U.S. FOOD & DRUG ADMINISTRATION

Multivesicular Liposomes: Physicochemical characterization and in vitro drug release testing

Complex Generic Drug Product Development Workshop

Session 3: Complex Formulations/Dosage Forms

September 12, 2018

Soumyarwit Manna, Ph.D.

Division of Therapeutic Performance,

Office of Research and Standards

OGD | CDER | US FDA

Outline

- Complex formulations – an introduction
- Current bioequivalence guidance on bupivacaine-multivesicular liposome (BPV-MVL)
- FDA internal research
  - Physicochemical characterization of BPV-MVL
  - In vitro drug release study on BPV-MVL
- Take home messages

Complex Formulations – an introduction

- Complex injectable formulations/dosage forms

  – Long-acting (LAI) parenteral drug products
    - Microparticles
    - Implants/inserts
    - Liposomes – unilamellar , multilamellar, multivesicular
    - Suspensions

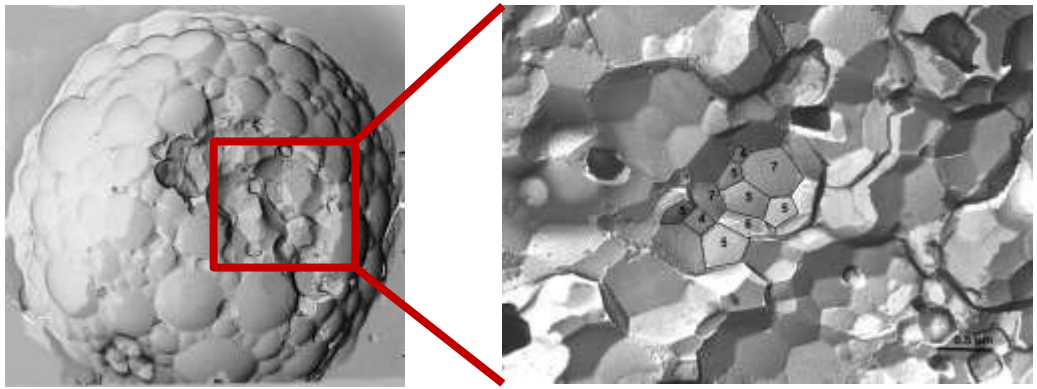
- Limited research conducted on Multivesicular Liposomes – lipid based micro-particles

  – Injectable drug products with nanotechnology
    - Nano size liposomes
    - Iron complex
    - Nano-suspensions

To demonstrate bioequivalence
- Qualitatively same – Q1
- Quantitatively same – Q2
- Physicochemical attributes – Q3

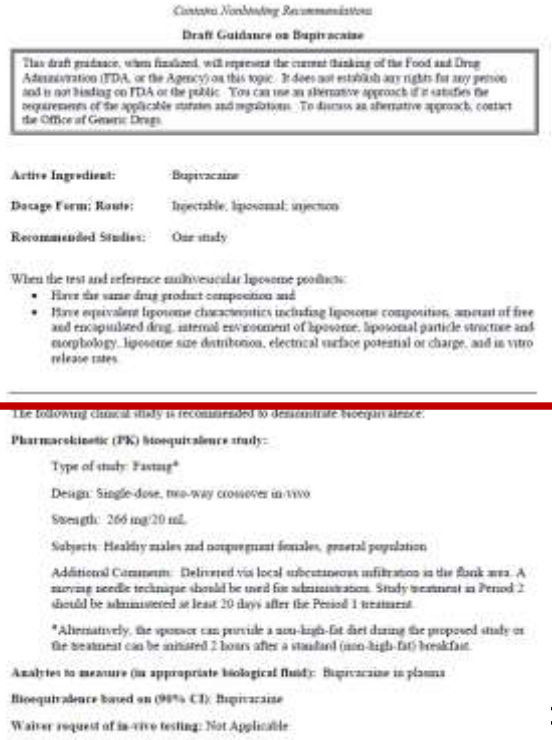
Case Study- Exparel®

- Model Complex Formulation - Exparel®
  - Bupivacaine-Liposome Injectable Injection - 13.3 mg/mL, in 10 mL and 20 mL (single use vial) approved on 10/28/2011
  - An amide local anesthetic, indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia
  - Sterile, non-pyrogenic white to off-white preservative-free aqueous suspension of ***multivesicular liposomes (MVL)*** - based on DepoFoam® drug delivery system



Current Draft Product Specific Guidance for BPV-MVL

- Composition
  - Lipid and non-lipid components (Q1, Q2 sameness)
  - Free and encapsulated drug
- Internal aqueous environment of liposor
  - pH – influence the ionization of the API
  - Osmolality – influence the transmembrane transport of th
  - Volume and composition – influence the encapsulation of
    mechanism
- Particle structure and morphology
  - Unique non-lamellar honeycomb structure and morpholog
    RLD and test product – influence the sustained-release of
- In vitro release kinetics
  - Methodology used for in vitro release testing (IVRT) should
    process variability in the production of the test formulatio



Contains Nonbinding Recommendations

Draft Guidance on Bupivacaine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Bupivacaine

