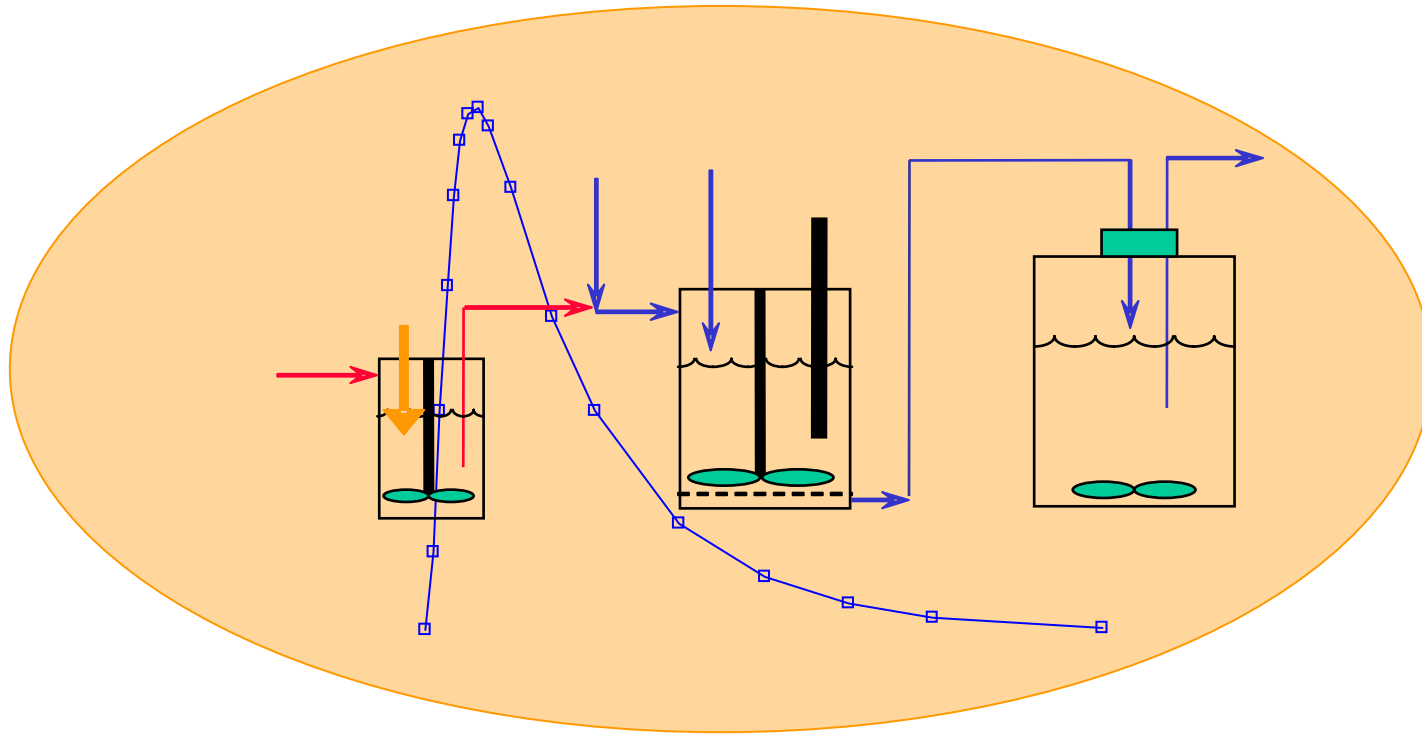




# FloVitro™ Technology

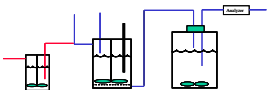


**Dr L. Hughes and Amie Gehris**  
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**Spring House, PA, USA**  
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# Overview

- Technology description
- Uses
- Qualification
- Operating windows
- Examples

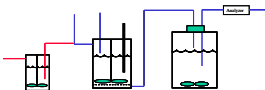




# New Approach to Dissolution Testing

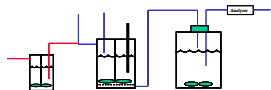
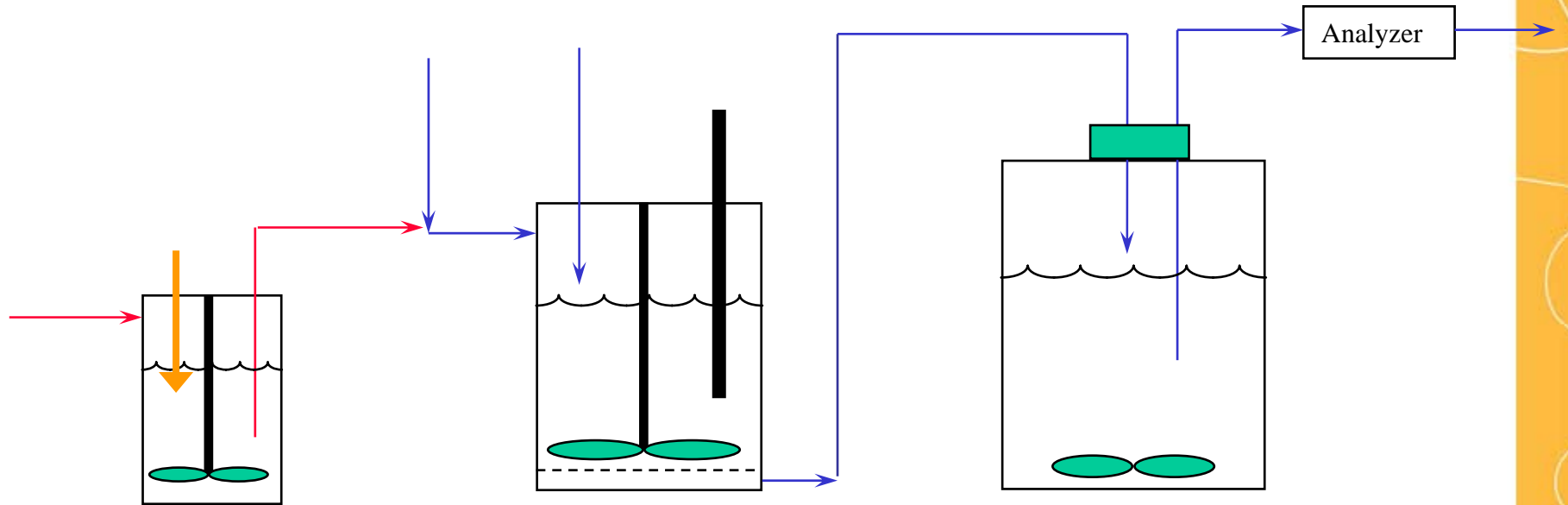
## Features:

- Level A IVIVC
- Three stirred cells in series
- Output does not require mathematical modeling
- Predictive across dosage forms of the same API
- Minimal method development



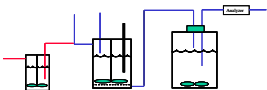
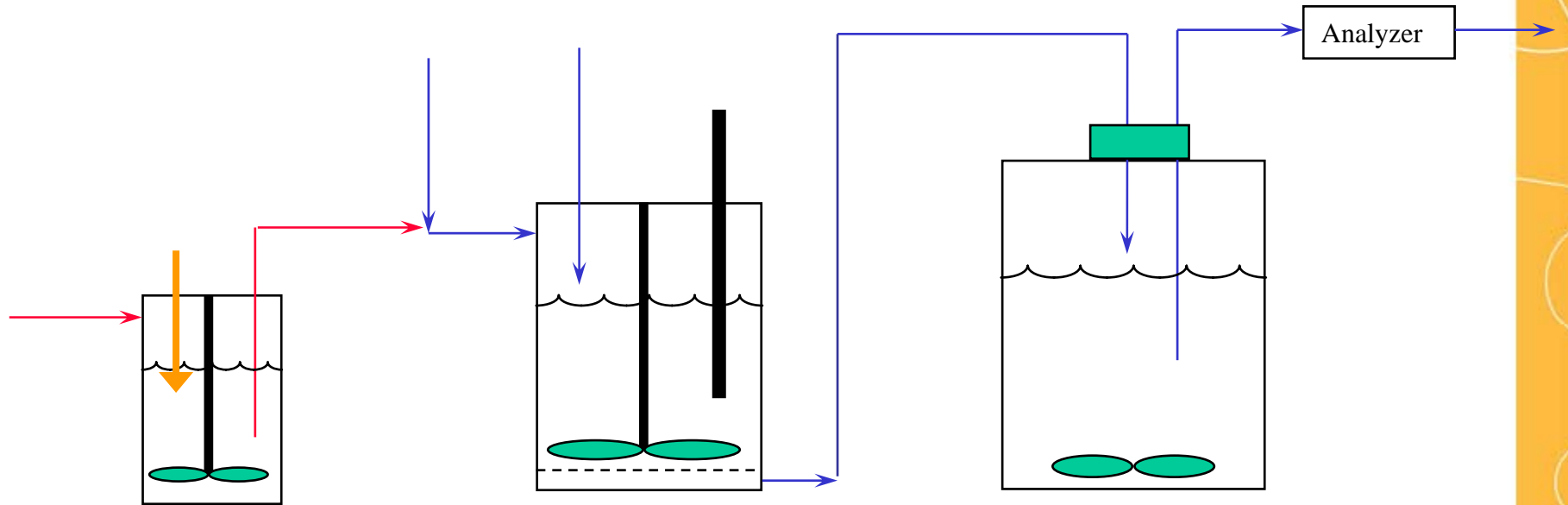


# Overall





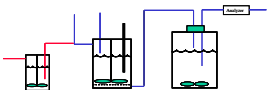
# Overall





# Effect represented

- Gastric disintegration
- Gastric dissolution
- Transfer from gastric to intestinal conditions
- Intestinal dissolution
- Variable intestinal pH
- Intestinal absorption
- Systemic clearance

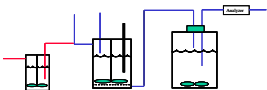




# Equipment



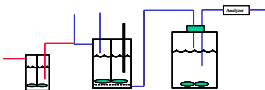
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# Predictability

Test method is predictive across dosage forms of the same API with the assumption that neither Absorption nor Clearance characteristics have changed



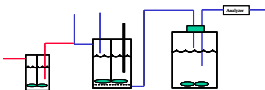


# API's tested

IVIVC demonstrated for:

- BCS I (High sol/High perm) - 7
- BCS II (Low sol/High perm) - 3
- BCS III (High sol/Low perm) - in progress
- BCS IV (Low sol/Low perm) - 3

