes. Working within a structured system of good recordkeeping, documentation, and good manufacturing practices is, in fact, a necessary foundation to successful scale-up. These topics are reported and discussed in chapters 7 to 9.

Section III, Chapters 10 to 13, is dedicated to *Testing and Measurements Methods*.

Carefully constructed and statistically designed experiments, facilitate the analysis of collected data in a logical and expeditious fashion. The cosmetic chemist works with a plethora of cosmetic raw materials which have to be carefully selected. Thus, to obtain a well-designed formulation it is necessary to organize sets of experimental batches to fit an experimental model that can make predictions within the range of parameters established. The rationale is to achieve an optimized product that will be the most cost-effective, while still offering the best overall performance and customer satisfaction. Furthermore, a well-planned statistical approach will provide in-depth knowledge and greater understanding of the product with a minimal amount of experimentation necessary to accelerate the speed-to-market and achieve cost-saving. Naturally a number of prototype-formulations have to be developed and evaluated before the approval of the final ones to be launched. Thus various rheological measurements have to be done to characterize the product, such as flow profiles, crepe/recovery, yield value measurements, viscosity recovery strain sweep and frequency sweep and so on, made by different instruments.

In conclusion a general guide to design and develop a target profile for topical formulations are reported and discussed by these four chapters.

Sensory and Elegancy is the topic of **Section IV, Chapters 14 and 15**. The key to gaining a profitable repeat business in the skin care market is to offer products that should be effective, having also an emotional appeal through their aesthetic appearance and performance. The cosmetic product, in fact, can make a person look better, providing him/her with a sense of wellbeing and helping to achieve success in a modern society that values physical attractiveness. The *what is beautiful is good* stereotype is, in fact, extended to the older also, so that unattractive elderly individuals are perceived significantly less favourably. Today, attractiveness is equated to youthfulness. Thus, the consumer is not only interested in what a product can do but also in the promise it holds. The expectation is, therefore, that cosmetics have to stir the emotions while performing on a high technical level, possessing both rational and emotional aspects. As a consequence the primary determining variable for engineering the tactile aspects of a topically applied emulsion is the emulsifier choice. Formulation chemist can help marketing professional, communicating aesthetics needs and desires by offering a wider array of emulsion options up front in the development process from which to choose. In any way, almost every ingredient in a personal care product plays a key role and has a practical function: emulsifier, preservative, emollient, and so on. However, fragrance seems to be the most important product attribute at the point of sale, influencing soon the consumer evaluation, as emotionally potent component of most personal care products. By using the information and the processes reported and discussed on these two chapters, more a aesthetically pleasing topical formulations that resonate with a target audience can be designed and scaled up to produce successfully cosmetics and short their development cost.

In any way, formulation scale-up may present unexpected complications, depending on the complexity of the formulation, compounding procedure design, and the availability of manufacturing equipment. Moreover, a well prepared product needs to be stable for at least three years. Thus, the necessity of the *stability testing* necessary to evaluate a product's ability to maintain its original aesthetic, physical and chemical characteristics designed under controlled conditions to accelerate the aging process. Such testing can provide and indicate many of the problems that may occur in formulations over time. Therefore, stability testing can guide the chemist during product development to ensure that it will remain safe to use, continuing to be aesthetically acceptable to the consumer for

use over time. The length of time a product remains fit and acceptable for use, is termed its *shelf life*. It should be sufficient to provide adequate time for manufacture and distribution, the expected time duration in retail, and the probable length of time the product will be used by the consumer, all under the environmental conditions anticipated in each segment.

The changes affecting a cosmetic product can be both chemical and physical and are often affected by environmental conditions, such as temperature, humidity, and sunlight exposure, as well as physical stresses such as what experienced in transport. Naturally the topical product' stability testing will depend up on the type of product and its stage of development. At this purpose, stability considerations with respect to the concepts of absolute and relative stability, the stage of product development, and the product/package interactions with both theoric and pragmatic applications of accelerated conditions are discussed in **Section V, Chapters 16 to 18**, *Stability and Preservation* reports all the key factors that have to be considered in the evaluation of topical product stability.

