Newsletter

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Phospholipid

Forschungszentrum/Research Center

Heidelberg

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Introduction

In 2017 the Phospholipid Research Center organised its 5th International Symposium on Phospholipids in Pharmaceutical Research on September 18th and 19th, 2017 in Heidelberg with overwhelming success (more information on page 5).

The team managing the Research Center has been strengthened by Dr. Dorothea Gutekunst, who joined the Center on August 1st, 2017. She is a pharmacist and finished her PhD in July 2017 at Kiel University, Germany at the department of Pharmaceutics and Biopharmaceutics under the supervision of Prof. H. Steckel and Prof. R. Scherließ. She is familiar with phospholipids because of her PhD project on „Phospholipid microemulsions for the dermal application of proteins: Prediction of in-vivo skin tolerability with full-thickness human skin equivalent“, which was partially funded by the Phospholipid Research Center. As a research scientist at Kiel University, Dorothea gained experience in formulation development with phospholipids for the dermal and parenteral application in various projects. We are very pleased that Dorothea joined us and wish her a good start.

Finally, at the end of this year 2017, we would like to thank all members for their valuable contributions and wish all of you a successful 2018!

Peter van Hoogevest

Managing Director
Phospholipid Research Center

Phospholipid Research Center – NEWS

General Meeting of the Phospholipid Research Center e.V.

The General Meeting of the Phospholipid Research Center e.V. (PRC) took place on September 19th, 2017 (Heidelberg, Germany) immediately after the Symposium. Ten members with voting rights and three guests from Lipoid LLC were present.

The new President of the PRC Prof. Dr. A. Blume welcomed all participants and called for a moment of silence to remember the in 2016 deceased President of the PRC Dr. Jürgen Zirkel.

All present participants confirmed Prof. A. Blume and Prof. C. Müller-Goymann as President and Vice President of the PRC, respectively and elected them for a period of three years.

The recently finished 5th International Symposium on Phospholipids in Pharmaceutical Research was discussed and improvements for the next event in 2019 were suggested.

Each member of the Phospholipid Research Center e.V. is very welcome to join the general meeting and to enrich this organisation with new ideas.

Meeting of the Scientific Advisory Council

The Meetings of the Scientific Advisory Council took place on January 16th, 2017 (Lipoid GmbH, Ludwigshafen) and on July 3rd, 2017 (Zentrum für Pharmaverfahrenstechnik, TU Braunschweig).

Participants:

Prof. A. Blume (President, PRC)
Prof. C. Müller-Goymann (Vice President, PRC)
Prof. G. Fricker (Scientific Board)
Dr. F. Martin (Scientific Board)
Dr. H. Rebmann (Honorary President, PRC)
Mrs. B. Rebmann (Guest)
Dr. R.-O. Quinkert (Scientific Board)
PD Dr. P. van Hoogevest (Managing Director PRC)

Prof. G. Storm (Utrecht University, Netherlands) was welcomed on July 3rd, 2017 as new member of the Scientific Advisory Council.
In 2017, the Phospholipid Research Center supported the following 24 projects.

Ongoing and New Funded Projects

Interactions of the Tumour-Targeting Vector Peptide pHLIP with Phospholipids.
Prof. S. Keller, University Kaiserslautern, Germany

Development of NLCs and nano-emulsions with monoacyl-phospholipids and investigation of their skin penetration and influence on skin barrier structure in vitro and in vivo.
Prof. C. Valenta, University Vienna, Austria

Assessment and better prediction of acute hypersensitivity and complement involvement upon administering liposomal drug products to human subjects.
Dr. J. Metselaar, University Twente, The Netherlands

Phospholipids as functional excipient in solid oral dosage forms.
Prof. R. Bodmeier, FU Berlin, Germany

Development of colloidal carrier systems (micro-emulsions) on the basis of phospholipids for dermal application.
Profs. R. Neubert/J. Wohlrab and G. Brezesinsky, University Halle/Potsdam, Germany

Treatment and diagnosis of early gastric cancer with lipid based formulated hypericin by applying photodynamic therapy.
Dr. F. Helm, University Heidelberg, Germany

Macrophage reprogramming by ultra-fast drug release from plasmonic liposome.
Dr. X. Li, University Dallas, United States

Phospholipid-Functionalized Calcium Carbonate Based DD System to Improve the Bioavailability of PWSD.
Prof. J. Huwyler, University Basel, Switzerland

Phospholipid based liquid-fill formulations for hard gelatin capsules.
Prof. H. Bunjes, University Braunschweig, Germany

Establishing a more rational design of thermo-responsive liposomes.
Prof. H. Heerklotz, University Freiburg, Germany

Targeted liposomal antioxidant and anti-inflammatory therapy for liver ischemic reperfusion injury.
Dr. L. Corvo, University Lisbon, Portugal

Modulating Tumor-Associated Macrophages using Cell-specific Targeted Liposomes.
Dr. J. Prakash, University of Twente, The Netherlands

Phosphatidylserine enriched phospholipids as anti-inflammatory agents
Prof. K. Mäder/PD Dr. A. Meister, University Halle (Saale), Germany

Liposomal oral drug delivery: The use of bipolar amphiphiles to stabilize liposomes.
Dr. S. Drescher, University Halle (Saale), Germany

Development of a phospholipid-based depot technology for sustained drug release.
Prof. P. Luciani, University Jena, Germany

Theranostic phospholipids-coated ultrasound contrast agents: response on demand.
Dr. K. Kooiman, MC Rotterdam, The Netherlands

Evaluation of cochleates as parenteral depot formulations.
Prof. J. Kuntsche, University South Denmark

