# Delivery systems for cosmetic actives

## How to deliver your actives through the skin barrier to their site of action
## In cosmetics trade show, Barcelona (Spain), April 15th 2015

Delivery systems are equally crucial as the active ingredients in a cosmetic formulation. In fact, active ingredients must be targeted to their optimal site of action through the skin barrier to achieve their beneficial actions. Moreover, very often, active ingredients are extremely sensitive to physical (light, UV radiation, heat) and chemical (oxidation, sensitiveness to acids or bases, etc.) degradation and require to be stabilised in the formulation in order to ensure that they retain their efficacy. In addition to that, if more actives are included in a formulation it could become crucial to avoid them from interacting before their effective use. Another problem could be represented by the fact that actives could not be directly soluble in the formulation. Finally, active ingredients could have unpleasant side effects or properties (e.g. cause irritation, have a bad odour give an unpleasant coloration, etc.) and must be masked in the final formulation.
Delivery systems are used to address and solve all these potential formulation issues. They incorporate, stabilise, protect, solubilise, mask and, last but not least, correctly target through the skin barrier the actives in a formulation. A plethora of delivery systems exist and are constantly bettered. The most commonly used delivery systems include liposomes, niosomes, microemulsions and nanoemulsions, micro and nanoparticles, polymeric micelles and cyclodextrin complexes.

The workshop will provide an introduction on the skin structure and the permeability properties of the *stratum corneum*. Subsequently, the effect cosmetic formulations can have on local gene expression patterns will be discussed. Finally, last but not least, specialists form university and industrial research (pharma and cosmetics) will provide an overview on different delivery system today available to cosmetic formulators.

### CRUCIAL ROLE OF THE TISSUE STRUCTURE FOR *STRATUM CORNEUM* PERMEABILITY

**Marek HAFTEK, MD, PhD**
Directeur de Recherches CNRS Laboratoire de Recherche Dermatologique, MatriX, Faculté de Médecine et de Pharmacie UCBL1, Lyon, France

***Abstract***

Stratum corneum is the final product of epidermal differentiation. This continuously renewed layer of dead cells, the keratinocyte-derived corneocytes, constitutes the permeability barrier at the skin surface. Functional competence of this vital barrier has been shown to largely depend on the presence and composition of the intercellular lipids. However, ultrastructure of the intercorneocyte spaces plays an equally important role, not to mention the structure of cellular elements, including cell-cell junctions. In this talk, we shall review the impact of structural variables on the stratum corneum function: in skin physiology, pathology, and upon contact with topically applied treatments.

***Short bio***

Marek Haftek, M.D., Ph.D., is a trained dermatologist working as a Research Director with CNRS (National Centre for Scientific Research). He specializes in the domain of epidermal barrier and its function. He studies, in particular, the intercellular junctions and elements of the extracellular matrix and their implication in the process of epidermal differentiation, i.e., formation of the horny layer and its desquamation, in normal and pathological conditions. He is an expert in ultrastructural and immunocytochemical exploration of the epidermal barrier.
He graduated from Warsaw Medical Academy, Poland (M.D.) in 1975; passed the board exams in dermatology and venereology in 1978-81 and Ph.D. thesis in 1979; became an Associate professor at Lyon University, France in 1985-6 and Researcher at CNRS in 1986. In 1994, he obtained the habilitation to direct research and the Research director degree in 1996. Since 2006 he is the acting Director of the research unit EA4169 "Fundamental, clinical and therapeutic aspects of the skin barrier function" at the University of Lyon.

### ENVIRONMENTAL BIOLOGICAL INFLUENCES ON SPHINGOLIPIDS METABOLISM IN EPIDERMIS

**Dr. Iuliana POPA**
University of Paris XI, School of Pharmacy, Châtenay-Malabry, France

***Abstract***

- Overview of metabolism of sphingolipids (precursors , final products and active enzymes) during differentiation of keratinocytes in epidermis: The way to skin homeostasis
- Sphingolipids metabolism as a key role in response to environmental cellular stress (i.e.: apoptosis, autophagy , aging, atopic skin)
- Exogenous sphingolipids and skin barrier integrity

First of all we should know that the word "sphingolipid" was given because of novel chemical structures making the link between lipids and sugars which was a mystery at that time as well as the signification of the enigmatic and mythological Sphinx. First discovered in the brain, now specific structures that

have been identified in different organs are found to be markers for sphingolipidoses (Fabry, Gaucher, ...), and also markers for differentiation in cancer diseases or in skin, such as protein-bound ceramides in atopic dermatitis and dry skin.
Why environmental changes in sphingolipids in epidermis? Maybe just because skin biology is influenced by external and internal factors (genetics, cytokines, etc.) and because sphingolipids play a major role in cell metabolism and in cell to cell, organ to organ signalisation.
In skin, many studies describe the lipid metabolism and the generation of ceramides in the *stratum corneum* as the latest step of communication with the external world insuring homeostasis.
We can describe how the sphingolipid metabolism is modified as a response to environmental stresses like aging or UV light, or how their synthesis is downregulated in dry skin or ichtyosis, although the underlying mechanisms are still poorly understood.
Then we spot out some of the emollient active sphingolipids manufactured that show a capability to restore the skin barrier and to alleviate the daily problems resulting from a dry skin.

