In Vitro Release Testing of Complex Parenteral Dosage Forms

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Applications of USP Apparatus 4

- *In vitro* release testing of complex parenteral dosage forms (such as polymeric microspheres, nano-sized formulations, implants, and semi-solid dosage forms)
- Development of *in vitro-in vivo* correlation for polymeric microspheres

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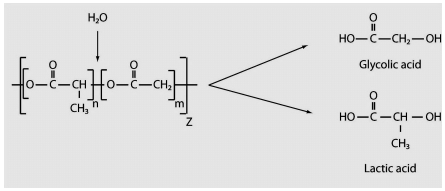
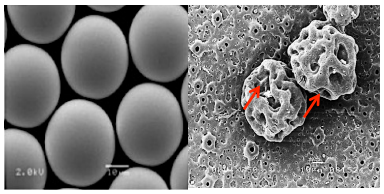
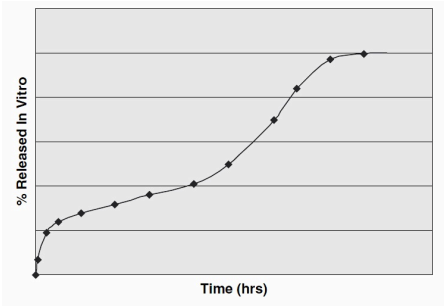
Case Study I_Polymeric Microspheres







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A. Rawat, D.J. Burgess. Int J. Pharm, 2012

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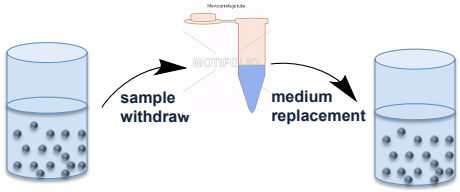
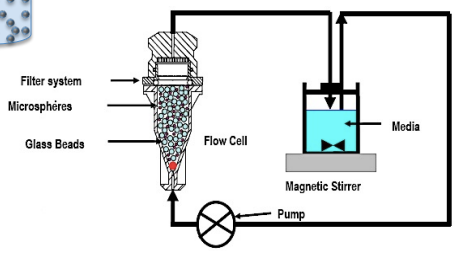
Case Study I_Polymeric Microspheres

Sample-and-Separate method



Continuous flow method



Advantages:

- ✧ **Prevents microsphere aggregation**
- ✧ **Better hydrodynamic conditions**
- ✧ **Flexibility of media volume**
- ✧ **Simulates *in vivo* environment (*e.g.* subcutaneous tissues)**

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Zolnik B.S., Burgess D.J., Dissol Tech, 2005

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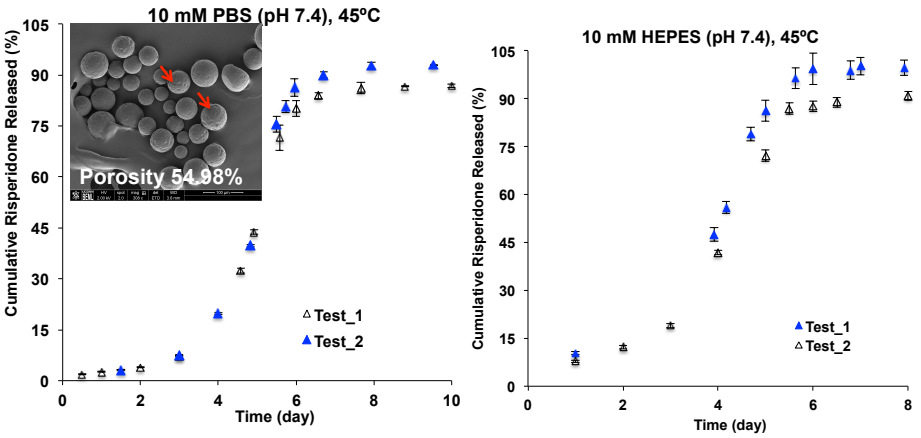
Comparison of Two Release Methods

