

Application of Adaptive Perfusion as In Vitro Release Testing Method to Improve Understanding and Assessment of Complex Products

Dongkai Zhu, Ph.D.

Staff Fellow
Office of Pharmaceutical Quality Research
Office of Pharmaceutical Quality
CDER | US FDA

[Scientific and regulatory considerations for IVRT for complex products] –
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Everyone deserves confidence
in their *next* dose of medicine.

Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

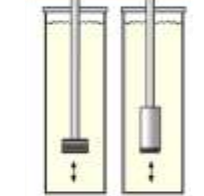
www.fda.gov

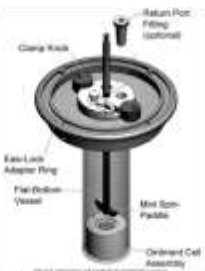
Overview



- Why we need better in vitro release testing (IVRT) methods for complex drug products:
 - Challenges
 - Needs
- Our internal approach to solve this problem:
 - Example: adaptive perfusion (AP)
 - Case study: ophthalmic emulsion
 - Other potential uses

Common IVRT Methods

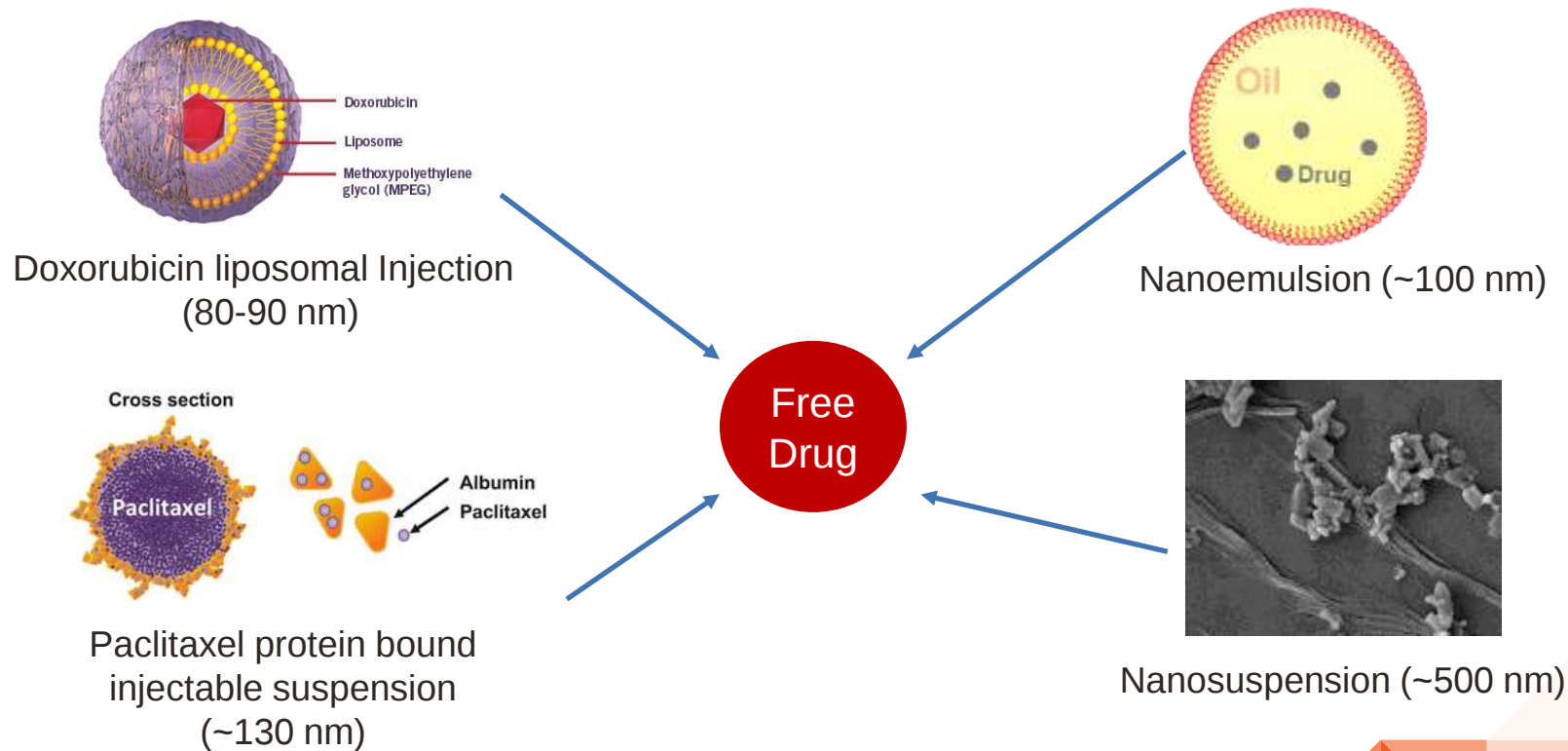
USP Apparatus 1	USP Apparatus 2	USP Apparatus 3	USP Apparatus 4	USP Apparatus 5	USP Apparatus 6	USP Apparatus 7
						