Dosage Form; Route: Injectable; liposomal; injection

Recommended Studies: One study

When the test and reference multivesicular liposome products:

- Have the same drug product composition and
- Have equivalent liposome characteristics including liposome composition, amount of free and encapsulated drug, internal environment of liposome, liposomal particle structure and morphology, liposome size distribution, electrical surface potential or charge, and in vitro release rates

The following clinical study is recommended to demonstrate bioequivalence:

Pharmacokinetic (PK) bioequivalence study:

Type of study: Fasting*

Design: Single-dose, two-way crossover in vivo

Strength: 266 mg/20 mL

Subjects: Healthy males and nonpregnant females, general population

Additional Comments: Delivered via local subcutaneous infiltration in the flank area. A surgical needle technique should be used for administration. Study treatment in Period 2 should be administered at least 20 days after the Period 1 treatment.

*Alternatively, the sponsor can provide a non-high-fat diet during the proposed study or the treatment can be initiated 2 hours after a standard (non-high-fat) breakfast.

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

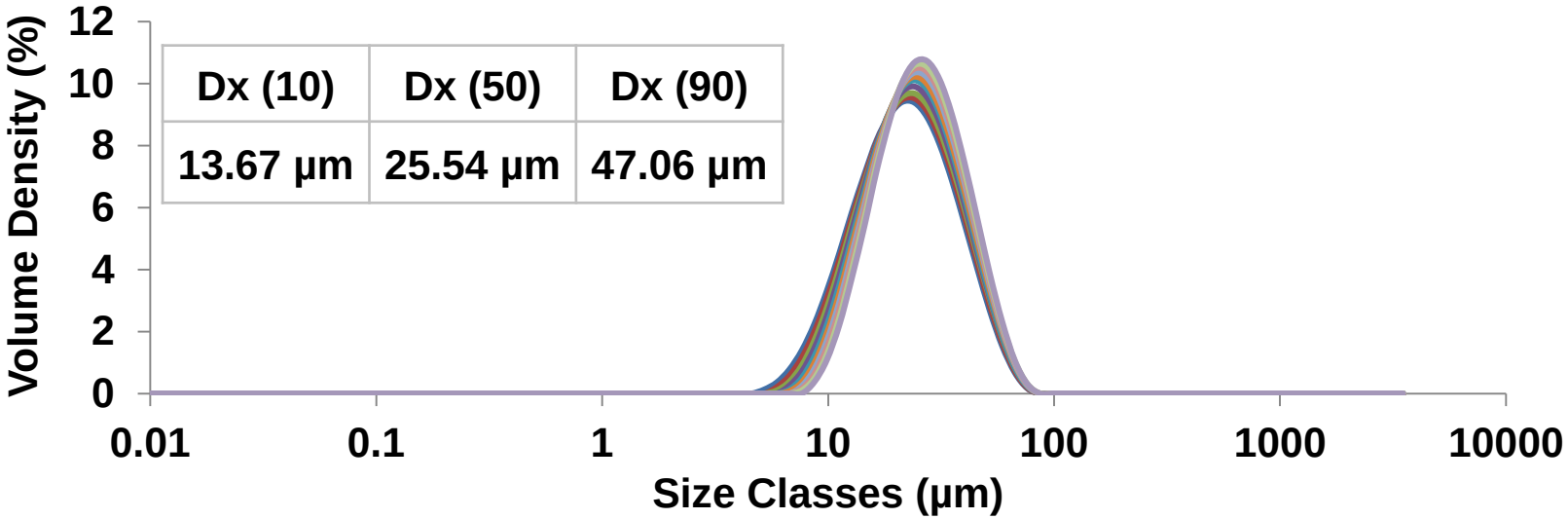
Bioequivalence based on (90% CI): Bupivacaine

Waiver request of in-vivo testing: Not Applicable

Scientific gaps in understanding the effect of change in morphology on the mechanism of release