Investigations on liposomal transdermal drug delivery by Raman microscopic imaging in combination with stable isotopic labelling.
Dr. C. Mattheaus, University Jena, Germany

Production of liposomes by centrifugation of water-in-oil emulsions.
Prof. H. Nirschl/Dr. G. Leneweit, KIT Karlsruhe, Germany

Synergy-based delivery system for combating sexually-transmitted bacterial infections: liposomal azithromycin-in-chitosan hydrogel.
Prof. Z. Vanic, University Zagreb, Croatia

Lipid nanovectors to use non-coding RNA oligonucleotides in glioblastoma in combination with standard therapy.
Prof. G. de Rosa, University Naples, Italy

Combination of PUFA-PC wih cytoskeleton-targeting drugs for overcoming Akt-dependent chemoresistance.
PD Dr. A. Koeberle, University Jena, Germany

Electrospun bioactive wound dressing containing phospholipid stabilized nano-dispersions of a Birch Bark Dry extract.
Prof. R. Daniels, University Tübingen, Germany

Antitubercular drug-loaded multi-liposomes vectors.
Prof. F. Bordi, University Rome, Italy

Publications

Following publications, related to projects supported by the Phospholipid Research Center were made during 2017:

Tran, T., Siqueira, S. D., Amenitsch, H., Müllertz, A., & Rades, T. (2017). In vitro and in vivo performance of monoacyl phospholipid-based self-emulsifying drug delivery systems. *Journal of Controlled Release*, *255*, 45-53.

Uhl, P., Pantze, S., Storck, P., Parmentier, J., Witzigmann, D., Hofhaus, & G. Fricker, G. (2017). Oral delivery of vancomycin by tetraether lipid liposomes. *European Journal of Pharmaceutical Sciences*, *108*, 111-118.

Wolf, M., Halper, M., Pribyl, R., Baurecht, D., & Valenta, C. (2017). Distribution of phospholipid based formulations in the skin investigated by combined ATR-FTIR and tape stripping experiments. *International Journal of Pharmaceutics*, *519*(1), 198-205.

Pratsinis, A., Zuercher, S., Forster, V., Fischer, E. J., Luciani, P., & Leroux, J. C. (2017). Liposome-supported enzymatic peritoneal dialysis. *Biomaterials*, *145*, 128-137.

Kolbina, M., Koerber, M., Bodmeier R. (2017). Saturated Phosphatidylcholine as Matrix Former for Extended Oral Drug Release. *Poster Presentation AAP Annual Meeting & Exposition*.

Wolf, M., Binder, L., Jatschka, J., Pribyl, R. & Valenta, C. (2017). Simultaneous detection of formulation compound and drug by ATR-FTIR and HPLC. *Poster Presentation CRS German Local Chapter 21th Annual Meeting.*

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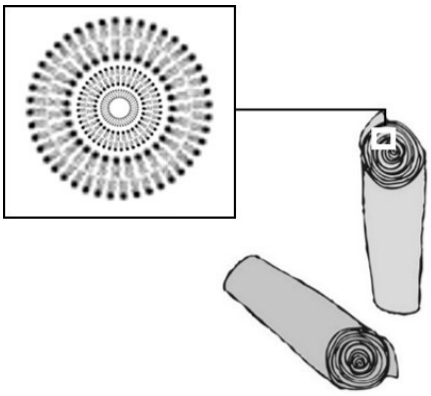
Congress Reports

5th Symposium on "Phospholipids in Pharmaceutical Research" 2017

Dorothea Gutekunst and Peter van Hoogevest

The Phospholipid Research Center Heidelberg, organised already its "5th International Symposium on Phospholipids in Pharmaceutical Research" from 18th – 19th September 2017 at the University of Heidelberg, Germany. 165 researchers from all over the world attended the meeting. International experts from academia and industry presented in their seminars innovative and new applications of phospholipids. Categorised in five topics: Analytics and Characterisation Techniques, in vitro/Physicochemical Properties, Drug Delivery, Technological Approaches and Skin Application; 69 scientists presented their posters on topics in phospholipid research.

The first day started with a general introduction to phospholipids. PD Dr. Peter van Hoogevest (Phospholipid Research Center, DE) and Dr. Ralf-Olaf Quinkert (Lipoid GmbH, DE) highlighted properties, manufacturing and analytics of phospholipids. An example for the versatile deployment of phospholipids presented Prof. Dr. Alfred Fahr (University of Jena, DE) vividly. His explanations focused on special lipid bilayers, comprising phosphatidylserine, arranged in cylindrical continuous sheets, called cochleates. For getting an idea of the structure, see the following figure.



Simplified representation of the fascinating structure of cochleates. (Adapted from Fahr, 2017).

The audience enthusiastically listened to these explanations and to the subsequent session on examples of the industrial use of phospholipids presented by Dr. Josbert Metselaar (University of Twente, NL), Dr. Daryl Drummond (Merrimack Pharmaceuticals, US) and Dr. Jürgen Schmitt (B. Braun Melsungen AG, DE). Next to the speakers, exhibitors of different companies facilitated an active exchange between academia and industry as well. Representatives of Particle Solutions Innovations B.V., Avestin Europe GmbH, Malvern Instruments GmbH, Microfluidics and Polymun Scientific presented their products and skills.

Research projects with a special focus on the parenteral administration of phospholipids were highlighted by the seminars of Prof. Jean-Christophe Leroux (ETH Zürich, CH) "Detoxification using parenteral lipid formulations" and Prof. Karsten Mäder (University of Halle, DE) "Phosphatidylserine enriched phospholipids as ant-inflammatory agents".

