CENTER FOR
DERMAL RESEARCH

Innovations in Dermatological Sciences

September 9-10, 2019

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New Jersey Center for Biomaterials

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Innovations in Dermatological Sciences

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CENTER FOR DERMAL RESEARCH

The Innovations in Dermatological Sciences Conference is an annual conference hosted by the Center for Dermal Research. Over the past six years we have covered many topics on advancements in the pharmaceutical industry as well as research and new innovative methods being introduced.

We have seen increased growth in engagement from the academics side, specifically the involvement of students. Each year more and more students are coming to the conference to learn from industrial and academic professionals. These students enjoy the opportunity to network with professionals from the fields they are looking to enter after graduation.

To accommodate this rapid growth of students present at the conference, we are excited to present the Young Scientist Mentor Program as a new addition to the Innovations in Dermatological Sciences Conference that was created with students and young professionals in mind. We hope that undergraduates, postdoctoral students and medical residents as well as industry scientists in the early years of their careers will participate in this new Program. The Mentors will be selected from a pool of mid-career professionals who can discuss current trends in the industry for young scientists and who have faced similar career choice dilemmas in their lives. We hope our Young Scientists will benefit from the advice provided, will expand their networking as well as interviewing skills and learn about different companies and possible career options that they may not have been aware of.

This conference program is designed to inspire and inform young minds in the areas of career development and opportunities in the following areas:

Clinical | Clinical Research | Academics | Pharmaceuticals
Cosmetics| Personal Care industries | Regulatory

Mentor Circle leaders include newly minted industrial/academic professionals who will advise on current and relevant trends in their individual areas of expertise.

All students registered for the conference are invited to a pre-conference dinner. We encourage students to submit poster abstracts, there will be a poster session on September 9th, 2019 from 5:00-5:30. Awards for posters will be announced on September 10th, 2019 at 12:25 PM. There will also be lunch and learns on both days of the conference led by mentors who are relatively new to the workforce. Mentors will discuss a topic relevant to their field of expertise/interest. Each young scientist will have the opportunity to select which mentor/topic is of interest to them at the beginning of each day of the conference. There will be a limit of 8 seats per mentor-led table. Once the slots are full, you must select another mentor table. The lunch and learn is a great way to network without stress and pressure, giving everyone the opportunity to have a casual conversation over lunch and hopefully develop into a reliable connection.

This new addition to the conference could not have been launched without the assistance of Kavita Beri, MD and Kristen Labazzo, PhD. These two ladies are exceptional and have been a major contribution to the success of the program. Dr. Beri brings in her expertise in cosmetic dermatology and Dr. Labazzo has a biomaterials background and is now a professor in Rutgers Biomedical Engineering department.

Program Committee:
Kavita Beri, MD- *Be Mind Body Skin*
Hannah Carter- *New Jersey Center for Biomaterials*
Kristen Labazzo, Ph.D., MBA- *Rutgers Biomedical Engineering*
Bozena Michniak-Kohn, Ph.D., FAPPS, M.R.Pharm.S.- *Rutgers Ernest Mario School of Pharmacy, Center for Dermal Research*

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Innovations in Dermatological Sciences Conference

Young Scientist Mentor Program

September 8-10, 2019

This program is a new addition to the Innovations in Dermatological Sciences Conference!
This conference program is designed to inspire and inform young minds in the areas of career development and opportunities in the following areas:

Clinical | Clinical Research | Academics | Pharmaceuticals
Cosmetics| Personal Care industries | Regulatory

Mentor Circle leaders include newly minted industrial/academic professionalswho will advise on current and relevant trends in their individual areas of expertise.

AGENDA:

September 8, 2019	
7:00PM-9:00PM	**Young Scientist Dinner (Destination Dogs-101 Paterson St, New Brunswick, NJ 08901)**
September 9, 2019	
12:25PM-1:45PM	**Mentor Circle Lunch - Somerset Ballroom**
September 10, 2019	
12:25PM-1:45PM	**Mentor Circle Lunch - Somerset Ballroom**

How Mentor Circle Lunch Works:
Mentors will discuss a topic relevant to their field of expertise/interest.
Each young scientist will have the opportunity to select which mentor/topic is of interest to them at the beginning of each day of the conference. There will be a limit of 8 seats per mentor-led table. The mentor lunch is a great way to network giving everyone the opportunity to have a casual conversation over lunch and hopefully develop into a reliable connections.

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Day 1 – September 9, 2019 Agenda

8:00-9:00 **Registration, Breakfast, Networking**

9:00-9:10 **Opening Remarks**

Joseph Barone, Pharm.D., FCCP–*Rutgers Ernest Mario School of Pharmacy*

David Kimball, Ph.D.–*Rutgers Office of Research & Economic Development*

Bozena Michniak-Kohn, Ph.D., FAAPS, M.R.Pharm.S.–*Rutgers Ernest Mario School of Pharmacy, Center for Dermal Research*

Plenary Session

9:10-9:45 **Understanding and Manipulating Skin Pigmentation**
David Fisher, MD, Ph.D.–*Massachusetts General Hospital, Harvard Medical School, Soltego, Inc.*

Session I: Epigenetics-Roots of Inheritance & Effects on Skin Health

Chair: Kavita Beri, MD–*Be Mind Body Skin*

9:45-10:10 **Harnessing the Potential of Epigenetic Therapy for Skin Disease**
Brian Capell, MD, Ph.D.–*University of Pennsylvania Perelman School of Medicine*

10:10-10:35 **Advancing Personalized Skin Care by Leveraging Epigenetics**
William Lee, MBA–*EpigenCare*

10:35-10:55 **Break**

10:55-11:25 **Epigenetics, Your Ally to Deliver Important Messages to the Skin**
Carine Mainzer, Ph.D.–*SILAB, Inc.*

Session II: Suncare & Hair Aging

Chair: Stephen Rumbelow, Ph.D.–*Croda Inc.*

11:25-11:55 **Broad Protection in Suncare**
Abhijit Bidaye, MS–*Croda Inc.*

11:55-12:25 **Hair Aging – A Novel Botanical for Reversing Hair Graying and Thinning**
Miri Seiberg, Ph.D.–*Seiberg Consulting, LLC*

12:25-1:45 **Lunch, Networking, & CDR Sponsor of the Year**

Session III: How the microbiome and skin nutrition modulate skin physiology

Chair: Inayet Ellis, Ph.D.–*Gattefossé USA*

1:45-2:05 **Plant Based Nutrition and Mindfulness and its effects on the Health of the Skin**
Moiz Kasubhai, MD, MRCP–*Lincoln Medical and Mental Health Center, Weill Cornell University*

2:05-2:25 **The Impact of the "Emotional Body" on the Microbiome-host Interaction and Skin Physiology**
Kavita Beri, MD–*Be Mind Body Skin*

2:25-2:45 **Unlocking the Skin Microbiome: From R&D to Product**
Arne Materna, PhD presenting on behalf of Nur Hasan, Ph.D., MBA–*CosmosID Inc.*

2:45-3:05 **Microbiome-derived Drugs for the Immunomodulation of Autoimmune Diseases- Psoriasis as a Clinical Model**
Ira Spector, Ph.D., MBA–*SFA Therapeutics, LLC*

3:05-3:20 **Break**

Session IV: FDA: Development of Complex Generic Topical Products

Chair: Sam Raney, Ph.D.–*FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance*

3:20-3:50 **Bioequivalence Fundamentals for Generic Topical Dermatological Drug Products: Development and Harmonization of Current Regulatory Standards**
Priyanka Ghosh, Ph.D.–*FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance*

3:50-4:20 **How to Structure Efficient Development Programs for Generic Topical Drug Products: Lessons Learned from Experience**
Tannaz Ramezanli, Pharm.D., Ph.D.–*FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance*

4:20-4:50 **Panel**

Priyanka Ghosh, Ph.D.–*FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance*

Tannaz Ramezanli, Pharm.D., Ph.D.–*FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance*

Sam Raney, Ph.D.–*FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance*

Markham Luke, MD, Ph.D.–*FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance*

4:50-5:00 **Adjourn**

5:00-5:30 **Poster Session**

5:30-7:00 **Reception**

Day 2 – September 10, 2019 Agenda

8:30-9:00 **Registration, Breakfast, Networking**

9:00-9:10 **Opening Remarks**
Bozena Michniak-Kohn, Ph.D., FAAPS, M.R.Pharm.S.–*Rutgers Ernest Mario School of Pharmacy, Center for Dermal Research*

Plenary Session

9:10-9:45 **Naked Eye to Nucleotide, Managing Skin Disease in this Era**
Babar Rao, MD, FAAD–*Rutgers Center for Dermatology, Rutgers Robert Wood Johnson Medical School*

Session V: Formulations, Delivery Challenges and Testing Methods

Chairs: Jamie Lynn Harden, Ph.D.–*Dermira Inc.*
Carine Mainzer, Ph.D.–*SILAB Inc.*

9:45-10:10 **Testing Topical Formulation In Vivo: Can We Improve Methods?**
Stuart Lessin, MD–*KGL Skin Study Center*

10:10-10:35 **Innovative Skin Imaging Solutions for Claims Substantiation**
Matthieu Jomier, MS–*Newtone Inc.*

10:35-10:55 **Break**

10:55-11:25 **A Look in the Rear View Mirror with an Eye on the Road Ahead – Topical Rx Product Development**
Debra Dow, Pharm.D., MBA–*Dow Development Labs, LLC*

11:25-11:55 **Encapsulated CBD for Skin Care**
Samuel Shefer, Ph.D.–*SALVONA Technologies*

11:55-12:25 **Comparisons of Topical Permeation Enhancers via Franz Cell Permeation Studies and Mass Spectrometry Imaging**
Stephen Rumbelow, Ph.D.–*Croda Inc.*

12:25-1:45 **Lunch, Networking, & Poster Awards**

Session VI: Formulations, Delivery Challenges and Testing Methods *(continued)*

Chair: Robert Falcone, Ph.D.–*HRA Pharma*

1:45-2:15 **The Advantage of Target Engagement Studies for the Optimization of Topical Drug formulations**
Alon Mantel, Ph.D.–*Tergus Pharma*

2:15-2:45 **Topical Formulation Strategy – From Concept to Marketed Formulation**
Thean Yeoh, Ph.D.–*Pfizer*

2:45-3:15 **Topical Formulation Possibilities with Penetration Enhancers**
Inayet Ellis, Ph.D.–*Gattefossé USA*

3:15-3:45 **Panel: To CBD or not CBD use in Cosmetics – Advantages & Challenges when considering using CBD and derivatives thereof in Cosmetic Products and Personal Care Applications**
Moderator: Nakissa Sadrieh, Ph.D.–*Food and Drug Administration*
Robert Falcone, Ph.D.–*HRA Pharma US Inc.*
David Steinberg, Ph.D., FRAPS–*Steinberg & Associates, Inc.*
Shahnam Sharareh, Pharm.D., RAC–*Fox Rothschild LLP*

3:45-4:00 **Break**

Chairs: Miri Seiberg, Ph.D.–*Seiberg Consulting, LLC*
Thomas Boyd, Ph.D–*Colgate-Palmolive*

4:00-4:20 **Topical Drug Development: The Changing Landscape**
Jon Lenn, Ph.D.–*MedPharm*

4:20-4:40 **Dermal Drug Discovery: What Physicochemical Properties can (and cannot) Do for You**
Leandro L. Santos, M.Sc.–*Incyte Corporation*

4:40-5:00 **Use of an Ex Vivo Human Skin Model to Assess the Efficacy of Novel Compounds and Topical Formulations**
Jamie Lynn Harden, Ph.D.–*Dermira, Inc.*

5:00-5:15 **Closing Remarks & Prize Drawings**

Speakers' Biographies – & – Abstracts

Innovations in Dermatological Sciences

Kavita Beri, M.D.

Be Mind Body Skin

The Impact of the "Emotional Body" on the Microbiome-host Interaction and Skin Physiology

Biography

Dr. Kavita Beri is a Board-Certified Physician, Scientist and author. She is the founder of BE MIND BODY SKIN, an integrative aesthetics and wellness spa with a "mind body & skin approach" to anti-aging- located in Ocean New Jersey, USA. Dr. Beri is an Adjunct Professor of Biomedical Engineering and Scientist at the Center for Dermal Research at Rutgers University New Jersey. Dr. Beri has published several scientific papers and presented both nationally and internationally on her research in vibrational and quantum healing, vibrational cosmetics, and microbiome science. She has recently authored a book on Tantra Yoga that is released worldwide on amazon and Kindle ebooks. Dr Beri has given talks at the Teen Vogue Summit, In-Cosmetics North America and has been interviewed by Woman's Health Magazine and Euro Cosmetics Magazine related to her work with microbiome, mindfulness and meditation. She is a founder of vegan skincare line KYVTA. Dr. Beri is a reviewer for several journals in Regenerative Medicine and also serves on the Editorial Board of the Future Science Journal and the H&PC Today Magazine. Her passion is in mind body and skin regeneration and their inter-connection. She is also a certified yoga teacher RYT who trains new yoga instructors on the Philosophy of Yoga and the Mind- Body- Soul connection. Her background in Tantra Yoga tradition and various other Yogic backgrounds (influenced from esoteric Egyptian and Vedic Doctrines), are the basis for her work in the Ether room of the spa, as well as the Educational Collaborations of the BE School of Light with Healthcare Organizations and Corporate Organizations. www.kavitaberimd.com

Abstract

Emotions play a strong on their impact on the mental state and in turn the overall health of the body. As the microbiome science has introduced a strong connection of the skin-gut and brain, we take a deeper look at how emotions and energetic states of the body impact the microbiome and the physiology of the skin.

Abhijit Bidaye, M.S.

Croda Inc.

Broad Protection in Sun Care

Biography

Abhijit Bidaye is the Applications Team Leader- Beauty Effects at Croda Inc. During his 21-year career in the personal care industry, he has spent 19 years of his employment on the supply side of the industry with Croda Inc. in the area of both Skin Care and Hair Care. His current focus is on Sun care and color cosmetics. Abhijit is a graduate of University of Cincinnati MS in Cosmetic Science program. He has BS in Pharmacy from University of Pune, India.

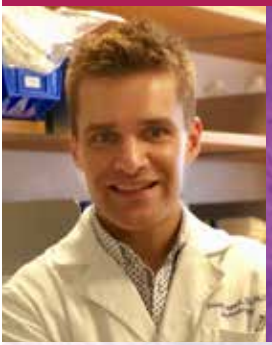
Abstract

UV light is known to damage skin, but visible and infrared (IR) light can also damage skin cells at levels found in sunlight. Cells and tissues exposed to all solar light wavelengths (including UV, visible and IR) sustain more damage than with UV alone.

