REVIEW ARTICLE

The Use of Phospholipids to make Pharmaceutical Form Line Extensions

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Abbreviations

ABC	accelerated blood clearance
AML	acute myeloid leukaemia
API	active pharmaceutical ingredient
AUC	area under the curve
CARPA	complement activation-related pseudoallergy
CINV	chemotherapy-induced nausea and vomiting
DEPC	1,2-dierucoyl-*sn*-glycero-3-phosphocholine
DMPC	1,2-dimyristoyl-*sn*-glycerol-3-phosphocholine
DMPG	1,2-dimyristoyl-*sn*-glycerol-3-phospho-(1'-*rac*-glycerol) (sodium salt)
DNA	deoxyribonucleic acid
DOPC	1,2-dioleoyl-*sn*-glycero-3-phosphocholine
DOPE	1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine
DOPS	1,2-dioleoyl-*sn*-glycero-3-phospho-L-serine (sodium salt)
DOTAP	dioleoyl-3-trimethylammonium propane
DPPC	1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine
DPPG	1,2-dipalmitoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (sodium salt)
DSPC	1,2-distearoyl-*sn*-glycero-3-phosphocholine
DSPG	1,2-distearoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (sodium salt)
EM	electron microscopy
EMA (EMEA)	European Medicines Agency
EPC	egg phosphatidylcholine
EPR	enhanced permeability and retention
ESM	egg sphingomyelin
EU	European Union
FDA	US Food & Drug Administration
GFR	glomerular filtration rate
GI	gastrointestinal
GPC	glycerophosphocholine
HSPC	hydrogenated soybean phosphatidylcholine
IP	intellectual property
IUPAC	International Union of Pure and Applied Chemistry
LMWH	low molecular weight heparin
LLOD	lower limit of detection
MDP	muramyldipeptide
MPEG 2000-DSPE	*N*-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine (sodium salt)

MPS	mononuclear phagocytic system
MRC	myelodysplasia-related changes
MSPC	monostearoylphosphatidylcholine (1-stearoyl-2-hydroxy-*sn*-glycero-3-phosphocholine)
MTP-PE	muramyltripeptide-phosphatidylethanolamine
NCE	new chemical entity
NDA	new drug application
NSAID	non-steroidal anti-inflammatory drug
OROS	osmotic release oral system
o/w	oil-in-water
PA	phosphatidic acid
PC	phosphatidylcholine
PE	phosphatidylethanolamine
PEG	polyethylene glycol
PG	phosphatidylglycerol
PGE1	prostaglandin E1
PI	phosphatidylinositol
PK	pharmacokinetic
PLGA	poly(lactic-*co*-glycolic acid)
POPC	1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine
PS	phosphatidylserine
R&D	research and development
RNA	ribonucleic acid
ROI	return of investment
SPC	soybean phosphatidylcholine
US	United States
USP	United States Pharmacopoeia
w/o/w	water-in-oil-in-water

PETER VAN HOOGEVEST is a pharmacist by training, with a PhD degree in biochemistry obtained 1984 at the Utrecht University (NL). In 1994, he became an adjunct professor in pharmacy at the University of Basel (CH). His industrial career started at Ciba-Geigy Ltd./Novartis AG in 1984. He was CEO of the company ADD Advanced Drug Delivery Technologies AG (Muttenz, CH). and Managing Director of Phares Drug Delivery AG (Muttenz, CH). Since 2012 he is Managing Director of the Phospholipid Research Center, Heidelberg (D) and Head of the Scientific Department of Lipoid GmbH, Ludwigshafen am Rhein (D).

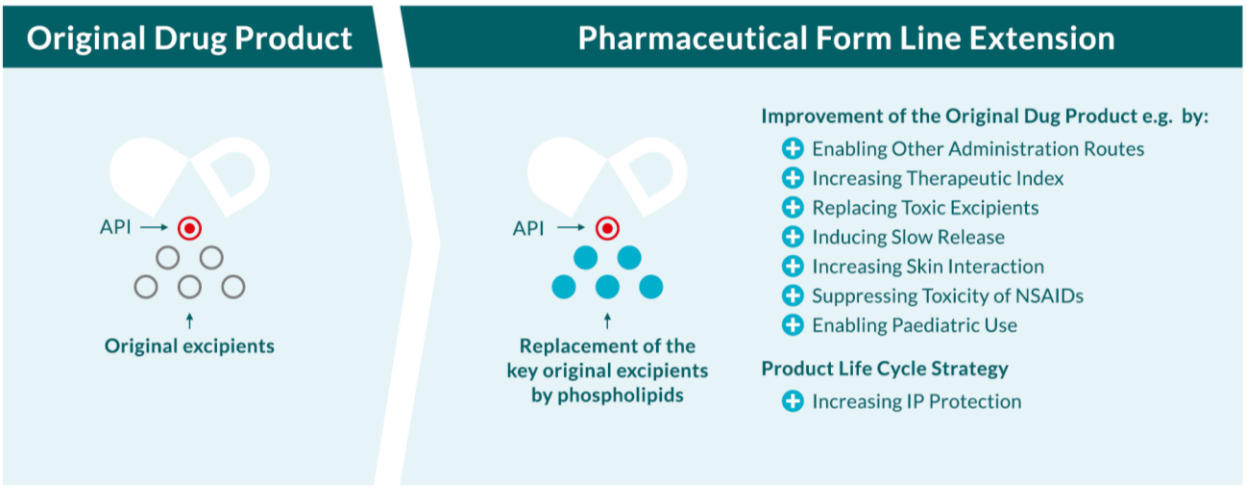
Abstract

This review describes the use of phospholipid excipients to make Pharmaceutical Form (Dosage Form) Line Extensions of existing drugs as part of a Product Life Cycle Management. We provide product examples and development candidates, which show the versatility of phospholipids as key excipients in formulations to develop line extension drug products for any administration route by reformulating existing products. The resulting products enable the application of a drug substance for another administration route or show an increased efficacy and/or reduced toxicity of the formulated drug substances, or enable a more convenient use, through reduction of dosing frequency, or adapt a product for regulatory requirements for specific patient populations. The patents related to the product examples are used to protect the substantially improved products. Parenteral line extensions for lipophilic drugs using non-toxic phospholipid-based solubilising formulations are clearly an alternative to products with solubilising synthetic detergents with the risk for allergic and anaphylactic reactions.

Practical Application

This review draws the attention to academic and industrial formulation scientist to consider using phospholipid excipients to reformulate existing products to improve the product properties by an active product life cycle management. Phospholipids are suitable for this purpose because they are biocompatible, biodegradable, non-toxic, and available at large scale and of pharmaceutical grade. Besides, they are well known to regulatory authorities.

Graphical abstract



Review on the use of phospholipid excipients to make Pharmaceutical Form (Dosage Form) Line Extensions of existing drugs as part of a Product Life Cycle Management.

Content

1. Introduction

1.1. General aspects

In search of the best possible therapies for the treatment of diseases, the pharmaceutical industry has two main ways to generate new products. Considering that such products comprise the drug substance and the dosage form, the first obvious option is to look for new drug substances, which are more efficacious in certain diseases and/or are less toxic. The development of such New Chemical Entities (NCEs) does require extensive preclinical resources, safety testing, and extensive clinical testing to prove its safe and superior efficacious use. The costs of such developments are immense and can only be carried by major pharmaceutical companies. In addition, the failure rates of such developments are high, but in case of success, such products may generate sales. Another challenge of such an approach is that the development stage may be so long that a considerable part of the life span of the protective patents, which secures the sales of such new products, is consumed. A second option is to employ new formulations of the NCE, which make, *e.g.*, the NCE suitable for another administration route, enable less frequent administration or lower doses, and suppress side effects or increase the efficacy.

Generic drug substances may be reformulated to generate innovative, patentable, drug products serving patients' needs. In this review, these (re)formulations related line extensions for NCEs as well as generic drug substances are called "Pharmaceutical Form Line Extensions".

In the European Union (EU), extensions of indications are subject to a line extension procedure when changes to strength, pharmaceutical form, and route of administration apply.[2] Such a procedure is necessary because, as compared to the original product, the new product may entail one or more of the following changes of product characteristics, caused by the new dosage form:[3]

- "change of bioavailability",
- "change of pharmacokinetics (PK), *e.g.*, changes in the rate of release",
- "change or addition of a new strength/potency",
- "change or addition of a new route of administration".

Line extensions require less research and development (R&D) as the initial discovery, and early-stage clinical research of a new molecular entity is not needed.[4] Further, the supply-side incentives that encourage innovation via patent exclusivity periods can often be applied to line extensions. Thus, line extensions are not subject to generic competition at the same time as the original product, but they are improved substitutes for the original products.

In the seventies of the previous century, reformulation development strategies, resulting in mostly intellectual property (IP)-protected product line extensions, were successfully explored and applied by companies like ALZA Corporation (Palo Alto, USA) and Ciba-Geigy Ltd. (Basel, Switzerland). These companies developed dosage form line extensions based on combining generic drugs and oral slow-release technologies (*e.g.*, osmotic release oral system, OROS) and transdermal delivery systems (*e.g.*, Nitroderm TTS, Estraderm TTS, Nicotinell TTS), respectively, both with impressive sales potentials. Also, the oral product Voltaren with diclofenac sodium was successfully reformulated in a topical dosage form line extension (Voltaren Emulgel) for local pain treatment of, *e.g.*, arthrosis-

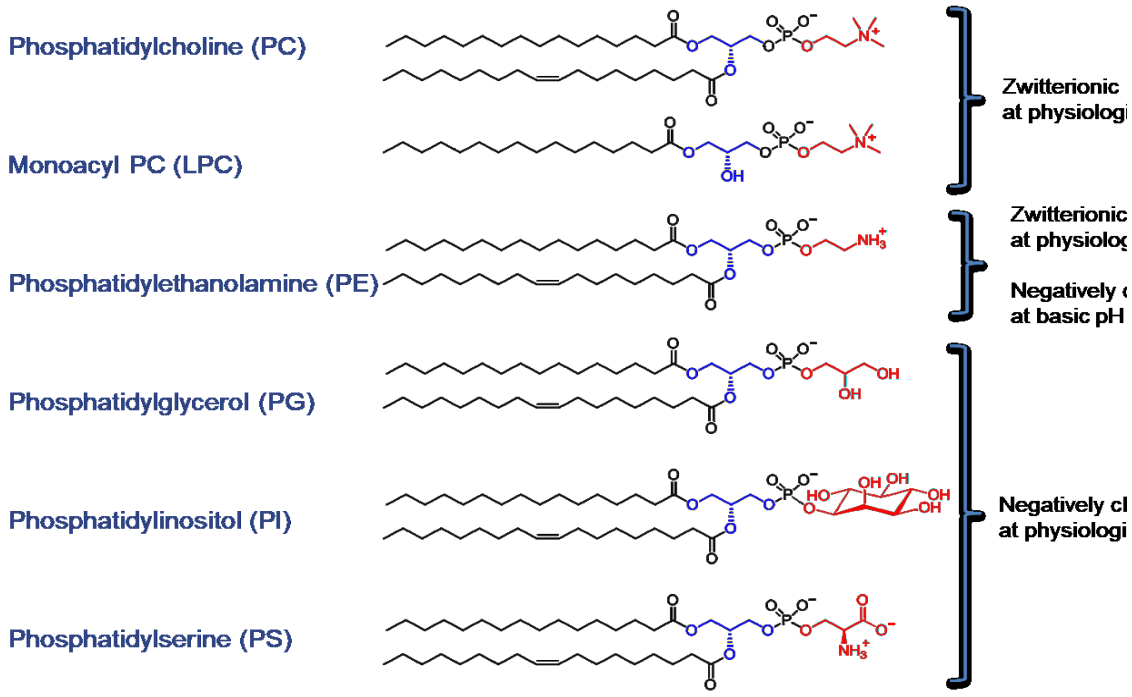
related complications. More examples of such successful product line extensions can be found in the literature.[6]

Needless to say, that successful reformulations require suitable excipients, which preferably have a broad scope of use, enabling the introduction of one or more of many new features that characterise the line extension for an established drug product. This review illustrates the many options, which exist to make Pharmaceutical Form Line Extensions with phospholipids as key excipients (as part of product life cycle management) and underscores these options by providing examples of these line extensions and patents which cover these products. The cited patents serve as examples to underscore the commercial impact of the developed line extension but do not represent the complete IP protection of these products. The review draws the attention to academic and industrial formulation scientists to consider using phospholipid excipients to reformulate existing products to yield innovative products with improves product properties compared to the original product as part of an active product life cycle management.

1.2. Phospholipids

The molecular structure of phospholipids comprises a glycerol backbone which is esterified in positions 1 and 2 with fatty acids and position 3 with phosphate. The systematic designation of, for example, phosphatidic acid (PA) is 1,2-diacyl-*sn*-glycero-3-phosphate, where "*sn*" means stereospecific numbering or stereo-specifically numbered, *i.e.*, the carbon atom that appears on top in the FISCHER projection showing a vertical carbon chain with the hydroxyl group at carbon-2 to the left is designated as C-1.[7] The specific and non-random distribution of substituents over the positions 1, 2, and 3 of the glycerol introduces chirality. In typical membrane phospholipids, the phosphate group is further esterified with an additional alcohol, for instance in phosphatidylcholine (PC) with choline, in phosphatidylethanolamine (PE) with ethanolamine, and in phosphatidylglycerol (PG) with glycerol (**Figure 1**).

Figure 1. Chemical structure of phospholipids.



Depending upon the structure of the polar region and pH of the medium, PE and PC are zwitterionic and have a neutral charge at pH values of about 7. The phospholipid may have two esterified fatty acids and are called “diacyl-phospholipids”, whereas phospholipids with one fatty acid are called “monoacyl-phospholipids” or “lyso-phospholipids”. In scientific literature, synthetic phospholipids are named in an abbreviated way according to “number of the position of fatty acids” – “type of fatty acid” – “phosphatidyl” – “alcohol”. The number of fatty acids could be “mono” or “di”, the fatty acids are described as, *e.g.*, oleoyl or palmitoyl (coming from oleic acid and palmitic acid, respectively), “phosphatidyl” describes the backbone of the phospholipid molecule which encompasses glycerol, further esterified with one or two fatty acid and a phosphate group, and finally the alcohol is mentioned as described above. The International Union of Pure and Applied Chemistry (IUPAC)[8] instead uses “glycero” – “phospho” – “alcohol”. Examples are POPC, 1-palmitoyl-2-oleoylphosphatidylcholine (IUPAC: 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine) or DOPE, 1,2-dioleoylphosphatidylethanolamine (IUPAC: 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine). The nomenclature of natural phospholipids is described in the discussion section below.

Technologically, phospholipids can be used as emulsifier, wetting agent, solubiliser, and liposome- and mixed micelle-former. From a pharmaceutical perspective, they are, for instance, used as excipients for solubilising hydrophobic drugs in mixed micelles, liposomes, and emulsions, where phospholipids act as emulsifier. Further on, controlled release or targeted delivery, increasing the therapeutic index of the formulated drug, can be achieved with the aid of phospholipids.[9]

Phospholipids are present in a range of pharmaceutical products and are for these reasons well-known to regulatory authorities. A broad variety of natural as well as synthetic phospholipids with pharmaceutical quality is available, which further increases the possibilities to generate improved (re)formulations of existing drugs.[9]

In the following, product and development examples of phospholipid-based Pharmaceutical Form Line Extensions are provided. The line extensions are systematically discussed in relation to their administration routes.

In all cases, illustrative examples, wherein the phospholipids play a crucial role in improving the pharmaceutical performance of the original products, are shown and commented on. The review does not intend to provide a complete and exhaustive list of all products containing phospholipid excipients. The description of the phospholipids in the corresponding products is taken from the references, which mention the composition of the products.

2. Parenteral Pharmaceutical Form Line Extensions

2.1. Converting from the oral to the parenteral administration route

In **Table 1**, the possibilities to use phospholipids to convert an oral drug product into a parenteral product are demonstrated with a few notable examples.

Table 1. Examples of Pharmaceutical Form Line Extensions using phospholipids as key excipients to convert an oral dosage form into a parenteral dosage form.

API (Class)	Originator Oral Product Dosage form and (product example)	Parenteral Line Extension Product Dosage form and (product)	Advantage of Line Extension
Aprepitant (Anti emetic)	Tablet (EMEND)	o/w emulsions with egg lecithin (Cinvanti)	Adequate solubilisation, without organic solvents / synthetic detergents
Carprofen (NSAID)	Tablet (Canidryl)	Mixed micelles with lecithin (Rimadyl)	
Dexamethasone palmitate (Corticosteroid)	Tablet (Dexamethasone USP)	o/w emulsions with egg yolk phospholipids (Limethason)	
Diazepam (Tranquilliser)	Tablet (Valium)	Mixed micelles with soybean lecithin (Valium MM) o/w emulsions with egg lecithin (Diazepam-Lipuro)	
Flurbiprofen axetil (NSAID)	Tablet (Ansaid, Flurbiprofen)	o/w emulsions with egg lecithin (Kaifen)	
Vitamin A, D, and E (Vitamin supplement)	Tablet (various)	Mixed micelles with soybean phospholipids (Cernevit)	
Estradiol (estrogen steroid hormone)	Tablet (Estradiol USP) (Estrace)	Skin flux enhancing component in adhesive layer with lecithin (Vivelle TTS)	Increasing skin penetration, general advantages of TTS *versus* oral treatment

The list of parenteral Pharmaceutical Form Line Extension in **Table 1** shows that phospholipid- based solubilisation technologies play an essential role in reformulation of particularly oral compounds with low water solubility for intravenous administration. The motivation to create parenteral line extensions may be of general reasons (*e.g.*, when patients are unable to take oral medication or to have a fast onset of action) and/or it may be a drug substance-specific issue, as described below.

Aprepitant

The lipophilic anti-emetic aprepitant is a substance P/neurokinin-1 (NK_1) receptor antagonist used for chemotherapy-induced nausea and vomiting (CINV) prevention, which is an oral product on the market (EMEND, 40-125 mg tablets).[10] The company Heron Therapeutics (San Diego, USA) found that aprepitant could be successfully reformulated in an oil-in-water (o/w) emulsion using egg lecithin as the main emulsifier to enable solubilisation of the drug[11] and the intravenous administration of the original drug. The egg lecithin is used in this product (Cinvanti) as an emulsifier

and is an essential component of this type of formulation. The same product is discussed in more detail in section 2.3 as a parenteral Pharmaceutical Form Line Extension where polysorbate as a potentially toxic excipient is replaced from the original product.

