Phospholipid Research Center

The Use of Phospholipids to make Pharmaceutical Form Line Extensions

LIPIDS 2021

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How to get new products in Pharmaceutical Industry

1. NCE (New Chemical Entity)

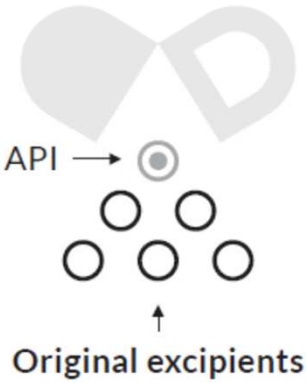
2. Pharmaceutical Form Line Extension

   - Another Dosage Form for the same Drug Substance

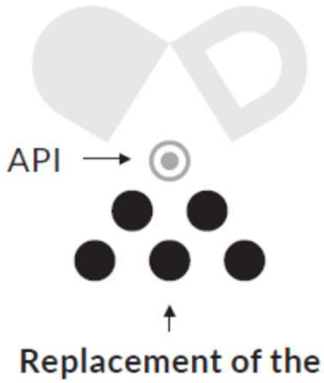
Reference:
van Hoogevest P, Tiemessen H, Metselaar JM, Drescher S, Fahr A, **2021**
The Use of Phospholipids to make Pharmaceutical Form Line Extensions,
Eur. J. Lipid Sci. Technol., 2000297.

How to get new products in Pharmaceutical Industry

Original Drug Product



Pharmaceutical Form Line Extension



Improvement of the Original Drug Product

- Enabling Other Administration Routes
- Increasing Therapeutic Index
- Replacing Toxic Excipients
- Inducing Slow Release
- Increasing Skin Interaction
- Suppressing Toxicity of NSAIDs
- Enabling Paediatric Use

Product Life Cycle Strategy

- Increasing IP Protection
- Prelonging Product Sales Period

Pharmaceutical Form Line Extensions: Several Administration Routes

(A) **Parenteral** Pharmaceutical Form Line Extensions

(B) **Inhalation** Pharmaceutical Form Line Extensions

(C) **Dermal** Pharmaceutical Form Line Extensions

(D) **Oral** Pharmaceutical Form Line Extensions

(E) Suitability of phospholipids for **paediatric** Pharmaceutical Form Line Extensions

Suitability of Phospholipids

Physiological excipients:

- Biocompatible
- Biodegradable
- Safe in use after oral, dermal, inhalation, and parenteral administration

Multifunctional technical use:

- Emulsifier
- Liposome former
- Wetting agent

Industrial availability:

- Natural and synthetic phospholipids

(A) Parenteral Pharmaceutical Form Line Extensions

- Conversion from oral to the parenteral administration route
- Improving the therapeutic index of parenteral drugs
- Replacing toxic excipients in parenteral dosage forms
- Extending release properties of parenteral dosage form

(1) Conversion from Oral to Parenteral

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 **PHOSPHOLIPIDS AS KEY EMULSIFIER/ SURFACTANT**
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)	

(1) Conversion from Oral to Parenteral: Role of Phospholipids

- Enable production of parenterally acceptable oil-in-water emulsions with Egg PC as emulsifier; the lipophilic drug substance is dissolved in the oil phase.

- Enable production of mixed micelles with soybean phospholipids and bile salts; the lipophilic drug substance is dissolved in mixed micelles.

(2) Improving Therapeutic Index of Drug Substance I

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)

(2) Improving Therapeutic Index of Drug Substance II

API (Class)	Originator Product Dosage form and (product example)	Line Extension Product Dosage form and (product)
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)

(2) Improving Therapeutic Index of Drug Substance: Role of Phospholipids

- Phospholipids are essential components of liposomes, which target the drug substance to the site of action (EPR effect; or macrophage targeting) and avoid tox-target organs.

(3) Replacing 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

(3) Replacing toxic excipients: Role of Phospholipids

- Act as alternative solubiliser or emulsifier in mixed micelles or emulsions, respectively, to avoid anaphylactic reactions caused by *iv* administration of synthetic detergents like polysorbates (Tween 20 or 80), Cremophor, or Solutol.

(4) Extending 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)
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)

(4) Extending release properties: Role of Phospholipids

- Form multivesicular liposomes which slowly release the encapsulated water soluble drug.