To explore the extent of this damage, 3D skin substitutes, primary skin cells and skin cell lines have been irradiated with components of solar light with measurements taken of the resulting radical generation and DNA damage. Radical generation in 3D skin models was measured using Electron Spin Resonance (ESR) to test the effects of high energy visible (HEV) light and sunscreen formulations. UV filters in formulations of spf 15 applied to this skin reduced radical generation on exposure to all wavelengths of solar light by 21-70%. When the skin was exposed only to HEV light wavelengths, these UV filtering formulations still reduced radical stress (by 20-75%). UVA filters were particularly important in reducing radical generation in both conditions. ESR also allows us to speculate on potential different mechanisms of radical generation in UV and HEV light by looking at the time course of radical formation.

Further wavelengths effects were examined by assaying Reactive Oxygen Species (ROS), during irradiation, in primary human skin cell monocultures. In keratinocytes from the epidermis, complete solar light generates the same level of ROS as UV does alone ($p > 0.05$). However in fibroblasts from the dermis, complete solar light generates 72% greater ROS than UV alone ($p < 0.001$). This greater damage with complete solar light is also seen when examined using nuclear DNA and mitochondrial DNA damage assays ($p < 0.001$). ROS can also be generated in fibroblasts with visible only irradiation ($p < 0.001$) and IR only irradiation ($p < 0.05$). This shows that all wavelengths in solar light have the potential to cause damage to the skin.

The solar radiation-induced generation of ROS in fibroblasts cell lines has been used as a screening technique for samples from Croda's compound library. This allows the testing of compounds in their ability to reduce damage rather than just their ability to absorb and reflect light, allowing all wavelength effects to be taken into account.



Brian Capell, M.D., Ph.D.

University of Pennsylvania

Harnessing the Potential of Epigenetic Therapy for Skin Disease

Biography

I am a board-certified dermatologist and currently an Assistant Professor of Dermatology in Genetics, core faculty member of the Penn Epigenetics Institute, and member of the Abramson Cancer Center at the University of Pennsylvania. Fascinated by the emerging field of epigenetics, following the completion of my clinical dermatology residency in July 2013, I pursued advanced postdoctoral training under the mentorship of Dr. Shelley Berger, a pioneer in the field of epigenetics and chromatin biology. Through these experiences, I have gained a unique combination of basic and translational research expertise in the interrogation of epigenetic and chromatin regulatory mechanisms in epithelial biology. I aim to harness these basic skills in combination with my clinical knowledge as I build my independent research program focused on answering fundamental questions regarding the epigenome and chromatin regulatory enzymes in the skin and other epithelial tissues, including how they are altered by intrinsic (i.e. aging) and extrinsic (i.e. ultraviolet radiation) environmental influences, and how these changes ultimately contribute to disease. Building off of my previous experiences working on aging and senescence during my Ph.D. with Dr. Francis Collins, and my postdoctoral work studying chromatin regulatory enzymes in cancer, my current work is focused on the following: 1) defining the role of the master epigenetic regulators, and some of the most frequently mutated genes in all of cancer (i.e. KMT2C (MLL3), KMT2D (MLL4), UTX (KDM6A), LSD1 (KDM1A)) in the skin; and 2) understanding how enhancer and epigenetic and epitranscriptomic dysfunction may play a role in epithelial development, differentiation, and carcinogenesis. I anticipate the concepts gleaned from my lab's studies combining human patient samples, primary cells, and mouse models will identify new epigenetic targets for prevention and treatment of inflammatory and neoplastic skin disorders.

Abstract

Epithelial tissues rely on a highly coordinated balance between self-renewal, proliferation, and differentiation. Epigenetic mechanisms provide this precise control through the regulation of gene enhancers and transcriptional networks in order to establish and maintain cell fate and identity. Disruption of these pathways can lead to a loss of proliferative control, ultimately driving cancer. Consistent with this, chromatin regulators are amongst the most frequently mutated genes in all of cancer, with an exceptionally high incidence of mutations in cancers of self-renewing epithelial tissues, such as squamous cell carcinoma (SCC). SCC is the most common type of cancer worldwide, affecting numerous epithelial tissues ranging from the skin and eyes to the lung, esophagus, and oropharynx. Despite this, precisely how disruption of epigenetic homeostasis may drive epithelial cancers such as SCC is poorly understood. In the Capell Lab, we combine cutting-edge epigenetic technologies, human patient samples, primary cells, and mouse models in order to solve these fundamental unanswered questions. Through this, we hope to identify new targets for prevention and treatment of these potentially deadly cancers.

Debra Dow, Pharm.D., MBA

Dow Development Labs, LLC

A Look in the Rear View Mirror with an Eye on the Road Ahead – Topical Rx Product Development

Biography

Debra Dow, PharmD, MBA, has spent over 25 years working on topical product development programs with emphasis on formulation and clinical development. Debra has four formulation patents and has developed products for the treatment of acne, oil control, dry skin, psoriasis, wound healing, ichthyosis, corticosteriod responsive dermatoses, KS, actinic keratosis and herpes labialis. Her direct formulation experience with active ingredients spans from peptides to retinoids, and topical antibacterials and antifungals to PDT compounds. Over the past 17+ years Dr. Dow has overseen clinical operations at Symbio LLC, a derm-focused clinical research organization with offices in NY and Germany. Phase I to phase III clinical studies have been designed and run in numerous dermatology indications including acne, rosacea, psoriasis, actinic keratoses, atopic dermatitis, antifungals, as well as dermal fillers, skin infections & wound healing studies and other dermatology, ophthalmology and women's health indications to support FDA approvals. Debra is currently President of Dow Development Laboratories, a topical product development specialty lab located in Northern California, and Vice President of Scientific Affairs at Symbio, LLC.

Abstract

Topical product development scientists face unique challenges related to their work. Over the past three decades a number of regulatory, scientific and marketplace landscape changes have put us where we are today. In order to successfully navigate topical product development in 2020 and beyond, it is important to understand from where we've come, in order to see where we are headed. A short review of some key regulatory events/happenings and their resulting influence, the evolution (evolving science) of topical generics, topical prescription product approvals over the recent past in various dermatology indications and recent areas of research will be reviewed.

Inayet Ellis, Ph.D.

Gattefossé USA

Topical Formulation Possibilities with Penetration Enhancers

Biography

Dr. Ellis is the Scientific Affairs Manager at Gattefossé USA where she provides, scientific, regulatory and quality support in use of lipid based excipients in USA and Mexico. Prior to Gattefossé, she worked at IPM, Sandoz and Kos Pharmaceuticals as formulation scientists. She has over 15 years of experience in development of various dosage forms from early stage to commercial manufacturing. She obtained her BSc degree in Pharmacy at Ankara University, MS and PhD in Pharmaceutics at University of Rhode Island. She was awarded a fellowship by Hoffmann-La Roche for her dissertation on lipid based drug delivery systems on poorly soluble drugs

Abstract

Poor solubility remains the main challenge for the pharmaceutical industry as it leads to poor penetration and permeation in skin delivery. For formulation of such challenging active pharmaceutical ingredients (APIs), the scientists seek emerging vehicles for such APIs for topical delivery. A safe and effective penetration / permeation enhancer that has emerged over the years is Transcutol®. In this presentation, the art and science of stable formulations with liquid solubilizers/ penetration enhancers in various semi-solid topical formulations such as creams, gels, foams etc that are also patient compliant will be discussed. Moreover, case studies of topical formulations for difficult actives with Transcutol® and other penetration enhancers will be presented.

David Fisher, M.D., Ph.D.

Massachusetts General Hospital

Understanding and Manipulating Skin Pigmentation

Biography

Dr. Fisher studies melanocyte and melanoma biology. His lab has particular interest in understanding pathways of transcriptional dysregulation in melanoma, and their interface with oncogenic signaling. These studies employ a diverse set of technologies including biochemical, molecular, genetic, cellular, animal model, and clinical investigations. Dr. Fisher Directs the Melanoma Program at MGH Cancer Center, where he also sees melanoma patients in the Medical Oncology clinic. He also serves as Chairman of the Department of Dermatology and Director of the Cutaneous Biology Research Center at MGH. He has extensive experience in collaborative studies, and also focuses his research largely on the translation of basic science observations to clinically tractable opportunities.

Abstract

Skin pigmentation plays a diversity of roles in human biology which span modulating risk of cutaneous malignancy to cosmetic and psychosocial influences. Studies in recent years have elucidated many mechanistic details underlying the control of pigmentation, within both skin and hair, which include both constitutive and adaptive (UV-induced) melanin biosynthetic pathways. The same pathways have also been found to modulate broader biologic responses, such as UV-seeking behaviors. This presentation will review our understanding of the molecular pathways underlying control of melanin synthesis, regulation of the "switch" between red/pheomelanin vs dark/eumelanin synthetic programs, and highlight recognized nodal points which may serve as targets for small molecule manipulation of pigment synthesis. The potential impact of strategies to alter skin pigmentation, such as related to UV or skin cancer protection, will also be discussed within the context of currently existing UV-protection strategies.

Priyanka Ghosh, Ph.D.

FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance

Bioequivalence Fundamentals for Generic Topical Dermatological Drug Products: Development and Harmonization of Current Regulatory Standards

Biography

Dr. Priyanka Ghosh is a pharmacologist within the Office of Research and Standards, Office of Generic Drugs. In her current role, Dr. Ghosh is responsible for research and regulatory (product-specific guidances for generic drug development, controlled correspondences, citizen petitions, Pre-ANDA meeting packages) projects in the dermal drug development area.

Abstract

The availability of generic topical dermatological drug products can make prescription drugs more affordable and enhance patient access to these critical medicines. However, there can be substantial uncertainty about specific aspects of how to approach the development of complex generic drug products. The goal of this presentation is to discuss scientific challenges related to the development of complex topical dermatological drug products and to describe how the United States Food and Drug Administration (FDA) has leveraged the results of research funded by the Generic Drug User Fee Amendments (GDUFA) to develop alternative, more efficient approaches by which to establish bioequivalence (BE) for these drug products. The presentation will also clarify the FDA's BE standards and recommendations related to topical dermatological products.

Jamie L. Harden, Ph.D.

Dermira, Inc.

Use of an Ex Vivo Human Skin Model to Assess the Efficacy of Novel Compounds and Topical Formulations

Biography

Jamie Harden, Ph.D. is the Associate Director of Immunology Research at Dermira - a biopharmaceutical company located in Menlo Park, California focused on bringing innovative treatments to patients with chronic skin disease. Jamie currently leads several early research programs focused on targeting inflammation in skin.

Jamie obtained her B.A. in Microbiology and Genetics from The Ohio Wesleyan University (2002-2006), and Ph.D in Immunology from the School of Medicine and Biomedical Sciences at the State University of New York at Buffalo (2006-2011). She then continued her training as a postdoctoral researcher at The Rockefeller University in the Laboratory for Investigative Dermatology under the direction of Dr. Michelle Lowes and Dr. James Krueger (2012-2015). In 2015, Jamie joined Dermira and has combined her immunology expertise with skin biology to develop new in-house methods for studying inflammatory skin diseases.

Abstract

The ability to assess the efficacy of novel small molecules and other therapeutics is critical to moving a research candidate into the development pipeline. Although cell culture and animal models can provide support of target engagement, they do not fully capture the complex inflammation occurring in human dermatological diseases. Dermira has developed a robust model using ex vivo human skin to evaluate the efficacy of novel compounds and topical formulations. Using surgical waste skin, the resident immune cell population can be 'coaxed' into a variety of inflammatory states, known to play a role in specific skin diseases. We call this model the skin Resident Immune Cell Assay (sRICA), and this model uniquely allows for an interplay between activated skin-resident immune cells and neighboring stromal cells. The sRICA model can then be utilized to evaluate the anti-inflammatory effects of novel therapeutics, including elucidating compound IC50's in situ, characterizing anti-inflammatory profiles, determining topical delivery potential, and aiding in formulation selection. Although the sRICA models are useful in elucidating anti-inflammatory mechanisms, no single model fully captures the inflammation occurring in actual patient tissue. Therefore, a final step in our evaluation of a novel therapeutic occurs by treatment of patient tissue ex vivo. By combining results from both the sRICA model and patient biopsies cultured ex vivo, we can more confidently support the development of early research candidates and enhance the likelihood of clinical success of novel treatments for inflammatory skin diseases.

Nur A. Hasan, Ph.D., MBA

CosmosID Inc.

Unlocking the Skin Microbiome: From R&D to Product

Biography

Dr. Nur A Hasan is a molecular microbiologist with experiences in microbial genomics, metagenomics, and molecular ecology. Dr. Hasan is the Chief Scientific Officer at CosmosID Inc. and an adjunct faculty at the Center for Bioinformatics and Computational Biology, University of Maryland, College Park, MD. Dr. Hasan received his Bachelor and Masters in Microbiology, M.B.A in Marketing and Ph.D. in Molecular Biology. He has authored over 75 peer-reviewed articles and over 70 conference proceedings. Currently, Dr. Hasan is leading an effort in developing the world's largest curated genome databases and ultra rapid bioinformatics platform for pathogen detection and cross-disciplinary microbiome research.

Abstract

As microbiome research advances and new therapeutic approaches progress along clinical pipelines, the technology for metagenomic sequencing and analysis is evolving to meet emerging regulatory standards. Robust, standardised, and validated workflows for sample preparation and sequencing are crucial to control the introduction of bias. The clinical actionable and informative unit in microbiology is a strain, not a genus or species. With declining costs for shotgun metagenomic sequencing, modern bioinformatic and database solutions are required to accurately delineate microbial communities down to strain-level. To this end CosmosID has developed most comprehensive microbiome analysis platform with world largest curated genome database and ultrafast bioinformatics tool and developed Clinical Laboratory Improvement Amendments (CLIA) certified Next Generation Sequencing Service Laboratories with integrated, reproducible, end-to-end "sample to answer" workflow, starting with appropriate study design, sample size calculation, laboratory optimized and validated SOPs for sample collection, processing and sequencing. Adequate standards and controls are used to reduce bias and ensure reproducibility. CosmosID has developed a cost effective shotgun metagenomics to help explore multi-kingdom microbial community, resistome, virulome and functional analysis of the skin microbiome, and demonstrate data unseen by traditional 16S analysis to accelerate discoveries and product development.

Matthieu Jomier, M.S.

Newtone Inc.

Innovative Skin Imaging Solutions for Claims Substantiation

Biography

Matthieu Jomier is currently managing director of Newtone Inc. (Princeton, New-Jersey) where he focuses on North and South America business development and support.

Matthieu received his B.S. and M.S in Electrical Engineering and Computer Science in 2002 from the ESCPE-Lyon (France) where he specialized in image processing, data modeling and computer vision.

He worked on a variety of projects in the areas of medical image processing, hyperspectral imaging and clinical image analysis. Matthieu developed in-vivo and in-vitro solutions to assess product efficacy in correlation with consumer perception.

Prior to joining Newtone, Matthieu was a research associate in the Neuro Image Analysis Laboratory at the University of North Carolina at Chapel Hill and worked for the Molecular and Ionic Spectroscopy research center in Lyon, France.

Abstract

Non-invasive skin imaging techniques have become increasingly available to evaluate the effectiveness of a wide range of cosmetic and personal care products. Whether for 2D or 3D analysis, innovative high sensitivity acquisition systems combined with specific image processing algorithms can be easily used for reliable and objective evaluation in clinical trials.

