Newsletter

Volume 10, Number 1

November 2016

Phospholipid
Forschungszentrum/Research Center
Heidelberg

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Introduction

Unfortunately, this Newsletter issue has to start with a sad announcement.

It was a shock for us all, when in July 2016, our President, Dr. Jürgen Zirkel, suddenly passed away during a business trip in India.

Since September 22nd, 2015 Dr. Jürgen Zirkel was President of the Phospholipid Research Center. As highly motivated manager, he guided from that day on the Research Center with the usual enthusiasm, devotion and care for the details.

We are grateful for the contributions he made from the very beginning on to the Phospholipid Research Center. Dr. Zirkel always attended the meetings of the Scientific Advisory Council and gave his opinions on the usefulness and quality of the research proposals in a clear and concise manner. Also the perfect organization in any detail of our biannual symposium was always very important for him. We will remember him as helpful person and also as bright scientist with a broad and impressive knowledge on any aspect of phospholipid excipients….

According to the by-laws of the Research Center, our Vice-President Prof. Alfred Blume, Emeritus of The University Halle/Saale, is now President of the Phospholipid Research Center.

We will organize again our biannual Symposium in Heidelberg on September 18th and 19th, 2017. Please reserve the dates!

Finally at the end of this year 2016, we thank all members for their valuable contributions and wish all of you a Successful 2017!

Peter van Hoogevest; Managing Director

Scientific Advisory Council Meetings

The Meetings of the Scientific Advisory Council took place on January 18th, 2016 and July 4th, 2016, both at the site of Lipoid GmbH, Ludwigshafen am Rhein.

The Phospholipid Research Center received in total in 2016 36 project proposals. The Scientific Advisory Council approved 11 proposals and invited 12 applicants to amend and resubmit their proposals.

The next meeting will take place on January 16th, 2017 at Lipoid GmbH in Ludwigshafen am Rhein. Proposals should be sent before November 30th, 2016. The future deadlines for the grant proposals will always be November 30th and June 30th in every calendar year.

It should be note that the degree of funding of research projects has been changed as well. The funding of a PhD Thesis project (for three years) and a Post-doc project (for one year) follows DFG guidelines. See for details:
http://www.dfg.de/formulare/60_12/60_12_en.pdf.

For more information about the funding of projects, and how to submit a research proposal, please visit our website: www.phospholipid-institute.com or contact us directly by phone or e-mail.

Approved projects

The following proposals were in 2016 approved for funding:

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

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

On-demand amplification of chemotherapy by ultra-fast drug release from plasmonic liposome, Dr. X. Li, University of Dallas, Dallas, USA.

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Change of WP3 into Characterization of phospholipid nanoparticles as carriers containing a bilayer core, Prof. S. Keller, University Kaiserslautern, Germany.

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

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

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

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

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

Inhibitory effect of phospholipids on the efflux transporter P-glycoprotein in intestinal mucosa, Prof. R. Schubert, University Freiburg, Freiburg, Germany.

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

Characteristics of Projects

Country origin

As derived from the presently 22 approved and ongoing projects, the universities that are being funded are located in: Germany (12), Switzerland (3), Denmark (2), The Netherlands (2), UK (1), Austria (1), USA (1).

Research fields

The projects were related to the oral (6), parenteral (10) or topical (skin) (4) administration and analytical aspects (2)

Workshop proposal

In 2016 no proposals on funding of workshops in the area of interest of the Phospholipid Research Center were received.

We would like to encourage our members to apply for a grant to support workshops and mini-symposia. These events are excellent tools for networking and in depth scientific discussions.

Publications

The following publications were made in 2016 with support of the Phospholipid Research Center:

Journals

Gautschi N, van Hoogevest P, Kuentz M 2016. Molecular insights into the formation of drug-monoacyl phosphatidylcholine solid dispersions for oral delivery. Eur J Pharm Sci pii: S0928-0987(16)30204-4.

Hinna AH, Hupfeld S, Kuntsche J, Bauer-Brandl A, Brandl M 2016. Mechanism and kinetics of the loss of poorly soluble drugs from liposomal carriers studied by a novel flow field-flow fractionation-based drug release−/transfer-assay. J Control Rel 232, 228–237.

Hinna AH, Hupfeld S, Kuntsche J, Brandl M 2016. The use of asymmetrical flow field-flow fractionation with on-line detection in the study of drug retention within liposomal nanocarriers and drug transfer kinetics. J Pharm Biomed Anal 124, 157–163.