Save the Date!

The **6th International Symposium on Phospholipids in Pharmaceutical Research** will be held on **September 9th – 10th, 2019**. Until then, you can become a member of the Phospholipid Research Center Heidelberg e.V. and apply for a grant to support your academic research project on phospholipids. For more information, please visit our homepage www.phospholipid-institute.com.

The first day concluded with a solemn announcement of the Thudichum-Award winners 2017. The Phospholipid Research Center donated the "Thudichum Award" for the second time. Named after the famous German physician and biochemist Johann Ludwig Wilhelm Thudichum (1829-1901), who isolated and characterised for the first time numerous compounds of the brain including phospholipids and related species. He recognised the physiological importance of phospholipids. This year, the members of the Scientific Advisory Council awarded Dr. Tom van Rooij (Erasmus MC, Rotterdam, NL) for his outstanding publications in pharmaceutical phospholipid research. Dr. Tom van Rooij examined in the group of Dr. Klazina Kooiman ultrasound contrast agents formulated in lipid-coated microbubbles for imaging and therapeutic applications. For the first time the "Thudichum Life Award" has been awarded. Dr. Herbert Rebmann (Honorary President of the Phospholipid Research Center) congratulated Prof. Daan Crommelin for his lifelong outstanding achievements in the field of phospholipid research. Prof. Daan Crommelin is a pioneer in the field of stabilisation and characterisation of phospholipids and liposomes.

Congratulations to

Prof. Daan Crommelin & Dr. Tom van Rooij

for their excellent scientific research!

The Thudichum Award winners 2017. Dr. Tom van Rooij (left) and Prof. Daan Crommelin (right).

After a first day of discussion, establishing new contacts but also happy reunions among the participants, we had a wonderful boat trip with a delicious dinner on the *Königin Silvia* at Neckar River.

Snapshot of the dinner event on the Königin Silvia.

The second day of the symposium started with a session on "Oral Administration of Phospholipids". Prof. Alexander Treusch (University of Southern Denmark, DK) summarised the latest results on the application of "Archaeal Lipids in the Oral Delivery of Therapeutic Peptides", whereas Prof. Anette Müllertz (University of Copenhagen, DK) elucidated the use of monoacyl-phospholipids in oral self-nanoemulsifying drug delivery systems. A new approach to improve the bioavailability of poor water-soluble drugs with a phospholipid-functionalised calcium carbonate based drug delivery system was presented by Prof. Jörg Huwyler (University of Basel, CH).

Phospholipids are versatile excipients.

Prof. Yvonne Perrie (University of Strathclyde, UK. Scotland) demonstrated, inter alia, the versatility of phospholipids as part of the development of lipid-based delivery systems for oral vaccination.

More focused on the mechanism of action of phospholipids in the human body was the following session. PD Dr. Andreas Koeberle (University of Jena, DE) presented the inhibitory effect of polyunsaturated phosphatidylcholine on Akt (also known as protein kinase B), as a potential treatment target in cancer therapy. Dr. Jai Prakash (University of Twente, NL) demonstrated a new approach in the field of cancer therapy using special liposomes, comprising carboxylated phospholipids, for targeting to tumor-associated M2 macrophages.

The mentioned seminars highlighted current innovative phospholipid research and development topics in Europe and North America.

What about phospholipid research in South America e.g. in Brazil?

The last session of the Phospholipid Symposium 2017 ended with a special seminar on phospholipid research in Brazil. Prof. Frédéric Frézard (Universidade Federal de Minas Gerais, BR) introduced main research fields, highlighted impressively current ongoing projects and pointed out promising research perspectives.

Traditionally, the symposium was concluded by the "Young Session" chaired by Prof. Christel Müller-Goymann (University of Braunschweig, DE). The students of six pre-nominated posters were invited to give a short presentation about their research. The following three posters were selected and awarded with a 500 € poster prize:

Joyce Azzi (Lebanese University, LB):
"Effect of liposome fatty acyl chains saturation on the photostability of encapsulated biomolecules."

Ana Ferreira-Silva (Universidade de Lisboa, PT): "Antagonist G-labeled long circulating liposomes actively targeted to lung tumor cells."

Philipp Uhl (University Hospital Heidelberg, DE):
"Cell penetrating liposomes enable oral delivery of vancomycin."

The success of the 5th International Symposium on Phospholipids in Pharmaceutical Research 2017 was based on the presence of many creative minds and inspiring scientists who demonstrated the versatile applications of phospholipids in pharmaceutical research.

Prof. Christel Müller-Goymann and the winners of the poster award (from left to right): Ana Ferreira-Silva, Philipp Uhl and Joyce Azzi.

We would like to acknowledge the speakers, poster authors, chairmen, Scientific Advisory Council and the University Heidelberg (Prof. Gert Fricker and his students) for their support. Special thanks go to Mrs. Britta Merz and Dr. Torsten Kromp for their contributions to the organisation and coordination of the symposium. Finally, we would also thank all participants for their enthusiastic contributions.

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Fahr, A. "Special colloidal structures with phospholipids: Cochleates,." *5th International Symposium on "Phospholipids in Pharmaceutical Research", Heidelberg, Germany*, 2017

Upcoming Events

Meeting of the Scientific Advisory Council

Monday, January 29th, 2018

The next meeting of the Scientific Advisory Council will be hosted by Prof. A. Blume at the University of Halle (Saale), Germany.

