2096

Development of *In Vitro-In Vivo* Correlation of Parenteral Naltrexone Loaded Polymeric Microspheres

J. V. Andhariya[1], J. Shen[1], Y. Zou[2], S. Choi[2], Y. Wang[2], 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
Janki.andhariya@uconn.edu; d.burgess@uconn.edu

INTRODUCTION

- ❖ Establishment of *in vitro-in vivo* correlations (IVIVCs) for parenteral polymeric microspheres has been challenging, due to their complex multiphase release characteristics as well as the lack of compendial *in vitro* release testing methods.
- ✓ The objective of the present study was: **To investigate whether a Level A IVIVC can be established for compositionally equivalent microspheres prepared with manufacturing differences.**

METHODS

1. Preparation of Microspheres: Three Q_1/Q_2 equivalent naltrexone microspheres were prepared using different manufacturing processes.

Sample	Preparation Method	Solvent System	Solvent Removal
Formulation 1	Magnetic Stirring	Methylene Chloride & Benzyl alcohol	Solvent Evaporation
Formulation 2	Magnetic Stirring	Ethyl Acetate & Benzyl alcohol	Solvent Extraction
Formulation 3	Homogenization	Ethyl Acetate & Benzyl alcohol	Solvent Extraction

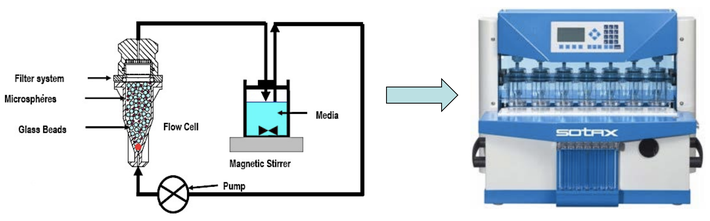
2. Evaluation of Critical Quality Attributes: The obtained naltrexone microspheres were evaluated for various critical quality attributes.

Critical Quality Attributes	Method of Determination
Drug loading	High Performance liquid chromatography
Particle size	Accusizer auto dilution particle sizing system
Porosity	Mercury porosimetry
Morphology	Scanning electron microscopy
Moisture Content	Karl-fischer titration
Glass transition temperature	Modulated temperature differential scanning calorimeter

3. *In Vitro* Release Testing:

- Briefly, ~ 10 mg of microspheres mixed with glass beads were put into flow through cells
- **Medium**: 10 mM phosphate buffer with Tween 20 and sodium azide, pH 7.4
- Testing Temperature: 37° C • Flow Rate: 8 ml/min

Developed USP apparatus 4 method



4. *In Vivo* Release Testing:

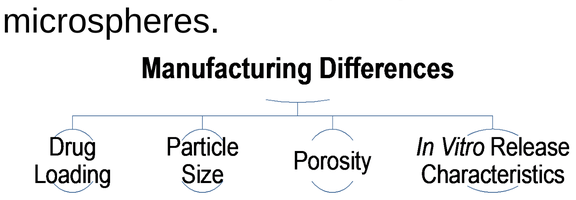
- Model: Rabbit
- Route: IM injection
- Dose: 11.69 mg/kg

- Blood sample collection: Periodically from marginal ear veins
- Analytical method: LC-MS

- Deconvolution of the *in vivo* naltrexone release using the Loo-Riegelman method.
- Comparison of the deconvoluted *in vivo* release profiles with the *in vitro* release profiles of the microspheres to determine if there is any correlation.

RESULTS AND DISCUSSION

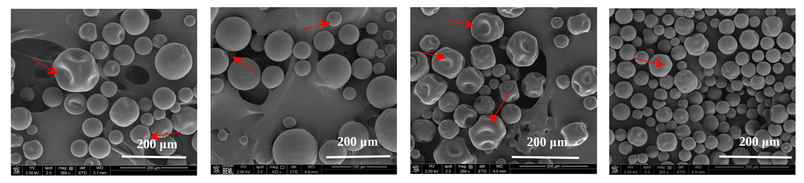
- It was observed that minor changes in manufacturing processes had significant impact on certain critical quality attributes of the microspheres.