Holzschuh S, Kaess K, Bossa GV, Decker C, Fahr A, May S 2016. Investigations of the influence of liposome composition on vesicle stability and drug transfer in human plasma: A transfer study. J Liposome Res 18, 1-39.

Nagarsekar K, Ashtikar M, Thamm J, Steiniger F, Schacher F, Fahr A 2016. Understanding cochleate

formation: insights into structural development. Soft Matter 12, 3797-3809.

Nagarsekar K, Ashtikar M, Thamm J, Steiniger F, Schacher F, Fahr A 2016. Micro-spherical cochleate composites: method development for monodispersed cochleate system. J Liposome Res 1–9, November.

Tran T, Xi X, Rades T, Muellertz A 2016. Formulation and characterization of self-nanoemulsifying drug delivery systems containing monoacyl phosphatidylcholine. Int J Pharm 502(1-2),151-160.

Fueloep A, Sammour DA, Erich K, von Gerichten J, van Hoogevest P, Sandhoff R, Hopf C 2016. Molecular imaging of brain localization of liposomes in mice using MALDI mass spectrometry. Scientific Repots 6:33791, DOI: 10.1038/srep33791.

PhD Theses

Broekgaarden M 2016. New strategies to enhance photodynamic therapy for solid tumors. University Amsterdam, The Netherlands.

Hinna AH 2016. Retention of Lipophilic Drug Compounds within Nano-particulate Drug Carriers. University of Southern Denmark Odense, Denmark.

Posters

Albold D, Scherließ R 2016. Suitability of Microemulsions as Vehicle System for Dermal Protein Application. DPhG Annual Meeting Munich.

Loeser K, Kazmaier U, van Hoogevest P, Werz O, Koeberle A 2016. Inhibition of Akt by Polyunsaturated Phosphatidylcholine - a Novel Approach for potentiating Liposomal Anti-Cancer Therapy. Medicinal Chemist Symposium EFMC-YMCS, Manchester.6

Self-Introduction Prof. Luciani

Dr. Paola Luciani received the offer from the Friedrich Schiller University in Jena in July 2015 and started her appointment September 2015 as endowed Professor with focus on “Phospholipids in Drug Development”.

In the following, Prof. Luciani introduces her past and future research interests. As young professor, she looks for cooperation options and you will find below certainly inspiration to contact her in that respect:

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Phospholipids for Drug Development in Jena, Germany

by Paola Luciani

The intriguing physico-chemical and biological properties of phospholipids represent an ideal ground to build up versatile research platforms for molecular imaging, for drug delivery, and for unravelling etiological factors underlying diseases. Moreover, phospholipids are crucial building blocks of cells and lipoproteins, and can themselves be active signal mediators.

As undergraduate chemistry student at the University La Sapienza in Rome, I had the luck of being involved in an interdisciplinary research project at the edge of chemistry, physics, biology and pharmacy, that introduced me to the fascinating complexity of lipid membranes. Through the years, during my PhD studies in Rome first, and afterwards as a visiting scholar at the Biomedikum in Helsinki, as postdoctoral fellow at the University of Florence, and as senior scientist at the ETH Zurich, I kept investigating the biophysical characteristics of biomembranes and their interaction with drugs, nucleic acids, proteins, and fluorophores, correlating the colloidal properties of phospholipid-based carriers with their *in vitro* and *in vivo* activity, paying increasingly attention to their translational potential.

Currently, my research at the Friedrich Schiller University of Jena, as part of my activities as endowed Professor, focuses on investigating the potential of phospholipids in drug development exploiting their dual nature of formulation components and active

elements in living cells, with a special attention to lipid-based tools for diagnostic molecular imaging and for targeted therapy of fibrotic diseases.

Despite the relentless efforts from an academic and industrial point of view, and the flourishing presence of several parenteral liposomal drug products on the market, from a pharmaceutical technology point of view still much has to be done in terms of optimization of liposome production for specific administrations, like the subcutaneous route for achieving sustained release of hydrophilic drugs. My new research group will indeed devote a special attention in this regard as well.

In the following, I summarize my research background and future interests.

