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Developing with Apparatus 4

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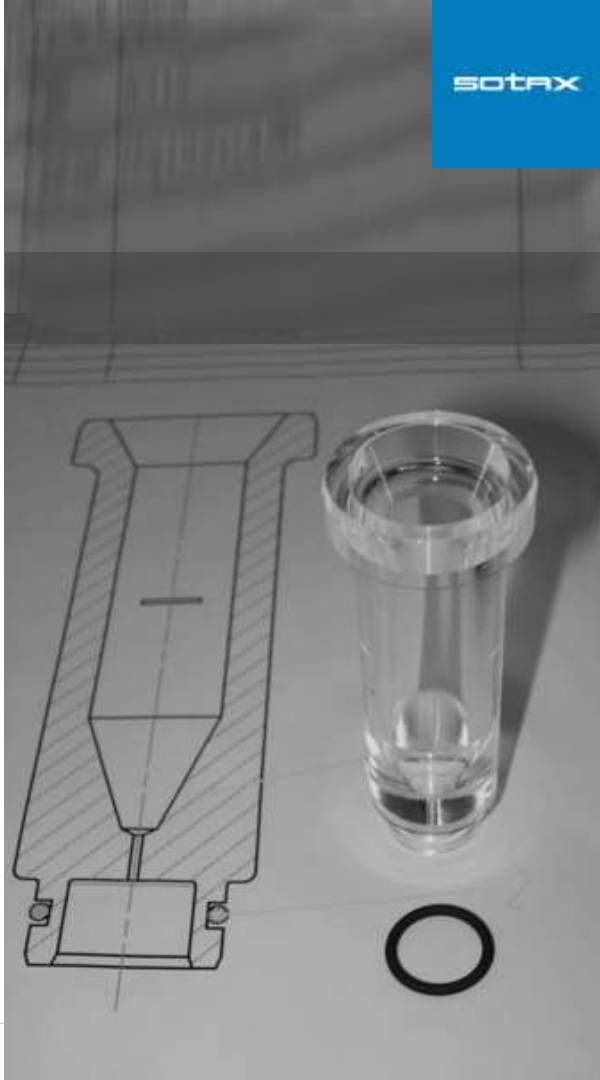
USP 4 | From USP <724>

"Consists of a reservoir, pump, flow through **cell immersed in a water bath maintained at 37 ± 0.5** C"