Particle Size Characterization

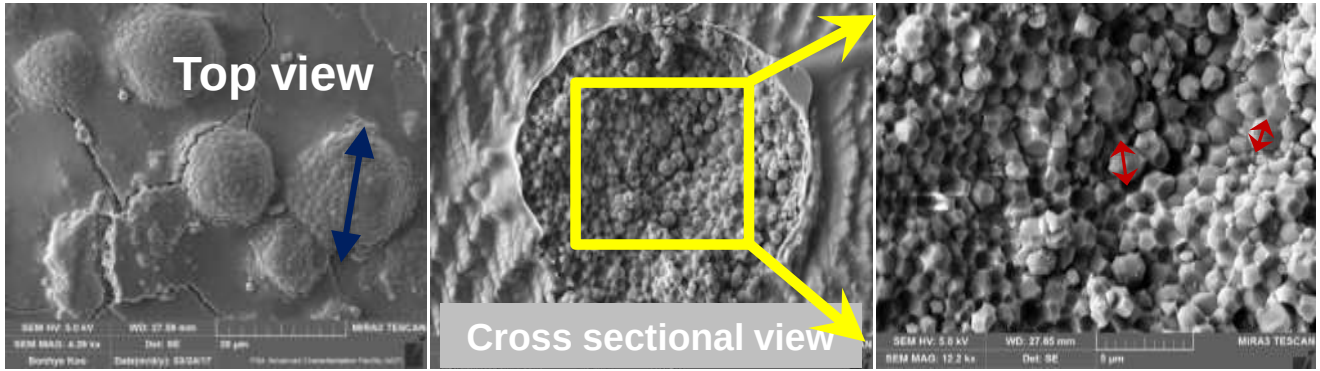
Method: Laser Diffraction

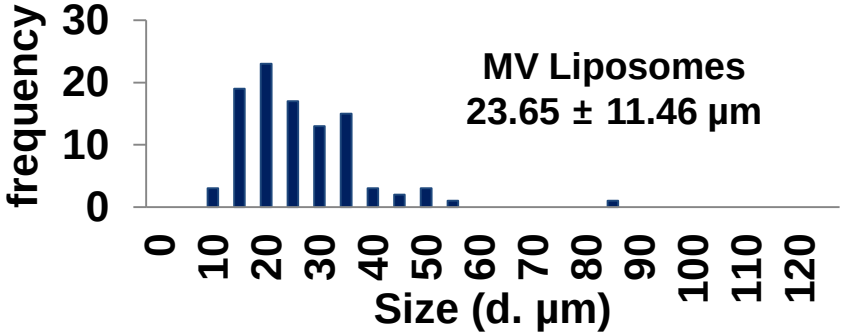


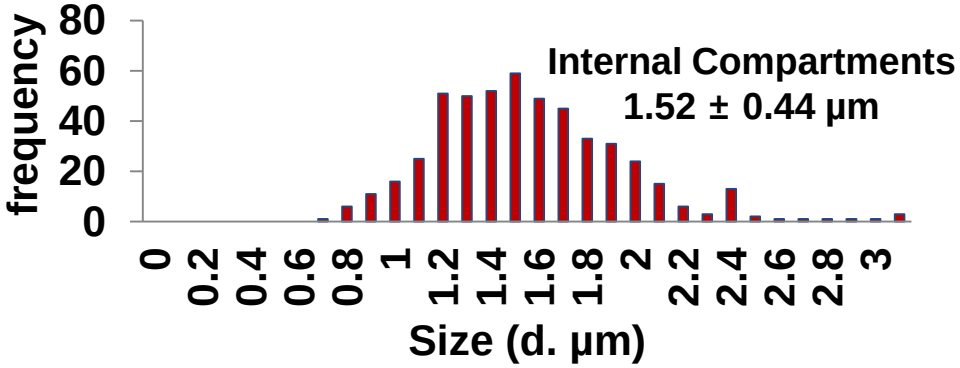
- Applicable for detection of size of the outer vesicles
- Cannot measure size of the inner vesicles
- Cannot be used for detection of size degradation of the vesicles during drug release
- Potential application restricted to assessment of size of the MVLs prior to any drug release study

Particle Structure and Morphology Characterization

Method: Cryo-Scanning Electron Microscopy



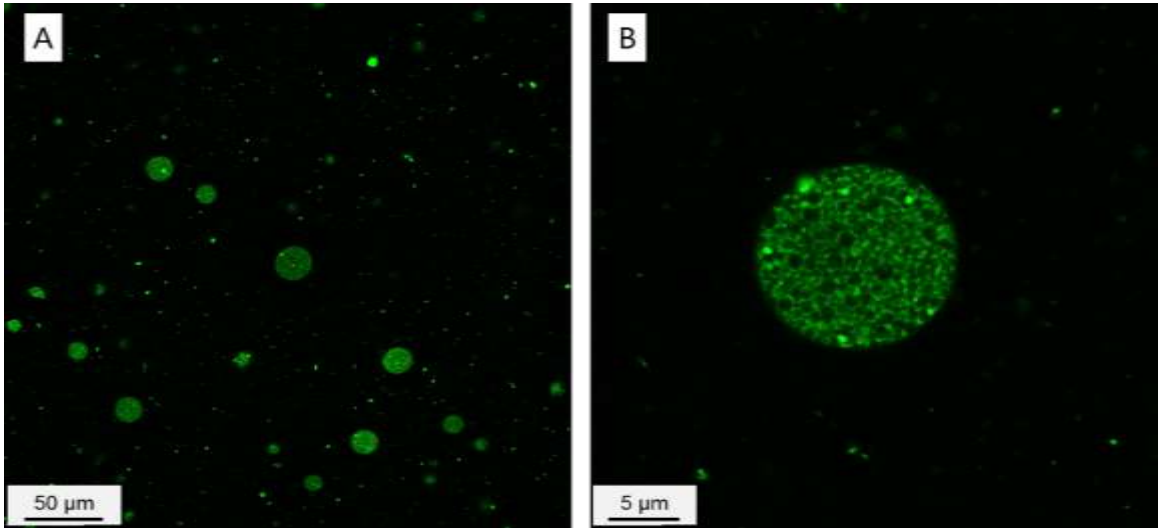




Mostly spherical shape structure; Size range of 10 - 60µm

Particle Structure and Morphology Characterization (Cont.)

