

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

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[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.







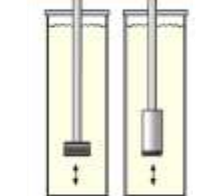

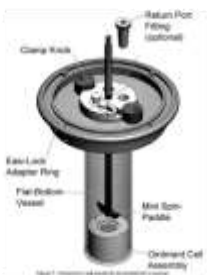


[www.fda.gov](http://www.fda.gov)

# 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

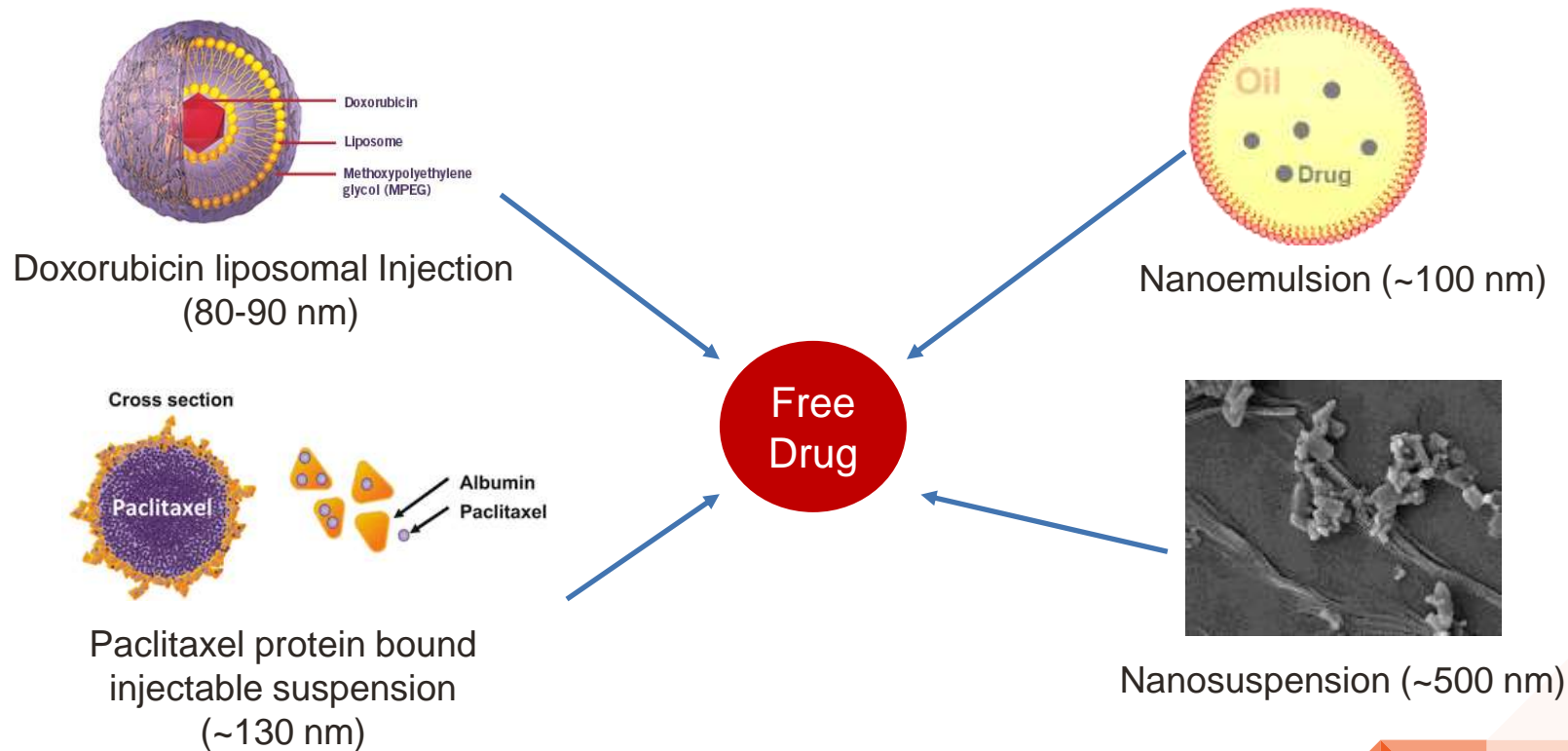
# Common IVRT Methods

<b>USP Apparatus 1</b>  Basket	<b>USP Apparatus 2</b>  Paddle	<b>USP Apparatus 3</b>  Reciprocating Cylinder	<b>USP Apparatus 4</b>  