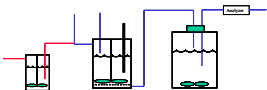
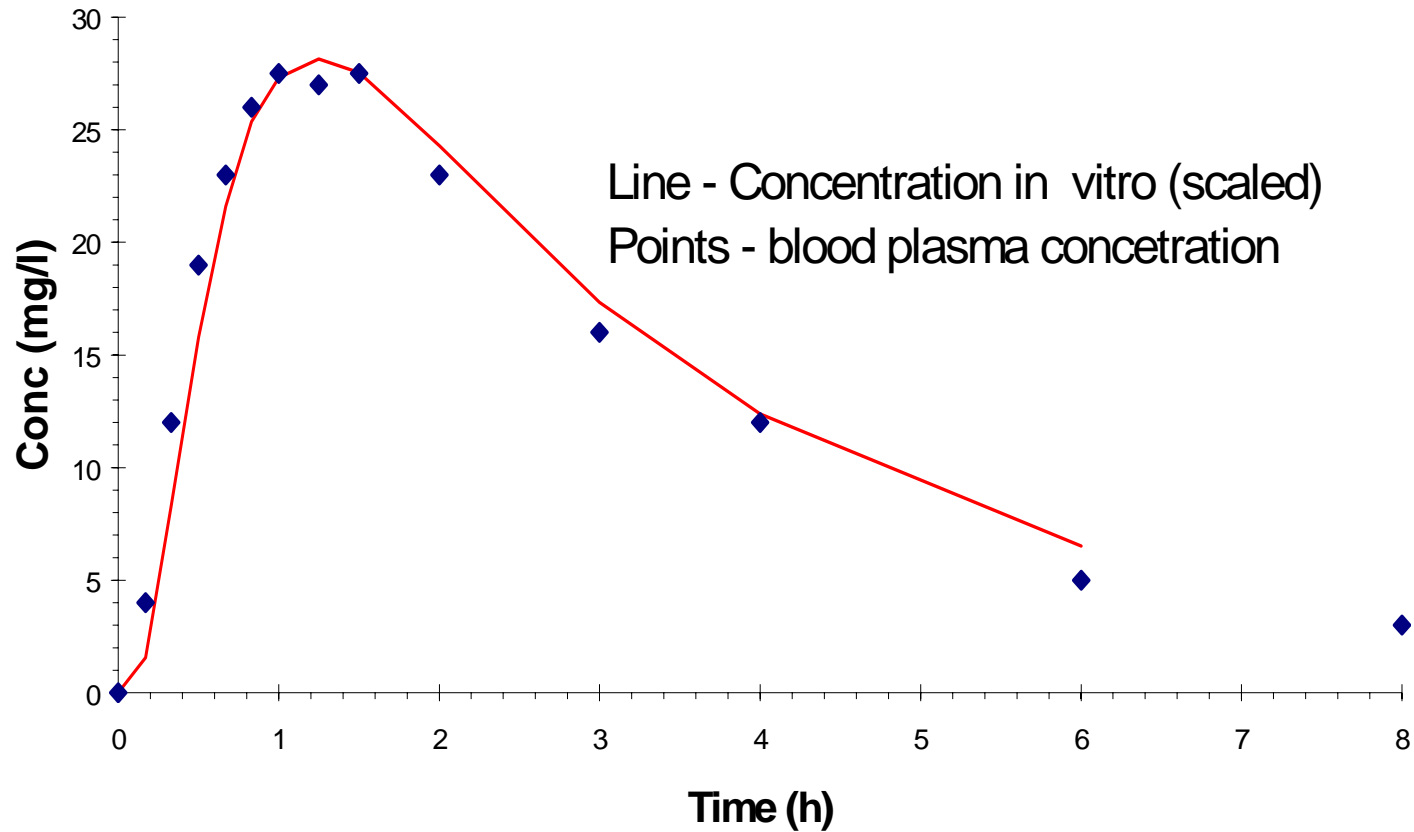
IVIVC for other drugs, but BCS class not known.





# IR dosage

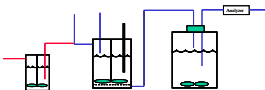
## Correlation of *in vivo* and *in vitro* data for Advil