***Short bio***
Iuliana Popa is associate professor at the Faculty of Pharmacy of the University of Paris XI, and board member of the French Society of Cosmetics.
She holds a PhD in Macromolecular Chemistry (Romania) and also a PhD in Biology (France) when she got into the study of gangliosides as sphingolipid markers in melanoma cancer in Lyon. During this time she worked on research subjects related to the ceramides as metabolic precursors in the skin in various diseases in dogs and humans (atopic dermatitis, ichtyosis, melanoma) and during aging. Currently, she is trying to promote the importance of the study of sphingolipids in skin biology in this university where this topic is not yet developed.

**LAST INNOVATIONS IN THE FIELD OF CARRIER SYSTEMS FOR COSMETIC ACTIVES DELIVERY**

**Dr. Gabriele BLUME**
Sopharcos, Research & Development, Consulting, Pharmacy & Cosmetics, Steinau an der Strasse, Germany

***Abstract***
For more than 40 years liposome are used in cosmetics and pharmacy as a penetrating carrier system for active ingredients. Liposomes have the ability to carry hydrophilic, lipophilic and amphiphilic substances and can be used for each of those actives.
Since that time a lot of new carrier systems have been introduced with main ability of stabilizing active ingredients. Most of them have not the ability of skin penetration.
One of the novel penetrating systems are micro-emulsions, colorless emulsions that are easy to manufacture. Their disadvantage is the high proportion of emulsifiers. It is very difficult to incorporate them into final formulations.
Another new carrier system are the Carri-Actives, special produced nano-emulsions . A variant of these penetrating vesicles can encapsulate lipophilic compounds in high concentration.
A second variant, a multiple nano-emulsion can encapsulate hydrophilic and amphiphilic actives. In comparison with conventional liposomes these multiple nano-emulsions show a higher loading efficiency of actives and better penetration ability.
These nano-emulsions are stable in final formulation.

***Short bio***
Dr. Gabriele Blume studied biology and biotechnology at the University of Essen where she graduated in 1985. Subsequently, she continued with Ph D studies at the technical University of Munich, finishing her dissertation in 1991 with the subject "Systemically applied liposomes in the medicine". Then she moved to the University of Utrecht (Netherlands) in order to take a post-doc position dealing with the "chemical modification of liposomes to enhance specific targeting" (stealth liposomes).
In 1992 she started working for IDEA GmbH (Munich) as manager R&D, which means the development and characterisation of topically applied liposomes (Transfersomes) for the pharmaceutical industry.
In 1996 she changed to ROVI GmbH (Schluechtern) as Vice president R&D for the development of flexible liposomes for the cosmetic and pharmaceutical industry. She collaborates effectively with different universities in Germany with specific research tasks to clarify the properties and efficacy of liposomes loaded with active ingredients.
Mid of 2010 she founded her own company "Sopharcos" and is working as consultant and contract developer for the pharmacy and cosmetics. She developed novel drug carrier systems for dermal application (4 new patents pending).

**DEVELOPING SUITABLE FORMULATIONS FOR SKIN APPLICATION CONTAINING LIPID NANOPARTICLE**

**Dr. Marilene Sofia RODRIGUES ESTANQUEIRO**
Laboratory of Pharmaceutical Technology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal

***Abstract***
In the last years, lipid nanoparticles, namely Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC), have been studied for cutaneous application, for both pharmaceutical and cosmetic uses. SLN and NLC have many features that are advantageous for cutaneous application, such as, the controlled release of active substances or ingredients, good tolerability and close contact with the *stratum corneum*, which allow an increase of skin hydration.
Despite the many advantages presented by aqueous dispersions of lipid nanoparticles, their inclusion in semisolid dermal carriers, like creams or gels, is required for topical application. Three options are commonly described: (a) mixing SLN/NLC with existing dermatological bases, (b) addition of viscosity enhancers to the aqueous phase to obtain a hydrogel or (c) the direct production of a first product containing only nanoparticles in a one-step process. This last one requires the use of a greater amount of lipids, which can negatively influence the homogenization, whereby the other two options are the most applied. When we talk in skin application it is also very important to consider the rheological behavior and the mechanical characteristics, such as firmness, and adhesiveness, of the formulations, which can affect the choice of the product, conditioning their acceptability by consumers.

The presentation will give an overview about the development process of semisolid formulations containing lipid nanoparticles as well as their technological characterization and the discussion of some results obtained by our group in this area.