Flow-through Cell	<b>USP Apparatus 5</b>  Paddle over Disk	<b>USP Apparatus 6</b>  Rotating Cylinder	<b>USP Apparatus 7</b>  Reciprocating Holder	
<b>Vertical Diffusion Cell</b> 		<b>USP 2 Immersion Cell</b> 		<b>Dialysis</b> 		<b>Bottle-shaking</b> Sample-and-separate 	<b>Others</b> <ul style="list-style-type: none"> <li>• Pulsatile Microdialysis (PMD)</li> <li>• Miniatured flow-through cell</li> <li>• MicroDiss™</li> <li>• MicroFLUX™</li> <li>• Scissor™ (sub-cutaneous)</li> </ul>

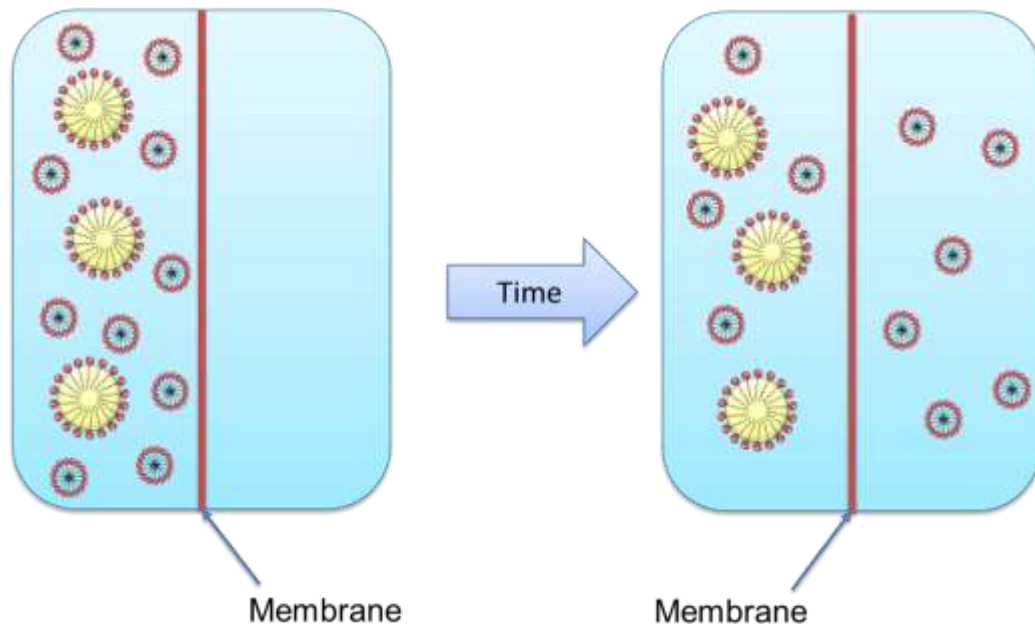
# A Good IVRT Needs to be:

- **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

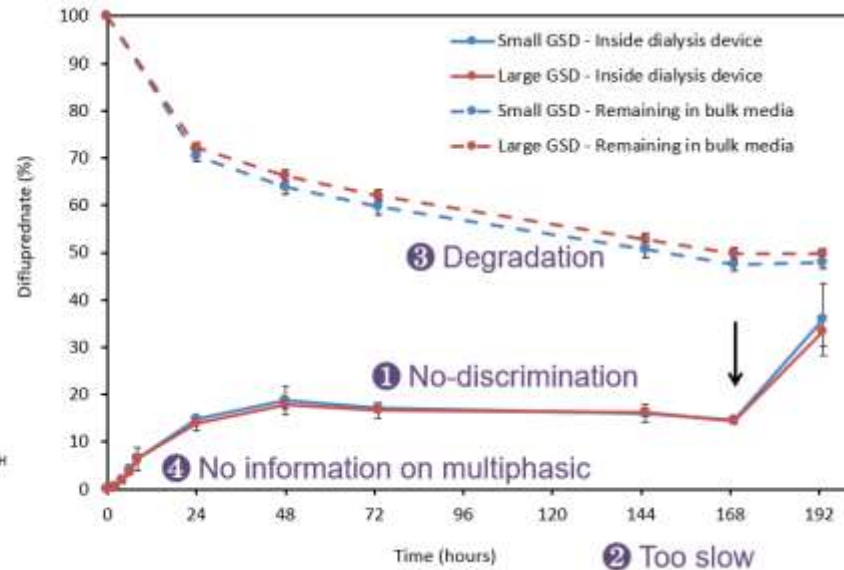
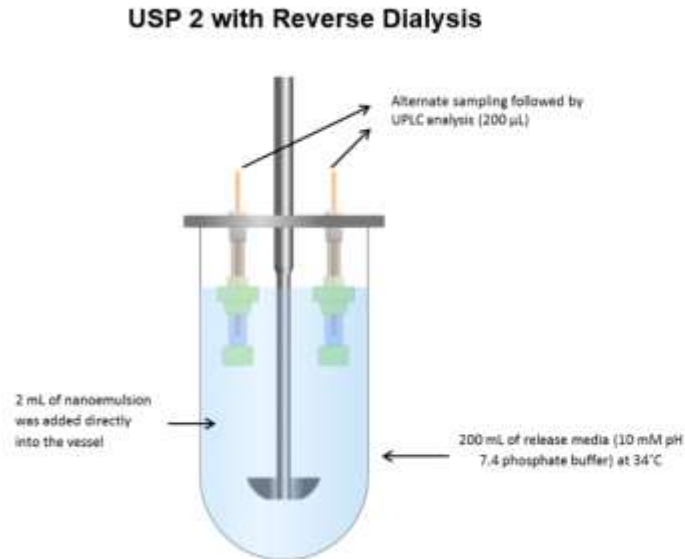


- Complex active ingredient (**complex mixtures of APIs**)
- Complex dosage form and formulation (**multiphasic, colloids**)
- Complex routes of delivery (**ophthalmic**)



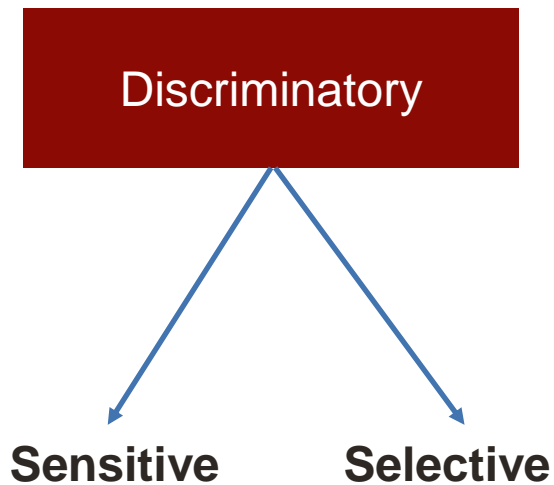
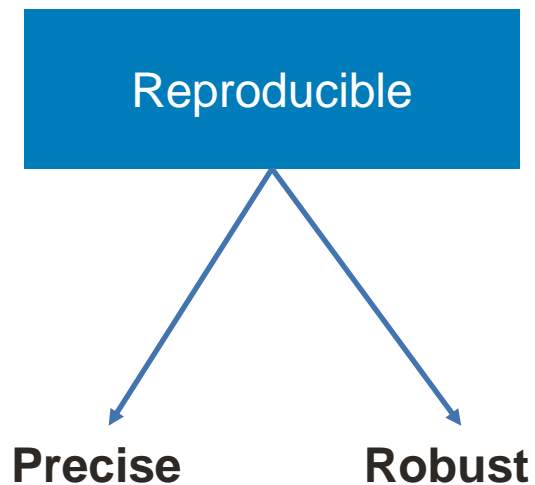
# IVRT by (Reverse) Dialysis: A Typical Example