# Possible Uses

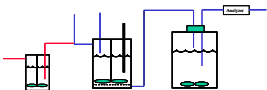
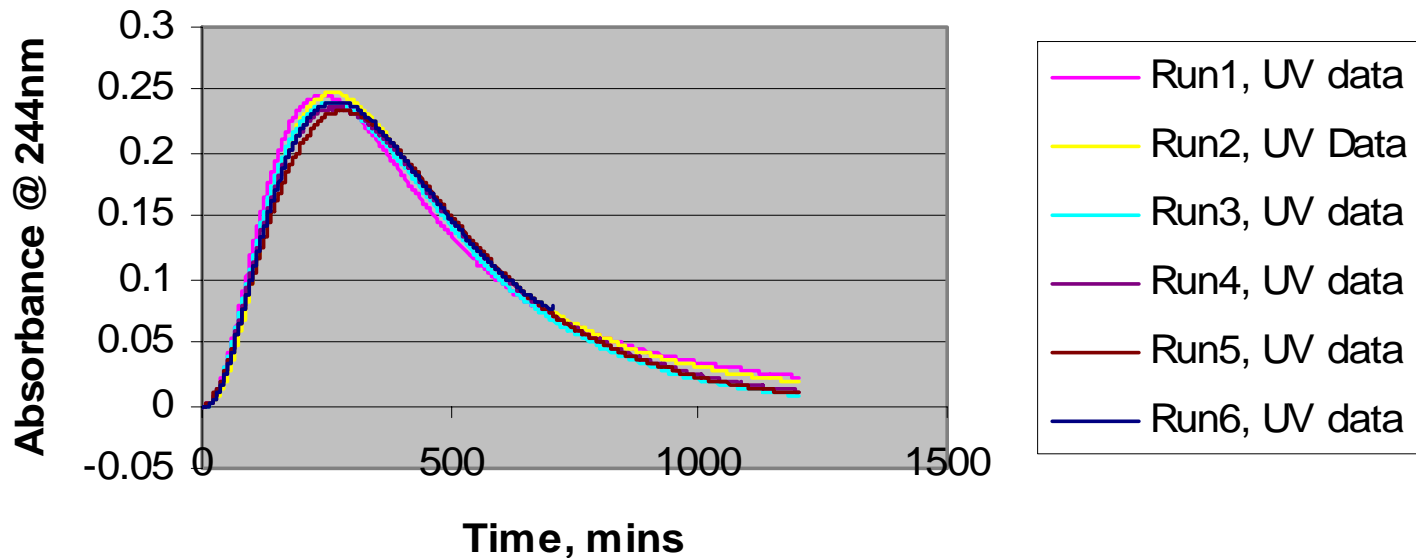
- Demonstrating Bioequivalence
- Support of scale-up/process modification
- Salt form selection
- Modified release product development
  - ✓ Test more options
  - ✓ Test options quicker
  - ✓ Increase probability of success
  - ✓ Reduce human or animal testing
  - ✓ Reduce costs and time-to-market





# Reproducibility: USP Prednisone Calibrator Tablets, 10mg

Rohm and Haas GI Dissolution Analysis with  
USP Prednisone Calibrator Tablets, 10mg

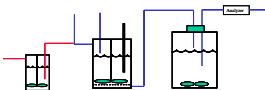




# Repeatability Prednisone Recoveries at 3 hours

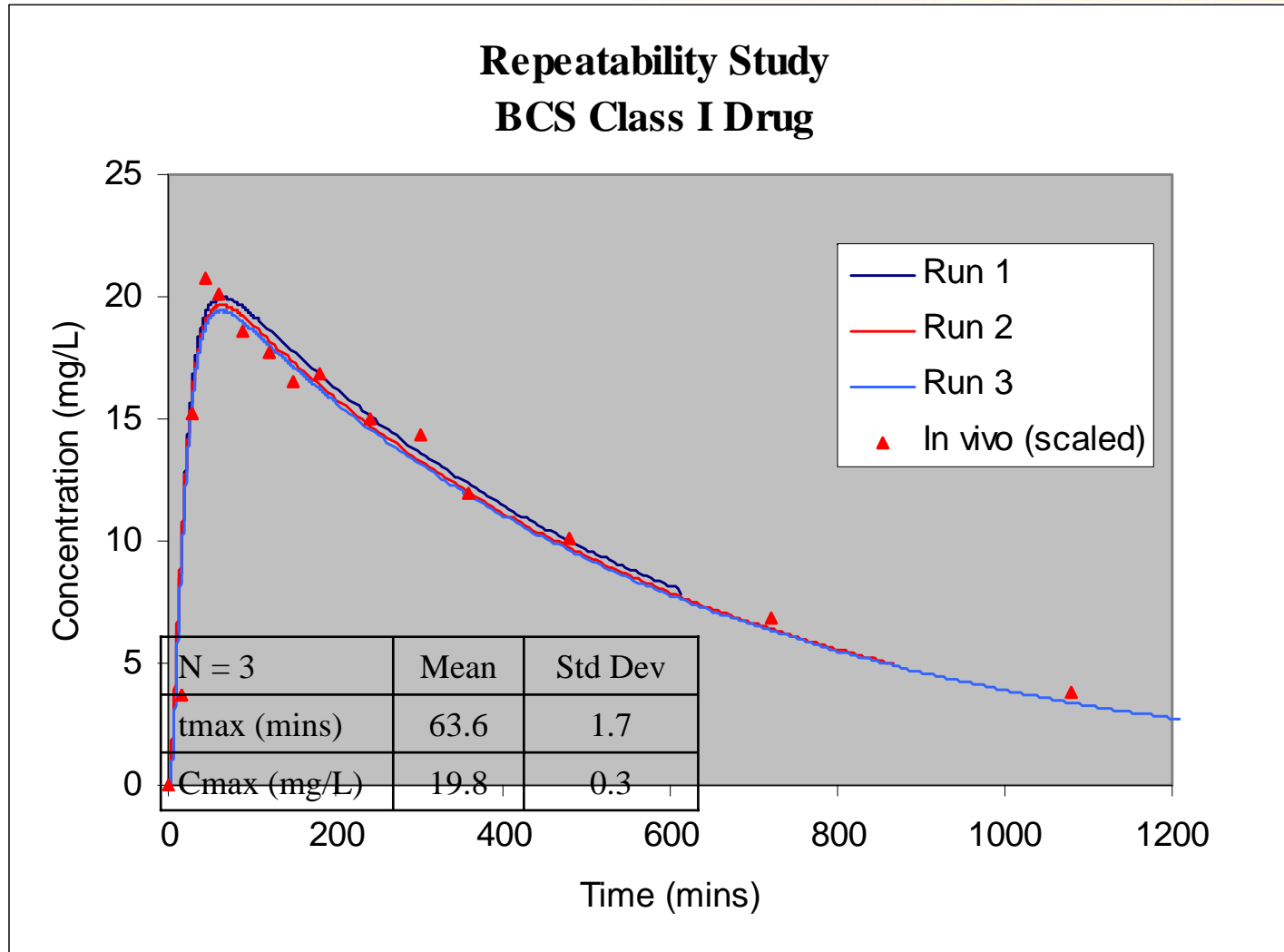
Expt	% Recovery @ 3 Hours
1	46.81
2	41.69
3	51.62
4	46.08
5	44.56
X	<b>46.15</b>
St Dev	<b>3.63</b>