(B) Inhalation Pharmaceutical Form Line Extensions

- Conversion a liquid inhalation form into a solid inhalation form
- Enabling local treatment
- Enabling systemic treatment with fast onset of action
- Extending release properties of the inhalation dosage form

(1) Converting a liquid into a solid dosage form

API (Class)	Originator Oral Product Dosage form and (product example)	Line Extension Product Dosage form and (product)
Tobramycin (Antibiotic)	Aqueous solution Tobramycin injection (Bethkis, inhalation solution)	Powder for inhalation with DSPC-$CaCl_2$ (Tobi Podhaler)

Role of Phospholipids:

- Phospholipids enable the formation of porous powder particles suitable for Dry Powder Inhaler devices to replace administration by means of a nebulizer.

(2) Enabling local lung treatment instead of oral systemic treatment

API (Class)	Originator Oral Product Dosage form and (product example)	Line Extension Product Dosage form and (product)
Ciprofloxacin (Antibiotic)	Tablet (Cipro)	Powder for inhalation with DSPC-$CaCl_2$ (Ciprofloxacin DPI, development stage)

Role of Phospholipids:

- Phospholipids enable the formation of porous powder particle suitable for Dry Powder Inhaler devices to replace oral systemic administration.

(3) Enabling systemic treatment with fast onset of action

API (Class)	Originator Oral Product Dosage form and (product example)	Line Extension Product Dosage form and (product)
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)

Role of Phospholipids:

- Phospholipids enable the formation of porous powder particle suitable for Dry Powder Inhaler devices to replace oral systemic administration.

(4) Extending release properties of the inhalation dosage form

API (Class)	Originator Product Dosage form and (product example)	Line Extension Product Dosage form and (product)
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)

Role of Phospholipids:

- Phospholipids are essential components of liposomes, which slowly release the hydrophilic drug substance after administration by means of a nebulizer.
- In addition, targeting to macrophages containing pathogens may be possible.

(C) Dermal Pharmaceutical Form Line Extensions

- Conversion from oral to dermal administration
- Conversion from parenteral to dermal administration
- Improving skin interaction

(1) Conversion from oral to dermal administration

API (Class)	Originator Product Dosage form and (product example)	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)	

Role of Phospholipids:

- Enable formulation of the drug substance in skin-compatible dosage forms, with the claim that the phospholipids (*e.g.* liposomes) enhance skin interaction.

(2) Conversion from parenteral to dermal administration

API (Class)	Originator Product Dosage form and (product example)	Topical Line Extension Product Dosage form and (product example)	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

(2) Conversion from parenteral to dermal administration: Role of Phospholipids

- Enable formulation of the drug substance in skin-compatible dosage forms, with the claim that the phospholipids (*e.g.* liposomes) enhance skin interaction.

(3) Improving skin interaction

API (Class)	Originator Product Dosage form and (product example)	Line Extension Product Dosage form and (product example)	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 Al)	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

Role of Phospholipids: As described before.

(D) Oral Pharmaceutical Form Line Extensions

- Suppressing gastric irritation of NSAIDs

(1) Suppressing gastric irritation of NSAIDs

API (Class)	Originator Product Dosage form (product example)	Line Extension Product Dosage form and (product example)	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)	

Role of Phospholipids:

- make complexes with the drug substance
- form protective layer of the gastric mucosa
- interferes with prostaglandin metabolism.

(E) Paediatric Pharmaceutical Form Line Extensions

- Intraveneous paediatric use
- Oral paediatric use

(1) Intravenous paedriatic use

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

(2) Oral paedriatic use

- Phospholipids of natural (soybean) origin are odourless or have a characteristic, slight nutlike odour and bland taste in contrast to polysorbates, which have a bitter taste.

- SPC is used in oral products; EFSA assessed the safety of oral use of lecithin (E 322, food codex): 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).

- 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.

PHOSPHOLIPIDS
IN LINE EXTENSIONS

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Natural Phospholipids

Soybean PC, Egg PC

- **Oral**
- **Dermal**
- **Parenteral**

Synthetic Phospholipids

DMPC, DMPG, DPPC, DSPC, etc.

- **Parenteral**

PHOSPHOLIPIDS
IN LINE EXTENSIONS

CONCLUSIONS

Phospholipids are interesting and unique excipients to develop pharmaceutical form line extensions as part of a product life cycle management strategy.

In accordance, with their excipient profile and physicochemical properties, they are used for any administration route, for drug targeting, slow release, increase of bioavailability and technological improvement of dosage forms.

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Thank you for your attention!