Nano-Size Complex Products In Vitro Release Testing (IVRT)

Thilak Mudalige, PhD
Research Chemist
Arkansas Laboratory
Office of Regulatory Affairs
US FDA

Advancing Generic Drug Development – September 24, 2024

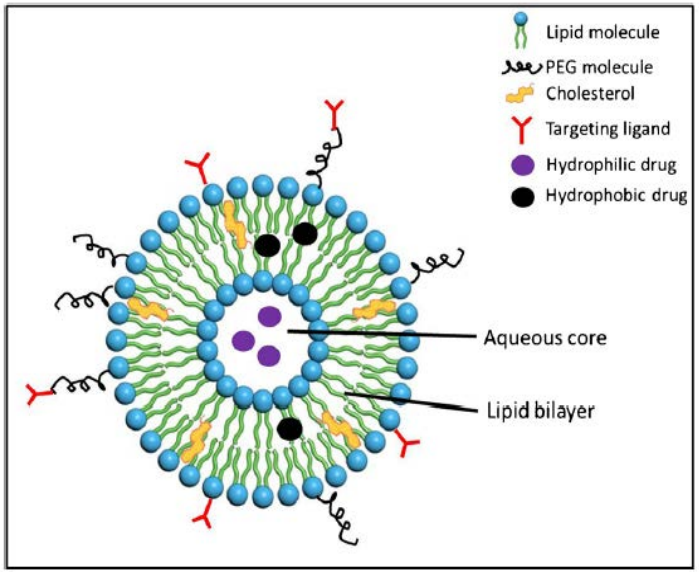
Outline

- Drug product containing nanomaterials
- Liposome and liposome drug products
- IVRT of complex products containing nanomaterials and challenges
- Innovative methods for IVRT

Complex Products Containing Nanomaterials

- Complex products: Drugs that are characterized by complex active ingredients, formulations or routes of delivery (MAPP 5240.10).
- Drug product containing nanomaterials: Submicron-sized particles with one or more therapeutic agents that are dispersed, adsorbed, or covalently bound in encapsulated vesicles, capsules, or polymer matrices
  - liposomes, polymer nanoparticles, protein nanoparticles, Emulsions, ion colloids

Liposome and Liposome Drug Products



Liposome

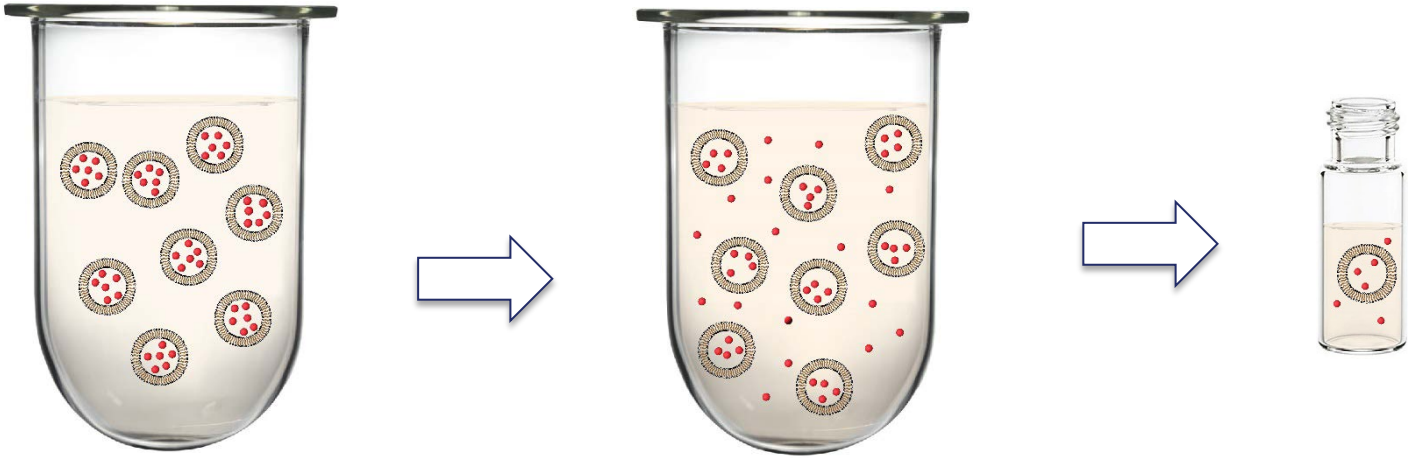
- Microvesicle composed of a bilayer and/or a concentric series of multiple bilayers separated by aqueous compartments formed by amphipathic molecules such as phospholipids that enclose a central aqueous compartment

Liposome Drug Product

- A drug product in which the active pharmaceutical ingredient (API) is contained in liposomes