Meeting of the Membrane Section of the German Biophysical Society: "Membrane Models for Biophysics"

March 5th, 2018 – March 7th, 2018

This workshop is supported by the Phospholipid Research Center and organised by the Department Physical Chemistry, University Halle (Saale), Germany. It will take place at the Drübeck Monastery located in Harz Mountains. For further information, please visit the following homepage: www.dgfb-membranes.uni-halle.de.

Researcher`s Day 2018

Monday, June 25th, 2018

In 2018 the Phospholipid Research Center will organise the Researcher`s Day in Ludwigshafen am Rhein, Germany. The main purpose of the meeting is to bring the researchers (funded by the PRC) together, discuss the projects and offer a platform for networking. The participants will be divided in three expert groups, Parenteral, Dermal and Oral. The final scientific program will be published in the week commencing June 2018 and will be available on our homepage (www.phospholipid-institute.com).

6th International Symposium on Phopsholipids in Pharmaceutical Research 2019

September 9th – September 10th, 2019

News and information will be published on our homepage. The Venue will be, as always; Heidelberg, Germany.

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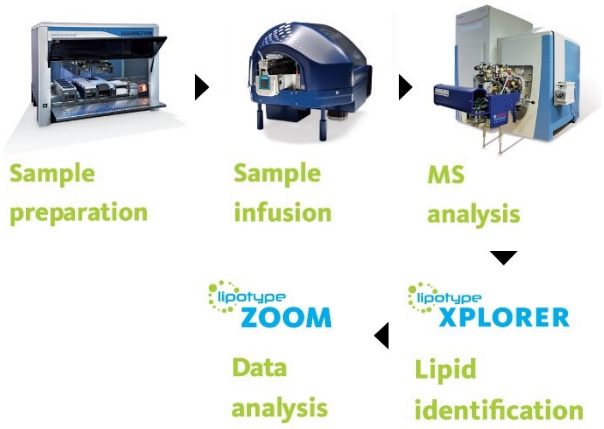
Lipid Analytics

Skin lipidomics: analyzing lipid-related skin aging at the molecular level

Christian Klose and Michal A. Surma

Lipotype GmbH, Tatzberg 47, Dresden, Germany

The Lipotype shotgun lipidomics workflow optimized for speed, throughput and convenience utilizing automation.



Skin as the largest human organ fulfills a number of vital functions which are all related to the interaction with or the protection from what is outside of us, i.e. our environment. This functionality, its physiology and pathophysiology, are derivative of structure and composition of its topmost layer, the *stratum corneum*. The barrier properties *of stratum corneum* are based upon its anatomy and physiology. The *stratum corneum* consists of a layered meshwork of corneocytes sealed with lipids arranged in lamellar fashion, where corneocytes act as "bricks" glued together by a lipid "mortar", consisting mostly of ceramides (CER), cholesterol and free fatty acids [2]. Acting on the skin surface, sebaceous glands are a major source of sebum lipids: triacylglycerol (TAG), diacylglycerol (DAG) and cholesterol esters (CE) [3]. Further constituents of skin lipid matrix are wax esters and squalene. Lipid studies of skin have demonstrated that age, gender, ethnicity, and season of the year affect the skin lipid composition [5]. Likewise, alterations of lipid profiles were linked to dermatological and systemic diseases, like atopic dermatitis [6], [7], hereditary ichthyosis [8] or Netherton syndrome [9]. Understanding skin surface lipid composition at the molecular level, i.e. the skin lipidome, would not only greatly facilitate our knowledge on skin physiology, but is also a prerequisite for understanding fundamental skin properties.

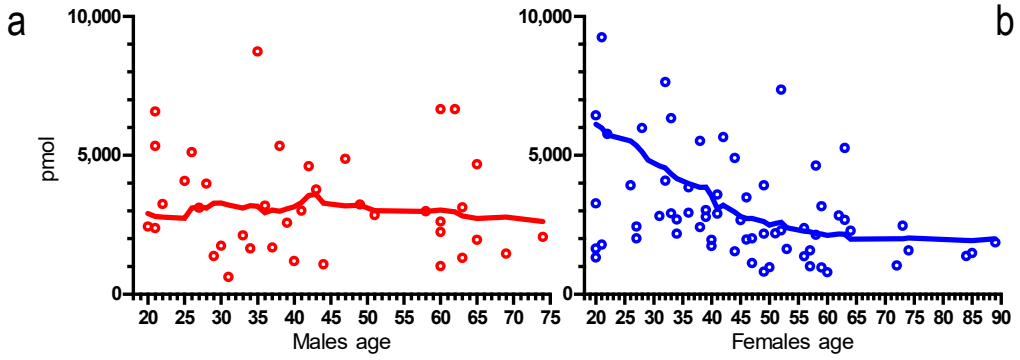


Figure 1. Inter-individual variation. (a,b) Amounts of lipids measured of (a) males and (b) females of different age (here the two most extreme pmol values are not shown to improve clarity). Lines represent 0-order polynomial smoothing function with 8 neighbors averaged.