Carprofen

Carprofen is a NSAID with low water solubility[12] used in veterinarian medicine for pain treatment as a result of arthrosis. Oral therapy (Canidryl tablets) may give rise to gastric irritation typical for NSAIDs.[13] For these reasons, a parenteral Pharmaceutical Form Line Extension was developed to permit parenteral administration. The resulting product Rimadyl comprises mixed micelles of lecithin and glycolic acid to solubilise the drug substance and to enable subcutaneous injection to dogs.[14] Lecithin is an essential component in the mixed micelles with non-allergenic properties and eliminating the haemolytic activity of the used bile salt.[9]

Dexamethasone

Dexamethasone is administered orally as a tablet.[15] To enable parenteral administration, the company Mitsubishi Tanabe Pharma (Osaka, Japan) followed a coordinated double line extension strategy: A prodrug of dexamethasone, a palmitate ester of dexamethasone, with high oil solubility was developed and formulated in the o/w emulsion product Limethason, suitable for parenteral administration, using egg yolk phospholipids (bearing 79% PC, 17% PE, and 4% other phospholipids by weight) as an emulsifier.[16] This emulsion product is also on the market in Germany (Lipotalon of Recordati Pharma, Ulm, Germany). The alternative approach to make dexamethasone suitable for parenteral administration using the water-soluble dexamethasone sodium phosphate—an inorganic ester of dexamethasone—is inferior, because Lipotalon has a more substantial inhibiting effect on the production of pro-inflammatory cytokines in peritoneal macrophages than dexamethasone sodium phosphate.[17] Lipotalon appears to be clinically, histologically more efficacious regarding T-cell reactions. In addition, dexamethasone palmitate formulated in an emulsion showed a 5.6-time higher efficacy in inflamed tissue compared to dexamethasone sodium phosphate.[18]

Diazepam

Diazepam was patented in 1959 by Hoffmann-La Roche AG (Basel, Switzerland).[19] It has been one of the most frequently prescribed medications in the world since its launch in 1963.[19b] Injectable diazepam is a valuable adjunct in status epilepticus and severe recurrent convulsive seizures. Diazepam is a useful premedication in patients undergoing surgery. Intravenously, prior to cardioversion for the relief of anxiety and tension and to diminish the patient's recall of the procedure.[20] Since diazepam is a compound with relatively low water solubility, solubilisation formulations are needed to enable intravenous administration. Consequently, Pharmaceutical Form Line Extensions were introduced on the market, which used mixed micelles of soybean lecithin and glycocholic acid (Valium MM, Roche)[21] and o/w emulsions with egg lecithin as emulsifier[22] (Diazepam-Lipuro, B. Braun Melsungen AG),[23] respectively. Diazepam dissolves in the mixed micelles or the oil phase of the o/w emulsion. In both cases, the phospholipid is an essential component in these formulations, which either eliminates the haemolytic effect of the bile salt in the mixed micellar formulation or serves as a non-toxic emulsifier in the o/w emulsion.[9] The o/w emulsion further prevents adsorption of the drug by infusion sets.[24] The mixed micellar product is, however, not on the market anymore.

Flurbiprofen axetil

Flurbiprofen is a member of the phenylalkanoic acid derivative group of NSAIDs available in 50-100 mg tablets. It is slightly soluble in water at pH 7.0 and readily soluble in most polar solvents.[25] To enable parenteral administration of this drug, to reduce gastric mucomembranous disturbances caused by oral flurbiprofen, and to enable a fast onset of action, a prodrug of flurbiprofen, flurbiprofen axetil, was developed. Due to its high solubility in oils, flurbiprofen axetil is formulated in o/w emulsion with egg yolk lecithin as the key excipient (Axetil, Kaken Pharmaceuticals Co. Ltd., Tokyo, Japan).[26]

Vitamin A, D, and E

Multivitamin supplements are on the market in oral tablets.[27] In some indications, the parenteral administration, in case of prevented or reduced food intake by, *e.g.*, oesophagus and GI stenosis, coma, persistent vomiting, is required.[28] These multivitamin preparations containing lipophilic vitamins such as vitamin A (retinol), vitamin D3 (cholecalciferol), and vitamin E (α-tocopherol), need solubilisation to enable parenteral administration. Mixed micelles containing soybean phospholipids and glycocholic acid are used in these Pharmaceutical Form Line Extension to solubilise these vitamins (Cernevit, Baxter Germany GmbH, Unterschleißheim, Germany).[28]

Interestingly, the lipophilic vitamin K1 (phytomenadion) is solubilised for oral and parenteral administration with the same mixed micelles. At this way, the developers of this formulation profited from the fact that mixed micelles are suitable for parenteral as well as oral administration and no additional reformulation from an oral to a parenteral line extension was necessary. Also, the orally used mixed micellar formulation may be better absorbed in children with cholestatic disease condition compared to the Cremophor-based products.[29] The mixed micellar formulation is also a clear improvement compared to polyoxyethylated fatty acid containing injectables,[30] which may cause fatal allergic reactions.[31]

Estradiol

A further example of a parenteral Pharmaceutical Form Line Extension is related to estradiol. Estradiol is available in oral dosage forms[32] and a transdermal system (Vivelle TTS). (Note: transdermal administration is grammatically considered as parenteral administration, since oral administration is avoided; however, from the pharmacopoeial point of view, parenterals are sterile dosage forms and transdermal dosage forms are considered as a distinct type of dosage form.) Vivelle, which belongs to parenteral administration forms, is a line extension with several benefits such as the application of a new transdermal system for once a week administration, instead of taking many tablets, and the assurance of a constant drug level for the entire duration of wear. The Vivelle system comprises three layers. Starting from the visible surface toward the surface attached to the skin, these layers are: 1) a translucent flexible film consisting of ethylene-vinyl alcohol copolymer, polyurethane, urethane polymer, and epoxy resin, 2) an adhesive formulation containing estradiol USP (United States Pharmacopoeia), acrylic adhesive, polyisobutylene, ethylene-vinyl acetate copolymer, 1,3-butylene glycol, styrene-butadiene rubber, oleic acid NF, lecithin, propylene glycol, bentonite NF, mineral oil USP, and dipropylene glycol, and 3) a polyester release liner that is attached to the adhesive surface, which must be removed before the system can be used.[33] Lecithin plays in this type of formulation the role as skin flux enhancer, probably in combination with propylene glycol and oleic acid.

2.2. Improving the therapeutic index

From a pharmaceutical-technological point of view, Pharmaceutical Form Line Extensions resulting in a more efficacious drug product and drug products with fewer side effects are most striking. Phospholipids can play a key role in this option, because they are the main building blocks of liposomes and o/w emulsions, as these dosage forms are quite often used to achieve this goal. Both colloidal types of formulations have the potentials to change the body distribution of the associated drug after parenteral administration, resulting in an enrichment of the drug in the diseased target tissues and/or avoidance of "tox-target" organs. In addition, they can replace synthetic detergents in parenteral formulations of whose parenteral application is hampered by the risk of allergic reactions up to anaphylactic shock.

To allow a systematic discussion of all these options, the parenteral Pharmaceutical Form Line Extensions are presented into three product categories which 1) show an improvement of the therapeutic index employing drug targeting to the diseased site and/or avoidance of "tox target" organs, 2) same as 1) and additionally eliminates potentially toxic excipients, and 3) show a less toxic formulation by removal of potentially toxic excipients.

The improvement of therapeutic index is qualitatively described by the increase of efficacy and/or improvement of the safety profile. The exact factor at which the therapeutic index is increased cannot be provided, because of the lack of clinical research data comparing directly, ideally in the same patient population, the line extension and the originator product. **Table 2** shows such product examples of the use of liposomes/emulsions to optimise the therapeutic index of intravenously administered drug substances. For more details on the characteristics of liposome products and sales, refer to CROMMELIN *et al.*, 2020.[34] Further line extensions, which increase the therapeutic index and additionally eliminate suspect potentially toxic excipients, are discussed in section 2.3. A recent update on the clinical performance of these line extensions based on liposomes can be found in BELTRÁN-GRACIA *et al.*, 2019.[35]

Table 2. Examples of parenteral Pharmaceutical Form Line Extension, based on liposomes/emulsions, resulting in an increased therapeutic index of the drug substance.

API (Class)	**Originator Product Dosage form and (product example)**	**Line Extension Product Dosage form and (product)**
Cisplatin (Cytostatic)	Aqueous solution (Platinol)	Liposomal suspension, with DPPG, HSPC, MPEG 2000-DSPE (Lipoplatin)
Daunorubicin citrate (Cytostatic)	Lyophilisate (Daunoblastin)	Liposomal suspension, with DSPC and cholesterol (DaunoXome)
Daunorubicin/ cytarabine (Cytostatics)	Lyophilisate/ aqueous solution (Daunoblastin/Cytarabin USP)	Lyophilised liposomal suspension, with DSPC, DSPG, and cholesterol (Vyxeos)

Doxorubicin HCl (Cytostatic)	Lyophilisate/ aqueous solution (Adriamycin, doxorubicin HCl injectable)	Liposomal suspension, with HSPC, MPEG 2000-DSPE and cholesterol (Doxil/Caelyx, Lipodox) Liposomal suspension, with EPC and cholesterol (Myocet)
Doxorubicin HCl (Cytostatic)	Liposomal suspension, with HSPC, MPEG 2000-DSPE, and cholesterol (Doxil/Caelyx, Lipodox) Liposomal suspension with EPC and cholesterol (Myocet)	Liposomal suspension with MPEG 2000-DSPE, DPPC, and MSPC (ThermoDox)
Irinotecan HCl (Cytostatic)	Lyophilisate (Camptosar)	Liposomal suspension with MPEG 2000-DSPE, DSPC, and cholesterol (Onivyde)
Mifamurtide (Immunomodulator)	Micelles MTP-PE (Development stage)	Lyophilised phospholipids followed by *in situ* preparation of liposomal suspension, with POPC and DOPS (Mepact)
Prostaglandin (Smooth muscle relaxant)	Lyophilizate, α-cyclodextrin complex (Prostavasin)	o/w emulsion with EPC (Liple)
Vincristine sulphate (Cytostatic)	Aqueous solution (Vincristine sulphate USP)	Lyophilised liposomal suspension with sphingomyelin and cholesterol (Marqibo)

Cisplatin

Cisplatin is a chemotherapy medication to treat several cancers. It is available as Cisplatin Injection, which is a sterile aqueous solution, each millilitre containing 1 mg of cisplatin and 9 mg sodium chloride in water for injection and hydrochloric acid and/or sodium hydroxide added to adjust pH to 3.5 to 4.5. It is indicated for metastatic testicular tumours, advanced bladder cancer, and metastatic ovarian tumours.[36]

For this cytostatic drug, a parenteral Pharmaceutical Form Line Extension was developed. On November 30, 2007 the European Medicines Agency (EMA, prior to 2010 named EMEA) granted the orphan drug status to liposomal cisplatin of Regulon Inc., Athens for the treatment of pancreatic cancer.[37] The product Lipoplatin is a liposomal formulation of cisplatin. The liposomes are composed of 1,2-dipalmitoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol), sodium salt (DPPG), hydrogenated soybean PC (HSPC), cholesterol, and *N*-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine, sodium salt (MPEG 2000-DSPE). It was developed to reduce the toxicity rendered by cisplatin and to improve the targeting of the drug to the primary tumour and metastases by enhancing its half-life circulation time in body fluids and tissues. Preclinical studies have shown Lipoplatin's lower toxicity in rats, in comparison to cisplatin.[38] Lipoplatin has also shown a high concentration in tumours and metastases at levels up to 200-fold higher compared to the adjacent normal tissue in surgical specimens from patients.[39] Phase I, II, and III studies have been published,[40] and a relevant patent for this product is US Patent 6,511,676.[41]

Daunorubicin

Daunorubicin is the hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of *Streptomyces coeruleorubidus*. It is provided as a sterile lyophilised powder in vials for intravenous administration only. Cerubidine (daunorubicin) is indicated for remission induction in acute non-lymphocytic leukaemia of adults and for remission induction in acute lymphocytic leukaemia of children and adults.[42] Myocardial toxicity may occur either during therapy or months to years after termination of treatment.[42]

To suppress the cardiotoxicity and possibly enhance the tumour efficacy, an improved parenteral Pharmaceutical Form Line Extension, DaunoXome, was developed based on the preparation of liposomes with lipid composition 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC) and cholesterol in a 2:1 molar ratio.[43] Based on imaging studies with ^{111}In-labelled liposomes, it was postulated that DaunoXome extravasates selectively into solid tumours through discontinuities in the capillary beads arising in tumour neovasculature. Preclinical studies have indicated that DaunoXome increases *in vivo* daunorubicin tumour delivery by about 10-fold over a conventional drug, yielding a comparable increase in therapeutic efficacy. Studies on the modes of delivery and action indicated that DaunoXome arrives at and accumulates within tumour cells primarily in an intact form. Once within the tumour cells, the liposomes release drug over a prolonged period (36 h or more), providing sustained, high levels of cytotoxic material within tumour cells.[44] Clinical PK paralleled findings from animal studies. In humans, DaunoXome produced daunorubicin plasma area under the curve (AUC) levels that were more than 35-fold higher than those reported for comparable doses of non-encapsulated drug at 80 mg/m^2. Cardiotoxicity was not clinically observed even for patients receiving more than 1 g/m^2 cumulative daunorubicin.[45]

Based on these findings, the orphan drug status was granted to DaunoXome for the treatment of Kaposi´s sarcoma.[46] Later, DaunoXome was granted the orphan drug status in the EU for the treatment of acute myeloid leukaemia.[47]

Daunorubicin/cytarabine

In oncology, often various cytostatic compounds are combined. For treatment of acute myeloid leukaemia, the combination of cytarabine and daunorubicin is being used.[48] They act synergistically, because daunorubicin inhibits deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis. Cytarabine, in turn, decreases DNA synthesis by inhibiting DNA polymerase. Daunorubicin is provided as a sterile lyophilised powder in vials for intravenous administration only (see above),[42] whereas Cytarabine for Injection USP, commonly known as ara-C, is provided as sterile lyophilised cytarabine for intravenous, intrathecal, or subcutaneous administration.[49]

The company CELATOR Pharmaceuticals Inc (Ewing, NJ, USA) later Jazz Pharmaceuticals plc (Dublin, Ireland) combined the use of the two co-encapsulated drug substances in liposomes to make a Pharmaceutical Form Line Extension.[50] Basically, this line extension is a double line extension by combining two drugs and additionally introducing a new dosage form of both combined drugs.

Liposomes containing daunorubicin and cytarabine at the same time are the first dual-drug liposomal encapsulation product approved by the US Food & Drug Administration (FDA). The fixed 1:5 molar ratio of daunorubicin/cytarabine was shown to be the most synergistic ratio for killing leukaemia cells *in vitro* and in murine models. The resulting product Vyxeos comprises, besides the drug substances daunorubicin and cytarabine, the following inactive ingredients: DSPC, 1,2-

distearoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol), sodium salt (DSPG), cholesterol, copper gluconate, triethanolamine, and sucrose.[51]

These daunorubicin/cytarabine liposomes are approved for the treatment of adults with newly diagnosed therapy-related acute myeloid leukaemia (AML) or AML with myelodysplasia-related changes (AML-MRC).[51-52] The efficacy of this liposomal combination of two cytostatic compounds is based on the fact that the liposomes have a propensity for uptake by the bone marrow, which is the target site for AML treatment. In leukaemia-bearing mice, the liposomes are taken up by leukaemia cells to a greater extent than by normal bone marrow cells, and the liposomes undergo degradation thereby releasing daunorubicin and cytarabine within the intracellular environment.[53]

This product is an exciting example of how liposome technology can be applied to deliver even combinations of (co-encapsulated) drugs to the diseased target sites.

Doxorubicin HCl

Doxorubicin Hydrochloride is a cytotoxic, anthracycline, topoisomerase II inhibitor isolated from cultures of *Streptomyces peucetius var. caesius*. Doxorubicin HCl for Injection USP, is a sterile lyophilised powder.[54] The occurrence of cardiomyopathy complicates the use of this drug. The risk of cardiomyopathy is proportional to the cumulative exposure with incidence rates from 1–20% for cumulative doses ranging from 300 mg/m² to 500 mg/m² when doxorubicin HCl is administered every three weeks. Doxorubicin HCl is indicated as a component of multi-agent adjuvant chemotherapy for treatment of women with axillary lymph node involvement following resection of primary breast cancer. Also, many other cancers can be treated with doxorubicin HCl.[54]

To suppress this cardiotoxicity, Pharmaceutical Form Line Extensions of doxorubicin HCl were developed based on the use of PEGylated liposomes (Doxil/Caelyx/Lipodox; Doxil and Caelyx are the brand names of the doxorubicin liposomes in the US and EU, respectively, whereas Lipodox is the generic version) and non-PEGylated liposomes (Myocet). Here, the abbreviation PEG stands for polyethylene glycol.

Doxil is a sterile, liposomal dispersion of so-called “stealth liposome” carriers, which are composed of cholesterol, HSPC, and MPEG 2000-DSPE. The “stealth effect” is related to the presence of PEG on the liposomal surface, which extends the blood-circulation time by reducing recognition by the mononuclear phagocyte system uptake. More than 90% of the drug is encapsulated in the PEGylated liposomes.

Doxil is considered as the first FDA-approved nano-drug (1995).[55] Its efficacy is based on four unrelated principles:

1) prolonged drug circulation time and avoidance of the premature clearance by the mononuclear phagocytic system (MPS) owing to PEGylation,
2) high and stable remote loading of doxorubicin driven by a transmembrane ammonium sulphate gradient, which also allows for drug release at the tumour,
3) having the liposomal lipid bilayer in a “liquid ordered” phase since HSPC—a lipid with a high transition temperature (T_m about 53 °C)—and cholesterol are used, making the liposomes stable in blood circulation and suppressing the leakage of the encapsulated drug substance. Due to the enhanced permeability and retention (EPR) effect, caused by the presence of the

PEGylated lipid in the liposomal membrane, Doxil is "passively targeted" to tumours, and its doxorubicin is released and becomes available to tumour cells.[55]

4) Finally, it is further proposed that the release of the drug substance from the liposomes within the tumour is triggered by the ammonia production caused by glutaminolysis.[56]

The Doxil line extension shows superior efficacy over former conventional therapy in case of Kaposi's sarcoma, recurrent ovarian cancer over comparator drug and equivalent efficacy in metastatic breast cancer and reduced cardiotoxicity compared to doxorubicin HCl. In addition, Doxil demonstrates a significant reduction of cardiotoxicity as compared to doxorubicin HCl in all settings.[55] A drawback of this new formulation is the occurrence of the so-called Palmar-Plantar Erythrodysesthesia Syndrome (Hand-Foot Syndrome), which has become the dose-limiting toxicity. Furthermore, the widespread use of this product revealed the possibility of (pseudo)allergic infusion reactions (often referred to as complement activation-related pseudoallergy or CARPA). Most of these hypersensitivity reactions are transient and mild, but life-threatening reactions also have been documented in hypersensitive patients (see, for example, VAN DEN HOVEN *et al.*[57] and references therein). These reactions usually occur at the start of infusion. While this seems to be a general side effect of intravenous administration of colloidal particles, it is currently unclear whether the specific lipid composition of the product plays a role. This CARPA effect can, however, be reduced by premedication and slowing down the initial infusion rate.[58]

Doxil was not protected by a formulation patent but indirectly by patents covering the use of a transmembrane gradient to load liposomes with weak bases like doxorubicin[59] and the use of PEGylated lipids to prolong the circulation time of liposomes.[60] Upon entering the USA market, Doxil sales benefited from 14 years of patent protection in the USA.

