Complex Injectable and Implantable Drug Products: Bioequivalence Considerations

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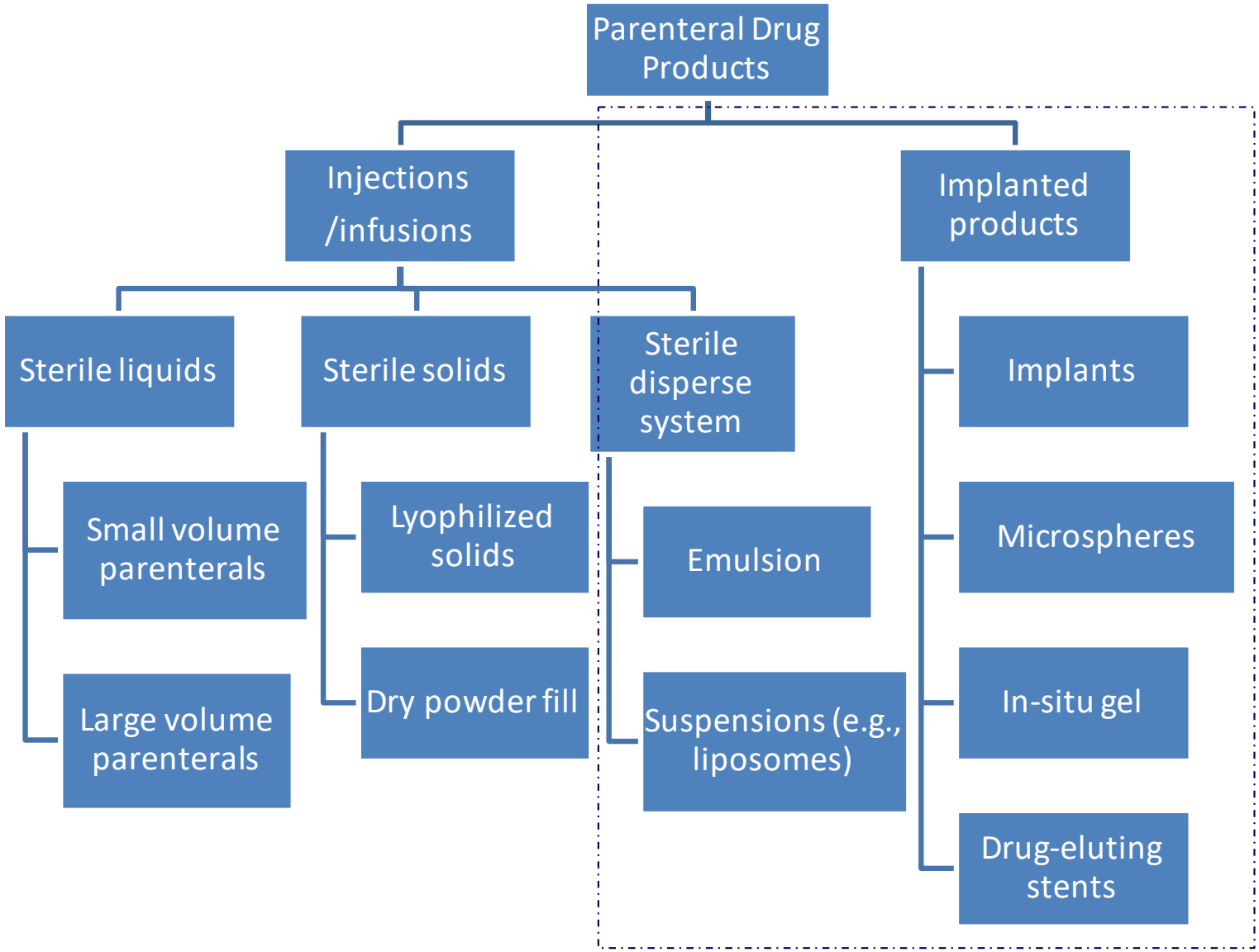
Parenteral Drug Products

- 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
Lyophilized solids
Emulsion
Microspheres
Large volume parenterals
Dry powder fill
Suspensions (e.g., liposomes)
In-situ gel
Drug-eluting stents
Complex

Bioequivalence (BE) Approaches

Approaches to Determining Bioequivalence (21 CFR 320.24)

- In vivo pharmacokinetic comparison
- In vivo pharmacodynamic comparison
- In vivo clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA

Parenteral solution

- Same active ingredients, strength, dosage form
- Qualitatively (Q1) and quantitatively (Q2) the same for the inactive ingredients
- In vivo BE study waived (320.22(b)(1)

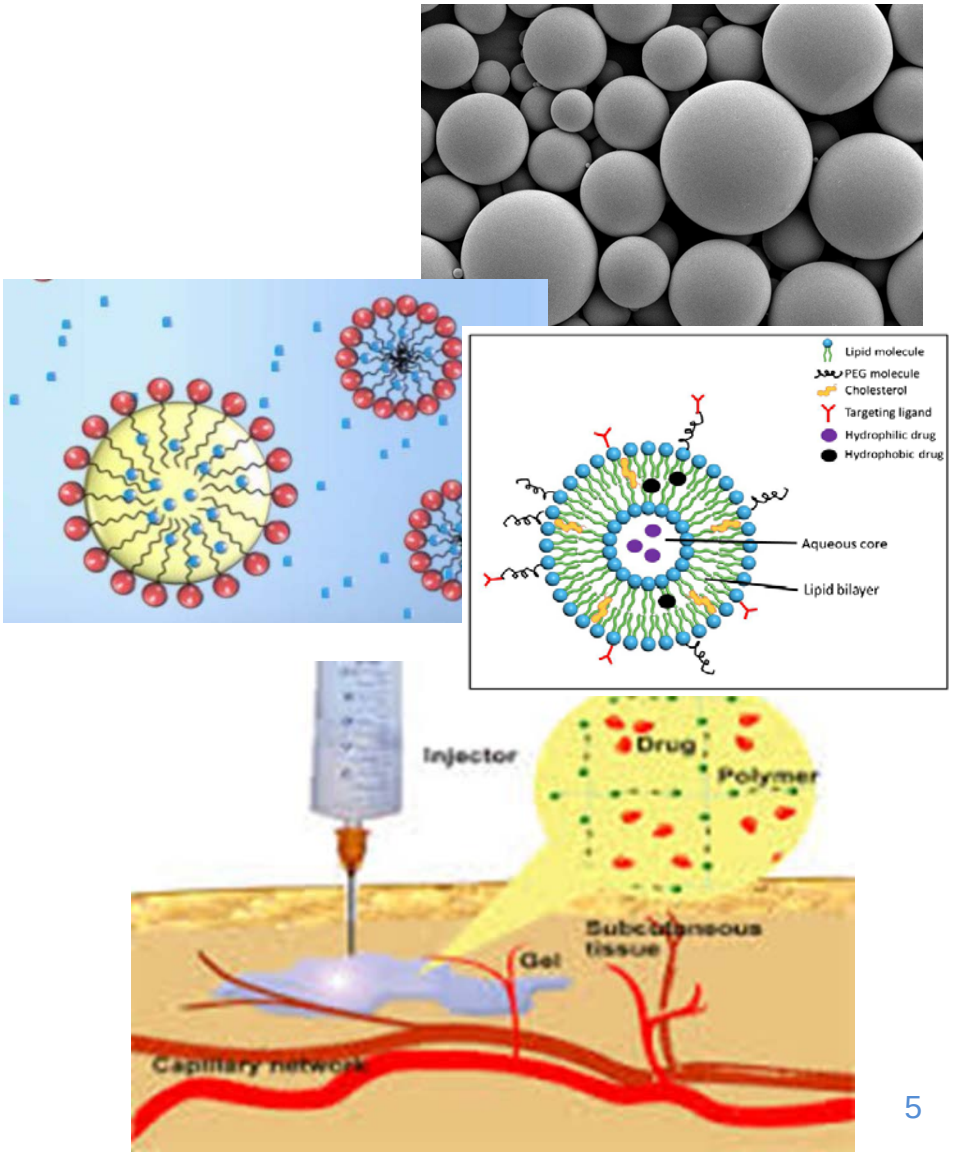
Tablets/capsules

- Same active ingredients, strength, dosage form
- Can have different inactive ingredients/design/release mechanisms
- Pharmacokinetic study preferred to demonstrate bioequivalence

Bioequivalence approaches for complex injectable and implantable products?