Basket	Paddle	Reciprocating Cylinder	Flow-through Cell	Paddle over Disk	Rotating Cylinder	Reciprocating Holder

Vertical Diffusion Cell	USP 2 Immersion Cell	Dialysis	Bottle-shaking	Others
			Sample-and-separate 	• Pulsatile Microdialysis (PMD) • Miniatured flow-through cell • MicroDiss™ • MicroFLUX™ • Scissor™ (sub-cutaneous)

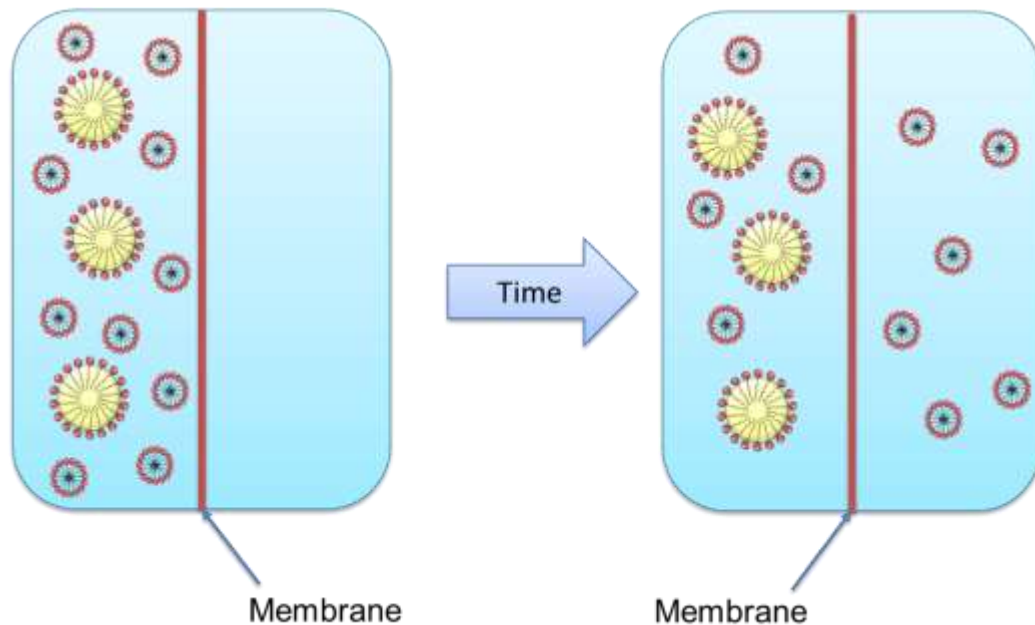
A Good IVRT Needs to be:

- **Reproducible:**
 - Precise: e.g., low CV%
 - Robust: e.g., against minor disturbance to method
- **Discriminatory:**
 - Sensitive: e.g., known changes in quantity like sample with 50%, 100%, 150% drug loading
 - Selective: e.g., able to detect differences in sample if Critical Quality Attributes (CQAs) changed, such as particle size

Membrane Diffusion: A Common Approach for Separation



Limitation of Membrane Separation in IVRT



- Driven by concentration gradient: High to Low
- Membrane transfer may become a rate-limiting step

