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] – September 24, 2024


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Pharmaceutical quality
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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

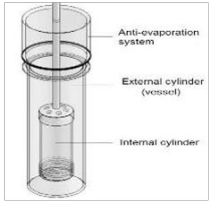
USP Apparatus 1

Basket

USP Apparatus 2

Paddle

USP Apparatus 3



Reciprocating Cylinder

USP Apparatus 4

Flow-through Cell

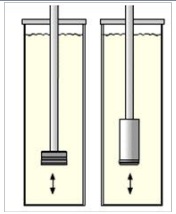
USP Apparatus 5

Paddle over Disk

USP Apparatus 6

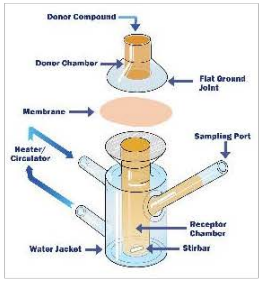
Rotating Cylinder

USP Apparatus 7

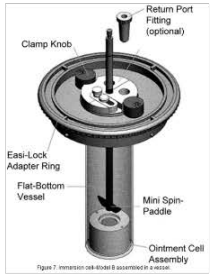


Reciprocating Holder

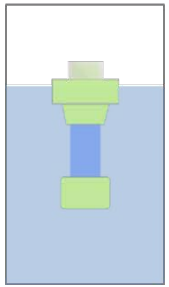
Vertical Diffusion Cell



USP 2 Immersion Cell



Dialysis



Bottle-shaking

Sample-and-separate

Others

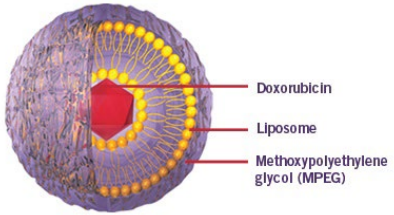
- Pulsatile Microdialysis (PMD)
- Miniatured flow-through cell
- MicroDiss™
- MicroFLUX™
- Scissor™ (sub-cutaneous)

A Good IVRT Needs to be:

- **Reproducible**:
  - Precise: e.g., low CV%
  - Robust: e.g., against minor disturbance to method

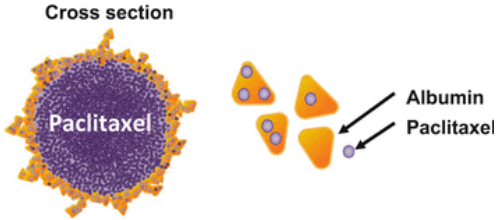
- **Discriminatory**:
  - Sensitive: e.g., known changes in quantity like sample with 50%, 100%, 150% drug loading
  - Selective: e.g., able to detect differences in sample if Critical Quality Attributes (CQAs) changed, such as particle size

Membrane Diffusion: A Common Approach for Separation



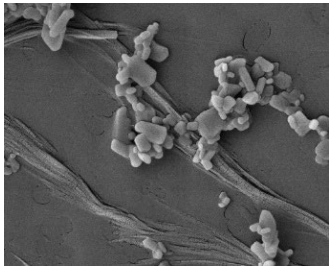
Doxorubicin liposomal Injection (80-90 nm)

Nanoemulsion (~100 nm)