Microbial contamination of topically applied formulations, in fact, can not only affect the cosmetic stability, but can be a consumer safety concern. At this purpose, it is to underline that also if the skin care products are typically not designed to be sterile, they need to adhere to appropriate regulatory criteria for safety with set limits. Most often, the presence of low levels of microorganisms is to be expected as long as they are inhibited from proliferation and are non-pathogenic. A product that adheres to such local regulatory qualifications is considered clean and safe. Preservation is, therefore, an integral part of the success, but it is still only a part of the requirements of a successfully cosmetic product. This is the reason why an adequate preservation of topically applied formulations is required to protect the consumer and the product during its normal intended use and shelf life. Thus, an essential aspect of stability of a formulation is establishing its microbiological safety, which determined through performing a preservative efficacy test, measures the capacity of a formulation's preservative system against microbial contamination.

In conclusion, formulation science is the art of combining a variety of ingredients creating a single coherent physical form while maintaining balance among all ingredients to maintain stability and effectiveness of the final product designed. *Color Cosmetics*, reported in **Section VI, Chapters 19 and 20**, is a particular cosmetic technology and formulation design that require specialized equipments, knowledge and expertise. Thus, for example, as lip product sales continue to grow worldwide, marketers and formulation chemists have to come up day by day with innovative ideas and claims to attract consumers. Moreover, while formulating lip care products is not an easy task, the market of this color cosmetic is highly competitive, with new trend emerging year after year. At this purpose, new ingredients and technology from skin care are now being introduced to provide moisturizing and antiaging benefits for colored lipsticks also.

On the other hand, nail lacquers are other color cosmetics characterized from a high market increase. Fingernails and toenails are, in fact, important anatomical structures that, regarding as an individual's *calling card*, require periodic maintenance for good overall hygiene and health. Thus, nail cosmetics are used to make fingernails and toenails look and feeling well groomed, attractive, and protected. These two chapters report the current developments of all the colours, the polymers and *green raw* materials, used to day for formulating innovative color Cosmetics sensitive to global environmental, safety, and regulatory issues.

The book ends with **Section VII, Chapters 21 and 22**, totally dedicated to *Sunscreens*.

The increasing awareness about the damaging effects of sunlight has led to a significant demand for

more protection from sunscreens and to an enlargement of the concept of sun protection toward global photoprotection. Thus, a topical and a nutritional activity to protect the skin against damages from sunlight are increasingly advocated to the General Public.

The use of UV filters in skin care and cosmetic products together with the oral intake of specialized and protective diet supplements represent, therefore, a key benefit that these products can provide consumers. The predominant physical forms of sunscreens currently on the market are emulsion-based lotions and alcohol-based continuous sprays. Solid sticks and oily formulations are also available. In any way, formulating effective sunscreens requires a number of considerations beginning with the selection and combination of approved UV filters for desired SPF and UVA protection.

In vitro and *in silico* methods can be very useful during development to estimate the right balance of filters within the FDA, Japan, Australia, or EU monographs. Being the lists of sunscreens different among these countries, harmonization of ingredients and efficacy testing methods is on going as well, to provide the end-consumer with adequate protection and clear label information. In any way, a limited menu of UV filters for incorporation into sunscreens is available for the formulating chemist, depending on regulatory requirements in an individual country or jurisdiction.

With the demand for higher SPF's, the trend has been to use more individual and a wider variety of agents in new products. But recent research in sunscreens efficacy has emphasized the need for products protecting skin and mucous membranes against the full UV spectrum with a limited number of available agents. However, while sunscreen efficacy depends on vehicle formulation also, solvents and emollients of the formulation can have a profound effect on the strength of UV absorbance by the active ingredients and at which wavelengths they absorb. Moreover, film formers and emulsifiers, which determine the uniformity and thickness of the film on the skin surface, may determine SPF level, durability, and water resistance of the final formulation also.

These are some of the problems and the challenges the formulator has in developing new and effective formulations. A detailed discussion of incorporating UV filters into various vehicles to achieve defined goals for efficacy and aesthetics is reported on these two chapters.

This interesting book completed with an updated references list and enriched with a glossary of terms, offers the formulator a simple and practical approach to design effective skin care products for topical use, helping him/her to select the right ingredients according with and respecting the today international rules. All the aspects of a modern cosmetic formulation from the selection of raw materials, to the scale-up and pilot production process completed by stability tests and the necessary marketing supports are reported.

Written with the support of well known experts, *Apply Topically* may be useful not only for students in chemistry who wish to know and understand philosophy and technologies necessary for formulating cosmetic products, but may be of useful support for cosmetic chemists in their daily work and for all people of the chemical and medical community who want to have a better technological specific knowledge on the fascinating field of Cosmetic Dermatology

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