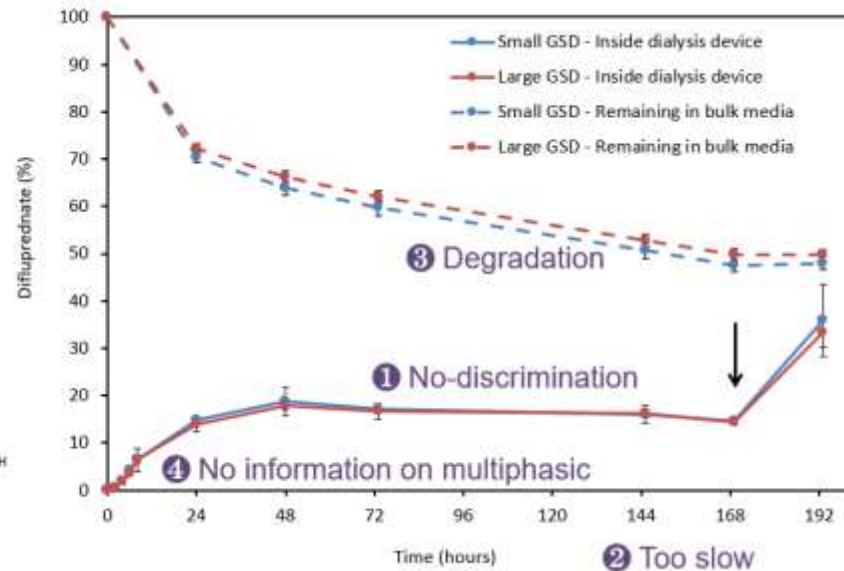
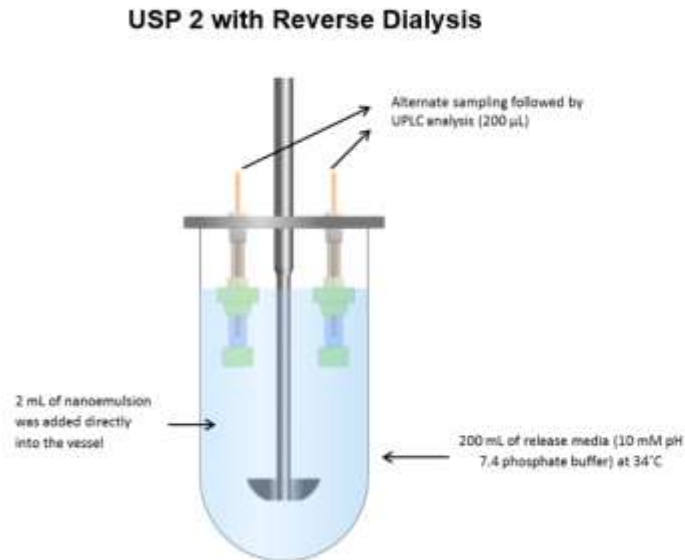
Ophthalmic Emulsions Can Be Challenging



- Complex active ingredient (**complex mixtures of APIs**)
- Complex dosage form and formulation (**multiphasic, colloids**)
- Complex routes of delivery (**ophthalmic**)

IVRT by (Reverse) Dialysis: A Typical Example

Difluprednate ophthalmic emulsion 0.05%

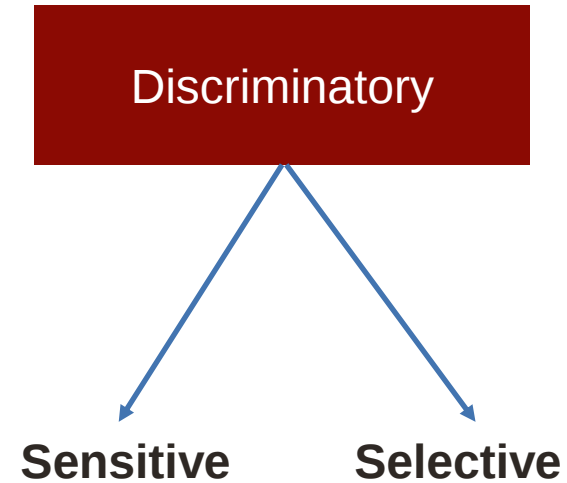
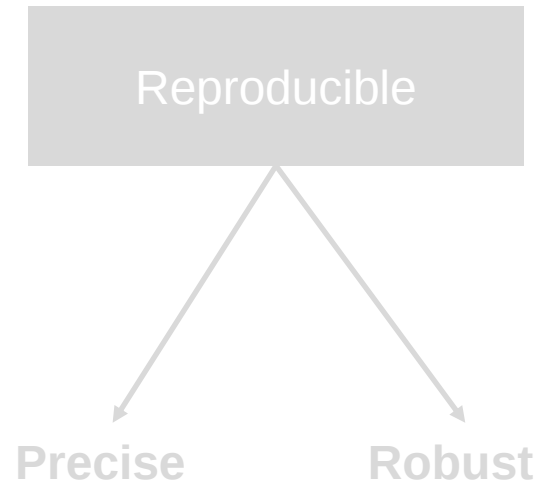