The non-PEGylated liposomal product Myocet with doxorubicin (initially developed by The Liposome Company, later Elan Pharmaceuticals, Princeton, NJ, USA and other companies) comprises the lipids cholesterol and EPC. US Patent 5,616,341, describing the compositions used for *in situ* loading of the liposomes with doxorubicin, covered the product.[61]

The liposomes show after intravenous administration an increased blood level of total doxorubicin over time suggesting a minor prolonged residence time in the blood circulation.[62] In clinical practice, Myocet shows comparable efficacy as doxorubicin HCl but, just like Doxil, reduced cardiotoxicity. In contrast to Doxil, there is no occurrence of the Hand-Foot Syndrome. Myocet is approved in Europe and Canada for treatment of metastatic breast cancer in combination with cyclophosphamide. Despite these positive features, the product is not popular. A severe limitation of Myocet is related to its administration form which is presented as a three‐vial system: Myocet doxorubicin HCl (lyophilised), Myocet liposomes (aqueous dispersion), and Myocet buffer, used for *in situ* loading of the liposomes with doxorubicin. Additionally, the high costs are a hindrance.[63]

A further Pharmaceutical Form Line Extension based on Doxil and doxorubicin HCl with the aim to further increase the therapeutic index of doxorubicin HCl, is ThermoDox. ThermoDox is an intravenous liposomal dosage form of doxorubicin, whose phospholipid composition is optimised to release the doxorubicin HCl content at localised tumour site or intratumourally by locally applied hyperthermia. The target indication of this line extension is the treatment of primary liver tumour, whereas the two original/parent products Doxil and doxorubicin HCl are not used for this indication.[54,64] This product has been developed by Celsion Corporation (Lawrenceville, NJ, USA)

and is covered by patents.[65] At present, ThermoDox has the orphan drug designation in EU[66] and US.[67]

The ThermoDox product comprises 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), the lysolipid 1-stearoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (monostearoylphosphatidylcholine, MSPC), and MPEG 2000-DSPE. The addition of MSPC to the composition accelerates drug release by a slight reduction in the transition temperature of DPPC enabling local release by hyperthermia treatment through non-invasive focused ultrasound. The presence of the PEGylated lipid helps in attaining lysolipid-induced permeability at a faster rate.[68] The use of these thermosensitive liposomes and the local release result in a 25-fold higher drug concentration at the target site as compared to intravenous infusion of the un-encapsulated drug and 5-fold higher drug concentration compared to Doxil. Despite these promising features, obtaining clinical evidence for the usefulness of this approach appears challenging.[69] Exploring other localised cancer indication such as bladder cancer may be a more promising indication.[70] An impression on the patents covering the product can be obtained from the web.[71]

Irinotecan

Irinotecan hydrochloride (Camptosar Injection) is an antineoplastic agent of the topoisomerase I inhibitor class. Camptosar is supplied as a sterile, aqueous solution.[72] Camptosar Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum and is indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy. The most significant adverse reactions reported were severe neutropenia and severe diarrhoea.

As with the previously discussed cytostatic compounds, the motivation to make a Pharmaceutical Form Line Extension was to improve either the efficacy and/or suppress the toxicity of irinotecan. It was found that irinotecan encapsulated in liposomes—liposomal irinotecan was originally developed by Hermes Bioscience (D. PAPAHADJOPOULOS) and patented,[73] further developed by Merrimack Pharmaceuticals, and now owned by Ipsen Biopharmaceuticals Inc.; the Onivyde trademark was filed in 2013[74]—showed in preclinical studies a maximum tolerated dose in normal mice of 80 mg/kg for free irinotecan and >320 mg/kg for the liposomal counterpart. Liposomal irinotecan showed markedly superior efficacy when compared with free irinotecan in human breast and colon cancer xenograft models.[68c,75] In clinical studies, it was found to be efficacious in the treatment of pancreatic cancer. In 2014, Onivyde received the orphan drug status from the FDA[76] and in 2015 from the EMA.[77] Onivyde is the first FDA-approved therapy in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. The formulation comprises cholesterol, DSPC, and MPEG 2000-DSPE. The drug is loaded into and kept inside the liposomes following a rather elaborate procedure using polymeric or non-polymeric highly charged anions and intra-liposomal trapping agents-like polyphosphate or sucrose octasulphate in combination with a high-pKa polyalkylamine gradient, which facilitates the encapsulation of irinotecan at a high drug-to-lipid ratio. An extensive IP umbrella covers the product and concomitant therapy (see orange book of the FDA,[78] owned by Ipsen Biopharmaceuticals Inc). It should be noted that the line extension is used for another cancer indication than the original parent product. The irinotecan HCl injectable was approved in the US in 1996, whereas Onivyde received FDA approval 19 years later.

Mifamurtide

The product based on mifamurtide (Mepact) is not a Pharmaceutical Form Line Extension derived from a parent drug product but is an example of the development of a line extension during the R&D stage to convert an aqueous solution of the drug into a liposomal dosage form, which showed an increased therapeutic index. The efficacy of the product is based on the finding that macrophages can be activated to a tumouricidal, microbicidal, and antiviral state by a wide variety of naturally occurring and synthetic agents. Muramyldipeptide (MDP) is the minimal structural unit of the cell wall of *Mycobacteria* with immune-potentiating activity[79] that is capable of activating macrophages.[80] A lipophilic analogue of MDP, MTP-PE (muramyltripeptide-phosphatidyl-ethanolamine), has been synthesised to obtain a more stable association with liposomes, because MTP-PE can be inserted into the phospholipid bilayer structure. Liposomal MTP-PE has been shown *in vitro* to enhance the activation of murine macrophages and human monocytes by 100-fold compared with free MDP. In addition, systemic administration of liposomes containing MTP-PE has been shown to eradicate spontaneous metastases in several animal tumour models, including dogs with autochthonous osteogenic sarcoma metastases.[81] Based on these findings, a stable and reproducible preparation of liposomal MTP-PE, with total entrapment of MTP-PE, was developed by Ciba-Geigy Ltd. (Basel, Switzerland) for clinical use in humans.[82]

This product, which can be considered as a double line extension (conversion of the water-soluble MDP to the phospholipid derivative MTP-PE with amphiphilic properties and simultaneously conversion of the micellar solution of MTP-PE to MTP-PE liposomes) comprises a sterile lyophilisate of the synthetic phospholipids POPC and 1,2-dioleoyl-*sn*-glycero-3-phospho-L-serine, sodium salt (DOPS) in a 7:3 weight ratio containing the MTP-PE at a 1:250 (w/w) drug-to-lipid weight ratio. The multilamellar liposomes are *in situ* prepared by addition of saline to the lyophilisate. The phosphatidylserine (PS) component in the formulation was selected to mimic the phospholipid components of the outer leaflet of the membrane of senescent erythrocytes, which are preferably taken up by macrophages. The application of this formulation in toxicity-sensitive species caused a 10-fold reduction in adverse side effects compared with free MTP-PE in aqueous solution.[83] At this way, the MTP-PE is efficiently targeted to (lung) macrophages, which activates their tumouricidal state. This therapy concept was explored in the clinic with children suffering from osteosarcoma to eradicate lung metastases after removal of the primary tumour by activated lung macrophages.[84] After assessment of the clinical efficacy by the EMA,[85] the European Commission formally granted in 2009 a centralised marketing authorisation for Mepact for the treatment of patients with non-metastatic, resectable osteosarcoma.[86] Mepact was already granted orphan medicinal product status in Europe in 2004 and in the US in 2001.[87] Mepact was protected by patents[88] and is nowadays marketed by Takeda Pharmaceutical Company (Tokyo, Japan) in Europe. This example illustrates how phospholipids can be used to deliver selected drugs to macrophages as part of immunotherapy.

Prostaglandin

Alprostadil (prostaglandin E1, PGE1) is one of the prostaglandins, a family of naturally occurring acidic lipids with various pharmacological effects. As an endogenous substance, PGE1 exerts its biological effects either directly or indirectly by regulating and modifying the synthesis and effects of other hormones and mediators. Alprostadil is a smooth muscle relaxant.

The drug substance is on the market in an injectable cyclodextrin formulation (Prostavasin). The purpose of the cyclodextrin is to solubilise the lipophilic prostaglandin compound.[89] The product is used for the therapy of peripheral arterial occlusive disease stages III and IV according to FONTAINE *et al.*[90].

Japanese researchers found that incorporation of the prostaglandin in an o/w emulsion with soybean oil as oil phase (10%) and EPC (1.8%) as emulsifier was more effective than the comparable cyclodextrin formulation for the treatment of peripheral vascular diseases.[91] The o/w emulsion product Liple of Mitsubishi Tanabe Pharmaceutical (Osaka, Japan)—initially developed by Green Cross and covered by US Patent 4,684,633[92]—, which is based on the described findings, is used for indications such as improvement of extremital ulcers, resting pains in chronic occlusive arterial diseases (BUERGER´s disease) and others.[93] The egg phospholipid permits the formulation of this drug substance in an emulsion and is, as emulsifier, a key component of this Pharmaceutical Form Line Extension.

Vincristine sulphate

Vincristine sulphate Injection (USP) is a sterile, preservative-free, single-use only solution available for intravenous administration. It is indicated in acute leukaemia and has also been shown to be effective in combination with other oncolytic agents in Hodgkin's disease, non-Hodgkin's malignant lymphomas, rhabdomyosarcoma, neuroblastoma, and Wilms' tumour. The most common adverse reaction is hair loss; the most troublesome adverse reactions are of neuromuscular origin.[94]

As pointed out by CULLIS,[95] vincristine sulphate was selected for inclusion in a phospholipid-based (liposomal) Pharmaceutical Form Line Extension for three reasons. First, it is one of the most commonly used anti-cancer drugs, second, vincristine is a cell-cycle specific drug and an extended release from liposomes may result in enhanced potency, and third, neurotoxicity as dose-limiting side effect of vincristine sulphate, which may be reduced as result of encapsulation in liposomes. Preclinical development indeed showed that the efficacy of the liposomal vincristine was increased and the general toxicity decreased, when the release from the liposomes in the blood circulation was delayed.[96] The optimal lipids were the natural lipids egg sphingomyelin (ESM) and cholesterol prepared as relatively small liposomes.

Based on these findings, a clinical dosage form was developed[97] showing an increased efficacy against non-Hodgkin’s lymphoma and reduced toxicity compared to the original vincristine sulphate injectable.[98] The clinical dosage form is a kit with three vials for *in situ* preparation of the vincristine sulphate liposomes, which comprises vials with vincristine sulphate injection, sphingomyelin/cholesterol liposome injection, and sodium phosphate injection, respectively. Just like the *in situ* preparation of Myocet, the procedure needs a controlled heating step in a water bath,[99] which makes the procedure elaborate.

Despite favourable phase II/III results in 2004, the FDA did not approve the product.[100] The FDA[101] granted the orphan drug status in 2007; the EMA did this in 2008.[102] The company Talon Therapeutics (San Francisco, CA, USA) took the vincristine sulphate liposomes successfully forward for another indication, that is Philadelphia chromosome-negative acute lymphoblastic leukaemia, and in 2012, it received approval by the FDA, 25 years after the market introduction of the Vincristine sulphate injectable originator product. The product is now marketed by Spectrum Pharmaceuticals (Irvine, CA, USA) under the trade name Marqibo. Marqibo is covered by several

patents;[103] data taken from ref.[104] This product is another example of the use of phospholipids to develop a superior parenteral Pharmaceutical Form Line Extension. However, Marqibo is only approved for one disease indication (acute leukaemia) compared to vincristine sulphate injection (see above).[94]

Several interesting line extension developments in this category are ongoing. In the following, a few selected examples are discussed.

Corticosteroid liposomes

The company Enceladus Pharmaceuticals BV (Naarden, The Netherlands) is developing Nanocort, which is a liposomal prednisolone formulation for treatment of acute manifestations of inflammatory diseases such as rheumatoid arthritis and ulcerative colitis.[105] Prednisolone is a glucocorticoid, which is available for oral therapy in, *e.g.*, tablet form or as injectable suspension for intra-articular administration (*e.g.*, Predni H Injekt of Winthrop Arzneimittel GmbH, Frankfurt am Main, Germany). Water-soluble esters such as the phosphate (Prednisolone Sodium Phosphate Injection USP) or hemisuccinate esters (Prednisolut, Mibe Arzneimittel GmbH, Brehna, Germany) are used for intravenous administration.

Glucocorticoids are highly effective anti-inflammatory drugs, but their use in arthritis therapy is controversial due to a high incidence of serious adverse effects occurring during chronic treatment.[106] As a result of rapid elimination from the circulation and unfavourable tissue distribution, systemic therapy with glucocorticoid results in poor target localisation of the drug, which often necessitates the use of high doses and intensive dosing schedules.[107] Targeted delivery of glucocorticoids may significantly increase the concentration of the drug in the inflamed tissue.[108] The liposomal formulation in development is composed of DPPC, cholesterol, and MPEG 2000-DSPE in a molar ratio of 1.85:1.0:0.15.[108a]

In 2016, Enceladus announced positive results from a Phase IIa study in patients with active rheumatoid arthritis or in ulcerative colitis using Nanocort.[109]

Another product under development by Enceladus is Oncocort,[105] which is liposomal dexamethasone for castration-resistant prostate carcinoma and metastasised multiple myeloma. In both indications, corticosteroids are part of the standard-of-care and have proven to be efficacious, albeit with limitations due to other potential side effects. Preclinical studies have shown that targeted delivery of corticosteroids in animal models for these indications can be a promising strategy to improve efficacy and reduce toxicity.[110]

Since infusion reactions as a result of complement activation as shown with PEGylated liposomal doxorubicin are less acceptable in a non-life-threatening disease such as inflammation, the development of Nanocort triggered further attempts to minimise these reactions.[111] Recently, it was discovered that a very slow initial rate of infusion followed by carefully step by step increasing the infusion rate is key for avoiding these reactions. These protocols are now implemented in clinical practice.[112] The glucocorticoid liposomes are covered by an extensive IP portfolio.[113]

Gemcitabine

Gemcitabine, a nucleoside analogue and deoxycytidine antimetabolite, is characterised by activity against many kinds of tumours. It is available as the HCl salt in lyophilised form (Gemzar)[114] for intravenous treatment of ovarian, breast, non-small cell lung, and pancreatic cancer. Primary dose-

limiting toxic effects are myelosuppression, neutropenia, leucopoenia, anaemia, and thrombocytopenia. The main limitation of using this active compound is the rapid inactivation by deoxycytidine deaminase following intravenous administration *in vivo*. As a result, the compound needs to be administered at a high-dose level, and because of the narrow therapeutic index, this high dosing may give rise to severe side effects.

In the past, several attempts were made to improve the therapeutic index of gemcitabine. High hopes were raised for liposomes as potential tumour delivery (*e.g.*, GemLip).[115] Although this approach seemed successful in the preclinic, this liposomal form of gemcitabine has never been clinically tested.

In addition, lipid derivatives of gemcitabine such as CP-4126 of Clavis Pharma ASA (Oslo, Norway) and Clovis Oncology Inc. (Boulder, CO, USA) were explored;[116] so far without success.[117] Nevertheless, the Japanese company Fujifilm (Tokyo, Japan) is now pursuing clinical research with a Pharmaceutical Form Line Extension based on liposomal gemcitabine (FF-10832) and presented favourable preclinical findings.[118] In contrast to the liposomal form of twenty years ago, which comprises hydrogenated EPC and cholesterol,[119] the liposomal dosage form of Fujifilm comprises cholesterol, HSPC, and MPEG 2000-DSPE in a 4:15:1 molar ratio and therefore has a longer circulation half-life. The optimised lipid composition allows for effective drug encapsulation over 97.5% for the total amount of gemcitabine (0.5 mg/mL). Electron microscopy (EM) data revealed that FF-10832 had a homogeneous appearance and consisted of unilamellar liposomes with a mean particle size of 80 nm.[118b] In 2018, Fujifilm started clinical trials in the US for its patented[120] anti-cancer agent FF-10832 to assess it as a potential treatment for advanced solid tumours.[121]

2.3. Replacing potentially toxic excipients

Organic solvents (for example ethanol and propylene glycol) and synthetic detergents such as polysorbates (*e.g.*, Tween 20 and 80) and Polyoxyl 35 Castor Oil (Kolliphor EL, Cremophor EL)[30] are used in some products to enable intravenous administration of poorly water-soluble drug substances. Depending on the type and quantity/concentration, organic solvents may cause side effects[122] such as pain at the injection site and/or thrombophlebitis.[123] Certain (synthetic) detergents, in turn, possess allergic properties after intravenous administration, which may even give rise to the occurrence of anaphylactic shocks. To avoid these undesired side effects, phospholipids can serve as alternative solubilisers in liposomes or mixed micelles or as emulsifier in solubilising o/w emulsions[9] to make superior Pharmaceutical Form Line Extensions. Examples of such reformulated products are presented in **Table 3.**

Table 3. Examples of parenteral Pharmaceutical Form Line Extension, eliminating potentially toxic excipients.

API (Class)	Originator Product Dosage form and (product example)	Line Extension Product Dosage form and (product)	Advantage of line extension
Aprepitant (Anti-emetic)	Aqueous polysorbate containing prodrug formulation (EMEND injection)	o/w emulsion, with egg lecithin (Cinvanti)	Replacement of polysorbate, no prodrug
Diazepam (Tranquilliser)	Organic solvent/ water mixture (Valium Roche)	Mixed micelles with soybean lecithin (Valium MM) o/w emulsion with egg lecithin (Diazepam-Lipuro)	Replacement of organic solvents, reduction of side effects at injection site
Etomidate (Anaesthetic)	Organic solvent/ water mixture (Hypnomidate)	o/w emulsion with egg lecithin (Etomidat-Lipuro)	Replacement of organic solvents, reduction of side effects at injection site
Propofol (Anaesthetic)	Cremophor-based formulation (Development stage)	o/w emulsion with egg yolk lecithin (Diprivan)	Replacement of Cremophor, reduction of side effects

Aprepitant

EMEND (fosaprepitant) for injection is a sterile, lyophilised formulation containing fosaprepitant dimeglumine. This is a prodrug of aprepitant, a substance P/NK_1 receptor antagonist, acting as antiemetic agent for the prevention of CINV. The final dosage form for intravenous infusion contains polysorbate 80. Hypersensitivity reactions including anaphylactic reaction[124] and irritation of blood vessels resulting in infusion-site pain have been reported.[125] In general, the allergic properties of polysorbates and other synthetic detergents are well described in the literature.[126]

To overcome the disadvantages of polysorbates, the company Heron Therapeutics (San Diego, CA, USA) developed a Pharmaceutical Form Line Extension based on an emulsion-like formulation with egg lecithin as the emulsifier (Cinvanti).[11] This product was approved by the FDA in 2017.[104,127] The weight ratio of the oil phase to phospholipid, ranging from 1.7 to 2.7 in the formulation, suggests, however, that this formulation may be better described as swollen liposomes than emulsion particles. Cinvanti is the first and only polysorbate 80-free, intravenous formulation of a NK_1 receptor antagonist.[128]

A similar product to the aprepitant formulation, but with another drug substance (Varubi, rolapitant) using polyoxyl-15-hydroxystearate (Kolliphor HS15, in the past termed as Solutol HS 15) as alternative emulsifier to EPC developed by TESARO Inc. (Waltham, MA, USA) was withdrawn from the market due to the high incidence of anaphylactic shocks[129] likely due to the polyoxyl-15-hydroxystearate component in the product. This event underscores the relative safe use of EPC as emulsifier compared to synthetic emulsifiers,.[130]

The Cinvanti product is covered by US patents,[131] which all expire in 2035.[104] Interestingly, the patents covering the original product expire in 2027, which means that the line extension could be launched ten years before the original product will lose its IP protection. This line extension showed that by considering lipid-based solubilisation technologies, the elaborate development of the EMEND formulation based on a pro-drug and a polysorbate formulation could have been avoided.