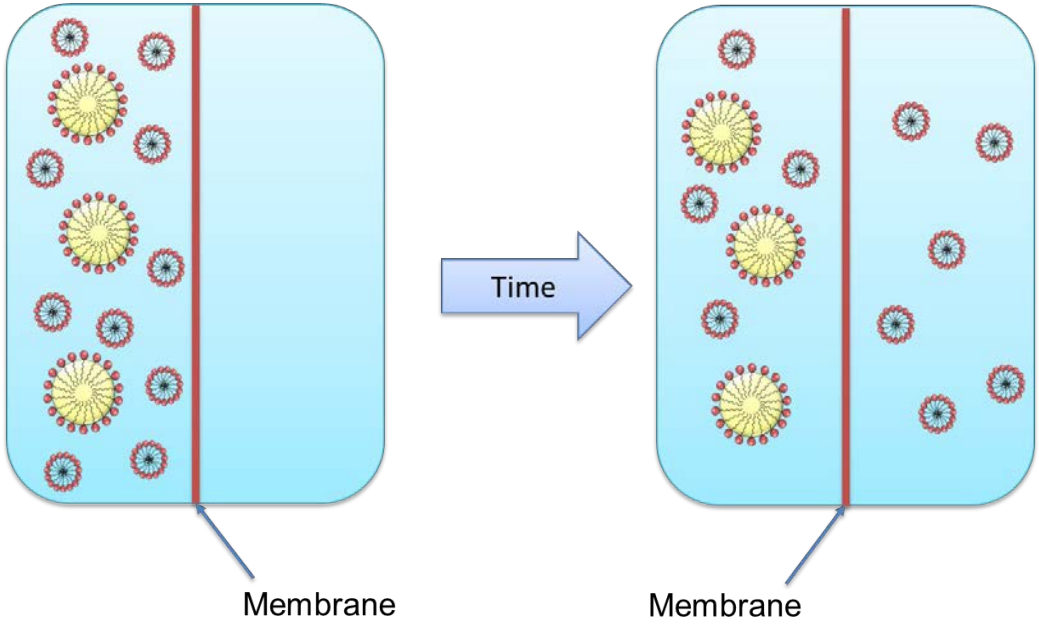
Paclitaxel protein bound injectable suspension (~130 nm)

Free Drug



Nanosuspension (~500 nm)

Limitation of Membrane Separation in IVRT



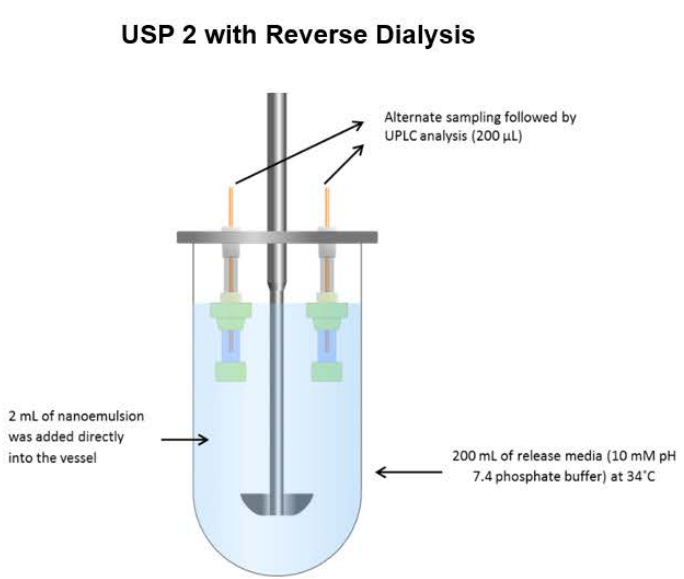
- Driven by concentration gradient: Hight to Low
- Membrane transfer may become a rate-limiting step