**USP spec for Apparatus 2 37-70% dissolved in 30 min**

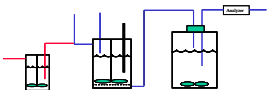




# Repeatability



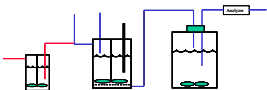
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# Operating Windows for Cell 1

Factorial design to identify major variables that affect solids transfer

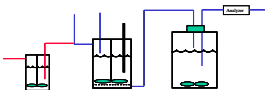




# Solids Transfer – Fractional Factorial Design

Half of a  $2^5$  (16 expts)

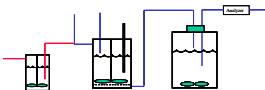
Agitation rate	100 and 300rpm
Dip tube length	3mm above agitator (long) 20mm above agitator (short)
Dip tube tip	Angled and square
Particle size	Coarse (100/120mesh) Fine (270/325 mesh)
Flow rate	1.0 and 4.0 ml/min





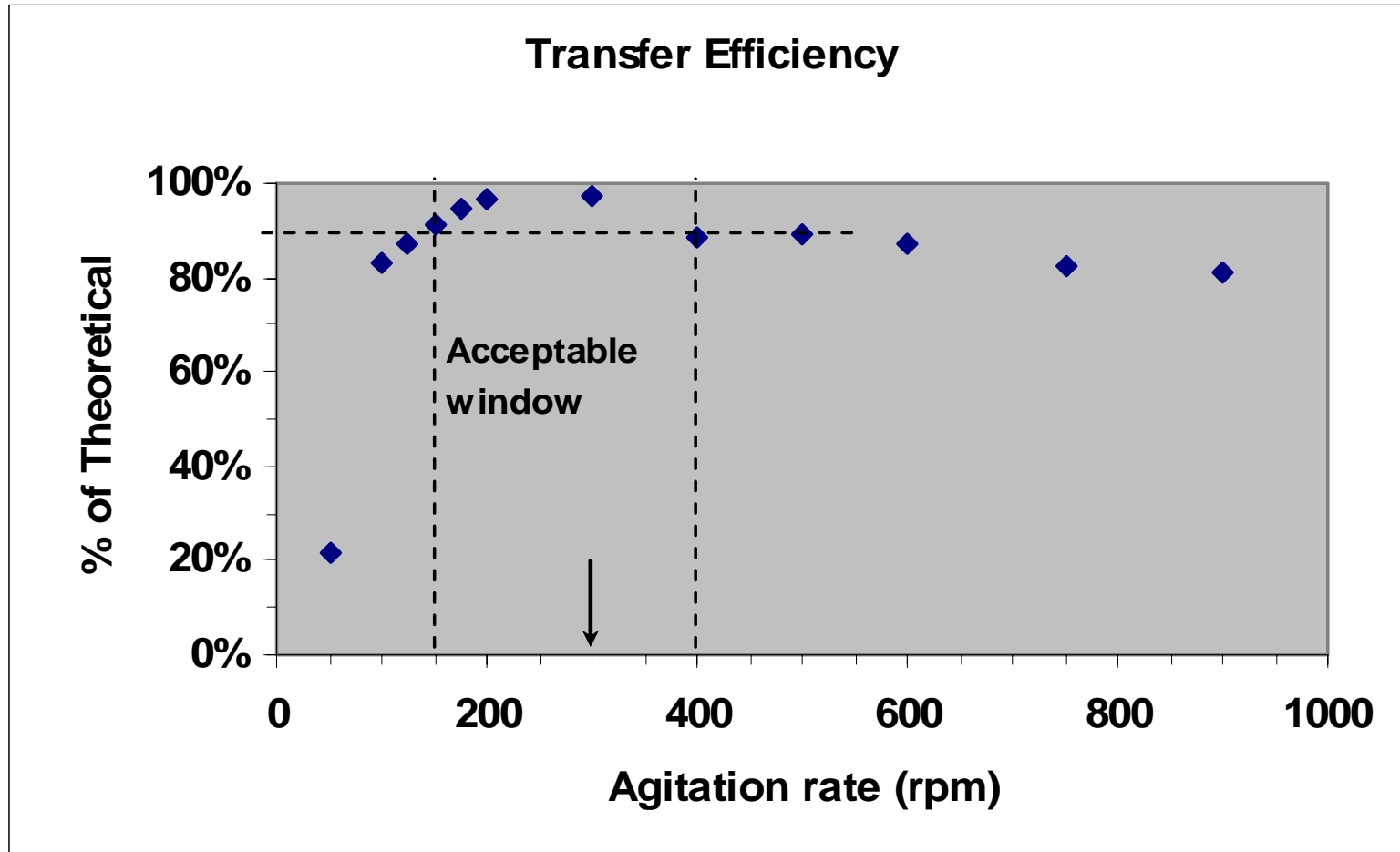
# Solids Transfer - Major effects

- Agitation Rate
- Particle size
- Dip tube length and shape only had effects outside typical operating conditions

