同写意论坛第 70 期活动

Excipients in Parenteral Drug Products

Wenlei Jiang, PhD
Senior Science Advisor
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

珠海·珠海德翰大酒店
2018年3月13-15日

Disclaimer: This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

目

录

- Parenteral drug product/excipients
- General consideration for parenteral excipient selection
- Excipients in complex parenteral products
- Challenges of excipient selection in generic complex parenteral product development and research opportunities

Parenteral Drug Products

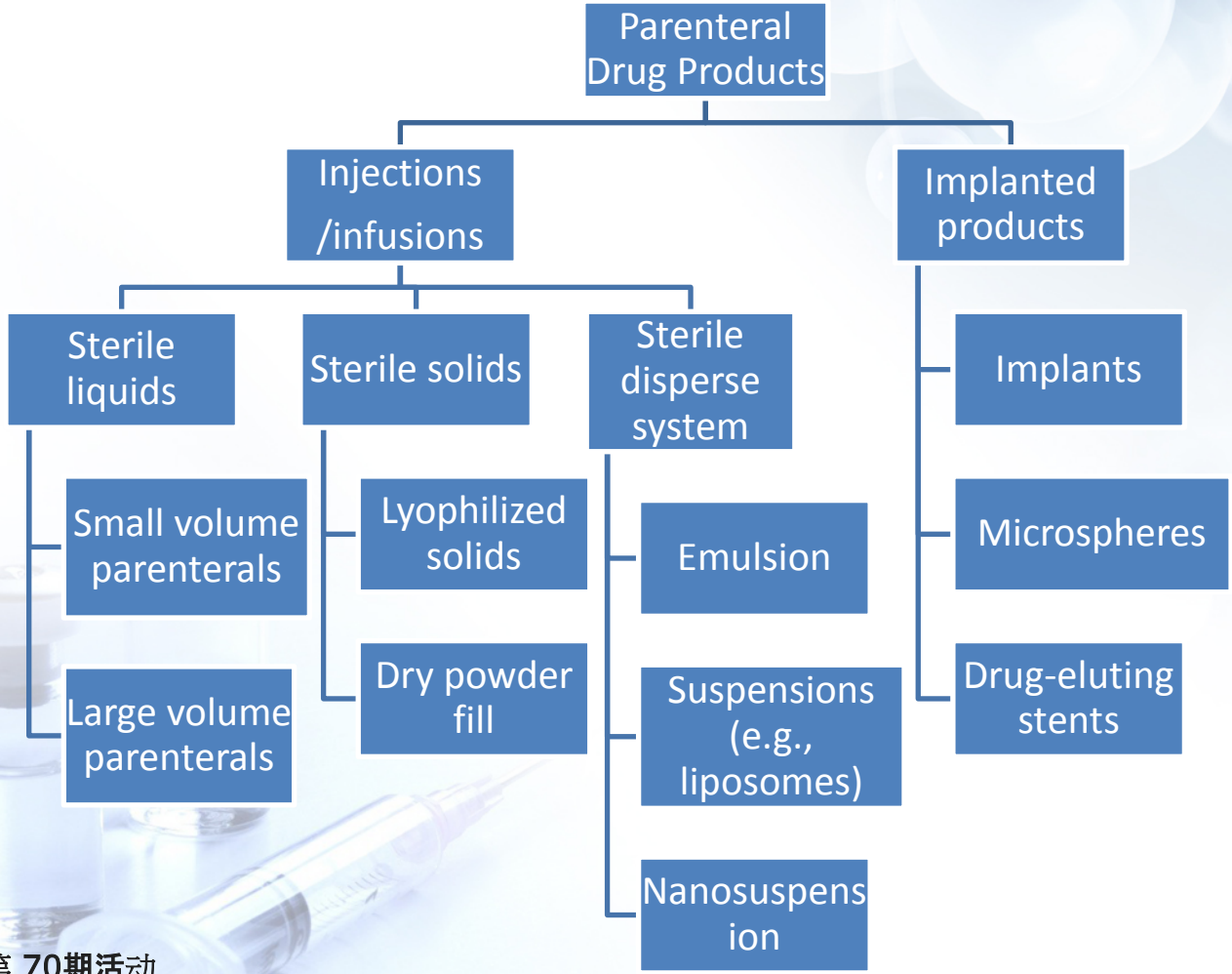
- Injections and implanted drug products

  - Injected through the skin or other external boundary tissue,

  - Implanted within the body to allow the direct administration of the active drug substances into blood vessels, organs, tissues, or lesions.