✓ Sample-and-Separate method



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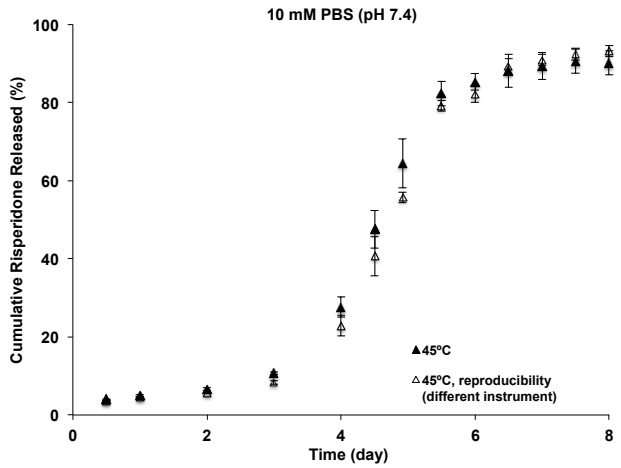
Comparison of Two Release Methods

✓ USP apparatus 4 method



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Case Study I_Polymeric Microspheres

- IVIVC

A predictive mathematical model describing the relationship between an *in vitro* property of a dosage form (e.g. rate or extent of drug release) and a relevant *in vivo* response (e.g. plasma drug concentration, amount of drug absorbed, and AUC).

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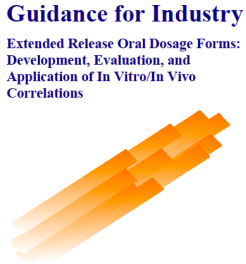
Development of IVIVC for CR Parenterals

- U.S. FDA Guidance for Industry (immediate and extended release oral dosage forms)



- Biorelevant *in vitro* release methods needed

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Categories of IVIVC

- **Level A:**
  - Generally linear and represents a point-to-point relationship between *in vitro* dissolution and *in vivo* input rate
- **Level B:**
  - The mean *in vitro* dissolution time is compared to either mean residence time or mean *in vivo* dissolution time
- **Level C:**
  - A single point correlation between a dissolution parameter (*e.g.* $T_{50\%}$) and a PK parameter (*e.g.* AUC, C_{max}, and T_{max})
- **Multiple Level C:**
  - Multiple dissolution time points with one or several PK parameters
- **Level D:**
  - Rank order correlations (qualitative) (not considered useful for regulatory purposes).

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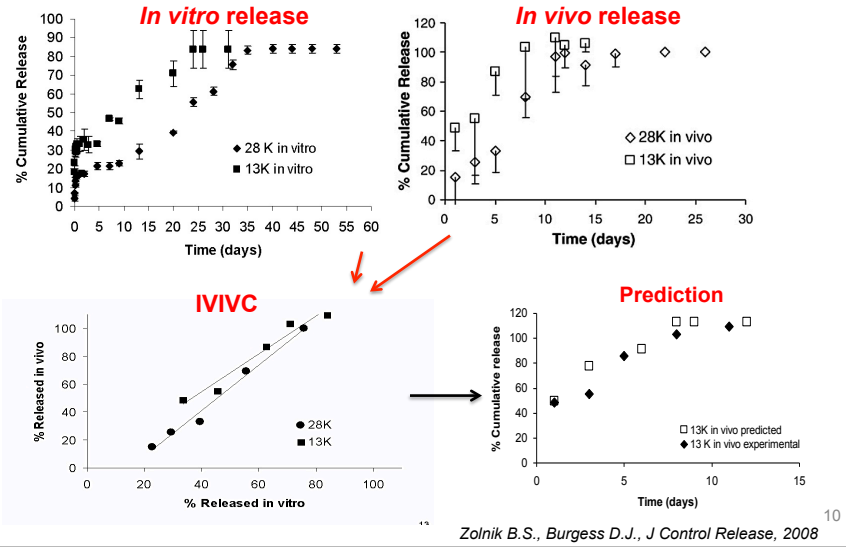
Dexamethasone Microspheres



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Zolnik B.S., Burgess D.J., J Control Release, 2008