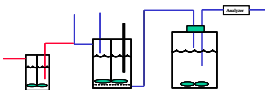




# Effect of Agitation Rate

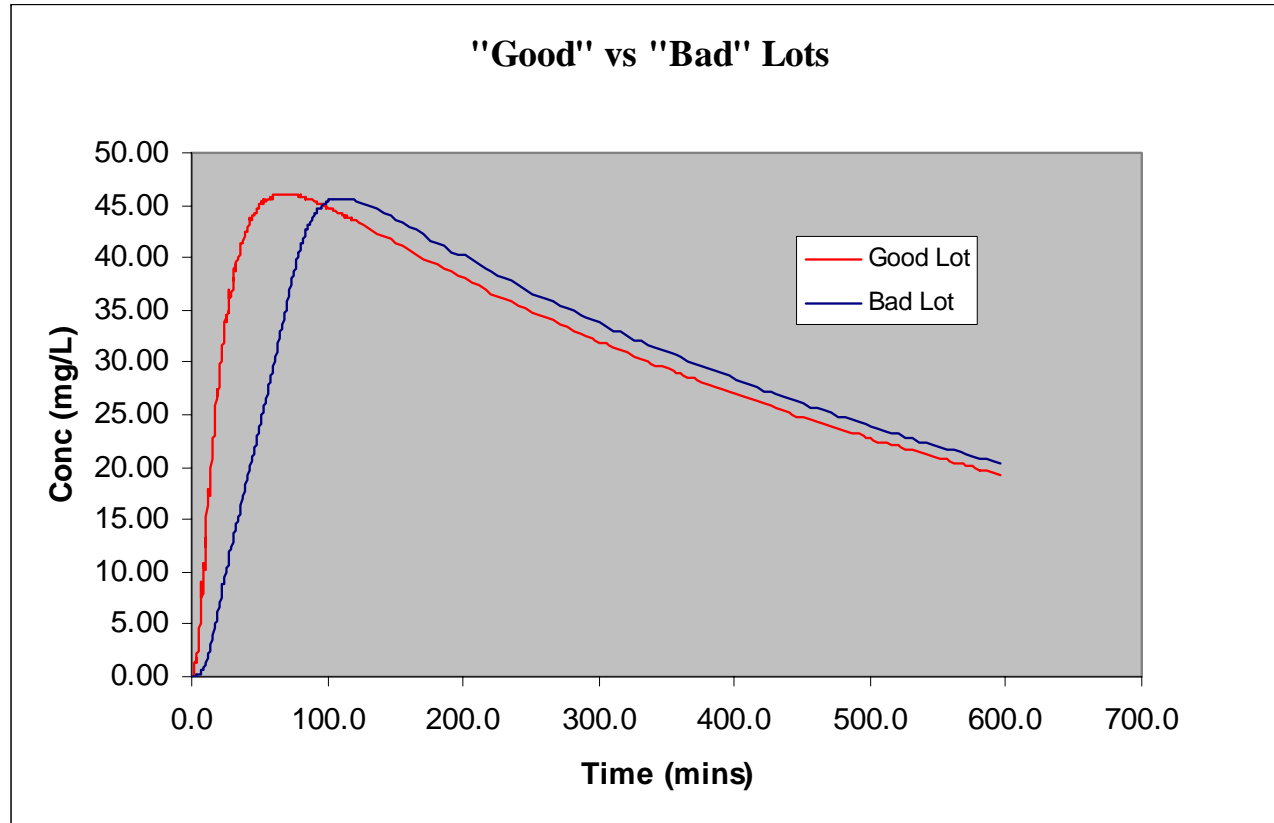


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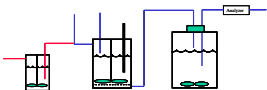