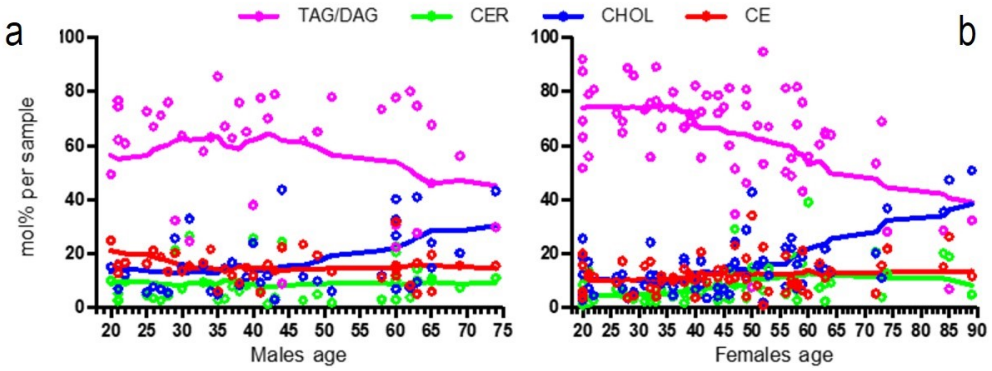


Figure 2. Inter-individual variation presented in the profiles of lipid groups of (a) males and (b) females of different age. Lines represent 0-order polynomial smoothing function with 8 neighbours averaged.

Quantifying the skin lipidome is a challenging task. First of all, the skin lipid complexity puts high demands on the methods to be applied. In particular, skin ceramides present a serious analytical problem, as they are represented by 12 different classes. The classes are defined by a combination of 4 different sphingoid bases (dehydrosphingosine, sphingosine, phytosphingosine and 6-hydroxy sphingosine) with 3 different acyl chains (non-hydroxy, alpha-hydroxy and esterified omega-hydroxy fatty acids) [2]. Ideally, a comprehensive analysis of the skin lipidome should encompass the analysis of ceramides together with all the other lipid classes present on and in the skin, preferably on a single analytical platform.

With our recently introduced a mass spectrometry-based skin lipidomics technology we aimed at addressing the presented challenges. We succeeded in achieving a high coverage of lipid classes, including both *stratum corneum* lipids (ceramides, cholesterol) as well as sebum lipids (TAG, DAG and CE), full quantitation and high-throughput [1]. The methodology is compatible with tape stripping, a convenient and minimally invasive skin sampling method. Lipotype skin lipidomics features the coverage of 16 lipid classes; absolute quantification at the level of individual lipid molecules; high reproducibility (technical variation of 7.4%) and high-throughput capabilities (200 samples per day). This method was applied in a large-scale lipidomic survey of human *stratum corneum* samples, where we investigated the impact of age and sex on lipidome variability in 104 healthy subjects [1]. Interestingly, the observed overall inter-individual variability in lipid amounts was considerable (57% coefficient of variation in males, 90% in females), as seen also in other studies [12] (Figure 1a,b). The amounts of TAG and DAG with respect to total lipid content markedly decreased with age in female skin (Figure 2b), while the relative amount of cholesterol increased. This phenomenon was less pronounced in the male population (Figure 2a). A previous investigation of human epidermis also discovered a decline of triglycerides in older subjects, as compared with younger subjects [3]. This finding was further corroborated by a study on 110 women, which showed that the sebum amount decreases with age [13]. We observed relative cholesterol ester and ceramide levels remaining constant. This indifference of ceramide content to age in skin was observed before [14].

In summary, our study revealed large inter-individual variability of skin lipidomes in samples collected from the volar forearm, comparable in magnitude to the intra-individual variability as measured at 14 sites on one male and one female [1]. Both absolute and relative amounts of sebaceous lipids were observed to decrease with increasing age, especially among females. However, male and female samples could not be distinguished by their lipidomes. In general, skin lipidome variability as assessed in this study is high and mainly driven by sebaceous lipids, which tend to decrease at old age. A possible explanation for gender-specific, age-dependent depletion of sebaceous lipids might be connected to hormonal regulation of sebum secretion [16]. It was shown, that at increasing age eccrine glands are either reduced in number or in functional capacity [17]. This could account for the pronounced decline of both absolute and relative amounts of sebaceous lipids among older women.

The applied lipidomic approach proved to be useful in assessing variability and changes in skin lipid composition caused by age and sex of subjects. An exciting future application of the skin lipidomics technology is studying the

effect of anti-aging cosmetics with respect to skin lipid composition and further correlation with functional skin parameters. This might prove an effective approach for substantiating anti-aging claims. If the product influences skin properties, then skin lipidomics is a direct way to prove its efficacy based on the molecular skin composition. The approach can be extended to the investigation of skin-damaging factors, many of which will be responsible for natural skin aging as well. Possibilities do not end at this point, as broad lipid coverage, absolute quantification and high-throughput makes shotgun mass spectrometry based skin lipidomics a well-suited tool for rigorous and systematic studies of various topics e.g. characterization of skin disorders, influence of drugs on the skin lipidome, mode-of-action studies related to skin lipid metabolism or the skin microbiome-lipidome relation, impact of cosmetic substances and actives on the skin lipidome supporting their efficacy.

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Update: Industry

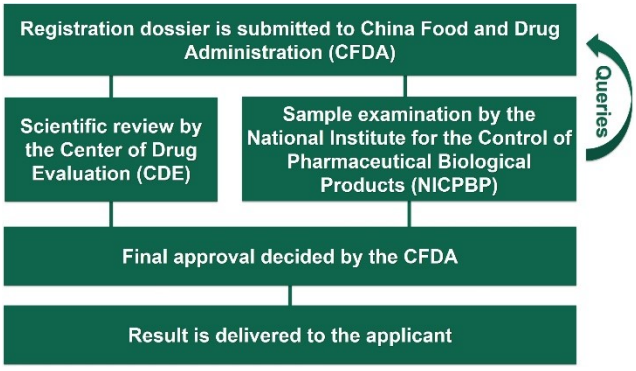
Registration of Phospholipids and other Lipids as Active Pharmaceutical Ingredients and Excipients in China

Torsten Kromp, Elvira Bindewald, Sebastian Horn, Marion Goll-Tillmann

Lipoid GmbH, Quality Assurance, Ludwigshafen, Germany

In China, the regulatory requirements for registration of pharmaceutical raw materials and active pharmaceutical ingredients (API) have to be considered and adopted for each product. The registration dossier contains information on the quality and manufacture of the raw materials used. Specific requirements have to be fulfilled and the structure and content of the dossier is strictly defined. Phospholipids as pharmaceutical excipients have to be registered together with the drug product producer (bundling review).