Difluprednate ophthalmic emulsion 0.05%

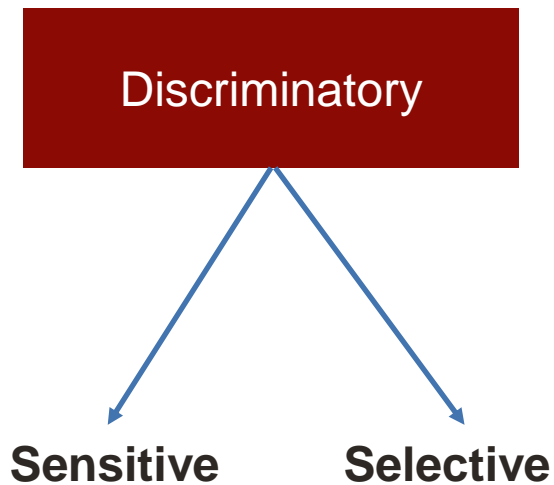
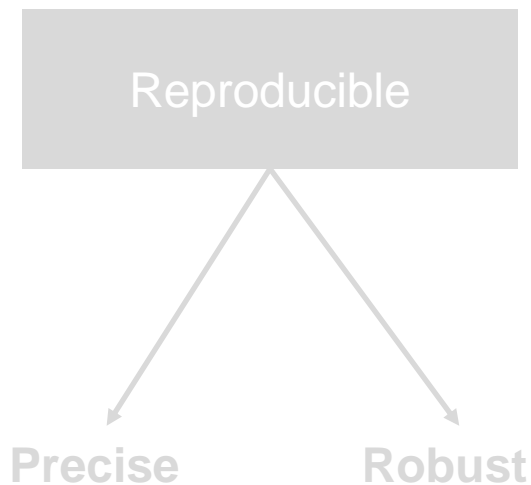


Patel D, Zhang Y, Dong Y, Qu H, Kozak D, Ashraf M, Xu X. Adaptive perfusion: An in vitro release test (IVRT) for complex drug products. Journal of Controlled Release. 2021 May 10;333:65-75.