Diazepam

The tranquilliser diazepam (described above) was originally on the market in an injectable dosage form comprising organic solvents and water. This dosage forms caused discomfort at the injection site and thrombophlebitis.[123] Compared to the formulation of diazepam using water-miscible solvents (40% propylene glycol, 10% alcohol, 5% sodium benzoate and benzoic acid added as buffers, and 1.5% benzyl alcohol added as a preservative),[132] o/w emulsions suppresses the risk for complications at the injection site such as pain and thrombophlebitis, and possible toxicity caused by the organic solvent can be avoided.[133] Also, when diazepam was formulated in mixed micelles of soybean lecithin and sodium glycocholate, no thrombophlebitis at the injection site was observed.[134] Both phospholipid-based Pharmaceutical Form Line Extensions appear to be superior formulations compared to the organic solvent formulation. Nevertheless, the injectable formulation based on mixed micelles, Valium Roche MM, is not on the market anymore for undisclosed reasons and in, *e.g.*, Germany still the organic solvent formulation of diazepam is being used.[135]

Etomidate

Etomidate is a short-acting, intravenous anaesthetic agent used for the induction of general anaesthesia and sedation for a short procedure such as the reduction of, *e.g.*, dislocated joints or tracheal intubation.[136] It was developed at Janssen Pharmaceutica N.V. (Beerse, Belgium) in 1964 and was introduced as an intravenous agent in 1972 in Europe and 1983 in the US.[137] The original product Hypnomidate, which was formulated in a mixture of propylene glycol and water,[138] causes severe pain at the injection site.[139] By incorporating the drug substance in an o/w emulsion (Etomidat-Lipuro, B. Braun Melsungen AG, Melsungen, Germany),[139a] with egg lecithin as a key emulsifier, a Pharmaceutical Form Line Extension was developed showing improved tolerability at the injection site. The product was protected by a general patent on emulsions[140] and was introduced on the German market in 1991.[141]

Propofol

Propofol (Diprivan; 2,6-diisopropylphenol) is an intravenous, sedative-hypnotic agent that can serve for initiation and maintenance of Monitored Anaesthesia Care sedation.[142] The anaesthetic properties of propofol were initially reported in 1973 by ICI (Cheshire, UK).[143] The first clinical trials were conducted in Europe in 1977 using a 1% preparation formulated in Cremophor EL,[144] but this formulation was not clinically tested in the US. High incidences of anaphylaxis with the Cremophor EL formulation prompted its withdrawal from development.[145] Propofol in an o/w or lipid-based emulsion was evaluated in clinical trials in Europe in 1983 and in the US in 1984.[143b] Its anaesthetic properties were found to be similar to the Cremophor EL formulation but without the anaphylactic reactions.[146] The emulsion formulation ultimately chosen for development was one having the same components as the parenteral fat formulation Intralipid (Kabi/Pfrimmer, Munich, Germany), comprising soybean oil and egg yolk lecithin as the key emulsifier.[142] Although this example is not a

classical line extension development in which an original product is converted in another product, it is an excellent example showing that also during the development phase the timely selection of line extensions with improved performance plays a role.

2.4. Improving both the therapeutic index and replacing potentially toxic excipients

The previously discussed advantages based on phospholipid-based line extensions, which on the one hand can be the increase of therapeutic index and on the other hand the elimination of potentially toxic excipients, can also be combined in a line extension product. In **Table 4** such product examples are provided.

Table 4. Examples of parenteral Pharmaceutical Form Line Extension, based on phospholipid formulations, resulting in an increased therapeutic index of the drug substance as well as allowing the replacement of potentially toxic excipients.

API (Class)	Originator Product Dosage form and (product example)	Line Extension Product Dosage form and (product)	Advantage of line extension
Amphotericin B (Antifungal)	Lyophilizate (Fungizone)	Lyophilised complex of drug with DMPC, DMPG (Abelcet) Lyophilised complex of drug with cholesterol sulphate (Amphotec) Lyophilised liposomal suspension, with HSPC, DSPG, and cholesterol (AmBisome) o/w emulsion with purified egg lecithin as emulsifier (Amphomul)	Increase therapeutic index and replacement of sodium deoxycholate by phospholipids
Cyclosporin (Immuno-suppressant)	Solution with Cremophor EL (Sandimmune)	o/w emulsion with phospholipids (NeuroSTAT, development stage)	Increased therapeutic index and replacement of Cremophor
Docetaxel (Cytostatic)	Concentrate with polysorbate and ethanol (Taxotere)	Liposomal suspension with PC and sodium cholesteryl sulphate (DoceAqualip)	Increased therapeutic index and replacement polysorbate and ethanol by phospholipids
Paclitaxel (Cytostatic)	Aqueous concentrate with Cremophor (Taxol)	Lyophilised liposomal suspension with lecithin and cholesterol (Lipusu) Liposomal suspension with DOPC and DOTAP (EndoTag; development stage)	Increased therapeutic index and replacement Cremophor by phospholipids

Amphotericin B

Fungizone contains amphotericin B, an antifungal polyene antibiotic obtained from a strain of *Streptomyces nodosus*.[147] Each vial contains a sterile, non-pyrogenic, lyophilised cake providing 50 mg amphotericin B and 41 mg sodium deoxycholate with 20.2 mg sodium phosphate as a buffer. Amphotericin B is insoluble in water. Therefore, the antibiotic is solubilised by the addition of sodium deoxycholate to form a mixture which provides a colloidal dispersion for intravenous infusion following reconstitution. Due to the presence of the strong detergent sodium deoxycholate, the product has haemolytic properties and may cause thrombophlebitis and pain at the injection site.[148] In addition, the drug is nephrotoxic. To increase the therapeutic index of amphotericin B and to replace the potentially toxic excipient sodium deoxycholate, several Pharmaceutical Form Line Extensions with phospholipids as key excipients were developed.

Abelcet (amphotericin B) is a lipid complex formulation, developed by The Liposome Company in 1995. Abelcet is a drug lipid complex with 1:1 drug-to-lipid weight ratio bearing the synthetic phospholipids 1,2-dimyristoyl-*sn*-glycerol-3-phosphocholine (DMPC) and 1,2-dimyristoyl-*sn*-glycerol-3-phospho-(1'-*rac*-glycerol), sodium salt (DMPG) in a 7:3 molar ratio.[149] PK studies demonstrate that there is deposition in the MPS.[150] This "depot" form releases the drug at local sites of infection, maybe through the action of lipases.[151] Compared to Fungizone, site-effects at the injection site and nephrotoxicity are reduced.[152] The product was covered by US patents.[153]

Amphotec, an amphotericin B cholesteryl sulphate complex for injection, in the past manufactured at Ben Venue Laboratories Inc. (Bedford, OH, USA), is another lipid-based line extension of Fungizone.[154] The formulation is based on the specific property of amphotericin B to form complexes with cholesterol, which is covered by US patents.[155] It shows that in particular cases also alternative lipids may be used attempting to increase the therapeutic index of amphotericin B and to eliminate suspect excipients from the formulation. The increased safety profile of Amphotec (compared to Fungizone) was demonstrated in preclinical[156] as well as clinical settings[157] and is possibly related with an accumulation of the drug in a non-toxic form in the MPS tissue. Amphotec was significantly less nephrotoxic than conventional amphotericin B and could be given to patients with renal disease. Despite these positive features, the sales of this product are discontinued.[158]

AmBisome, developed initially by NeXstar Pharmaceuticals Inc. (Boulder, CO, USA), is the best-selling lipid-based injectable of amphotericin B.[34] AmBisome is a liposomal formulation with low content of amphotericin B.[159] The lipid bilayer of AmBisome is composed of HSPC, cholesterol, DSPG, and amphotericin B in a 2:1:0.8:0.4 molar ratio.[160] Amphotericin B forms a complex in the liposomal membrane with cholesterol. The superiority of this line extension compared to Fungizone is underscored by preclinical data reports showing negligible haemolysis caused by AmBisome.[159] In addition, AmBisome demonstrated increased safety in animal models with systemic fungal infection. It was tolerated at doses higher than those of conventional amphotericin B and possessed a higher therapeutic index.[160] The product was protected by several patents.[161]

Further liposomal formulations of amphotericin B and line extension of Fungizone, not discussed here in detail, are PhoSome, AmBil, Lambin, AmbiHope, Lipholyn, Ampholip, and Fungisome. For details please refer to ADLER-MOORE *et al.*[162]

Besides liposomes or lipid complexes, also an o/w emulsion with purified egg lecithin as essential component[163] can be used to suppress the toxicity of amphotericin B and, hence, as a solubilising

formulation of amphotericin B. An example of such a Pharmaceutical Form Line Extension is the product Amphomul, which comprises soybean oil as oil phase, glycerol as isotonising agent, and purified egg lecithin. Amphomul is manufactured by Bharat Serum and Vaccines Ltd (Mumbai, India). This product is covered by patents.[163-164] After administration of Amphomul, amphotericin B gets released from the oily phase in the monomeric form, which is less toxic compared to oligomeric form present in conventional (Fungizone) formulation. In rodents, Amphomul is at least 80-fold less toxic than conventional deoxycholate formulations of amphotericin B. Amphomul gets distributed rapidly into the MPS and, hence, a rapidly increased amphotericin B concentration is achieved in liver and spleen, the target organs in patients of Visceral leishmaniasis (kala-azar).

In general, all liposome-based Pharmaceutical Form Line Extensions of amphotericin B show a similar increase in therapeutic index in preclinical studies.[165] However, comparative clinical studies have never been performed. A conclusion on which line extension is best can therefore not be drawn.

Cyclosporine

Cyclosporine, the active ingredient in Sandimmune, is a cyclic polypeptide immunosuppressant agent. The injectable form of cyclosporin is formulated with Cremophor EL. Sandimmune is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. The injectable form is always to be applied with adrenal corticosteroids. Sandimmune Injection (cyclosporine injection, USP) is mostly used shortly before and after transplantation and when patients are unable to take the Sandimmune Soft Gelatin Capsules or Oral Solution.[166] This daily single-dose is continued postoperatively until the patient can take the Sandimmune Soft Gelatin Capsules or the Oral Solution. This switch should be performed as soon as possible after surgery.

While cyclosporine has been widely used to prevent graft rejection in patients undergoing organ transplantation, it was also used to treat several systemic and local autoimmune disorders. The neuro- and cardio-protective effects of cyclosporine were tested in phase II and III trials with an o/w emulsion formulation with phospholipids as the key emulsifier[167] including 1.2% egg phospholipid and 10% soybean oil as oil phase (NeuroSTAT). This product received orphan drug status from FDA and EMA in 2010.[168] The reformulation strategies focused on developing Cremophor EL-free formulations.[169] This intravenous formulation of cyclosporine did not significantly affect the glomerular filtration rate (GFR) in an acute nephrotoxicity rat model, while the Cremophor EL-based Sandimmune and the Cremophor EL itself reduced GFR to approximately 70% and 75%, respectively, of the baseline level. These results indicate that the main contributor to the acute nephrotoxic effects in this model was associated the Cremophor EL in the vehicle.[133,170]

In 2016, NeuroVive Pharmaceutical AB (at present Abliva, Lund, Sweden) announced that the phase II clinical trial, although well conducted, showed that patients treated with CicloMulsion during open heart surgery had no benefit from the treatment in terms of preventing acute kidney injury. The company therefore discontinued the development.[171] The development of the other cyclosporine o/w formulation (NeuroSTAT), for treatment of traumatic brain injury, is still continuing.[172]

Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxoid family. The docetaxel injectable product (Taxotere) contains 20 mg docetaxel (anhydrous) in 0.54 g polysorbate 80 and 0.395 g dehydrated alcohol solution to solubilise the poorly water-soluble drug. Severe hypersensitivity reactions

characterised by generalised rash/erythema, hypotension, bronchospasm, or very rarely fatal anaphylaxis have been reported even in patients who received a 3-day dexamethasone premedication.[173] To eliminate these side effects probably caused by polysorbate 80, a Pharmaceutical Form Line Extension was developed by the Indian company Intas (Ahmedabad, India) in cooperation with the US company Jina Pharmaceuticals Inc. (Libertyville, IL, USA).[174] This product is based on the Nanoaqualip technology in which the therapeutic drugs are formulated in an aqueous medium without the use of any toxic solvents during the manufacturing process yielding a homogenous nano-sized product comprising PC and sodium cholesteryl sulphate. DoceAqualip is protected by patent.[175] The phospholipid in the formulation plays an essential role as (co)solubiliser together with the sodium cholesteryl sulphate, possibly forming mixed micelles. DoceAqualip is indicated for treatment of breast cancer, non-small cell lung cancer, prostate cancer, cancer of head and neck, which are the same indications as for Taxotere.[176]

Paclitaxel

Paclitaxel is on the market in an injectable form bearing Cremophor EL (Kolliphor EL, polyoxyl 35 castor oil) (Taxol, approved by the FDA in 1992). The injectable has as side effects anaphylaxis and severe hypersensitivity reactions characterised by dyspnoea, hypotension, angioedema, and generalised urticaria. These side effects have occurred in 2 to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication.[177]

For these reasons, this product has been reformulated to a Pharmaceutical Form Line Extension with more efficacy and reduction of undesired side-effects by the elimination of Cremophor EL from the product and encapsulating the drug in liposomes.[178] While not yet approved in American or European countries, this liposomal paclitaxel product, called Lipusu (initially developed by Sike Pharmaceutical Nanjing, Jiangsu, China[179]), received market approval in China in 2003. This freeze-dried intravenous liposome formulation is prepared with lecithin and cholesterol at a mass ratio of 87:13.[180] Compared to Taxol, Lipusu shows comparable activity against breast, gastric, and non-small lung cancer, but with less severe side effects. In phase I clinical trials, Lipusu was administered at 175 mg/m^2, the same dose as Taxol, premedicated with corticosteroids.[181] Side effects included diarrhoea, anaemia, neutropenia, thrombocytopenia, hepatotoxicity, and chest pain, but these were milder than those of patients treated with Taxol.[182] In addition, it was shown that due to the elimination of Cremophor EL from the formulation, Lipusu displayed a much higher safety margin and did not induce hypersensitivity or hypersensitivity-related lung lesions, which may be associated with the fact that Lipusu did not activate the complement system or increase histamine release *in vivo*. Indeed, Lipusu did not promote complement activation in healthy human serum *in vitro*.[183] Lipusu has been approved for the treatment of ovarian cancer, breast cancer, and non-small cell lung cancer in China.[184] Luye Pharma claims that Lipusu has more favourable clinical and industrial advantages over albumin-bound Paclitaxel (Abraxane) in terms of safer formulation medium, less dosage needed and the ease of production.

Lipusu was the most popular pharmaceutical product for cancer treatment in China in 2018, as well as the most popular paclitaxel product in China in 2018. The patents Luye holds with respect to Lipusu will expire in 2021. This paclitaxel liposome product is a prominent example of how phospholipids can be used to increase the therapeutic index of the formulated drug and to eliminate potentially toxic excipients from the original formulation.

An alternative liposomal formulation of paclitaxel (EndoTag), containing dioleoyl-3-trimethylammonium propane (DOTAP) as positively charged lipid and 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) in a 53:47 molar ratio, is in the clinical development stage since a long time.[185] The company Medigene AG (Martinsried, Germany) started the development based on favourable preclinical findings in tumour models.[186] Due to the presence of the positive charge in the liposomes, the encapsulated paclitaxel is targeted to tumour endothelium. In 2006, Medigene AG exclusively licensed the newly issued patent.[187] In 2015, Medigene AG transferred the product development to the company SynCore Biotechnology Co., Ltd. (Taipei City, Taiwan).[188] In 2006, an orphan designation was granted by the European Commission to Medigene AG for paclitaxel (liposomal) for the treatment of pancreatic cancer.[189] In 2019, clinical trials with EndoTag in China were announced by SynCore Biotechnology.[190] Further alternative lipid-based line extensions for paclitaxel, which are in the development stage, can be found in Sun *et al.*[182b]

2.5. Extending release properties

In the 1980s, the possibility to use liposomes as parenteral slow release vehicle for encapsulated water-soluble drugs, especially for proteins, was explored at the preclinical level.[191] This research direction was driven by the advent of highly potent (biological) drugs with a shorter biological half-life for which the oral administration route is not feasible. Therefore, dosage forms allowing a lower frequency of injection and avoiding probable toxic drug plasma level after bolus injection needed to be developed.

For obtaining a depot effect at an intramuscular or subcutaneous injection site it is necessary that the depot formulation stays at the injection site. It was shown that larger liposomes with diameters above 300 nm were indeed retained at the subcutaneous or intramuscular injection site.[192] In addition, the entrapped water-soluble drug or model compound was slowly released from the aqueous compartment(s) of the liposomes.[193]

A technological breakthrough in this area was obtained after introduction of the DepoFoam technology initially developed for delivering proteins and peptides.[194] This technology is based on the use of large multivesicular liposomes. This structure renders a higher aqueous volume-to-lipid ratio and a much larger particle diameter (about 24–31 µm) than ordinary single-vesicle liposomes. More recently, the FluidCrystal injectable depot technology, based on the *in situ* formation of a lipid depot, with PC as an essential component, was also used to develop lipid-based products.

Several Pharmaceutical Form Line Extensions based on these technologies for low molecular weight drugs were introduced on the market (**Table 5**).

Table 5. Examples of parenteral Pharmaceutical Form Line Extensions, based on liposomes, with extended drug release properties.

API (Class)	Originator Product Dosage form and (product example)	Line Extension Product Dosage form and (product)
Bupivacaine HCl (Local anaesthetic)	Aqueous solution (Marcaine, Sensorcaine)	Liposomal (DepoFoam) suspension with DEPC, DPPG, tricaprylin, and cholesterol (Exparel)
Buprenorphine HCl (Opioid-related disorders)	Sublingual tablet (Subutex, Sublocade)	Lipid-based solution for subcutaneous injection with phosphatidylcholine (soybean) glycerol dioleate, and ethanol anhydrous (Buvidal)
Cytarabin (Cytostatic)	Aqueous solution (Cytarabin for Inj. USP)	Liposomal (DepoFoam) suspension with DOPC and DPPG (DepoCyt)
Morphine sulphate (Anaesthetic)	Aqueous solution (Infumorph, Duramorph)	Liposomal (DepoFoam) suspension with DOPC and DPPG (DepoDur)

Bupivacaine HCl

Bupivacaine HCl injectable solution is a prescription medication used as a local anaesthetic (numbing medicine). Bupivacaine is available under the following different brand names: Marcaine and Sensorcaine. Marcaine was introduced on the market by Hospira Inc. (Lake Forest, IL, USA) in 1984.[195]

Bupivacaine is a potent local anaesthetic with increased cardiotoxicity risks compared to lidocaine.[196] In general, long-acting local anaesthetic formulations hold great promise for the management of acute pain, as long-lasting analgesia could be realised with a single dose administered after surgery or trauma. Liposomal bupivacaine formulations prolong analgesic duration in animals and humans. The slow release of drug from the liposomal depot decreases the potential for systemic toxicity and allows for administration of a higher bupivacaine dose.[197] In addition, the better and more prolonged the local anaesthesia is acting the further use of systemic opioids to suppress pain after the operation is reduced.