General registration procedure:



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Announcement issued by CFDA on matters in relation to bundling review and approval of packaging materials and pharmaceutical excipients (No. 134 in Year 2016)

China as an emerging market is of great interest for the pharmaceutical industry. The regulatory requirements for registration of Active Pharmaceutical Ingredients (API) and excipients are constantly changing. Therefore, the more or less specific requirements in regards to the registration of pharmaceutical raw materials and APIs have to be considered and adopted for each product. Basically, all documents have to be registered at the corresponding competent authorities. The registration dossier should contain information on the quality and manufacture of the raw materials used.

In China, the registration shall be done by the company branch or an entrusted agency on site. It is essential to translate the documents and follow up of the registration proceeding continuously. If an external agency is used, the respective agent is the contact person between registration authorities and the foreign applicant. The registration dossier has to be submitted to the CFDA (China Food and Drug Administration) in Beijing. The documents for API registration will be checked. Then the evaluation of the submitted documents starts through several official bodies, until the final approval is done by the CFDA.

A new regulation for excipient registration in China came into force in 2016 replacing the former Import Drug License (IDL) registration. The most important change in the registration procedure is that the excipient now has to be registered bundled together with the drug product and cannot be registered alone anymore. The structure and content of the registration dossier is strictly defined. These standards have to be followed exactly, representing the major challenge for regulatory affairs departments.

Challenges

- Changing contacts prolonged the registration period
- Clarification and answering of queries from the CDE/NICPBP
- Agreements with costumers for bundled registration

Tips

- Send experts to the test center or CDE and discuss open issues
- Local agency as contact (e.g. manage the communication, track the registration status)

Alerts of Phospholipid Based Products from Pharma Industry

Pulmocare®

Abbot Nutrition announced Pulmocare which is an oral product designed for people with chronic obstructive pulmonary disease (COPD), cystic fibrosis, or respiratory failure. Patients may benefit from a high-calorie, modified carbohydrate and fat, enteral formula that may help reduce diet-induced carbon dioxide production. It is a vanilla flavoured liquid filled in tubes for oral feeding. Beside fat and cabohydrates Pulmocare contains various vitamins, minerals, trace elements and soybean lecithin. In Pulmocare soybean lecithin acts as an oral multifunctional excipient. On the one hand, it gives stabilisation to the emulsion; on the other hand it is an important source of essential fatty acids and calories.

Abbot Nutrition, Product Flyer, July 31st, 2017

Cinvanti™

Heron Therapeutics Announces U.S. FDA Approval of Cinvanti (aprepitant) injectable emulsion for the prevention of acute and delayed Chemotherapy Induced Nausea and Vomiting (CINV). Cinvanti is a substance P/neurokinin-1 (NK1) receptor antagonist, indicated in adults, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin and initial and repeat courses of moderately emetogenic cancer chemotherapy.

Cinvanti injectable emulsion contains the active ingredient, aprepitant. Aprepitant is a lipophilic, poorly water soluble substance P/neurokinin 1 (NK1) receptor antagonist, an antiemetic agent. It is the first and only polysorbate 80-free, intravenous formulation of an NK1 receptor antagonist indicated for the prevention of acute and delayed CINV. The emulsion contains the following inactive ingredients: egg lecithin, ethanol, sodium oleate, soybean oil, sucrose and water for injection. In the past, pharmaceutical formulations containing polysorbate 80 have been linked to hypersensitivity reactions, including anaphylaxis and irritation of blood vessels resulting in infusion-site pain.

Cinvanti is an excellent example of a parenteral emulsion with egg phospholipid as superior emulsifier, compared to synthetic emulsifiers which may rise the risk for anaphylactoid reactions, to solubilize a lipophilic dug substance.

The U.S. Commercial Launch of Cinvanti is planned for January 2018,

Heron Therapeutics, Press Release, November 9th, 2017

Kisqali®

Novartis Kisqali (ribociclib) receives EU and FDA approval as first-line treatment for HR+/HER2- locally advanced or metastatic breast cancer in combination with any aromatase inhibitor. Ribociclib is a selective cyclin-dependent kinase inhibitor, a class of drugs that help slow the progression of cancer by inhibiting two proteins called cyclin-dependent kinase 4 and 6 (CDK4/6). These proteins, when over-activated, can enable cancer cells to grow and divide too quickly. Targeting CDK4/6 with enhanced precision may play a role in ensuring that cancer cells do not continue to replicate uncontrollably.

Kisqali are film-coated tablets supplied for oral use containing 200 mg of ribociclib free base. The tablets also contains as colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide red, polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide, xanthan gum and soybean lecithin as suspension stabiliser. The surface active and viscosity increasing properties of soybean lecithin make it favourable for the formulation stability as well as in the coating process. Soybean lecithin as film coating excipient in Kisqali underlines the usability in classical pharmaceutical formulations and the broad field of application.