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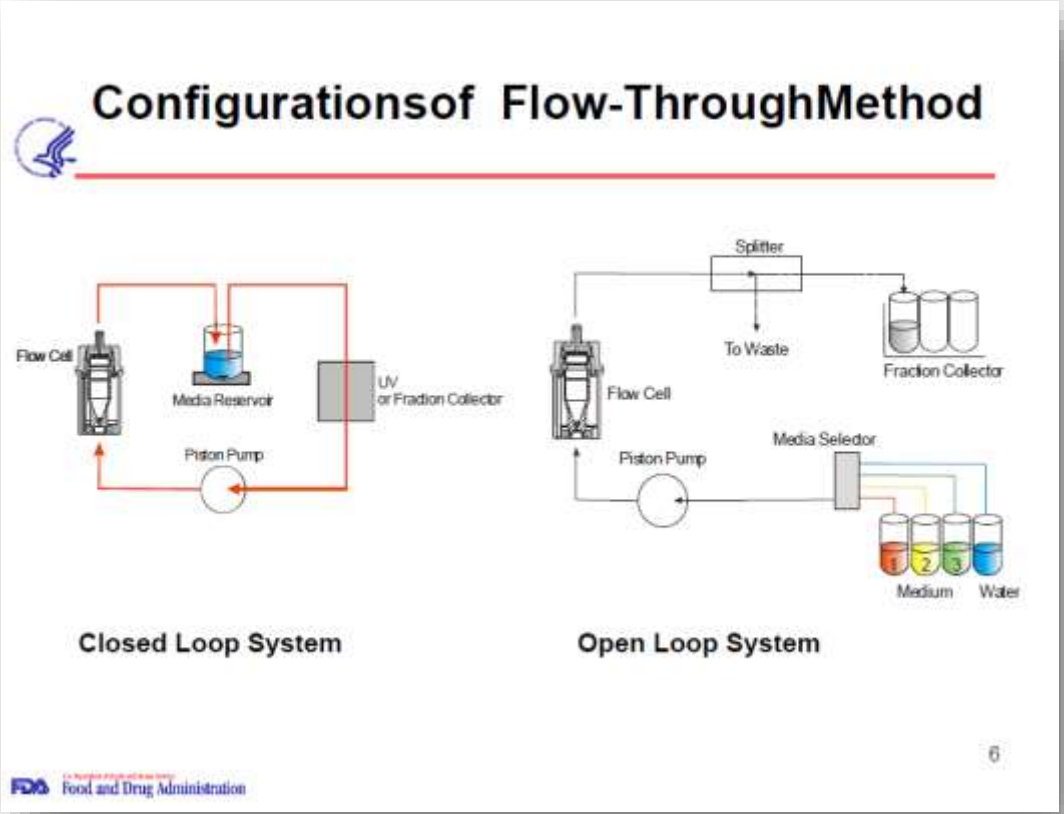
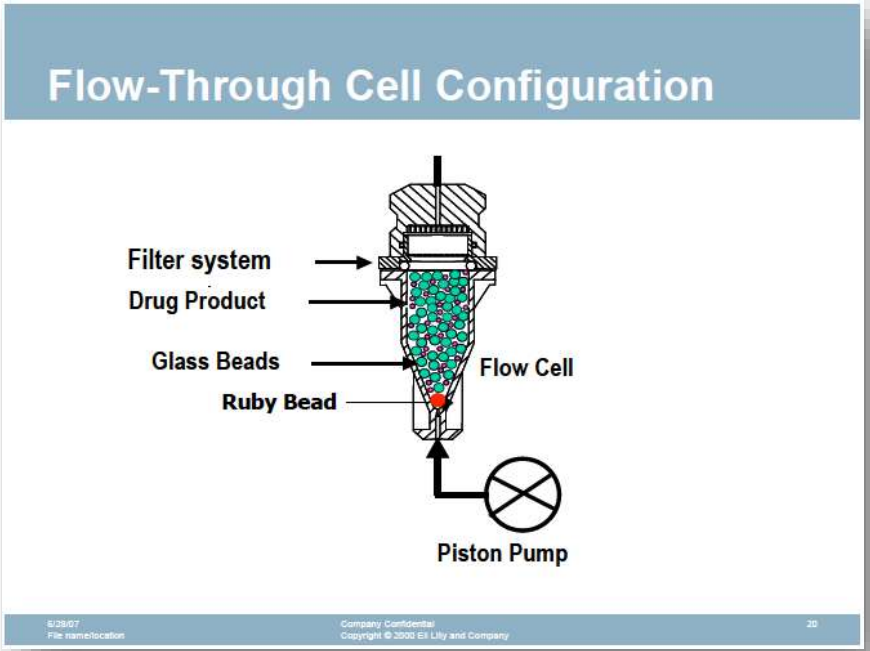
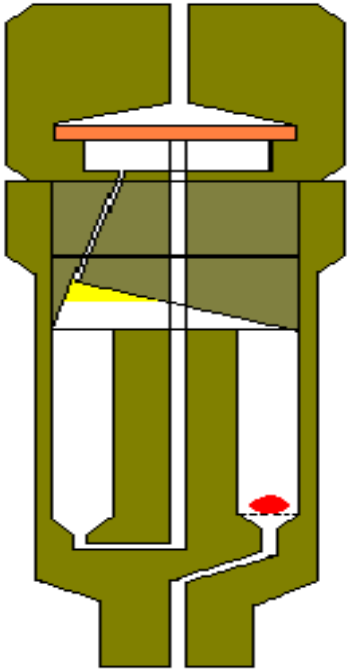
Method Review


Configurationsof Flow-ThroughMethod
Flow Cell
Media Reservoir
UV
or Fraction Collector
Piston Pump
Closed Loop System
Splitter
To Waste
Fraction Collector
Flow Cell
Media Selector
Piston Pump
1
2
3
Medium
Water
Open Loop System
6
Food and Drug Administration

Method Review | Cells

- Many cells available for your dosage forms
  - Tablet, Capsule, Soft Gel/Lipid, Implant, Device, Powder/API, Patches, Gels, etc
- Custom cells available