The Pharmaceutical Form Line Extension developed for these reasons for bupivacaine Exparel (a bupivacaine liposome injectable suspension) by DepoTech Corp. (San Diego, CA, USA) and SkyePharma Production SAS (Saint-Quentin-Fallavier, France) was introduced on the US market in 2011 by Pacira Pharmaceuticals (Parsippany, NJ, USA)—27 years after the introduction of the original bupivacaine injectable. The product is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks. Exparel combines bupivacaine with DepoFoam, a drug delivery technology that delivers medication over a desired period (see above). The liposomes comprise the lipids 1,2-dierucoyl-*sn*-glycero-3-phosphocholine (DEPC), DPPG, cholesterol, and tricaprylin.

Exparel represents the first and only multivesicular liposome local anaesthetic that can be utilised in the peri- or post-surgical setting. By utilising the DepoFoam platform, a single dose of Exparel delivers bupivacaine over time, providing significant reductions in cumulative pain scores with up to a 78% decrease in opioid consumption. The clinical benefit of the opioid reduction was not demonstrated. The product is covered by US patent.[198]

Buprenorphine HCl

Buprenorphine HCl is an opioid used to treat opioid use disorder, acute pain, and chronic pain.[199] The compound is available in sublingual tablets (Subutex[200]) and also in extended release injectable form (Sublocade[201]). The Sublocade (buprenorphine extended-release) injection is a clear, sterile solution for subcutaneous injection only. It is designed to deliver buprenorphine at a controlled rate over a one-month period. Buprenorphine is dissolved in the ATRIGEL delivery system at 18% by weight. The ATRIGEL delivery system is a biodegradable 50:50 poly(DL-lactide-*co*-glycolide) polymer and a biocompatible solvent, *N*-methyl-2-pyrrolidone (NMP). The usage safety of NMP is, however, controversial discussed.[202]

Camurus AB (Lund, Sweden) developed an alternative line extension to this product by applying their FluidCrystal injectable depot technology. A liquid solution with low viscosity comprising soybean phosphatidylcholine (SPC), glycerol dioleate, and a small amount of alcohol (in the weekly formulation) or NMP (in the monthly formulation)[203] is transformed into a controlled-release liquid crystal gel matrix *in situ* on contact with minute quantities of aqueous fluid at the site of injection. It is claimed that the release duration can be tuned to meet dosing interval specifications ranging from once-daily to once-weekly or once-monthly.[204] In a Phase III study, it was shown that subcutaneous buprenorphine delivered weekly or monthly was well tolerated, with a systemic safety profile consistent with the known profile of sublingual buprenorphine. Both the weekly and monthly injectable were associated with high retention rates and low levels of illicit opioid use throughout this study.[205]

The product Buvidal received market authorisation in the EU in 2018.[206] In the US, the registration status of this product is complicated. Braeburn Inc. (Princeton, NJ, US)—obtaining a licence for the product from Camurus AB in the US[207]—announced that it is eligible for marketing approval for Brixadi (the product name in the US) as of 2020. This follows from the decision by the FDA to grant Braeburn's Citizen Petition (filed in 2019) and thereby revoke Indivior PLC's (Chesterfield Court House, Virginia, US) orphan designation for buprenorphine treatment for opioid use disorder. By revoking Indivior's orphan designation, Sublocade injection is not eligible for any period of orphan exclusivity.[208] Patents protecting the product are US 9937164[209] and EP 3045162.[210]

Cytarabine

To address the need for an improved therapy of leptomeningeal cancer dissemination, a Pharmaceutical Form Line Extension for cytarabine was developed.[211] Cytarabine was encapsulated in multivesicular liposome preparation using the DepoFoam technology. This product, known as DepoCyt,[212] was introduced on the US market in 1999 by Pacira Pharmaceuticals (Parsippany, NJ, USA) and SkyePharma Production SAS (Saint-Quentin-Fallavier, France). The liposomal formulation comprises DOPC, DPPG, cholesterol and triolein.

The encapsulation of the drug in lipid changes drastically the PK of the free cytarabine released by liposomes in the cerebrospinal fluid, such that the mean elimination $t_{1/2}$ of the depot formulation of free cytarabine in the cerebrospinal fluid is between 130 and 277 h *versus* 3.4 h for native cytarabine.[213] Furthermore, the cytotoxic concentrations of the slow release formulation of the cytarabine in cerebrospinal fluid were maintained for as long as 14 days or more, depending on the target cell threshold concentration that is cytotoxic.[211] In addition, DepoCyt has distinct advantages for the patients compared to the standard therapy of leptomeningeal cancer dissemination fusing intrathecal injection of methotrexate at a lower frequency of administration. However, DepoCyt was discontinued in 2017.

Morphine sulphate

Infumorph by Hikma Pharmaceuticals USA Inc. (Eatontown, NJ, USA) is a sterile solution of morphine sulphate intended for use in continuous micro-infusion devices for intraspinal administration in the management of pain. This product was introduced on the market in 1984.[214]

DepoDur is a Pharmaceutical Form Line Extension of morphine sulphate injectable. It is an extended-release liposome injection, developed by Endo Pharmaceuticals (Chadds Ford, PA, USA) and SkyePharma PLC (London, UK) intended for single-dose administration by the epidural route for the treatment of pain following major surgery. DepoDur is administered prior to surgery or after clamping the umbilical cord during caesarean section.[215] DepoDur was introduced on the market in 2004—eighteen years after introduction of the regular morphine sulphate injection.[104] The product comprises multivesicular liposomes with DOPC, DPPG, cholesterol, and triolein as lipid components.[215]

Administered epidurally as a single dose either before or during surgery, DepoDur provides sustained release of morphine sulphate for as long as 48 hours. As stated by RIOS, the release profile is a considerable improvement over current therapy, which requires the use of an in-dwelling epidural catheter and/or administration via continuous intravenous infusion with patient-controlled analgesia.[216] The pharmaceutical profile of the drug product is described in ref.[217] The product was marketed by Pacira Pharmaceuticals and covered by patents which last expiry date in 2017.[104] In spite of the positive features of the product, sales of the product were discontinued in 2012.[218]

3. Inhalation Pharmaceutical Form Line Extensions

Interestingly, phospholipids are used/explored in many ways in dosage forms for inhalation. They are used 1) to replace a solution for nebulisation by a dry powder inhalation formulation (example tobramycin), 2) to convert a dosage form of a drug, which is usually orally and parenterally administered into an inhalation form enabling local lung treatment (example ciprofloxacin), 3) to allow slow release of the drug substance reducing the administration frequency (examples amikacin and ciprofloxacin), and 4) to enable systemic administration with a fast onset of action (examples levodopa and acetyl salicylic acid). These options are summarized in **Table 6**. Options 2) and 3) are also designed to reduce systemic side effects as result of the local administration.

Table 6. Example of inhalation Pharmaceutical Form Line Extensions using phospholipids as key excipients.

API (Class)	**Originator Oral Product Dosage form and (product example)**	**Line Extension Product Dosage form and (product)**
Converting a liquid inhalation form into a solid form (dry powder inhalation form)		
Tobramycin (Antibiotic)	Aqueous solution Tobramycin injection (Bethkis, inhalation solution)	Powder for inhalation with DSPC-$CaCl_2$ (Tobi Podhaler)
Enabling local treatment with a dry powder inhalation form		
Ciprofloxacin (Antibiotic)	Tablet (Cipro)	Powder for inhalation with DSPC-$CaCl_2$ (Ciprofloxacin DPI, development stage)
Enabling systemic treatment		
Levodopa (Parkinson's disease)	Oral tablets in combination with carbidopa (Sinemet)	Powder for inhalation with DPPC (Inbrija)
Acetylsalicylic acid	Oral tablets (Aspirin)	Powder for inhalation with DPPC (Asprihale, development stage)
Extending release properties		
Amikacin (Antibiotic)	Aqueous solution (Amikacin sulphate injection)	Liposomal suspension with DPPC and cholesterol (Arikayce)
Cisplatin (Cytostatic)	Aqueous solution (Cisplatin injection)	Liposomal suspension with DPPC and cholesterol (Inhaled Lipid Complex of cisplatin, development stage)
Ciprofloxacin (Antibiotic)	Aqueous solution (CIPRO intravenous injection)	Liposomal suspension with HSPC and cholesterol (Pulmaquin, later Linhaliq)

The safety of administration of phospholipids to the lung was already proven in 1964 when phospholipids were administered to infants to treat the Respiratory Distress Syndrome caused by lack of phospholipid surfactants in these infants. Interestingly, lung tissues comprise saturated phospholipids,[219] which are the same phospholipids as used to make suitable inhalable formulations (utilising their powder forming properties and slow-release features) as will be demonstrated in the following section.

3.1. Converting a liquid form into a solid form

Tobramycin is available as an injection and in an ophthalmic ointment and solution. It is also available as solution for inhalation as an antipseudomonal antibiotic for chronic pulmonary infections in patients with cystic fibrosis.[220] The solutions for inhalation of tobramycin and the use of nebulisers require prolonged administration and cleaning times and high administration frequency, resulting in a high treatment burden in this patient population. A dry powder formulation for inhalation, eliminating these disadvantages, would therefore be a viable alternative.
The dry powder Pharmaceutical Form Line Extension of tobramycin, Tobi Podhaler, was developed using PulmoSphere technology—initially developed by Chiron Corporation (Emeryville, CA, USA)—wherein phospholipids are key excipients.[221] PulmoSphere particles are manufactured by an emulsion-based spray-drying process, designed to create porous particles with a sponge-like morphology.[222] The availability of a dry powder formulation for inhalation offers a genuine alternative to oral administration. It provides substantially improved intrapulmonary deposition efficiency, faster delivery, and more convenient administration over nebulised formulations. The availability of more efficient and convenient treatment options may improve treatment adherence and thereby therapeutic outcomes in cystic fibrosis.

The dispersed oil droplets are stabilised against coarsening by a monolayer of the saturated long-chain phospholipid DSPC. Such saturated long-chain PCs, for example DPPC, are the principal components of endogenous pulmonary surfactant.[223] The active pharmaceutical ingredient (tobramycin) is incorporated in the emulsion by dissolving it in the continuous water phase. Owing to the short spray drying time (in the order of milliseconds), tobramycin is present as an amorphous solid in the spray-dried particles. DSPC acts as emulsifier and hydrophobic shell former. The product was introduced on the market in 2013. The product and technology are covered by various patents (see ref.[224] for details).

3.2. Enabling local treatment

The same technology is used for the antibiotic ciprofloxacin, to create a dry powder inhalation form and to enable treatment of local infections in the lung.
Ciprofloxacin is an antibiotic used to treat several bacterial infections.[225] This includes bone and joint infections, intra-abdominal infections, certain types of infectious diarrhoea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections. Ciprofloxacin is on the market in several dosage forms, that are tablet and injectable form.[226] A Pharmaceutical Form Line Extension for ciprofloxacin, the Ciprofloxacin DPI, whereas DPI stands for “dry powder inhaler”, is in development as a long-term, intermittent therapy to reduce exacerbations in patients with non-cystic fibrosis bronchiectasis and evidence of respiratory pathogens using the same PulmoSphere technology as for tobramycin.[227] Besides, this formulation approach would have the advantages of a dry powder inhalation form.

As with Tobi Podhaler, the principal excipient is DSPC. Although DSPC makes up just 21.5% w/w of the bulk composition, the surface of the PulmoSphere particles comprises more than 96% DSPC. The porous hydrophobic phospholipid shell formed with DSPC reduces interparticle attractive forces, enabling efficient powder dispersion and delivery of ciprofloxacin inhalation powder to the lungs. Following deposition of ciprofloxacin inhalation powder, DSPC is catabolised and ultimately recycled by type II cells in the lungs.[228] The other excipient, calcium chloride, is present in ciprofloxacin

inhalation powder at a concentration of 1.5% w/w and helps to modify the phase behaviour of the phospholipid by binding to the phosphate portion of the PC headgroup on DSPC.

3.3. Enabling systemic treatment

Remarkably, the dry powder inhalation approach with synthetic saturated phospholipids can also be used to achieve enhanced systemic delivery via uptake by the lungs as opposed to local lung delivery as shown with the example antibiotic formulation described above. This can be advantageous for drugs that require a fast onset of action. Here, the added phospholipid also acts as a diluent excipient to develop a suitable dry powder formulation for inhalation.

Levodopa

Levodopa (L-Dopa, L-3,4-dihydroxyphenylalanine) crosses the protective blood–brain barrier, whereas dopamine itself cannot.[229] Thus, L-DOPA is used to increase dopamine concentrations in the treatment of Parkinson's disease and dopamine-responsive dystonia.

Quite recently (in 2019), a dry powder formulation product for inhalation, Inbrija[230] by Arcoda Therapeutics Inc. (Ardsley, NY, USA) and Civitas Therapeutics Inc. (Chelsea, MA, USA; which is a subsidiary of Arcoda) was introduced on the market as parenteral Pharmaceutical Form Line Extension of the oral levodopa products (in combination with carbidopa, an inhibitor of dopamine decarboxylase[231]). Inbrija, which acts systematically after inhalation, is intending to treat symptoms during 'off' periods that occur while patients are taking their usual treatment, a combination of levodopa and carbidopa. The advantage of this line extension is the faster onset of action of levodopa. This product contains DPPC as excipient in the powder formulation,[232] with two main advantages. Firstly, on the technical side it is the improved flowability of the powder and the high powder density enabling high drug dose inhalation.[233] Secondly, on the physiological side, it is the compatibility of saturated phospholipids with the lung tissue. Since after inhalation the active ingredient is systemically absorbed. Hence, this treatment belongs to parenteral administration. The product was introduced on the market in the US in 2018 and in the EU in 2019. The IP related to the product is found in ref.[233]

Acetylsalicylic acid

Concerning Inbrija, it is worth mentioning that also acetylic salicylic acid (commonly orally administered) is being developed by the company Otitopic Inc. (Los Angeles, CA, USA) in a Pharmaceutical Form Line Extension for inhalation, using DSPC as essential formulation component, with a fast onset of systemic action. The company Otitopic Inc. claims that the effects of their product Asprihale are distinctly more rapid, potent, and assure a consistent pharmacodynamic response in the treatment of acute thrombotic conditions such as stroke and heart attack than the current standard of care.[234] It is touted as revolutionising the myocardial infarction management by providing a portable, single-use therapy for the treatment of acute myocardial infarction.[235] Several patent applications have been published and patents have been granted.[236] The phospholipid component is added to coat the active, suppressing its bitter taste and irritation potential upon inhalation and simultaneously acts as a viable alternative for lactose, which is typically used to blend powders for inhalation.[236c]

3.4. Extending release properties

Phospholipids in the form of liposomes also have the potential to act as slow-release formulation for drug substances after inhalation to reduce the required frequency of inhalation dosing for local treatment of lung diseases. Pharmaceutical Form Line Extensions based on this principle were discussed by CIPOLLA *et al.*[237] In this article, CIPOLLA mentions: "*There have been a wide range of drugs evaluated in liposomal formulations with the intention to treat lung disease. The earliest examples were liposomal formulations of oncology compounds to target lung cancer […]*".

Later development efforts have focused on the antibiotics ciprofloxacin and amikacin, resulting in (for the time being) a clinical failure for ciprofloxacin and a successful market introduction of a liposomal amikacin slow-release inhalation product (Arikayce).
The discussed products do not have direct comparators as original product, being the same inhaled drug substances without a slow-release formulation, but in **Table 6**, the original intravenous products are provided. In fact, tobramycin and aztreonam (Cayston) are the only antibiotics approved for inhalation therapy of lung infections in the US and polymixins (colistin and the related colomycin) are the only ones in Europe.[238] Inhaled cytostatics are not on the market. Therefore, the liposomal slow-release formulations for amikacin or ciprofloxacin would also represent the first inhalation therapy with these antibiotics and the inhalation form of cisplatin would be the first inhaled cytostatic. Thus, these line extension products can also be considered as conversions of the parenteral dosage forms used for the original administration routes.

In general, delivery of an antibiotic formulation *via* the inhalation route has the potential to provide high concentrations at the site of infection with reduced systemic exposure to limit systemic side effects. A slow-release liposomal formulation may improve tolerability controlled release, thereby reducing the dosing frequency, enhanced penetration of biofilms and better treatment of intracellular infections.[239] The same rationale may apply for inhaled cytostatics but the potentially resulting in a more efficacious local tumour treatment.

Amikacin

Amikacin sulphate is a semi-synthetic aminoglycoside antibiotic derived from kanamycin. It is on the market in the US (Amikin) since 1994 as an injectable dosage for intravenous and intramuscular use. The injectable form is also used for the treatment of respiratory infections. Aminoglycosides are, however, potentially nephrotoxic and ototoxic.[240] The development of an injectable Pharmaceutical Form Line Extension with amikacin sulphate using liposomes was explored by Gilead Sciences Inc. (La Verne, CA, USA) named MiKasome.[241] MiKasome showed substantially reduced nephrotoxicity and reduced ototoxicity in preclinical studies. In humans, however, it was assumed that therapeutic dose monitoring would virtually eliminate the toxicity in control arms in clinical studies for the cystic fibrosis indication, and so proof of improvement and label claim would be very difficult to obtain. With these issues, there was less commercial incentive leading to cessation of further development of this product.[241]

Still, local administration of this product was considered a potentially viable therapeutic strategy, and the company Transave (South Brunswick Township, NJ, USA) decided to develop liposomal amikacin (Arikace, later named Arikayce) originally for treatment of *Pseudomonas* lung infections and lung infections due to non-tuberculous *Mycobacteria* in cystic fibrosis patients.[242] After obtaining the orphan drug status in the US and EU, Insmed Inc. (Bridgewater Township, NJ, USA)

acquired Transave and further developed the product. This product is a liquid dispersion of liposomes composed of DPPC and cholesterol.

Although it could be shown that targeting amikacin (without liposomes) to the lung by inhalation leads to a >3000-fold increased lung-to-serum drug concentration ratio as compared to intravenous administration,[239] the liposomal product is until now only registered in the US (in 2018; 24 years after introduction of the original product) and only for a limited population, and only as part of a combination antibacterial drug regimen.[243] In addition, the product is still nephrotoxic and ototoxic. It has additional product-specific side effects such as respiratory adverse reactions including, hypersensitivity, pneumonitis, haemoptysis, bronchospasm, or exacerbation of the underlying pulmonary disease.[244] In the EU, the marketing authorisation application for Arikayce was withdrawn in 2016.[245] Clinical research for other indications like non-cystic fibrosis bronchiectasis is, however, ongoing.[246] Several patents protect Arikayce; the most recent ones[247] expire in 2035 at the latest.