Phospholipid-based treatment for liver fibrosis

Fibrosis is a regenerative response of the organism, essential in tissue repair and wound healing. When the scar formation is excessive and dysregulated, the functionality of the tissue is altered. Among several fibrotic pathologies, liver fibrosis is a particularly interesting phenomenon to investigate from a therapeutic perspective, especially because it has been shown that organ function in early fibrosis can be restored upon removal of the underlying etiological factor.

With the aim of treating areas where the growth of collagen is uncontrolled, specific anti-fibrogenic drugs, such as terguride, able to prevent the activation of tumor growth factor–β (TGF–β), one of the major profibrogenic cytokines, in hepatic stellate cells (HSC), can be loaded into the liposomes via an active loading method, or silymarin, that can be encapsulated in the lipid bilayers, optimizing previously reported protocols. Besides more conventional drugs, anti-inflammatory mediators described as pivotal players released by human mesenchymal stem cells, could be used for anti-fibrotic cell therapy. Encapsulation of these small proteins in liposomes could represent a strategy - with an interesting potential to be scaled-up - to lower the TGF-β1/TGF-β3 balance, compromised during the progression of the fibrotic diseases.

A specific class of phospholipids, polyene phosphatidylcholines, already used in formulations as therapeutic entity, has been shown to exert a powerful action in lowering reactive oxygen species (ROS) production in human HSC. Formulating liposomes with its main component, dilinoleoylphosphatidylcholine, has been reported particularly effective in reverting fibrosis in rats. The use of this phosphatidylcholine in formulating anti-fibrotic liposomes can be contemplated, with the aim of exploiting a synergistic therapeutic effect. Additionally, understanding the antifibrotic mechanisms of polyene phosphatidylcholines in terms of intercellular communication and effect on imbalanced lipid droplet homeostasis could open new avenues for the design of novel treatments.

Oxidative stress: intracellular, extracellular, membrane

Among the various pro-fibrotic modulators, ROS exert a prominent role in the initiation and perpetuation of the fibrosis. Monitoring their real-time production represents a powerful tool for a better understanding and diagnosis of the early stages of the disease progression, and for a dynamic and longitudinal evaluation of the therapeutic efficiency of new treatments. To date, ROS quantification *in vivo* lacks appropriate specificity.

Hydrocyanines are newly described ROS-specific probes that can be easily prepared from commercially available cyanine dyes. Hydrocyanines are extremely versatile molecules, and they can be easily conjugated to biocompatible molecules, such as peptides, nucleic acids, phospholipids, PEG-ylated phospholipids. Once the liver fibrosis-specific liposomes

will be optimized, hydrocyanine derivatives could be used as a working tool for real-time screening of the ROS-induced response in tissue samples to new treatment in fibrotic tissues. Hydrocyanine-based ratiometric contrast agents recently developed in collaboration with Prof. Jean-Christophe Leroux during my years at the ETH Zurich, Switzerland, represent an ideal starting platform to shed new light in this direction.

Liposomes as diagnostic tools

The possibility of an early diagnosis to detect the evolution of liver disease to liver fibrosis remains a Holy Grail in hepatology. The lack of accurate, reproducible, and easily applicable methods for the assessment of hepatic fibrosis has been the major limitation for both the clinical management and research in liver diseases. Liver biopsy remains the gold standard to reach the certainty of diagnosis. The nature of the procedure, however, creates a quest for a less invasive diagnostic modality through which the evolution of the disease and the effectiveness of the anti-fibrotic therapies could be more easily followed. The identification of biomarkers, specific for enzymes responsible for the early alterations of liver microstructure, combined with a non-invasive optical imaging modality, could guide the clinicians towards a timely therapeutic strategy. The biomarkers, indeed, could be also used as targeting moiety to achieve a highly specific treatment in the fibrosis-affected areas in the liver. Liposomes represent an optimal platform to combine diagnostic accuracy and therapeutic efficiency.

In my years in Zurich I started to screen for novel biomarkers for human lysyl oxidase, an enzyme that initiates the cross-linking of collagen and elastin fibrils in the extracellular matrix, and that plays a crucial role in fibrotic pathologies, and in tumor progression and metastases. Such markers will be used as a targeting ligand to be conjugated to liposomes as diagnostic tools for diverse diagnostic modalities.