Method: Confocal Microscopy



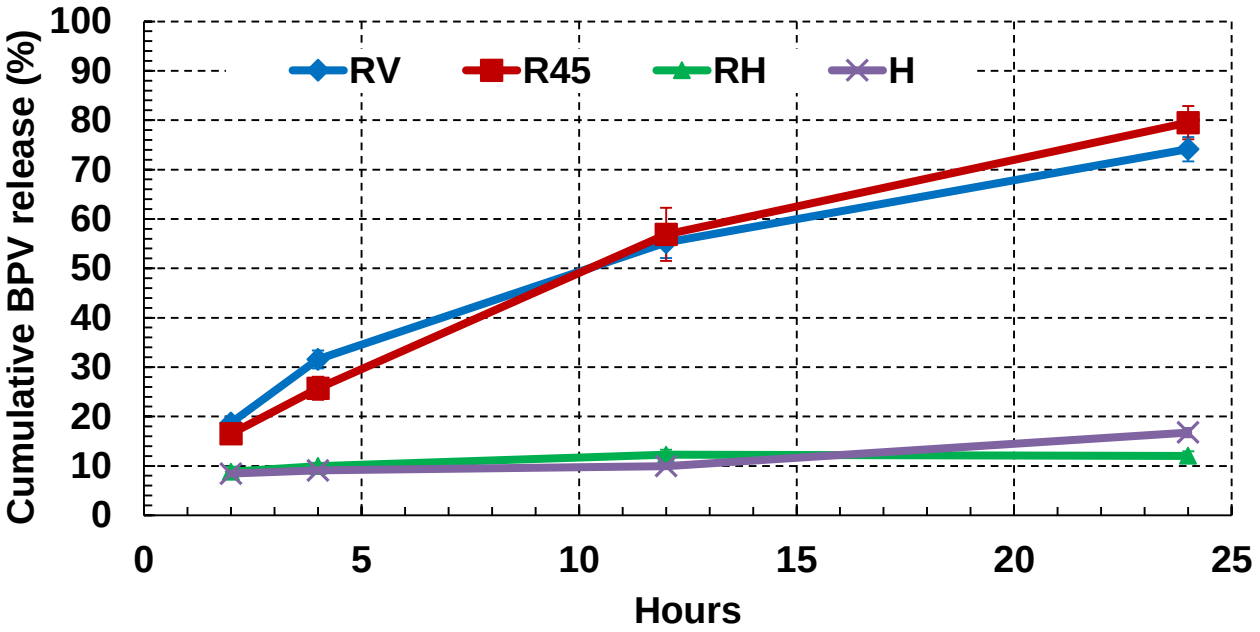
- Internal compartments show the characteristic “honeycomb” structure
- Range of 1 - 2 µm - consistent with cryo-SEM results
- Can be used as a complimentary method to cryo-SEM

In Vitro Release Test (IVRT) – Release Mechanism

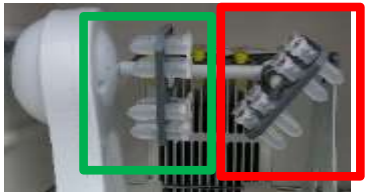
- Sample-and-separate method (water bath shaker)
  - Orientation / agitation
  - Composition of dissolution media – with / without human serum albumin
  - Dissolution media – phosphate buffer (pH 7)

- Dialysis coupled with in-situ UV-Vis probe in a USP II apparatus
  - MWCO of dialysis membrane – 10 kDa, 20 kDa, 50 kDa and 100 kDa
  - Temperature - 25°C, 31°C, 37°C, 40°C at pH 7, 120 rpm
  - pH of dissolution media – pH 5, pH 6, pH 7 at 37°C, 120 rpm
  - Agitation speed – 120 rpm and 240 rpm at pH 7, 37°C

Sample-and-Separate Method Release Profiles – Orientations

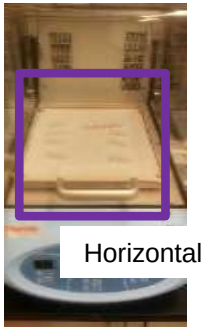


Tubes rotated – Vertical (RV)



Tubes rotated– Horizontal (RH)

