CRS 2023

The Apparatus IV and Complex Dosage Forms

For Experts.
By Experts.

Vivek Shah

Obligatory Topics Page

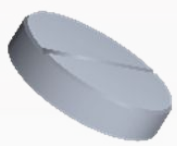
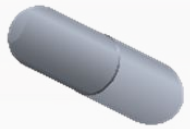
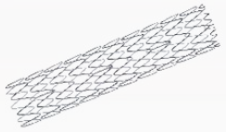
8 AM in Vegas, What Will We Be Discussing?

- Complex Dosage Forms and Apparatus IV
- Case Study with Emulsion
- Case Study with Implant

What Are These Complex Dosage Forms?

What's the Fuss All About?

sotax

DOSAGE FORM							
	• MR, CR, SR and ER tablets	• API's • Powders • Granules	• Capsules • Pellets	• Medical devices • Drug-eluting beads & stents • Implants • Coated ocular implants & lenses	• Suppositories • Soft-gelatin capsules	• Parenterals • Emulsions • Suspensions • Microspheres • Semi-solids
CHALLENGES	• pH change • Poorly soluble	• Low dose • Hydrodynamic control	• Floating • Capsule interference	• Low dose	• Lipid interference	• Low dose • Small particles • Dialysis often required

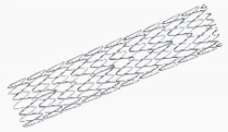
Expertise with novel dosage forms
Long are gone the days of the immediate release tablet

An understanding of FDA requirements for complex dosage forms
Limited Guidance Available

What Are These Complex Dosage Forms?

What's the Fuss All About?

sotax

DOSAGE FORM			
			
	• API's • Powders • Granules	• Medical devices • Drug-eluting beads & stents • Implants • Coated ocular implants & lenses	• Parenterals • Emulsions • Suspensions • Microspheres • Semi-solids
CHALLENGES	• Low dose • Hydrodynamic control	• Low dose	• Low dose • Small particles • Dialysis often required

The dosage forms that will be discussed with techniques to address their inherent challenges

Knowledge Is Powder

Solutions for Powder Formulations

sotax

Challenges Associated with Handling Powders for Dissolution:

- Powder Fineness
- Loss of Hydrodynamic Control
- Particle Size and Filtration *(more to come on this topic)*

Why the Apparatus 4 over the Apparatus 1 or 2:

- Apparatus 4 for API Powder via **Apparent Dissolution**
- Powders in a vessel with Apparatus 1 or 2 tend to result in high variability
- Apparatus 4 is an excellent tool in the pre-formulation space
- *Cell Setup addresses many of the challenges associated with Powders in dissolution*

Knowledge Is Powder

Solutions for Powder Formulations

sotax

Cells for Apparatus 4 Powder Dissolution

22.6 mm Compendial Cell, with beads

22.6 mm Compendial Cell *bead sandwich*

In most cases, attempt to evaluate a compendial approach first before attempting nuanced approaches

Knowledge Is Powder

Solutions for Powder Formulations

sotax

Cells for Apparatus 4 Powder Dissolution

The powder cell is an alternative to the 22.6mm compendial cell.

The cell adds a sieve with multiple locations to place a filter and a different hydrodynamic environment.

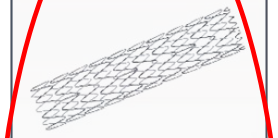
The powder cell can be difficult to assemble but with proper training you can impress your peers with your newly obtained dexterity

I spent more than 5 minutes trying to center this thumbs up image

What Are These Complex Dosage Forms?

What's the Fuss All About?

sotax

DOSAGE FORM			
			
	• API's • Powders • Granules	• Medical devices • Drug-eluting beads & stents • Implants • Coated ocular implants & lenses	• Parenterals • Emulsions • Suspensions • Microspheres • Semi-solids
CHALLENGES	• Low dose • Hydrodynamic control	• Low dose	• Low dose • Small particles • Dialysis often required

The dosage forms that will be discussed with techniques to address their inherent challenges

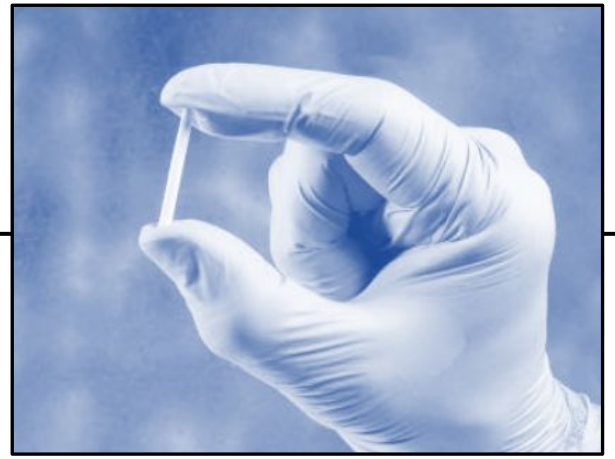
Implanting Success

Solutions for Implant Formulations

sotax

Challenges Associated with Optimizing Dissolution Methods for Implants:

- Long Run Times
- Addressing the Polymer



Why the Apparatus 4 over the Apparatus 1 or 2:

- Apparatus 4 cells and flow better simulate the target environment of most implants
- Volume flexibility and hydrodynamic control make Apparatus 4 more appealing for many implant programs

Implanting Success

Solutions for Implant Formulations

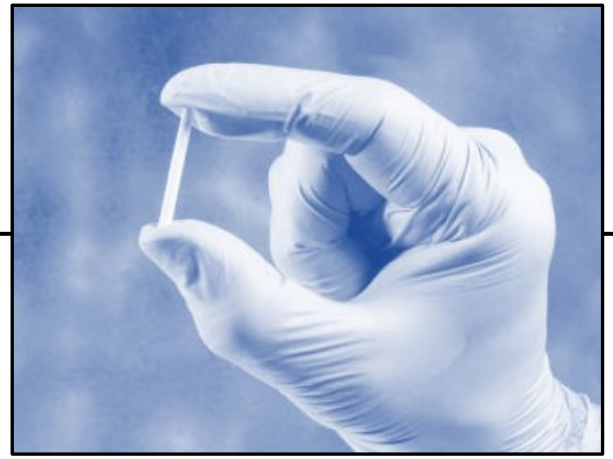
sotax

The Necessities When Approaching Implant Dissolution:

Understand the Polymer and API Localization, the polymer is likely not your friend and the devious formulators are to blame

Real Time In Vitro Release vs. Accelerated Dissolution

API Stability Information, the more the merrier



Implanting Success

Solutions for Implant Formulations

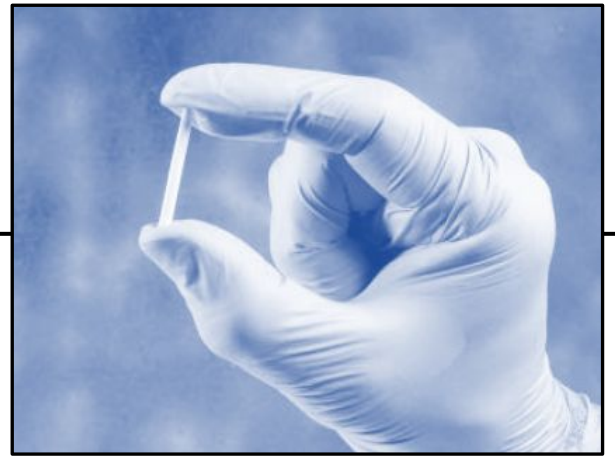
sotax

Cells for Apparatus 4 Implant Dissolution

22.6 mm Compendial Cell, Implant vertically seated in beads

22.6 mm Compendial Cell Ultem cell, more chemically resistant material

Implant Cell, can provide increased agitation due to small surface area



I Feel Stentamental

Solutions for Stent Formulations

sotax

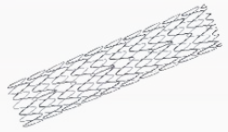
Base CE7 was modified to be able to fit Large Stents

Large Stent Apparatus 4 Cells

What Are These Complex Dosage Forms?

What's the Fuss All About?

sotax

DOSAGE FORM			
			
	• API's • Powders • Granules	• Medical devices • Drug-eluting beads & stents • Implants • Coated ocular implants & lenses	• Parenterals • Emulsions • Suspensions • Microspheres • Semi-solids
CHALLENGES	• Low dose • Hydrodynamic control	• Low dose	• Low dose • Small particles • Dialysis often required

The dosage forms that will be discussed with techniques to address their inherent challenges

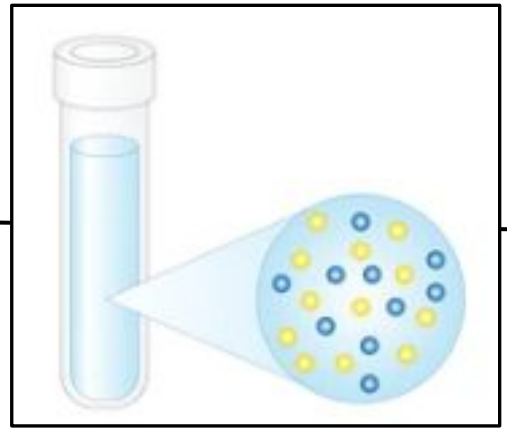
The Suspension Is Killing Me

Solutions for Suspension / Emulsion Formulations

sotax

Challenges Associated with Handling Suspensions/Emulsions for Dissolution:

- Particle Size and Filtration
- Viscosity and Sample Loading
- Reproducibility and Variability



Why the Apparatus 4 over the Apparatus 1 or 2:

- Apparatus 4 cells and flow better simulate the target site of most parenteral solutions
- Volume flexibility
- *Cell Setup addresses many of the challenges associated with Suspensions / Emulsions in dissolution*

The Suspension Is Killing Me

Solutions for Suspension / Emulsion Formulations

sotax

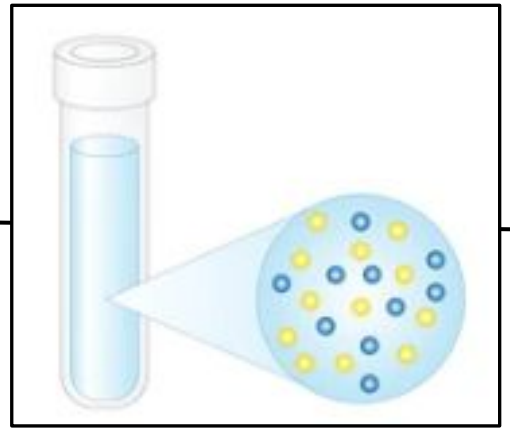
The Necessities When Approaching Suspension and Emulsion Dissolution:

Know Your Available Techniques and When to Use Them

Ultrafine Filtration

Float-A-Lyzer

Microdialysis



The Suspension Is Killing Me

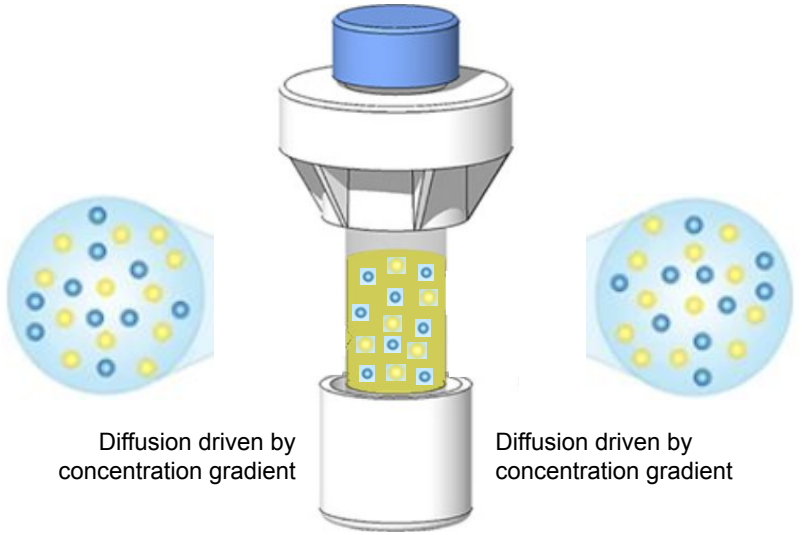
Are FALs our Pals?

sotax

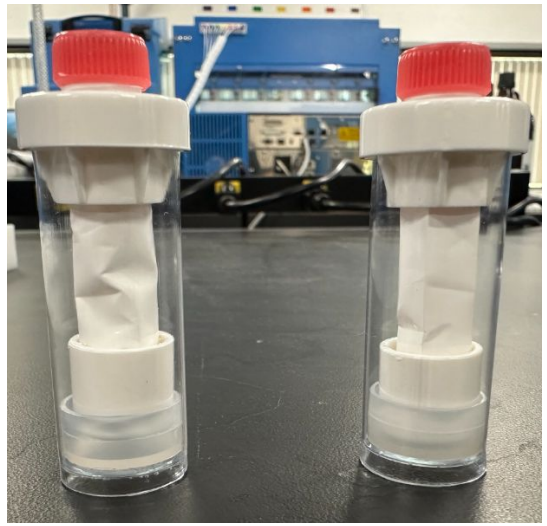
Float-A-Lyzer (FAL)

FALs are manufactured by Molecular Weight Cutoff (MWCO) ranging from 0.1 kD to 1000 kD

- In our experience, it is recommended to use a 300 kD or 1000 kD
- FALs slow down release rate substantially via diffusion, not *dissolution*



The issue with FALs:



- This was how the FALs were received, the membrane often appears different from FAL to FAL.
- The dimensions of the membrane are different from FAL to FAL, greatly impacting the variability
- Membrane material options limited