# Challenges with Current IVRT Method



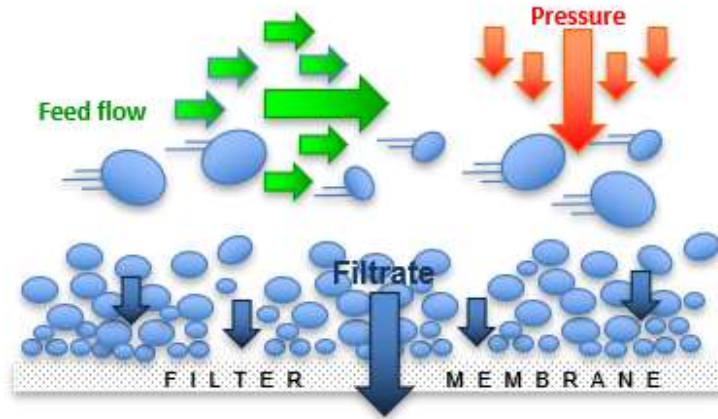
# Challenges with Current IVRT Method



# How can we improve IVRT?

# One Example: Adaptive Perfusion (AP)

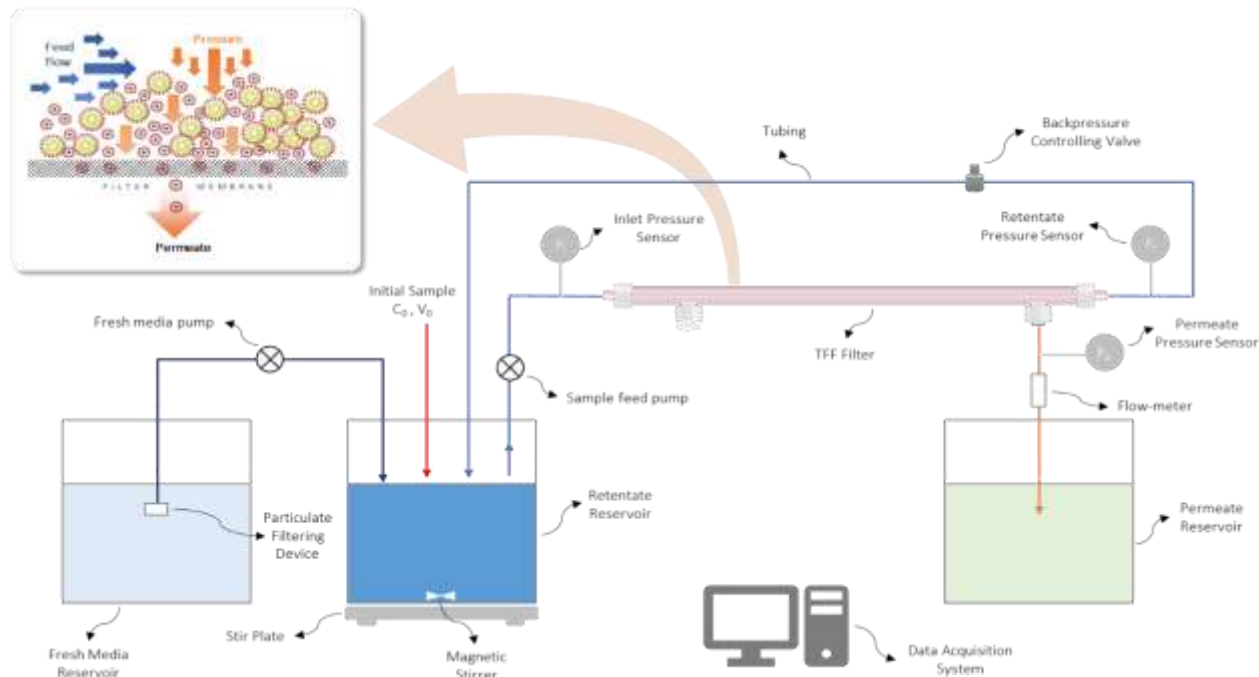
## Tangential Flow Filtration (TFF)



- Measures:

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

# Schematic Diagram



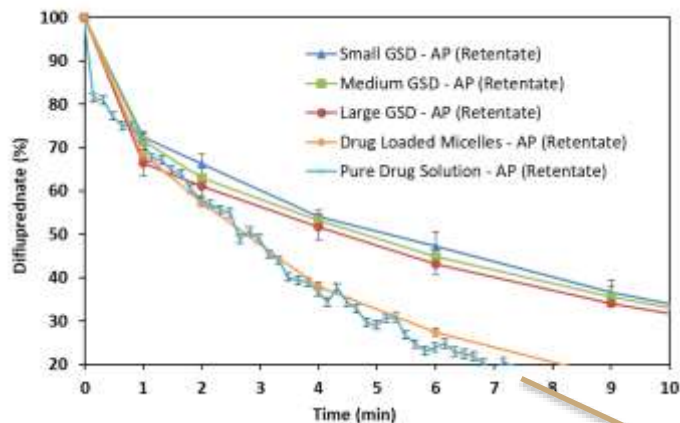
Patel D, Zhang Y, Dong Y, Qu H, Kozak D, Ashraf M, Xu X. Adaptive perfusion: An in vitro release test (IVRT) for complex drug products. Journal of Controlled Release. 2021 May 10;333:65-75.

# Case Study: Formulation with Varying Globule Size Distribution

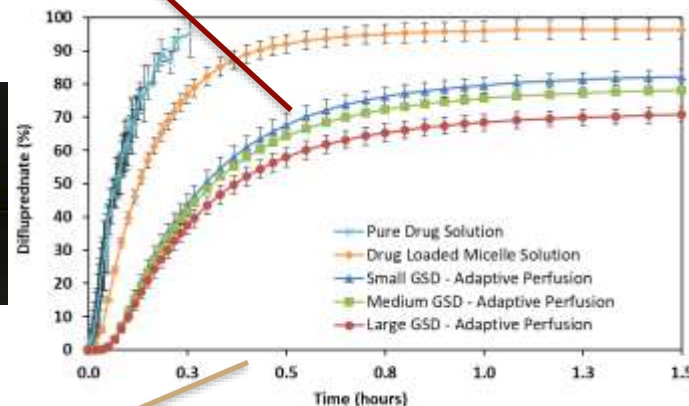


## 2 Discrimination

Retentate Profile (n=3)



Permeate Profile (n=3)