Left - Slide from Eli Lilly Suspension on CE 7smart | SOTAX user meeting
Right – Soft Gel Cell

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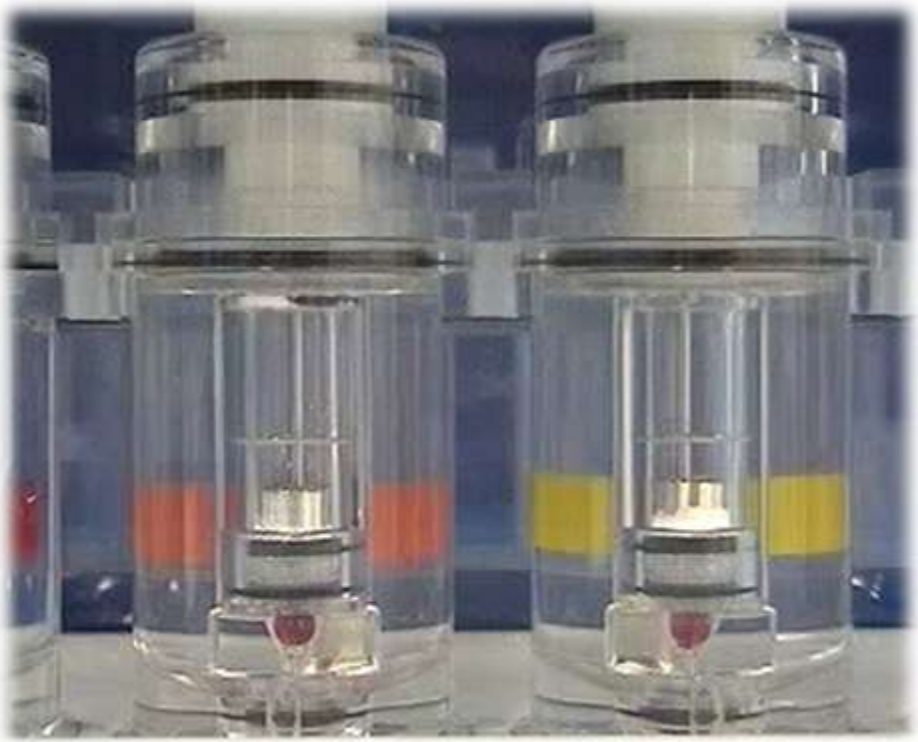
Method Review | Cell Set-up examples



Method Review | Cell Set-up examples

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Why USP 4?

Flexible Set-up

Poorly soluble today, lipid filled soft gels tomorrow

Have the ability to use the USP 4 instrument in multiple configurations to study your products

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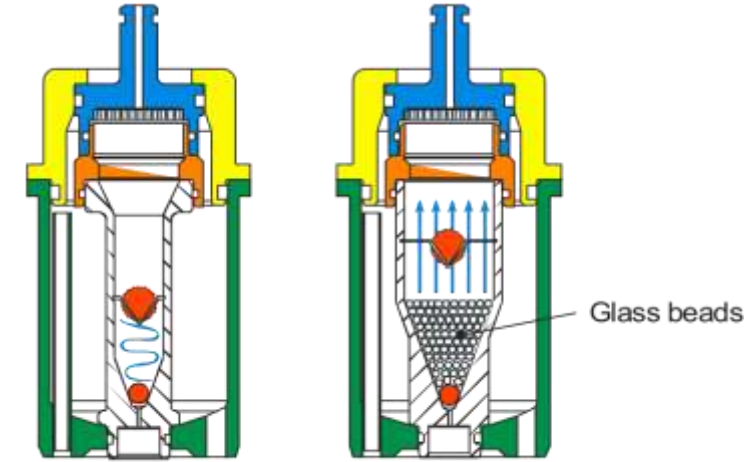
Cells Options

Set-up cells to take advantage of the controlled flow past the dosage form



Why USP 4?