Bioequivalence Demonstration of Complex Injectable and Implantable Drug Products

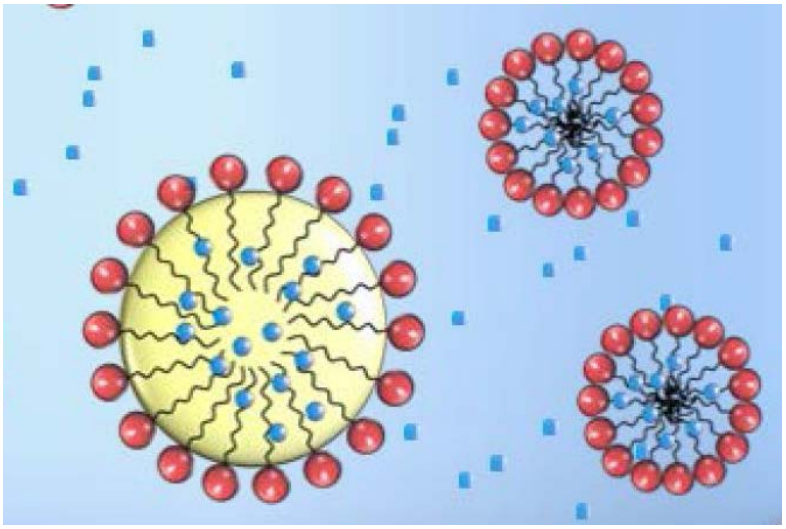
- Product complexity
- Current FDA approaches for BE demonstration
- Recent scientific and regulatory advances with the support of GDUFA funding



GDUFA: Generic Drug User Fee Amendment

GUDFA regulatory science
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm567695.htm

Injectable Emulsion Drug Products



Trade name	Active ingredient	Route	Initial Approval Date
RESTASIS	Cyclosporine	Ophthalmic	10/10/2003
DIPRIVAN	Propofol	Intravenous	10/02/1989
CINVANTI	Aprepitant	Intravenous	11/9/2017
VARUBI	Rolapitant HCl	Intravenous	10/25/2017

Emulsion: Dispersion made up of two immiscible liquid phases which are mixed using mechanical shear and stabilized with surfactant

Types of Emulsions:

Oil in Water (O/W)
Water in Oil (W/O)
Water-in-Oil-in-Water (W/O/W)
Oil-in-Water-in Oil (O/W/O)

Complexity

- Complex formulation
- Some products intended for local action

Injectable Emulsion Drug Products Bioequivalence Demonstration

In vitro option

- Formulation qualitatively (Q1) and quantitatively (Q2) the same
- Acceptable comparative physico-chemical characterization
- Acceptable comparative in vitro release

In vivo option

- Permissible non-Q1/Q2 formulation (21CFR 314.94(b)(9)(iii))
- In vivo pharmacokinetic BE study or comparative clinical endpoint BE study

Challenges

- Emulsion globule size comparison
- Development of discriminative in vitro release method
- Insensitive clinical endpoint

Product-Specific Guidance for Propofol Emulsion

Active Ingredient: Propofol
Dosage Form; Route: Injectable; injection
Strength: 10 mg/ mL
Recommended Study: Two options: In vitro or In vivo studies

I. In vitro option:
To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which "any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all the following criteria should be met:
i. The Test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterization of the Test and RLD formulations. The comparative study should be performed on at least three exhibit lots of both Test and Reference products.

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential of the formulation and at physiological pH, osmolality, free acid concentration, and amount of propofol partitioned in the aqueous and oil phases.

The sponsor should also demonstrate that the test product is stable when diluted with 5% Dextrose Injection USP, according to label instructions.
Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) based on D50 and SPAN (alternatively harmonic intensity weighted average particle diameter and polydispersity index derived from cumulant analysis of the intensity size distribution) for the globule size distribution only

iii. Acceptable comparative in vitro drug release rate tests from 12 units of each of the test and RLD formulations.
An in vivo pharmacokinetic bioequivalence study is requested for any generic propofol injection, 10 mg/mL that has a different inactive ingredient from the RLD4 or unacceptable data from in vitro comparative studies.

II. In vivo option:
Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 10 mg/mL
Dose rate: 30 mcg/kg/min
Subjects: Healthy males, non-pregnant and non-lactating females, general population 18 to 55 years of age
Analytes to measure (in appropriate biological fluid): Propofol in plasma
Bioequivalence based on (90% CI): Propofol
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM506910.pdf

Statistic Method for a Whole Profile Analysis of Emulsion Globule Size

The AAPS Journal (2018) 20: 62
DOI: 10.1208/s12248-018-0212-y

Research Article

Equivalence Testing of Complex Particle Size Distribution Profiles Based on Earth Mover's Distance

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Abstract. Particle size distribution (PSD) is an important property of particulates in drug products. In the evaluation of generic drug products formulated as suspensions, emulsions, and liposomes, the PSD comparisons between a test product and the branded product can provide useful information regarding *in vitro* and *in vivo* performance. Historically, the FDA has recommended the population bioequivalence (PBE) statistical approach to compare the PSD descriptors D50 and SPAN from test and reference products to support product equivalence. In this study, the earth mover's distance (EMD) is proposed as a new metric for comparing PSD particularly when the PSD profile exhibits complex distribution (e.g., multiple peaks) that is not accurately described by the D50 and SPAN descriptor. EMD is a statistical metric that measures the discrepancy (distance) between size distribution profiles without a prior assumption of the distribution. PBE is then adopted to perform statistical test to establish equivalence based on the calculated EMD distances. Simulations show that proposed EMD-based approach is effective in comparing test and reference profiles for equivalence testing and is superior compared to commonly used distance measures, e.g., Euclidean and Kolmogorov–Smirnov distances. The proposed approach was demonstrated by evaluating equivalence of cyclosporine ophthalmic emulsion PSDs that were manufactured under different conditions. Our results show that proposed approach can effectively pass an equivalent product (e.g., reference product against itself) and reject an inequivalent product (e.g., reference product against negative control), thus suggesting its usefulness in supporting bioequivalence determination of a test product to the reference product which both possess multimodal PSDs.

KEY WORDS: earth mover's distance; equivalence test; particle size distribution; profile comparison.