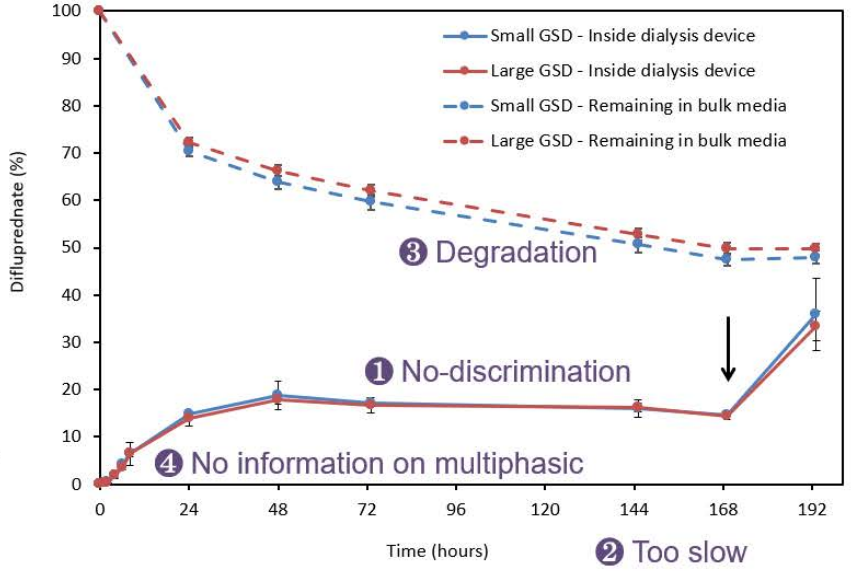
Ophthalmic Emulsions Can Be Challenging

- 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.

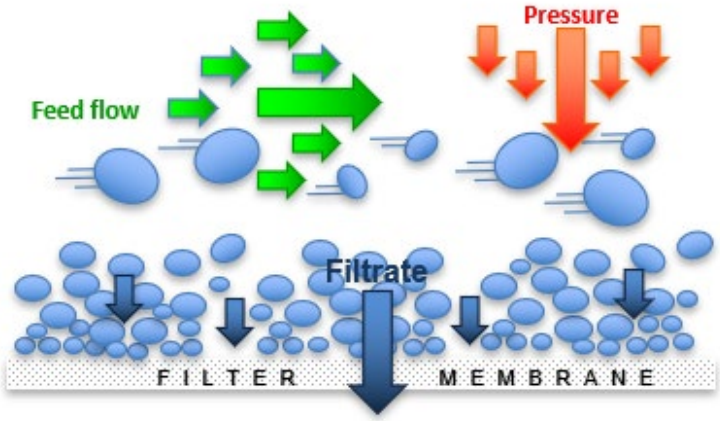
Challenges with Current IVRT Method

Challenges with Current IVRT Method

How can we improve IVRT?

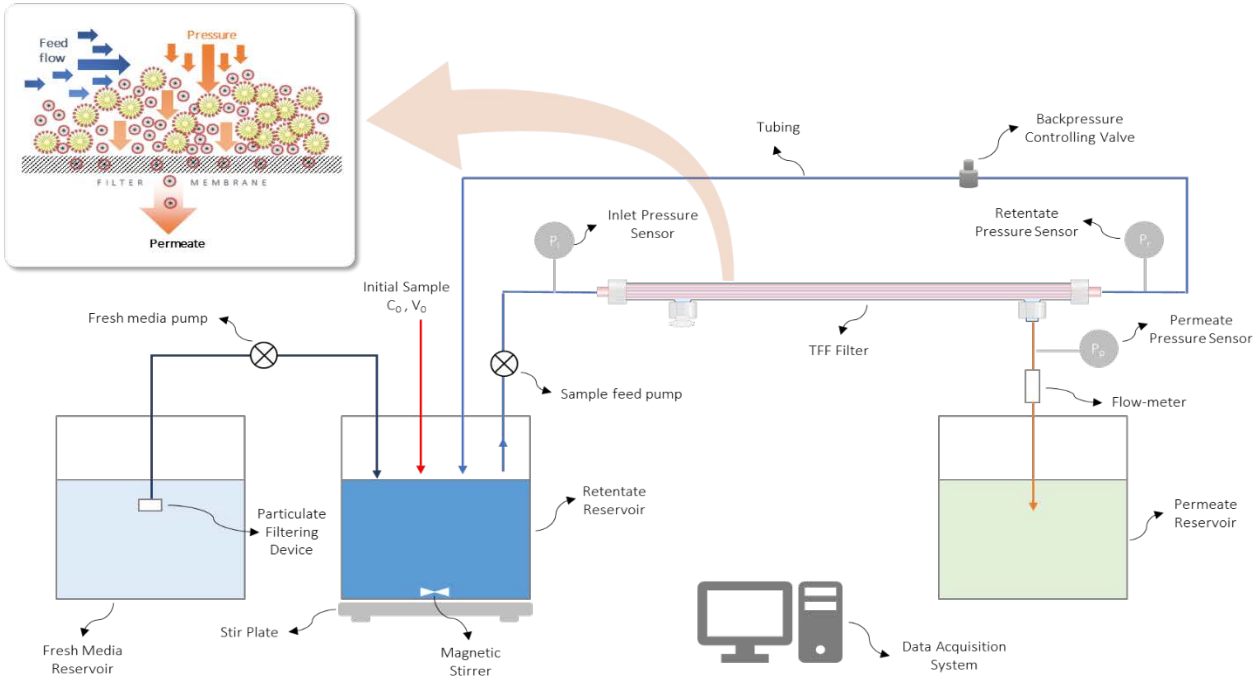
One Example: Adaptive Perfusion (AP)

