Evaluation of effect of minor manufacturing changes and establishment of IVIVC for compositionally equivalent parenteral microsphere drug products

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OBJECTIVES

- ***PLGA*** microspheres - complex processing methodologies and hence, minor manufacturing changes have the potential to affect microsphere physicochemical characteristics.
- Moreover, establishment of *in vitro-in vivo correlation* (IVIVCs) for parenteral polymeric microspheres has been very challenging, due to their complex multiphase release characteristics as well as the lack of compendial *in vitro* release testing methods.

The objectives of present study were: 1) To investigate the effect of minor changes in the manufacturing process on the physicochemical properties of various compositionally equivalent parenteral PLGA microsphere drug products; ***2)*** to develop *in vitro* release testing methods to ensure product quality and predict *in vivo* performance; and ***3)*** to establish Level A *in vitro-in vivo* correlations (IVIVCs) for the compositionally equivalent PLGA microspheres.

METHODS

1. Preparation of Q1/Q2 Equivalent Microspheres with Manufacturing Differences:

Table 1. Naltrexone Microspheres[1]

Sample	Preparation Method	Solvent System
Formulation 1	Magnetic Stirring	DCM/BA
Formulation 2	Magnetic Stirring	EA/BA
Formulation 3	Homogenization	

DCM: Methylene Chloride, EA: Ethyl Acetate, BA: Benzyl Alcohol

Table 2. Risperidone Microspheres[2]

Sample	Preparation Method	Solvent System
Formulation 1	Homogenization	DCM_Dry Sieving
Formulation 2		DCM_Wet Sieving
Formulation 3	Vortexing	EA/BA
Formulation 4	Homogenization	

Table 3. Leuprolide Acetate Microspheres

Sample	Solvent System	Homo. Speed (RPM)
Formulation F1	DCM/MeOH	13 to 14 K
Formulation F2		8 to 9 k
Formulation F3	DCM/DMSO	13 to 14 K
Formulation F4		8 to 9 k

MeOH: Methanol, DMSO: Dimethyl sulfoxide

- ***Single Emulsion Solvent Evaporation method***

Drug+Polymer +Organic Solvent ⇨ Primary Q/W Emulsion using PVA+Water (DP) ⇨ Transfer to large Aqueous phase (CP) ⇨ Solidify, Collect and Dry

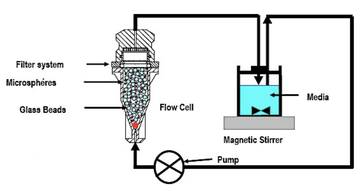
2. Evaluation of Critical Quality Attributes (CQAs):

CQA	Method of Determination
Drug loading (DL)	High performance liquid chromatography
Particle size	Accusizer auto dilution particle sizing system
Porosity	Mercury porosimetry

3. *In Vitro* Release Testing:

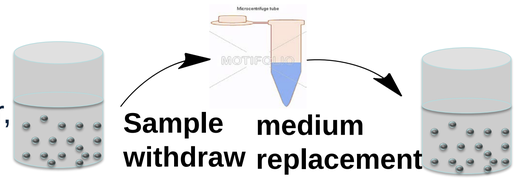
Risperidone and Naltrexone Microspheres

- Developed USP apparatus 4 method
- 10 mM phosphate buffer, 37° C



Leuprolide Acetate Microspheres

- Sample-and-separate method
- 33 mM Phosphate buffer, 37° C



4. *In Vivo* Release Testing:

- Model: Rabbit
- Route: IM injection
- Blood Sample collection

5. Development of IVIVC:

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

RESULTS

1. Physicochemical Properties:

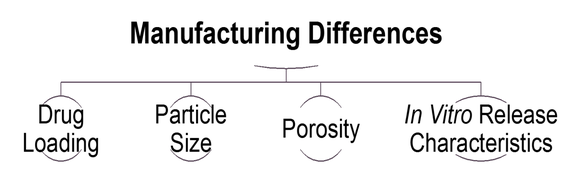


Table 4. Naltrexone Microspheres[1] Q1/Q2 – 30% DL

Formulation	Particle Size (µm) (Mean±SD)	% Porosity
Formulation 1	121.11±3.61	49.83
Formulation 2	105.49±8.63	58.32
Formulation 3	68.56±1.52	65.08
Vivitrol®	108.40±7.4	50.21

Table 5. Risperidone Microspheres[2] Q1/Q2 – 35% DL

Formulation	Particle Size (µm) (Mean±SD)	% Porosity
Formulation 1	22.77±11.71	43.97
Formulation 2	46.05±0.81	43.19
Formulation 3	43.79±1.07	46.04
Formulation 4	34.39±31.44	54.98
Risperdal Consta®	58.43±5.21	61.75

Table 6. Leuprolide Acetate Microspheres Q1/Q2 – 8% DL

Formulation	Particle Size (µm) (Mean±SD)	% Porosity
F1	45.52±1.64	57.06
F2	72.69±11.82	52.65
F3	40.71±3.80	61.01
F4	91.36±16.02	56.48
F5	52.13±6.11	62.16