Patel D, Zhang Y, Dong Y, Qu H, Kozak D, Ashraf M, Xu X. Adaptive perfusion: An in vitro release test (IVRT) for complex drug products. *Journal of Controlled Release*. 2021 May 10;333:65-75.

Challenges with Current IVRT Method



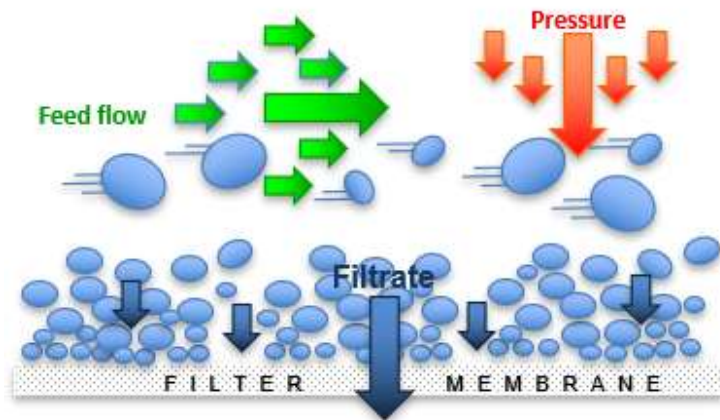
Challenges with Current IVRT Method



How can we improve IVRT?

One Example: Adaptive Perfusion (AP)

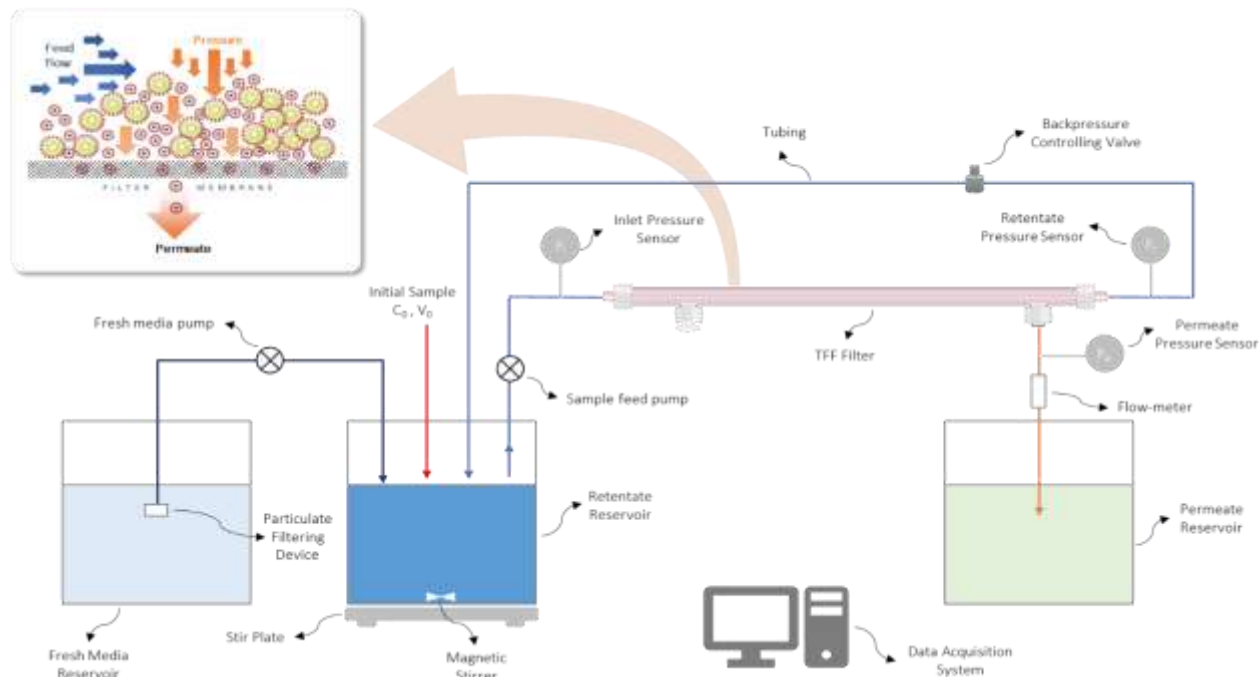
Tangential Flow Filtration (TFF)



