508361

Development of *In Vitro-In Vivo* Correlation of Peptide Microspheres – Possibility and Challenges

J. Andhariya[1], R. Jog[1], J. Shen[1] Y. Zou[2], Y. Wang[2], S. Choi[2], and D.J. Burgess[1]

1-University of Connecticut, School of Pharmacy, Storrs, CT 06269

2- FDA/CDER, Office of Generic Drugs, Office of Research and Standards, Silver Spring, MD 20993

CONTACT INFORMATION: janki.andhariya@uconn.edu

PURPOSE

***In vitro-in vivo* correlation (IVIVC):**

- *In vitro response* **IVIVC** *In vivo response*
  Predictive mathematical model
- Challenging for the microspheres – complex release characteristics
- However, developed Level A IVIVC (rabbit model) –

Peptide Microspheres -

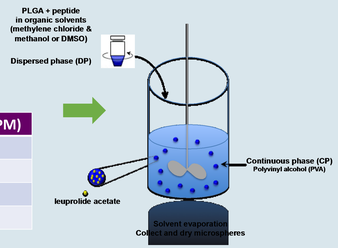
- Further explore the concept of IVIVC development
- **Challenges:** Larger size, hydrophilic, high burst release –Variable

OBJECTIVE: To understand challenges involved and possibility of establishing level A IVIVCs (rabbit model) for peptide microsphere drug products.

METHOD(S)

Model Drug: Leuprolide Acetate **Polymer:** Poly(lactic-co-glycolic acid) (PLGA)

Preparation Method:
Single emulsion (O/W) solvent evaporation



Process variables

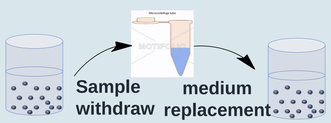
Formulations	Solvent systems	Homogenization Speed (RPM)
F1	DCM/MeOH	13 to 14 K
F2		8 to 9 k
F3	DCM/DMSO	13 to 14 K
F5		8 to 9 k

Characterization of microspheres:

1. **Critical quality attributes:** Drug loading, particle size, porosity

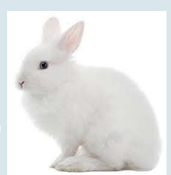
***2. In Vitro* Release Testing**:

- Sample-and-separate method
- Medium: 33 mM phosphate buffer, pH 7.4
- Testing Temperature: 37°C



***3. In Vivo* Release Testing**:

- Model: Rabbit
- Route: IM injection
- Blood Sample collection over the period of time



***4. In vitro-in vivo* correlation (IVIVC):**

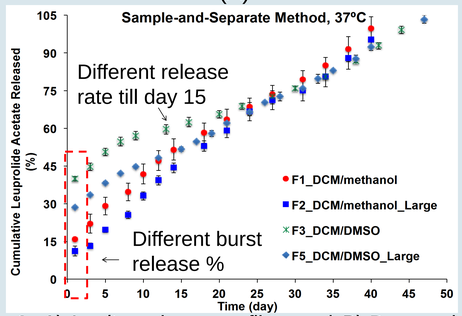
- 2- Stage deconvolution Approach (Loo-Riegelman method)
- Validation of the model: Internal as well as external
- Estimation of % Prediction Error (%PE)

RESULT(S)

Table 1. Physicochemical properties of the prepared leuproplide acetate (LA) microspheres

Formulations	Drug Loading (%W/W)	Particle Size (µm)	Porosity (%)	Pore Diameter (nm)
F1	~ 8 %	45.52	57.06	814.5
F2		72.69	52.65	712.7
F3	Q1/Q2	40.71	61.01	964.0
F5		52.27	56.48	814.1

(A)



(B)