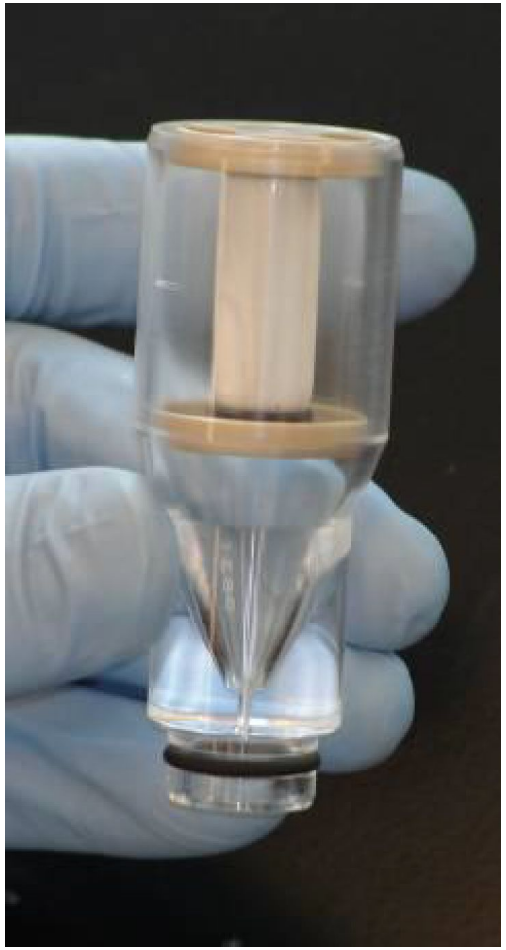
The Suspension Is Killing Me

Are FALs our Pals?

sotax

A4D Adaptor

Self assembled with membrane of choice to fit within an Apparatus 4 Compendial Cell



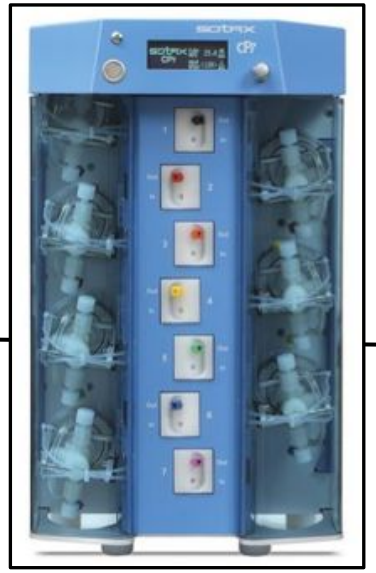
The Suspension Is Killing Me

Solutions for Suspension / Emulsion Formulations

sotax

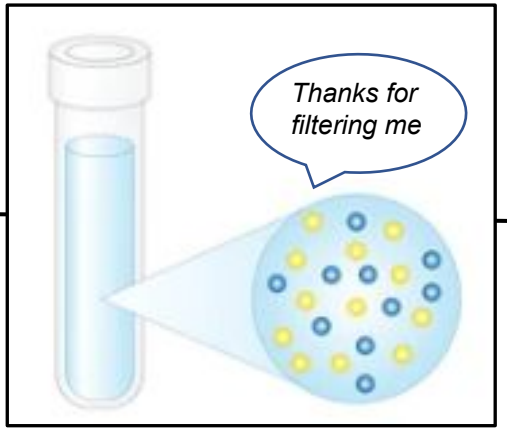
Ultrafine Filtration

Suspension / Emulsion formulations can be manufactured with very small API particle sizes, adding complexity to proper filtration of samples



Manipulate pump **RPM** and Flow Rate to account for backpressure from low particle size filters

Mixed Cellulose Ester filters manufactured by Millipore, go down to a 25 nm pore size



The Suspension Is Killing Me

Adapting to the Future

sotax

Microdialysis

Hollow Fiber Filters (HFFs) have shown to provide adequate discriminatory power for specific suspensions and emulsions

3D Printing is nifty, custom printed plate to attach TFFs to the back of the Apparatus IV

The issue with Microdialysis:

- Sample Loading is done within the TFF, considerations for **hydrodynamic control** must be evaluated
- TFFs are $200/ea, the testing requires at least 6, relatively expensive Dissolution Test and to make it feasible, the TFFs need to be cleaned properly