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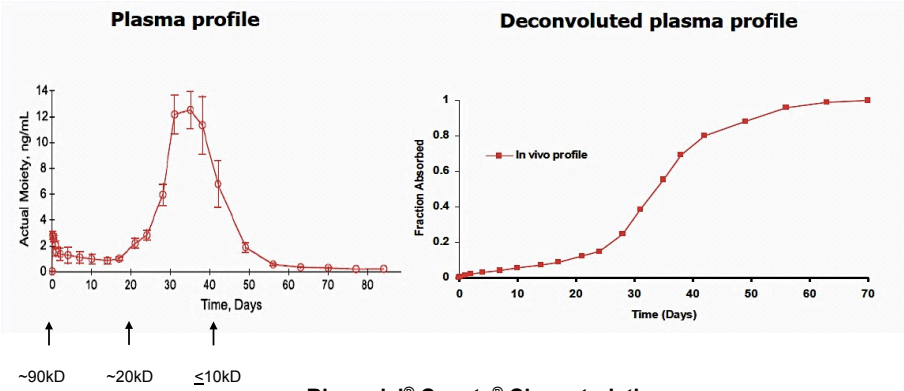
Comparison of IVIVC of Risperdal® Consta®



Risperdal® Consta® Characteristics

- Drug loading: 38% w/w
- Particle Size: 25 to 150 µm
- Burst release: <1%
- Lag phase: 3 weeks

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Schizophrenia Research, 70 (2004): 91-100

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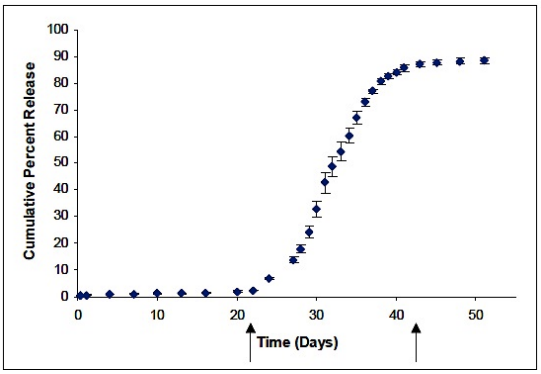
Comparison of IVIVC of Risperdal® Consta®

- ***In vitro*** **release profile using USP apparatus 4, at 37°C**



- *In vitro* release profile (USP 4 data) shows burst release (<1%) followed by a lag phase of 3 weeks in accordance with the published *in vivo* results. The fas release phase starts after 3 weeks and plateaus by week 6.

Rawat A., Bhardwaj U., Burgess, D.J., Int J Pharm, 2012

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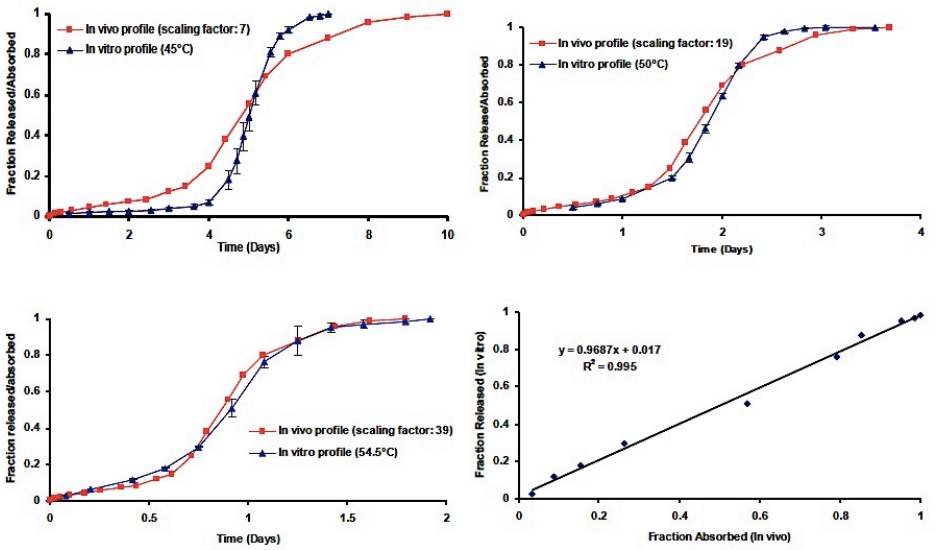
Comparison of IVIVC of Risperdal® Consta®