Phospholipid-based depot technology

Phospholipid-based formulations successfully attained the market for several distinct administration routes. Notwithstanding, much can still be improved in terms of industrial process and final applicability. One example is represented by phospholipid-based depot injectables. By slow release of the drug at the site of action, injectable depot formulations enable to limit the immediate exposure of the active principle at a systemic level and to reduce the frequency of administration. A reliable, steady, and prolonged drug release achieved with a sterile biocompatible injection system that can be conveniently produced and administered is an appealing solution to address various unmet clinical needs. Novel manufacturing processes for lipid-based depots as an alternative to current technologies could be developed with a special focus on hydrophilic drugs and biomacromolecules.

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Industry News

Pacira Pharmaceuticals Announces Official Launch of EXPAREL to the Oral Surgeon Community to Treat Pain Following Oral and Maxillofacial Procedures

New research presented at AAOMS 2016 shows EXPAREL is safe and effective for pain relief following removal of wisdom teeth
PARSIPPANY, N.J., Sept. 21, 2016 (GLOBE NEWSWIRE) -- Pacira Pharmaceuticals, Inc. (NASDAQ:PCRX) today announced new data regarding the benefit of EXPAREL® (bupivacaine liposome injectable suspension) for patients undergoing third molar (wisdom teeth) extraction, marking the official launch of the product to the oral surgeon community. EXPAREL is a local analgesic that provides prolonged non-opioid postsurgical pain control.
As the nation battles the opioid addiction crisis, there is a particular opportunity to offer opioid alternatives to treat postsurgical pain in oral surgery patients.
The formal launch of EXPAREL to the oral surgeon community coincides with the presentation of new data on the safety and efficacy of the product in this patient population, which is occurring this week at the annual meeting of the American Association of Oral and Maxillofacial Surgeons (AAOMS) in Las Vegas, Nevada. The data were generated from a prospective, randomized, double-blind, placebo-controlled study during which patients having all four wisdom teeth removed were randomized to receive a lidocaine nerve block followed by infiltration with either EXPAREL 133 mg (10 mL; 59 subjects) or placebo (10 mL saline; 30 subjects). A total of 166 subjects were enrolled in the study; 77 subjects were excluded due to protocol deviations.

Patients receiving EXPAREL demonstrated a numerically lower overall mean opioid consumption compared to patients administered placebo. Other key findings included:

- Significantly lower pain scores at 48 hours (P=0.0226), the primary endpoint of the study. Pain scores were also significantly lower compared to placebo at 24 hours (P=0.0192), 72 hours (P=0.0469), and 96 hours (P=0.0450).
- No difference in adverse event rates between the EXPAREL and placebo groups were observed; treatment-emergent adverse events were mild or moderate.

This preliminary study data provides encouraging support for both the strong safety profile of EXPAREL and its potential to deliver prolonged pain management following oral surgery. When considering oral surgery procedures, especially third molar extraction, postsurgical pain often ranks among patients' top concerns so the ability to ease anxiety and offer a non-opioid option that provides ample pain management during the first few days after surgery—when pain is often at its worst—is a real benefit to both clinicians and our patients, alike.

Comments: Exparel comprises the use of multivesicular liposomes which, because of their large size, reside at the injection site and slowly release the encapsulated water soluble drug.

US FDA grants orphan drug status to TLC178 to treat cutaneous T-cell lymphoma

Taipei City Friday, October 21, 2016, Taiwan Liposome Company (TLC) announced that product candidate TLC178 has been granted an orphan drug designation for the treatment of cutaneous T-cell lymphoma (CTCL) by the US Food and Drug Administration (FDA). Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). T-cell lymphomas account for approximately

15 percent of all cases of NHL in the US, with cutaneous T-cell lymphoma being one of the most common forms of T-cell lymphoma. TLC178 is a liposomal-encapsulated formulation of the chemotherapy drug vinorelbine that applies the NanoX nanotechnology platform to decrease the toxicity of the drug. Lower toxicity is likely to expand applications for TLC178 from the current vinorelbine indications of non-small cell lung cancer (NSCLC) to lymphomas and other advanced solid tumors. TLC has recently received US FDA approval for its phase 1/2 open-label, dose-escalation study investigating the safety, tolerability and pharmacokinetics of intravenous TLC178 administration. This phase 1/2 clinical trial is planned for sites in both Taiwan and the US trial in Taiwan will be initiated once approval is granted by the Taiwan FDA. According to a recent report from GBI Research, the global market for the treatment of non-Hodgkin's lymphoma is expected to reach $9.2 billion by 2020, reflecting a compound annual growth rate (CAGR) of 7.4% from a market of $5.6 billion in 2013.