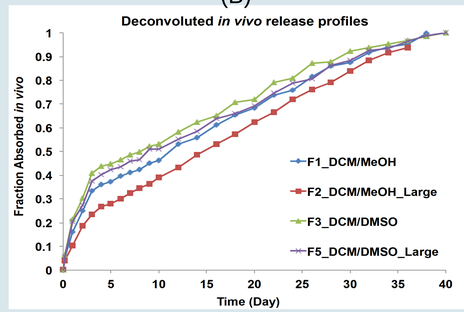
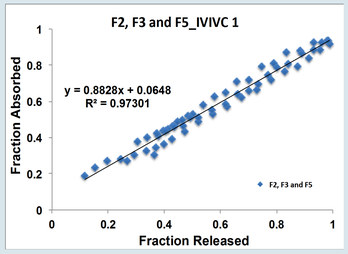


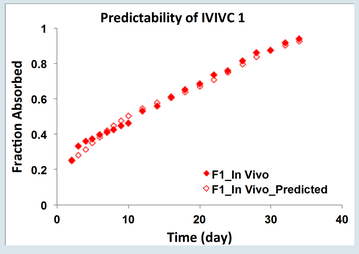
Figure 1. *A) In vitro* release profiles; and *B)* Deconvoluted *in vivo* release profiles of the prepared Q_1/Q_2 equivalent LA microspheres

Development of *in vitro-in vivo* correlation (IVIVC)

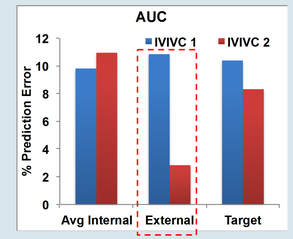


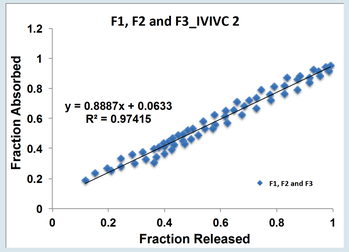
- **1:1 Linear Correlation – Level A**

T(In vivo)= (Time (In vitro) *a)+b
a=Time scaling factor = 1.6, b= time shifting factor = 1



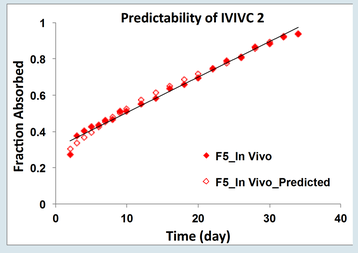
% Prediction Error (PE) of IVIVC 1

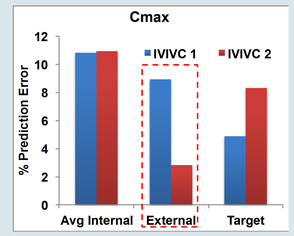




- **1:1 Linear Correlation – Level A**

T(In vivo)= (Time (In vitro) *a)+b
a=Time scaling factor = 1.6, b= time shifting factor = 1





CONCLUSION(S)

- ✓ The size, porosity and release characteristics of LA microspheres appeared to be sensitive to manufacturing changes.
- ✓ Despite the differences in the *in vitro* and *in vivo* release profiles (% burst release and release rate), an affirmative level A IVIVC was developed using the developed *in vitro* release testing method in a rabbit model for peptide microspheres.
- ✓ This indicates that the developed *in vitro* release testing method has the potential to predict the *in vivo* performance of microspheres.

FUNDING

- Support was provided by the Office of Generic Drugs/Office of Research Standards, U.S. FDA (Grant Award 1U01FD004931-02).
- **Disclaimer**: This poster reflects the views of the authors and should not be construed to represent FDA'S views or policies.

REFERENCES

1. Andhariya J. V., Shen J. and Burgess D. J. *et.al.*, Journal of Controlled Release, 2017, 255, 27-35. 2.Shen J. and Burgess D. J. *et.al.*, Journal of Controlled Release, 2015, 218, 2-12. 3.. FDA Guidance for Industry: extended release oral dosage forms: development, evaluation and application of in vitro/in vivo correlation, Rockville, MD, 1997.