# Formulation Problem



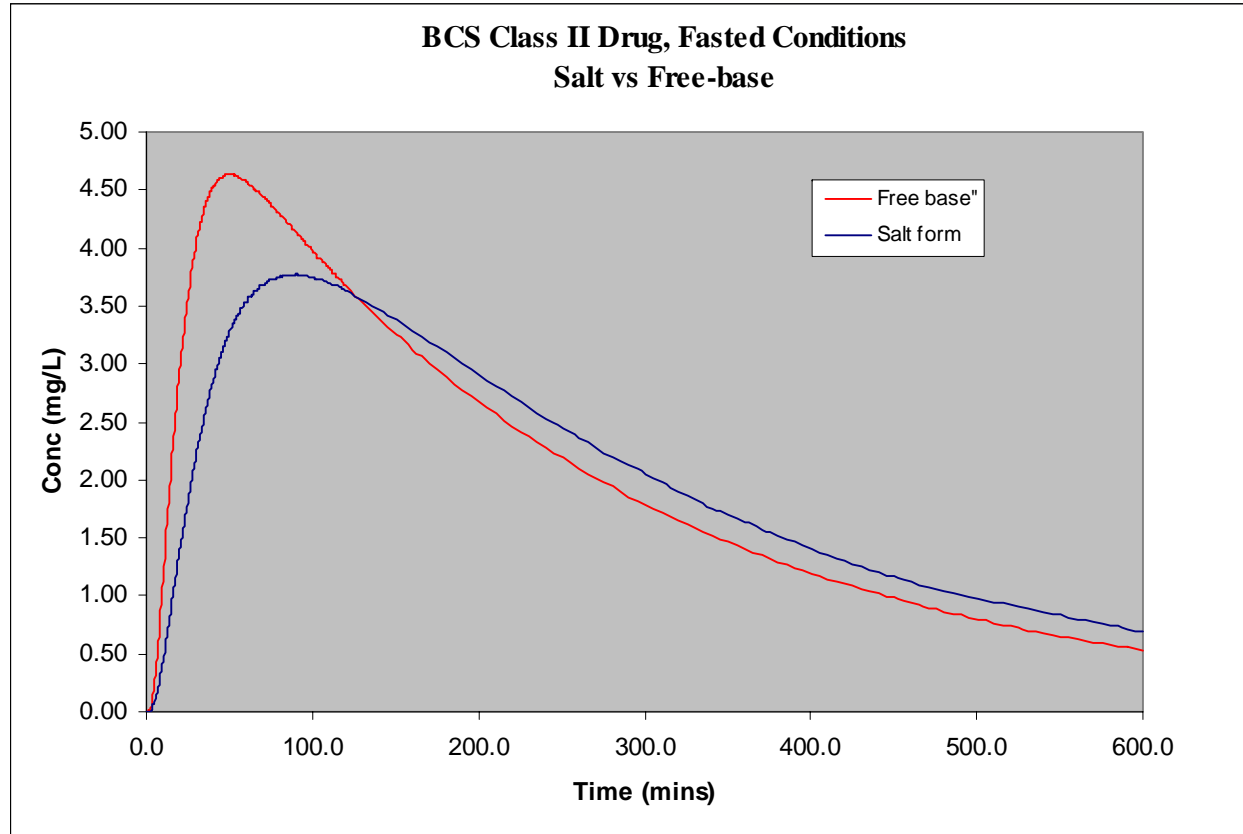
$t_{\max}$  values correlated well with *in vivo* data

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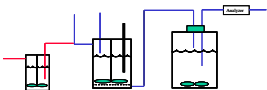


# Salt form



Dissolution rates counter-intuitive, but correlated with other studies.