Pulsatile Microdialysis (PMD) for Dissolution of Emulsion Drug Products

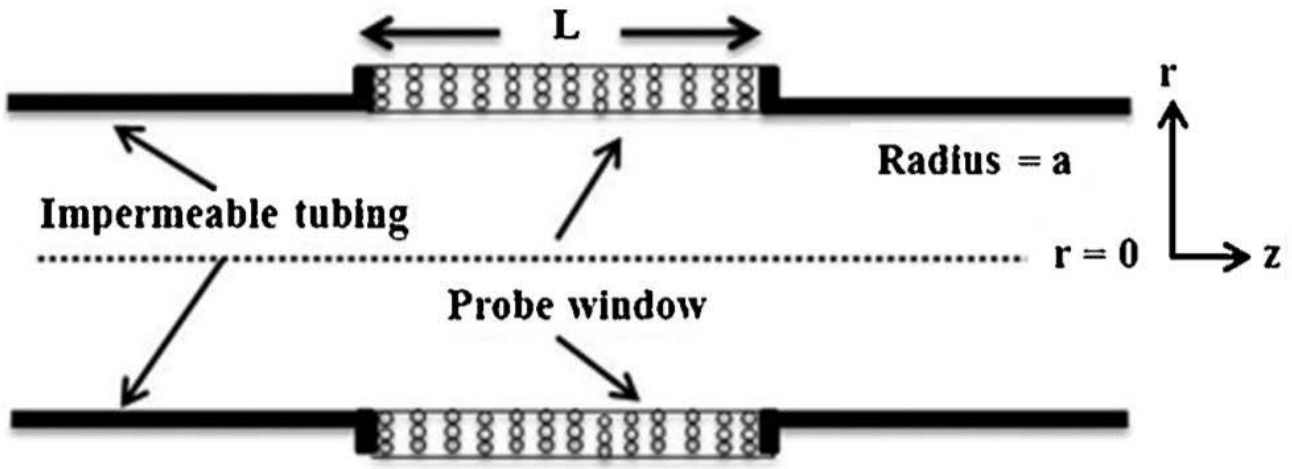
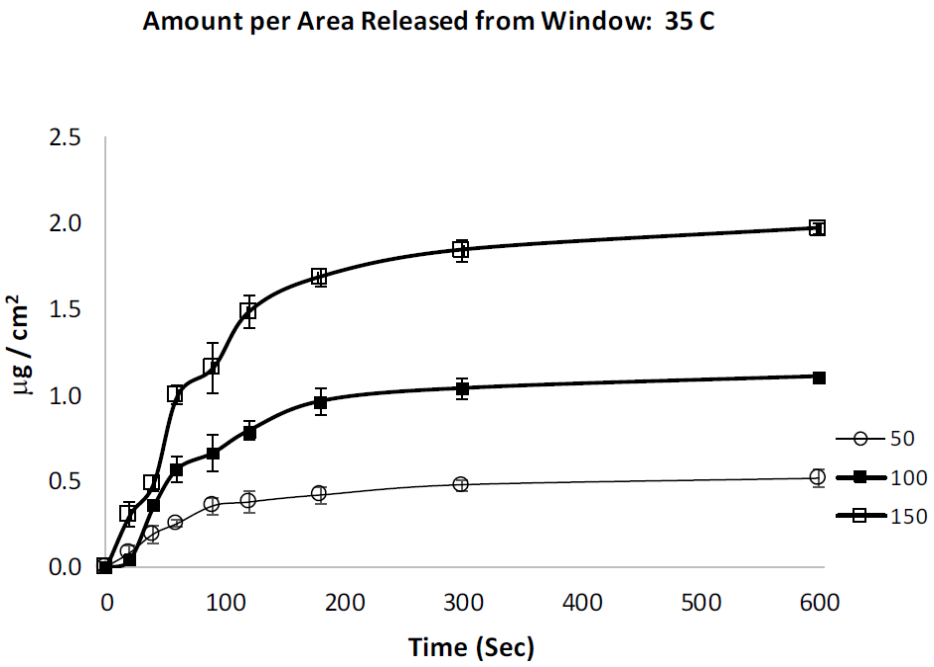
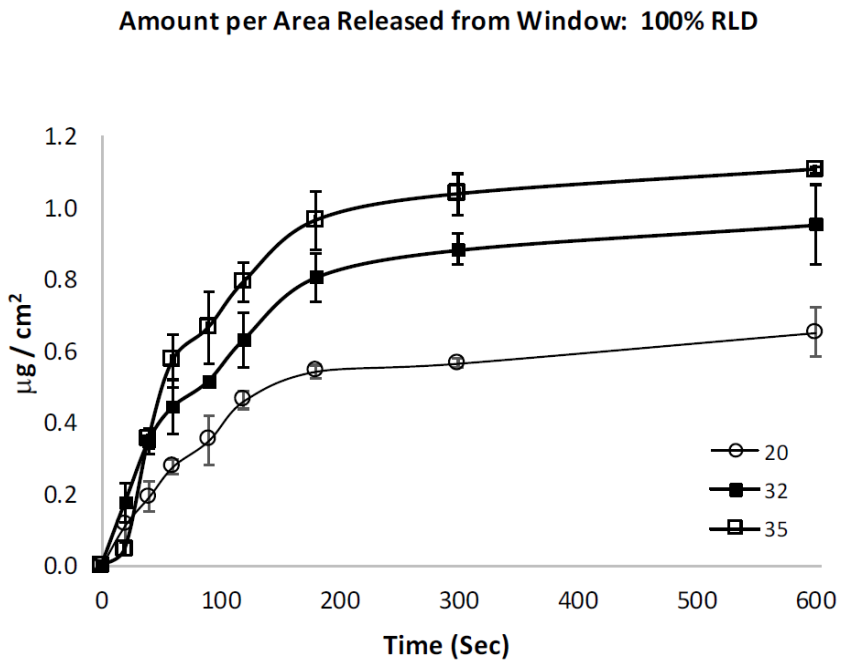


Fig. 1. A schematic diagram of a microdialysis probe.

Shah, KB et al., Int J Pharm 468 (2014) 64-74.

In Vitro Release Testing of Cyclosporine Emulation Formulations

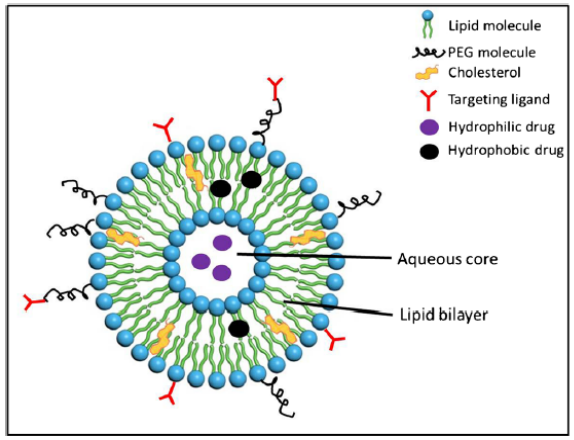


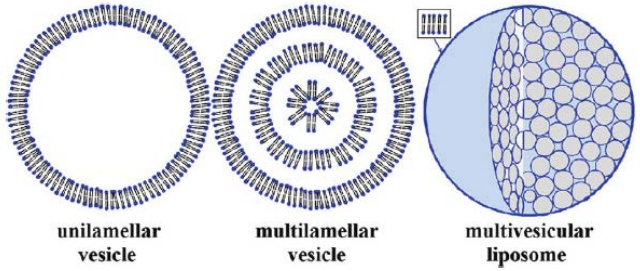


Q1/Q2 cyclosporine ophthalmic emulsions containing 50%, 100%, 150% drug load relative to the RLD (left), or 100% drug load relative to the RLD (right). The x-axis corresponds to resting time, and the y-axis is the amount of cyclosporine released from the PMD probe window per area. The receiver medium was either (A) kept at 35 °C or (B) varied between 20 °C, 32 °C, and 35 °C. Data points represent the average from three replicates ± standard deviation. Courtesy of Robert Bellantone, Physical Pharmaceutica, LLC.

This work was partially funded by FDA Contract HHSF223201610105C.

