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ADME Studies in Support of Development of Liposomal Formulations of Marketed Chemotherapeutics

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Presentation Outline

- Review of Liposomal Drug Delivery
- Regulatory Requirements for ADME/PK Data
- Case Study: CPX-351
  - Introduction to CPX-351 Development
  - Non-clinical ADME Study Results
- Summary

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Liposomal Drug Delivery

Liposomes – General Properties

- A **liposome** is an artificially-prepared spherical vesicle composed of a lipid bilayer.

- Liposomes are often composed of phosphatidylcholine-enriched phospholipids and may also contain mixed lipid chains with surfactant properties such as egg phosphatidylethanolamine. The major types of liposomes are the multilamellar vesicle (MLV), the small unilamellar vesicle (SUV), the large unilamellar vesicle (LUV), and the cochleate vesicle.

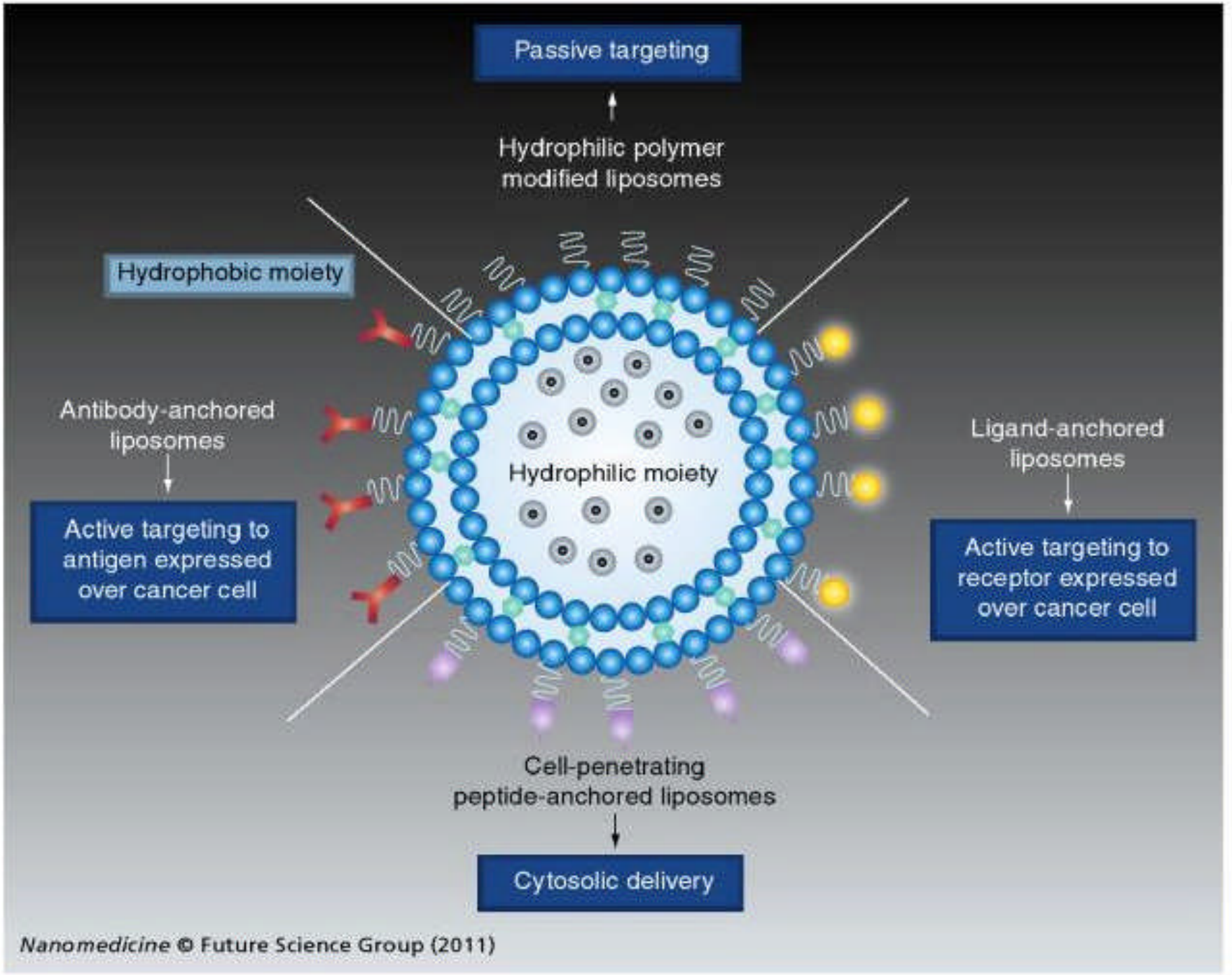
- A liposome encapsulates a region of aqueous solution inside a hydrophobic membrane; dissolved hydrophilic solutes cannot readily pass through the lipids. Hydrophobic chemicals can be dissolved into the membrane, and in this way liposome can carry both hydrophobic molecules and hydrophilic molecules.