***Short* bio**

Marilene Estanqueiro has a Master Degree in Pharmaceutical Sciences by the Faculty of Pharmacy, University of Porto in 2011 and has a post-graduation course in Pharmaceutical Technology, in 2014. Since 2012 is an invited professor of Laboratory of Pharmaceutical Technology, in the same faculty. In the field of cosmetics, her research interest includes development and technological characterization of cosmetic formulations, as well as efficacy evaluation. Based on this field, during the last years she was worked with sunscreens, geomaterials, extracts and with lipid nanoparticles. She has around eight peer-reviewed articles on international scientific journals and about twenty-five communications (oral and poster) in national and international congresses. She is a member of the Portuguese Society of Cosmetic Sciences.

**INNOVATIVE SYSTEM FOR ACTIVES DELIVERY IN COSMETIC FORMULATION: BALANCING THE INNOVATION WITH THE REGULATORY REQUIREMENTS**

**Serena TONGIANI, Ph.D.**
R&D Director, ANGELINI, S. PALOMBA, Acraf S.p.A., S. Palomba, Pomezia (RM), Italy

***Abstract***

World consumers are expecting the latest technology advances to be incorporated into innovative formulations, both in terms of active ingredients (entering the perimeter of cosmeceutics) and in terms of delivery technologies. To obtain cosmetic formulations with optimized sensory benefits, not only the active ingredients but also the delivery systems play crucial roles. Cosmetics formulators today are looking to mutuate technologies from the pharmaceutical world. This cross-contamination between pharmaceutical and cosmeceutical technologies is very important to promote innovation, and can also maximize the return of the research investment for companies that have a pipeline involving both types of products. However, the challenge is not only to respect regulatory requirements that are constantly evolving in the cosmetic and cosmeceutics world, but also to offer new, smart carrier systems that are able to deliver the active ingredients to one or more skin layers minimizing the systemic adsorption.
In this presentation we will look at the many challenges that Cosmetic Active Ingredient Delivery is facing and at the novel (and not so novel) technologies that may represent an innovative path.

***Short bio***

Serena Tongiani graduated from University Perugia, Italy, with a diploma in Pharmaceutical Science and received a PhD in Chemistry and Pharmaceutical Science from University of Urbino, Italy.
From 2002 to 2005 she worked at the University of Kansas as research associate conducting research on new drug delivery technologies. During this time she synthesized and structurally characterized a new family of cyclodextrin derivatives with superior binding capacity, known as sulfoalkyl-alkyl ether cyclodextrins. These derivatives provide a universal tool to formulate more efficient anti-cancer drugs. They have superior binding ability and low toxicity levels and grant her the opportunity to work in projects funded by the National Cancer Institute. In 2005 Dr. Tongiani joint Schering Plough Corporation, and started to work in the oral and solid formulation product development group. There she followed the development of new chemical entities from bench to commercialization scale up.
In 2010 she took over the position of Head of Preclinical Development departments in ACRAF, Angelini, located in Santa Palomba, Rome. In this responsibility she has led the non clinical research group to develop drug products for various therapeutic area supporting the company portfolio across multiple disease areas. Serena Tongiani in May 2011 became R&D Director of ACRAF, Angelini. As R&D director she balanced the Angelini R&D pipeline to include projects in early development in the main company core areas (Pain and Inflamation, Nervous System and Antinfectives) and projects that support the life cycle management of the products already included in the company portfolio. She also started a dynamic approach to the Angelini's R&D pipeline that gained to the group several partnerships with center of excellence around the world.

**MODERATOR**

**Florian T. E. WEIGHARDT, Ph.D**
Associate Editor, Molecular and Cell Biologist, H&PC Today, TeknoScienze Srl.

**Short bio**

Florian Weighardt was born in Bruxelles – Uccle (B) in 1967. He graduated in 1990 in Biological Sciences at the University of Pavia where he also obtained the PhD in Molecular and Cell Biology. From 1990 to 1999 he has been grant-holder and post-Doc researcher in the field of nuclear RNA binding proteins and nucleo-cytoplasmic shuttling proteins in the Institute of Biochemical and Evolutional Biochemistry (IGBE) of the Italian National Council of Research (CNR) in Pavia. Afterwards, he worked for two years as Telethon Fellow at the Ospedale San Raffaele in Milan. From 2001 to 2004, he worked for Food Products Unit of the Joint Research Centre of the European Commission in Ispra providing scientific support to the implementation of the European Regulatory Framework on genetically modified organisms (GMOs). Subsequently, he worked in the Ichthiology and Aquaculture laboratory of the University of the Insubria in Varese. He joined the TeknoScienze Srl. editorial group in Milan as editorial assistant at the beginning of 2009. Florian Weighardt is author of over twenty peer reviewed articles on international scientific journals and acts today as Associate Editor and scientific writer specialized in technical reviews, essays, interviews and reports for the journals of the TKS editorial group.