26M0200

Effect of Manufacturing Processes on *In Vitro* and *In Vivo* Performance of Naltrexone Microspheres

Janki V. Andhariya[1], Jie Shen[1], Stephanie Choi[2], Yan Wang[2], Wen Qu[3], Yuan Zou[2] , Diane J. Burgess[1]
[1]University of Connecticut, School of Pharmacy, CT 06269 [2]FDA/CDER/OGD/ORS, MD 20993

2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13–17, 2016
COLORADO CONVENTION CENTER, DENVER

PURPOSE

- Manufacturing changes may affect various microsphere physicochemical characteristics such as particle size and porosity, which in turn may affect the *in vitro* and *in vivo* release characteristics of these complex parenteral dosage forms.
- **The objectives** of the present study were:
  1) To understand how manufacturing processes affect drug release from compositionally equivalent naltrexone microspheres;
  2) To explore whether the developed *in vitro* release testing method can be potentially used to predict *in vivo* release characteristics of the prepared qualitatively (Q_1) and quantitatively (Q_2) equivalent naltrexone microspheres.

METHOD

1. Preparation and Characterization of Microspheres

Three Q_1/Q_2 equivalent naltrexone microspheres were prepared using different manufacturing processes.

Sample	Preparation Method	Solvent System	Solvent Removal
S_DCM_EVA	Magnetic Stirring	Methylene Chloride	Solvent Evaporation
S_EA	Magnetic Stirring	Ethyl Acetate	Solvent Extraction
H_EA	Homogenization	Ethyl Acetate	Solvent Extraction

Physicochemical properties of the microspheres (such as particle size and porosity) were characterized.

2. *In Vitro* Release Testing

Method: Modified USP apparatus 4
Release medium: phosphate buffer saline (pH=7.4)
Temperature: 37°C (real-time)

3. *In Vivo* Release Testing

Model: Rabbit
Route: IM injection
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 see if there is any correlation.

RESULTS

1. Physicochemical properties:

Sample	Drug Loading (%, w/w)	Particle Size (μm) (Mean±SD)	% Porosity
S_DCM_EVA	28.74±1.64	121.11±3.61	49.83
S_EA	29.70±1.11	105.49±8.63	58.32
H_EA	29.57±1.75	68.56±1.52	65.08

2. *In vitro* release testing:

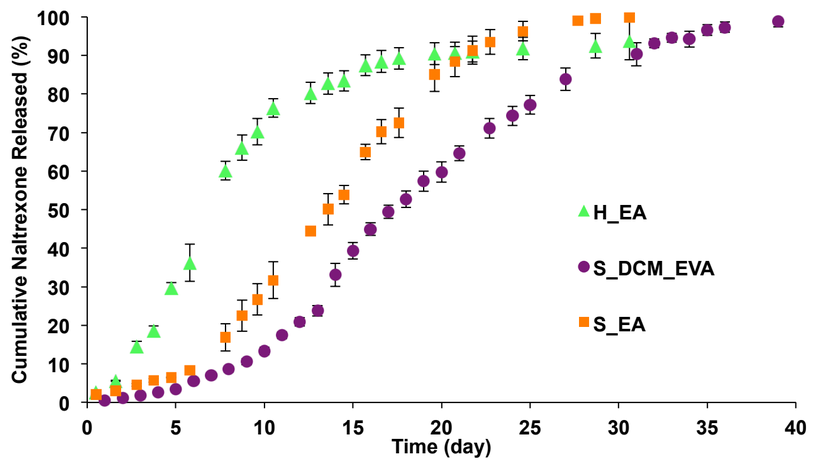

Figure 1. *In vitro* release profiles of the prepared Q_1/Q_2 equivalent naltrexone microspheres (*n*=3).

3. *In vivo* release testing:

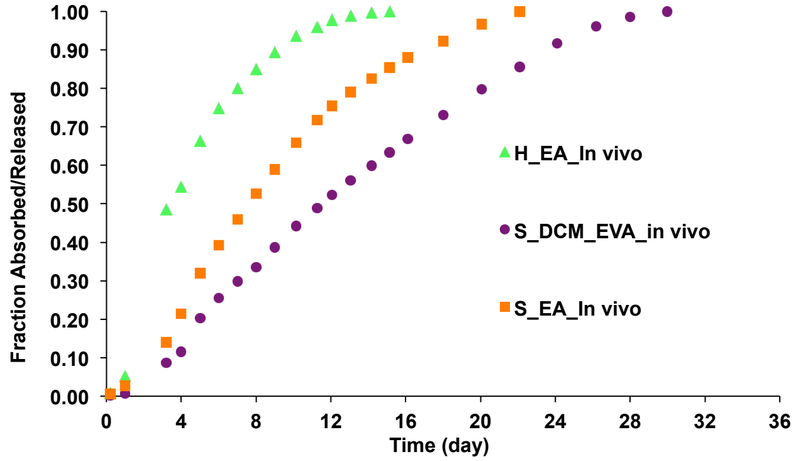

Figure 2. Deconvoluted *in vivo* release profiles of the prepared Q_1/Q_2 equivalent naltrexone microspheres (*n*=6).

CONCLUSIONS

1. Physicochemical properties as well as *in vitro* and *in vivo* performance of complex parenteral polymeric microspheres are sensitive to minor manufacturing changes.
2. Even with equivalent composition, naltrexone microspheres with manufacturing differences had different *in vitro* and *in vivo* performance.
3. The developed *in vitro* release testing method is capable of detecting manufacturing differences, and has the potential of predicting the *in vivo* performance of the prepared Q_1/Q_2 equivalent naltrexone microspheres.

REFERENCE

1. A. Rawat, D.J. Burgess, *et al.* Validation of USP apparatus 4 method for microsphere *in vitro* release testing using Risperdal® Consta®. *Int J Pharm*, 2011; 20 (2): 198-205.

FUNDING/DISCLAIMER

- The authors would like to thank the Office of Generic Drugs/Office of Research Standards, U.S. FDA (Grant Award 5U01FD004931-02) for funding the project.
- 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.