- To deliver the molecules to sites of action, the lipid bilayer can fuse with other bilayers such as the cell membrane, thus delivering the liposome contents. By making liposomes in a solution of DNA or drugs (which would normally be unable to diffuse through the membrane) they can be (indiscriminately) delivered past the lipid bilayer.

Liposomal Drug Delivery

- By encapsulating a drug(s) in a liposome, the PK/PD profile may be improved compared to the non-liposomal form.

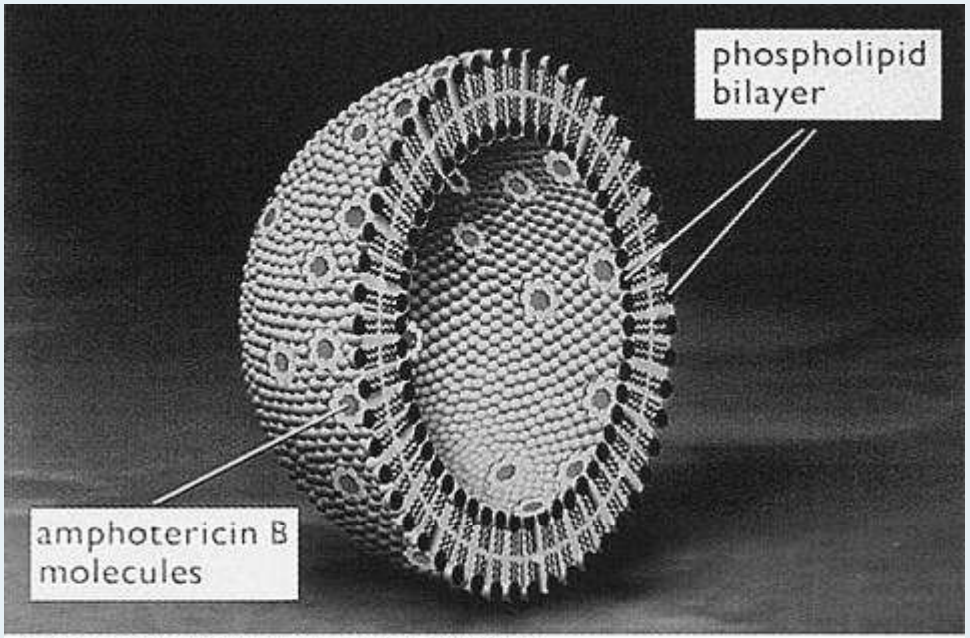
- Liposomal drug delivery systems may be designed to shape the drug disposition profile to:
  - increase the circulation time within the body (e.g. via protective PEGylation) avoiding detection “steath”, thus increasing the exposure profile to disease cells/tissues,
  - target (active (peptide or mab) or passive) and release within specific disease tissue types, and
  - minimize the harmful effects on healthy tissues (e.g. cardio or liver toxicity).


Passive targeting
Hydrophilic polymer modified liposomes
Hydrophobic moiety
Antibody-anchored liposomes
Active targeting to antigen expressed over cancer cell
Hydrophilic moiety
Ligand-anchored liposomes
Active targeting to receptor expressed over cancer cell
Cell-penetrating peptide-anchored liposomes
Cytosolic delivery
Nanomedicine © Future Science Group (2011)