Guidance for Industry. Liposome drug products, chemistry, manufacturing, and controls; human pharmacokinetics and bioavailability; and labeling documentation. U.S. Food and Drug Administration. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070570.pdf (2018)

IVRT of Products Containing Nanomaterials



Drug release conditions

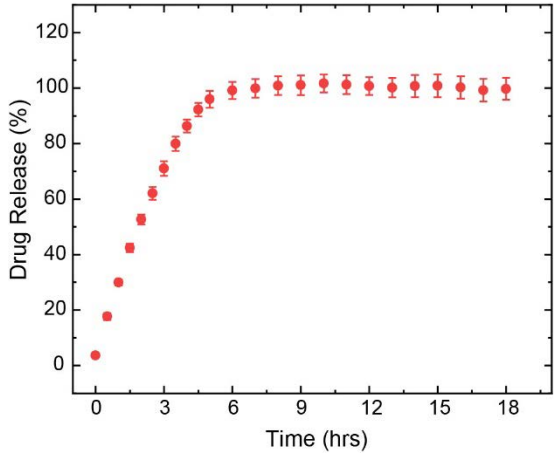
- pH
- Temperature
- Release media composition

Time correlated sampling

IVRT of Products Containing Nanomaterials

Analysis (separation and quantitation)

Generating drug release profile



Challenge

- **Both nanoparticles and released APIs are in same size scale**
- **Difficult to separate by conventional methods**
- **Nanoparticle has delicate structures**

Separation Methods and Challenges

Sample and separation

- Filtration: API Binding to membrane, disintegration of nanoparticles
- Centrifugation: Difficulty in separating nanoparticles

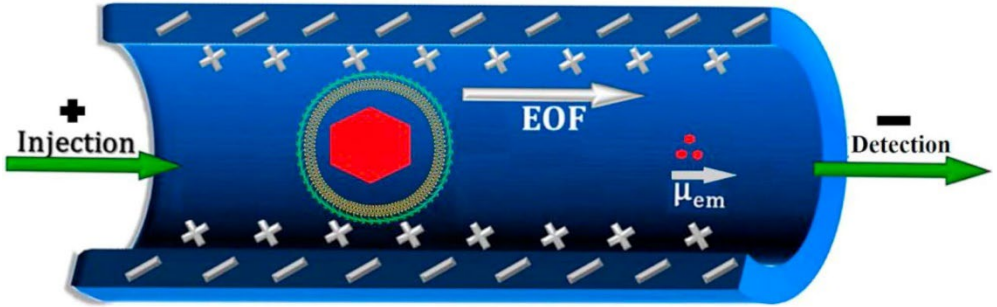
Membrane diffusion method

- Dialysis sack: API binding to membrane, non-sink conditions
- Dialysis sack with continuous flow: API binding to membrane, non-sink conditions

Conditions for New Methods

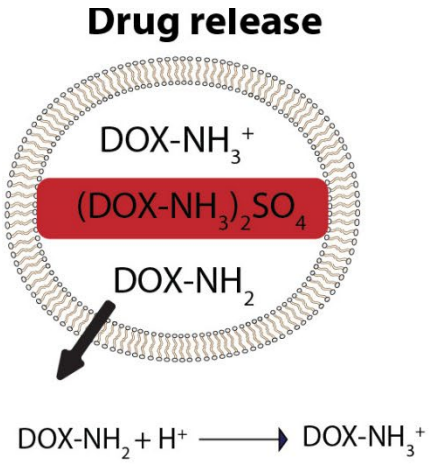
- Eliminate manual separation
- Avoid artifact associated with disruption of nanoparticles
- Automation
- Real-time sampling and analysis

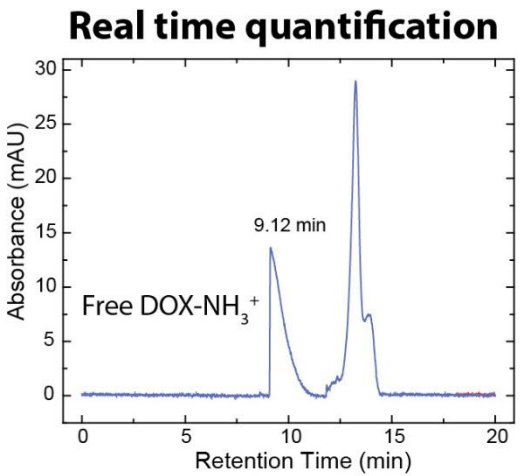
Capillary Electrophoresis (CE)-based IVRT