1. Physicochemical Properties:

Sample	Drug Loading (%, w/w)	Particle Size (µm) (Mean±SD)	% Porosity
Formulation 1	28.74±1.64	121.11±3.61	49.83
Formulation 2	29.70±1.11	105.49±8.63	58.32
Formulation 3	29.57±1.75	68.56±1.52	65.08
Vivitrol®	33.50±1.43	108.40±7.4	50.21

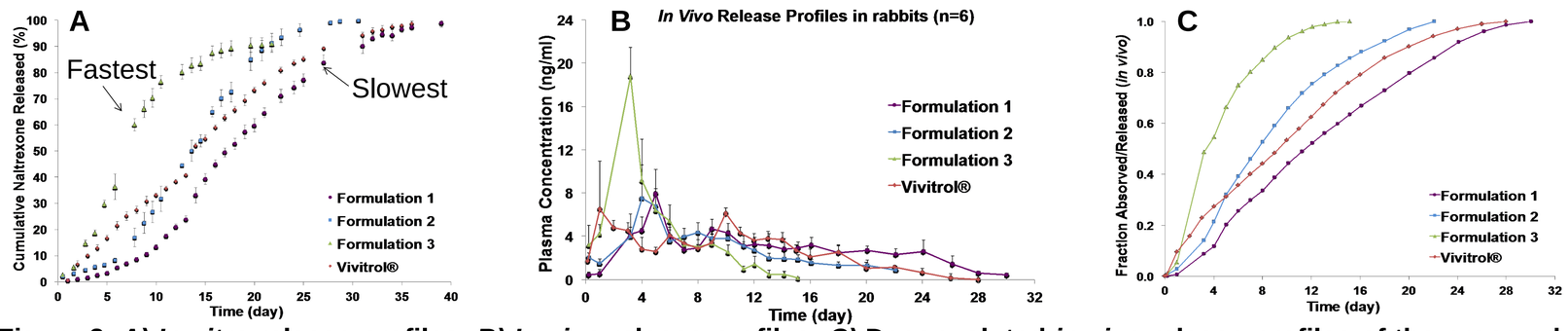
Morphology:



Vivitrol® Formulation 1 Formulation 2 Formulation 3

Figure 1. SEM monographs of the prepared Q_1/Q_2 equivalent naltrexone microspheres and Vivitrol®

2. *In vitro* and *in vivo* release testing:

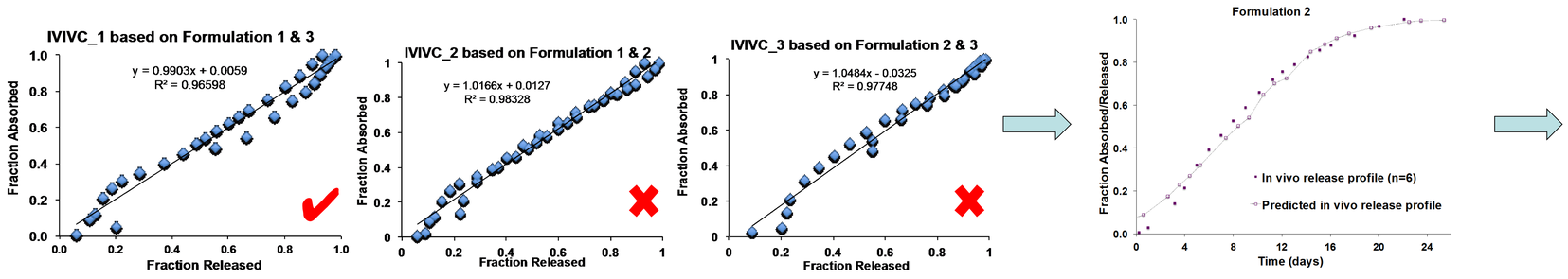


Pharmacokinetic Parameters

Formulation	$t_{½}$ (day)	T_{max} (day)	C_{max} (ng/ml)	AUC_{last}
Formulation 1	15.13	5	5.3	53.41
Formulation 2	6.17	4	5.0	41.92
Formulation 3	2.12	3	12.5	48.14
Vivitrol®	3.78	1	7.54	74.60

Figure 2. *A) In vitro* release profiles; *B) In vivo* release profiles; *C)* Deconvoluted *in vivo* release profiles of the prepared Q_1/Q_2 equivalent naltrexone microspheres (n=3)

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



% Prediction Error (PE) of IVIVC_1

Formulation	Parameter	Observed	Predicted	%PE
Avg Internal	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

CONCLUSIONS

1. Various physicochemical properties (such as particle size, porosity and drug loading) appeared to be sensitive to minor changes in manufacturing processes, which in turn affect *in vitro* drug release characteristics.
2. Level A IVIVC was developed using the developed modified USP apparatus 4 *in vitro* release testing for the prepared naltrexone microspheres with manufacturing differences.

REFERENCES

1. J. Andhariya, D.J. Burgess, *et.al.* Development of *in vitro-in vivo* correlation for parenteral naltrexone loaded microspheres. J Control Release, 2017; 255 :27-35.
2. FDA Guidance for Industry: extended release oral dosage forms: development, evaluation and application of in vitro/in vivo correlation, Rockville, MD, 1997.

ACKNOWLEDGEMENT

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