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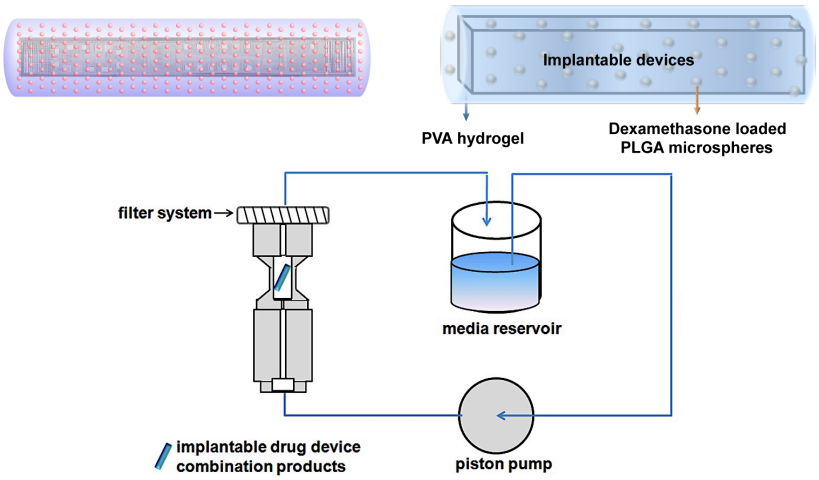
Case Study II_Implants/Drug Eluting Devices



Shen J., Burgess D.J., Int. J. Pharm., 2012

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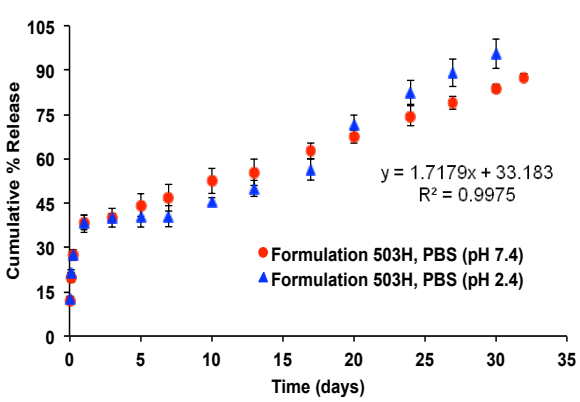
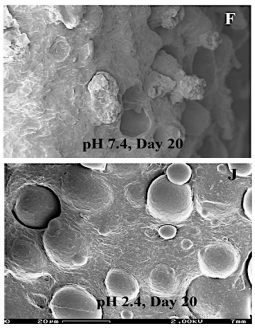
Case Study II_Implants/Drug Eluting Devices

- **Accelerated *in vitro* release testing-extreme pH conditions**





- Microspheres release for ~ 34 days at 37°C in PBS buffer (burst release ~ 39%).

Shen J., Burgess D.J., Int. J. Pharm., 2012

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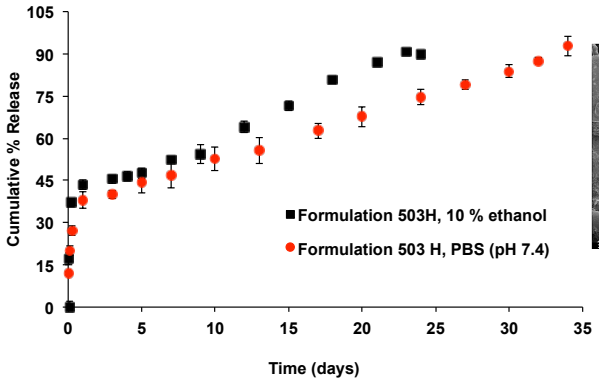
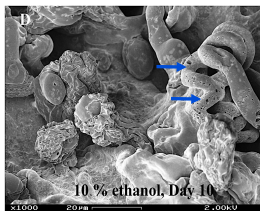
Case Study II_Implants/Drug Eluting Devices

- **Accelerated *in vitro* release testing in a hydro-alcoholic medium**





Shen J., Burgess D.J., Int. J. Pharm., 2012

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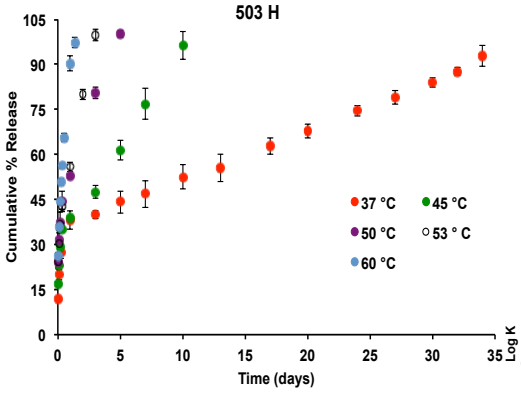
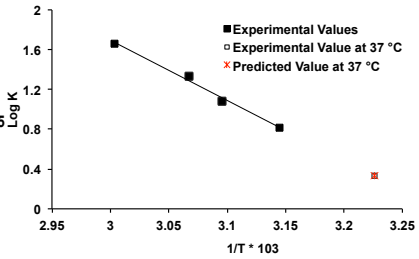
Case Study II_Implants/Drug Eluting Devices