Liposome Drug Products





Trade name	Active Ingredient	Route	Approval Date
DOXIL	Doxorubicin HCl	Intravenous	11/17/1995
DAUNOXOME	Daunorubicin Citrate	Intravenous	4/8/1996
AMBISOME	Amphotericin B	Intravenous	08/11/1997
DEPOCYT	Cytarabine	Intrathecal	04/01/1999
VISUDYNE	Verteporfin	Intravenous	04/12/2000
DEPODUR	Morphine Sulfate	Epidural	05/18/2004

Liposome: Microvesicle composed of a bilayer and/or a concentric series of multiple bilayers separated by aqueous compartments formed by amphipathic molecules such as phospholipids that enclose a central aqueous compartment

Complexity

- Complex formulation and lipid excipients
- Complex manufacturing process
- Scale up challenges
- Complex in vivo behavior

Injectable Liposome Drug Products Bioequivalence Demonstration

In Vitro Option

- Formulation Q1 and Q2 the same
- Acceptable comparative physico-chemical characterization

For Immediate-Release Liposomes, e.g., verteporfin liposomes

In Vivo Option

- Formulation Q1 and Q2 the same
- Equivalent physico-chemical characteristics
- In vivo pharmacokinetic BE study

For Non Immediate-Release Liposomes, e.g., doxorubicin HCl liposomes

Challenges

Lack of standard in-vitro release method

In vivo pharmacokinetic BE studies

- Total drug alone is insufficient to demonstrate BE
- Limited number of patients for BE study
- Intensive pharmacokinetic sampling not feasible for certain physiological sites, e.g., cerebrospinal fluid (CSF).

Product-Specific Guidance for Doxorubicin HCl Liposome Injection

Active Ingredient: Doxorubicin hydrochloride

Dosage Form; Route: Injectable, liposomal

Recommended Studies: Two studies: in vivo and in vitro

To be eligible for the bioequivalence studies recommended in this guidance, the Test product should meet the following criteria:

- Qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD)
- Manufactured by an active liposome loading process with an ammonium sulfate gradient
- At least one batch of the Test product should be produced by the commercial scale process and be used in the in vivo bioequivalence study
- Equivalent liposome characteristics including liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and in vitro leakage rates comparable to the Reference Standard (RS).

In Vivo Study:

Type of study: Fasting*
Design: Single-dose, two-way crossover in vivo
Strength: 50 mg/vial or 20 mg/vial
Dose: 50 mg/m2
Subjects: Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy and who are already receiving or scheduled to start therapy on doxorubicin hydrochloride (liposomal).

In Vitro Study:

1. Type of study: Liposome Size Distribution

   Design: In vitro bioequivalence study on at least three lots of both Test and RS product. At least one lot of the Test product should be produced by the proposed commercial scale manufacturing process.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf

Product-Specific Guidance for Doxorubicin HCl Liposome Injection

- In vitro leakage under multiple conditions: In vitro drug leakage testing to characterize the physical state of the lipid bilayer and encapsulated doxorubicin should be investigated to support a lack of uncontrolled leakage under a range of physiological conditions and equivalent drug delivery to the tumor cells. Below are some examples of proposed conditions.

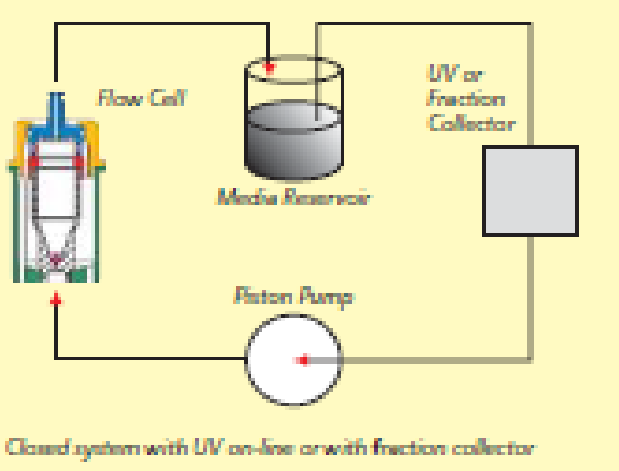
Table 1. Examples of in vitro leakage conditions of doxorubicin liposomes

In Vitro Drug Leakage Condition	Purpose	Rationale
At 37°C in 50% human plasma for 24 hours	Evaluate liposome stability in blood circulation.	Plasma mostly mimics blood conditions.
At 37°C with pH values 5.5, 6.5, and 7.5 for 24 hours in buffer	Mimic drug release in normal tissues, around cancer cells, or inside cancer cells	Normal tissues: pH 7.3 Cancer tissues: pH 6.6 Insider cancer cells (endosomes and lysosomes): pH 5-6 (Endosome and lysosomes of cancer cells may be involved in liposome uptake and induce drug release).
At a range of temperatures (43°C, 47°C, 52°C, 57°C) in pH 6.5 buffer for up to 12 hours or until complete release	Evaluate the lipid bilayer integrity	The phase transition temperature (Tm) of lipids is determined by lipid bilayer properties such as rigidity, stiffness and chemical composition. Differences in release as a function of temperature (below or above Tm) will reflect small differences in lipid properties
At 37°C under low-frequency (20 kHz) ultrasound for 2 hours or until complete release.	Evaluate the state of encapsulated drug in the liposome.	Low-frequency ultrasound (20 kHz) disrupts the lipid bilayer via a transient introduction of pore-like defects and will render the release of doxorubicin controlled by the dissolution of the gel inside the liposome.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf

USP Apparatus 4-Flow Through Cell Dissolution for Liposome Drug Products

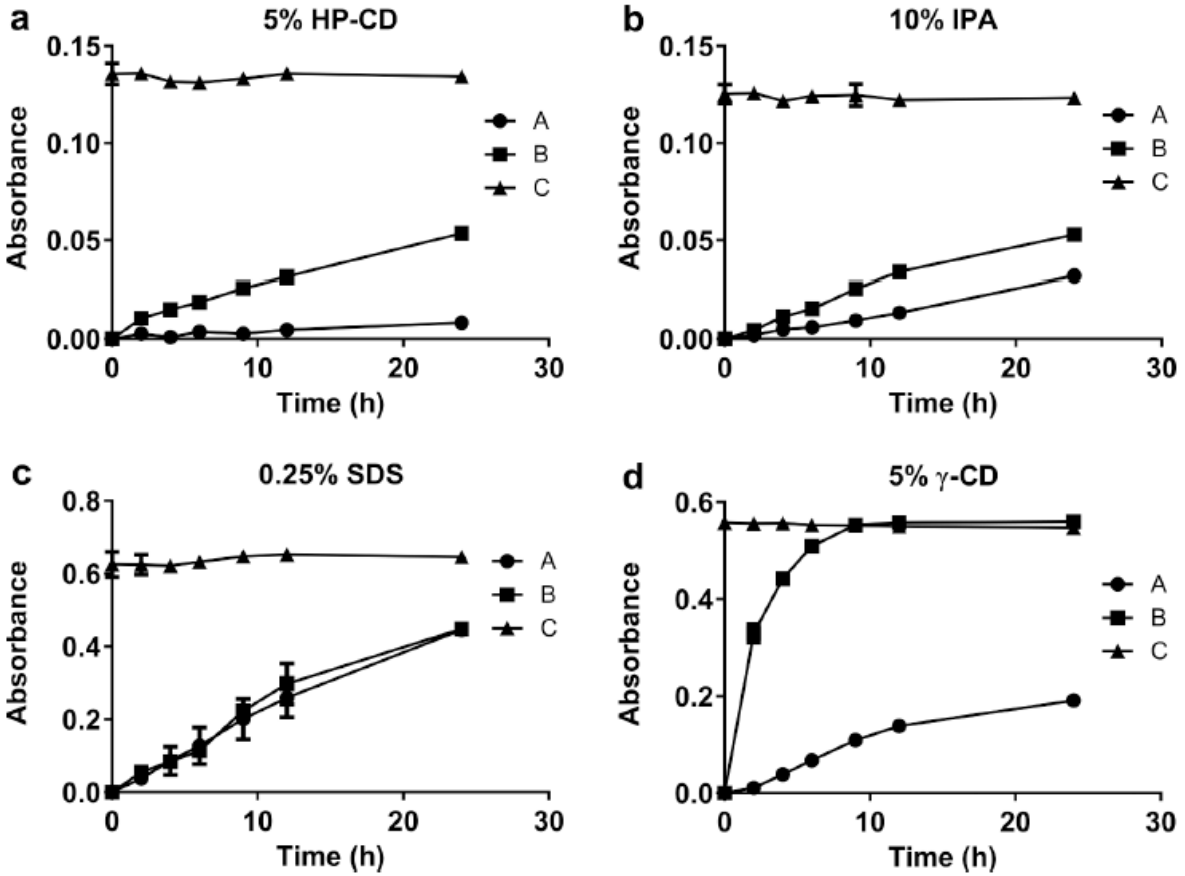
CE 7smart cell



Closed system with UV on-line or with fraction collector

http://www.teknokroma.es/UserFiles/Test%20Disolucion/SOTAX%20CE%207smart.pdf

Selection of Dissolution Media for Amphotericin B Liposomes



An addition of 5% w/v of γ-cyclodextrin to the release media of 5% sucrose, 10 mM HEPES, and 0.01% NaN3 (pH = 7.4) prevented Amp B precipitation and facilitated drug release.

Fig. 1. The effect of solubilizer addition to the release media on Amp B release from AmBisome® in the single-unit vial-based IVR assay at 45 °C, including 5% HP-CD (a), 10% IPA (b), 0.25% SDS (c) or 5% γ-CD (d). Lines represent: A. AmBisome® in Float-A-Lyzer® (●); B. Free Amp B solution in Float-A-Lyzer® (■); C. Free Amp B in release medium (▲). The final Amp B concentration in the release media is 10 μg/mL for all the groups

Tang J et al. Development of a flow-through USP 4 apparatus drug release assay for the evaluation of amphotericin B liposome. European Journal of Pharmaceutics and Biopharmaceutics 134 (2019) 107–116

This work was supported by FDA grant U01FD005249-01.

In Vitro Drug Release from Different Amphotericin B Drug Products

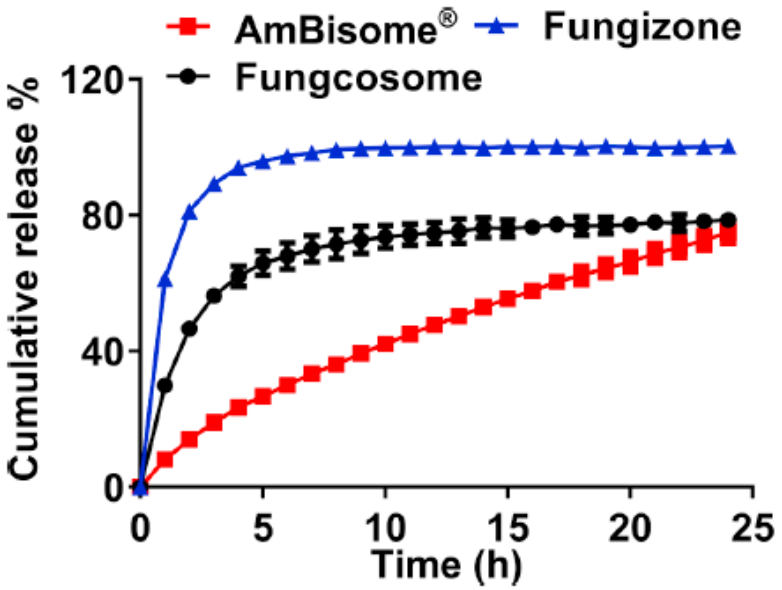


Fig. 5. The cumulative release of different commercial Amp B formulations on Sotax® at 55 °C. 5% γ-CD was added into media, and total Amp B concentration is 10 µg/mL for all the groups based on reported package insert drug concentrations.

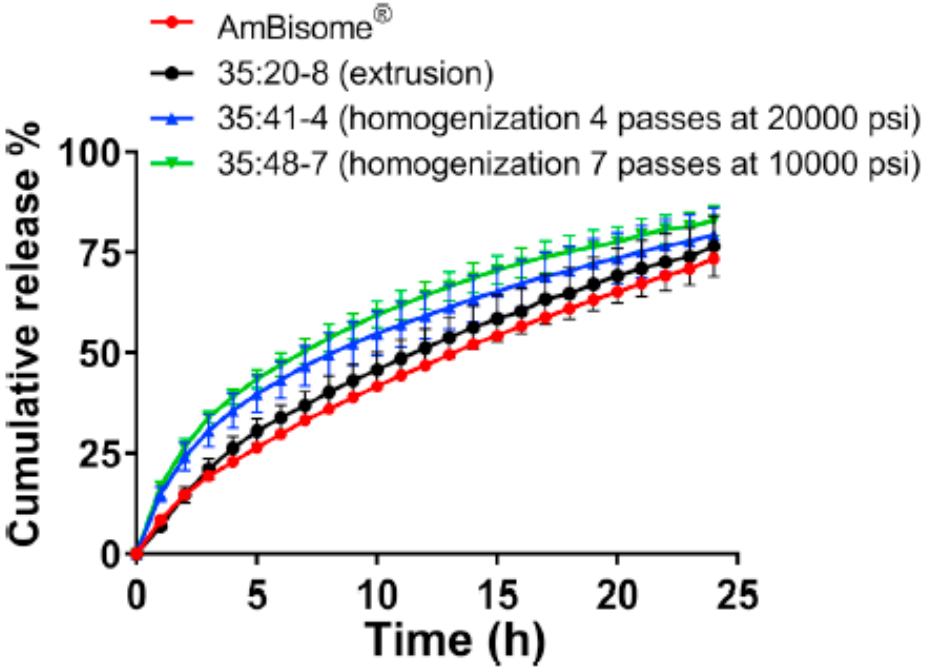


Fig. 6. The cumulative release of different liposomal Amp B formulations prepared by extrusion and homogenization from Z1P on Sotax® at 55 °C. 5% γ-CD was added into media, and total Amp B concentration is 10 µg/mL for all the groups.

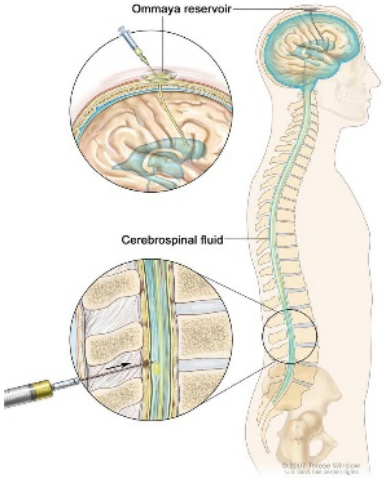
Tang J et al. Development of a flow-through USP 4 apparatus drug release assay for the evaluation of amphotericin B liposome. European Journal of Pharmaceutics and Biopharmaceutics 134 (2019) 107–116

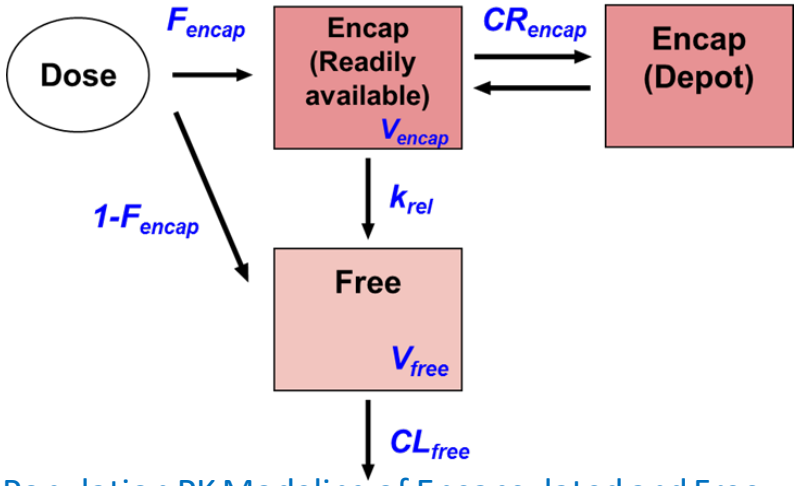
This work was supported by FDA grant U01FD005249-01.