Solves challenges of non-compendial elution
floating, swelling, sticky, multi-particulate, sampling problems, etc

Fewer apparatus parameters which affect the test
flow rate, flow type, and cell type

Unique cells for different formulations and new types of dosage forms

Increasing potential for IVIVC studies

Expedite the understanding of your products' release characteristics

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FDA Draft Guidance
EPA – Soft Gelatin Capsules

"Based on the information available to the Agency, as well as the recommendation given in the USP Pharm Forum,1 USP Apparatus 4 (flow-through cell) has been shown to be the most appropriate apparatus for drugs with poor solubility, compared to the conventional USP Apparatus 1 (basket) and Apparatus 2 (paddle)"

"In addition, the use of surfactant is also critical in the in vitro drug release method development for an icosapent ethyl drug product. "

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FDA Draft Guidance
EPA – Soft Gelatin Capsules

1. Dissolution medium and volume
2. Surfactant and concentration
3. Filter type and size for sample collection and preparation, where applicable
4. Enzyme and concentration, where applicable
5. Rotation speed (USP Apparatus 2 (paddle))
6. Flow rate (USP Apparatus 4 (flow-through cell))

Other parameters for US Apparatus 4:

7. System mode (closed versus open)
8. Type of cell (size in mm)
9. Glass beads (size in mm)
10. Glass bead loading (weight in gm)
11. Sample load (volume in mL)
12. Split ratio (%)
13. Size of sample tube (volume in mL)

Example Method Development Week

Monday:
- Unpack and Install CE7
- Perform functional tests

Tuesday:
- Planning meeting
- Execute test #1 and #2 of a Soft Gel sample

Wednesday:
- Execute test #3 and #4 of a Soft Gel sample
- Uninstall and Pack CE7 for Transport

Thursday:
- Present Work from the week

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Run #1
Soft Gel 'Guiding Samples'
Flow Rate Study

'Guiding Samples' are first draft methods. Sample results help to guide the method optimization.

- N=2
- Cell = Lipid Cell
- Flow rate = 8, 16, 24 mL
- Media = 0.05 M pH 6.0 citrate buffer with pepsin, sample #1 = 1% SLS media addition @20min

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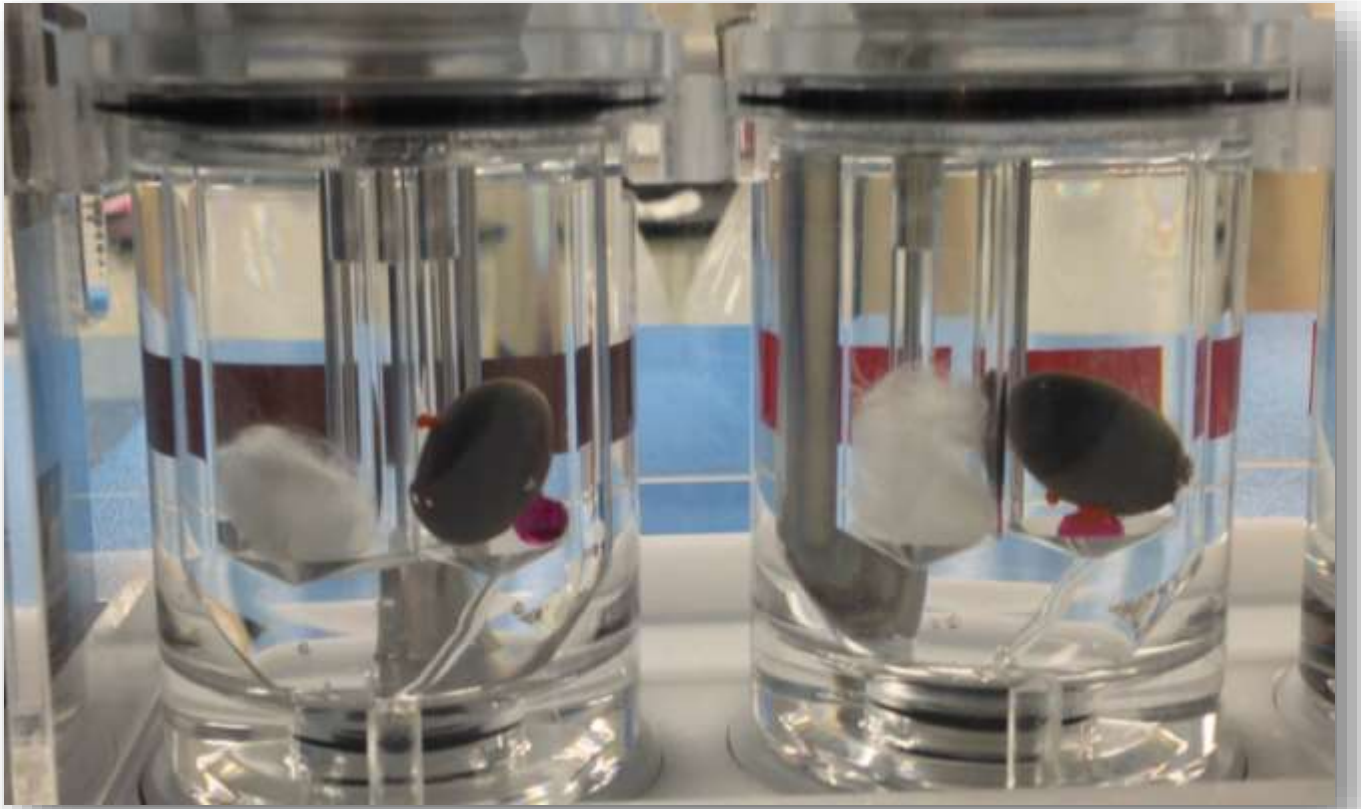
Method Review | Soft Gel Example