- Routes of administration

  intravenous (i.v.), intramuscular (i.m.), subcutaneous (s.c.), intraventricular, intra-arterial, intra-articular, intrathecal, intracisternal, and intraocular


Parenteral Drug Products
Injections /infusions
Implanted products
Sterile liquids
Sterile solids
Sterile disperse system
Implants
Small volume parenterals
Large volume parenterals
Lyophilized solids
Dry powder fill
Emulsion
Suspensions (e.g., liposomes)
Nanosuspension
Microspheres
Drug-eluting stents

Unique Aspects of Parenteral Drug Products

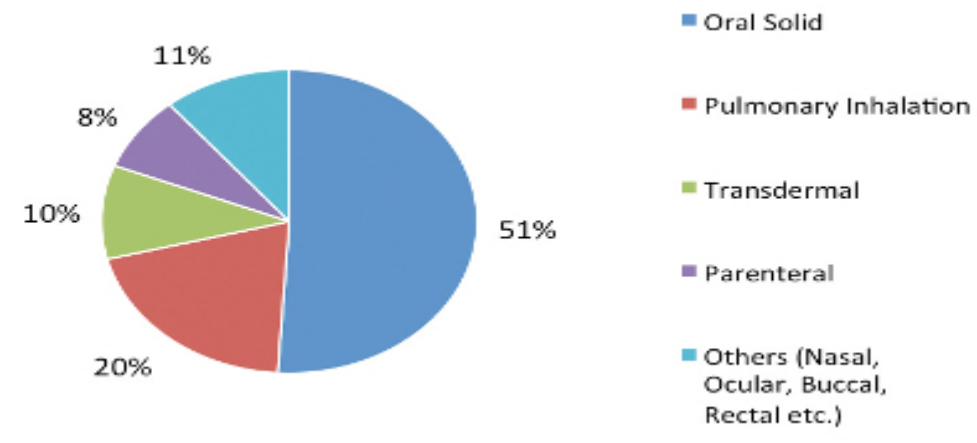
- Sterile
- Pyrogen free
- Free of particulate matter (for solutions)
- No coloring agent solely for the purpose of coloring
- Isotonic (preferably)
- Administration device needed

Excipients

- Excipients are components of a finished drug product other than the active pharmaceutical ingredient (API)

- Excipients are added during formulation for a specific purpose

Unique Aspects of Parenteral Excipients



http://www.americanpharmaceuticalreview.com/Featured-Articles/182921-Drug-Shortages-and-Excipient-Opportunities-A-Parenteral-Excipient-Market-Analysis/

- Ultra high purity grades
- Bioburden and endotoxin limits of excipients shall be stated.
- Withstand terminal sterilization or aseptic processing
- Higher cost, low volume, limited supplier base
- GRAS (Generally Recognized as Safe) excipient not necessarily deemed safe for use in parenteral products

Types/Functions of Parenteral Excipients

- Solvents and cosolvents
- Solubilizing, wetting, suspending, emulsifying, or thickening agents
- Chelating agents
- Antioxidants
- Preservatives
- Buffers
- Bulking agents, protectants, and tonicity adjusters
- Other special functions

Impact of Excipients on Parenteral Drug Products

- Solubility
- Stability
- Sustained release functions
- Manufacturability
- Safety
- Injection/infusion site irritation
- biocompatibility

Parenteral Excipient Selection with Drug Property in Mind

- Use salt formation/co-solvent/surfactant/complex approach to improve solubility
- Select proper pH, buffer, antioxidants, and/or manufacturing process to reduce drug degradation
- Choose additional excipients to support appropriate manufacturing process to improve drug stability