List of Clinically Approved Liposomal Drugs as of 2012

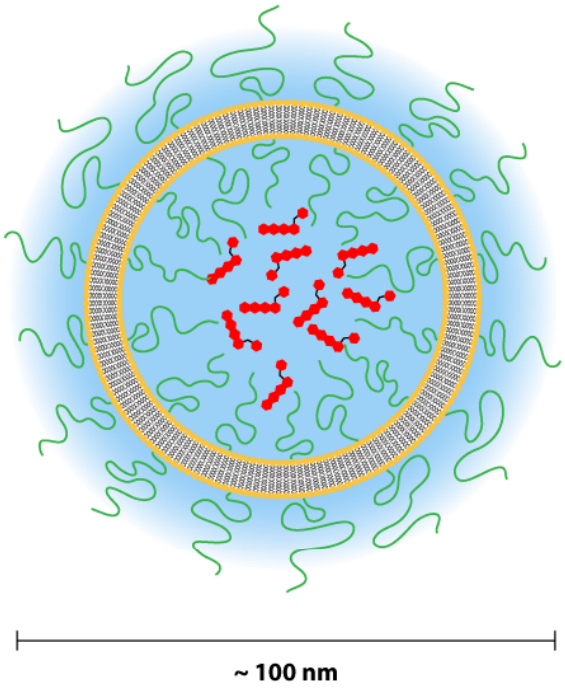
Name	Trade name	Company	Indication	Liposomal Excipients
Liposomal amphotericin B	Abelcet	Enzon	Fungal infections	DMPC, DMPG
Liposomal amphotericin B	Ambisome	Gilead Sciences	Fungal and protozoal infections	HSPC, Cholesterol, DSPG
Liposomal cytarabine	Depocyt	Pacira (formerly SkyePharma)	Malignant lymphomatous meningitis	DOPC, Cholesterol, DPPG
Liposomal daunorubicin	DaunoXome	Gilead	HIV-related Kaposi's sarcoma	DSPC, Cholesterol
Liposomal doxorubicin	Myocet	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer	LIPOVA-E120, Cholesterol
Liposomal IRIV vaccine	Epaxal	Crucell	Hepatitis A	LECIVA-S70
Liposomal IRIV vaccine	Inflexal V	Berna Biotech	Influenza	LECIVA-S90
Liposomal morphine	DepoDur	SkyePharma, Endo	Postsurgical analgesia	DOPC, Cholesterol, DPPG
Liposomal verteporfin	Visudyne	QLT, Novartis	Age-related macular degeneration pathologic myopia ocular histoplasmosis	Egg PG, DMPC
Liposome-proteins SP-B and SP-C	Curosurf	Chiesi Farmaceutici, S.p.A.	pulmonary surfactant for Respiratory Distress Syndrome (RDS)	Leciva-S90
Liposome-PEG doxorubicin	Doxil/Caelyx	Ortho Biotech, Merck	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer	MPEG-DSPE, HSPC, Cholesterol
Liposomal vincristine	Marqibo	Spectrum Pharmaceuticals	Acute Lymphoblastic Leukemia (ALL) and Melanoma	Cholesterol and egg sphingomyelin

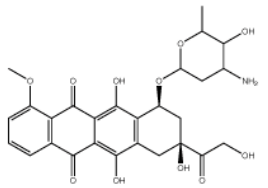
Lipid Soluble Drug in the Bilayer



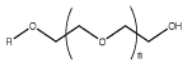
CROSS SECTION VIEW OF LIPOSOME

Hydrophilic Drug Contained within the Liposome





Doxorubicin



Polyethylene glycol [PEG]

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Liposomal Drug Development

Regulatory Requirements for ADME/PK Data

FDA *Draft* - Guidance for Industry (Aug, 2002)

Liposomal Drug Products – CMC; Human Pharmacokinetics and Bioavailability; Labeling and Documentation

Introduction

…"A drug substance in a liposome formulation is intended to exhibit a different pharmacokinetic and/or tissue distribution (PK/TD) profile from the same drug substance (or active moiety) in a nonliposomal formulation given by the same route of administration. ***The complete characterization of the PK/TD profile of a new liposome drug product is essential to establish the safe and effective dosing regimen of the product****"…*

This guidance does not cover clinical efficacy and safety studies or bioequivalence studies of those to document sameness.

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

III. Human Pharmacokinetics and Bioavailability

A. Bioanalytical Methods… *for liposomal drug products the bioanalytical method should also be capable of measuring encapsulated and unencapsulated drug substance.*

B. In Vivo Integrity (Stability) Considerations…*if the bioanalytical method can distinguish between encapsulated and unencapsulated drug substance, the in vivo stability of the liposome should be determined.*

The liposome is considered stable in vivo, if over time (from PK study), the:

- *Drug substance, when in circulation, remains substantially in the encapsulated form.*
- *Ratio of unencapsulated to encapsulated drug substance remains constant*

*When the liposome is stable in vivo, the **total** drug substance can be measured to determine the PK and Bioavailability.*

C. Protein Binding

D. In Vitro Stability

FDA Draft Guidance – Liposomal Drug Products, 2002

III. Human Pharmacokinetics and Bioavailability

E. Pharmacokinetics and Bioavailability

- ADME/PK parameters may be different between the liposome and nonliposome drug products.

- Conduct comparative MB/PK studies between the liposome and nonliposome drug products when (1) the two products have the same active moiety, (2) the two products are given by the same route of administration, and (3) one of the products is already approved for marketing.

