

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

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

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Outline

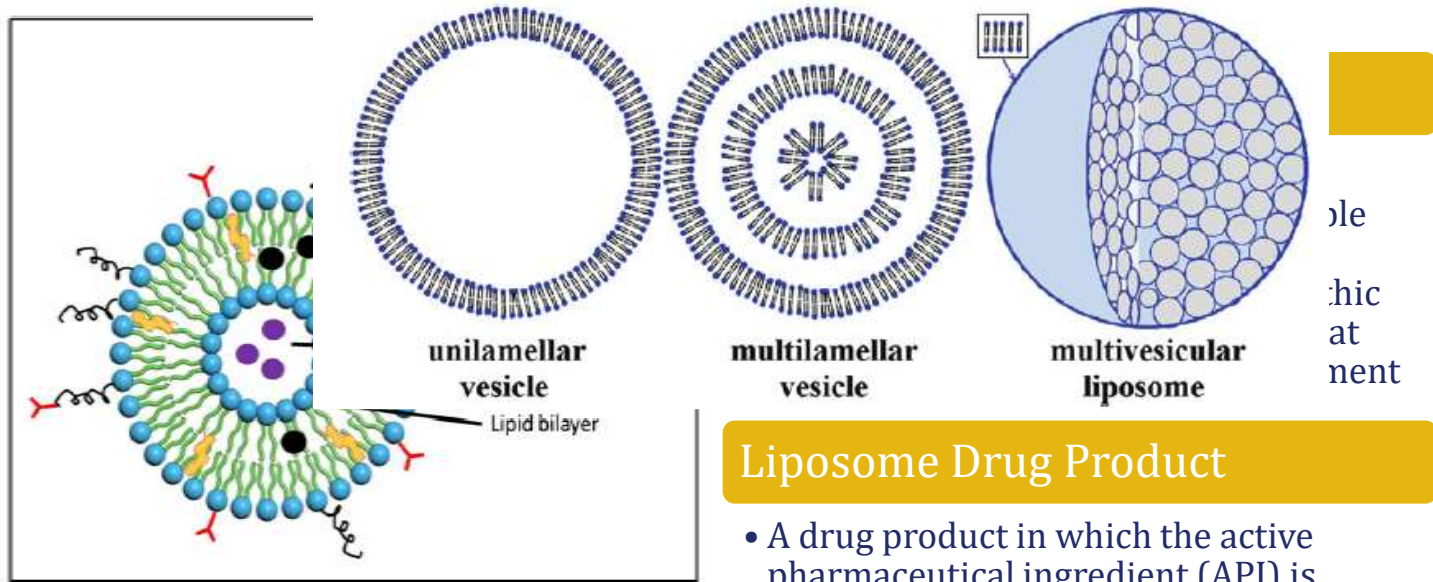
- Drug product containing nanomaterials
- Liposome and liposome drug products
- IVRT of complex products containing nanomaterials and challenges
- Innovative methods for IVRT