Cisplatin

Eleison Pharmaceuticals LLC (Princeton, NJ, USA) is developing an inhaled cisplatin lipid complex with sustained-release properties for prevention and treatment of lung metastases as a result of paediatric osteosarcoma. Approximately 35% of patients fail first-line therapy, mostly with metastatic recurrence only in the lungs, and with poor prognosis (five-year survival of such patients is below 25%).[248] In 2013, the product received the orphan drug designation from the EMA.[249]

Eleison is currently enrolling patients in a phase II clinical study by leading osteosarcoma clinical investigators throughout the US, to evaluate the safety and efficacy of inhaled lipid cisplatin in patients with osteosarcoma lung metastases. The product comprises cisplatin (1 mg/ml), DPPC (16 mg/ml), and cholesterol in 0.9 % NaCl.[250]

Eleison has sub-licensed the marketing rights of inhaled lipid cisplatin for the Chinese market to an emerging Hong Kong-based pharmaceutical company. In conjunction with this agreement, Eleison and the Chinese partner plan to commence in 2020 a large phase II study of inhaled lipid cisplatin in patients with non-small cell lung cancer, the leading cause of cancer deaths worldwide. Eleison cooperates with Windtree Therapeutics (Warrington, PA, USA) to further develop inhaled lipid cisplatin.[251]

Ciprofloxacin

For ciprofloxacin it is known that intravenous administration of this antibiotic to treat lower respiratory tract infections or severe pneumonia is often ineffective for patients infected with *Pseudomonas aeruginosa*. Observations included failure to eradicate the organism, persistence of infection, and the emergence of resistance. Thus, an inhaled ciprofloxacin product achieving higher drug concentrations in the lung may be more effective and simultaneously reduce the potential for the development of resistance.[239]

The company Aradigm Corp. (Hayward, CA, USA) explored the inhalation use of liposomal ciprofloxacin. This product, Pulmaquin, was a successor of Lipoquin of the same company. The difference between Lipoquin and Pulmaquin is that with Lipoquin practically all ciprofloxacin is liposome-encapsulated, while with Pulmaquin, a portion of the drug is not encapsulated to provide an initial high peak concentration of ciprofloxacin in the lung. Pulmaquin comprises the lipids HSPC

and cholesterol.[252] Linhaliq, the later tradename for Pulmaquin, was intended for once-daily inhalation with the additional aim to reduce adverse lung reactions such as bronchospasm that have historically hampered the development of inhaled antibiotics in bronchiectasis.

PK studies in a mouse model showed that aerosolised Lipoquin (1 mg/kg) provides an AUC_{0-24} in the lungs that is over 80-fold larger than oral ciprofloxacin (50 mg/kg), which is rapidly eliminated from the lungs (half-life 4.2 h). In contrast, aerosolised Lipoquin has an 80% longer half-life (7.4 h).[253] Despite a promising preclinical profile and clinical results showing that Linhaliq was safe and, compared with placebo, its use extended the time before a patient experienced a pulmonary exacerbation and Linhaliq-treated patients experienced a decrease in the frequency of severe exacerbations including those that required antibiotic treatment,[254] the FDA rejected the New Drug Application (NDA) for Linhaliq in 2018 because of concerns related to the clinical data, human factors validation study (that is usage of devices by intended users without serious use errors), and the product quality.[255] In Europe, Aradigm withdrew its application in 2019.[256] The development and marketing rights were then acquired by the Spanish company Grifols SA (Barcelona, Spain) in 2020.[257] The product was further licensed in April 2020 to Savara Pharmaceuticals (West Lake Hills, TX, USA) for bronchiectasis, and this company plans a confirmatory Phase III trial of ciprofloxacin (for inhalation) in non-cystic fibrosis-related bronchiectasis.[258]

4. Dermal Pharmaceutical Form Line Extensions

4.1. Converting from the oral to the dermal administration route

Phospholipids can also be used to convert oral products into Pharmaceutical Form Line Extensions for topical administration to the skin or mucosa. The choice of phospholipids is motivated by their excellent skin compatibility and the potential of liposomes to enhance the skin interaction with drugs. In general, for this type of line extensions topical administration should result in less systemic side effects compared to oral therapy. The original products mentioned in **Table 7** are also available in injectable form to treat emergency (*e.g.*, lumbago in case of NSAIDs). The presented topical line extensions are not intended for treatment of emergency indication but serve more as an alternative for more prolonged treatment with an oral product.

Table 7. Examples of Pharmaceutical Form Line Extensions using phospholipids as key excipients to convert an oral form in a dermal/vaginal form.

API (Class)	Originator Product Dosage form and (product)	Line Extension Product Dosage form and (product)	Advantage of line extension
Diclofenac sodium (NSAID)	Tablet (Voltaren)	Liposomal gel with PC (Diclac Liposomal Gel, Voltaren Spray, and other)	Improved skin interaction; lower systemic availability compared to oral administration
Ketoprofen (NSAID)	Capsule (Orudis)	Ethanolic solution with soybean lecithin (Ketospray)	
Nimesulide (NSAID)	Tablet (Nisulid)	Foam formulation with HSPC (Erreflog topical foam)	

Diclofenac

The dermal NSAID Pharmaceutical Forms Line Extensions were developed as an alternative to oral medications with this class of drug products to circumvent gastric side effects of these drugs.[259] Several formulation approaches to achieve this goal have been described. In addition, certain salt forms of diclofenac, such as diclofenac hydroxyethyl pyrrolidine[260] and diethylamine, respectively,[261] can permeate through the human stratum corneum from aqueous solutions, whereas diclofenac sodium seems to profit from phospholipid-based formulations.[262] It is, however, unclear whether the phospholipids should be used in form of liposomes or mixed micelles. Anyway, several clinical studies in animals (veterinarian) and osteoarthritis patients showed the benefit of this type of phospholipid-based products—gels[263] (Diclac Schmerzgel, Hexal AG, Holzkirchen, Germany) including "(3-*sn*-Phosphatidyl)-choline" and sprays[264] (Voltaren spray, Novartis Consumer Health, Munich, Germany) with de-oiled soybean phospholipids—on their own in relief of pain and morning stiffness. Still, in all cases, no critical comparison with a comparator having a different formulation composition has been made.[265] Also, the justification for the selection of the phospholipid type (saturated or unsaturated) is not presented in any study. However, it is known that the phase transition temperature of phospholipids dramatically influences whether phospholipids are suitable for skin penetration or skin barrier enhancement.[266] The concept of local treatment of arthritis inflammations was underscored by a study showing that after administration of a diclofenac sodium 4% spray gel, the diclofenac concertation was found to penetrate the skin locally in substantial amounts. The median diclofenac concentration was approximately 10- to 20-fold higher in synovial tissue of the knee than in synovial fluid or plasma.[267] For this reason, such NSAID products can be considered not only as dermatological products, but also as partially parenteral products since they are aimed for an enrichment of the drug in the synovial compartments or tissues surrounding joints, without further systemic bioavailability.

Ketoprofen and Nimesulide

A similar type of studies, with the same lack of comparators, can be found for other NSAIDs, which are on the market as oral products and are reformulated for dermal use bearing phospholipids as key excipients. These are ketoprofen and nimesulide.[268]

Ketoprofen is on the market as Ketospray (CYATHUS Exquirere Pharmaforschungs GmbH, Bisamberg, Austria) which contains soybean lecithin as stabiliser to enable the formulation of the high concentration (10%) of ketoprofen. It is further claimed that the lecithin acts together with ethanol and isopropanol in the formulation as flux enhancer.[269] The efficacy and tolerability of these spray products have been shown in a safety study as it is defined by Article 21 of the European Clinical Trials Directive 2001/20/EC.[270]

Nimesulide was found to have excellent skin interaction when using multilamellar liposomes. Anti-inflammatory studies, using the carrageenan-induced rat paw oedema model, indicated significantly higher efficacy of liposomal entrapped nimesulide in comparison to the marketed gel formulation and the Carbopol gel containing nimesulide.[271] In Italy, a cream and a spray formulation are on the market, including nimesulide.[272]

Although the scientific evidence that phospholipids exclusively enhance the skin interaction of NSAIDs is on debate, the corresponding products enjoy much interest in local symptomatic treatment in arthrosis patients.

4.2. Converting from the parenteral to the dermal administration route

There are a few parenteral products for which a dermal Pharmaceutical Form Line Extension could offer a more convenient alternative. For instance, for an antifungal that needs to be repeatedly intravenously injected to treat local infections, a topical product can be a less painful and more cost-effective alternative. Examples at which phospholipids play a key role in such line extensions are provided in **Table 8**.

Table 8. Examples of Pharmaceutical Form Line Extensions using phospholipids as key excipients to convert a parenteral form into a topical form.

API (Class)	Originator Product Dosage form and (product example)	Topical Line Extension Product Dosage form and (product)	Advantages of line extension
Amphotericin B (Antifungal)	Parenteral micellar solution or liposome (Fungizone or Ambisome)	Liposomal gel, with HSPC and cholesterol (Fungisome)	Drug solubilisation and improved skin interaction
Minoxidil (Hair loss)	Solution, intradermal injection (Minoxidil injection)	Solution with SPC (Morr F) (Tugain, spray)	Increased tolerability and improved skin interaction
Heparin (Venous thrombosis)	Solution (Heparin Sodium Injection, USP)	Liposomal suspension with soybean lecithin (ViaTromb spray)	Improved skin interaction
Lidocaine HCl (Local Anaesthetic)	Solution Xylocaine (lidocaine HCl and epinephrine Injection, USP)	Liposomal gel with HSPC (LMX cream)	Improved skin interaction

Amphotericin B

Amphotericin B was first on the market in a parenteral dosage form (Fungizone) which used sodium deoxycholate as solubiliser[147] to enable injection of this water-insoluble drug (see above). In 2007, a parenteral and dermal Pharmaceutical Form Line extension was developed by the company Lifecare Innovations Pvt Ltd. (Gurgaon, Haryana India), based on a liposomal formulation of amphotericin B with HSPC and cholesterol as liposome components.[162] For the dermal treatment of acute and recurrent chronic fungal infections of the skin and cutaneous leishmaniosis, the liposomes were formulated in a gel (Fungisome gel).[273] The liposomes solubilise amphotericin and offer a formulation with less irritation potential and increased skin interaction.

Minoxidil

The drug minoxidil is on the market for treatment of hair loss (androgenic alopecia) and is available in tablet form (Minoxidil Tablets, USP)[274] and administered through intradermal injection (Minoxidil Injection of Swiss Healthcare Pharmaceutical Ltd; Montreux, Switzerland), respectively. As Pharmaceutical Form Line Extension, Morr F by Intas Pharmaceuticals Ltd (Ahmedabad, India) and JINA Pharmaceuticals Inc (Libertyville, IL, USA), a dermal liquid comprising minoxidil liposomes based

on US patent 9,750,812[275] was introduced. In addition, a dermal spray/foam with phospholipids is on the market (Tugain of Cipla Ltd, Mumbai, India).

The benefits of liposomal forms for skin treatment, in general,[276] and of minoxidil (SPC dissolved in isopropyl alcohol-propylene glycol-water solution) in comparison to a minoxidil solution (isopropyl alcohol-propylene glycol-water), for treatment of androgenic alopecia are well described in the literature.[277] A topical formulation of Morr F (combination of Minoxidil and Finasteride) was shown to have clinically significant improvement in terms of hair growth as compared to Minoxidil alone.

Heparin

Heparin acts as an anticoagulant, preventing the formation of clots and extension of existing clots within the blood. Heparin and its low-molecular-weight derivatives (low molecular weight heparin, LMWH), for example, enoxaparin, dalteparin, or tinzaparin, are effective in preventing deep vein thromboses and pulmonary emboli in people at risk[278] and is given as a subcutaneous injection. Since a topically applied dosage form of heparin would be a more convenient way to administer the drug compared to injection, dermal Pharmaceutical Form Line Extensions were developed. In addition, liposomal dosage forms to enhance the skin penetration of heparin were explored. Just like with dermal forms of NSAIDs, the clinical applicability of the dermal use of heparin in liposomes is controversial. BETZ *et al.*[279] found that the extent of LMWH penetration was independent of the formulation. LMWH, however, showed a trend to accumulate in deeper epidermal layers of the liposomal formulation compared to the aqueous formulation. The molecular weight of the heparin and liposomal formulations influenced the penetration pattern of heparin in the epidermis. They could not conclude whether the concentration of LMWH achieved at the blood capillaries is sufficient to exert a pharmacological effect. For these reasons, such applications are more suitable to treat superficial venous thrombosis rather than deep venous thrombosis. Indeed, GÓRSKI *et al.*[280] were able to clinically prove that the dermal application of a liposomal heparin spray (Lipohep spray gel) combined with compression shows a comparable efficacy as subcutaneous administration of LMWH in the treatment of superficial thrombosis.[280b]

VECCHIO and FRISINGHELLI[281] reviewed the literature on dermally applied heparins for the treatment of vascular disorders. They concluded that still more clinical research is needed to clarify which formulation is best regarding the treatment of thrombosis and that so far, all reviewed products are about the same in efficacy and tolerability. Nevertheless, a product such as ViaTromb by CYATHUS Exquirere Pharmaforschungs GmbH (Vienna, Austria) uses the “magic” of the liposome (with soybean phospholipids[282]) in the product to suggest a superiority of this dermal heparin product *versus* products without liposomes, which makes, despite the absence of convincing clinical evidence, such Pharmaceutical Form Line Extensions from marketing perspective attractive products.

Lidocaine

Lidocaine is another drug substance used for local anaesthesia through injection (Xylocaine; lidocaine HCl and epinephrine Injection, USP),[283] which could be made more attractive for the patient by reformulating the drug in a dermal dosage form. An example of such product is LMX4 (ELA-Max), a lidocaine cream (4 weight%) of Ferndale Pharmaceuticals Ltd (Wetherby, UK), which contains benzyl alcohol, carbomers, cholesterol, hydrogenated soy lecithin, polysorbate 80, propylene glycol, trolamine, vitamin E acetate, and purified water.[284] LMX4 is a liposomal

formulation in a gel base, which because of the presence of liposomes[285] enhances the skin penetration of the drug, leading to a rapid onset of action,[286] and prevents metabolic degradation at the application site. This, in turn, leads to a prolonged duration of action[287] and further helps in sustained release of the drug.[288] More extensive clinical research and comparison with eutectic mixture of local anaesthetics (composed of lidocaine 25 mg/ml and prilocaine 25 mg/ml, polyoxyethylene fatty acid esters that are emulsifiers, carboxypolymethylene that is a thickening agent, distilled water with pH adjusted approximately to 9, and without any preservative) was performed. It was shown that LMX4 and the product of an eutectic mixture of local anaesthetics were equally efficacious.[289] These results indicate that the presence of liposomes in the LMX4 product may act as an additional sales/marketing factor to create an attractive Pharmaceutical Form Line Extension.

4.3. Improving interaction with the skin

Phospholipids can also be used as key excipients in Pharmaceutical Form Line Extension to improve (either in the form of skin penetration or restoring the skin barrier) the skin interaction profile of the formulated drug in existing skin products. Some examples are provided in **Table 9**.

Table 9. Examples of dermal Pharmaceutical Form Line Extensions.

API (Class)	Originator Product Dosage form and (product example)	Line Extension Product Dosage form and (product)	Advantages line extension
Azelaic acid (Antibiotic, anti-acne)	Cream 20% (Azelex)	Gel 15% with lecithin (Skinoren Gel/Finacea)	Increased efficacy
Clindamycin phosphate (Antibiotic)	Cream (Cleocin)	Water-in-oil-in-water (w/o/w) emulsion with soybean lecithin as emulsifier (Clindesse intravaginal cream)	Increased efficacy
Dexpanthenol (Provitamin)	Ointment, gel solution (Bepanthen)	Spray with HSPC (Sensiderm, Physiogel AI)	Cooling effect, excellent spreading and skin interaction
Diclofenac sodium (NSAID)	(Voltaren Emulgel)	Liposomal gel with PC (Diclac)	Equivalent to original product
Dithranol/salicylic acid (Anti-psoriatic)	Ointment (Psoralon MT)	Liposomal Gel with egg lecithin (Psorisome)	Efficacy enhancement (50% less dithranol); no salicylic acid; increased skin interaction

Azelaic acid

Azelaic acid, a naturally-occurring saturated dicarboxylic acid, is used to treat mild to moderate acne, both comedonal acne and inflammatory acne.[290] Azelaic acid was introduced on the US market in a topical gel by Amirall S.A. (Barcelona, Spain) in 1995, for treatment of rosacea, due to its ability to

reduce inflammation.[290b] This product, Azelex cream (20%),[291] contains cetearyl octanoate, glycerine, glyceryl stearate, cetearyl alcohol, cetyl palmitate, cocoglycerides, PEG-5 glyceryl stearate, propylene glycol, and purified water as excipients. Benzoic acid is present as a preservative.

As Pharmaceutical Form Line Extension—initially developed by Schering AG (Berlin, Germany)—, an alternative dermal product containing lecithin for the same indication containing less azelaic acid (15%) compared to Azelex was introduced on the US market by Leo Pharma AS (Ballerup, Denmark) in 2015; twenty years later. This product, Finacea/Skinoren Gel, has been developed to meet the needs of acne patients with greasy skin.[292] A reason to select 15% drug content instead of 20 % was that the galenically acceptable maximal concentration in the gel was only 15%.[292b] The Austrian product approval documentation mentions that SPC is used as phospholipid component.[292b] BURCHACKA *et al.*[293] found in a Franz cell diffusion system that a liposomal gel formulation showed a higher concentration of azelaic acid in the stratum corneum compared to the standard non-liposomal product. The only preclinical experiment to study skin PK, which has been published with azelaic acid containing hydrogels by Schering, was a test on an *in vitro* skin penetration, using hairless mouse skin. Azelaic acid containing hydrogels delivered a higher dose fraction into the viable skin layers than Skinoren cream. Since the number of experiments was low and since the variation between the single experiments was high, these differences should not be overestimated.[292b]

Schering performed two phase II/III clinical studies with Skinoren Gel controlled by the azelaic acid-free vehicle ("placebo") and 5% benzoyl peroxide hydrogel, respectively. Moreover, Schering has performed a phase II study between Skinoren Gel and Skinoren Cream in small groups of 15 patients each to underscore the clinical efficacy. No clinical studies in comparison with the cream formulations were made.[292b]

Since the phospholipid-containing product Finacea, which bears 15% azelaic acid, and the Azelex cream product containing 20% azelaic acid are used for the same indication, it can be assumed that the phospholipid-based line extension product shows an increased efficacy.[292b] To underscore the commercial importance, this product is protected by patents.[294]

Clindamycin

For treatment of local vaginal infections clindamycin is used in a cream formulation.[295] The Pharmaceutical Form Line Extension Clindesse was originally developed by the company KV Pharmaceutical Company, which was acquired by the company Perrigo (Dublin, Ireland). The Clindesse product is covered by patents.[296] Clindesse is indicated for the treatment of bacterial vaginosis in non-pregnant women.[297] The formulation comprises a pH neutral o/w emulsion, which oil globules have two phases, an internal water-soluble phase and an external water-insoluble phase. The internal water phase contains the clindamycin and has an acidic buffer.[296a] The phospholipid (SPC)[296b] probably acts as essential emulsifier in this complex water-in-oil-in-water (w/o/w) emulsion formulation. In a clinical study, which compared Clindesse with a conventional vaginal cream, it was shown that Clindesse was more efficacious compared to a conventional cream since a single dose of Clindesse was equivalent in safety and efficacy to a regimen of once daily for seven days of the conventional cream, Cleocin, in the treatment of bacterial vaginosis.[295,298]

Dexpanthenol

Dexpanthenol (provitamin B5) is a well-known substance used in skincare and topical treatment of skin and mucous membrane related diseases. Most of these diseases are characterised by a decrease or damage of the barrier function of the skin or mucous membrane. A popular method to strengthen the barrier function is to add, together with the drug substance, hydrogenated natural phospholipids such as HSPC to the formulation, generating dermatological interesting Pharmaceutical Form Line Extensions. These phospholipids have a phase transition temperature above skin temperature, which brings these molecules in the rigid gel state. Together with other high-melting lipids in the formulation, they form lamellar structures able to form a skin barrier increasing lipid film.[266,299] In the case of dexpanthenol, the product Sensiderm are using this "lamellar" technology.[300] A similar use of hydrogenated phospholipids from soybean can be found in the product Physiogel AI of GlaxoSmithKline (London, UK)[301] for treatment of atopic dermatitis and in the product Repithel of Mundipharma Deutschland GmbH & Co. KG (Frankfurt/Main, Germany) containing polyvinyl-pyrrolidone iodine of for the local treatment of burn wounds.[302]

Diclofenac sodium

Diclofenac sodium (Voltaren) was introduced as oral NSAID by Ciba-Geigy Ltd (Basel, Switzerland) in 1973/1974.[303] Based on the success of this product as an anti-inflammatory drug, topical Pharmaceutical Form Line Extensions were developed for local anti-inflammatory effects in, *e.g.*, joints, also to eliminate possible systemic side effects. The first topical product to achieve this was Voltaren Emulgel of Ciba Geigy Ltd. This Voltaren gel containing the diethylammonium salt of diclofenac received US regulatory approval as the first topical prescription treatment for pain associated with osteoarthritis in 2007.[304] To circumvent patent protection of this topical product,[305] liposome-based dermal Pharmaceutical Form Line Extensions of diclofenac (for example Diclac of Hexal AG including 1% diclofenac and SPC)[263,306] was developed, having at least the same benefits as the original Emulgel product.[307]

Dithranol

The drug substance combination of dithranol (patented by Bayer AG, Leverkusen, Germany in 1916) and salicylic acid is topically applied to the skin for a short period for treatment of psoriasis. A side effect of the use of dithranol is a reversible brown colouration of the skin. This combination is on the market in the product Psoralon MT ointment (including 0.5–3% dithranol) with paraffin and vaseline of Hermal Kurt Herrmann GmbH & Co oHG (Reinbek, Germany).[308] A further problem is the oxidative sensitivity of dithranol.