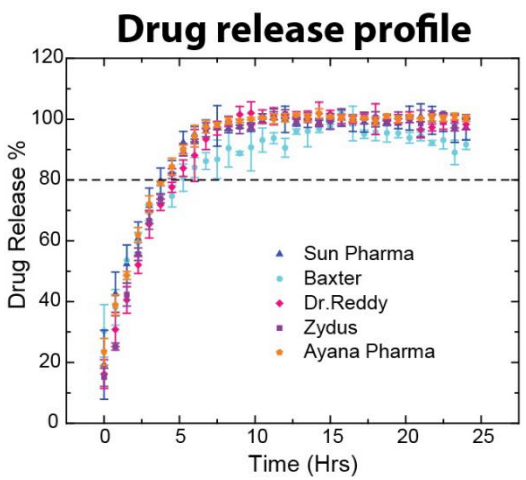


- Automated drug release profiling
- Liposome compatible analysis media
- Small sample volume
- Simultaneous sampling, separation and quantitation

CE-based IVRT for Liposomal Doxorubicin

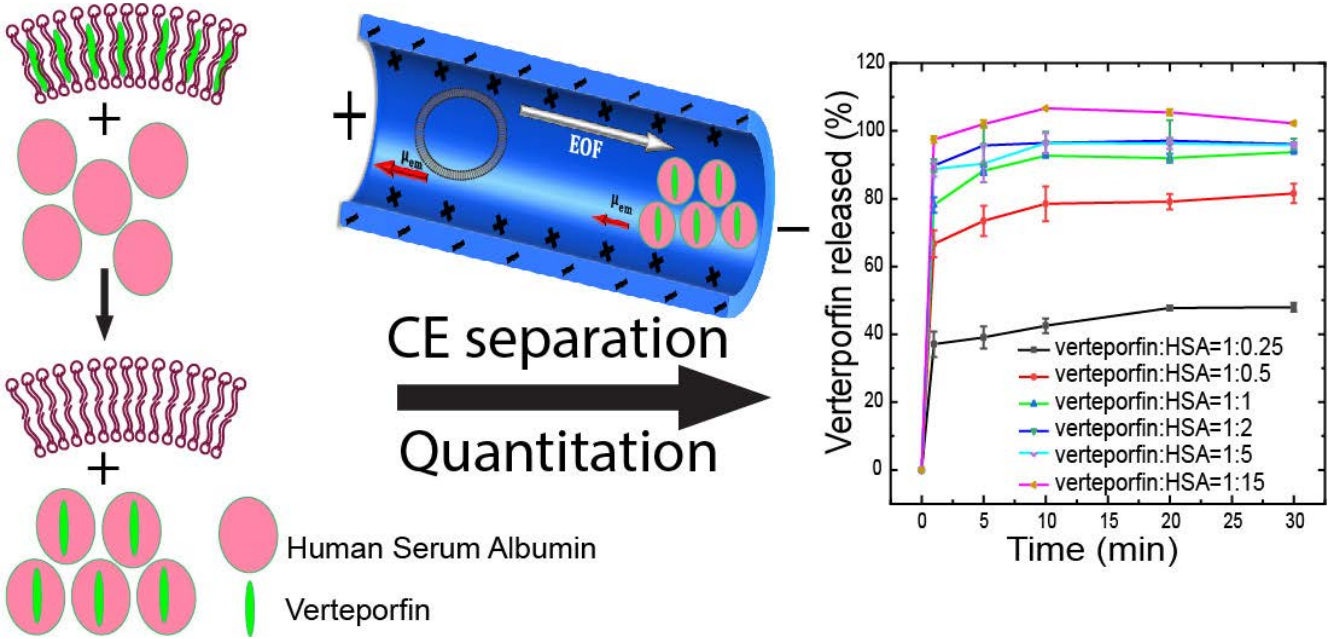






Jayaraj et al, J. Pharm. Sci., 113(2024) 4, 1088-1093

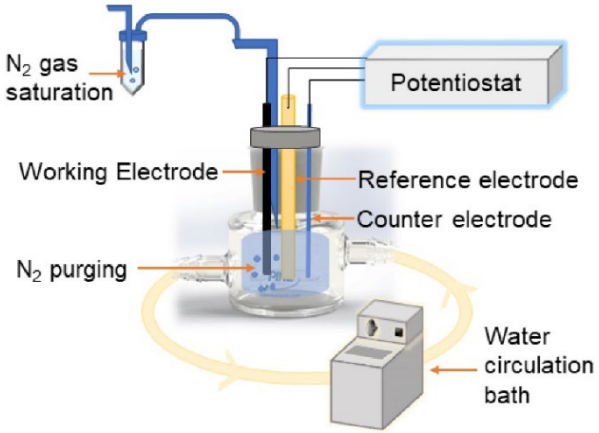
CE-based IVRT for VISUDYNE® (verteporfin for injection)