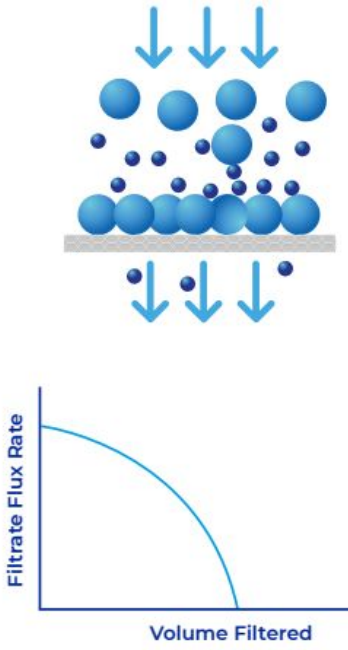
The Suspension Is Killing Me

Adapting to the Future

sotax

Microdialysis

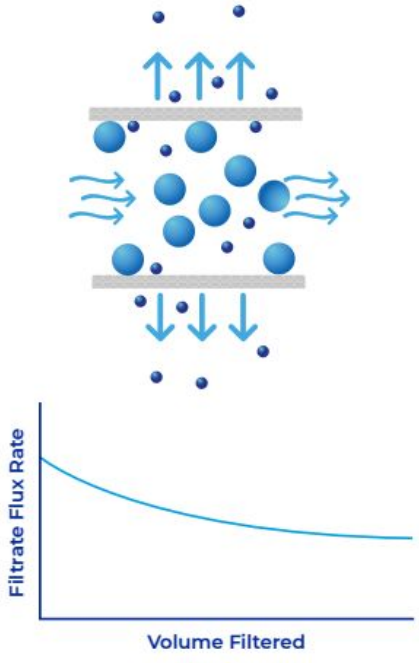
Figure 2
Direct Flow Filtration Process



The feed is directed into the membrane. Molecules larger than the pores accumulate at the membrane surface blocking the flow of liquid and smaller molecules that could pass through. This layer of large molecules is referred to as a "gel layer".

As the volume filtered increases, fouling increases and the flux rate decreases rapidly, resulting in the membrane blocking and the end of the filtration.

Figure 3
Tangential Flow Filtration Process



Sample solution flows through the feed channel and tangentially along the surface of the membrane. The crossflow prevents the build-up of molecules at the surface of the membrane. This disruption of the gel layer allows for the flow of molecules that are small enough to pass through the pores of the membrane to continue into the filtrate. The TFF process prevents the rapid decline in flux rate seen in direct flow filtration allowing a greater volume to be processed per unit area of membrane surface.

Mandatory Transition Slide

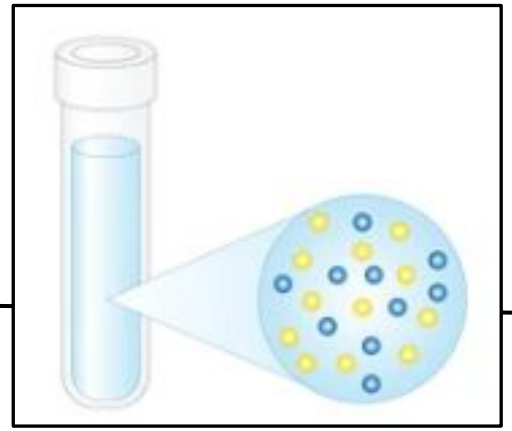
Obligatory Topics Page

8 AM in Vegas, What Will We Be Discussing?

- Complex Dosage Forms and Apparatus IV
- Case Study with Emulsion
- Case Study with Implant

The Curious Case of the Emulsion

Purpose:
Develop a dissolution method able to discriminate differences with critical processing parameters



Challenges:
- D_{90} of the API is 35 nm
- Low Viscosity, can leak through the cell
- Oil-in-Water Emulsion
- Discrimination

Addressing the Challenges

D_{90} of the API is 30 nm
1. Try to use compendial approach with ultrafine filtration
2. Assess viability of FAL
3. Compare results to Microdialysis

Low Viscosity
1. Try to load enough glass beads in the compendial cell to prevent leakage
2. Using a FAL will prevent leaking
3. Using a TFF will prevent leaking

Oil-in-Water Emulsion

Test for oil in samples, ideally components of formulation are kept within the hydrodynamically controlled environment

Discrimination

Develop a discriminatory method able to pick up differences in globule size, drug load, and excipient differences

The Curious Case of the Suspension

Initial Dissolution Approach

Use well understood dissolution approach with Apparatus IV, load beads to compendial cell, depot the emulsion on top of the beads