Comments: a typical and another example to use liposomes to increase the therapeutic index of generic oncology drugs to develop line extension products.

LATITUDE Pharmaceuticals Receives USPTO Notice of Allowance for Novel Injectable Depot Formulation Platform

MENAFN Press - 21/09/2016 (MENAFN Press
SAN DIEGO, CA, U.S.A., September 20, 2016 /EINPresswire.com. LATITUDE Pharmaceuticals, Inc. (LATITUDE), announced that it has received a notice of allowance from the United States Patent and Trademark Office (USPTO) for a U.S. patent application covering LATITUDE's PG (Phospholipid Gel) Depot, a phospholipid gel composition that enables sustained localized or systemic drug delivery for small molecules, peptides or proteins with up to one-week release from a single intramuscular or subcutaneous injection. LATITUDE's PG Depot properties are particularly well-suited for prolonged delivery of drugs that require a high dose and/or frequent injections as well as drugs with poor stability or solubility. Individual PG Depot formulations can be custom-tailored to create optimized drug-release kinetics, including peak-less profiles. The PG Depot is composed entirely of FDA-approved injectable ingredients, and its simple production process is significantly less expensive than other injectable depot technologies such as PLGA microspheres and liposomes. LATITUDE's PG Depot has proven to be safe for both human as well as veterinary applications, with human product candidates already in Phase II clinical studies.

Comments: This technology competes with the technology used by Pacira (see above).

Public summary of opinion on orphan designation Mifamurtide for the treatment of hepatocellular carcinoma EMA/COMP/449076/2016 Committee for Orphan Medicinal Products, 5 September 2016

On 14 July 2016, orphan designation (EU/3/16/1700) was granted by the European Commission to Delta Proteomics SAS, France, for mifamurtide for the treatment of hepatocellular carcinoma.

What is hepatocellular carcinoma?

Hepatocellular carcinoma is a primary cancer of the liver (a cancer that starts in the liver, rather than one that has spread to the liver from elsewhere in the body). It is more common in men than in women, and occurs mostly in people who have liver scarring (cirrhosis) or after hepatitis B or C infection. Features of the disease include yellow skin, pain and swelling in the abdomen, easy bruising, weight loss, weakness, loss of appetite and nausea.

Hepatocellular carcinoma is long-term debilitating and life-threatening, with patients surviving on average for around 6 to 20 months after diagnosis.

What is the estimated number of patients affected by the condition?

At the time of designation, hepatocellular carcinoma affected approximately 1.6 in 10,000 people in the European Union (EU). This was equivalent to a total of around 82,000 people*, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

At the time of designation, some patients with early stage hepatocellular carcinoma were treated with surgery to remove part of the liver or radiofrequency ablation (directing heat and electricity through a needle to destroy cancer cells). Chemotherapy (medicines to treat cancer) was generally used if surgery was not possible or the disease had spread to other parts of the body (metastatic disease). Nexavar (sorafenib) was authorised in the EU for use in hepatocellular carcinoma.

Comments: This product comprises multilamellar liposomes composed of MTP-PE (muramyltripeptide-phosphatidylethanolamine), POPC and DOPS, originally developed by Ciba-Geigy in the 80`s of last century.

Literature alerts

Development of risperidone liposomes for brain targeting through intranasal route. Narayan R, Singh M, Ranjan O, Nayak Y, Garg S, Shavi GV, Nayak UY. Life Sci. 2016 Oct 15;163:38-45. doi: 10.1016/j.lfs.2016.08.033.

This study is aimed at development of functionalized risperidone liposomes for brain targeting through nasal route for effective therapeutic management of schizophrenia. The risperidone liposomes were prepared by thin film hydration method. Various parameters such as lipid ratio and lipid to drug ratio were optimized by using Design-Expert(®) Software to obtain high entrapment with minimum vesicle size. The surface of the optimized liposomes was modified by coating stearylamine and MPEG-DSPE for enhanced penetration to the brain. The formulations were evaluated for vesicle size, zeta potential, and entrapment efficiency. The morphology was studied by Transmission Electron Microscopy (TEM). In vivo efficacy was assessed by performing pharmacokinetic study in Wistar albino rats following intranasal administration of the formulations in comparison to intravenous bolus administration of pure drug. The mean vesicle size of optimized liposomes ranged from 90 to 100nm with low polydispersity index (<0.5). The entrapment efficiency of optimized liposomes was between 50 and 60%, functionalized liposomes showed maximum entrapment. The TEM images showed predominantly spherical vesicles with smooth bilayered surface. All formulations showed prolonged diffusion controlled drug release. The in vivo results showed that liposomal formulations provided enhanced brain exposure. Among the formulations studied, PEGylated liposomes (LP-16) had shown greater uptake of risperidone into the brain than plasma. High brain targeting efficiency index for LP-16 indicating preferential transport of the drug to the brain. The study demonstrated successful formulation of surface modified risperidone liposomes for nasal delivery with brain targeting potential.