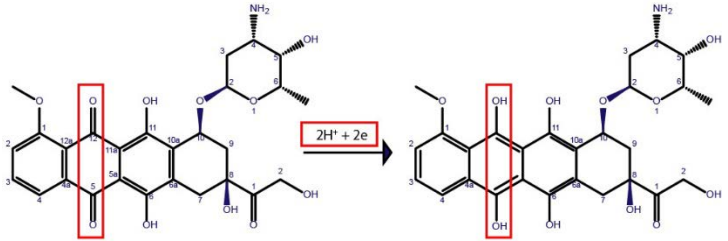


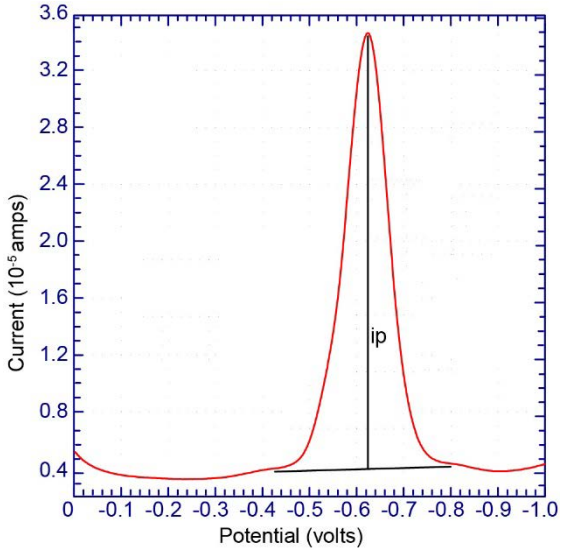
fda.gov/cdersbia

Siriwardane et al, Int. J. Pharm., 946 (2023) 123449

Electroanalysis-based IVRT



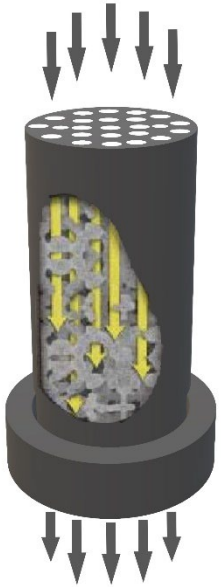


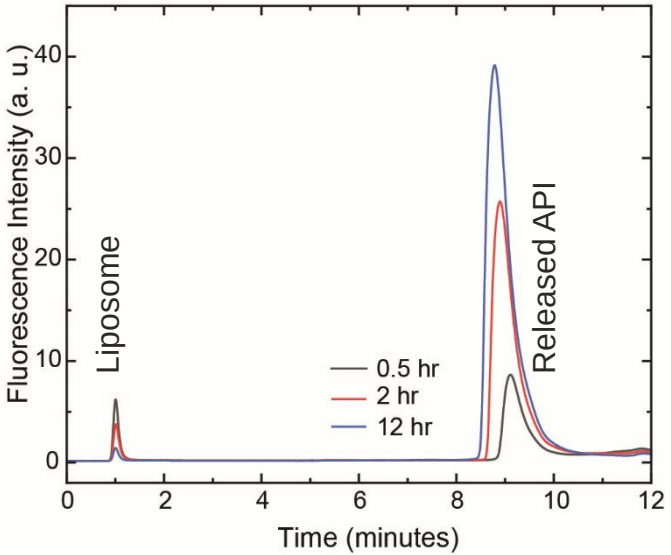


Redox reduction of doxorubicin

Yurtsever et al, J. Pharm. Sci., 113(2024) 3, 791-797

Chromatography-based IVRT





- Polyvinylpyrrolidone (PVP) coated monolithic silica column
- One micron through pores
- Mesopores (10 nm)

Niyonshuti et al, J. Pharm. Sci., 1134(2024) 9, 2837-2842

Major Advantages and Limitations

Method	Advantages	Limitations
CE	• Small sample volume • Delicate separation	• Need charged APIs
Electroanalysis	• No separation • No sampling	• Works with electroactive APIs only
Chromatography	• High accuracy • Multiple detectors possible	• Requires specialized monolithic silica column • Possibility of liposome rupture

Summary

- Innovative IVRT methods were developed to achieve real-time sampling and analysis of liposomal products.
- API specific physical and chemical properties should be considered for selecting IVRT.
- These methods can be utilized for other liposomal products.

Acknowledgements

Arkansas Laboratory

Dumindika Siriwardane

Savithra Jayaraj

Isabelle Niyonshuti

Fatma Yurtsever

Michael Wichman

ORS/OGD/CDER

Wenlei Jiang
Lei Zhang
Robert Lionberger

Office of Regulatory Science /ORA

Paul Howard

Selen Stromgren

Sean Linder

Daniel Rice

Marilyn Khanna