Challenges and Solutions for In-Vivo Bioequivalence Study of Cytarabine Liposomes

Generic Name:
Cytarabine liposome injection

Indication and Regimen:
50 mg, administered intrathecally (intraventricular or lumbar puncture) every 14 days for treatment of lymphomatous meningitis





Population PK Modeling of Encapsulated and Free Cytarabine

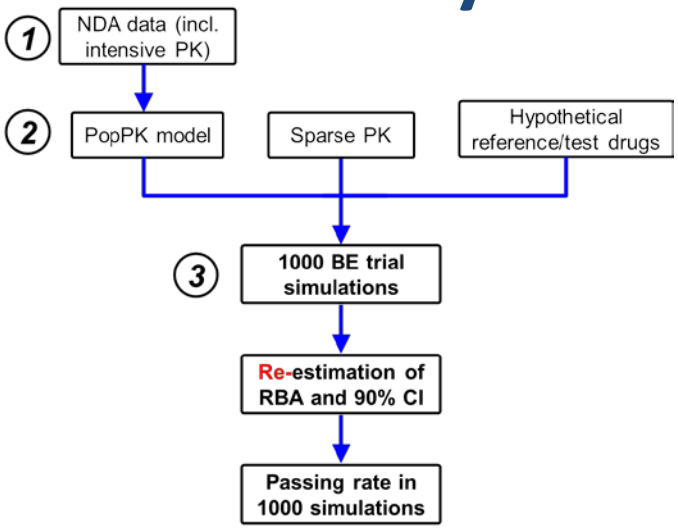
There is sustained release of cytarabine from the liposomes and the terminal half-life of free cytarabine was prolonged in cerebrospinal fluid (CSF).

Bioequivalence Study Challenges

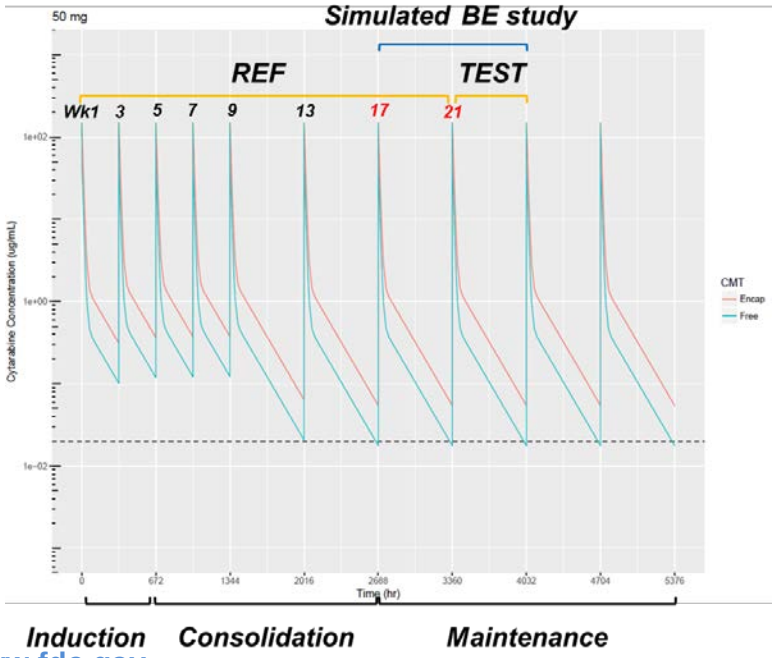
- Difficult to enroll patients
- Intensive PK sampling from CSF is not feasible
- High inter- and intra-individual variability

Parameter	Definition
Fixed effects	
F_{encap}	Fraction of encapsulated cytarabine in the formulation
k_{el}, h^{-1}	Release rate constant from encapsulated cytarabine
V_{encap}, mL	Volume of distribution of encapsulated cytarabine
V_{free}, mL	Volume of distribution of free cytarabine
CL_{free}, mL/h	Clearance of free cytarabine
CR_{encap}, mL/h	Conversion rate between encapsulated cytarabine (readily available form) and the depot

Model-based Bioequivalence Method for Cytarabine Liposomes



Limit	Minimal number of subjects
80.00 – 125.00%	68
70.00 – 142.86%	28
66.67 – 150.00%	24
60.00 – 166.67%	20
50.00 – 200.00%	8



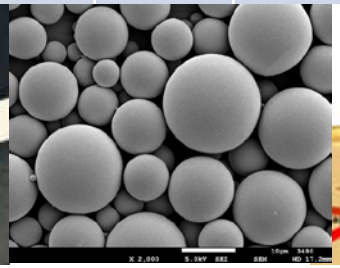
RBA	20 patients with limit of 60 – 167%	8 patients with limit of 50 – 200%	
100% (= BE)	89.6	82.0	= estimate of power
167% (= BIE)	1.7	26.3	= estimate of type-I error

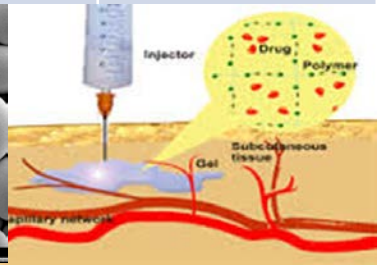
The model-based BE evaluation method with a minimal 20 subjects and a widened BE limit of 60.00–166.67% provided reasonable statistical power and type-I error rate.

Ken Ogasawara, Alejandro Pérez-Pitarch, Jia Chen, Myong-Jin Kim, Liang Zhao, Lanyan Fang. Bioequivalence Evaluation for a Complex Drug Product, Cytarabine Liposome Injection, Using Modeling and Simulation Approaches. American Conference of Pharmacometrics 2018, San Diego, CA

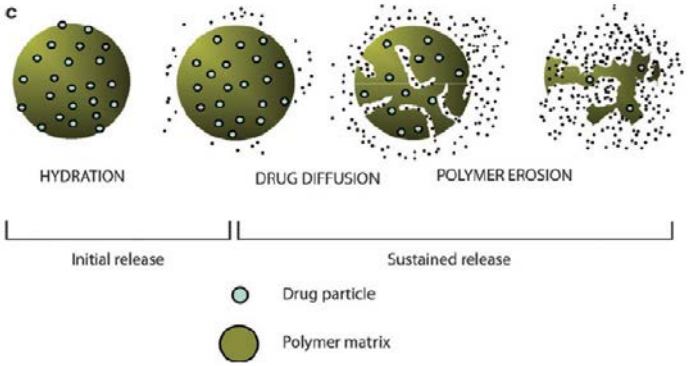
Long-acting Polymeric Microspheres, In-Situ Gels, and Implants