New smartphone-based acquisition solutions are now available to capture skin data directly from the consumer at home, increasing the number and frequency of acquisitions during clinical studies. Other imaging techniques, such as hyperspectral imaging of the entire face, can still play a very important role in the quantitative analysis of skin components and thus provide new methods for substantiating claims.

Finally, thanks to significant advances in artificial intelligence or automatic learning methods, it is now possible to use a large volume of generated data to optimize the correlation between in vivo instrumental measurement, expert ranking and visual consumer perception.

Moiz Kasubhai, M.D., MRCP

Lincoln Medical and Mental Health Center,
Weill Cornell University

Plant Based Nutrition and Mindfulness and its Effects on the Health of the Skin

Biography

I have practiced as a Physician in India, United Kingdom and United States and the accumulated experience has given me an in-depth perspective of Healthcare. The acute management of diseases, be it traumatic or non-traumatic, and prevention by way of immunizations, clean drinking water and safe environment is excellent in the western world. But the focus individually is on sick care and not on keeping one's mind and body robust and resilient. The predominant curriculum of teaching our medical student and doctors in training is also based on sick care, because that is where reimbursements are from the payers of healthcare.

Many of us have started this new journey of keeping the citizens of this country healthy in mind and body and some of the tools we have are Mindfulness and Plant Based Nutrition. This scientific movement will only gain in momentum and is now being noticed by lay people, healthcare policy experts and payers and will yield immense benefits in reducing sick care.

Abstract

Mindfulness is an age old practice, which is now backed with evidence based medicine showing its amazing benefits in stress reduction, reducing negative thoughts, improving memory and focus, all of which have a direct bearing on improving relationships, work satisfaction and better quality of life. This translates to improvement of skin conditions along with conventional medical treatment.

Plant Based Nutrition is the approach one takes in improving one's health by increasing intake of vegetables, beans, whole grains and fruits. These are nutrient rich foods, which fill you up and leave less room for less healthy foods. They decrease the risk of chronic diseases such diabetes, hypertension and heart disease by decreasing the likelihood of gaining weight, lowering blood sugar and cholesterol and decreasing abdominal fat. Vitamins, carotenoids, tocopherols and flavonoids possess anti-oxidant properties to improve the skin.

William Lee, MBA

EpigenCare Inc.

Advancing Personalized Skin Care by Leveraging Epigenetics

Biography

William Lee is co-founder of EpigenCare Inc., a new consumer epigenetics company that recently debuted its personalized skincare solution SKINTELLI. He has over 10 years of experience in the biotechnology sector and is also a shareholder and senior executive of EpiGentek, a reagent and services provider for epigenetic research. In his spare time, he enjoys writing music and hiking a scenic trail. William graduated from New York University with honors and obtained his MBA from the Tepper School of Business at Carnegie Mellon University.

Abstract

Epigenetics is the study of biological mechanisms that can silence or express genes, with one of the most well characterized mechanisms being DNA methylation. Despite having been proposed as the first true epigenetic mark over 40 years ago as well as having structured research initiatives in the last 20 years, DNA methylation has yet to fulfill its potential for in vivo dermatological applications. In this presentation, we explore the importance of the dynamic aspect of DNA methylation and how its interplay with individualized environmental factors can regulate protein production essential to skin quality and appearance. By focusing on cosmetic as opposed to purely clinical applications with this epigenetic mechanism, we can expect a more strategic approach to data accumulation and correlation, and ultimately rapid development towards true consumer personalization in skincare.

Jon Lenn, Ph.D.

MedPharm

Topical Drug Development: The Changing Landscape

Biography

Jon Lenn has direct responsibility for setting MedPharm's scientific technology strategy. Since joining in 2015 he has led MedPharm's development of cutting edge performance models for assessing penetration and activity of clients' products targeted towards key biochemical pathways. He has over 17 years' experience in developing dermatological projects with Connetics, Stiefel and GSK and has been directly involved with the development and approval of 8 products. He received his PhD on the topical delivery of macromolecules from the University of Reading.

Abstract

The approval of monoclonal antibodies has revolutionised the management of psoriasis and more broadly dermatology and the global dermatology market is forecast to increase to $36.6 billion in 2023 with a growing interest in areas such as 'omics' and gene therapy. As the boundaries of molecular targets continue to be pushed both biologics and small molecular weight drugs require topical delivery; at least until the nanobots are here to save the day. Thus, alternate technologies for drug delivery to the skin and product development are required to increase the chances of success. This presentation will cover these challenges including the areas that are ripe for innovation in topical delivery and formulation development along with the advancing performance testing 'tool box' which is making real differences in the time required and expense of topical product development.

Stuart R. Lessin, M.D.

KGL Skin Study Center

Testing Topical Formulations In-Vivo: Can We Improve Methods?

Biography

Stuart R. Lessin, M.D. serves as Medical Director of KGL Skin Study Center, a Philadelphia-based independent clinical research facility providing safety and efficacy testing of cosmetics, personal care products and pharmaceutical drugs and devices. He is a board certified dermatologist with over 30 years of laboratory and clinical research experience including topical drug development and testing, from IND to NDA submission. He is a former lab chief at the University of Pennsylvania where he developed techniques for molecular diagnosis of cutaneous lymphomas. He is the former Director of Dermatology at the Fox Chase Cancer Center in Philadelphia, PA where he created and directed clinical care programs and a clinical trial unit. He currently serves as Vice-President of the Dermatology Foundation.

Abstract

Testing the safety of topical formulations is an essential element in the development of cosmetics, personal skin care products and pharmaceuticals. The avoidance of animal testing has made in-vivo testing in humans the de facto method for validating in-vitro testing. Repeat insult patch testing (RIPT) involves the repeated application of an ingredient or formulation to the skin, under occlusion for variable periods of time. RIPT protocols have been developed for assessing potential development of contact sensitization (allergy), primary and cumulative irritancy, photosensitivity (phototoxicity and photoallergy) and comedogenicity. Contact allergy is a major complication of topical product use and is responsible for a large clinical burden. The current RIPT method of testing for contact allergy potential supported by United States Food and Drug Adminstration guidance is labor intensive with unspecified sensitivity. Validation of simpler and more sensitive methods is needed and will be discussed.

Carine Mainzer, Ph.D.

SILAB, Inc.

Epigenetics, Your Ally to Deliver Important Messages to the Skin

Biography

Dr. Carine Mainzer joined SILAB Inc in 2016 as a Scientific Support Manager, a position at the crossroads between academic and industrial research, where scientific and innovative ideas are applied to the field of personal care to support the development of natural active ingredients for healthy and compromised skin. In this search of breakthrough innovations, she works actively with universities to identify and develop sustainable partnerships throughout the US. Prior to joining SILAB Inc, Dr. Mainzer has worked with Johnson & Johnson Consumer France and Natura. She has a background in tissue engineering, epidermal differentiation and skin barrier function. She holds a Ph.D. from the University of Lyon (France) and completed her postdoctoral fellowship under the supervision of Dr. Peter Elias and Dr. Yoshikazu Uchida in the Department of Dermatology at the University of California, San Francisco. She has authored several peer-reviewed publications and blog articles for the New York Society of Cosmetic Chemists (NYSCC) and The Cosmetic Chemist; and performed several presentations at dermatology and cosmetic conferences. She is part of the scientific committee of the NYSCC.

Abstract

Throughout its lifetime, an individual will encounter several epigenetic modifications that will alter the way its genes are expressed, with consequences at multiple levels in the body including hair and skin. Because of this central role in biological processes, we have made of epigenetic our research signature to help us understand the epigenome/hair and skin relationship and develop adapted natural solutions to restore their homeostasis.

In this context, one particular study that we focused on was to characterize the epigenetic impact in photo-aged skin and understand specifically how miRNA modulate the expression of mRNA coding for extracellular matrix components. Our experimental model consisted of fibroblasts and human skin explants that were irradiated repetitively with solar simulated radiations to induce a photo-aged phenotype that was assessed through broad spectrum aging markers. We next analyzed both the miRNome and the transcriptome (miRNA and mRNA profiles respectively) on irradiated fibroblasts in the search of potential interdependent interactions. Our analysis revealed multiple variations in miRNAs and mRNAs expression profiles, and notably a specific reduction in the expression of both miR-22-5p and -199a-5p that was correlated with an increased expression in extracellular matrix disruptor MMP1 in both irradiated fibroblasts and human skin explants. These functional correlations were supported by the overexpression of each miRNA mimics in a model of transfected fibroblasts.

Altogether this study highlighted, for the first time in dermo-cosmetic research, the functional characterization of epigenetic regulations on photo-aged skin and supported the development of a natural active ingredient protecting skin against environmental stress and aging.

Alon Mantel, Ph.D.

Tergus Pharma

The Advantage of Target Engagement Studies for the Optimization of Topical Drug Formulations

Biography

Dr. Alon Mantel brings over 15 years of practical knowledge of human skin structure, function and pathology. He received his PhD training in skin biology at the department of dermatology at the University of Rochester, NY, and continued his scientific career at the Skin of Color Research Institute at Hampton University in VA. His work contributed greatly to the understanding of the molecular pathways involved in epidermal differentiation, abnormal scar formation, and progression of skin cancer. His work on human skin function and disease has been published in top journals and received several awards and recognitions by his peers. Currently, Alon serves as a senior skin biologist at Tergus Pharma where he develops novel assays using ex-vivo human skin. Such studies, designed to address challenges in development of topical formulations, include validation of target engagement, skin irritation testing, effects on pigmentation, evaluation of skin barrier function and more.

Abstract

Topical formulations for drug delivery are becoming increasingly popular. The biggest advantage of topicals is the ability to deliver drugs more selectively to a specific site, thus, reducing the risk of systemic adverse effects. Successful delivery however, relies heavily on having the optimal formulation because even a small change in the composition or properties can make a large difference in treatment efficacy. Good formulation development process is usually supported by data from stability, irritation/toxicity, in-vitro release testing and skin penetration studies. While such experiments provide important information regarding drug distribution and the physical properties of the formulation, they lack the capacity to determine whether the drug engages its molecular target. Thus, target engagement studies designed to evaluate the biological activity of a drug should be considered for formulation optimization, and for improved chances for successful outcomes in the clinic.

Tannaz Ramezanli, Pharm.D., Ph.D.

FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance

How to Structure Efficient Development Programs for Generic Topical Drug Products: Lessons Learned from Experience

Biography

Tannaz Ramezanli currently serves as a staff fellow within the Office of Research and Standard (ORS) at Office of Generic Drugs (OGD) at the U.S. FDA. She works as a reviewer within the Topical and Transdermal Team at ORS. She is responsible for the development of product-specific bioequivalence guidances, reviewing and responding to controlled correspondences and Pre-ANDA meetings. Tannaz Ramezanli is also engaged in the development of regulatory science research initiatives related to topical and transdermal drug products through FDA-funded collaborations with research institutions around the world. She received her Ph.D. in Pharmaceutical Sciences from Rutgers University and her Pharm.D. from Tehran University of Medical Sciences.

Abstract

The goal of this presentation is to discuss specific issues of scientific or regulatory complexity related to developing topical dermatological drug products and how to communicate with and get feedback from the United States Food and Drug Administration (FDA) during product development. This presentation utilizes case studies to illustrate how to efficiently navigate complex product development issues for different topical dermatological drug products, discusses what kinds of evidence can be used to demonstrate bioequivalence (BE) for different types of prospective generic topical products, and illustrates how the evidence for characterization-based BE standards is modular and scalable, as appropriate to the nature and complexity of the drug product.

Babar Rao, M.D., FAAD

Rutgers Center for Dermatology,
Rutgers Robert Wood Johnson Medical School

Naked Eye to Nucleotide, Managing Skin Disease in this Era

Biography

Dr. Babar K. Rao is board certified in both Dermatology and Dermatopathology and is a leading authority on pigmented lesions, as well as a pioneer in Dermoscopy and Reflectance Confocal Microscopy (RCM). Doctor Rao has completed residency training and fellowships at the University of London, UT Southwestern, New York University, and Cornell University, and currently serves as Clinical Professor of Dermatology and Dermatopathology at Rutgers – Robert Wood Johnson Medical School. Doctor Rao is also an Associate Clinical Professor of Dermatology at Weill Cornell Medical College at Cornell University and president of the American Confocal Group.

Abstract

Traditionally if a concerning skin lesion is not diagnosable by the naked eye, it is biopsied and analyzed histologically thereafter. Similarly, for understanding treatment effects (medical or aesthetic) for a given skin condition, a biopsy is generally required. Biopsies are invasive procedures, and result in scarring in addition to pain/discomfort and other psychological effects. Many skin lesions that look abnormal to the naked eye, especially nevi, are biopsied, but usually reveal a benign histology. If most of these lesions are benign, then continuing to perform invasive biopsies in this era, is questionable. Therefore, there is a need for other, non-invasive technologies to diagnose these lesions without cutting. Several such tools exist, many of which are computerized readings that tell you whether or not to biopsy a lesion. Others, such as OCT and ultrasound generate the overall architecture of the tumor, but lack the same resolution of a histology slide [1]. Reflectance Confocal Microscopy (RCM), on the other hand, is gaining popularity with clinicians because the high-quality resolution of the images, and the main difference from histology being that they instead have grey-scale images. There are numerous studies proving the diagnostic accuracy of RCM, which is currently being used in various clinical settings, including for treatment monitoring [2]. Additionally, there are numerous other tools which can provide further details into the cellular activity and chemical reactions in the cell and tissues. A systematic review of managing skin lesions beginning with the naked eye, all the way into the nuclear changes, will be discussed in this presentation.

Stephen Rumbelow, Ph.D.

Croda Inc.

Comparisons of Topical Permeation Enhancers via Franz Cell Permeation Studies and Mass Spectrometry Imaging

Biography

Steve Rumbelow is the Research and Technology Manager for the Innovation Support and Health Care for Croda Inc. Steve has been in this position since 2014, managing a Health Care team responsible for both generating new high purity excipients for the pharmaceutical industry. This includes products for all major delivery routes and applications, ranging from emulsifiers and dispersants through to solvents and permeation enhancers and the team is also very active in generating accompanying performance and application data for such applications, with a particular emphasis on the impact of excipient purity on drug delivery and performance. The Innovation Support team (formerly Analytical) closely support this teams activities as well as supporting other R&D teams within Croda, covering a wide variety of industries, including Personal Care and Performance Chemicals.

Steve graduated from Leeds University with a PhD in 1982 and started his career in the food and fine chemical industries, developing his skills in analytical chemistry (primarily chromatography and mass spectrometry) covering areas ranging from trace analysis through to polymer characterization, during which he has worked with a combination of conventional and novel separation techniques to resolve complex problems. Starting his career with Cadbury Schweppes in the UK, Steve joined ICI in 1995 before moving to the US division of Uniqema (an ICI business) 1999 before finally joining the R&D team in Croda in 2007. During his career he has authored more than 40 scientific presentations, posters and articles and has been involved on several industry specific and technique-based groups and expert panels (including most recently, the USP). Current memberships include the AAPS, American Society of Mass Spectrometry and the Controlled Release Society.