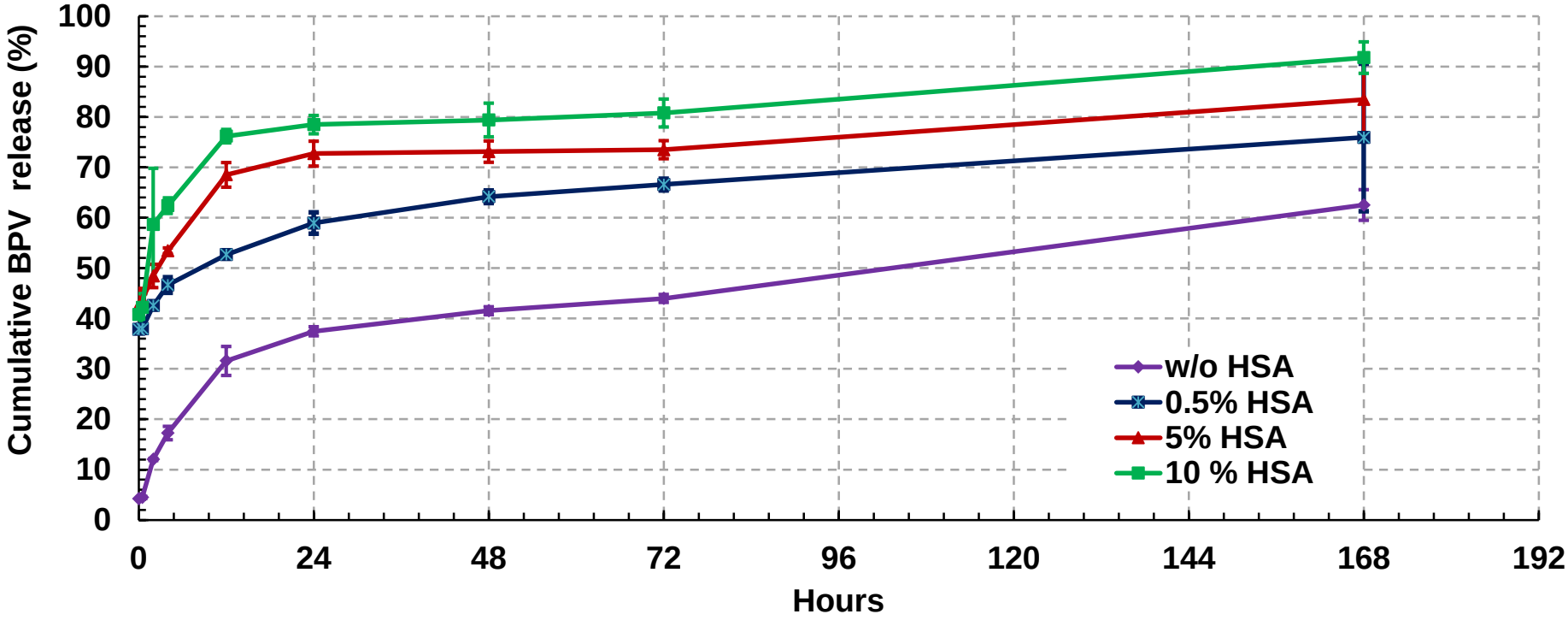
Tubes rot.– 45˚ (R45)



Horizontal (H)

Different orientations resulted in difference in release profiles:
RV and R45 position exhibited more release compared to other orientations

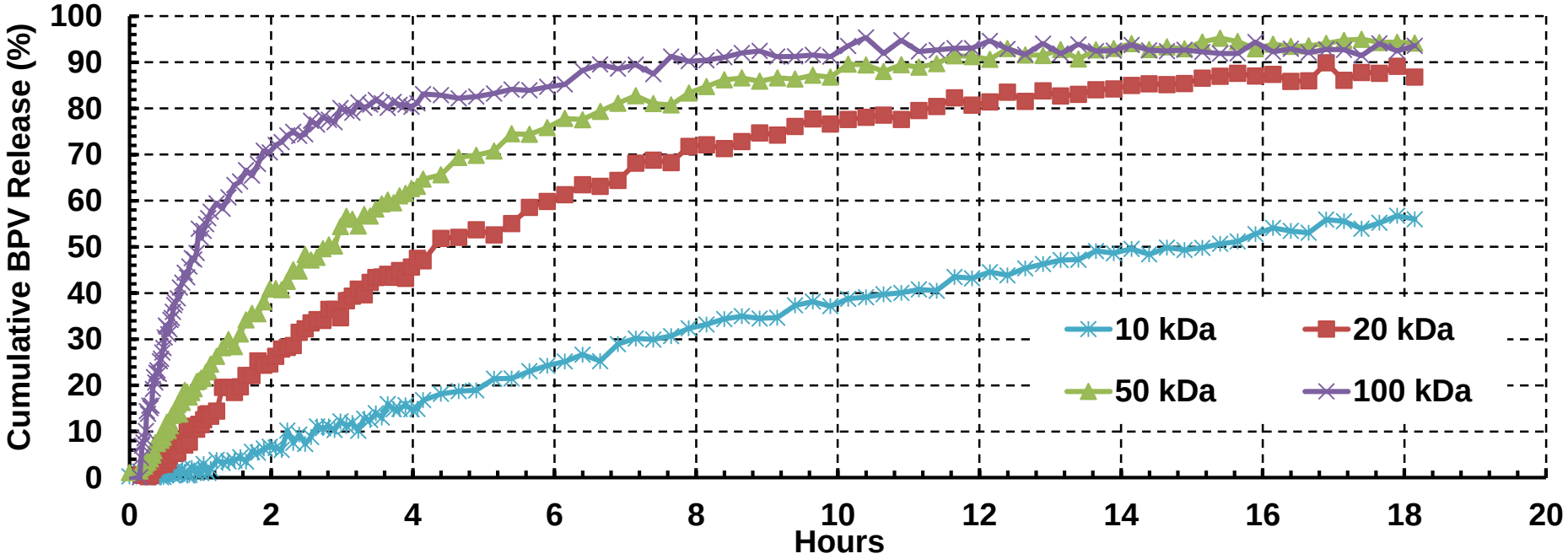
Sample-and-Separate Method
Release Profiles – Influence of HSA