- Measures:

- Retentate (remaining drug) and permeate (removed drug)
- Rate (how fast drug is released) and extent (how much drug is released)

Schematic Diagram



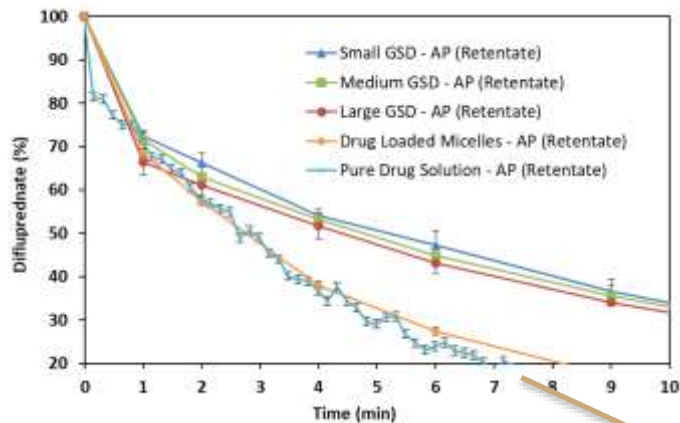
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Case Study: Formulation with Varying Globule Size Distribution

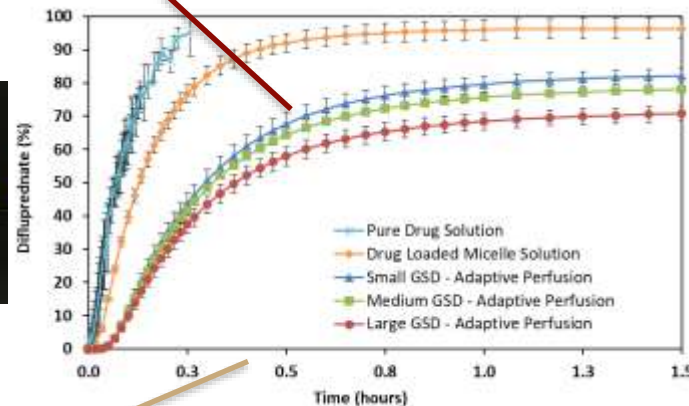


2 Discrimination

Retentate Profile (n=3)



Permeate Profile (n=3)