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Method Review | Soft Gel Example

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Run #1
Soft Gel 'Guiding Samples'
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- N=2
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- Media = 0.05 M pH 6.0 citrate buffer with pepsin, sample #1 = 1% SLS media addition @20min

Soft Gel Sample

Sample	% Folic Acid	% B2	Manual Results
1 – SLS	35.9	32.3	84%, 79%
2 – no SLS	-	-	

Run #2
Cell Setup Study

- N=4
- Cell = N=2, Lipid Cell | N=2, packed 22.6mm Tablet Cell
- Flow rate = 25 mL/min
- Media = 0.05 M pH 6.0 citrate buffer with pepsin, 1% SLS media addition @20min

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Run #2 – Cell Selection

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Run #2 – Cell Selection

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Run #2
Cell Set-up

- N=4
- Cell = N=2, Lipid Cell | N=2, packed 22.6mm Tablet Cell
- Flow rate = 25 mL/min
- Media = 0.05 M pH 6.0 citrate buffer with pepsin, 1% SLS media addition @20min

Soft Gel Sample

Sample	% Folic Acid	% B2	Manual Results
Lipidic Cell	33.3	28.5	84%, 79%
22.6 mm - Packed	-	5.9	

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Run #3
Media Screen

- N=4
- Cell = N=2, Lipid Cell | N=2, **un-packed** 22.6mm Tablet Cell
- Flow rate = 30 mL/min
- Media = 0.05 M pH 6.0 citrate buffer with pepsin,
  N=2, 2% SLS media addition @20min
  N=2, 5% SLS media addition @20min

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Method Review | Media Screen