Presence of HSA in 50 mM PBS caused faster release of BPV from the MVLs

Dialysis coupled with in-situ UV-Vis probe in a USP II apparatus

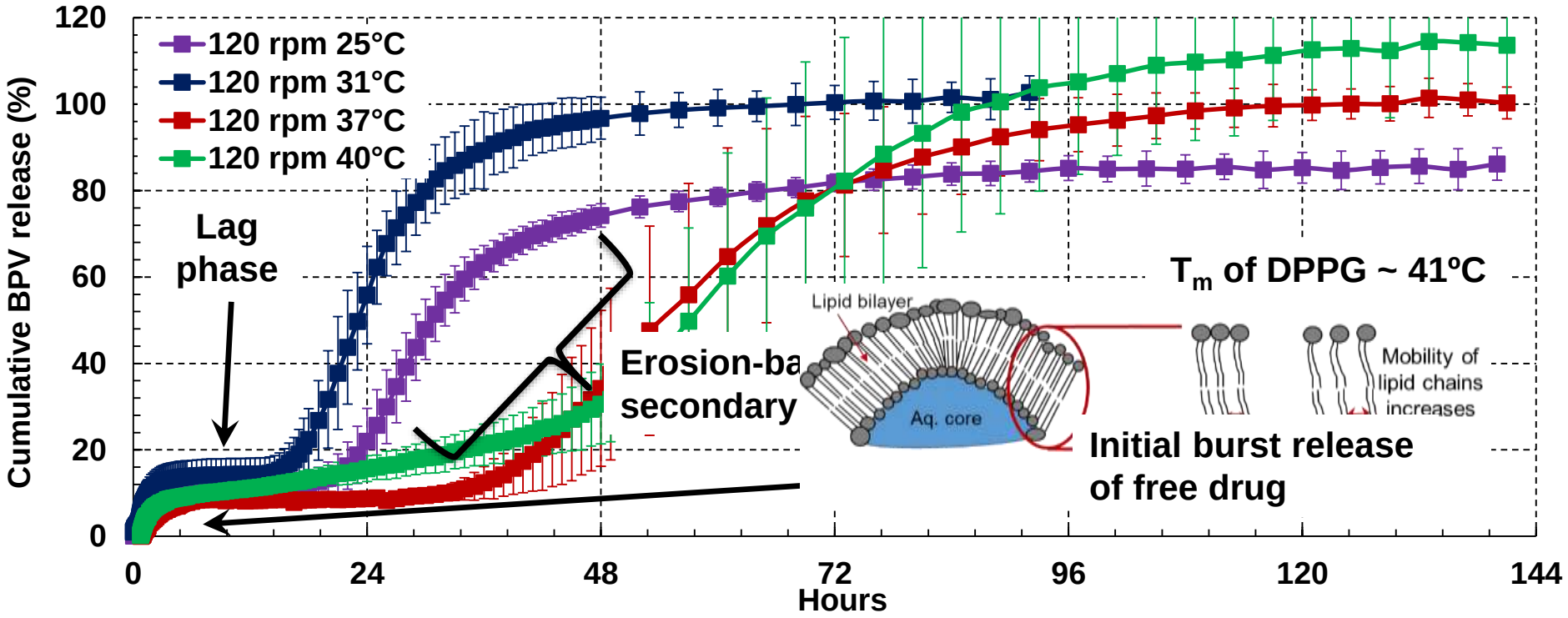
- Effect of MWCO of Dialysis Membrane on the Diffusivity of BPV



- Initial diffusion rate of BPV was proportional to the MWCO of the dialysis membrane
- 100 kDa membranes exhibited the fastest rate of diffusion among the tested membranes
- 100 kDa membranes also showed the typical diffusion profile ~ 2 h for most drugs