Novartis, Press Release, March 13th/Apr. 24th, 2017

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Phospholipid
Forschungszentrum/Research Center
Heidelberg

Special Application Systems with Phospholipids

SOLUTHIN® MD H:

A fast-dispersible hydrogenated phospholipid formulation increasing the dissolution of poorly soluble actives in water

A. Schulte, C. D. Heidecke, A. Ahmeti, P. van Hoogevest

Lipoid GmbH, Frigenstraße 4, 67065 Ludwigshafen, Germany

Hydrogenated phospholipids (PL) from lecithin are natural products useful for pharmaceutical and cosmetic applications. Due to their higher T_C than unsaturated phospholipids, hydration of the phospholipids to form liposomal dispersions requires higher temperatures. SOLUTHIN® MD H is a dry mixture of maltodextrin with pre-formed liposomes made from hydrogenated PL from non-GMO soybean with not less than 18% hydrogenated soybean phosphatidylcholine (HSPC). It was shown to be readily dispersible in water at 25 °C, forming stable dispersions and capable of solubilizing a lipophilic compound in water as well as in a medium simulating the fed state gastrointestinal tract (GI).

Saturated phospholipids are commonly used for liposomal encapsulation of water-soluble actives. For intercalation of poorly soluble actives, to date only Amphotericin B is used in the lyophilized liposome product AmbiSome® [1] Freeze-dried drug-containing liposomal dispersions of HSPC using carbohydrates as cryoprotectants previously showed that hydration of hydrogenated phospholipids at room temperature is possible [2]. A dry mixture of these lipids with an active could be useful for in-situ preparation of a dispersion medium for poorly water-soluble compounds. The purpose of the present work was to demonstrate the rapid dissolution of SOLUTHIN® MD H itself and the effect of the aqueous dispersion of SOLUTHIN® MD H on the dissolution of an active in water or in a medium simulating the fed state GI [3]. Curcumin was chosen as a model active with poor solubility and bioavailability [4].

SOLUTHIN® MD H and LIPOID P 75-3 (ca. 70% HSPC) were utilized from Lipoid GmbH, Ludwigshafen, Germany. All other materials were of analytical grade. Dispersions of solids in water or medium (2-(*N*-morpholino)ethanesulfonic acid buffer at pH 6.50 with 0.15 g/kg Polysorbate 80) resulted in a phospholipid content of 1.5%. They were produced by stirring for 30 min at 25 °C or 37 °C, respectively, using a standardized setup.

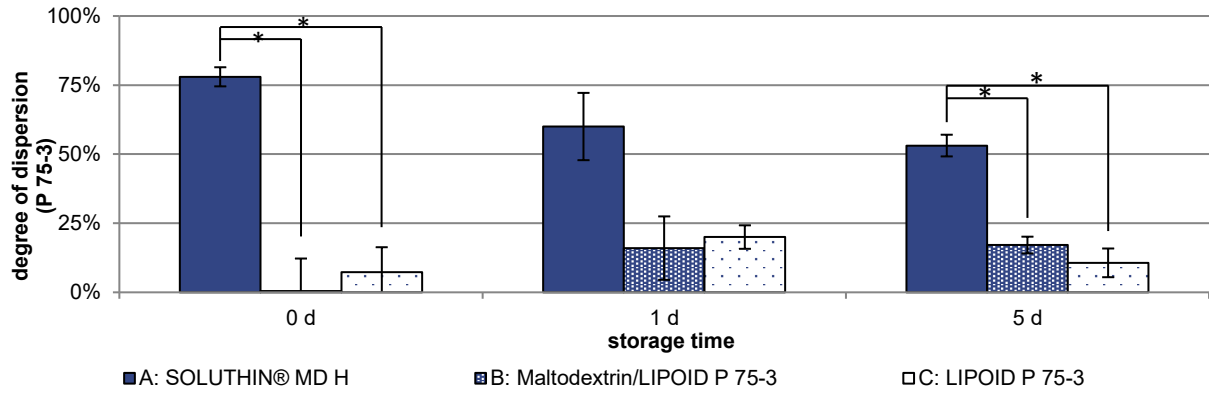

*Figure 1. Degrees of dispersion of LIPOID P 75-3 in water at 25 °C: unformulated and formulated in SOLUTHIN® MD H and a physical mixture with maltodextrin. *: one-sided t-test (Welch model), p ≤ 5%.*

After filtration through syringe filters (Sartorius, DE), the dry matter concentration (DM) of the filtrate was determined in triplicates using a moisture analyzer (Sartorius MA-45). Degrees of dispersion were calculated by dividing the measured DM by the expected DM (1.5%). In formulations, the divisor is calculated by the difference of the expected total DM (5.0%) and the measured DM of a maltodextrin solution (3.6 ± 0.1%). The first standard deviation interval is depicted and normally did not exceed 10%.

A dispersion of SOLUTHIN® MD H and a solution of maltodextrin were filtered through different pore sizes. While a decrease in yield was observed when filtered through 0.7 µm and 0.45 µm, no significant change was observed after filtration through 5 µm. The dissolution rates of SOLUTHIN® MD H in water at 25 °C and in medium at 37 °C were determined by measuring dry matter (DM) with and without prior filtration through 5 µm. In both solvents, the dissolution nears completion after stirring times of 2.5 min. Accordingly, dispersions were produced by stirring for 30 min at 25 °C and their DM were measured after filtration through 5 µm. The degrees of dispersion of LIPOID P 75-3, formulated in SOLUTHIN® MD H (**A**), in a physical mixture with maltodextrin (**B**), and as single component (**C**), were determined directly and after 2 d and 5 d storage at room temperature (Fig. 1). Directly after stirring for 30 min, the degree of dispersion of LIPOID P 75-3 formulated in SOLUTHIN® MD H (**A**) is 70% higher than unformulated (**C**). It is 80% higher than in the physical mixture of maltodextrin with LIPOID P 75-3 (**B**).