Abstract

This talk will feature the results of our initial investigations into the combined use of Franz cell permeation studies and MALDI-MS imaging techniques, enabling us to more accurately compare the performance of different permeation enhancers in topical applications. Through this combination of techniques, it is possible to compare the efficacy of these products in terms of flux, lag times, permeability constants, distribution and localization within human cadaver skin.

Leandro L. Santos, M.Sc.

Incyte Corporation

Dermal Drug Discovery: What Physicochemical Properties can (and cannot) Do For You

Biography

Leandro is currently Associate Director, Clinical Sciences, at Incyte Corporation. He holds a double major in Pharmaceutical Sciences and Biochemistry from the University of Sao Paulo (Brazil) and a Master of Science in Analytical Chemistry from the University of North Carolina at Chapel Hill. He joined Incyte in 2019 as a clinical scientist with focus on late-stage development of drugs for treatment of inflammatory diseases after spending 14 years in Nonclinical Discovery and Development at Stiefel/GlaxoSmithKline and Dermavant, and has worked in different areas of Rx and Cx dermal product development, including analytical, formulation, preformulation, DMPK, and drug delivery. He has led projects focused on various stages of development, as well as conceptualized and implemented tools used in in silico, in vitro and in vivo workflows. He has co-authored nonclinical sections of regulatory submissions, as well as patents and papers in peer-reviewed journals, and contributed to the development of several assets currently in clinical stage of development.

Abstract

Physicochemical properties such as molecular weight, lipophilicity, molecular volume and polarizability have been primarily utilized in Dermatology as a starting point for prediction of skin flux values and relative ranking/selection of molecules prior to preformulation and/or formulation development. Considering that new molecular entities (NMEs) in topical Dermatology are typically rare, with an annual average of less than one compound approved by the FDA for the past 10 years, drug repurposing is more commonly observed, typically using an oral drug. While the ideal physicochemical properties of oral and topical/dermal molecules overlap to a certain extent, dermal drug discovery can provide an opportunity for designing and selection of better compounds properly tuned for skin delivery. Additionally, medium-throughput and small scale assays can be designed to provide an early assessment of compound suitability for topical formulation development and dermal delivery during lead optimization stage, de-risking the candidate selection process. The presentation will provide an overview of in silico and in vitro workflows and tools which can be applied in dermal drug discovery.

Miri Seiberg, Ph.D.

Seiberg Consulting, LLC

Hair Aging: A Novel Botanical for Reversing Hair Graying and Thinning

Biography

Miri Seiberg is a skin and hair R&D expert with a track record of research innovation. She has initiated and managed research and development programs in the fields of skin, hair and mucosal tissue biology, resulting in novel drug candidates and successful consumer products (AVEENO, Neutrogena). Miri is involved in R&D projects of active ingredients, botanical extracts, skin health and aging, skin pigmentation, hair growth, hair pigmentation, skin cancer, skin diseases, wound healing, skin tissue engineering and regenerative medicine, and is supporting the development of drugs, devices and consumer products.

Miri Seiberg received her BSc from Tel Aviv University, Israel, and her MSc and PhD from the Weizmann Institute of Science, Israel, in collaboration with Princeton University, USA. She authored more than 60 peer-reviewed publications, reviews and book chapters, and has more than 80 patents. Miri spent 20 years at the Johnson & Johnson Skin Research Center, where she received numerous awards, including the Johnson Medal, the most prestigious award given for research and development at J&J. She is currently involved in skin and hair R&D consulting and in the development of botanicals for skin and hair unmet needs.

Abstract

The graying and the thinning of the hair are visible signs of the aging process, which many cultures wish to hide or reverse. While the anti-aging industry provides numerous solutions to facial skin aging, very limited options are available for hair aging. The most often used hair graying remedy is hair dyeing ("coloring"), which unfortunately involves harsh chemicals, and is only effective for a short term. Minoxidil, a hair loss treatment, produces noticeable hair growth results after months of use, but has no effect on hair graying. Few natural remedies claim effectiveness for hair loss or graying, however there is no scientific or clinical confirmation to these claims.

Numerous mechanisms, acting at different levels and follicular locations, contribute to hair graying, and they are all affected by oxidative damage. A key follicular graying mechanism is the marked reduction in catalase expression and activity. This decrease results in millimolar accumulation of hydrogen peroxide, leading to melanocyte malfunction and death. A pseudo-catalase small molecule treatment for vitiligo induced re-pigmentation of eyelashes, providing a proof of concept for "anti-gray" treatments that act like catalase.

The discovery and development of a botanical with catalase-like activity will be discussed. A pilot human hair study documented the statistically significant reversal of hair graying and thinning.

Samuel Shefer, Ph.D.

Salvona Technologies, LLC

Encapsulated CBD for Skin Care

Biography

Sam Shefer is the founder and president of Salvona Technologies, a company focused on the development and manufacturing of microspheres technologies for topical cosmetic and dermatological products. Salvona was established 20 years ago and most recently relocated to Hamilton, NJ to meet the needs of its organic growth. The company offers custom encapsulation as well as a large catalog of encapsulated items of most common APIs and functional ingredients that are used in the field. Sam earned degrees in Life Sciences and Chemical Engineering, and a postgraduate degree with Prof. Robert Langer at the Massachusetts Institute of Technology. The Biomaterial center of Rutgers University honored Sam as the Entrepreneur of the Year in 2016.

Abstract

We developed a novel delivery system for CBD (Cannabidiol) for use in topical applications to enhance its benefits when used in skin and hair care products. CBD is extracted from Cannabis Sativa in a multiple step process to produce either Full, Broad (does not contain any detectable levels of THC) and Isolate CBD that contains 99% CBD. The Full spectrum CBD is a true reflection of the natural extract consisting of CBD as well as THC and other terpenes. CBD is available commercially in solid and soft solid forms that are not soluble in water and is highly sensitive to low and high pH values, temperature and light. CBD is identified to be effective when applied topically due to the presence of receptors (CB2) in sensory neurons, keratinocytes, sebocytes, and in the dermal immune cells among other cells in the skin. There is a need to protect the CBD in order to make it commercially available for topical applications such as lotions, rubs, washes etc. The encapsulation is based on Salvona's proprietary microsphere production that is based on entrapping of the CBD in semi solid lipids with different properties including crystallization and molecular entanglements while homogenizing under high shear and high pressure and temperature drop, to form spheres with an average diameter of 1-10 microns. The created spheres are made of 100% natural and sustainable ingredients, exhibit 150% higher stability, and are easy to formulate in the production process of variety of topical product forms.

Ira C. Spector, Ph.D., MBA

SFA Therapeutics, LLC

Microbiome-derived Drugs for the Immunomodulation of Autoimmune Diseases – Psoriasis as a Clinical Model

Biography

Dr. Ira Spector is an experienced drug developer, with over 25 years of experience in drug and medical device development. He has helped develop 34 approved drugs and 12 medical devices. Ira has held leadership roles on teams that developed EnbrelTM for rheumatoid arthritis and other autoimmune indications, EffexxorTM for depression, ProtonixTM for GERD, Prevenar TM for preventing pediatric pneumonia and Prevenar-13TM for preventing adult pneumonia, ToriselTM for kidney cancer, MylotargTM for Acute Myelogenous Leukemia (the first targeted cytotoxin-Monoclonal Antibody conjugate for a difficult to treat form of leukemia), and many other major drugs. At Wyeth/Pfizer he was Vice President of Clinical Operations and Vice-Chief of Development, responsible for all clinical trials from phase 1-4 in oncology and phase 2-4 in all other diseases. While at Wyeth, Ira was responsible for managing one of the world's largest adult vaccine trials, in Community Acquired Pneumonia in adults, with 85,517 subjects, that led to the approval of Prevenar-13TM; one of the largest global Alzheimer's disease trials, with 4,000 subjects (bapineuzumab); and one of the largest clinical programs in breast cancer (neratinib), now approved as NerlynxTM for HER2+ breast cancer, with over 4,000 subjects. He then went on to Allergan, where he helped develop OzurdexTM for Diabetic Macular Edema and Retinal Venous Occlusion, BotoxTM for Overactive Bladder, BotoxTM for Chronic Migraine, JuvedermTM XL and BotoxTM for Cerebral Palsy.

Prior to joining Wyeth, he was Vice President and Partner at the PA Consulting Group, an international management consulting organization, where he was responsible for their US Healthcare Practice. Among the interesting projects he ran there was the selection of the CCD camera chip that enabled J&J Ethicon and Olympus to create the first flexible endoscope, and Ethicon's first surgical instruments for minimally-invasive surgery. Before founding SFA Therapeutics, Ira was Executive Vice President of Analytics & Consulting at ICON, a global contract research organization, where he built their scientific consulting organization. In addition to SFA Therapeutics, Ira has helped found three other startup companies; Diamonex/CrystallumeTM for diamond thin films (sold to Monsanto), QMACTM for semiconductor process controls (spun out to Versum), and an infrared materials business (DOD classified).

Dr. Spector is a co-founder of SFA Therapeutics, a development-stage bio-pharmaceutical company focused on a new advancement in the treatment immuno-inflammatory diseases, using small molecules first identified in the GI microbiome. SFA's initial focus is in psoriasis and liver cancer (hepatocellular carcinoma, also known as HCC), the fifth leading cause of cancer death. Patents have been granted in preventing the progression of hepatitis B, which afflicts 270 million people, to hepatocellular carcinoma, which causes almost 1 million cancer deaths per year; and in treating liver cancer directly; with additional patents expected in a wide range of immuno-inflammatory diseases, including preventing cytokine release syndrome (also known as cytokine storm), a major fatal side effect in CAR-T (immunotherapy in oncology); and in preventing relapse/recurrence in leukemia and lymphoma.

Ira holds BS degrees in Physics and Electrical Engineering from Washington University (St. Louis), where he was a Langsdorf Fellow and Dean's Scholar, an MBA from Drexel University (Philadelphia), and a PhD in Clinical Health Sciences (specializing in biostatistics and epidemiology) from the University of Medicine and Dentistry of NJ (Newark, now Rutgers University).

Abstract

Despite numerous brands and attempts to develop drugs for psoriasis, it remains a disease with serious unmet medical needs. With over 100 million patients, and growth of over 9% per year, treatment for patients with moderate-severe disease is still a major unmet need, due to patient concerns regarding the safety of existing drugs. SFA Therapeutics, a development-stage bio-pharmaceutical company, is focused on a new way to treat chronic inflammatory diseases, based on GI microbiome metabolites. Chronic inflammation has been implicated in a wide range of diseases, including rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease (IBD), Crohn's Disease, psoriasis, liver disease (hepatitis B, NASH and hepatocellular carcinoma (HCC), the predominant form of liver cancer caused by hepatitis B. Our initial focus is in psoriasis and liver disease. SFA will present human data in psoriasis from a translational research study where each patient showed significant improvement. Our psoriasis drug, SFA002, is oral, eliminating the need for injections or infusions, which patients strongly dislike, and should have a much better side effect profile than current drugs. Success in psoriasis will lead to treatments in other diseases that have the similar underlying mechanisms of action, such as rheumatoid arthritis, Crohn's, and other autoimmune diseases.

This talk will review our work to-date, forward plans and overview of our research.

Thean Yeoh, Ph.D.

Pfizer

Topical Formulation Strategy – From Concept to Marketed Formulation

Biography

Thean Yeoh, Ph.D. is a drug delivery expert who currently leads the formulation design and development of small molecule topical and transdermal products at Pfizer. His responsibilities span all stages of global product development involving NMEs and life-cycle compounds. In recent years, he has guided innovative approaches to the design and selection of topical NME's and has developed new strategies to de-risk topical formulation designs and programs. Thean has 25 years of drug product design and development experience. Prior to joining Pfizer, he was with Alkermes and Proctor & Gamble. He obtained his doctorate training in industrial and physical pharmacy from Purdue University's School of Pharmacy.

Abstract

Abstract: Topical formulation is an important component for any topical development program. Decisions on formulation design and development strategy can have far-reaching consequences on the technical complexity and timeline of the topical development program. This presentation will review formulation design informing experiments for compound selection, early formulation examples, critical elements for marketed formulation design and evaluation strategies. We will also discuss a case study to showcase how scientific understanding of material attributes resulted in influencing process design to produce a better PEG based ointment formulation.

Robert Falcone, Ph.D.

HRA Pharma US Inc.

Biography

Education: BS Chem (Physical Chemistry), MSChE (Kinetics, Catalysis & Pharmaceutical Processes), PhD (Materials Science & Engineering) – Medical Devices & Combination Products (Transdermal Delivery Systems)

Work: Office of Naval Research, ICI - Advanced Materials / Zeneca - Pharmaceuticals & Personal Care Technologies, Hartz Mountain Corporation - Veterinary Pharmacological Product Development, Church & Dwight Corp. –Program Manager - Veterinary & Personal Care (Skin-OTC and Rx), US Nonwovens – Director-Regulatory & OTC (Medical Devices and Combination Products), Peter Thomas Roth - Skin & Hair Care – Director, ProductDevelopment & Regulatory Affairs - Cosmetic, Rx & OTC products. Vantage Specialty Ingredients – Global Compliance Manager – Cosmetic, Personal Care, OTC and Rx (APIs). Integris Biosolutions – Global Regulatory Manager – Rx (NDA, ANDA), Medical Devices, Rx to OTC Switches, OTC, Cosmetics, Supplements (Human & Animal), DMF, ASMF and US Agent (EU, LATAM & ASIA to US). HRA Pharma US Inc., Rx, Rx to OTC Switches, OTC, Medical Devices and Cosmetics for US and Canadian Markets. US Agent to FDA & Canada.

Working on DMFs (US and Canada), ASMFs, NDA, ANDAs, CMC (Modules (1-4)), CSFs and Labels (FDA, EPA and EMA compliant).

Professional Affiliations: American Association of Pharmaceutical Scientists (AAPS), Regulatory Affairs Professional Society (RAPS), American Academy of Dermatology (AAD), Society of Cosmetic Chemists (SCC) ACS, Tau Beta Pi(National Honor Engineering Society), Sigma Xi (National Honor Research Society) & Alpha Sigma Mu (National Honor Materials Science & Engineering Society).

Markham Luke, M.D., Ph.D.

FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance

Biography

Markham C. Luke serves as Supervisory Medical Officer and Director of the Division of Therapeutic Performance (DTP) in the Office of Research and Standards, Office of Generic Drugs at FDA. DTP is responsible for facilitating pre-application development of generic drugs by conducting and promoting regulatory science research to establish standards to ensure therapeutic equivalence of new generic drug products. Markham has an MD and a PhD in Pharmacology from Johns Hopkins University and is a dermatologist by training. Markham has research interests in dermatopharmacology, clinical pharmacology, clinical study design and endpoints assessment (including patient-reported outcomes) for medical, surgical, and aesthetic products and serves as consultant dermatologist to various parts of FDA. Markham has been at FDA since 1998 serving various roles, including as the Lead Medical Officer for dermatology drugs, Chief Medical Officer and Deputy Director for the Office of Device Evaluation in the Center for Devices and Radiologic Health, and as Acting Director for Cosmetics in the Center for Food Safety and Applied Nutrition. In each of these roles including his current one, Markham has been involved in programs and initiatives dealing with product innovation as related to Public Health for our nation.