Dialysis coupled with in-situ UV-Vis probe in a USP II apparatus

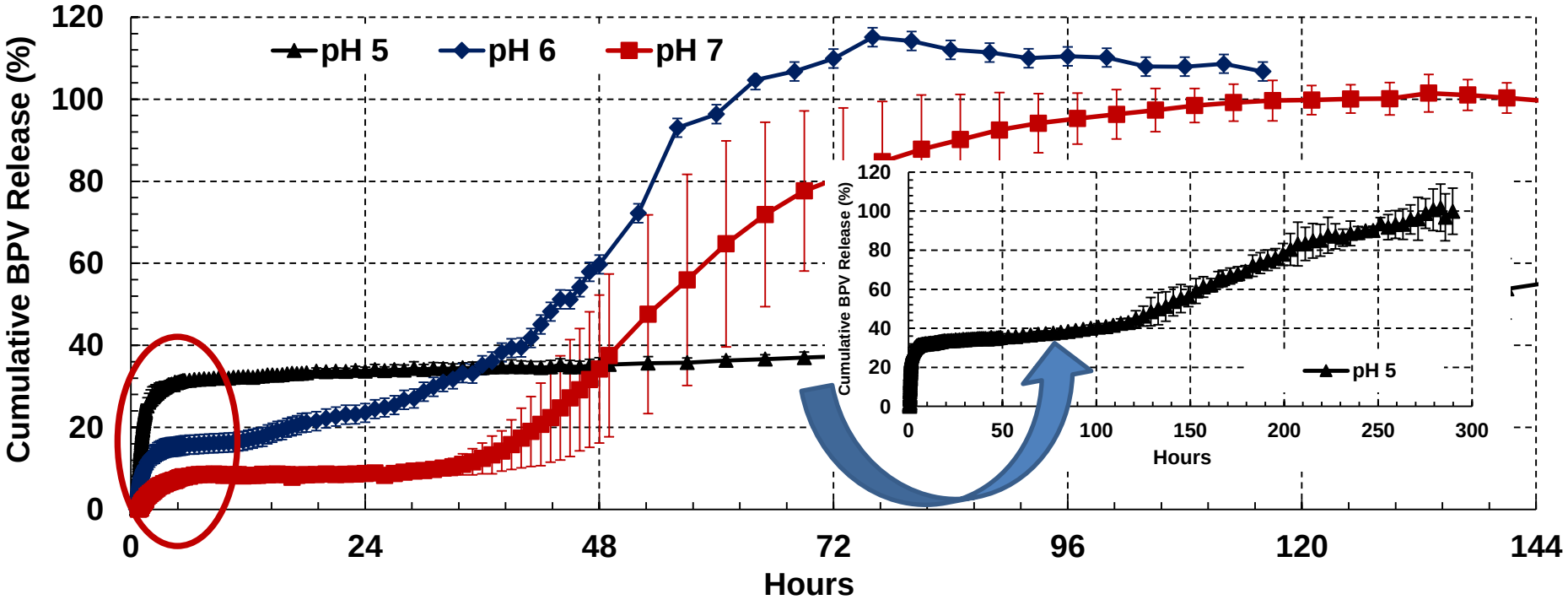
- Effect of Temperature



- Change in temperature influences the lag phase and the secondary release phase
- Temperatures close to T_m of the lipids cause more variable release in the secondary release phase

Dialysis coupled with in-situ UV-Vis probe in a USP II apparatus

- Effect of pH

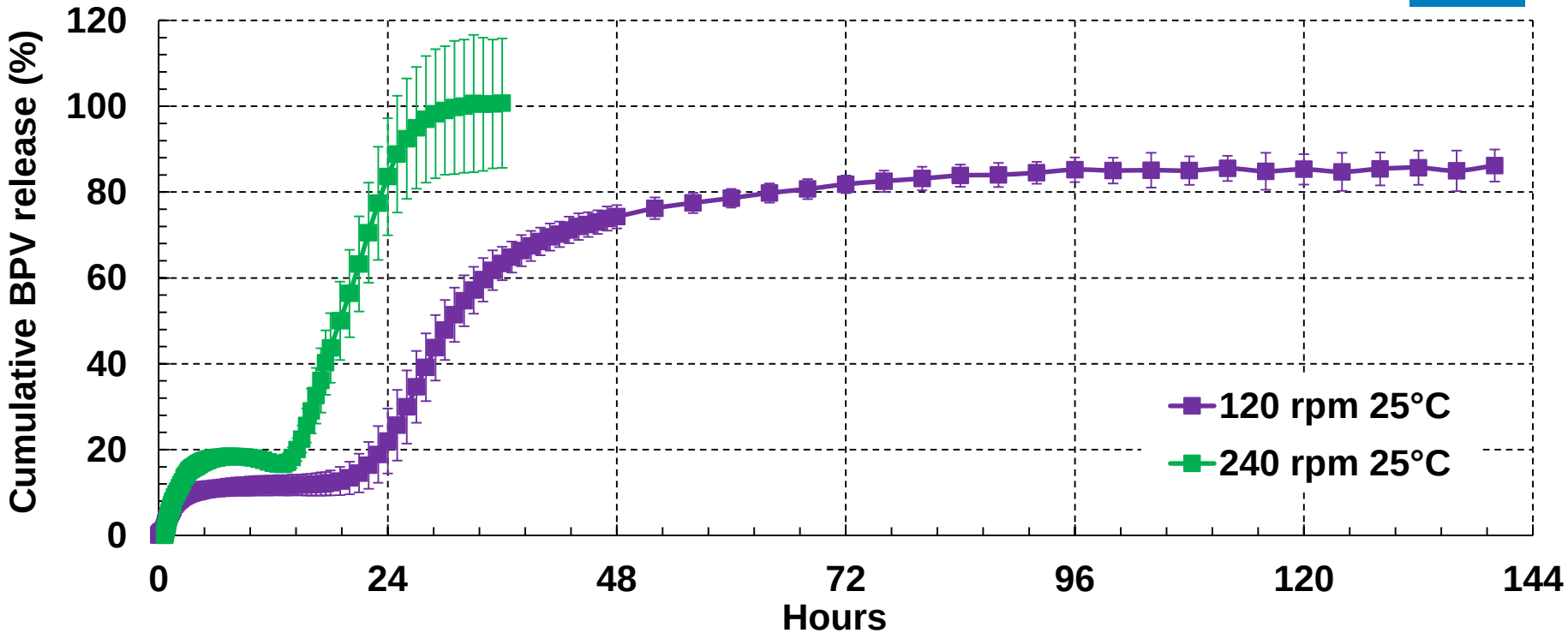


[1]Shah and Maniar, J Con Rel; 1993

- pH ↓ higher solubility of BPV (~ 40 mg/mL)[1] ↑
- pH ↑ ionization of BPV (pKa = 8.4) ↓

