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In Vitro and *In Vivo* Performance Testing of Risperidone Microspheres

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OBJECTIVE

- To develop *in vitro* performance testing methods capable of discriminating risperidone microspheres that are qualitatively (Q1) and quantitatively (Q2) equivalent in inactive ingredients but with manufacturing differences and to predict *in vivo* performance of these microspheres.

INTRODUCTION

Microspheres are considered high risk products as they are designed to release drug over long periods of time and they have complex formulations and processing methodologies. Minor manufacturing changes have the potential to affect microsphere physicochemical characteristics, which in turn may affect their *in vivo* performance. Therefore, in order to ensure their performance and safety, as well as assist in the product development, *in vitro* performance tests, particularly *in vitro* drug release tests, must be performed.

In the present study, a discriminatory USP apparatus 4 method was used for *in vitro* release testing of risperidone microspheres that are Q1/Q equivalent but with manufacturing differences. In addition, *in vivo* release performance of these risperidone microspheres was testing in a rabbit model.

METHODS

Preparation and Characterization of Risperidone Microspheres: Risperidone PLGA microspheres were prepared using an oil-in-water (o/w) emulsion-solvent extraction method under different manufacturing processes (*e.g.* homogenization and vortex mixing). Critical physicochemical properties (such as drug loading, particle size and size distribution, glass transition temperature, morphology, as well as water content) of the prepared risperidone microspheres were determined. The physicochemical properties of the commercial product (Risperdal® Consta®) were also determined.

***In Vitro* Release Testing:** *In vitro* release testing of the prepared risperidone microspheres and Risperdal® Consta® was investigated under "real-time" conditions (37˚ C) in USP apparatus 4. Briefly, 10 mg of microspheres were mixed with glass beads (1 mm) and placed in the USP 4 dissolution cell. 250 ml of PBS (10 mM, pH 7.4) with 0.01% (w/v) sodium azide was circulated through the flow through cells at a flow rate of 8 ml/min at 37˚ C. At pre-determined time intervals, one ml samples were withdrawn and replenished with fresh medium. All the measurements were conducted in triplicate and the mean values and standard deviations were reported.

***In Vivo* Release Testing:** *In vivo* release testing of the prepared risperidone microspheres and Risperdal® Consta® was studied using a rabbit model. Briefly, rabbits were randomly assigned to cages and treated with different risperidone microspheres that were suspended in the dilute of Risperdal® Consta® and injected into the rabbit thigh muscle. Blood samples were collected at pre-determined time intervals and analyzed *via* LC-MS/MS.

RESULTS

Table 1. Physicochemical properties of the prepared risperidone microspheres.

Sample	Inherent Viscosity (dL/g)	Preparation Method	Drug Loading (%)	Mean Particle Size (μm)	Tg (°C)	Water Content (%, w/w)
Risperdal® Consta®	-	-	39.42±1.92	104.5±1.06	40.79	0.173
Formulation_1	0.61	Homogenization	33.03±0.23	104.63±3.69	39.99	0.127
Formulation_2	0.61	Vortex	35.50±0.75	106.89±3.45	43.1	0.126

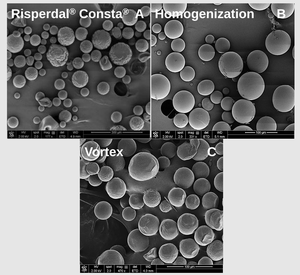

Figure 1. SEM micrographs of Risperdal® Consta® (A); and risperidone microsphere formulations Homogenization (B), and Vortex (C).

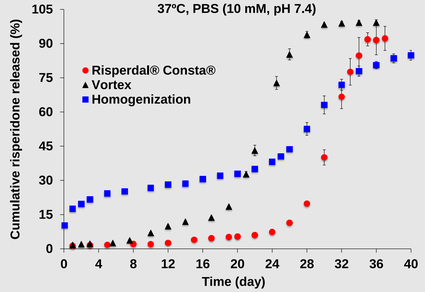

Figure 2. *In vitro* release profiles of Risperdal® Consta® and the prepared risperidone microspheres in 10 mM PBS (pH 7.4) at 37˚ C using USP apparatus 4. (Mean±std dev; *n*=3).

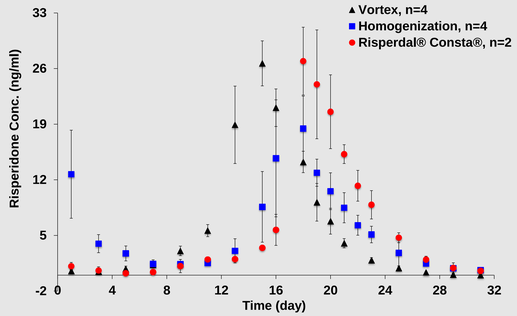

Figure 3. *In vivo* release profiles of risperidone microspheres in a rabbit model.

Table 2. Pharmacokinetic parameters of risperidone microspheres (*i.m.*).

Sample	Mean Cmax (ng/ml)	Mean Tmax (Day)	Mean $AUC_{(0-t)}$ (ng/ml*d)	Mean $MRT_{(0-t)}$ (Day)	Mean $t_{1/2}$ (day)
Risperdal® Consta®	29.41±0.77	18.5±0.71	168.58±9.77	19.10±0.52	1.88±0.37
Homogenization	20.83±2.62	18±0	166.79.03±37.15	14.96±1.40	2.33±0.48
Vortex	26.65±3.27	15±0	181.12±26.70	15.19±0.11	1.71±0.13

CONCLUSIONS

The critical physicochemical properties of risperidone microspheres with Q1/Q2 equivalence are very sensitive to manufacturing differences. An *in vitro* release testing using USP apparatus 4 demonstrated excellent discriminatory ability for risperidone microspheres that are Q1/Q2 equivalent in inactive ingredients but with manufacturing. In addition, this USP apparatus 4 method demonstrated the potential to predict the *in vivo* performance of these microspheres.

ACKNOWLEDGEMENTS

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