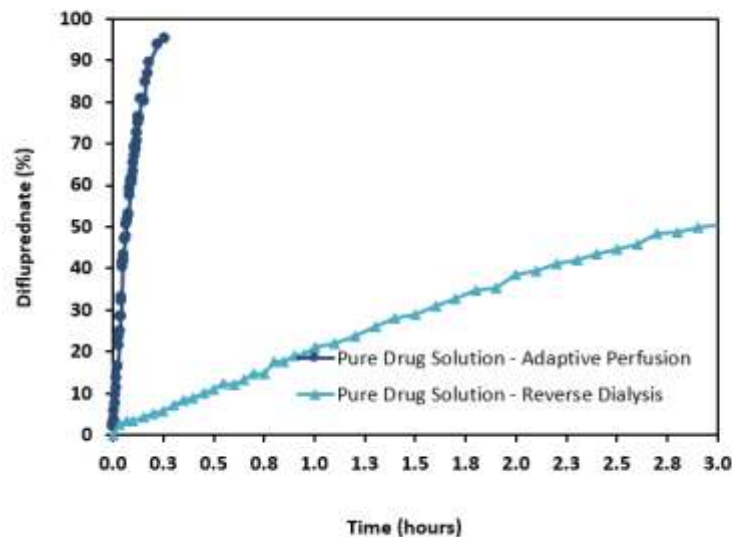


1 Fast

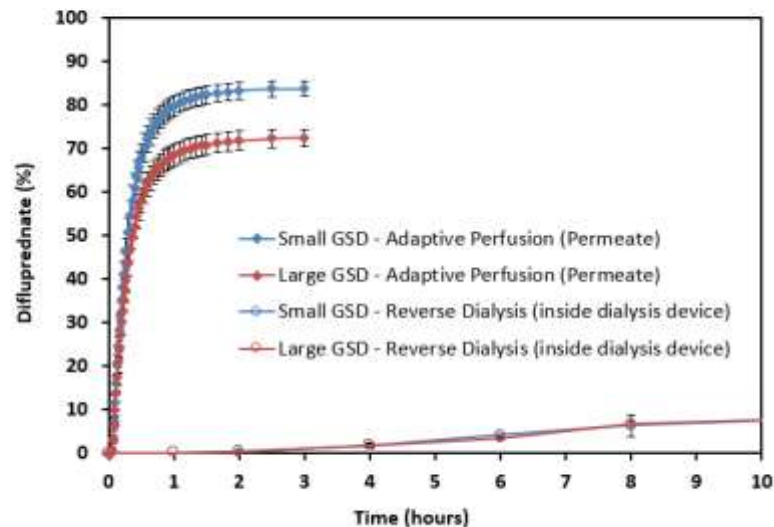
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Comparison to Traditional Dialysis

Pure Drug Solution (n = 3)

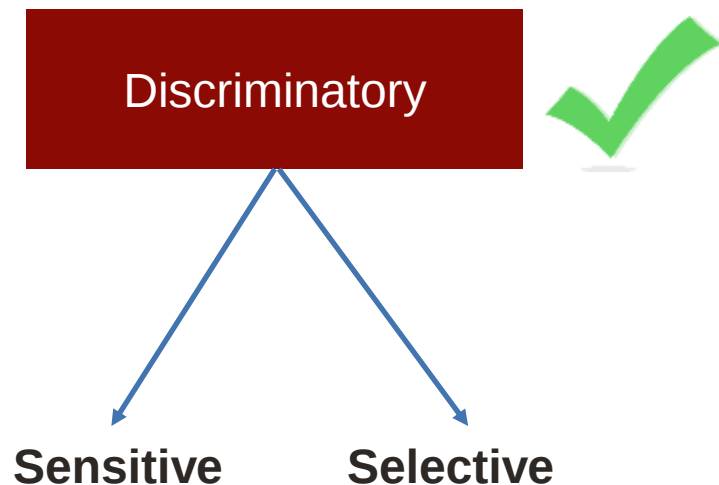
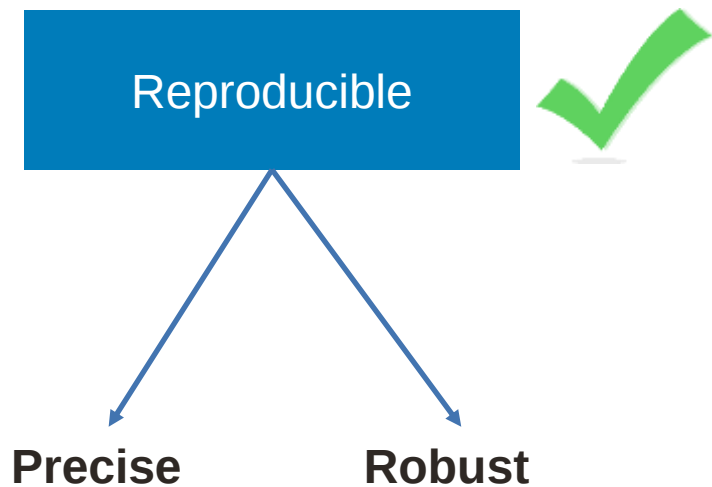


Small and Large GSD nanoemulsions (n = 3)