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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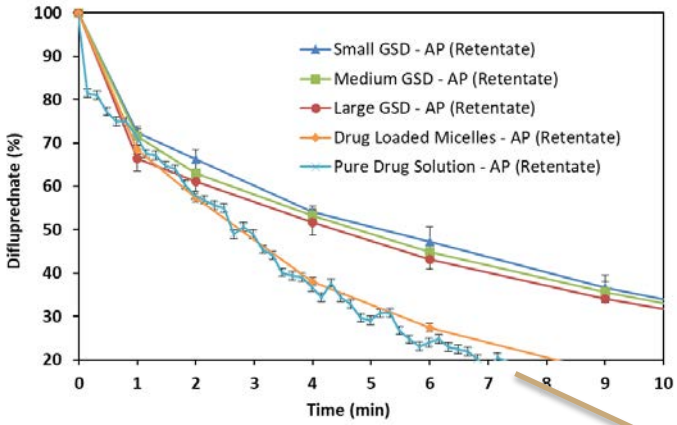
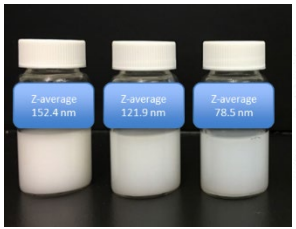
Case Study: Formulation with Varying Globule Size Distribution

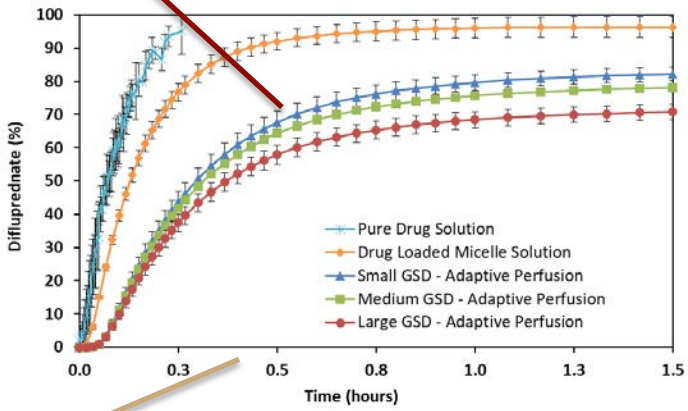
2 Discrimination

Retentate Profile (n=3)





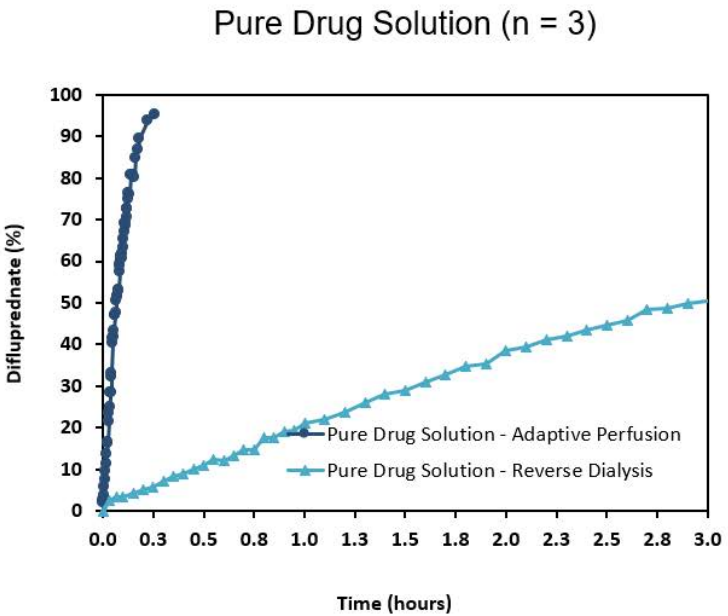
Permeate Profile (n=3)