Both results are statistically significant (p = 2.5% and p = 2.9 %, respectively). The differences between **A** and the formulation **B**, as well as between **A** and the pure **C** were still significant after storage for 5 d at ambient temperature (p = 2.9% and p = 2.5%, respectively).

The degrees of solubilization of curcumin in water at 25 °C as well as at 37 °C in medium by SOLUTHIN® MD H and microcrystalline cellulose (MCC) as a control were determined by measuring the curcumin concentration by TLC after filtration through 5 µm and comparing with the expected concentration. A constant mass of the active and volume of the excipient were applied to simulate the application in a 0.48 ml capsule (Figure 2).

The results show that SOLUTHIN® MD H nearly completely disperses in water after stirring for 2.5 min at 20 °C with significantly higher degrees than its unformulated hydrogenated PL component or physical mixtures of the PL with maltodextrin. It is effective in increasing the concentration of actives (e.g. curcumin) in water and in a medium simulating the fed state GI.

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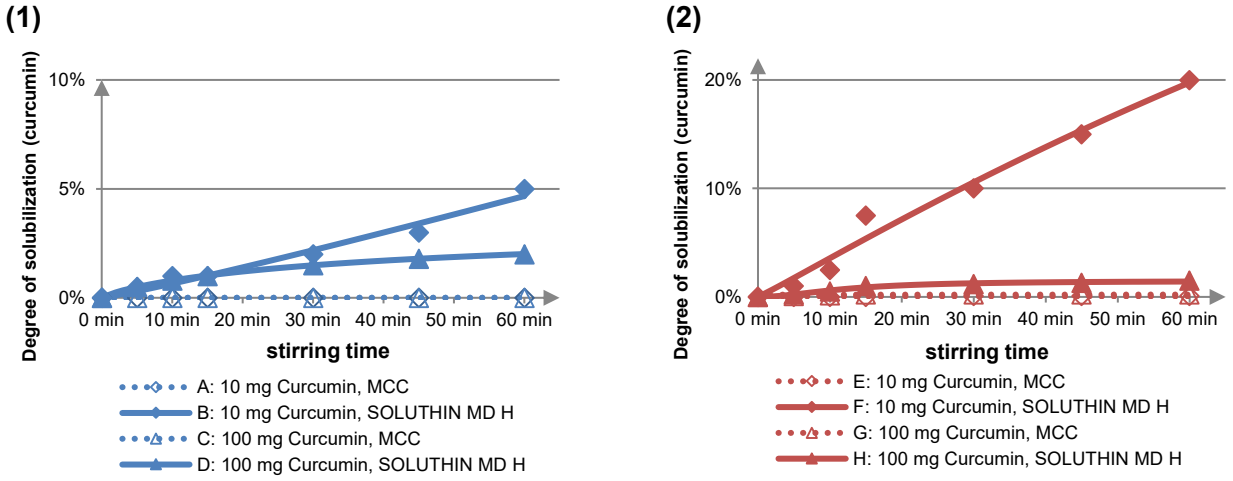
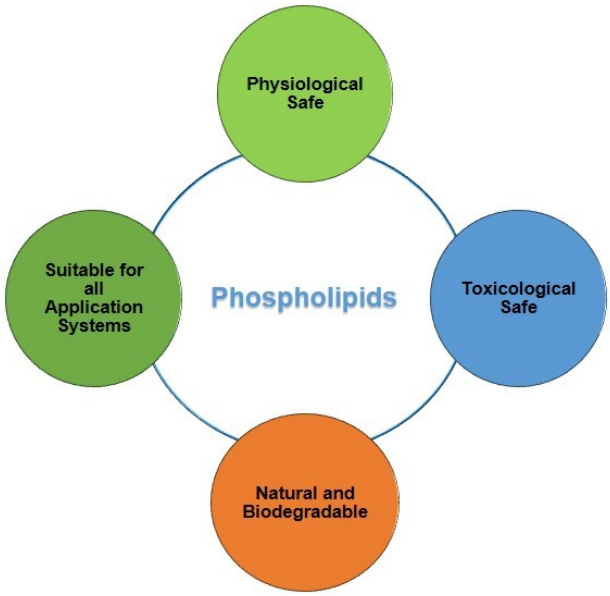


Figure 2. Degree of solubilization of curcumin in water at 25 °C (1) and medium at 37 °C (2) with SOLUTHIN® MD H or MCC.

Phospholipid
Forschungszentrum/Research Center Heidelberg

The **Phospholipid Research Center** is a non-profit organisation that promotes and provides a foundation for the use of phospholipids in pharmaceutics. Phospholipids are multipurpose excipients for pharmaceutical use. To expend this knowledge, the Phospholipid Research Center was founded.



The Phospholipid Research Center sponsors your PhD-, Postdoc projects and workshops on phospholipid-related scientific issues!

We looking forward to your research proposal!

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Impressum

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Editor Dr. Peter van Hoogevest
Co-editor Dr. Dorothea Gutekunst
Feature authors Dr. Torsten Kromp, Dr. Adrian Schulte, Dr. Christian Klose
Layout Dr. Dorothea Gutekunst

Contact

Phospholipid Research Center
Im Neuenheimer Feld 515
69120 Heidelberg, Germany
Phone: +49 (0)6221 / 588 8360
Fax: +49 (0)6221 / 651 5665
Email: info@phospholipid-institute.com

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