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

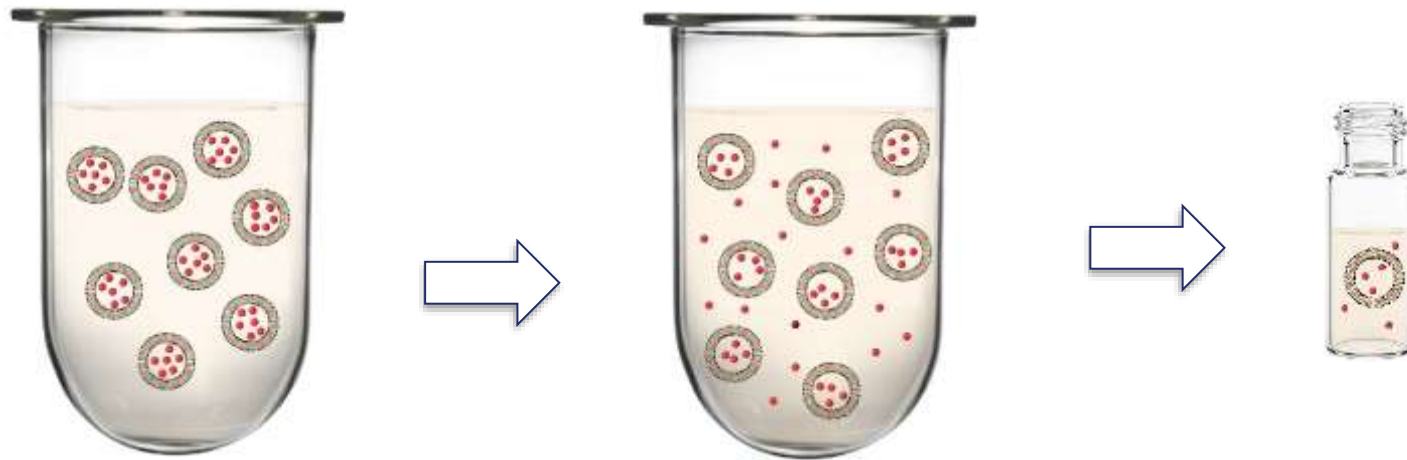
Liposome and Liposome Drug Products



Liposome Drug Product

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

IVRT of Products Containing Nanomaterials



Drug release conditions

- pH
- Temperature
- Release media composition

Time correlated sampling

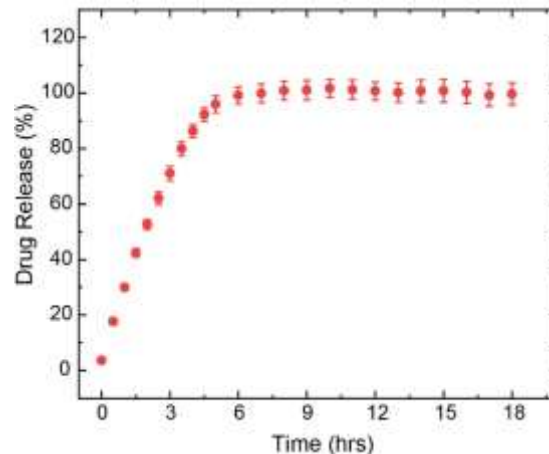
IVRT of Products Containing Nanomaterials



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

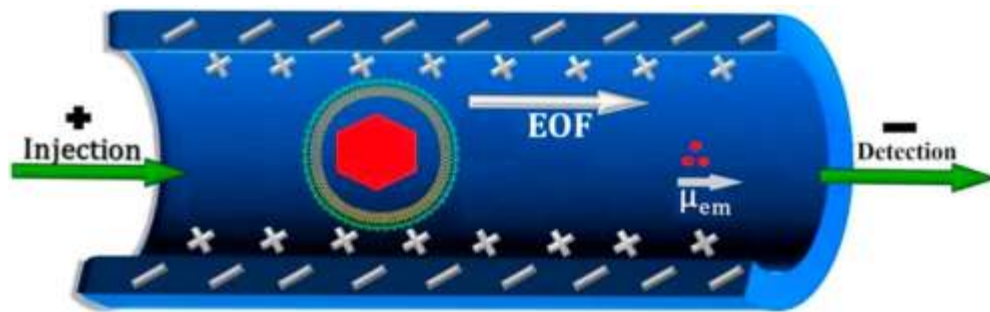
Membrane diffusion method

- 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

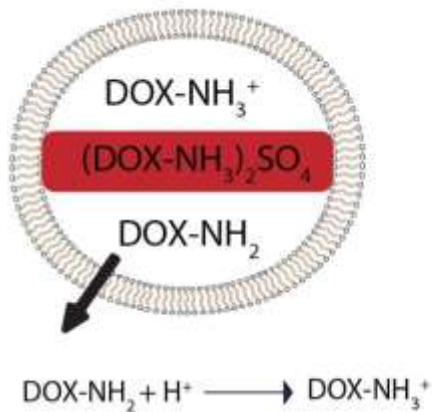


- Automated drug release profiling
- Liposome compatible analysis media
- Small sample volume
- Simultaneous sampling, separation and quantitation