Sam Raney, Ph.D.

FDA Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance

Biography

Dr. Sam Raney is a thought leader in topical and transdermal drug products, with over 25 years of experience producing numerous research manuscripts, review articles, book chapters and patents in pharmaceutical product development. Dr. Raney has been a researcher and adjunct professor within academia, a principal or sub investigator on over 400 pharmaceutical product studies, has held senior management roles in industry, serves as an expert panel member in the U.S. Pharmacopeia., and is the Lead for Topical and Transdermal Drug Products in the FDA Office of Generic Drugs. Dr. Raney holds a Bachelors in Molecular Biophysics & Biochemistry from Yale University, and a Ph.D. in Biochemistry & Molecular Biology from the University of British Columbia in Canada.

Shahnam Sharareh, Pharm.D., RAC

Fox Rothschild LLP

Biography

Shahnam is a patent attorney with 17 years' experience in preparing and prosecuting U.S. and international patent applications in a wide range of technologies, including chemistry, pharmaceuticals, pharmacology, biotechnology, medical diagnostic and cosmetic products. Shahnam represents life science and university based as well as fortune 500 companies in various regulatory, technology transfer, clinical trials and other transactional projects involving research and development activities and collaborations in drug delivery, small and large therapeutics products. He frequently advises clients with a Medical Cannabis and CBD platform. He is a Regulatory Affairs Certified (RAC) professional and works with clients on developing their FDA regulatory, marketing and advertising strategies relating to drug, dietary supplement and cosmetic products.

David C. Steinberg, Ph.D., FRAPS

Steinberg & Associates, Inc.

Biography

David C. Steinberg, BS Chemistry, Drexel U., MBA Management, Pace U. Fellow status in Society of Cosmetic Chemists, Regulatory Affairs Professional Society. Founder of Master's degree at Fairleigh Dickinson U, in Cosmetic Sciences. Currently President of Steinberg & Associates, Inc.

Poster Abstracts

Innovations in Dermatological Sciences

Dina Ameen

Rutgers University–Center for Dermal Research

Development and In Vitro Evaluation of Pressure Sensitive Adhesive Patch for the Transdermal Delivery of Galantamine

Authors: Dina Ameen[1, 2] , Bozena Michniak-Kohn[1, 2]

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Purpose: Galantamine (GAL) is used for treatment of mild-to-moderate Alzheimer's disease with dual mode of action. It was shown to improve patient cognitive and global function, ability to perform activities of daily living and behavior compared to placebo and baseline, and also it reduced caregiver burden. However, it is associated with gastrointestinal side effects and induced weight loss that necessitates gradual increase in dose to improve tolerability. The transdermal route offers an attractive alternative route of drug administration especially for Alzheimer's disease patients through eliminating gastrointestinal side effects and ultimately improving compliance. In this study, we prepared an optimized drug-in-adhesive patch for the transdermal delivery of galantamine free base with ex vivo and in vitro evaluation.

Methods: Four pressure sensitive adhesives with different functional groups; ten penetration enhancers and four drug loadings were tested to determine the optimized patch. GAL patches were prepared by mechanically mixing the adhesive solution in ethyl acetate with a calculated amount of GAL as a solution in ethyl acetate to prepare 8, 10, 12, and 15% GAL in dry polymer weight. The mixture then was applied onto the release liner using a micrometer adjustable wet film applicator at a wet film with thickness of 500µm. Penetration enhancers at 5% of dry polymer weight each were added to the mixture of the polymer and GAL and mixed well and then casted as above. The wet patches were kept at room temperature for 15 min and then baked in a vacuum oven at 80° C for 20 min. The dried patches were laminated with the backing layer and kept at ambient temperature until further testing. The ex vivo permeation of the different formulated patches through human cadaver skin was tested using vertical Franz diffusion FT-IR and rheological studies were done to determine the potential interactions of the polymer with the drug and/additives. In addition, patches were visualized under the microscope to investigate the crystallization potential. Drug release from the patches was also performed using Franz to determine the kinetic model for drug release.

Results: Showed that GELVA GMS 788 was the best pressure sensitive adhesive among the tested polymers. FT-IR and rheological studies results showed the possibility of hydrogen bonding between the drug and PSA, and that the additives had a plasticization effect causing increased flexibility of the polymer chains. Penetration enhancers ranked as follows: oleyl alcohol > decyl oleate >limonene= octyldodecanol > terpineol > caproyl 90 > lauroglycol™ FCC >labrafac lipophile™ > Propandiol. Crystallization study showed that formulation with limonene was most stable and oleic acid was added to inhibit crystallization upon storage. The combination of limonene and oleic acid increased the flux of galantamine by 2.7 fold compared to 1.7 fold when limonene was used alone. The optimized patch exhibited diffusion release kinetics and fitted well to Higuchi's model and yielded an ex vivo permeation rate of 32.4 ± 1.41 µg/cm²/h across human cadaver skin.

Conclusion: The optimized patch was composed of 10% w/w galantamine, 5%w/w Limonene, 5% w/w oleic acid, GELVA GMS 788 as PSA, and was casted on ScotchpakTM1022 release liner and laminated with Scotchpak 9723 as a backing film. The selected additives showed a synergistic enhancement of GAL permeation while successfully inhibiting the drug crystallization. Based on the results, the optimized patch was shown to be capable of achieving therapeutic plasma level patch size of about

15 cm2, which indicates that GAL transdermal patch was a promising drug delivery system for the treatment of Alzheimer's disease. Further pharmacokinetic and in vivo studies should be conducted to confirm the results.

Kevin Chen

Rutgers University–Center for Dermal Research, Ernest Mario School of Pharmacy

Antifungal Drug Delivery using Different Nail Formulations

Authors: Kevin Chen[1,2], Vinam Puri[1,2], Emily Yuasa[1,2], Jiayi Yuan[2], Bozena Michniak[1,2]

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Nearly 1/4th of the world population is affected by dermatophytes. Nail fungal infections affect a major percent of global population. Treatments for Onychomycosis are challenging because oral antifungals are associated with severe adverse effects while the topical therapy is limited in effect. Terbinafine hydrochloride (TBH) and econazole nitrate (ECN) are effective antifungal moieties that need to be delivered into the nail unit effectively. We have designed nail patches containing TBH and a nail lacquer containing ECN for topical delivery.

Nail patches were made using drug loaded matrix (DLM) and pressure sensitive adhesive loaded drug (PLD) methods. They were then tested for drug uniformity, release and permeation using Franz diffusion cells modified with nail adapters. Nail lacquers were made using a hydrophobic and hydrophilic polymer mix in a hydroalcoholic solvent system and tested for the above-mentioned characteristics. The drug concentrations were measured using validated HPLC methods. The DLM patches showed higher drug uniformity than the PLD patches. Release was achieved after some modifications in the patch components. A lacquer formulation for the ungual delivery of ECN was achieved. Novel formulations for antifungal drug delivery to the nail have been achieved.

Future Scope

A comparative study to determine the better delivery system as well as antifungal activity using the delivery systems is needed to be tested. Drug delivery using these systems is also needed to be tested on diseased nails.

Aaron Cohen

Colgate-Palmolive

In Vitro Release Test (IVRT) of Retinol Formulations

Authors: Aaron Cohen, Junhong Mao

Retinol is an extremely popular active in many topical skincare products and has diverse benefits in areas like anti-aging and anti-acne. Retinol is often present in an "encapsulated" form to slow its rate of release out of a formulation. Excessively high levels of retinol release can lead to unsightly skin reddening and irritation. In vitro release testing (IVRT) can be used to measure the rate of retinol release between different commercially available products and thus assess different methods of retinol encapsulation.

This poster describes the IVRT of a new encapsulated retinol product from PCA Skin and compares its rate of release to two products from a competitor. IVRT was performed using a Franz diffusion cell. Particular emphasis is on method development by discussing the optimization of such parameters like the appropriate membrane material and receiver medium needed to generate reliable and reproducible IVRT results. Ultimately, we showed that the retinol product from PCA Skin had a rate of retinol release about two times higher than the competitor's product.

Kevinn Eddy

Susan Lehman Cullman Laboratory for Cancer Research, Rutgers University

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Preclinical Study using Trigriluzole and Anti-Pd-1 in a Spontaneous Melanoma-Prone Mouse Model

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Much progress has been made in understanding melanoma pathogenesis within the last few years through targeted therapies and immunotherapies. However, resistance to small molecule inhibitors remains an obstacle in many patients. Immunotherapies such as check point inhibitors against PD-1/PD-L1 lead to durable responses but only in a subset of melanoma patients. Mouse models reflecting human cancers have provided invaluable tools towards the translation of basic science discoveries to clinical therapies, but many of these in vivo studies are short-term and do not accurately mimic circumstances which patients undergo during treatments. Our lab has demonstrated that ectopic expression of metabotropic glutamate receptor 1 (GRM1), in melanocytes leads to cell transformation in vitro and spontaneous metastatic melanoma in vivo. In addition, aberrant GRM1 expression is detected in > 90% of late-stage melanoma patients, suggesting that aberrant GRM1 mediated signaling and expression may be involved in some melanomas. Our ongoing longitudinal in vivo study is using our melanoma-prone transgenic mice which are being treated with a functional inhibitor of GRM1-mediated signaling plus anti-PD-1. Our preliminary results suggest that the addition of a checkpoint inhibitor, anti-PD-1, does not provide any additional benefit in reducing tumor progression. Molecular changes are being assessed for alterations in cytokines/chemokines, in addition the immune cell population are being profiled within these mice to better understand the long-term consequences of treatments. Our goal for this longitudinal study is to mirror patient circumstances during treatment regimens, to better design a rational treatment modality based on changes which transpire within these animals.

Anna Froelich

Poznan University of Medical Sciences

Microemulsions and Microemulsion-Based Gels with Mixed Non-Ionic Surfactants for Topical Delivery of Indomethacin

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Microemulsions are liquid systems composed of polar and non-polar phases stabilized by one or more surfactants and usually a cosurfactant. According to the literature reports, the diameter of the dispersed phase droplets does not exceed 100 nm [1] which makes them transparent. Because of an extremely low interfacial tension occurring between polar and non-polar domains, microemulsions reveal thermodynamic stability which is a unique feature among the oil and water dispersions. One of the most important of the advantages related to the application of microemulsions as drug delivery systems is their ability to improve bioavailability of active ingredients [2]. It is noteworthy that in the case of formulations applied to the skin the components of microemulsions may act as permeation enhancers [3].

In this study we present the design and characterization of microemulsions and microemulsion-based polymer gels with incorporated indomethacin, a non-steroidal anti-inflammatory drug revealing low water solubility. The extent of the isotropic region was assessed with the use of pseudoternary phase diagrams. The structural studies allowing for the determination of microemulsion type and domain/droplet diameter were based on the electrical conductivity of these systems and the results of dynamic light scattering experiments. Moreover, rheological studies were performed both for liquid microemulsions and semisolid microemulsion-based gels in order to assess the impact of the composition on the properties of the final product. Finally, drug release studies were performed with the use of vertical Franz diffusion cells.

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Benjamin Goodyear

Rutgers University–Center for Dermal Research, Ernest Mario School of Pharmacy

Quality by Design (QbD) Approach for Developing Nanocapsules as a Promising Topical Drug Delivery Platform for BCS II Drugs

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Abstract: Topical NSAID'S are used to treat both acute and chronic pain from Rheumatoid Arthritis & sports related injuries. Nanocapsules are a nano-sized delivery system used to deliver drugs from BCS Class II in order to reduce common negative side effects associated with oral drug administration routes. Using a systematic QbD approach, the goal of this research was to identify the Critical Material Attributes (CMA's) & Critical Processing Parameters (CPP's) which impact nanocapsule particle size distribution (PSD), Poly Dispersity Index (PDI), Encapsulation Efficiency (%EE), & Zeta Potential. A solvent evaporation technique was used to successfully manufacture nanocapsules to use for further testing and evaluation. CMA's identified were oil, co-surfactant, API, & polymer concentration; while CPP's were temperature, solvent type, mixing rate, and addition rate. The data from this work demonstrates the previously mentioned factors all play an important role in the formation of nanocapsules.

James V Gruber

BotanicalsPlus

Measuring Activation of the NLRP Inflammasomes In Vitro via Active Caspase-1 Release: Implications in Understanding Epidermal Inflammatory Responses

Authors: James V Gruber[1], Robert Holtz[2]

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In 2002, a key component of cellular inflammatory response was discovered when the NLRP Inflammasomes were isolated and identified [1]. When skin cells are attacked by endogenous threats, the NLRP proteins oligomerize to form Inflammasomes. The Inflammasomes release Active Caspase-1 (ACase-1), which cleaves Pro-IL-1 and Pro-IL-18 present in the skin cells creating active interleukin cytokines. Activated IL-1 and IL-18 initiate a process of inflammation response that leads to accumulation of downstream curative moieties [2]. NLRP Inflammasomes have been linked to many skin abnormalities such as acne, dandruff, atopic dermatitis, and other skin problems. Inflammasomes are also linked to inflammation caused by external insults like UV radiation, chemical and allergenic agents, and bacterial and fungal attacks. The NLRP1 Inflammasome appears to be the key sensor for UV stress in human keratinocytes, while the NLRP3 Inflammasome has been implicated in wound healing in skin [3,4]. We describe in vitro studies examining the role of various NLRP activators on Normal Human Epidermal Keratinocytes (NHEKs) to elicit upregulation of ACase-1. Two key activators, UVB energy and ATP, cause significant upregulation of the NLRP Inflammasomes measured by release of ACase-1. The release of ACase-1 is delayed from the time of exposure to both NLRP activators. Various external topical treatments that include polysaccharide- and antioxidant-based ingredients were examined for their impact on the expression of ACase-1 in Inflammasome-activated NHEKs.

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Anika Haq

Rutgers University–Center for Dermal Research, Ernest Mario School of Pharmacy

Thymoquinone Loaded Polymeric Films for the Treatment and Management of Wounds

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Purpose: In the wound healing processes, bacterial infections occur frequently, and the selection of the anti-bacterial agent and treatment regimen often determines the therapeutic outcome. The purpose of this study was to synthesize and characterize a biocompatible novel topical polymeric film system that has the potential to deliver a naturally-derived anti-bacterial/anti-inflammatory agent thymoquinone (TQ) directly to the skin target site that may have potential use in wound treatment.