Parenteral Excipient Selection with Manufacturing Process in Mind

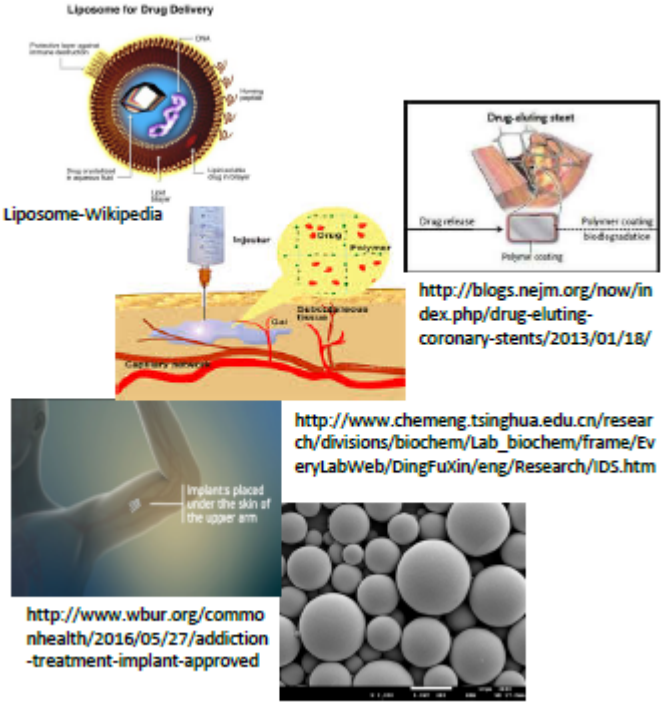
- Lyophilized products
  - Additional bulking agents for lyophilized formulation if needed
  - Select buffers with a small Δp*K*a/°C.
  - Select buffers that do not crystalize out but remain amorphous
  - Select buffers and preservatives not sublime
- Process equipment compatibility
  - Preservatives may be adsorbed by rubber tubes or filters

Parenteral Excipient Selection with Product Safety in Mind

- Note hemolytic potential of co-solvents
- Avoid mineral oil or paraffin which the body cannot metabolize
- Select optimal buffer strength to avoid infusion site irritation
- Use antimicrobial preservatives for multi-dose parenterals
- Caution excipient tolerability in special population/administration route
  - No preservatives for injections in contact with brain tissues or cerebrospinal fluid
  - Specific gravity
  - Children

Complex Parenteral Products

- Emulsions
- Liposomes
- Nanosuspensions
- In situ forming gels
- Drug-eluting stents
- Implants
- Microspheres



Emerging Parenteral Excipients

- Natural products, including naturally occurring polymers and derivatives
- Synthetic polymers or modifications
- Small molecules
- Modifications of natural products with synthetic polymers
- Modifications of natural products or polymers with small molecules

Tocopherol-PEG-succinate (antioxidant or solubilizer)

Sulfobutyl ethers of cyclodextrins (solubilizer)

Shireesh P.Apte* and Sydney O. Ugwu. A Review and Classification of Emerging Excipients in Parenteral Medications. *Pharmaceutical Technology MARCH 2003*

Generic Parenteral Products

- Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the [RLD] identified by the applicant under paragraph (a)(3) of this section.

- However, an applicant may seek approval of a drug product that ***differs from the [RLD] in preservative, buffer, or antioxidant*** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

21 CFR 314.94(a)(9)(iii)

Parenteral Products Labeling Requirements

- The United States and Europe require all excipients to be declared, along with their quantity, on the label

- In Japan only the excipient names are required in the labeling

Challenges of Excipient Selection for Generic Complex Parenteral Products

- Most complex parenteral products involve complex parenteral excipients which are mixtures or polymeric in nature
- Excipients can be from different origins and have concomitant (production related) components or processing aids
- Polymer degradation in the product may increase the difficulty of determining the molecular weight of the starting polymer material
- Lot-to-lot excipient variability
- Source-to-source excipient variability

↓

Difficult to define qualitative sameness of complex parenteral excipients

Excipients in Parenteral Emulsions

- Lipids
  - long-chain triglyceride (LCTs): triolein, soybean oil, safflower oil, sesame oil, and castor oil
  - Medium-chain triglyceride (MCTs): fractionated coconut oil, Miglyol® 810, 812, Neobee® M5, Captex® 300
- Emulsifiers
  - Lecithin
- Tonicity modifier
  - Glycerin, sorbitol, or xylitol
- Antioxidants
  - α-tocopherol, ascorbic acid, and deferoxamine mesylate
- Preservatives
  - sodium benzoate and benzyl alcohol