Research in the nineties showed that dithranol incorporated in liposomes shows a favourable skin interaction.[309] The Indian company Lifecare Innovations Pvt Ltd. (Haryana, India) developed a Pharmaceutical Form Line Extension based on liposomes. This new dosage form should increase the stability of the drug and enhance skin penetration at a lower dithranol dose and formation of a micro reservoir in the skin. Lifecare Innovations claims that the resulting product Psorisome (without salicylic acid) has minimised cloth-staining and discolouration problems, reduced irritation, perilesional erythema, burning, sensation, sustained moisturising effect, improved patient acceptability, dose reduction up to 50%, and improved drug stability.[310] The product is covered in the EU by a patent.[311] In this patent, clinical research on the comparison between a dithranol ointment with salicylic acid and a liposomal formulation with egg lecithin is presented. The lecithin

containing formulations were found to be non-irritating and therapeutically more effective even at dithranol concentrations of 0.5% as compared to a dithranol ointment containing 1.1% dithranol.

5. Oral Pharmaceutical Form Line Extensions

5.1. Suppressing gastric irritation of NSAIDs

Phospholipids can also be used to optimise oral products. An example is to use phospholipids to make Pharmaceutical Form Line Extension to reduce gastric side effects of NSAIDs (**Table 10**).

Table 10. Examples of oral Pharmaceutical Form Line Extensions of NSAID with reduced gastric side effects.

API (Class)	Originator Product Dosage form, (product example)	Line Extension Product Dosage form and (product)	Advantages of line extension
Acetylsalicylic acid (NSAID)	Aspirin	Complex of API with PHOSAL 35 SB* (Vazalore)	PLxGuard delivery system, decrease stomach irritation
Ibuprofen (NSAID)	Ibuprofen USP tablets (*e.g.*, Motrin)	Complex of API with phospholipid (PL1100/PL1200 Ibuprofen, development stage)	

*For composition of PHOSAL 35 SB refer to van Hoogevest[312]

Gastric mucosal injury occurs when the causative agents such as gastric acid and NSAIDs overwhelm the mucosal defence. It is well documented that external application of phospholipids to the stomach had the potential to reduce gastric side effects of oral NSAIDs such as ibuprofen and acetylsalicylic acid.[313] Also, the gastric irritation caused by acetylsalicylic acid (Aspirin) could be reduced in preclinical models by using PHOSAL 35 SB (the composition of PHOSAL 35 SB can be found in ref.[312]). These observations were the impetus for the commercial development of PL2200 Aspirin (Vazalore) by PLx Pharma Inc. (Houston, USA) combining aspirin with PHOSAL 35 SB.[314] Vazalore was approved in 2013[315] for temporary relief of minor aches and pains associated with a cold, headache, backache, toothache, premenstrual and menstrual cramps, minor pain of arthritis, and for a temporary reduction in fever. Several US patents cover this product.[316] The focus of the clinical development is to provide patients with vascular disease and diabetic patients, who are candidates for aspirin therapy with more reliable and predictable antiplatelet efficacy as compared to enteric-coated aspirin, while also reducing the adverse gastric events common in an acute setting. PLx Pharma is reported to perform soon a bioequivalence study of Vazalore 325 mg dose (in comparison of the original formulation of 2013 and a new formulation), and a corresponding sNDA (subordination, non-disturbance and attornment agreement) submission is expected by year-end of 2021.[317] The company develops similar phospholipid-based Pharmaceutical Form Line Extensions for ibuprofen (Phase I), indomethacin, and diclofenac, which show improved GI safety in preclinical models.

5.2. Alternative bioequivalent oral liquid form

Phospholipids can also be used in liquid oral dosage forms as an alternative to a solid dosage form. The typical example of such a liquid dosage form is the product, based on the use of a non-aqueous PC concentrate from soybean PHOSAL 50 PG trademark of PHOSPHOLIPID GmbH (Cologne, Germany),[318] developed for the lipophilic compound sirolimus, marketed under the trade name Rapamune by Wyeth-Pharmaceuticals (Madison, USA; a subsidiary of Pfizer Inc).[312] Sirolimus is a naturally occurring compound which is mainly used to prevent rejection of kidney transplants. The inactive ingredients in Rapamune Oral Solution are PHOSAL 50 PG (including PC, propylene glycol, mono- and di-glycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and Tween 80. Rapamune Oral Solution contains 1.5–2.5% ethanol and is supplied in amber glass bottles with 60 mg sirolimus per 60 ml. The sirolimus product based on the liquid PHOSAL formulation got the generic status in the US in 2019.[319]

Although this liquid dosage form was the first oral dosage form developed for this product and the solid dosage form, based on the use of nanocrystals, came later, both forms can be considered as line extensions of each other. In fact, sirolimus was the first approved drug using nanocrystal technology. The tablet form provides a common administration form, but the liquid form may be more convenient for a flexible-dose regime.[320] The systemic availability of sirolimus is low and was estimated to be approximately 14% after the administration of Rapamune Oral Solution. In healthy subjects, the mean bioavailability of sirolimus after administration of the tablet is approximately 27% higher relative to the solution. Sirolimus tablets are not bioequivalent to the solution; however, clinical equivalence has been demonstrated at the 2-mg-dose level.[312]

6. Suitability of phospholipids for paediatric Pharmaceutical Form Line Extensions

Regulatory authorities require the development of paediatric line extensions, *i.e.*, dosage forms suitable for paediatric use for products developed exclusively for adults.[321] Formulators are then possibly forced to replace excipients in formulations for adults by excipients which are unproblematic or approved for paediatric use. Phospholipids can be found in many products for paediatric use and may offer viable alternative solubilisers/dispersants to polysorbates, ethanol, and propylene glycol.[322]

Polysorbates (Tween 80, Tween 20) and polyoxyl castor oil derivatives are particularly problematic because, as outlined above, they may cause hypersensitivity reactions, especially after parenteral administration. In addition, the use of Tween 80 and 20, respectively, may give rise to the occurrence of the E-Ferol syndrome observed with Low-Birth-Weight Infants.[323] Phospholipids present an alternative when parenteral formulation should contain wetting agents (for suspension injections) or a solubiliser to enable unproblematic parenteral administration. In that respect, products containing solubilising formulations such as mixed micelles, o/w emulsions, and liposomes are approved for application in children explained as follows. Mixed micelles with SPC containing the lipophilic vitamin K is allowed for oral and intravenous use in children.[324] The product Diprivan comprising an o/w emulsion with EPC as essential emulsifier as solubilising formulation for the lipophilic drug propofol can be used in children ≥3 years for induction of general anaesthesia and in children of ≥ 3 months for maintenance of general anaesthesia. Paediatric patients, aged one month

to 16 years, with presumed fungal infection (empirical therapy), confirmed systemic fungal infections or with visceral leishmaniosis have been successfully treated with AmBisome comprising amphotericin B and the phospholipids HSPC and DSPC[325] as well as with Abelcet (DMPC/DMPG).

Phospholipids could also be used in injectable products for poorly water-soluble drugs to replace organic solvents such as ethanol and propylene glycol as solubilisers. Both solvents should be avoided in paediatric formulations. Accumulation of propylene glycol can occur in neonates and young children as they cannot adequately metabolise and eliminate the excipient. This reduced metabolism and elimination can lead to depression of the central nervous system.[322,326]

The permitted paediatric use of phospholipids after intravenous administration can be derived from the prescribing information of phospholipid-based products for intravenous use (**Table 11**).

Table 11. Intravenous products with phospholipids permitted for paediatric use.

Product	**Paediatric Use (Age category)**	**Phospholipid Component**
Abelcet[152a]	1 month – 16 years	DMPC and DMPG
AmBisome[327]	1 month – 18 years	HSPC and DSPG
Konakion MM[328]	From born before finishing 37th pregnancy week; or less than 2500 g birthweight – 18 years	SPC
Intralipid[329]	From born before finishing 37th pregnancy week; or less than 2500 g birthweight – 18 years	Egg yolk phospholipids
Mepact[86]	2 years – 18 years	POPC DOPS monosodium salt

Since for oral administration liquid products for paediatric use are preferred, excipients with a bitter taste need to be avoided in these liquid products and could be replaced by phospholipids. Phospholipids of natural (soybean) origin are odourless or have a characteristic, slight nutlike odour and bland taste[330] in contrast to polysorbates, which have a bitter taste.[331] Phospholipids are even able to suppress bitter taste without affecting other taste qualities.[332] SPC is used in oral products[9] and the European Food Safety Authority recently assessed the safety of oral use of lecithin (E 322, food codex) and concluded that there was no safety concern for the general population from more than one year of age and infants (from 12 weeks up to 11 months of age) at the refined exposure assessment for the reported uses of lecithins (E 322) as a food additive.[333] The product Konakion MM, containing SPC, can be orally administered to children from born before finishing 37th pregnancy week; or less than 2500 g birthweight – 18 years.[328b]

The acceptability of paediatric dermal use of soybean phospholipids (which are mainly present in dermatological products) in children can also be derived from the product prescribing information. For instance, the product LidoGalen (including lidocaine) containing HSPC can be used in children older than one month. The product ViaTromb Spray gel (including heparin), which contains soybean lecithin, can be used in children older than two years.[334]

7. Discussion

This review shows the manifold options to make Pharmaceutical Form Line Extensions with the aid of phospholipid excipients. These numerous options are the result of favourable physiological properties of phospholipids such as biocompatibility, biodegradability, and non-toxicity in combination with their multifunctional technological properties as surfactant excipient, being emulsifier, solubiliser, liposome former, and wetting agent. Regarding the versatility, phospholipids are superior compared to synthetic non-biodegradable excipients which are not always suitable for every administration route and which are, by definition, non-physiological.

Phospholipids are a family of compounds differing in fatty acid composition and polar headgroup, which give the specific species unique properties and use in pharmaceutical technology. Also, the availability of both natural and synthetic phospholipids provides the formulation scientist with a valuable treasure of options to optimise phospholipid-based line extension products.[9] The use of phospholipids (documented by drug master files according to 21 CFR 314.420 of the FDA)[335] in many registered products all around the world render them well-known to regulatory authorities. Therefore, when phospholipids need to be selected for formulation development, phospholipids documented through a drug master file are preferred. In case natural phospholipids derived from hen egg yolk or soybean are selected, attention should be paid to the grade of the product regarding minimal PC-phospholipid content, which is dependent on the administration route. For oral and dermal administration, natural phospholipids with at least 45% PC can be used, whereas for parenteral use at least 70% PC is typical.[336] For specific high-tech parenteral products more expensive, high purity, synthetic phospholipids may be the best choice, whereas for dermal and oral administration cost-effective natural phospholipids are the first choice.

The product examples provided in this review rely on the official description of the composition and phospholipids therein found in the literature. With synthetic phospholipids, there are hardly any question marks as to which phospholipid has been used in a product. In the case of natural phospholipids, it is much harder to find out which phospholipid grade actually has been used. An important reason for the poor description of phospholipids relates to the confusion that exists, especially in American literature, regarding the difference between the term “lecithin” and “phosphatidylcholine”. According to the USP Convention, 2014, lecithin is a complex mixture of acetone-insoluble phosphatides (*i.e.*, phospholipids), which consist chiefly of PC, PE, phosphatidylinositol (PI), and PA, present in conjunction with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates, as separated from the crude vegetable oil source. Unfortunately, “lecithin” is also used as a synonym of PC, which is the pure compound. Description of the phospholipid component in a product as “lecithin” leaves open which lipid was used. We therefore recommend to use for natural phospholipids the term “lecithin” only when the product contains less than 80% by weight total phospholipids (which could be, *e.g.*, PC, PE, PA); the term “phospholipids” is used when the product contains 80–100% by weight phospholipids (which could be, *e.g.*, PC, PE, PA); the specific phospholipid is mentioned (*e.g.*, PC) when the product contains more than 90% by weight of that specific phospholipid. The European Pharmacopoeia, the USP, and the Chinese Pharmacopoeia are continuously upgrading and extending the monographs on phospholipids, and the nomenclature used in these pharmacopoeias should unequivocally define the phospholipids used in pharmaceutical products.

The product and development examples described in this review only represent a fraction of the ongoing activities in the pharmaceutical industry regarding the use of liposomes and other phospholipid-based formulations. Reference is made to, for instance, www.orpha.net, www.clinicaltrials.gov, the United States Patent and Trademark Office (www.uspto.gov), and the European Patent Office (www.epo.org) databases.

The examples of conversion of an oral dosage to a parenteral dosage form are mainly related to poorly water-soluble drug substances in need for low toxic solubilisation formulation to enable parenteral administration (**Table 1**). The provided examples encompass also transdermal and inhalation products (**Table 6**), which are, because of the obtained systemic bioavailability, considered as parenteral dosage forms: they again underscore the versatility and suitability of phospholipids for any route of administration. The (parenteral) inhalation line extensions Inbrija and Asprihale (**Table 6**) with systemic activity show the use of phospholipids to create line extension products with fast onset of action. In contrast, phospholipids can also be used in liposomal form to develop inhalation line extensions with (local) slow-release properties (**Table 6**). From a pharmaceutical technological perspective, saturated phospholipids are a viable alternative for lactose as diluent for inhalation powders.
The parenteral line extensions, which show an increased therapeutic index of the employed drug substance (without discarding of a potentially toxic solubiliser in the original formulation) compared to a formulation without phospholipids, are mainly related to (water-soluble) cytostatics for cancer treatment (**Table 2**). These, in most cases, cytostatics have a narrow therapeutic index and/or drug-specific toxicity (for instance cardiotoxicity for doxorubicin HCl) and are reducing the quality of life of cancer patients. The increase of efficacy of the liposomal dosage forms and/or the reduction of toxicity may be linked to the EPR effect, which results in an enrichment of the liposomal cytostatic in tumour tissue and simultaneously avoidance of "tox target" organs, as demonstrated with the Doxil product. JENSEN and HODGSON[241] reviewed the properties of DaunoXome in comparison to Doxil and mention the short shelf-life of the DaunoXome product. In addition, DaunoXome is only applied to treat liquid tumours, whereas Doxil is used for both liquid and solid tumours.

The resulting line extensions mainly aim to the same disease indications as the original product. An example that the line extension is used for another cancer indication as the original product is Onivyde (pancreas cancer). It is remarkable to note that the original non-liposomal injectables with a worse therapeutic index are still on the market. This may be the consequence of the fact that in the clinical research stage, the liposomal products are compared to another anticancer drug.[337] For instance, liposomal doxorubicin has only once tested (crossover, double-blind) against the original product of doxorubicin HCl.[338]

The provided examples (**Table 2**) display that a plethora of lipids are applied in liposomes. A minimal requirement is that the liposomes employed are not leaky for the encapsulated drug to carry the cargo efficiently to the tumour site. Many lipid compositions and different methods such as ion gradient to keep the drug in the liposomes are now available to achieve the desired targeting profile. An interesting example in this direction is provided by the liposomal forms for doxorubicin HCl, Doxil (Caelyx) and Myocet (both used in combination with cyclophosphamide). Both have reduced cardiotoxicity, but Doxil is using PEGylated lipids to prolong the circulation time after intravenous administration, whereas Myocet and DaunoXome do not contain PEGylated liposomes.[241,339]

The Hand-Foot Syndrome is a major side effect of Doxil, whereas Myocet does not show this syndrome. Myocet seems to be expensive and requires an elaborate *in situ* preparation method of the dosage form for injection (needing a controlled heating step in a water bath[340]) whereas Doxil is a ready-for-use liquid injectable dosage form. From this comparison, it looks like that Myocet is the interesting alternative line extension from a clinical use point of view. A conclusion, however, cannot be drawn, since clinical trials comparing these two line extensions were never performed.

A further remarkable observation regarding these line extensions is that the original product, although being more toxic and/or less efficacious than the liposomal line extension (*e.g.*, doxorubicin HCl, vincristine sulphates etc.) is still registered and clinically used for the same medical indication and not withdrawn from the market. A rational explanation for that can be found in the fact that the original products are probably much cheaper and/or clinicians still are not convinced that the liposomal line extension is better. Another explanation could be that oncologists tend to use combination therapies and such combinations with the liposomal line extensions are not approved/tested, whereas for the non-liposomal form such combinations have a long(er) track record of use.

The product Mepact, in this class of (development stage) line extensions, is an example of a different way (instead of EPR effect) to use phospholipids/liposomes to increase the therapeutic of an immunomodulator by using liposomes which are optimised to interact with macrophages, to activate them to become tumouricidal to eliminate metastases. Also, parenteral emulsions, with EPC as emulsifier, can be used to optimise the efficacy of an oil-soluble drug-like prostaglandin (PGE1) for the treatment of peripheral vascular diseases.