Methods: Polyvinyl pyrrolidone (PVP) matrix-type films containing TQ were prepared by the solvent casting method using dibutyl phthalate as a plasticizer and Azone (laurocapram) as a penetration enhancer. The surface morphology of the film was recorded with a Zeiss field emission scanning electron microscopy (FESEM) (FSD PRE-AMP 4CH, Germany). The PVP/TQ films were characterized in terms of film thickness, drug content uniformity, weight variation, flatness, folding endurance, the percentage of moisture content and uptake. In vitro, skin permeation studies were performed on human cadaver skin by using Franz diffusion cells (FDC). Human dermal fibroblasts (HDF, Passage 2-4) and HaCaT (Passage 37-39) cells were counted and were seeded onto 24 well plates at a density of 50000 cells/well for HDF and 250k cells/well for HaCaT. After reaching confluency, the culture media was replaced with sterile base media and scratch wounds were created in the cell monolayer using a sterile pipette tip (200 uL). TQ in DMEM at different concentrations (1 ng- 1000 ng) was placed into the culture media and the experiment was continued for 24 hours for HDF and six days for HaCaT cell line. Base media was used as a control and 100 ng FGF-2 (Fibroblast Growth Factor) was used as a positive control. On the other hand, 10% DMEM was used as a positive control for HaCaT. Images were taken at 0, 4, 8, 12 and 24 hours for HDF and at 0, 24, 48, 72 and 144 hours for HaCaT.

Results: Thickness, drug content uniformity, weight variation, flatness, folding endurance, percentage of moisture content and uptake were found to 1.17 ± 0.04 mm, 100 ± 6.4 %, 82.04 ± 1.9 mg, 100%, 68 ± 2.38, 14.12 ± 0.42 %, and 2.26 ± 0.47 % respectively. These results indicated that the process employed to prepare films in this study could produce films with uniform drug content and minimal film variability. The flatness study showed that the films had the same strip length before and after cutting, indicating 100% flatness. These data also indicate 0% constriction in the films meaning they could maintain a smooth surface when applied onto the skin. In other words, the films provided intimate contact with skin and hence better drug permeation. Folding endurance test results indicated that the films would not break and would maintain their integrity when folded. The low moisture uptake at laboratory ambient condition protects the material from microbial contamination and avoids extra bulkiness of the films. The moderate moisture content of the prepared films could assist the formulation stability by preventing drying and brittleness. FESEM photographs of TQ film showed polymer networks inside the film and homogeneous dispersion of drug inside the polymer networks. In vitro skin permeation studies on human cadaver skin produced a flux of 3.4 µg/cm2/h. It was

found that TQ showed significant positive effects on wound healing activities of HDF and HaCaT cell lines. TQ (100 ng) showed significant wound closure activity with HDF compared to both control ($p = 0.0014$) and positive control ($p = 0.0004$). 77% of wounds were closed with 100 ng TQ at 12 hours followed by 100% wound closure at 24 hours. The strong proliferative activity of TQ was reflected in the ability of the cells to increase in number to cover the scratched wound areas after 24 hours. The number of fibroblast cells in the scratched area was found to increase between 10 ng to 200 ng TQ and then decrease with the increased concentration of TQ. 100 ng TQ showed a significant increase in the number of fibroblast cells compared to all other experimental conditions. Using the HaCaT cell line 100 ng TQ showed 85% wound closure activity at day six which is significantly higher ($p = 0.0001$) than the experimental control. Rapid wound closure activity was observed between day three and day six at all TQ concentrations (1-1000 ng).

Conclusions: In this study, novel TQ loaded polymeric films were developed. The data indicated that TQ, a natural compound, can be utilized in a film for wound treatment. The TQ film prepared with hydrophilic PVP polymer containing Azone as a permeation enhancer showed in vitro skin permeation and wound healing activity. In summary, the TQ/PVP films developed in this study have potential which will be explored further for the treatment and management of wounds.

Tim Houser

Dermico LLC, University of Cincinnatti James Winkle College of Pharmacy

Capacitance Imaging of the Volar Forearm of Carriers and Individuals Affected by Ectodermal Dysplasia

Authors: Tim Houser, Gary Grove, Gerald Kasting

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a congenital disorder in which structures of ectodermal origin may be absent or abnormally formed. In affected XLHED children, there is significant morbidity and mortality due to hyperthermia, caused by an inability to sweat. In the present investigation, we have utilized a novel Dynamic Capacitance Imaging sensor (DCI) to attempt to classify differences in skin surface topography and moisture in individuals affected by ectodermal dysplasia, as well as known carriers and unaffected individuals. Casual analysis was performed to determine whether any differences were apparent without induction of sweating. This may be useful in determining whether eccrine sweat gland activity affects the hydration and topography of the stratum corneum and whether an individuals' condition can be determined through casual assessment.

Hwan June Kang

Rutgers University

Self-assembled Nanoparticles for Enhancing Diabetic Chronic Wound Healing

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Introduction: Chronic non-healing wounds are considered one of the most significant chronic complications of diabetes due to the accumulation of advanced glycation end products (AGEs), which

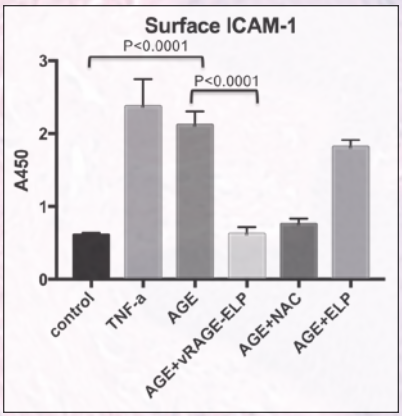

Figure 1. **Surface ICAM-1 Expression.** TNF-a: 10ng/mL, AGE: 100ug/mL, vRAGE-ELP: 1mg/mL, NAC (N-acetylcystein): 30mM, ELP: 1mg/mL (N=6)

form when proteins and lipids react with reactive sugars in the presence of high glucose. The binding of AGEs to their receptor (RAGE), which is found on vascular endothelium and several types of immune-competent cells, increases the generation of intracellular reactive oxygen species (ROS), activates the pro-inflammatory transcription factor, NF-□B, and eventually results in the increased expression of several pro-inflammatory genes including intercellular adhesion molecule-1 (ICAM-1) as well as RAGE itself. The soluble form of RAGE (sRAGE) is thought to act as a competitive inhibitor and thus prevent AGE-RAGE binding. It is also known that the extracellular domains of RAGE consist of V, C1 and C2 and that it is the V domain of RAGE (vRAGE) that binds AGEs. However, the highly proteolytic diabetic wound environment may still be a major challenge to treating the wounds with exogenous sRAGE or vRAGE since such exogenous peptides might degrade quickly. We propose a self-assembled nanoparticle system containing fusion proteins of elastin like polypeptides (ELPs) and vRAGE. ELPs are derivatives of tropoelastin with pentapeptides repeats of Valine-Proline-Glycine-Xaa-Glycine, where Xaa can be any amino acid except proline. ELPs reversibly self-assemble above a transition temperature, thus enabling the formation of nanoparticles containing vRAGE and protecting it from proteases. Here, we developed a nanoparticle system containing vRAGE-ELP fusion proteins, which bind to AGEs, inhibit AGE-RAGE bindings, suppress the RAGE-mediated signaling pathway and enhance wound healing in diabetic mice.

Materials and Methods: Full length encoding sequence for the V domain of human sRAGE was synthesized and fused to 50 repeats of an ELP encoding cassette. The expression vector was transformed into E. coli, BLR(DE3) strain. The bacteria were grown in Terrific Broth and the protein expression was induced by adding 1mM IPTG. Cells were lysed by sonication and the vRAGE-ELP fusion proteins were purified by centrifuging the lysates above and below the transition temperature (~35°C) three times. Successful purification of the fusion proteins was confirmed by running SDS-PAGE gels followed by Western blotting. The transition temperature was determined by measuring the solution turbidity using a spectrometer at 350nm. The sizes of nanoparticles at various temperatures were measured by dynamic light scattering. To test the bioactivity of vRAGE-ELP, Human Umbilical Vein Endothelial Cells (HUVECs) were stimulated by adding AGEs to cell cultures with or without treatments of vRAGE-ELPs to see if the fusion proteins could suppress the generation of ROS and expression of a pro-inflammatory marker (ICAM-1). To investigate the effect of vRAGE-ELP in vivo, excisional full-thickness wounds were created on the back of genetically modified diabetic mice (BKS.Cg-Dock7m +/+ Leprdb/J). Mice were treated with control vehicle (fibrin gel), empty ELP nanoparticles, free sRAGE or vRAGE-ELP and photos of injury sites were taken at days 1, 3, 7, 14, 21, 28, 35 and 42. The areas of open wounds were measured using ImageJ and the wound closure rates were calculated.

Results and Discussion: SDS-PAGE and Western Blotting results confirmed the presence of vRAGE-ELP in the purified products. The transition temperature was around 35°C, where a sharp change of solution turbidity was observed. The radius of nanoparticles at 37°C was 720 ± 55 nm at 25 μM. The intracellular ROS level was significantly decreased in vRAGE-ELP treated groups. The expression of ICAM-1 was suppressed in vRAGE-ELP treated groups while non-fused empty ELP proteins alone did not suppress the expression (Figure 1). Furthermore, a faster wound closure was observed in the

vRAGE-ELP-treated group compared to other control groups with statistically significant differences in wound closure observed starting at day 21 through day 42.

Conclusions: vRAGE-ELP fusion proteins that forms nanoparticles at physiological temperature have been developed and characterized in this project. The use of ELP enabled a relatively easy purification of the fusion proteins and provided a delivery system for the binding domain of RAGE to AGE. In vitro study results suggest that these nanoparticles inhibit AGE-RAGE binding and thus the RAGE-mediated pro-inflammatory signaling pathways. In vivo study showed that vRAGE-ELP treatment enhanced the healing of skin wounds in diabetic mice compared to all other groups. Future studies will analyze the epidermal and dermal thickness of skin samples collected from the in vivo study.

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Megan Kelchen

U.S. Food and Drug Administration

Strategic Analysis of the Roadmap for Implementing Characterization-Based Bioequivalence Approaches in Product-Specific Guidances for Generic Topical Dermatological Drug Products

Authors: Megan N. Kelchen, Priyanka Ghosh, Tannaz Ramezanli, Sam G. Raney

Purpose: Characterization-based bioequivalence (BE) approaches are efficient methods to establish BE of generic topical dermatological drug products compared to comparative clinical endpoint BE studies, which are considered to be the least accurate, sensitive, and reproducible method of establishing BE for these products. With the advancement in research of advanced analytics and in vitro characterization methods, the Office of Generic Drugs (OGD) has begun recommending these characterization-based approaches within product-specific guidances (PSGs). The first PSG wherein such an approach was comprehensively implemented was for acyclovir topical cream, 5% in 2016, after which these approaches were developed for a handful of topical dermatological drug products. By 2018, characterization-based BE approaches were demonstrated to be a generalizable approach for all classes of topical dermatological semisolid dosage forms. As part of the Generic Drug User Fee Amendments (GDUFA) Regulatory Science Priorities for fiscal year (FY) 2018, OGD intends to "expand characterization-based BE methods across all topical dermatological products." However, the implementation of this priority has been complex due to technical challenges, scientific unknowns, and limited resources to manage this goal. Therefore, a strategic roadmap was necessary based on a gap analysis of the essential steps for establishing characterization-based methods for all types of generic topical dermatological drug products.

To successfully transition the standards for establishing BE for topical dermatological drug products to characterization-based methods, four critical steps are necessary (Figure 1). Through GDUFA-funded research conducted over the past five years, general critical quality attributes for common topical dermatological dosage forms have been established (Step 1), leading to the identification of ten fundamental properties of semisolid drug products. Filling this gap in knowledge has facilitated the development of characterization-based BE approaches for specific drug products, which are then incorporated into their respective PSGs. The purpose of this study was to assess the progress in this transition by surveying the current recommendations for establishing BE within PSGs for topical dermatological drug products for each dosage form.

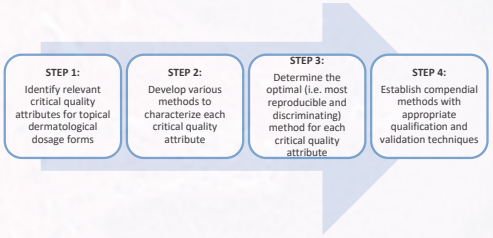

Figure 1. A roadmap for implementing characterization-based BE approaches for generic topical dermatological drug products.

Methods: Through GDUFA-funded research, a conceptual framework for identifying the failure modes for BE for generic topical dermatological products was established. The general critical quality attributes of topical semisolid dosage forms were identified and various methods for evaluating these quality attributes were developed. Common trends among the dosage forms were identified and used to develop characterization-based BE approaches within PSGs for various generic topical dermatological drug products. The PSGs for generic topical dermatological drug products published prior to July 2019 were classified based on the recommended approaches for establishing BE and categorized based on common semisolid dosage forms.

Results: By FY 2012 (prior to GDUFA I), approximately 27% of topical dermatological reference products had a published PSG. Currently, 200 PSGs (approximately 62%) have been published for the 322 topical dermatological reference drug products (Figure 2). In vivo studies (e.g., comparative clinical endpoint BE studies and vasoconstrictor studies) are currently recommended in most of the published PSGs and characterization-based BE approaches are recommended for only 6% of topical dermatological reference products overall and within 10% of the published PSGs.

Overall, PSGs are available for 68% (67/99) of topical cream reference products, 80% (39/49) of topical gel reference products, 67% (28/42) of topical ointment reference products, and 68% (21/31)

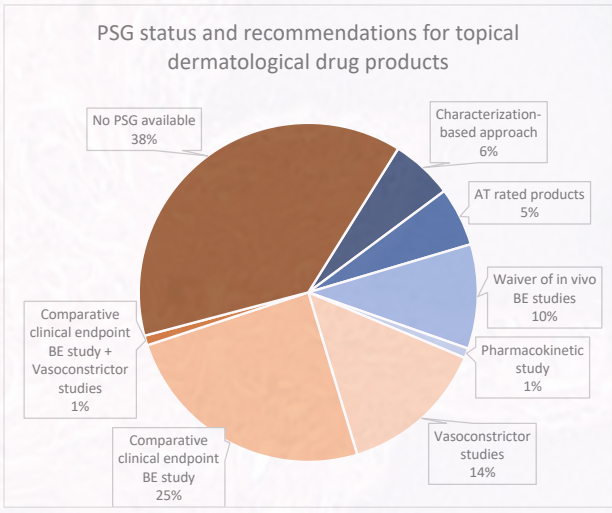

Figure 2. Current status of PSGs (n=200) for topical dermatological reference products (n=322). Blue sections represent efficient approaches for establishing BE; orange sections represent approaches for establishing BE that are less efficient.

of topical lotion reference products. Within these PSGs, an in vivo comparative clinical endpoint BE study is most commonly recommended (for 51% of cream PSGs and 79% of gel PSGs, for example). A smaller proportion of published PSGs include recommendations for characterization-based BE approaches for topical creams (12%), gels (10%), ointments (14%), and lotions (10%).