2. *In vitro* and *in vivo* release testing of LA microspheres:

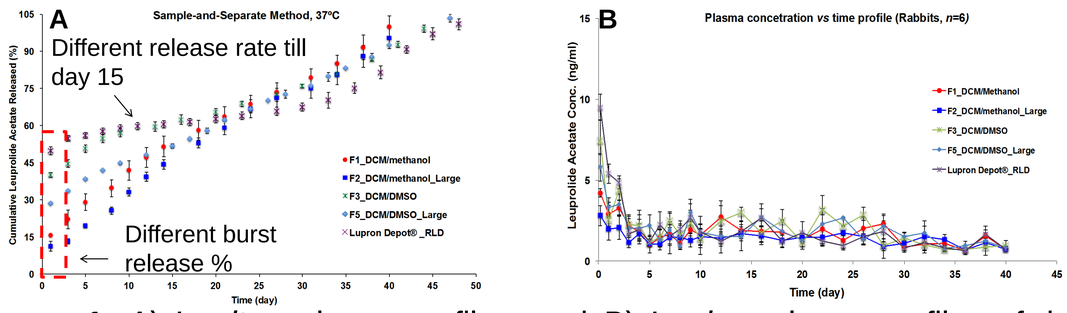
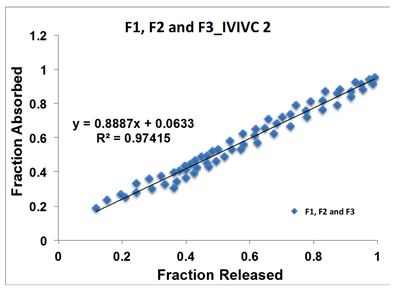


Figure 1. *A) In vitro* release profiles; and *B) In vivo* release profiles of the prepared Q_1/Q_2 equivalent LA microspheres

3. Development of *in vitro-in vivo* correlation (IVIVC) for LA microspheres:

1:1 Linear Correlation



% Prediction Error (PE) of IVIVC_1

Formulation	Parameter	Observed	Predicted	%PE	
Avg Internal	AUClast	66.05	64.17	10.94	←>10%
	Cmax	4.84	4.45	9.52	
F5 External	AUClast	74.69	72.58	-2.83	
	Cmax	5.80	5.71	-1.52	
Lupron Depot®	AUClast	69.03	63.29	-8.31	<±10%
	Cmax	9.49	10.29	8.40	

2. Naltrexone Microspheres

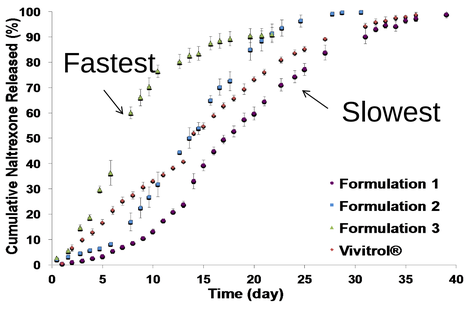


Figure 2. *In vitro* release profiles

% Prediction Error (PE) of IVIVC_2

Formulation	Parameter	Observed	Predicted	%PE
Avg Internal (F1,F3)	AUClast	70.89	76.50	7.04
	Cmax	11.22	13.38	11.96
Formulation 2 External	AUClast	69.14	62.78	10.13
	Cmax	7.74	7.49	3.38
Vivitrol®	AUClast	81.70	74.60	9.53
	Cmax	6.84	7.54	-9.27

3. Risperidone Microspheres

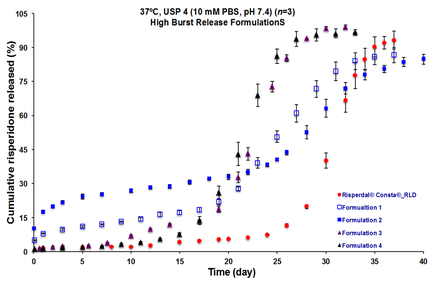


Figure 3. *In vitro* release profiles

% Prediction Error (PE) of IVIVC_3

Formulation	Parameter	Observed	Predicted	%PE
Avg Internal (F2, F3,F4)	AUClast			6.46
	Cmax			37.32
Formulation 1 External	AUClast	206.92	231.51	10.61
	Cmax	27.99	26.71	-4.56
Risperdal Consta®	AUClast	248.50	248.69	0.08
	Cmax	38.29	41.32	7.90

CONCLUSIONS

1. The critical quality attributes *(e.g.*, particle size and porosity) and hence, drug release characteristics (such as burst release phase of peptide microspheres, and release rate) appeared to be sensitive to minor manufacturing changes for both types of microsphere drug products.
2. The developed *in vitro* release testing methods – Can be used as a quality control tool as well as a biorelevant method.
3. Level A IVIVC for the different microsphere drug products ⇨ shows the feasibility of achieving IVIVCs for such complex drug products in humans.

REFERENCES

1. Andhariya J., Burgess, J.Control Rel, 255, 2017
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