Brand	Drug	Route	Dosing frequency	Dosage Form
RISPERDAL CONSTA	Risperidone	IM	2 weeks	Micospheres
SANDOSTATIN LAR DEPOT	Octreotide	IM	1 month	Micospheres
VIVITROL	Naltrexone	IM	1 month	Micospheres
LUPRON DEPOT	Leuprolide	IM	1, 3, 4, 6 months	Micospheres
BYDUREON	Exendatide	SC	1 week	Micospheres
ZOLADEX	Goserelin	IM	1, 3 months	Implant
ELIGARD	Leuprolide acetate	SC	1, 3, 4, 6 months	In-situ gel





Poly (lactic-co-glycolic acid) (PLGA) Microspheres



Complexity

- Complex formulation and polymeric excipients ingredients
- Complex manufacturing process
- Scale up challenges
- Long residence in vivo

Long-acting Polymeric Microspheres Bioequivalence Demonstration

In Vivo Option

- Formulation Q1 and Q2 the same
- In vivo pharmacokinetic BE study

Equivalence Challenges

Formulation sameness

- Demonstrate Q1 and Q2 sameness of the polymeric excipients

Discriminative in vitro release within reasonable timeframe

Bioequivalence studies

- Long duration
- Conventional BE matrix may not be sufficient to capture multiphasic in vivo release

Product-Specific Guidance for Risperidone Suspension

Active Ingredient: Risperidone

Dosage Form; Route: Injectable; intramuscular

Recommended Studies: Two studies: in vitro and in vivo

1.

Type of study:	In vitro drug release
Strength:	25 mg/vial
Medium:	Dissolution medium (pH 7.4) prepared as indicated below
Volume:	400 mL (200 mL for each temperature)
Apparatus:	Cylinder bottle
Temperature:	37 °C and 45 °C (water bath)
Sampling Times:	Day 1 and Day 21 for 37 °C Multiple time points from Days 0 to 8 for 45 °C. Two sampling time points, that bracket $T_{50\%}$ (which is defined as the time of 50% drug release), are to be linearly interpolated to determine $T_{50\%}$.

Parameters to measure: Cumulative drug release at Days 1 and 21 at 37 °C, cumulative drug release at Day 8 at 45 °C, and $T_{50\%}$ at 45 °C.

Bioequivalence based on (90% CI): $T_{50\%}$. The 90% confidence interval of the test/reference ratio of $T_{50\%}$ should be within 80-125%.

2. Type of study: In vivo, two-period, crossover steady-state
Strength: 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, 50 mg/vial
Subjects: Male and nonpregnant female patients with schizophrenia or bipolar I disorder who are already receiving a stable regimen of risperidone long-acting injection via the intramuscular route. Patients who are receiving any dosage regimen of risperidone long-acting injection every two weeks would be eligible to participate in the study by continuing their established maintenance dose.
Additional comments: FDA recommends that studies not be conducted using healthy subjects or patients on a different antipsychotic treatment. All strengths of the test product need to be from the same bulk in order for all strengths of the Test to be administered in the PK BE study.

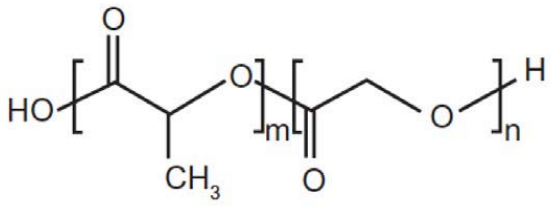
Analytes to measure (in appropriate biological fluid): Risperidone in plasma

Bioequivalence based on (90% CI): Risperidone

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

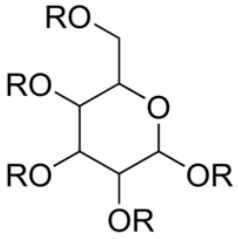
Poly(lactic-*co*-glycolic acid) (PLGA) copolymer

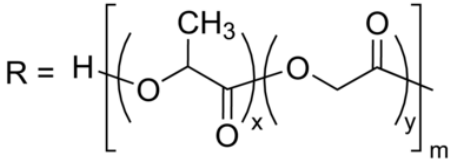


PLGA

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.
This work was supported by FDA grant U01FD05168.

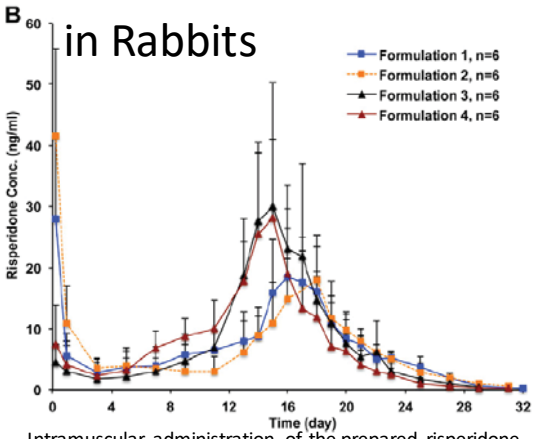
FDA Recommended Dissolution Methods for Microspheres

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Triptorelin Pamoate	Intramuscular Suspension	II (Paddle)	75	50 mL of methanol to 950 mL of water	950	1, 8, 24, 96, and 168 hours	11/16/2017
Triptorelin Pamoate	Injectable Suspension	II (Paddle)	200	Water-Methanol (95:5); Reconstitute vial in 2 mL Water for Injection, add to 500 mL medium at 37°C	500	1, 6, 12, 23, 48, and 72 hours	07/14/2008
Naltrexone	Injectable Suspension	Develop an in vitro release method using USP IV (Flow-Through Cell), and, if applicable, Apparatus II (Paddle) or any other appropriate method, for comparative evaluation by the Agency		Phosphate buffered saline with 0.02% Tween 20 and 0.02% Sodium azide, pH 7.4 (final osmolality should be 270 ± 20 mOsm), or any other appropriate medium, at 37°C.			09/01/2011
Octreotide	Injectable Suspension	Develop a dissolution method using USP IV (Flow-Through Cell), and, if applicable, Apparatus II (Paddle) or any other appropriate method, for comparative evaluation by the Agency					12/23/2010

https://www.accessdata.fda.gov/scripts/cder/dissolution/

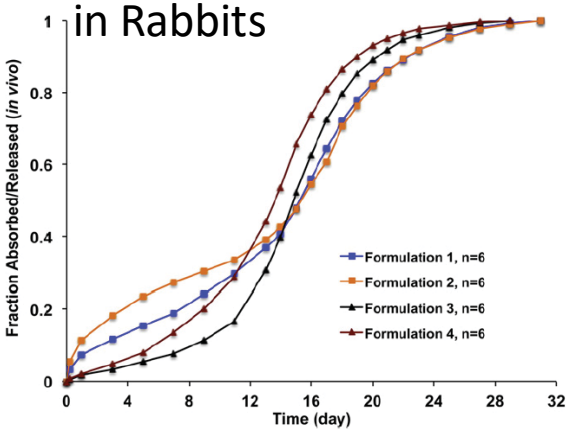
In Vitro-In Vivo Correlation (IVIVC) of Parenteral Risperidone Polymeric Microspheres

Plasma Concentration Profile in Rabbits



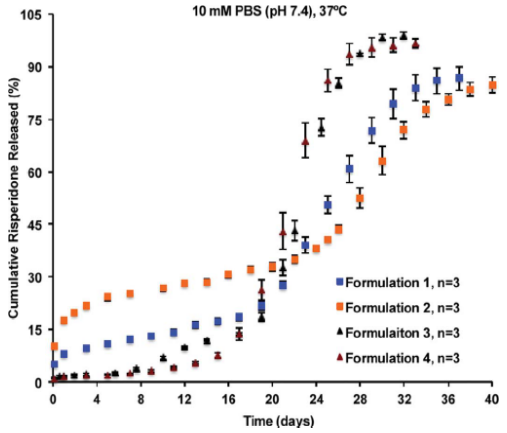
Intramuscular administration of the prepared risperidone PLGA microspheres at a single dose of 1.92 mg/kg) in rabbits. (mean±SD, n = 6)