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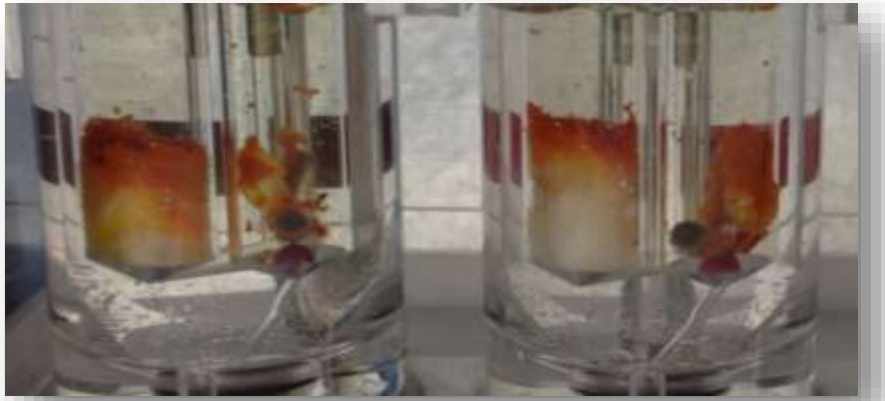
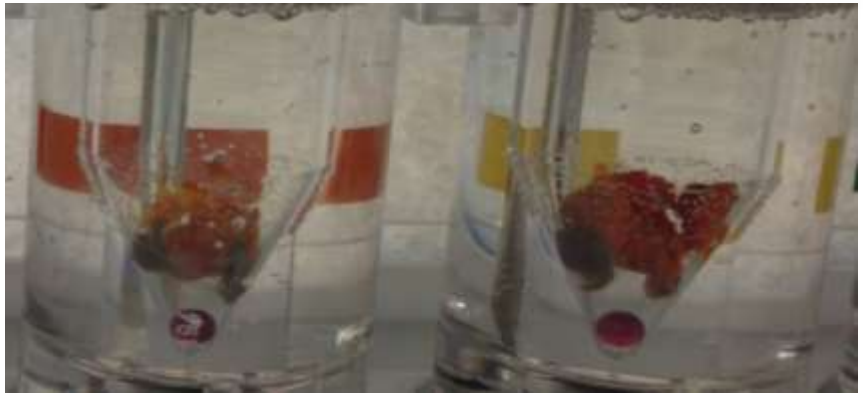
Method Review | Media Screen





- N=4
- Cell = N=2, Lipid Cell | N=2, packed 22.6mm Tablet Cell
- Flow rate = 25 mL/min
- Media = 0.05 M pH 6.0 citrate buffer with pepsin, 1% SLS media addition @20min

Soft Gel Sample

Sample	% Folic Acid	% B2	Manual Results
Lipidic Cell – 2% SLS	84.2	79.1	
Lipidic Cell – 5% SLS	53.1	48.0	84%, 79%
22.6 mm – 2% SLS	-	-	
22.6 mm – 5% SLS	-	-	

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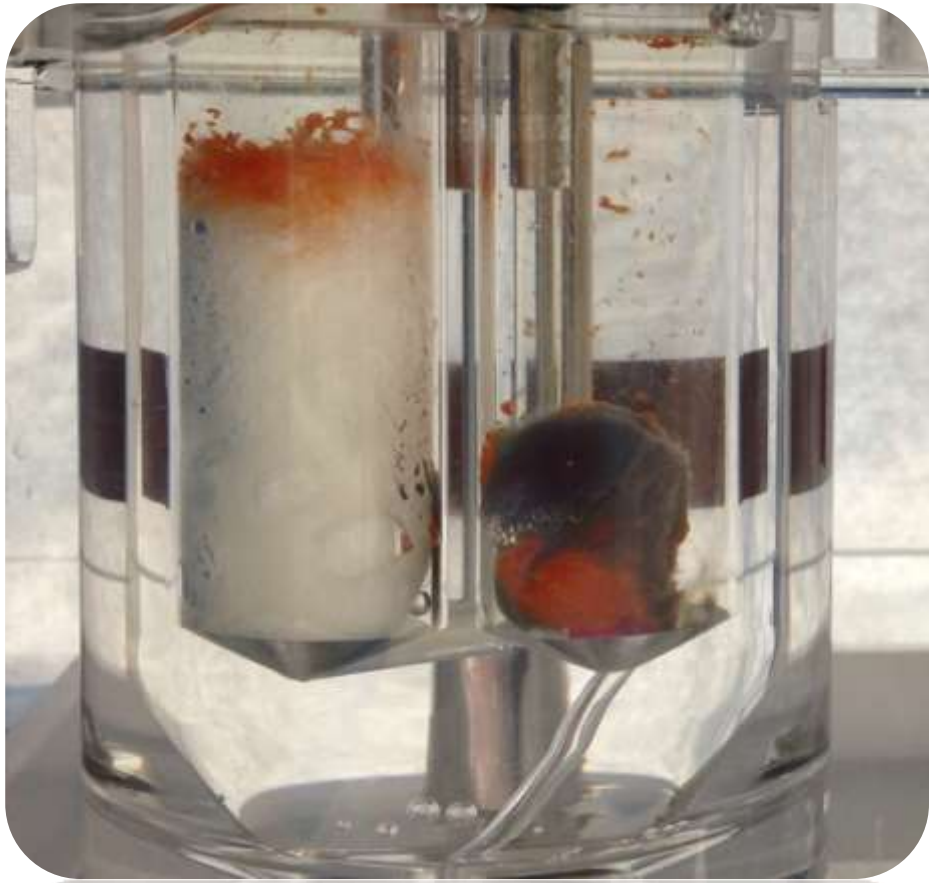
Run #4
Surfactant Screen