Conclusion: Over the last decade, characterization-based BE approaches have been recommended as an alternative in vitro BE approach to in vivo studies for many topical dosage forms based on the knowledge obtained in Step 1 of the roadmap. Incorporation of the characterization-based BE approaches in all PSGs for generic topical dermatological drug products continues to be a priority for OGD. Research has been ongoing to develop various methods of characterizing the critical quality attributes (Step 2). However, it is evident from this analysis that it is imperative to determine the optimal method for each critical quality attribute (Step 3) and develop compendial standards for these methods (Step 4) in the future to establish the infrastructure that is necessary to accomplish the goal of establishing characterization-based BE approaches for all topical dermatological drug products, which in turn will improve patient access to high quality generics.

Mitchell Klausner

MatTek Corporation

Application of In Vitro Skin Models for Cosmetic Product Efficacy: UV Protection, Skin Lightening, Skin Hydration and Anti-aging

Authors: Mitchell Klausner, Alexander Armento, Bridget Breyfogle, Gina Stolper, Jonathan Oldach. MatTek Corporation

In vitro skin equivalent models offer the capability to screen for safety and efficacy of raw cosmetic materials and formulations intended for topical application. Here we describe three commercially available skin tissue models, EpiDerm, EpiDermFT and MelanoDerm that are amenable to multiple applications of interest related to cosmetic product development and efficacy testing. EpiDerm, produced from normal human keratinocytes, is widely used for assessment of irritation, percutaneous absorption, cytotoxicity, cytokine release and has recently been utilized for evaluation of skin hydration. EpiDermFT is a full thickness in vitro skin equivalent produced from primary keratinocytes and primary fibroblasts containing a functional barrier and fully developed basement membrane. This model is well suited for evaluating cosmeceutical endpoints such as UV protection (e.g. CPD analysis) and skin aging biomarkers related to extracellular matrix (ECM) remodeling. MelanoDerm, a tissue containing primary keratinocytes and melanocytes, is used to evaluate skin lightening following treatment with topically or systemically applied cosmetic ingredients allowing for measurement of macroscopic darkening and melanin production. Utilization of these tissue models for cosmetic product testing can be highly valuable in streamlining product development efforts and reducing the use of animals for testing purposes.

Benjamin A. Kuzma

Long Island University

Estimation of In-Vivo Percutaneous Permeation (Flux) and Cumulative Amount Input of Metronidazole Formulations in Mini-Pigs' Dermis

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Purpose

Dermal microdialysis (dMD) quantitatively measures the rate and extent at which a topically administered drug becomes available in dermis, at or near the site of action in the skin. The observed exposure in dermis is the result of the rate at which the drug reaches the dermis as well as disposition (distribution and elimination) within dermis. However, in order to build efficient predictive in-vitro/in-vivo (IVIVC) models, it would be desirable to measure the in-vivo flux (the equivalent of the input-rate for oral administrations) independent of local disposition. Typically, a systemic disposition function (Unit Impulse Response, UIR) is estimated from IV administrations, a type of drug delivery that by-passes the absorption step. By analogy, we sought to estimate the disposition of a drug in skin, by delivering the drug directly into dermis using a dMD probe. The objectives of this study were: (i) to estimate the dermis disposition function (UIR) of metronidazole (MTZ) with a combination of microdialysis/retrodialysis techniques, and (ii) to calculate the in-vivo flux and cumulative amount input by deconvoluting the dermis concentration profiles that were obtained following application of MTZ topical formulations with the estimated UIR.

Methods

An experiment was conducted to assess the effect of formulation removal on dermis exposure from the application of two MTZ topical dermatological formulations. In 3 Yucatan mini-pigs, twenty probes were placed under formulation application sites and two additional dMD probes were inserted into the dorsum of each pig at a site distant from the formulations. The formulation application sites were wiped off at pre-determined times of 6hr, 12hr, and no wipe off. The two additional dMD probes were perfused with a 40 ng/mL solution of MTZ at a flow rate of 0.5µL/min for 10 hours (retrodialysis phase). The perfusion solution was then switched to plain lactated ringer solution and MTZ – D3 solution as internal standard (microdialysis phase). Samples were collected every hour until the end of the experiment (48 hr) and analyzed for MTZ content. Dermis clearance was calculated from the retrodialysis data at steady state by Equation 1, where X2.5-9.5 is the amount delivered by the probe between 2.5 to 9.5 hours, and AUC2.5-9.5 is the area under the curve from 2.5 to 9.5 hours.

Results

Dermis concentrations declined mono-exponentially. Dermis elimination half-life of MTZ was 1.35 hr (0.5) (geometric mean (CV%)) whereas half-life of MTZ at the formulation sites for the 6hr, 12hr and no-wipe off were 9.01 (30.29), 10.51 (34.06), 10.32 (32.84) hours for the gel and 7.32 (25.95), 10.50 (57.75), 23.86 (86.74) hours for the cream, respectively. The significantly longer half-life of

$$CL_{dermis} = \frac{X_{2.5-9.5}}{AUC_{2.5-9.5}}$$ Equation 1

The amount delivered was calculated as:

$$X_{2.5-9.5} = \left(C_{perfusate} - C_{ss}\right) \times V_{perfused(2.5-9.5)}$$ Equation 2

Where $C_{perfusate}$ is the MTZ concentration in the perfusate or Cin, Css is the concentration of the MTZ in dialysate exiting the probe, $V_{perfusate}$ is the volume of solution perfused through the probes in that seven hours. The dermis apparent volume of distribution was calculated as $V = {CL}/{k}$ where k is the slope of the elimination phase. The dermis disposition function (UIR) was built as follows:

$$UIR = \frac{1}{V} e^{-kt}$$ Equation 3

The Phoenix® (Certara, Princeton, NY) deconvolution module was used to calculate the cumulative amount delivered to the skin and the input-rate.

the formulations' sites compared to that of the formulation independent half-life suggests that the rate of absorption is the limiting process for the apparent elimination of MTZ from the dermis, apparently demonstrating flip/flop kinetics, typically defined as an increased terminal elimination half-life following oral dosing of a drug, as compared to its intravenous half-life. These results indicate that MTZ permeation across the upper layers of the skin is a long, sustained process. The average dermis apparent volume of distribution, and clearance were 0.12 ± 0.06 mL, and 0.057 ± 0.03 mL/hr, respectively. Figure 1 shows the in-vivo flux and cumulative amount input profiles sorted per formulation and wipe-off scheme.

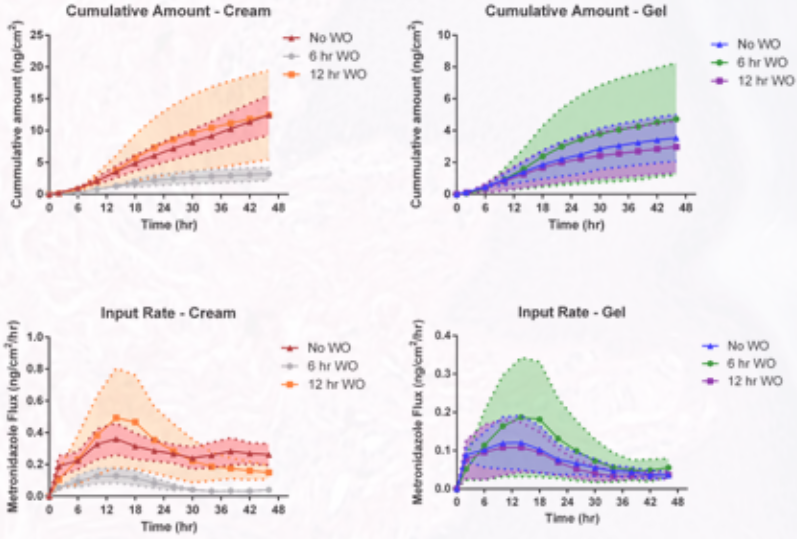

Figure 1 – Average In-vivo flux and cumulative amount input profiles sorted per formulation and wipe-off scheme. The shaded areas represent standard deviation. Data are presented as mean ± SEM (n=3 for 6hr and 12hr wipe off, n=5 for No WO).

Conclusion

The estimation of dermis disposition is a promising tool by which to estimate in-vivo flux and cumulative amount inputs that can be directly compared with in-vitro permeation (IVPT) data. The characterization of the absorption process independent of local disposition may be helpful for the development of quantitative IVIVC using IVPT and dMD data to improve the comprehension of in-vivo percutaneous permeation that is important for the successful development of new formulations and for the assessment of bioequivalence of topical dermatological products.

Min Li

Colgate–Palmolive Company

3D Mapping of Human Skin Metabolomics and Microbiome with a Facial Cleanser

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Abstract

Human skin harbors a variety of microorganism and molecules as well. The molecules can be from human cells, microbes that live on the skin, and the surrounding external environment. Our daily routine, including hygiene and beauty products, also contribute to the chemical composition of the human skin. This interplay creates a unique chemical niche environment on the human skin surface that results in region specific ecosystems. In previous work, a 3D topographical mapping model has been developed to visualize the body distribution of molecules and microbial communities present on the skin and to correlate bacteria and metabolites. The aim of this study is to specifically understand the impact of a Colgate facial cleanser on human face metabolomics and microbiome profiles using 3D mapping model. Six subjects, including 2 control individuals and 4 individuals who used the facial wash, were recruited in this pilot study. The study was performed over a period of 6 weeks, including 4 weeks washout period without using any personal care products on face, and 2 weeks wash with a facial cleanser twice daily. Nine skin swabs were collected from the different sites of each subject's face at baseline, right after, 4h, 8h and 24h after the first wash and 2wks after the last wash. The metabolite profiling of the skin swabs was performed using mass spectrometry, and microbial inventories were generated using 16S rRNA sequencing. Multivariate statistical analyses were used to compare molecular and bacterial profiles over time and to identify variations associated to facial cleanser wash. 3D mapping was applied to visualize the distribution of skin metabolites and bacteria. The results show that the facial metabolomics profiles of the subjects who washed with the facial cleanser were significantly different from the control subjects who washed with water only. Salicylic acid, the key active in facial cleaner was detected on the skin surface right after the first wash and persisted up to 24h. Some other unidentified metabolites were also changed by the facial cleanser. On the other hand, the facial microbiome was not significantly impacted by the cleanser. This study provides insights into the impact of the Colgate facial cleanser on skin metabolomic profile, and helps to understand the mode of action of the product efficacy.

Taylor Oswald

Rodan and Fields

Multitargeted Approach for Cutibacterium Acnes Antimicrobial Screening

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Acne is characterized by four main etiologies: inflammation, dysseborrhea, hyperkeratinization, and overgrowth of Cutibacterium acnes bacteria1. Consequently, topical treatment routinely consists of antimicrobials to control the bacterial population and associated inflammation, though these materials frequently exhibit unwanted side effects. Identification of new antimicrobials that avoid these negative implications requires a unique approach to in vitro screening compared to traditional methods.

Identification of new antimicrobial substances relies on traditional minimum inhibitory concentration (MIC) or zone of inhibition assays. However, these methods are limited in scope, as they do not account for biofilm virulence factors, induction of bacterial resistance, or harsh side effects caused by high use levels of antimicrobials2,3. In order to account for these factors, a multi-pronged testing platform was designed to screen for antimicrobials, or combinations of antimicrobials, targeting C. acnes. This screening platform includes traditional MIC determination, biofilm disruption MIC (evaluated via multiple staining procedures), and checkerboard MICs to identify potential synergy. Results indicate that antimicrobials traditionally utilized in acne treatment can be used in both lower concentrations and in combination with non-traditional antimicrobials in order to improve efficacy.

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Vinam Puri

Rutgers University–Center for Dermal Research, Ernest Mario School of Pharmacy

Ungual Delivery of Ketoconazole using Solid Lipid Nanoparticles

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Introduction: Nail fungal infections affect about 20% of the global population with challenging treatments as the infection is embedded within the nail. Oral antifungals are associated with serious side effects while the topical therapy is not effective.

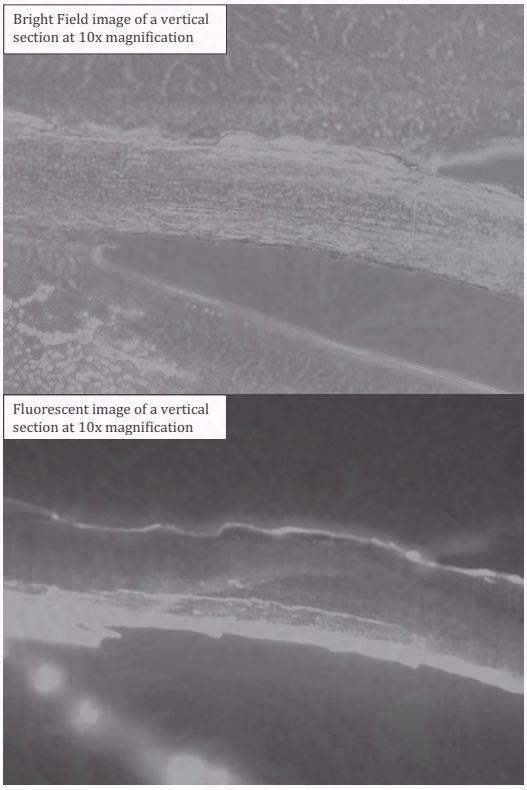
Ketoconazole (KTZ) is a broad-spectrum antifungal, practically insoluble in water, high logP (4.74) and a large molecular weight (531.4 g/mol). It also produces redness and irritation on skin. The nail

plate comprises high water content and for significant nail permeability, high aqueous solubility is desired. We used Solid Lipid Nanoparticles (SLNs) to enhance water solubility of KTZ up to 2% w/v and to mask its irritation. SLNs show occlusive properties on application which hydrate the underlying tissue and enhance permeability.

Methods: KTZ-SLNs (2%) were prepared using Glyceryl behenate, Phospholipid, PEG 600, and Tween 80 and hot high-pressure homogenization technique. Using design of experiments (DOE) the formulation was developed and optimized (response surface methodology; RSM) for maximal loading, entrapment and minimal size. Factor screening was done using Taguchi design (seven factors, at two levels).

Developed KTZ-SLNs and fluorescein (Fl) probe labeled SLNs were applied on the human cadaver nails obtained from Science Care using Franz diffusion cells modified with nail adapters (Permegear) to determine permeation into the nails. KTZ was quantified in nails and cross-sections (Leica Cryostat) were observed using fluorescent microscopy. Nail characterization was done at different time points using transonychial water loss, thickness and weight as parameters. Topical safety of the formulation was established using MTT cell viability assay on fully differentiated (3D) human epidermis, EpiDermTM SIT Kit (MatTek Corporation) and inflammatory mediator/cytokine assay using Human IL-1a/IL-IF1 Immunoassay Quantitative ELISA Kit (R&D Systems).

Results: Systematic optimization and critical quality attributes evaluation identified an optimized formulation with particle size of 336.2 ± 4.6 nm and high entrapment efficiency (84.6 %).



Fluorescent images of nail sections showed penetration into all layers (figure attached). Diffusion cell permeation studies also revealed significant permeability of KTZ into nails when applied as SLNs following single application.

The MTT tissue viability assay (in vitro skin irritation) showed remarkably higher relative viability (149.2%) in comparison to positive control (5% sodium dodecyl sulfate; 4.0 ± 0.26 %). Elisa test demonstrated the absence of IL-1a secretion (-21.85 pg/ml for KTZ SLNs compared to 241.17pg/mL for positive control).