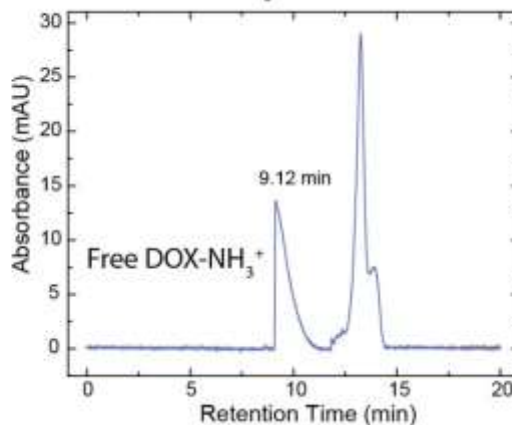
CE-based IVRT for Liposomal Doxorubicin



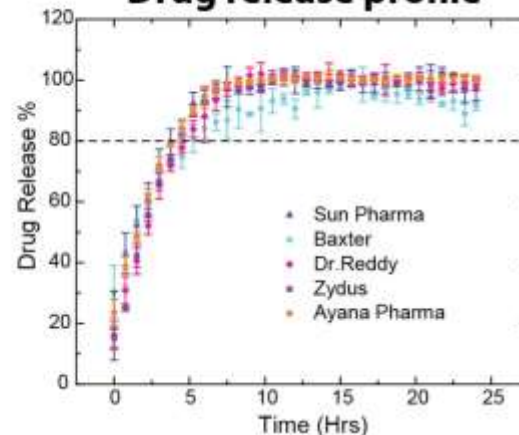
Drug release



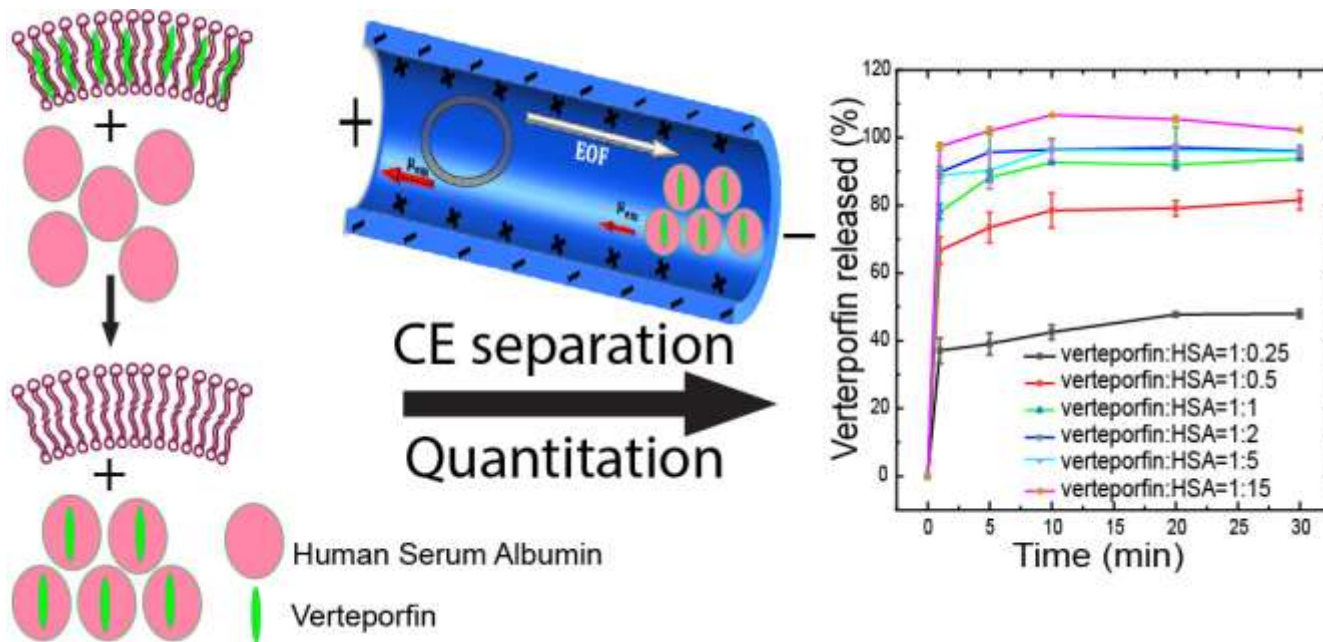
Real time quantification



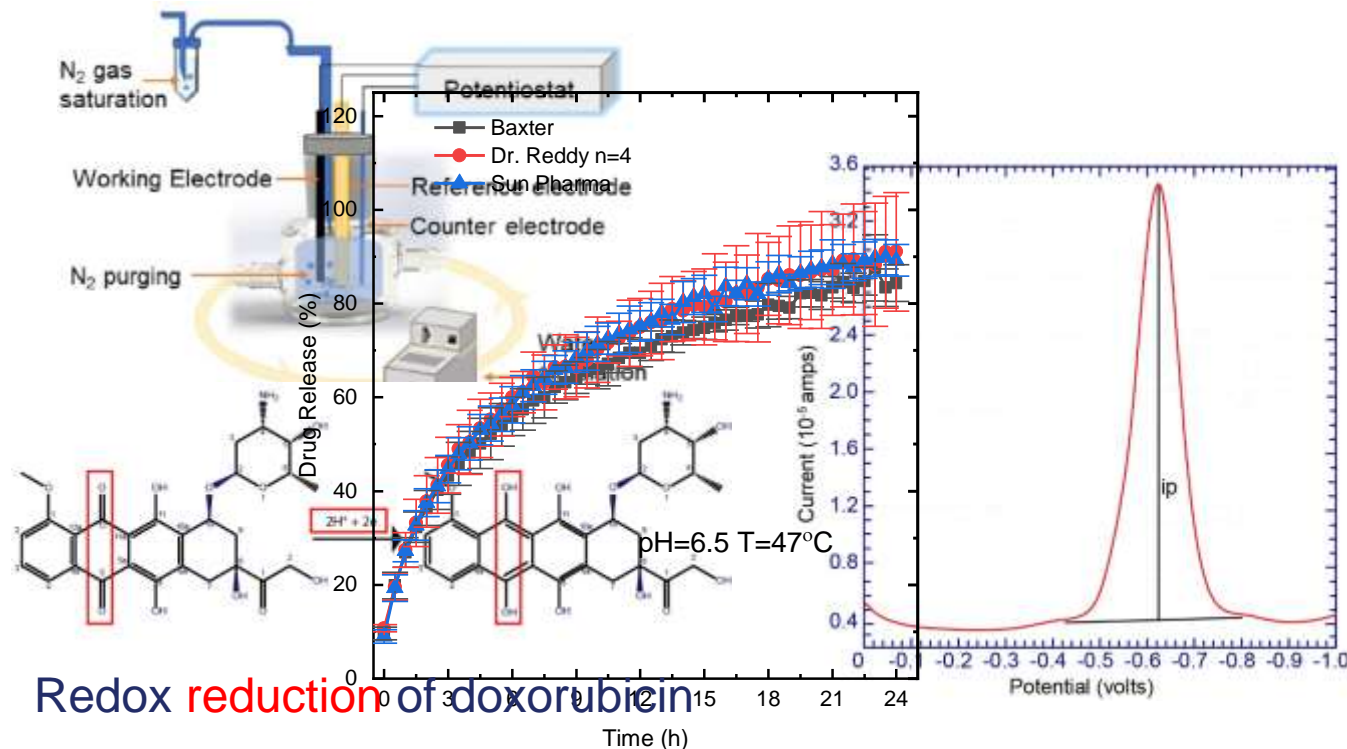
Drug release profile



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



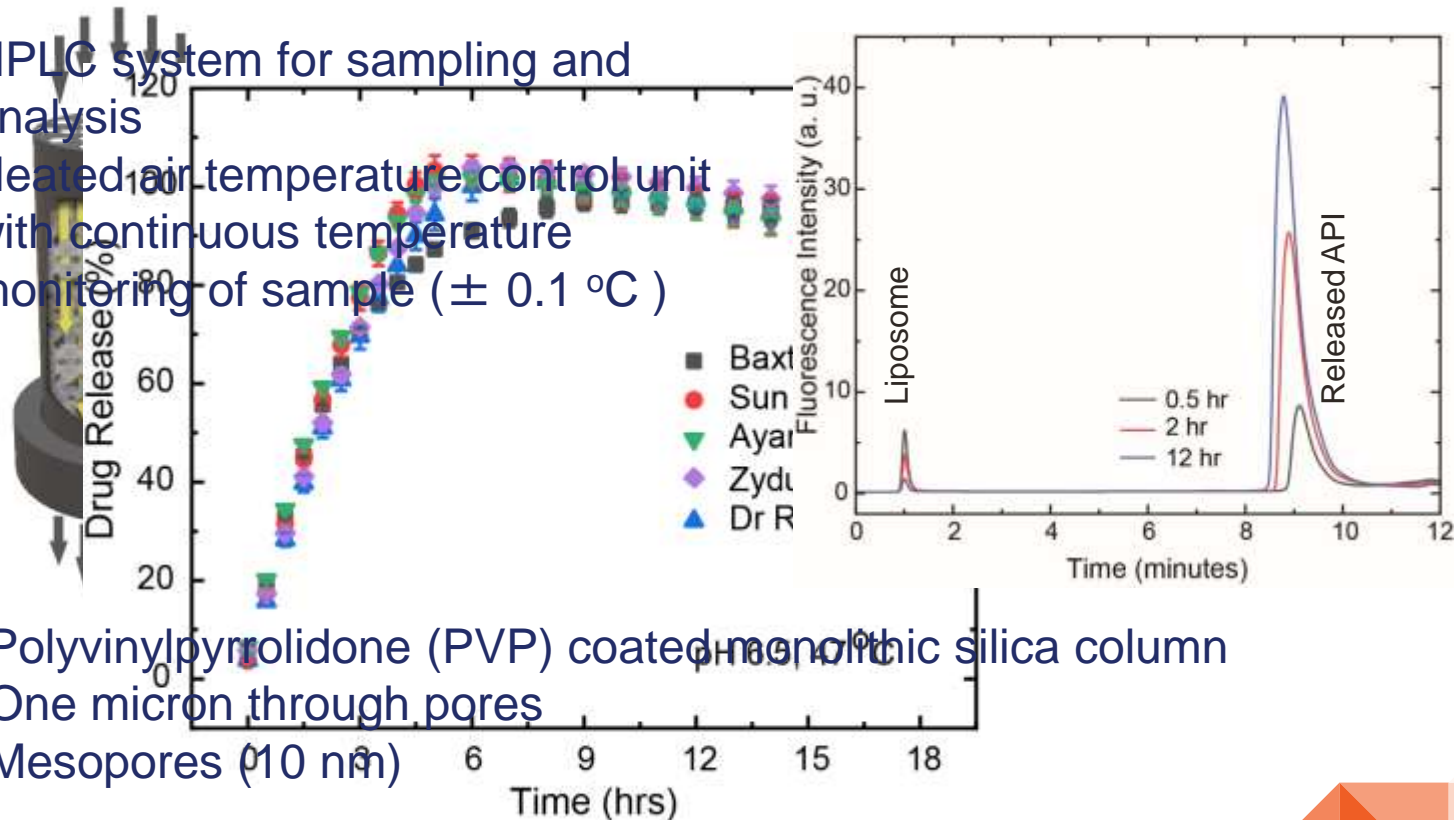
Electroanalysis-based IVRT



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

Chromatography-based IVRT

- HPLC system for sampling and analysis
- Heated air temperature control unit with continuous temperature monitoring of sample ($\pm 0.1^\circ\text{C}$)



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

Major Advantages and Limitations



Method	Advantages	Limitations
CE	<ul style="list-style-type: none">• Small sample volume• Delicate separation	<ul style="list-style-type: none">• Need charged APIs
Electroanalysis	<ul style="list-style-type: none">• No separation• No sampling	<ul style="list-style-type: none">• Works with electroactive APIs only
Chromatography	<ul style="list-style-type: none">• High accuracy• Multiple detectors possible	<ul style="list-style-type: none">• 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.



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