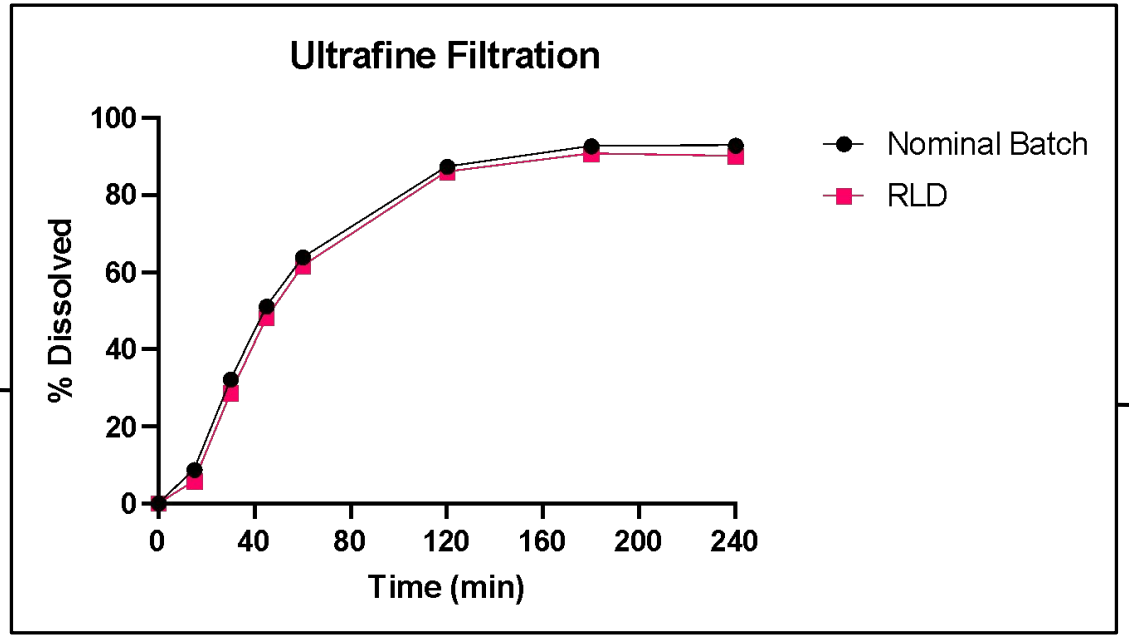
Attempted to use 0.2 um filters, even though this did not cover the D90

The Curious Case of the Suspension

Ultrafine Filtration

Use well understood dissolution approach with Apparatus IV, load beads to compendial cell, depot the emulsion on top of the beads

Evaluated 25 nm and 50 nm filters, this was used to contain components of the formulation and address the particle size



Advantages
- Short run time
- Simple approach

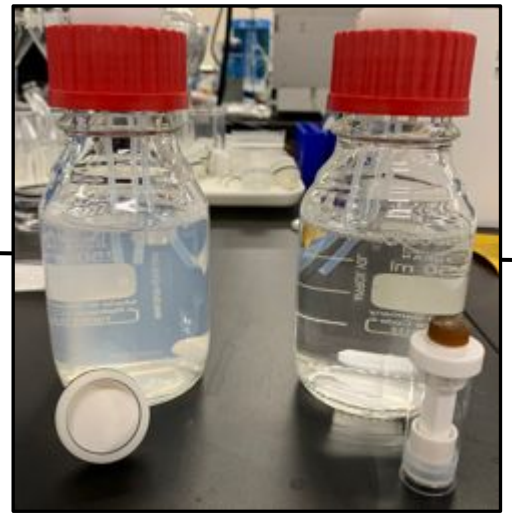
Shortcomings
- Backpressure from filters
- For this particular product, globule size discrimination was not achieved

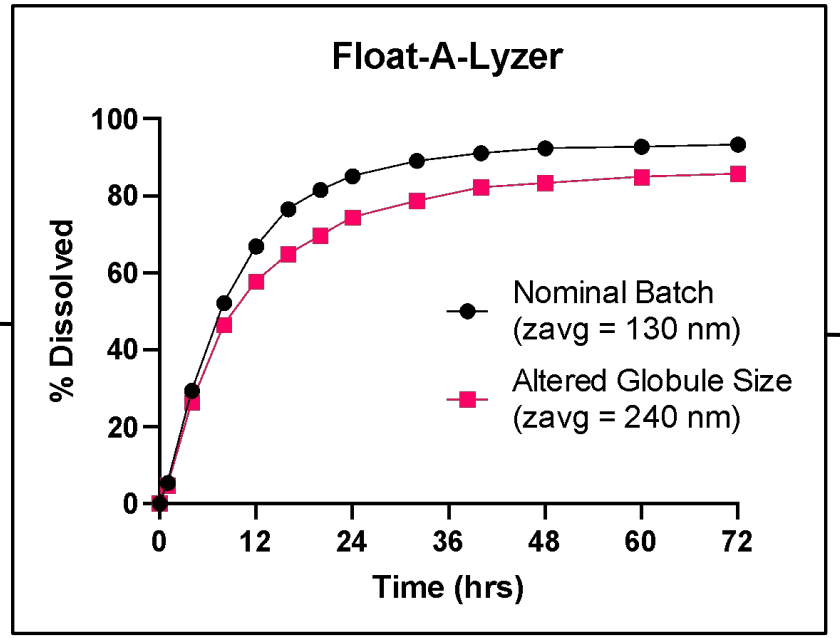
The Curious Case of the Suspension

sotax

Evaluation of FAL

Use the FAL within the Apparatus 4 to attempt to achieve discrimination and keep formulation components within cell





Advantages:
- Achieve discrimination (for this product)