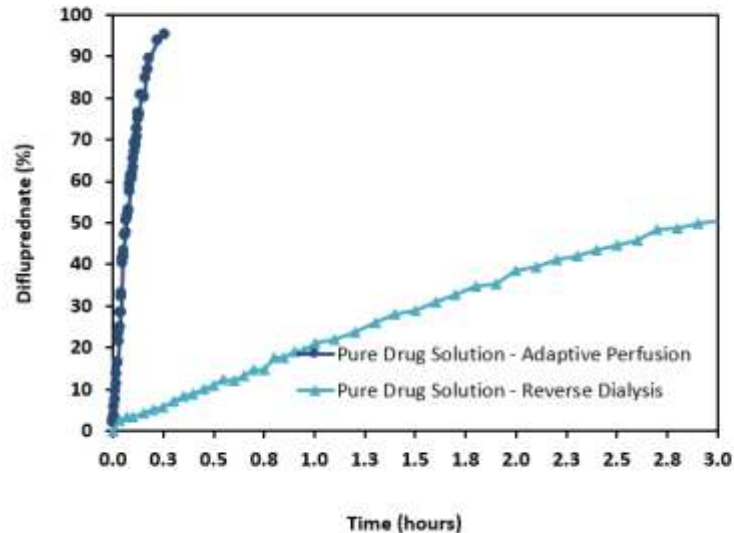


## 1 Fast

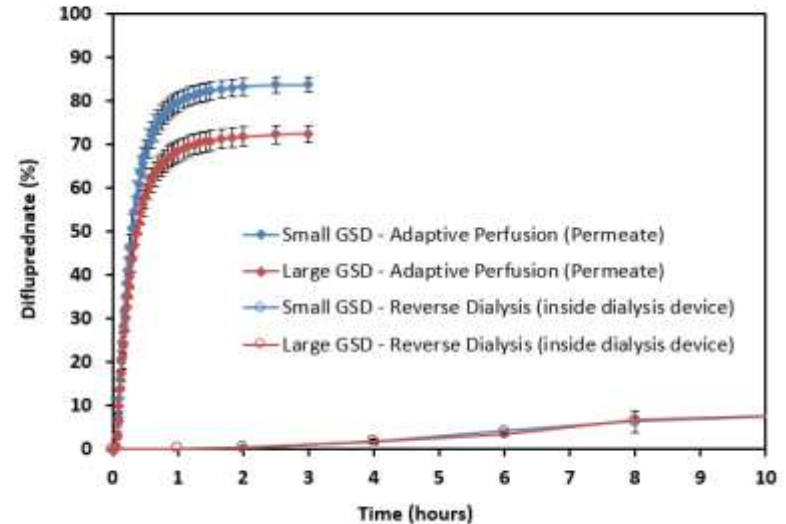
Patel D, Zhang Y, Dong Y, Qu H, Kozak D, Ashraf M, Xu X. Adaptive perfusion: An in vitro release test (IVRT) for complex drug products. Journal of Controlled Release. 2021 May 10;333:65-75.

# Comparison to Traditional Dialysis

Pure Drug Solution (n = 3)



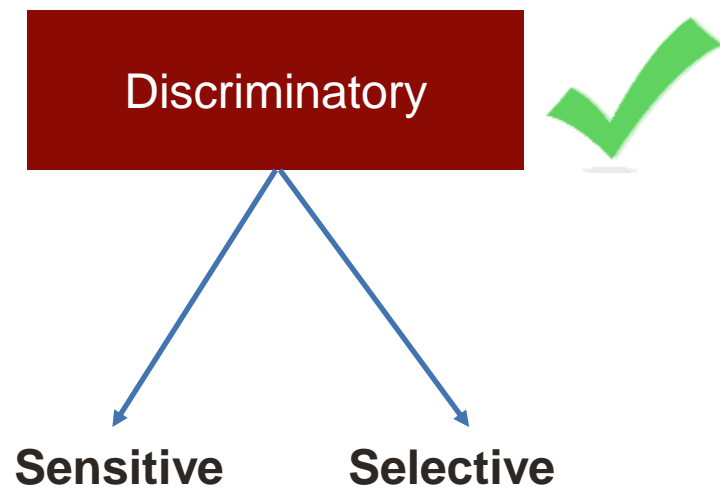
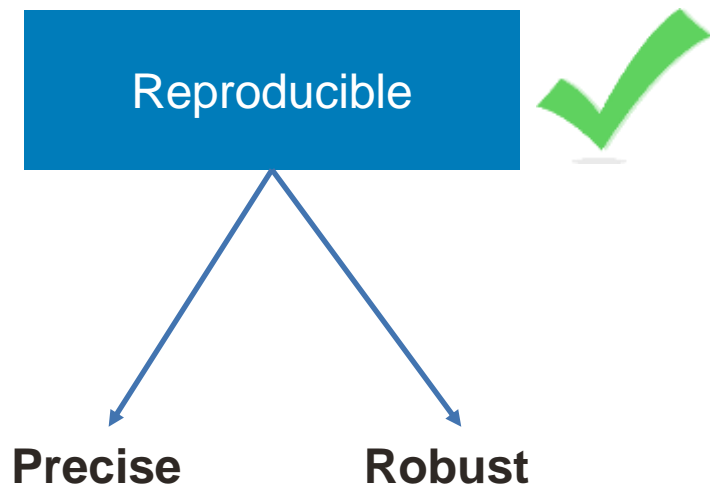
Small and Large GSD nanoemulsions (n = 3)