- Accelerated *in vitro* release testing at elevated temperature



$$K=Ae^{-Ea/RT}$$
$$LogK=logA-Ea/2.303RT$$



Shen J., Burgess D.J., Int. J. Pharm., 2012

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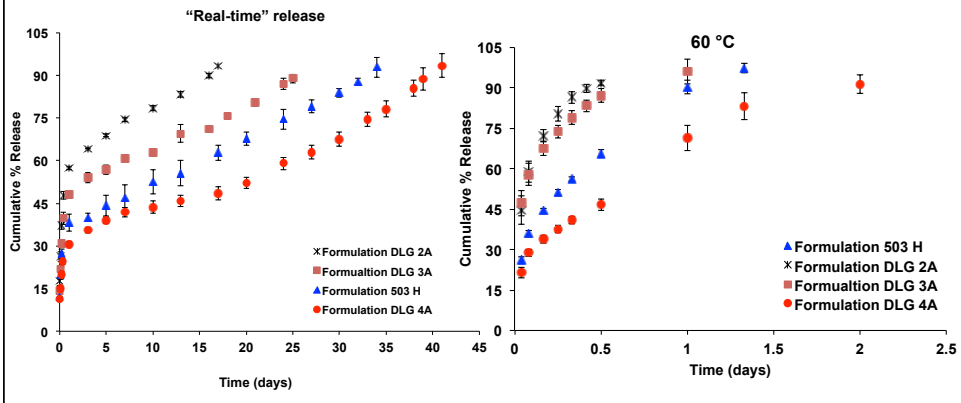
Case Study II_Implants/Drug Eluting Devices

- Discriminatory ability test



Shen J., Burgess D.J., Int. J. Pharm., 2012

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Case Study III_Nanoparticulate Systems

- **Challenges**
  - ✓ **Difficulty in separating nanoparticles in a rapid and efficient way**
  - ✓ **Complexity of nanoparticulate systems**
  - ✓ **Lack of understanding of *in vivo* drug release mechanism(s)**

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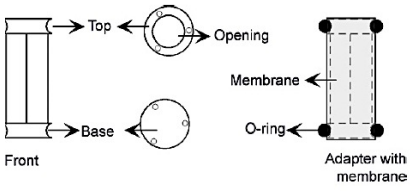
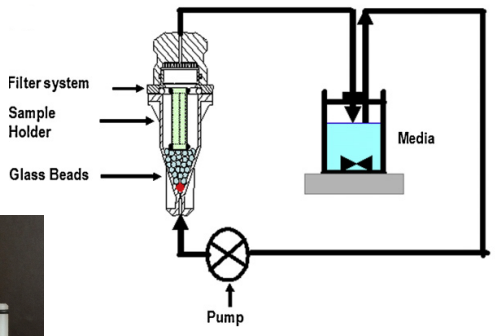
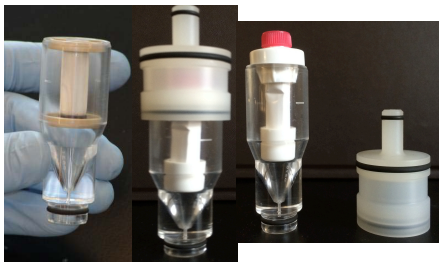
Case Study III_Nanoparticulate Systems