Complex Nature of Excipients in Parenteral Emulsion

Lipids	USP/NF	Definition	Additional requirements for injectables
Soybean oil	USP	refined fixed oil obtained from the seeds of the soya plant Glycine max Merr. (Fam. Fabaceae). It may contain suitable antioxidants	Unsaponifiable Matter, Acid Value, Peroxide Value, and Water
Castor oil	USP	Castor Oil is the fixed oil obtained from the seed of Ricinus communis L. (Fam. Euphorbiaceae). It contains no added substances.	
Medium chain triglycerides	NF	a mixture of triglycerides of saturated fatty acids, mainly of caprylic acid and capric acid.	
Lecithin	NF	a complex mixture of acetone-insoluble phosphatides	NMT 3.0% of lysophosphatidylcholine NLT 70.0% phosphatidylcholine

Different Standards in Different Regulatory Directives

Table 15. Description of soybean lecithin in regulatory directives

Pharmacopeia/directive	Food chemicals codex	231/2012 EC	NF 31	CP 2010	JPE 2004
Monograph number	INS: 322	E 322	–	–	106893
Monograph title	Lecithin	Lecithins	Lecithin	Soya lecithin	Soybean lecithin
Special characteristics	From soybeans and other plant sources	Animal or vegetable origin; additional specifications for hydrolysed lecithins	Origin from the crude vegetable oil source	Extracted and refined from soybean	From soybean, composed mainly of phospholipid
Acetone-insoluble matter	n.l.t. 50.0%	n.l.t. 60.0%	n.l.t. 50.0%	n.l.t. 90.0%	n.l.t. 60%
Toluene-insoluble matter	–	n.m.t. 0.3%	–	–	–
Hexane-insoluble matter	n.m.t. 0.3%	–	n.m.t. 0.3%	n.m.t. 0.3%	–
LPC content/ LPE content	–	–	–	n.m.t. 3.5% /n.m.t. 0.5%	
Water content or loss on drying	n.m.t. 1.5%	n.m.t. 2.0%	n.m.t. 1.5%	n.m.t. 1.5%	n.m.t. 1.5%
Peroxide value	n.m.t. 100	n.m.t. 10	n.m.t. 10	n.m.t. 5	n.m.t. 10
Acid value	n.m.t. 36	n.m.t. 35	n.m.t. 36	n.m.t. 30	n.m.t. 40
Iodine value	–	–	–	n.l.t. 75	–

n.l.t., not less than; n.m.t., not more than.

Peter van Hoogevest and Armin Wendel, The use of natural and synthetic phospholipids as pharmaceutical excipients. Eur. J. Lipid Sci. Technol. 2014. 116, 1088-1107

Excipients in Liposome Formulations

Product	Drug name	Administration route	Approval date	Lipids used
Doxil	Doxorubicin liposome	Intravenous	11/17/1995	Cholesterol, fully hydrogenated soy phosphatidylcholine (HSPC), MPEG-DSPE
DaunoXome	Daunorubicin liposome	Intravenous	04/08/1996	Distearoylphosphatidylcholine (DSPC), cholesterol
AmBisome	Amphotericin B liposome	Intravenous	08/11/1997	Hydrogenated soy phosphatidylcholine (HSPC), cholesterol, distearoylphosphatidylglycerol (DSPG)
Visudyne	Verteporfin	Intravenous	04/12/2000	egg phosphatidylglycerol, dimyristoyl phosphatidylcholine
Marqibo	Vincristine sulfate liposome	Intravenous	08/09/2012	Sphingomyelin/Cholesterol
Onivyde	Irinotecan hydrochloride	Intravenous	10/22/2015	1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE)

Complex Nature of Liposome Excipients

- Cholesterol, the only liposome lipid excipients which has NF monographs, in product label
  - No information about the stabilizer
  - No information about the source

- Multiple sources of lipids (synthetic, natural, semi-synthetic)

- Phospholipids isolated from animal sources may sometimes be complicated by the occasional occurrence of animal diseases

Regulatory Consideration on Phospholipid Selection

- Same origin of lipids used in the generic formulation
- Same details as the API
- Control of lipid components