The analysis of the parenteral line extension products in this review (**Table 3** and **Table 4**), characterised by the replacement of potentially toxic excipients by phospholipids, shows that phospholipid-based formulations such as mixed micelles, o/w emulsions, and liposomes are clearly an alternative, with reduced risks for anaphylactic reactions compared to formulations with synthetic detergents such as polysorbates, Kolliphor EL (Cremophor EL, Polyoxyl 35 Castor Oil), and Polyoxyl-15-hydroxystearate for solubilising poorly water-soluble drugs for parenteral administration. In addition, these phospholipid-based formulations can avoid or reduce formulations with potentially toxic organic solvents. Regarding the latter issue, it is remarkable that the injectable form of diazepam with mixed micelles has now been replaced by the original manufacturer by an organic solvent formulation which causes pain at the injection site.

A recent exciting example replacing synthetic detergents in parenteral formulations is the product Cinvanti, which belongs to two categories of line extensions: it enables the parenteral administration of the original oral product and, simultaneously, replaces the polysorbate in the injectable formulation of the prodrug of the original compound.[124] The original Emend for Injection product is an example of suboptimal pharmaceutical development. When lipid-based formulation alternatives would have been considered adequately, the development of the prodrug and its salt form and the addition of polysorbate, which makes the co-administration of dexamethasone necessary, probably to suppress hypersensitivity reactions, would not have been necessary.

The examples in **Table 4** show that the use of phospholipids in parenteral line extensions has, in comparison to the original product, two advantages simultaneously: replacement of excipients (eliminating corresponding infusion reactions) and further improving the therapeutic index of the drug by means of targeting. One of these examples, AmBisome, is considered as an improvement

compared to the original product Fungizone, but still Fungizone is on the market. This may be related to the costs of treatment and reimbursement policies of health insurances. This same price pressure and medical need in developing countries (treatment of kala-azar, *visceral leishmaniasis*) urged local companies to develop their own line extensions. Which line extension of amphotericin B is clinically best cannot be judged, since comparative clinical trials have never been performed. The line extensions with docetaxel and paclitaxel are only present in India and China, respectively.

Although, parenteral mixed micelles and o/w emulsions are clearly alternative solubilisers compared to synthetic detergent containing formulations, it should be noted that intravenous administration of (especially PEGylated) liposomes as part of such Pharmaceutical Form Line Extensions is also not without complications. Repeated administration of PEGylated liposomes can cause an Accelerated Blood Clearance (ABC) phenomenon. ABC involves the production of antibodies towards nano-carrier components, including PEG, which reduces the safety and effectiveness of encapsulated therapeutic agents.[341] Another immune response is the hypersensitivity or infusion reaction referred to as CARPA.[341] In that respect, it is of interest to compare the clinical data of these liposomal products and alternative (solubilising) formulations regarding the occurrence of infusion-related hypersensitivity reactions.

The available product leaflet on Caelyx (that is the product name of Doxil in Europe) mentions that serious and sometimes life-threatening reaction may occur within minutes after the start of the intravenous infusion of the PEGylated liposomes. After resolving the symptoms, in most patients, the treatment can be continued, without reoccurrence of the hypersensitivity symptoms. It is recommended to start the first infusion with an infusion rate of less than 1 mg drug substance per minute to reduce the risk for hypersensitivity reactions.[338,342] This recommendation agrees with SZEBENI *et al.*[58] who recommended to slow the rate of administration to an initial rate of 0.1–0.15 mg Doxil per minute in the first Doxil treatment. If the patient does not experience any reaction or other symptoms, this infusion rate can be gradually increased after 10–15 min up to 1–1.5 mg per minute. Non-PEGylated liposomes such as AmBisome show the same infusion reactions, but also here it is mentioned that these reactions can be prevented by applying slow infusion rates.[343]

In contrast to liposomes, other intravenous phospholipid-based solubilising formulation types such as o/w emulsions and mixed micelles show hardly any infusion-related reactions. The available product leaflet of the intravenous mixed micellar products comprising SPC and sodium glycocholate in the product Konakion MM mentions that side effects regarding the immune system are scarce, meaning that the frequency of occurrence is less than 1 out of 10.000.[324] An intravenous o/w emulsion with EPC as emulsifier used for parenteral nutrition (Intralipid) show in less than 1% of the administrations, an increase of body temperature and chills, which cannot be considered as severe hypersensitivity reactions. In addition, it is mentioned that the reporting frequency of other undesired side effects is less than 1 out of a million.[329a]

In sharp contrast, the synthetic detergent-containing solubilising formulations show a higher tendency towards the occurrence of hypersensitivity infusion reactions. For instance, Taxotere containing polysorbate 80 shows very often (*i.e.*, ≥ 1/10 cases) the event of significant reactions; 5.3% with grade 3/4. In addition, it is not allowed to repeat the treatment.[344] Also, paclitaxel shows significant hypersensitive response in less than 1% of the patients. Repeating the treatment is also not allowed. The Cremophor EL (Polyoxyl 35 Castor Oil) component is mentioned as a possible cause for the hypersensitivity reactions.[345] Also Polyoxyl-15-hydroxystearate (Kolliphor HS15, in the past

Solutol HS 15) failed as solubiliser because an aprepitant product using this solubiliser (Varubi) was withdrawn from the market due to the high incidence of anaphylaxis shock.[129] In addition, synthetic detergents may be disadvantageous after oral administration as well. Recent studies on the impact of polysorbate 80 on the microbiome in the gut showed that polysorbate may cause bacterial translocation across the intestinal epithelium, intestinal inflammation, and metabolic syndrome.[346]

Although phospholipids on their own do not have an allergy potential, phospholipids derived from soybean and hen egg yolk must be labelled as potential allergens because of the soy and egg origin.[347] It is known that residues of soy and egg proteins may cause these allergies. In purified soybean phospholipids used for pharmaceutical application, the protein residues were found to be below the lower limit of detection (LLOD) of a soybean specific ELISA (enzyme-linked immunosorbent assay) assay which was 3 ppm.[348] The egg protein content of purified egg lecithin for parenteral administration was tested by Lipoid GmbH.[349] The most sensitive immunological detection method of proteins showed less than a LLOD of 2 ppm of egg protein in purified egg phospholipids. However, from the immunological perspective regardless of any protein present, the origin of such products has, according to regulatory authorities, to be labelled to alert allergic individuals. In a recent study on propofol emulsion with soybean oil and egg lecithin as emulsifier and its parenteral use in children with allergies to egg, peanut, soybean, or other legumes, it was concluded that genuine severe allergic reaction to the product was rare and was not reliably predicted by a history of food allergy.[350]

Based on these findings, the authors believe that as part of pharmaceutical development activities, (phospho)lipid-based systems should always be considered as viable alternatives to synthetic detergent formulations for solubilising poorly water-soluble compounds for intravenous administration. In contrast to synthetic detergent formulations, liposomes, mixed micelles, and o/w emulsions are preferred as solubilising formulations, as there is no hypersensitivity risk. Due to the presence of bile salts, mixed micelles are typically used for small volume parenterals as well as oral liquids. A significant advantage is that a mixed micellar solution is thermodynamically stable and can be produced without high pressure homogenisation. The rare incidence of allergic reactions to purified natural phospholipids is restricted to small patient populations, which are mostly aware of their allergies. In contrast, allergic reactions to synthetic detergents may occur in any patient.

The examples in **Table 5** show that liposomes/phospholipids can also be used for making injectable line extensions with retarded release properties. So far, this approach is limited to the use of the DepoFoam technology (see above). This technology is challenging with respect to manufacturing since the entire production process must be carried out under aseptic conditions. A terminal sterilisation procedure is not possible. Therefore, it is to be expected that alternative technologies will be developed. Ideas in this direction are using *in situ* aggregated negatively charged liposomes[351] or injectable extrudates with hydrogenated soybean phospholipids as depot formulations.[352] These depots should cover the drug release window from days up to 2–4 weeks, which are presently not covered by formulations with polymers like poly(lactic-*co*-glycolic acid) (PLGA). The FluidCrystal injectable depot technology of Camurus, based on *in situ* formation may be a simpler alternative. The introduction of the slow-release injectable for buprenorphine (Buvidal/Brixadi) on the market underscores the viability of this technology.

Conversion from an oral dosage form to an inhalation form, which should act locally, show an interesting novel use of saturated phospholipids and $CaCl_2$ to develop inhalation powders (**Table 6**).

Also, in this case, the physicochemical properties of these phospholipids are ideally combined with the biocompatibility of these saturated phospholipids with lung tissue, which also contains saturated phospholipids.[353] The resulting products with antibiotic allow the local treatment of lung infections. The possible clinical benefits of Tobi Podhaler were, however, only compared to a placebo and not to the oral therapy with Tobramycin.[354]

The phospholipid-based line extension for inhalation purposes are challenging from clinical and technical development point of view (**Table 6**). For administration of antibiotic for local effects, the PulmoSphere technology had to be developed, and the usefulness of the inhaled antibiotic had to be proven clinically. For tobramycin this is the case, for ciprofloxacin not (yet). The inhalation forms of levodopa and acetylsalicylic acid use saturated phospholipids to make powders for inhalation, which must meet the highest requirements for particle size, particle size distribution, and flowability. The clinical development of this type of line extensions maybe less demanding compared to the locally acting line extensions because a fast onset of action and systemic absorption is envisaged, the latter one being well-described for the original oral products. Much more demanding is the development of liposomes for a desired slow-release use for antibiotics acting locally. Such development requires nebulisation of the liposomes, analysis of change of particle size, loss of encapsulated drug, co-administration of an initial dose, etc. The development of such a concept was successful for amikacine (Arikayce) but failed for ciprofloxacin. The Arikayce product is, however, for the time being only approved for a very limited medical indication in the US. The EMA was not convinced by the therapeutic profile of this product. The development difficulties of this type of slow-release formulations may be related to the absence of data of the inhaled antibiotics without liposomes. Basically, two steps towards potentially better products have been made simultaneously, by exploring inhalation therapy with an antibiotic which has never been used like that before and on top of that the development of a sophisticated, technologically challenging, dosage form.

Conversion from an oral dosage form to a dermal product using phospholipids (**Table 7**) is mainly related to the reputation of liposomes and their claimed excellent skin interaction. It cannot be objectively assessed whether the favourable skin interaction of the developed dermal Pharmaceutical Form Line Extension is caused exclusively by the liposomes. Alternatively, these positive effects may be achieved by other dosage forms (either without phospholipids or alternative phospholipid-based formulations such as o/w emulsions or mixed micelles). Nevertheless, the liposomes represent a skin-compatible and cosmetically appealing formulation with an excellent marketing story. The drug class in focus of this approach are the NSAIDs. The popularity of this approach offering a local treatment without systemic side effects (mainly gastric irritation) underscore that this type of line extensions are valuable products, also in terms of sales of such products.

The conversion from a parenteral dosage form to a dermal dosage form (**Table 8**) addresses the medical need that for some indications only local treatment may be beneficial while the toxicity of systemic administration of the drug can be avoided/suppressed (*e.g.*, example with amphotericin B). Such line extensions also address that some patients have a needle phobia. For instance, a locally acting anaesthetic instead of a local injection is a relief for such patients. Such an approach requires that the guaranteed effect obtained by the local injection is maintained after local treatment with a dermal dosage form during an adequate period. In case of heparin (LMWH), the liposomal formulation cannot penetrate that deeply into the skin as an injectable since the dermal form is more suitable to treat superficial venous thrombosis rather than deep venous thrombosis.

The dermal line extensions provided in **Table 9** are examples of products containing phospholipids with claimed advantages. The azelaic acid gel with phospholipid contains a lower concentration of the active compared to the cream, suggesting that the gel is more efficacious. The actual reason to take the lower percentage of azelaic acid was, however, not a difference in efficacy, but a galenical issue preventing a higher percentage of azelaic acid in the line extension with the phospholipid-containing gel formulation. As far this increase of efficacy is caused by the presence of the phospholipid is unclear, since systematic studies on this aspect are missing.

The dermal products (*e.g.*, Sensiderm and Physiogel AI) with added saturated phospholipids like HSPC are claimed to have skin barrier restoring effect, due to the presence of skin-like, lamellar structures, which ideally fit in the skin structure.

The Diclac liposomal gel is an interesting example to circumvent existing patents protecting an attractive commercial product, which does not contain phospholipids. The Diclac gel demonstrates that the skin interaction of the liposomal gel with diclofenac sodium is equivalent to the Emulgel which uses a specific lipophilic diethylamine salt of diclofenac. The liposomal gel with dithranol was at least as clinically efficacious as a dithranol ointment with salicylic acid. The phospholipid-containing formulations were found to be non-irritating and therapeutically more effective even at dithranol concentrations of 0.5% as compared to a dithranol ointment containing 1.1% dithranol. The specificity of the effect caused by solubilisation of the compound in comparison with other solubilising formulations has not been presented. As mentioned above, regarding line extension converted to the dermal application, the value of these line extensions is also based on marketing statements rather than sound scientific evidence. The comparison of the degree of skin interaction of original and line extension product using *in vitro* models using healthy (fresh) skin samples (*e.g.*, Franz Cell) may show qualitative differences but may be irrelevant for the diseased skin on the patient. Also, preclinical assessment using animal skin models are at the maximum indicative for differences in skin interaction because the skin of animals is different from the human skin. In the assignment of a claimed skin effect on a specific component, the presence of other excipients in a dermal product must be considered which may have overlapping properties.

The oral line extensions in **Table 10** are based on the property of phospholipids to complex with NSAIDs and to suppress the gastric irritation potential of this compound class. It appears that the product development of these products takes a very long time. The future will show whether these products with acetylsalicylic acid and ibuprofen, respectively, can conquer significant market shares of the oral NSAIDs. Another example of oral use of phospholipids is demonstrated by the product Rapamune. A non-aqueous concentrate of phospholipids (*e.g.*, PHOSAL 50 PG) is utilised here to solubilise the poorly soluble drug substance. The liquid oral dosage form is a viable line extension and it is used as immunosuppressant besides tablets, which contain the nano-sized drug substance. Such liquid concentrates may accelerate the pharmaceutical dosage form development, gives great dose flexibility, and enable a quick introduction of the product on the market.[312]

Most databases on the paediatric use of excipients only mention the excipients, which may cause problems for this patient population.[355] The developer of a dosage form would like to know as well which excipients can be used. Based on the prescription information and the phospholipid compositions, this review should provide some information on the paediatric intravenous administration of selected phospholipids. The paediatric oral use of phospholipids (soybean) is in general allowed, of course with precautions for soybean allergy. Sunflower phospholipids, with no

allergy warnings, are available today. Also, the paediatric dermal use of soybean phospholipids, natural and hydrated, is unproblematic.

It is out of the scope of this review to analyse the ROI of the provided line extensions. Anyway, the presented products were, in most cases, protected by additional patents. It is not exceptional that patents covering the line extensions have been issued 10–20 years after the market introduction date of the original product. These patents should carefully describe the phospholipids, which are suitable and preferred for the envisaged products. To do this accurately, a piece of in-depth knowledge on the availability of the many eligible phospholipids and formulation options is necessary to define the protecting IP of the product accurately. It is also clear from the description of the obtained line extensions that in all cases, such products must represent clear advantages for the patients. Together with the existence of these products on the market, it can be assumed that the line extensions represent commercially attractive products.

From the mentioned companies involved in the development of the line extensions, it can be derived that mostly small and mid-size companies are playing a role nowadays. In contrast, most big-pharma companies do not pursue the development of line extension products as a priority but may prefer to license in commercially attractive options. An example how such line extension enters the market is Doxil, which was developed by the small liposome company LTI (Menlo Park, CA, USA) and through the acquisition of Alza Corporation (Palo Alto, CA, USA) ended at J&J Pharmaceuticals. Gilead Sciences Inc.[241] and Taiwan Liposome Company,[356] respectively, are examples of companies pursuing and exploring especially liposome-based line extensions. Since mainly smaller companies are involved, it is no surprise that many line extensions change their owner or even developer during the development phase and marketing phase. The available resources of such companies are apparently not adequate to perform and finance the complete technical and clinical development.

Recently, METSELAAR and LAMMERS reviewed the challenges in nanomedicine clinical translation.[4] They define the challenges in the categories of commercial and practical feasibility, clinical development feasibility, translating preclinical efficacy to clinical outcome, bridging preclinical toxicity to patient safety, and fulfilling CMC (chemistry, manufacturing, and control) requirements. These considerations partially overlap with the general challenges a developer of Pharmaceutical Form Line Extension is facing. They apply particularly for liposomal products with increased therapeutic index. These authors refer to comparator products as a clinical reference. In most cases of line extensions, the comparator is the original product without the nano-medicine carrier, in this case, the liposome. The clinical research strategy is clear most of the time: suppression of toxicity and at least maintenance of efficacy of the original product. Recently, JENSEN and HODGSON[241] presented a few examples of the development of liposomal line extensions at Gilead. They conclude that also technical issues, such as lack of stability or cumbersome manufacturing methods, may be hurdles. At the end of the day, however, the overall ROI of such line extensions played a decisive role. Other line extensions, not related to challenging intravenous carriers like liposomes, which change the distribution and kinetics of the drug substance, may have lower technical hurdles to develop. The clinical development may, however, be equally challenging, dependent on the benefits the line extensions should have and which product will be used as a comparator (placebo or original product). The technological hurdles for the Pharmaceutical Form Line Extensions are relatively low because of the versatility, biocompatibility, and biodegradability of the phospholipids in combination with standard formulation technology. Also, the large-scale availability of pharmaceutical-grade phospholipids is helpful. In some cases, however, the dosage form development for the inhalation

route may be quite challenging. The presented products in this review demonstrate that phospholipid-based Pharmaceutical Form Line Extensions are not restricted to parenteral liposome products, but that phospholipids are well-suited pharmaceutical excipients in many other formulation types and any route of administration.

8. Conclusions

This review describes the use of phospholipids as key excipients for the development of Pharmaceutical Form Line Extensions as part of Product Life Cycle Management. Based on the provided product and development examples, conclusions can be drawn that phospholipids 1) are suitable to convert dosage forms for other administration routes, 2) can act as an alternative solubiliser to reformulate products containing potentially toxic synthetic detergents and/or organic solvents for parenteral administration of lipophilic compounds, 3) can be used in liposomal form to increase the therapeutic index of toxic cytostatics and antifungals for parenteral administration, 4) allow in liposomal form for slow release of the encapsulated drug substance, 5) serve to formulate inhalation products, for local treatment, systemic treatment, or local slow release, 6) improve the oral administration of NSAIDs, 7) may serve as a component in liquid oral dosage forms as alternative to solid dosage forms for lipophilic compounds, 8) are suitable in dermal products for enhancing the skin interaction of the drug substance, and 9) are very well suited for application in paediatric products.

These versatile properties are related to the non-toxicity, biodegradability, and biocompatibility of phospholipids for any administration route and their technical function as natural surfactant with emulsifying, wetting, liposome forming properties, which are very suitable to make dosage forms with drug targeting, solubilising, bioavailability enhancing, and drug release retarding properties.

The resulting line extensions present more attractive innovative products. Compared to the original products, they may have a better safety profile and/or are more efficacious and, in general, they may have an increased convenience of use.

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Conflict of interest

Peter van Hoogevest is also Head of the Scientific Department of Lipoid GmbH, Ludwigshafen am Rhein, Germany.

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