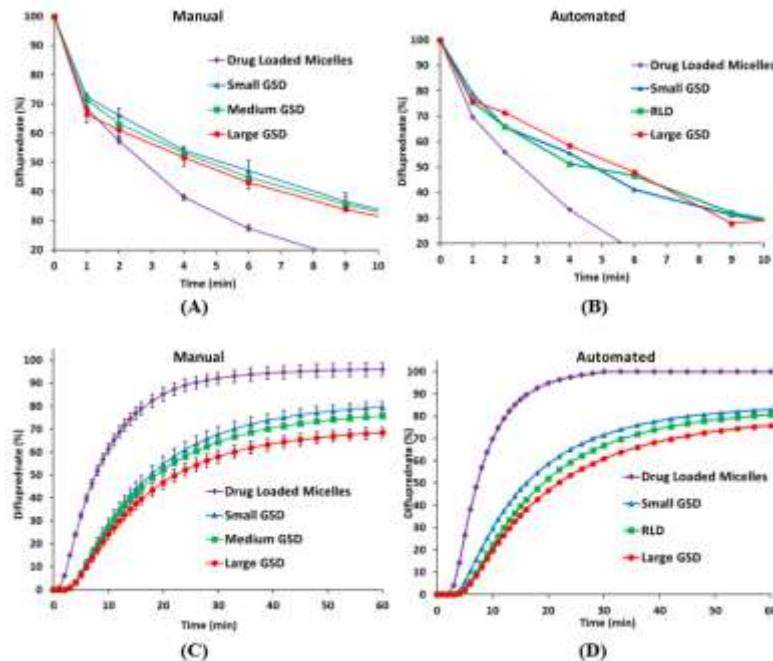
Patel D, Zhang Y, Dong Y, Qu H, Kozak D, Ashraf M, Xu X. Adaptive perfusion: An in vitro release test (IVRT) for complex drug products. Journal of Controlled Release. 2021 May 10;333:65-75.



# Both Goals Achieved with AP

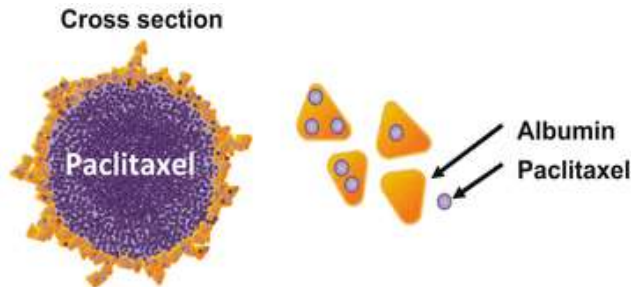


# Automation for Further Improved Reproducibility



# Other Potential Use #1:

## Paclitaxel Protein Bound Injectable Suspension



### Challenges:

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

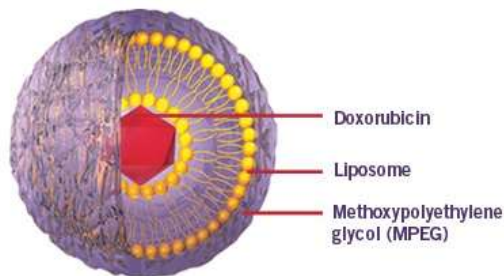
### Impact:

- 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](https://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.

# Acknowledgement



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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?

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