Conclusions: The developed KTZ-SLNs could overcome the well-known topical irritation of KTZ and can be a successful ungual delivery carrier for fungal infections.

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Learning Objectives:

Demonstrate effective anti-fungal ungual drug delivery.

Formulate SLNs as carriers for anti-fungal drugs.

Evaluate permeation as well as non-toxicity of the formulation on human tissue.

Raj Shah

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Concurrent Targeting of Glutaminolysis and Metabotropic Glutamate Receptor 1 (GRM1) Reduces Glutamate Bioavailability in GRM1$^+$ Melanoma

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Abstract

Aberrant glutamatergic signaling has been implicated in altered metabolic activity in several types of cancer including melanoma. Previously, we illustrated the role of metabotropic glutamate receptor 1 (GRM1) in neoplastic transformation of melanocytes in vitro and spontaneous development of metastatic melanoma in vivo. Glutamate, the natural ligand of GRM1, is one of the most abundant amino acids in humans and the predominant excitatory neurotransmitter in the central nervous system. Using a set of isogenic cell lines, we demonstrated correlations between GRM1 and glutaminase (GLS) expression. Metabolomics reveals elevated levels of glutaminolytic mitochondrial tricarboxylic acid (TCA) cycle intermediates especially glutamate in GRM1+ melanoma cells. Elevated intracellular pool of glutamate to satisfy the demand to fuel the growing tumor cells is the result of increased conversion of glutamine to glutamate via GLS. Using a rational drug-targeting strategy, we critically evaluate metabolic bottlenecks with the goal to limit glutamate availability in tumors. CB-839, a potent, selective, and orally bioavailable inhibitor of GLS, plus riluzole, a functional inhibitor of glutamatergic signaling, inhibited cell proliferation in vitro and significantly suppressed tumor growth in vivo in two independent xenograft mouse models of melanoma, with no obvious symptoms

of toxicity. Western blot analysis on excised tumor lysates demonstrated reduced ERK and AKT activities. Rigorous evaluation of the xenograft studies revealed gender biased responses to treatment strategies. Using LCMS analysis, we determined that the circulating blood plasma concentration of treatment modalities may provide explanations to differential treatment responses. Currently we are performing stable isotope tracing to determine the source of carbon fluxing into glutamate. These insights, combined with our data, support the rationale to target glutamate bioavailability to combat GRM1+ human neoplasia.

Jemima D. Shultz

Rutgers University–Center for Dermal Research

Skin Retention Study (In Vitro) of Dermatological Formulations Containing Ascorbyl Glucoside – AA2G Associated with Clay Minerals

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Introduction

Natural raw materials intended for topical application have always been subject of research and development studies, aiming for a variety of uses in the cosmetic and pharmaceutical industries. Among these raw materials, clay minerals have been object of many studies in a large variety of areas, especially in the pharmaceutical and cosmetic field where the clay minerals have no longer been used only as adsorbents / absorbents, excipients to stabilize emulsions or suspensions and to modify the rheological behavior of these systems, but also this group of minerals has been considered most recently as a potential material to modify the release rate of drugs1. Clay minerals are layered materials with a number of peculiar features, which find many relevant applications for natural products. In particular, clay minerals have been increasingly utilized in dermocosmetics and major advances have been achieved in the research and innovation related to these materials1.

The vitamin C derivative known as ascorbic acid 2-glucoside or ascorbyl glucoside (AA-2G) has a conjugated glucose in the carbon-2-hydroxyl which increases the stability of the active, specially protecting the vitamin C molecule degradation due to high temperature, pH and metal ions. Once applied topically, AA-2G is hydrolyzed by a cellular □-glucosylase and it is converted to L-ascorbic acid (vitamin C) which exerts antioxidant activity. In addition, the vitamin C has been used topically to treat photoaged skin by the fact that increases collagen synthesis, and it has also been reported to decrease melanin synthesis and has therefore been used topically as a skin whitener 2.

Objective

The development of a dermatological emulsions containing different clay minerals and skin retention study of the active ascorbyl glucoside (AA2G).

Methods and materials

Five dermatological formulations classified as O/W emulsion was developed and evaluated in in vitro permeability study during 8 hours on static vertical Franz diffusion cells using human skin. After 8 hours, the application site on the skin was washed 10 times using PBS buffer pH 7.4. and

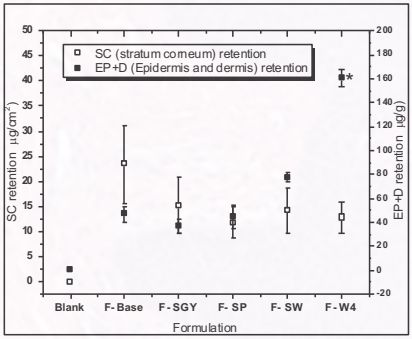

Figure 1: The amount of ascorbyl glucoside retained into the stratum corneum (SC), epidermis and dermis (EP+D) skin layers are presented on the Y-axis at the graph. The statistical data is expressed as mean±SE (n=5); p-value < 0.05 (*) was considered to be statistically significant between the amount of ascorbyl glycoside retained in the epidermis and dermis layers for formulation F-W4 containing the sodium smectite clay W4.

the tape stripping technique was performed to separate the stratum corneum from epidermis and dermis skin layers. A total of 10 tapes were applied to remove the SC, remaining (epidermis + dermis). The 10 tapes were placed together in a 50 mL falcon tube and 5 mL of PBS buffer pH 7.4/ methanol (75:25) solution was added for extraction of the active (AA2G). The remaining skin was scored and the amount of active present was extracted with the same solution, adding a tissue homogenizer for 10 minutes and sonication for 30 minutes. Then, the volume of ~500 µL of the sample was filtered through a 0.45 µm pore filter and analyzed using a valid HPLC method.

Results

The result shows that the retention of ascorbyl glucoside is significantly more expressive for the formulation containing the sodium smectite clay W4 than for the formulations containing kaolinite clays or control formulation (no clay mineral). The advance of have a vitamin C derivative as ascorbyl glucoside retained in the SC and or EP+D skin layers is the fact that it can be easily hydrolyzed into ascorbic acid (vitamin C) and glucose by □-glucosidase enzyme, which naturally exists in the skin cell membranes. As the continuous conversion of Ascorbyl Glucoside, it incessantly provides vitamin C for skin. It is known in the scientific literature that the vitamin C has powerful antioxidant properties, inhibits the synthesis of melanin, lightening the skin, promote the formation of collagen, which can reduce photo-aging and cell damage and also increase the expression of cytokeratin10, 28, 36

Conclusion

The sodium smectite clay has the ability to retain more amount of ascorbyl glucoside between the skin layers than the kaolin clay does. Considering that the research on different types of clay minerals have been able to attract great interest of the pharmaceutical and cosmetic industries and to make room for greater use of this type of material in various applications, particularly when the goal is dermal topical application. More research that focus on the development of new clay-based dermocosmetic formulations along with detailed analyses of their physicochemical stability are required, specially due to the chemical interactions between the active drug and the clay mineral into the formulation.

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Acknowledgements

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Hequn (Tracy) Wang

Johnson and Johnson Consumer Companies, Inc.

Novel Confocal Raman Microscopy Method to Investigate Hydration Mechanisms in Human Skin

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Abstract

Background: Skin hydration is essential for maintaining stratum corneum (SC) flexibility and facilitating maturation events. Moisturizers contain multiple ingredients to maintain and improve skin hydration although a complete understanding of hydration mechanisms is lacking. The ability to differentiate the source of the hydration (water from the environment or deeper skin regions) upon application of product will aid in designing more efficacious formulations.

Materials and Methods: Novel confocal Raman microscopy (CRM) experiments allow us to investigate mechanisms and levels of hydration in the SC. Using deuterium oxide (D2O) as a probe permits the differentiation of endogenous water (H2O) from exogenous D2O. Following topical application of D2O, we first compare in vivo skin depth profiles with those obtained using ex vivo skin. Additional ex vivo experiments are conducted to quantify the kinetics of D2O diffusion in the epidermis by introducing D2O under the dermis.

Results: Relative D2O depth profiles from in vivo and ex vivo measurements compare well considering procedural and instrumental differences. Additional in vivo experiments where D2O was applied following topical glycerin application increased the longevity of D2O in the SC. Reproducible rates of D2O diffusion as a function of depth have been established for experiments where D2O is introduced under ex vivo skin.

Conclusion: Unique information regarding hydration mechanisms are obtained from CRM experiments using D2O as a probe. The source and relative rates of hydration can be delineated using ex vivo skin with D2O underneath. One can envision comparing these depth-dependent rates in the presence and absence of topically applied hydrating agents to obtain mechanistic information.

Julia Zhang

Rutgers University- Center for Dermal Research, Ernest Mario School of Pharmacy

Dermal and Transdermal Delivery of Oxicams Using Deformable Liposomes

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Purpose

Oxicams, BCS Class II drugs belonging to the class of NSAIDS (non-steroidal anti-inflammatory drugs) are potent hydrophobic compounds indicated in conditions of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis in which rapid onset of drug action is desired to reduce inflammation and pain. However, many adverse effects (such as Nausea, upset stomach, diarrhea, dizziness etc.) are reported when they are administrated orally. The objective of this study is to develop deformable liposomes of meloxicam (model drug) to enhance the solubility and permeation for topical drug delivery across the stratum corneum for local (dermal), or systemic (transdermal) effects, to significantly reduce inflammation and pain and thereby greatly reduce the side effects.

Methods

Meloxicam loaded deformable liposomes were prepared by the thin film hydration method followed by sonication. Chemical analysis was performed by using an HPLC method for the quantitation of meloxicam to determine its entrapment efficiency and amount found in human skin samples following permeation studies. Physical characterization of particle size and zeta potential were determined using a Malvern Zetasizer DLS (Dynamic Light Scattering). Morphology, thermodynamic and visualization tests, such as transmission electron microscopy (TEM), differential scanning calorimetry (DSC), confocal microscopy (CLSM), were utilized to characterize the vesicles and understand the mechanism of penetration of these deformable liposomes. After the characterization, an in vitro skin permeation study was performed using Franz diffusion cells with human cadaver skin samples.

Results

As summarized in Table 1, the deformable liposomes of meloxicam (MX) were composed of phospholipid (PL), cetylpyridinium chloride (CPC), cholesterol (Chol) and/or permeation enhancer menthol (Men), anti-oxidant poplyphenol-1 (PP-1) and polyphenol-2 (PP-2). Formulations 1 to 4 were prepared based on the studies conducted by Duangjit1. Formulation 5 was prepared to study the effect of menthol in the liposome formulation. Formulations 6 and 7 were made using two different polyphenol compounds, which acted as both anti-oxidants and additional anti-inflammatory drugs.

The results indicated that these deformable liposomes of meloxicam provided substantial enhancement of meloxicam solubility compared to conventional liposomes (controls: F1 and F2), demonstrating

Table 1. Characterization Results of Different Liposome Formulations

Formulation ID	Sample Description	Formulation Components	%Entrapment Rate	Ave Diameter (nm)	PDI	Zeta Potential (mV)
F1	Conventionl Liposome	MX+PL	20.24	126.2	0.259	0
F2	Conventionl Liposome	MX+PL+Chol	21.10	125.7	0.274	-0.2
F3	Transfersome	MX+PL+Chol+CPC	91.01	136.7	0.351	20
F4	Menthosome	MX+PL+Chol+CPC+Men	82.66	97.5	0.303	21.5
F5	Menthosome w/o surfactant	MX+PL+Chol+Men	7.17	114.7	0.203	2.9
F6	Polyphenol-1	MX+PL+Chol+CPC+PP-1	95.48	118.2	0.243	22.9
F7	Polyphenol-2	MX+PL+Chol+CPC+PP-2	103.72	102.9	0.201	15.3

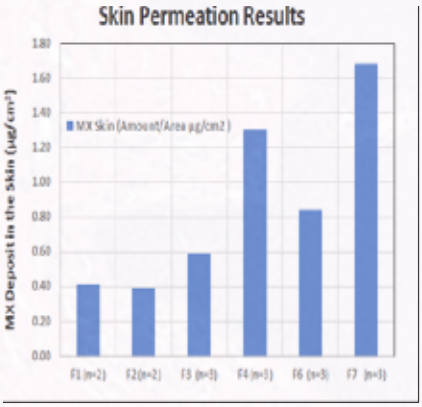

Figure1. Meloxicam Deposited in the Whole Skin

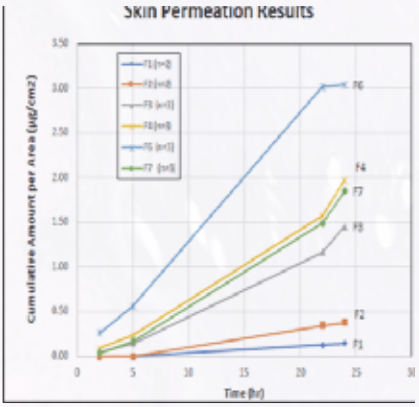

Figure 2. Cumulative Amount of MX Per Area in Receptor Compartment

much higher entrapment rates (70-100% vs 20%) and smaller, homogeneous particles, as shown in Table 1. Notably, the deformable liposomes containing polyphenols showed higher entrapment rate compared to transfersomes and menthosomes transdermal technology platforms.

Preliminary skin permeation study has been conducted using Franz Diffusion Cells on human cadaver skins. The obtained results also revealed meloxicam loaded deformable liposomes improved permeability, as demonstrated in Figures 1 and 2.

Specifically, permeation results of Formulation 7 (containing PP-1) showed the highest amount of meloxicam resided in the skin, while that of Formulation 6 displayed the highest amount of meloxicam penetrated through the skin and detected in receptor compartments.

Conclusion

Different compositions of deformable liposomes have been developed with high drug entrapment rate, homogeneous particle size and improved solubility and permeability. The dermal and transdermal delivery using deformable liposomes can be a promising alternative to conventional oral delivery of NSAIDS with enhanced local and systemic onset of action and reduced side effects.

Reference: 1. Duangjit S, et al. Comparative study of novel ultradeformable liposomes: menthosomes, transfersomes and liposomes for enhancing skin permeation of meloxicam. Biol Pharm Bull. 2014;37(2):239-47.

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Research Interests at the CDR

- Optimization of topical, transdermal & transmucosal drug delivery; development of novel skin permeation models & computational modeling.
- Design & evaluation of novel dermal penetration enhancers and retardants and their structure-activity relationships. Using enhancers for transdermal delivery of actives for the treatment of Alzheimer's disease, dementia, multiple sclerosis and other CNS disorders.
- Design and testing of novel nanosphere and siRNA topical formulations for the treatment of acne and melanoma respectively.
- Visualization of drug transport pathways in skin using Raman, Fourier Transform Infra-Red spectroscopy, electron and confocal microscopy.
- Development of novel human tissue cultured skin equivalents for permeability testing.
- Computational approaches to predicting skin transport of drugs.
- Design & evaluation of orodispersible polymer films for drug delivery.
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