  1. Mass Balance (MB) Study
     - a crossover or non-crossover design
     - drug substance tagged with a radioactive label (e.g. ^{14}C, ^{3}H)
  2. PK Studies
     - Single Dose, Multi-dose, dose proportionality *(measure encapsulated and unencapsulated drug substance **if needed**)*
  3. Additional PK Studies
     - Food-Effect
     - Drug Interaction and/or Special Populations
     - Exposure-response

FDA Draft Guidance – Liposomal Drug Products, 2002

EMA (European Medicines Agency) CHMP (Committee for Human Medicinal Products) – 21 Feb 2013

Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product

Introduction

"…liposomal medicinal products have formulation and manufacturing-specific distribution characteristics after intravenous administration and similar plasma concentrations may not correlate with therapeutic performance… the complete characterisation of the stability, ***pharmacokinetics (including tissue distribution)*** *of a new liposomal product is critical to establish safe and effective use. This is because differences between the applicant's product and innovator product with regard to manufacturing process steps and formulation may substantially modify efficacy/safety due to changes in specific liposome-cell interactions and liposome distribution characteristics which are not detectable by conventional bioequivalence testing alone".*

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500140351.pdf

3.2 Non-Clinical and Clinical Requirements

- ✓ Significant changes in pharmacokinetic characteristics are evident when an active substance is administered in a liposomal formulation, i.e. volume of distribution and clearance may be reduced and half-life prolonged. The clearance of the liposomal active substance is dependent on:
  1. the clearance of the liposomal carrier itself,
  2. the rate of release of entrapped drug from the liposomal carrier, and
  3. the clearance and metabolism of unencapsulated drug upon its release.

- ✓ The rate and location of in vivo drug release is a crucial parameter which can affect toxicity and efficacy.

- ✓ Therefore, the pharmacokinetics of the developed liposomal product should always be compared with the innovator's product. Only certain aspects of the conventional bioequivalence approach are applicable and in some cases additional requirements should be set on a case-by-case basis.

- ✓ Comparative human pharmacokinetic investigations should demonstrate not only the similarity of exposure of the total, unencapsulated and liposome encapsulated drug, but they should also demonstrate **similar distribution and elimination characteristics**.

EMA Reflection Paper – 2013

3.2.3 Non-clinical Studies *(ADME requirements!)*

Non-clinical pharmacokinetic studies

- Some pharmacokinetic aspects of liposomal products with regard to their performance in humans can be predicted by animal and, where applicable, cell-based models. However, the choice of appropriate species and models to investigate the in-vivo release of the drug from liposomes should be justified with special emphasis on areas such as accumulation and retention in target organs, pharmacokinetics and distribution. In addition to the systemic exposure, similarities in the distribution and elimination should be demonstrated. **These studies provide pivotal evidence of the comparability of disposition of liposomal drug products, as it is not possible to have a full picture of the distribution in man from blood/plasma data alone**.

- Sampling time points and sampling duration should be carefully selected so as to accurately quantify the time course of unencapsulated and total drug and metabolite in tissues balancing the need to quantify early drug release from liposomes (e.g. over first 15 min) and persistence of drug in particular tissues. If due to analytical reasons free concentrations cannot be measured then attempts should be made to compare the metabolite concentrations in the target organs.

- *Analytes to be measured*
  - The kinetics (including tissue distribution and excretion) of both the unencapsulated drug and the encapsulated drug should be investigated if feasible.

EMA Reflection Paper – 2013

Combination Chemotherapy

- For most patients with cancer, standard of care usually involves the use of combinations of individual drugs. For example, the use of cytarabine in combination with an anthracycline (such as daunorubicin) is the standard of care for the treatment of patients diagnosed with acute myeloid leukemia (AML).

- Individual drugs are combined at their “maximum tolerated dose” (MTD), the dose at which a drug has been shown to deliver maximum benefit balanced by an acceptable level of toxicity.

- Complementary mechanism of actions

Understanding the Impact of Drug Ratios

- Dosing individual drugs at MTD does not always produce combination drug regimens that deliver maximum efficacy.
- The same drugs combined at different ratios can result in distinctly varied efficacy and safety profiles. Depending on the ratio of the combined drugs, the outcome can be:

  Additive – the anti-cancer effect of the drugs is equal to the sum of the individual drugs.
- **Synergistic –** the anti-cancer effect of the drugs is greater than the sum of the individual drugs.

  Antagonistic – the anti-cancer effect of the drugs is less than the sum of the individual drugs.

Summary

Non-clinical ADME Studies to support Liposomal Drug Development

- Comparative studies of free vs. encapsulated forms of radiolabel drug(s) provide key information required by agencies for approval.

- May help to reduced the number and scope of additional clinical trials required for regulatory approval.

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Thank you