Comments: The intranasal route has long been considered to overcome the blood brain barrier for water soluble compounds: Reference is made to: Lu C-T, Zhao Y-Z, Wong HL, Cai J, Peng L, Tian X-Q. Current approaches to enhance CNS delivery of drugs

across the brain barriers. Int J Nanomed 2014; 9:2241-2257. doi:10.2147/IJN.S61288.

Development of paclitaxel-loaded liposomal nano-carrier stabilized by triglyceride incorporation Hong S-S, Choi JY, Kim JO, Lee M-K, Kim S-H Lim S, J International Journal of Nanomedicine 2016:11 4465–4477.

Studies have highlighted the challenge of developing injectable liposomes as a paclitaxel (PTX) carrier, a challenge attributable to the limitations in liposomal stability caused by PTX loading. Poor stability of PTX-loaded liposomes is caused by PTX-triggered aggregation or fusion of liposomal membranes and is exacerbated in the presence of PEGylated lipid. In the present study, the effect of triglyceride incorporation on the stability of PTX-loaded/PEGylated liposomes was explored. Incorporation of a medium chain triglyceride Captex 300 into saturated phosphatidylcholine (PC)-based liposomes (1,2-dimyristoyl-sn-glycero-3-phosphocholine [DMPC]:cholesterol [CHOL]:N-(Carbonyl-methoxypolyethyleneglycol 2000)-1, 2-distearoyl-sn-glycero-3-phosphoethanolamine [PE-PEG]), produced a fine, homogeneous, and membrane-filterable PTX-loaded liposomes fulfilling the requirement of an injectable lipid formulation. Triglyceride incorporation also greatly inhibited the time-dependent leakage of PTX from saturated PC-based liposomes, which appears to be mediated by the inhibition of liposome fusion. In contrast, triglyceride incorporation induced the destabilization and PTX leakage of unsaturated PC-based liposomes, indicating the opposite effect of triglyceride depending on the fluidity status of PC constituting the liposomal membrane. PTX release profile and the in vitro and in vivo anticancer efficacy of triglyceride-incorporated DMPC:CHOL:PE-PEG liposomes were similar to Taxol® while the toxicity of liposomal PTX was significantly lower than that of Taxol. Taken together, triglyceride incorporation provided an injectable PTX formulation by functioning as a formulation stabilizer of PEGylated/saturated PC-based liposomes.

Comments: Liposomoiogists tend to manipulate the permeability properties of the liposomal membrane by the selection of saturated or unsaturated phospholipids cholesterol and even lysolecithin. This study points to use of triglycerides for this purpose for this specific drug.

In vitro determination of the solubility limit of cholesterol in phospholipid bilayers. Epand RM, Bach D, Wachtel E. Chem Phys Lipids. 2016 Sep;199:3-10. doi: 10.1016/ j.chemphyslip.2016.06.006. Epub 2016 Jul 21.

Cholesterol has limited solubility in phospholipid bilayers. The solubility limit is strongly dependent on the nature of the lipid with which the cholesterol is mixed while properties of the crystals formed can be modified by phospholipid-cholesterol interactions. In this review we summarize the various methods that have been developed to prepare hydrated mixtures of cholesterol and phospholipid. We point out some of the factors that determine the form adopted when cholesterol crystallizes in such mixtures, i.e. two- or three-dimensional, monohydrate or anhydrous. These differences can greatly affect the ability to experimentally detect the presence of these crystals in a membrane. Several methods for detecting cholesterol crystals are discussed and compared including DSC, X-ray and GIXRD diffraction methods, NMR and EPR spectroscopy. The importance of the history of the sample in determining the amount and nature of the cholesterol crystals formed is emphasized.

Comments: Biophysical studies are useful in terms of applying analytical methods to address the maximal solubility of lipophilic drugs in liposomal membranes.

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