Deconvoluted In-vivo Release in Rabbits



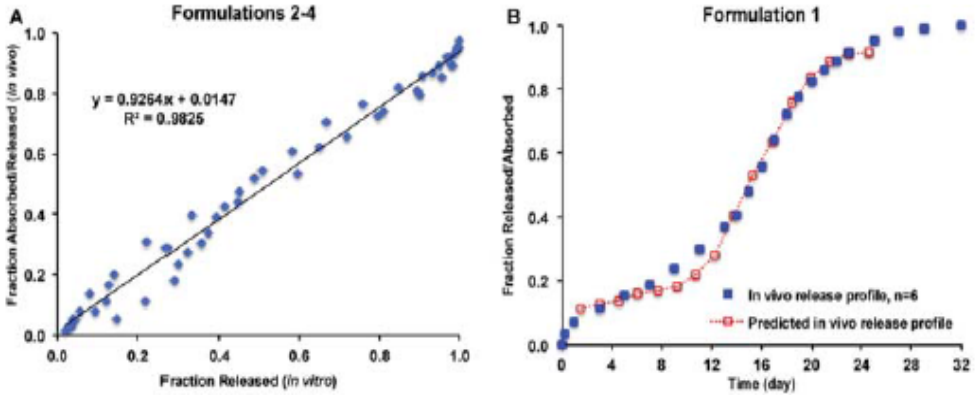
Deconvoluted using the Loo-Riegelman method

In-vitro Drug Release



USP apparatus 4 method at 37°C in 10 mM PBS (pH 7.4) (n=3).

Level A IVIVC



Shen J et al. In Vitro-in Vivo Correlation of Parenteral Risperidone Polymeric Microspheres. J Control Release. 218:2-12. (2015)

This work was supported by FDA (1U01FD004931-01).

Drug Release from Implants

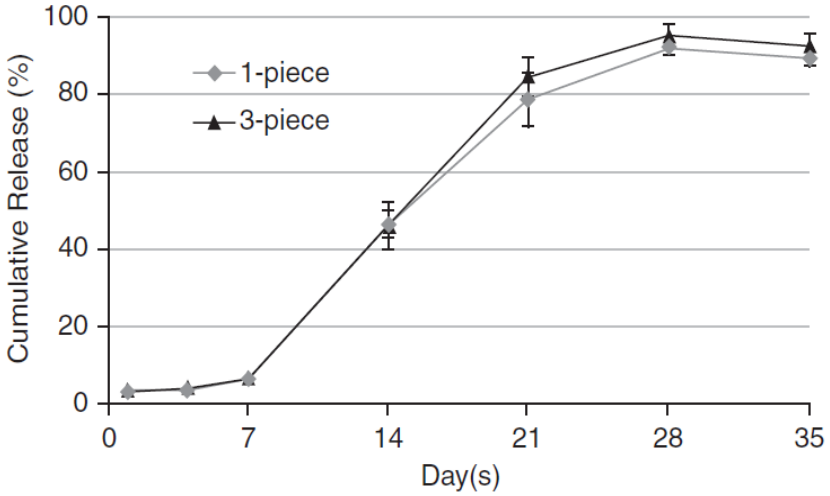


FIG. 1. Cumulative release of dexamethasone from 1-piece and 3-piece dexamethasone intravitreal implants (DEX implants) *in vitro*. Results are expressed as mean percentage ± standard deviation based on 6 replicates per time point.

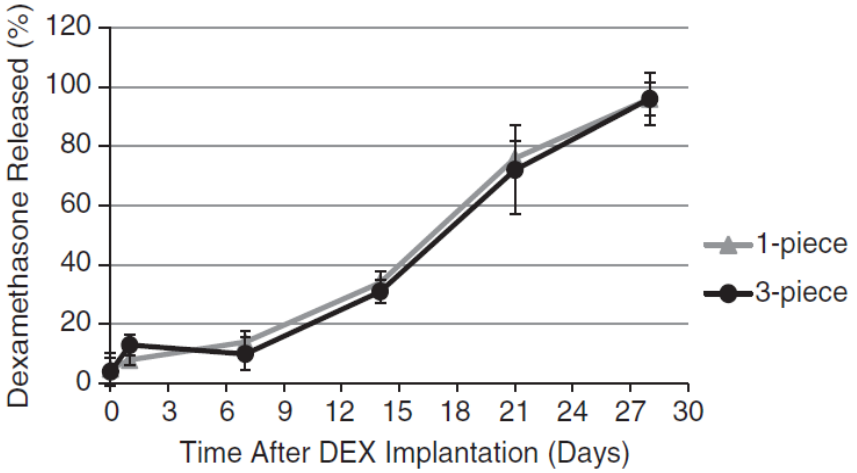


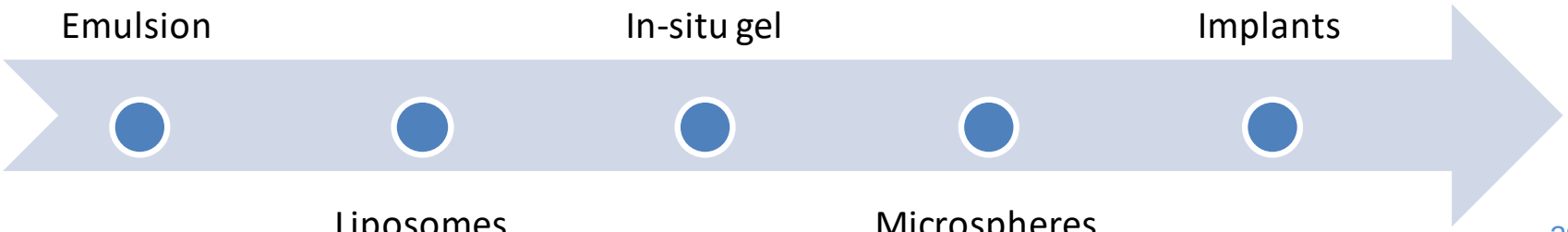
FIG. 2. Cumulative release of dexamethasone in the vitreous humor of rabbits after implantation of 1-piece or 3-piece DEX implants in the posterior segment of opposing eyes. Results are expressed as mean percentage ± standard deviation based on 6 replicates per time point. $P = 0.025$ at day 1, but not significant at any other time point.

Intact implants vs. Fragmented implants

Bhagat R. et al. Comparison of the release profile and pharmacokinetics of intact and fragmented dexamethasone intravitreal implants in rabbit eyes. J Ocular Pharmaco Therap. 30: 854-858. 2014

Equivalence Demonstration of Complex Injectable and Implantable Drug Products

- Formulation qualitatively (Q1) and quantitatively(Q2) sameness
- Physico-chemical properties
- Comparative in-vitro drug release
- Pharmacokinetic equivalence



Summary

- Complex injectable and implantable drug products have unique complexity and challenges for generic development
- In vitro and/or in vivo options are recommended for bioequivalence demonstration of complex injectable and implantable drug products
- Significant progress made in bioequivalence demonstration of these products with the support of GDUFA research funding
  - In vitro release testing method development
  - Statistic method development for particle size profile comparison
  - Model-based bioequivalence method
  - Excipient sameness consideration
  - IVIVC development

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  - Dr. Diane Burgess (University of Connecticut)

U.S. FOOD & DRUG ADMINISTRATION

Thank You!

Any question?

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