  A. Description and characterization of lipid components
  B. Manufacture of lipid components
  C. Specification for lipid components
  D. Stability of lipid components

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070570.pdf

Parenteral Implants, Microspheres and Excipients

Approved Products	Dosage forms	Drug	Administration route	Polymer used
Probuphine	Implant	Burprenorphine	Subdermal	Ethylene vinyl acetate (EVA)
Ozurdex	Implant	Dexamethasone	Intravitreal	Poly (D,L-lactide-co-glycolide) PLGA
Zoladex	Implant	Goserelin	Subcutaneous (SC)	D,L-lactic and glycolic acids copolymer
Risperdal Consta	microspheres	Risperidone	Intramuscular (IM)	75:25 polylactideco-glycolide (PLG)
Sandostatin LAR depot	microspheres	Octreotide	IM	biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer
Vivitrol	microspheres	Naltrexone	IM	75:25 polylactideco-glycolide (PLG)
Lupron Depot	microspheres	Leuprolide	IM	Polylactic acid
Trelstar	microspheres	Triptorelin	IM	Poly-d,l-lactide-co-glycolide
Bydureon	microspheres	Exendatide	SC	50:50 poly(D,L-lactide-co-glycolide) polymer

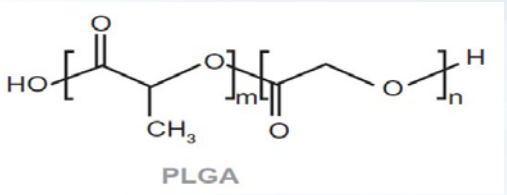
Parenteral In-situ Gels and Excipients

Product	Drug	Regulatory status	Administration route	Gel forming mechansims	Polymer used
Eligard	Leuprolide acetate	Approved	SC	In situ phase separation, solvent exchange	poly (DL-lactide-co-glycolide) (PLGH or PLG)
Atridox	Doxycycline hyclate	Approved	into the peridontal pocket	Same as above	poly(DL-lactide) (PLA)
Product A	N.A.	In development	N.A.	Same as above	**sucrose acetate isobutyrate**
Product B	N.A.	In development	N.A.	Same as above	**sucrose acetate isobutyrate**
Product C	N.A.	Development halted	N.A.	Thermally-induced	PLGA-PEG-PLGA

Regulatory Consideration on PLGA Sameness

- **Characterization of PLGA**
  - Polymer composition (L to G ratio)
  - Molecular weight and weight distribution
  - Polymer architecture (linear vs star-shaped)
  - Intrinsic viscosity
  - Glass transition temperature
  - Polymer end-cap
  - Crystallinity

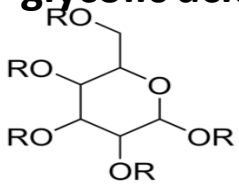
Poly(lactic-*co*-glycolic acid) (PLGA) copolymer

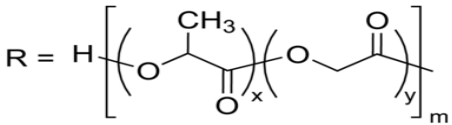


PLGA

m = number of units of lactic acid
n = number of units of glycolic acid
- Ratio of lactic acid to glycolic acid
- Molecular weight ~5kDa -100kDa

Glucose star polymer, D,L-lactic and glycolic acids copolymer





Garnera J et al. A protocol for assay of poly(lactide-co-glycolide) in clinical products. International Journal of Pharmaceutics 495 (2015) 87–92

Parenteral Excipient Research

- Conduct PLGA characterization
- Characterize cholesterol and other lipid excipients from different sources, lots, and manufacturers
- Investigate the Impact of different cholesterol/phospholipids on liposome formation and stability
- Harmonize regulatory standards for complex parenteral excipients

Conclusions

- Unique regulatory requirements for parenteral excipients
- Consideration of drug property, safety, and manufacturing process for parenteral excipient selection
- Emerging complex excipients for complex parenteral drug products
- Research opportunities for complex excipient characterization and excipient impact on complex parenteral drug products

Thank you!

Any Question?

wenlei.jiang@fda.hhs.gov

同筑技术人生路
写意中国新药魂

同写意
tongxieyi.com

www.tongxieyi.com

txy@tongxieyi.com

010-83634290　83634390

公众号：tongxieyi