- **Dialysis adapters for nanoparticulate systems**







Bhardwaj U., Burgess D. J., Int J Pharm., 2010

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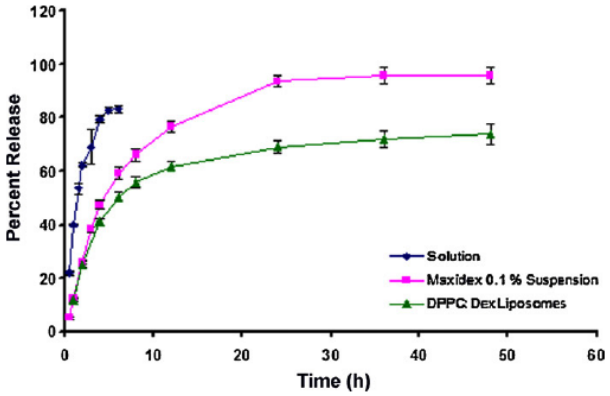
Case Study III_Nanoparticulate Systems

- ***In vitro*** **dissolution profiles of a solution, suspension and DMPC liposomes obtained using USP apparatus 4**



Bhardwaj U., Burgess D. J., Int J Pharm., 2010

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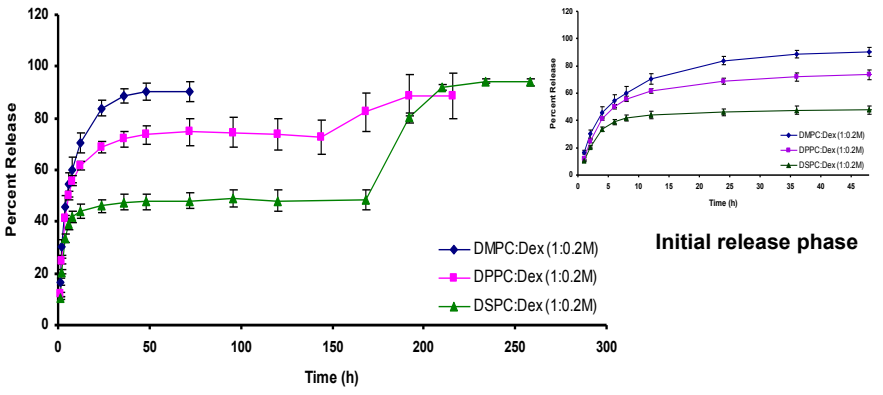
Case Study III_Nanoparticulate Systems

- **Discrimination against different liposomal formulations**



Bhardwaj U., Burgess D. J., Int J Pharm., 2010

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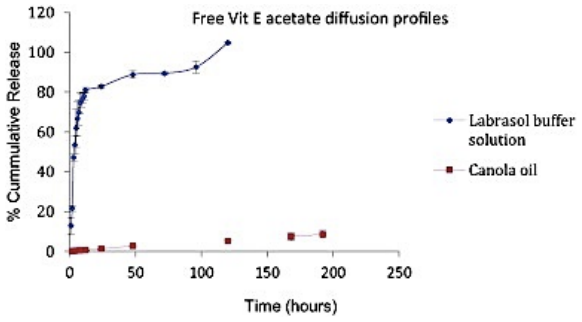
Case Study III_Nanoparticulate Systems

- **Selection of suitable release media for *in vitro* release testing of Vitamin E nanoemulsions**



Morais J.M, Burgess D.J. Int J Pharm. 2014

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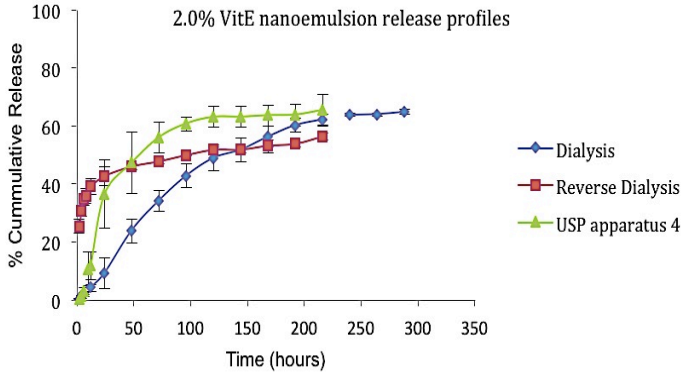
Case Study III_Nanoparticulate Systems

- ***In vitro* release profiles of vitamin E nanoemulsions obtained using different release testing methods**



Morais J.M, Burgess D.J. Int J Pharm. 2014

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Current lab members

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Dr. Upkar Bhardwaj
Dr. Archana Rawat
Dr. Jacqueline Morais

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