Dialysis coupled with in-situ UV-Vis probe in a USP II apparatus

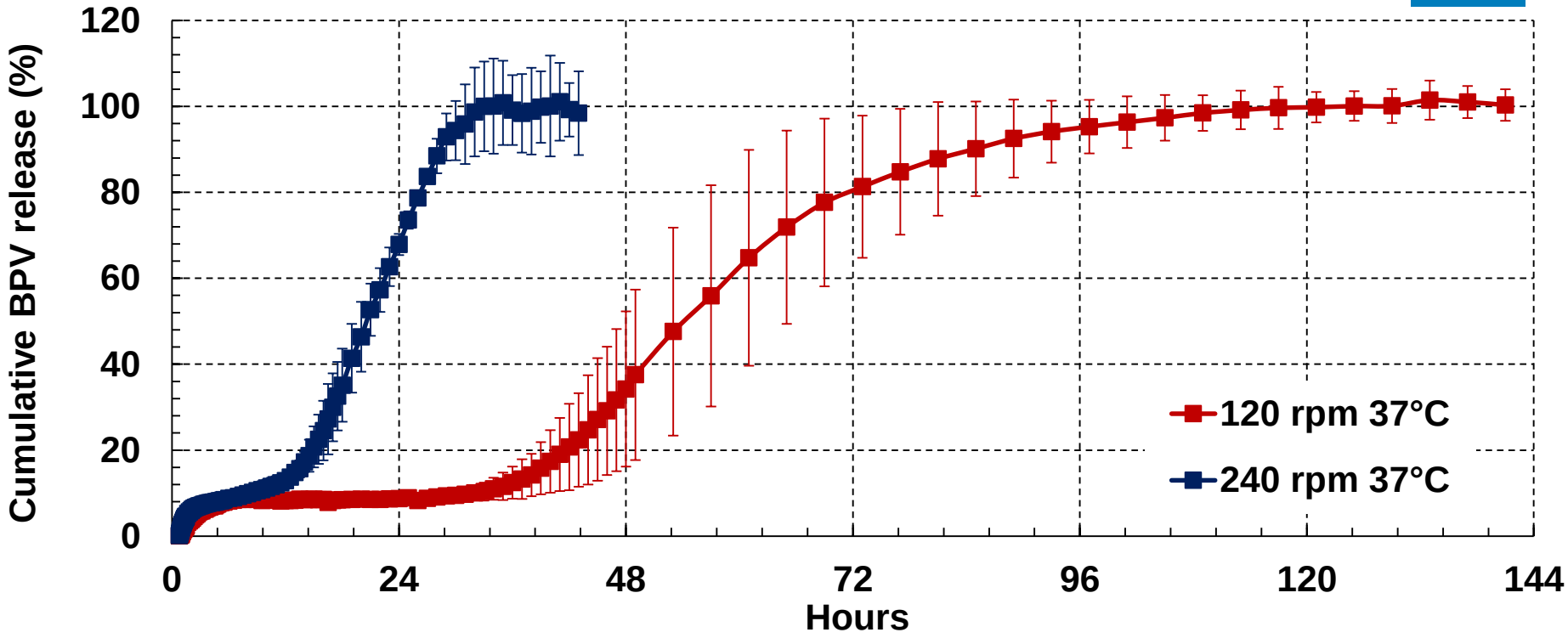
– Effect of Agitation - 25°C



Higher agitation releases the drug faster

Dialysis coupled with in-situ UV-Vis probe in a USP II apparatus

– Effect of Agitation - 37°C



Higher agitation releases the drug faster, irrespective of the temperature

Take Home Messages

- Potential methods to evaluate particle structure/morphology of the MVLs and the size distribution:
  - Cryo-SEM
  - Confocal microscopy
  - Laser diffraction
- Experimental factors that should be considered when develop and validate an IVRT method for BPV-MVLs include but are not limited to:
  - Temperature – changes the mobility of the lipid chains
  - pH – change the ionization of the drug
  - Agitation – causes disruption of liposomes
  - Composition of the release media – causes disruption of liposomes
  - MWCO of the dialysis membrane if applicable – influences diffusion of drug

Acknowledgements

- FDA / CDER / OGD / ORS / DTP
  - Yan Wang
  - Darby Kozak
  - Stephanie Choi
  - Bonhye Koo
  - Lynn Chen
  - Peter Petrochenko
- FDA / CDRH / DBCMS
  - Jiwen Zheng
  - Yong Wu
  - Berk Oktem
- FDA / CDER/ OPQ / OTR / DPQR
  - Xiaoming Xu
  - Yixuan Dong
- Characterization Facilities
  - FDA Advanced Characterization Facility (ACF, Formerly Nanotechnology Core Facility) at CDRH
  - CDRH/OSEL/DBCMS lab
  - CDER/OPQ/OTR/DPQR lab


FDA
U.S. FOOD & DRUG
ADMINISTRATION