Shortcomings:
- Long Run Times
- Results can be variable

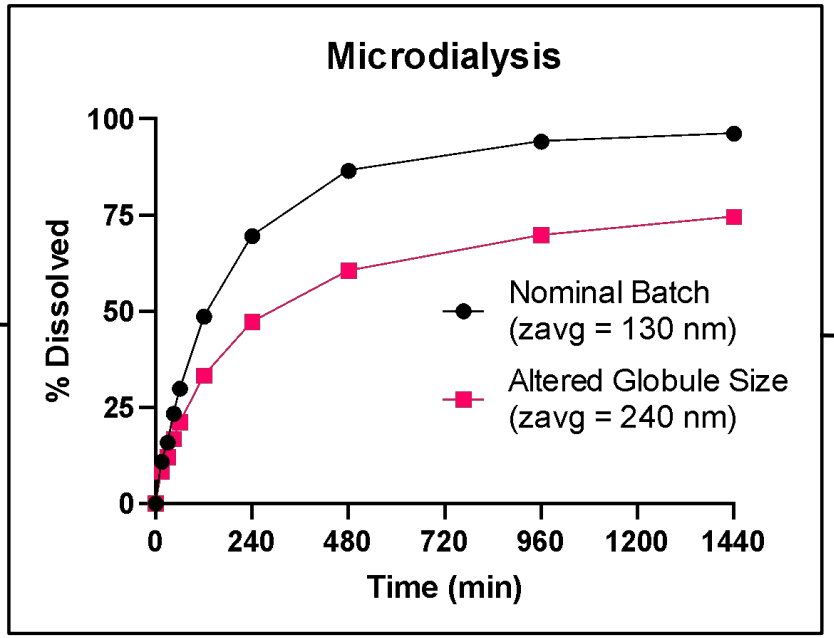
The Curious Case of the Suspension

sotax

Microdialysis

Suspension / Emulsion formulations can be manufactured with very small API particle sizes, but also the *viscosity* can be problematic for sample loading

Newly established as a potential way to test very specific types of suspensions/emulsions



Advantages:
- Achieve discrimination (for this product)
- Shorter run time than FAL (for this product)

Shortcomings:
- Cleaning
- Cost per run

We tested Microdialysis for a lyophilized cake that was suspended in water, great initial results and discriminatory power but unable to reproduce the results after a rigorous clean of the filters.

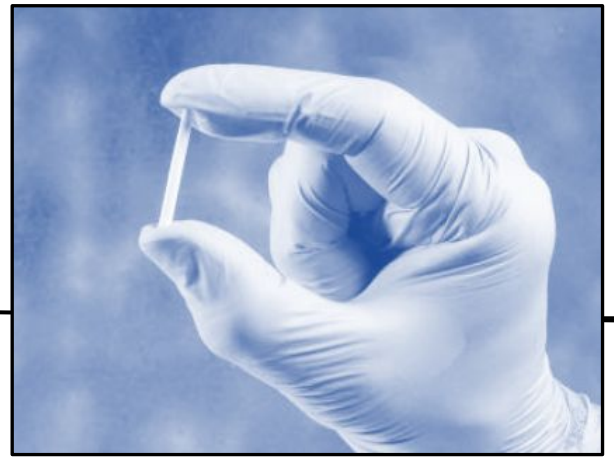
Obligatory Topics Page

8 AM in Vegas, What Will We Be Discussing?

- Complex Dosage Forms and Apparatus IV
- Case Study with Emulsion
- Case Study with Implant

The Curious Case of the Implant

Purpose:
Develop an *accelerated* dissolution method able to discriminate differences with critical processing parameters



Challenges:
- API diffusion through polymer can lead to long run times
- Accelerated conditions can require high temperatures and aggressive medias

Addressing the Challenges

API Diffusion Through Polymer
1. Approach or go above glass transition temperature of polymer
2. Break polymer down with media