- N=2
- Cell = N=2, Lipid Cell
- Flow rate = 30 mL/min
- Media = ***with-out pepsin***,
  N=1, 2% SLS in 0.05 M pH 6.0 citrate buffer
  N=1, 2% CTAB in 0.05 M pH 6.0 citrate buffer

Method Review | Media Screen



Method Review | Media Screen

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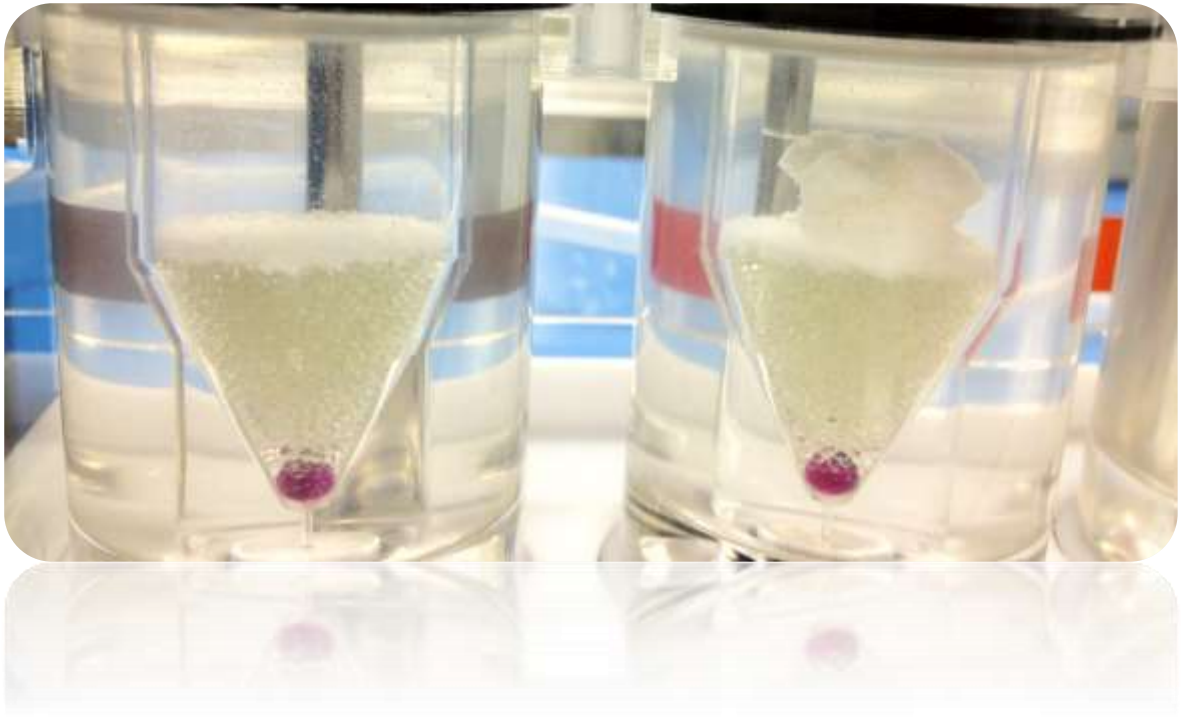
Run #4
Surfactant Screen

- N=2
- Cell = N=2, Lipid Cell
- Flow rate = 30 mL/min
- Media = ***with-out pepsin***,
  N=1, 2% SLS in 0.05 M pH 6.0 citrate buffer
  N=1, 2% CTAB in 0.05 M pH 6.0 citrate buffer

Soft Gel Sample

Sample	% Folic Acid	% B2	Manual Results
Lipidic Cell – SLS	86.4	75.2	84%, 79%
Lipidic Cell – CTAB	72.8	70.1	

Method Review | Poorly Soluble Example



Method Review | Poorly Soluble Example

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SPS
Pharma Services

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