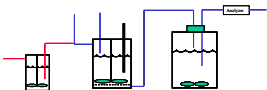
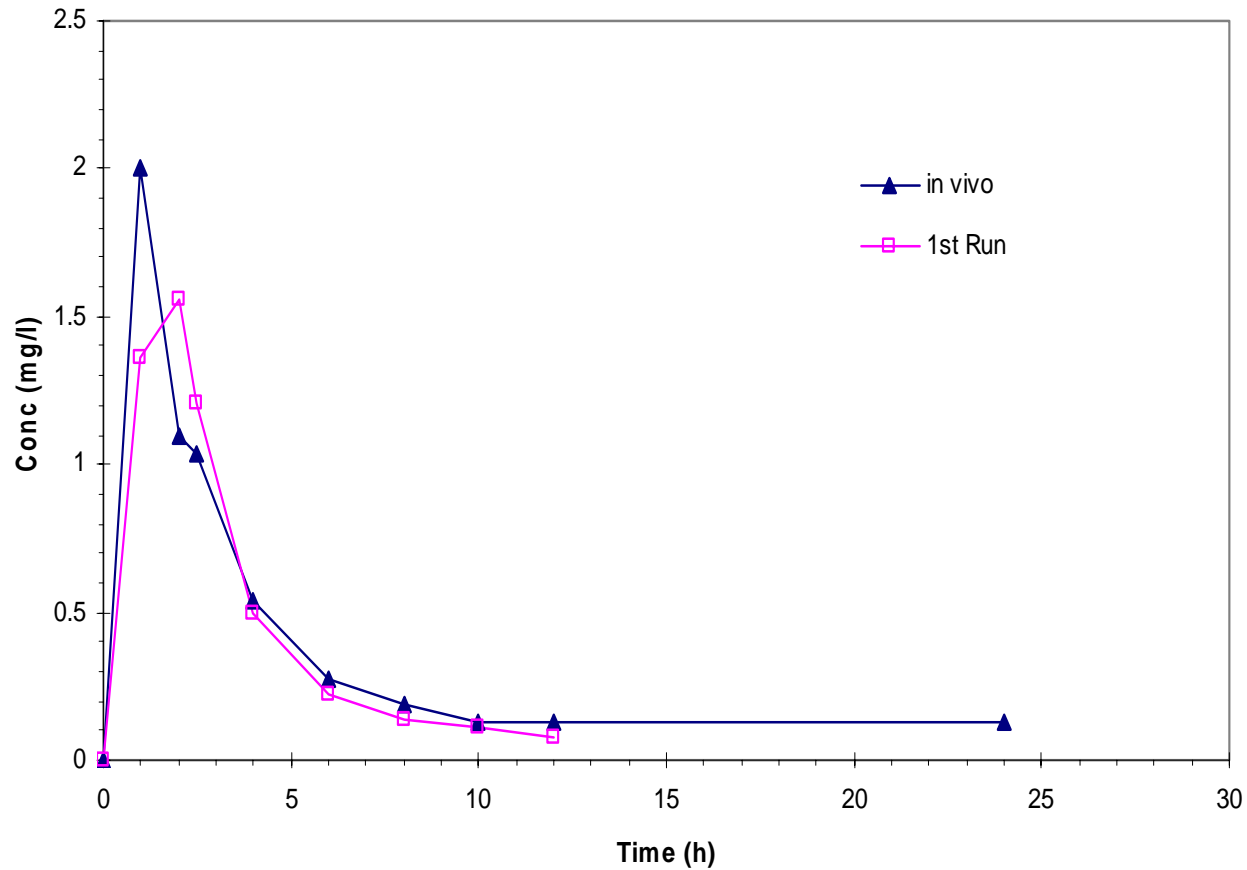
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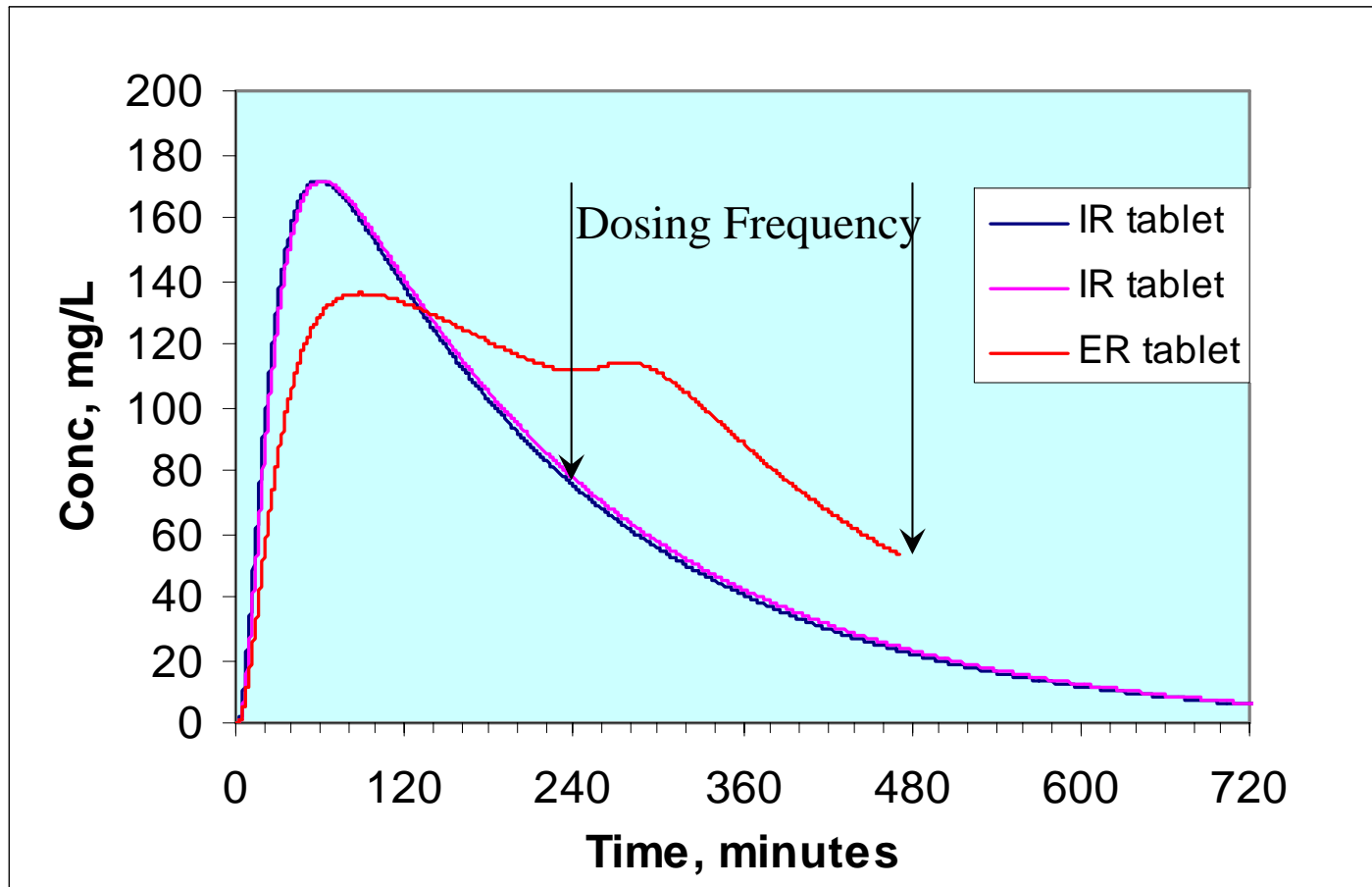
# Diclofenac – IR vs ER

Diclofenac Resinate *in vitro* - *in vivo* Correlation  
(concentration scale normalized by LSR)

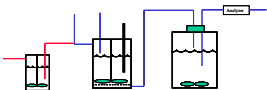




# Tylenol – IR vs ER



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# Summary

- A GI dissolution test that gives Level A IVIVC without mathematical modeling.
- A GI dissolution test that is predictive for extended release dosage forms.
- Defined repeatability using Prednisone
- Defining operating windows for Cell 1
- Valuable tool for bioequivalence, product development and troubleshooting