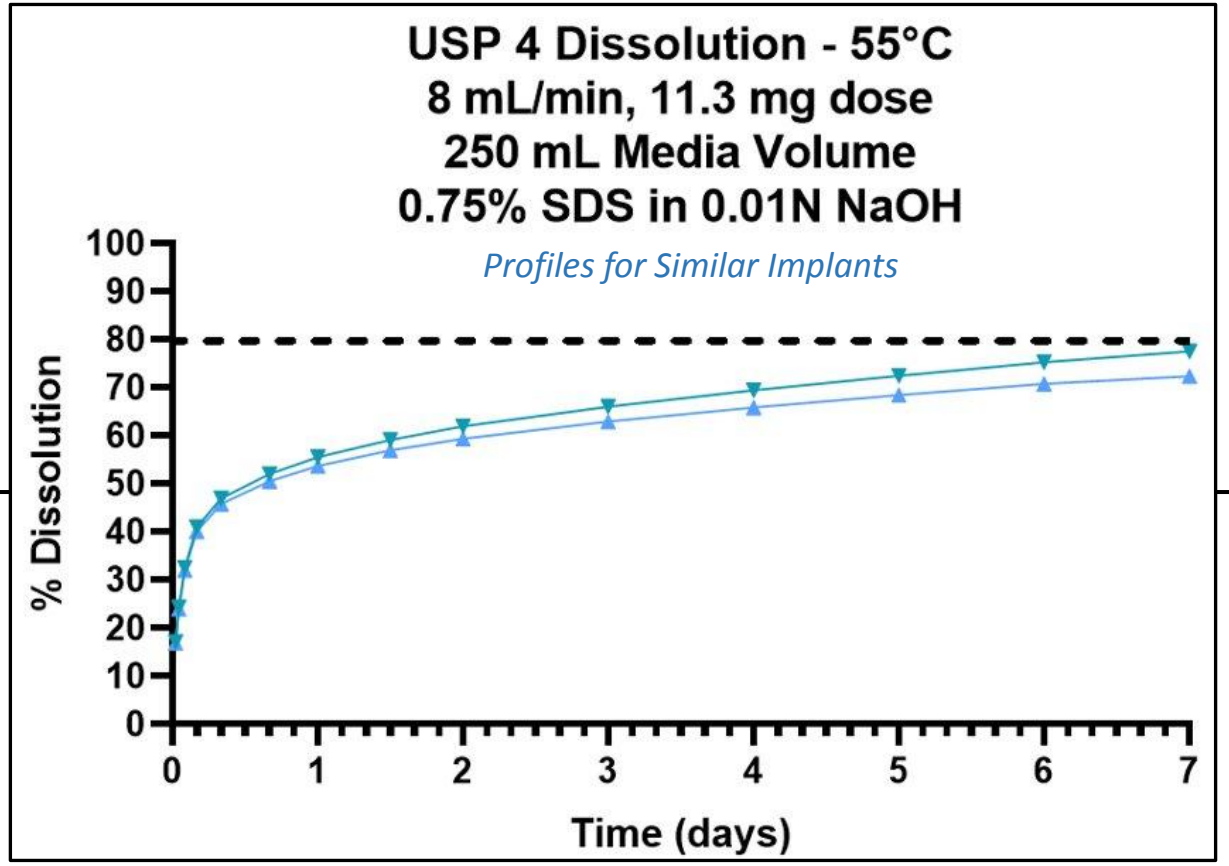
Awareness of Possible Issues:
- Running high temperatures can lead to evaporative loss
- Media choices and temperatures can impact API stability

The Curious Case of the Implant

An overview look at the CE7, CP7, and Autosampler C 615

The Curious Case of the Implant

Simple cell setup, Ultem Cell with glass beads and implant propped up



Real time release for this product is 1 year, accelerating release by hydrolyzing the polymer and using an elevated temperature, *method duration was 14 days*

Commonly Asked Questions

Q: How much can I accelerate the release profile?
A: For a QC method, you want to keep the core principles in place, reproducibility, discriminatory power, etc.

Q: Which cell should I use?
A: Always start with a compendial cell (22.6mm or 12mm) and justify moving towards the more specialized cells with data.

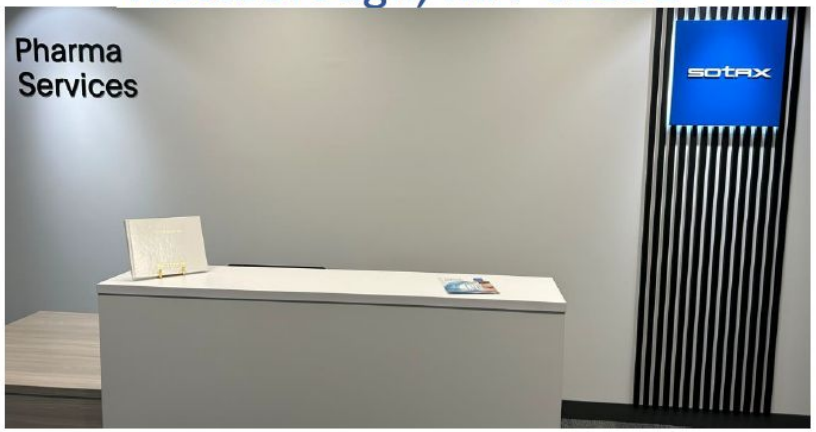
Q: What does the media compatibility looks like and what conditions I can I subject the system to?
A: Reach out to us, there are workarounds that we are discovering as we push the system to it's limits.

Thank You For Your Time!

Booth 201

SOTAX Corporation
2400 Computer Drive
Westborough, MA 01581

CRS2023
ANNUAL MEETING & EXPOSITION JULY 24-28, 2023
Paris Hotel » Las Vegas, NV, USA
THE FUTURE OF DELIVERY SCIENCE



Visit SOTAX at Booth 201:

Jerome Morris and *Sam Stern* will be there to show you the equipment and/or field any questions that pop up