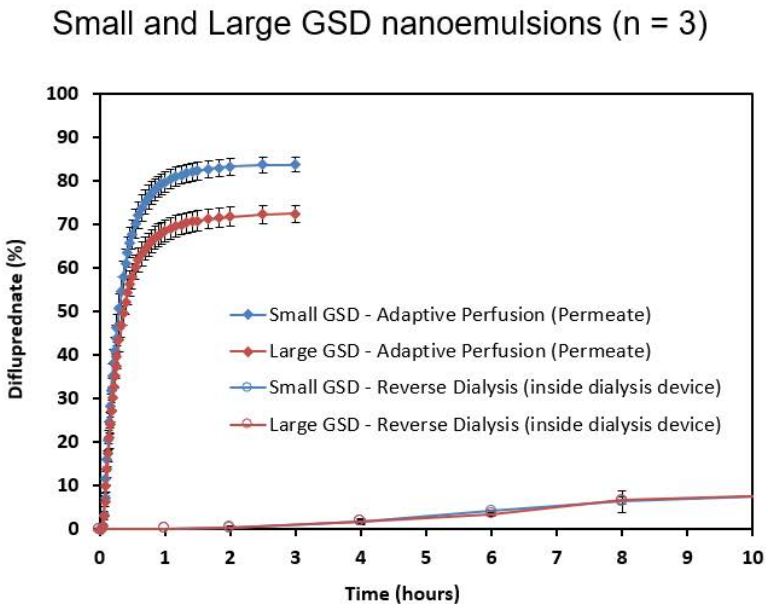


1 Fast

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





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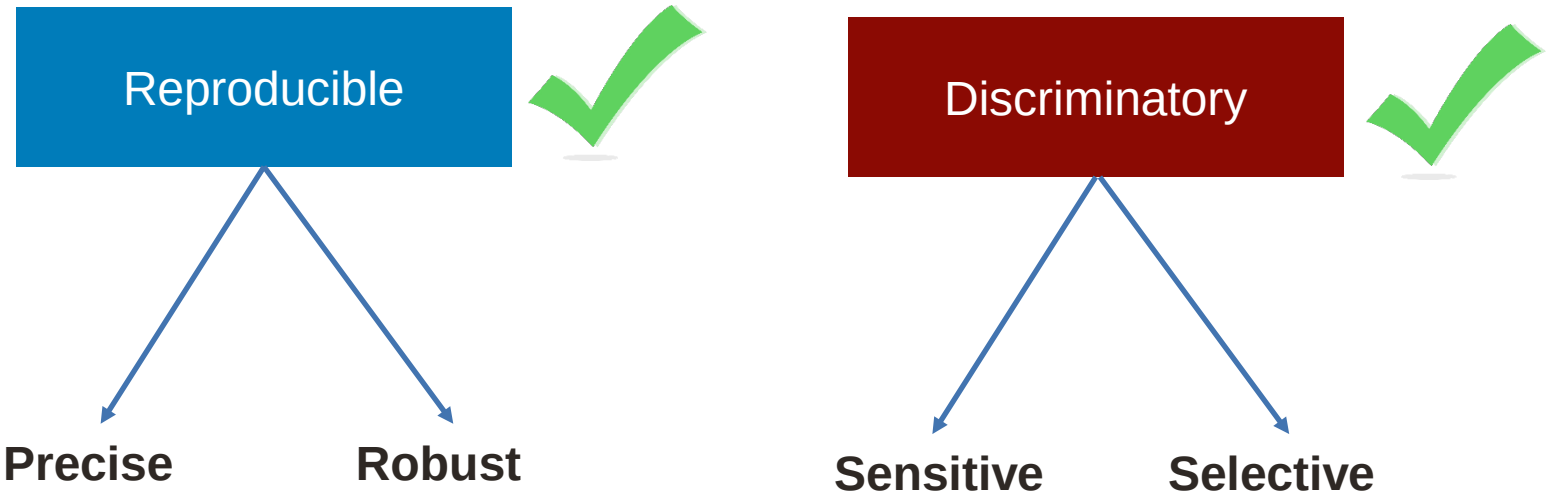
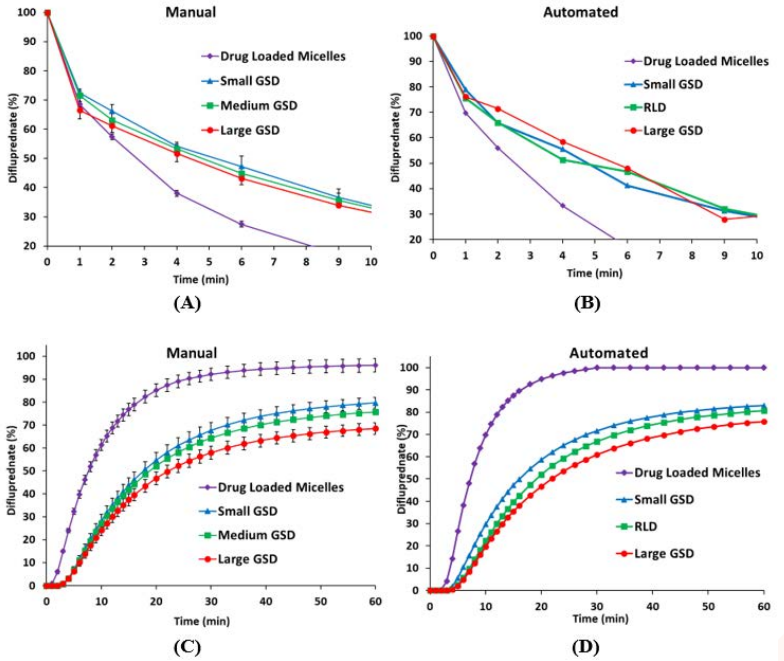
Both Goals Achieved with AP

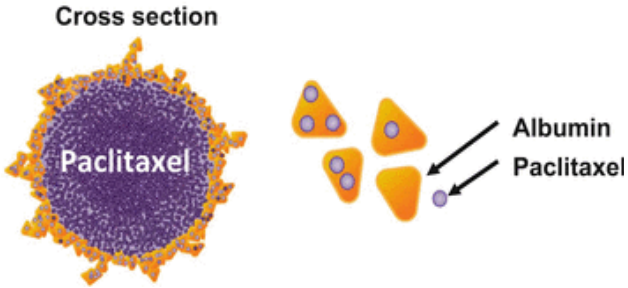


Automation for Further Improved Reproducibility



Other Potential Use #1:

Paclitaxel Protein Bound Injectable Suspension



Challenges:

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

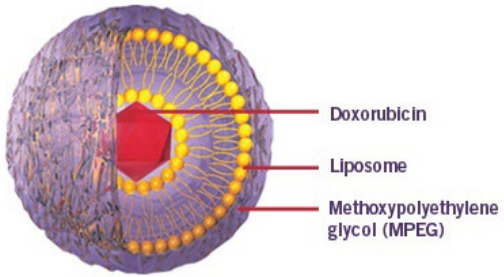
Impact:

- Understanding the role of **ELECTOLYTE**, 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

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

Questions?

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