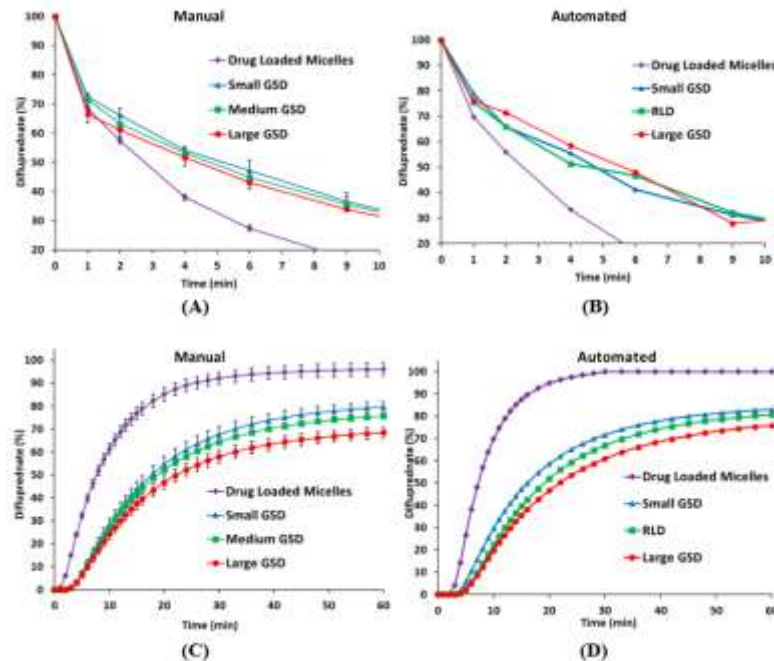


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Both Goals Achieved with AP

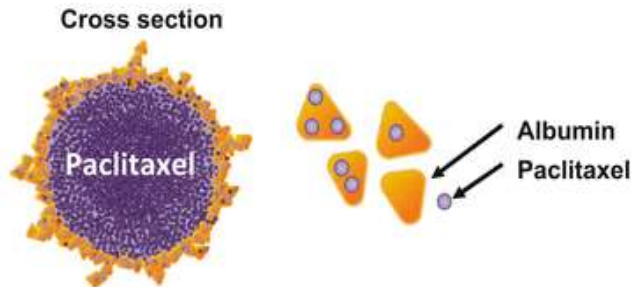


Automation for Further Improved Reproducibility



Other Potential Use #1:

Paclitaxel Protein Bound Injectable Suspension



Challenges:

- **RAPIDLY** and **SENSITIVELY** measure dissolution of protein bound drug particle system

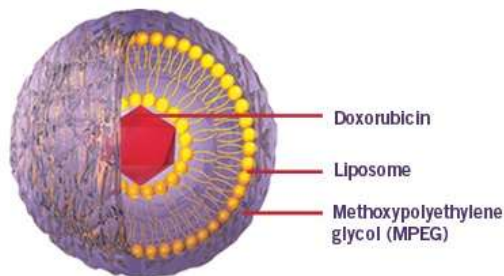
Impact:

- Understanding the role of **ELECTROLYTE**, in **STABILIZATION** and **RELEASE** mechanism

Otagiri M, Chuang VT, editors. Albumin in medicine: pathological and clinical applications. Springer; 2016 Nov 1

Other Potential Use #2:

Doxorubicin Liposomal Injection



Challenges:

- The DELAYED RELEASE mechanism is difficult to study using traditional IVRT method.
- Lack of the understanding of PARTICLE MORPHOLOGY on release.

Impact:

- LIPOSOMES share many SIMILARITIES with LIPID NANOPARTICLES (LNP).
- An ideal PLATFORM to study and facilitate the assessment of future LNP submissions.

<https://www.fiercepharma.com/m-a/updated-j-j-releases-more-doxil-its-popular-cancer-med-has-been-dogged-by-supply-issues>

fda.gov/cdersbia

Summary



- IVRT approach for complex drug products can be challenging and needs more concerted effort to improve.
- A new IVRT method was developed that can improve the understanding of in vitro release behavior of complex drug products.
- We encourage the development of more innovative and fit-for-purpose IVRT methods.

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Challenge Question #1

True or False? To develop suitable IVRT method for complex products, compendial apparatus should be used.

True

False

Challenge Question #2

Which of the following is NOT critical for developing a suitable IVRT for complex drug products?

- A. Sensitivity
- B. Selectively
- C. Robustness
- D. In vitro-in vivo correlation



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Questions?

Dongkai Zhu, Ph.D.

Staff Fellow

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