In Vitro-In Vivo Correlation of Risperidone Microspheres

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ABSTRACT SUMMARY

The objective of the present study was to develop an *in vitro-in vivo* correlation for risperidone microspheres that are equivalent in formulation composition and components but with manufacturing differences. A Level A IVIVC was established using the deconvolution approach for the prepared compositionally equivalent risperidone microsphere formulations. Results demonstrated that the developed *in vitro* release testing method using USP apparatus 4 can differentiate compositionally equivalent risperidone microspheres with distinctly different physicochemical properties and most importantly, this method can predict the *in vivo* performance of these microsphere formulations.

INTRODUCTION

Due to their complex formulation and manufacturing process, critical physicochemical characteristics of complex parenteral microsphere drug products are sensitive to even minor manufacturing changes (*e.g.* manufacturing site or instrumentation changes). Consequently, even with the sameness in terms of formulation composition and components, microsphere formulations may or may not be bioequivalent and therefore, bioequivalence studies are warranted. Accordingly, it is crucial to understand and develop appropriate *in vitro* performance testing methods to discriminate the effect of process variables on critical quality attributes (CQA) of compositionally equivalent microsphere formulations and to predict their *in vivo* performance.

In the present study, risperidone was used as a model drug, and PLGA with similar molecular weight as that used in the commercial product Risperdal® Consta® was used to prepare risperidone microspheres *via* different manufacturing processes. *In vitro* and *in vivo* performance of the prepared risperidone microspheres were investigated. Furthermore, the obtained *in vivo* release profiles of these microsphere formulations were compared with their *in vitro* release profiles.

EXPERIMENTAL METHODS

PLGA with similar molecular weight as that used in Risperdal® Consta®, was used to prepare compositionally equivalent risperidone microspheres with manufacturing differences (*e.g. via* homogenization and vortex, as well as different solvent systems). Critical physicochemical properties (such as drug loading, particle size and particle size distribution, porosity, and morphology) of the prepared microspheres were determined. Different manufacturing processes and processing parameters were optimized to obtain compositionally equivalent risperidone microspheres with distinctly different physicochemical properties.

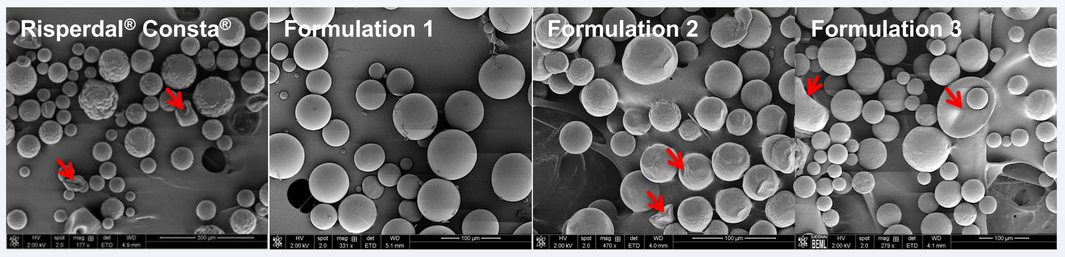
In vitro release testing of the prepared risperidone microsphere formulations was performed using a USP apparatus 4 method under “real-time” (37°C) testing conditions. In addition, *in vivo* release profiles of these microsphere formulations were investigated using a rabbit model and the data obtained were deconvoluted for comparison with the *in vitro* release profiles. Lastly, an *in vitro-in vivo* correlation of the compositionally equivalent risperidone microspheres was developed.

RESULTS AND DISCUSSION

Table 1. Physicochemical properties of risperidone microspheres.

Formulation	Preparation Process	Solvent	Drug Loading (%, w/w)	Particle Size (D50, μm)
Formulation 1	Homogenization	Methylene chloride	37.67±0.94	103.89±2.66
Formulation 2	Vortex	Ethyl acetate	37.33±0.60	104.22±4.63
Formulation 3	Homogenization	Ethyl acetate	36.45±1.23	74.04±7.53
Risperdal® Consta®	-	-	39.42±1.92	106.43±2.55

The critical physicochemical properties of the prepared compositionally equivalent risperidone microspheres are shown in **Table 1**. All risperidone microsphere formulations prepared had a similar drug loading (~37%). Formulations 1 and 2 had similar particle size compared to Risperdal® Consta®, while Formulation 3 had significantly smaller particle size ($p < 0.05$). Morphology (using scanning electron microscopy, SEM) and porosity studies (using Mercury Porosimeter) revealed that Formulation 1 had a less porous structure compared to Formulations 2 and 3 despite that Formulations 1 and 2 had similar particle size (**Figure 1**). Interesting, Risperdal® Consta® had a similar porosity (43.97%) as Formulation 1, even though it showed similar morphology to that of Formulations 2 and 3.



Porosity: 43.97% Porosity: 46.04% Porosity: 54.98% Porosity: 61.75%

Figure 1. Morphology and porosity testing results of the prepared risperidone microspheres. Red arrows indicate indentations on the surface of the microspheres.

As shown in **Figure 2**, the developed USP apparatus 4 method demonstrated good discrimination between the compositionally equivalent risperidone microsphere formulations under “real-time” (37°C) testing conditions. Overall, risperidone release from more porous microspheres (*i.e.* Formulations 2 and 3) appeared to be faster than that from less porous microspheres (Formulations 1).

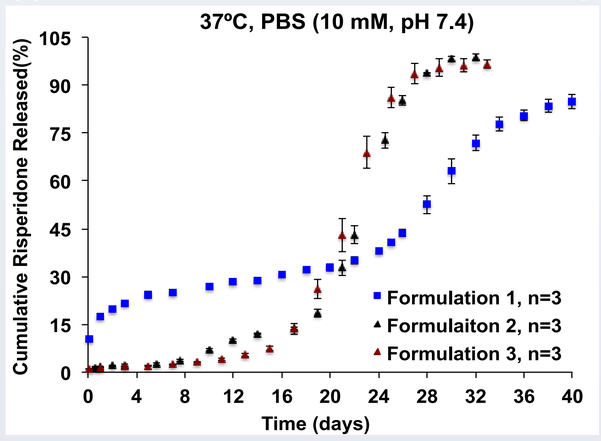


Figure 2. *In vitro* release profiles of the compositionally equivalent risperidone microspheres with manufacturing differences using USP apparatus 4 at 37°C in 10 mM PBS (pH 7.4) (n=3).

The mean plasma concentration-time profiles following intramuscular (i.m.) administration of the prepared risperidone microspheres and the deconvoluted plasma profiles (using the Loo-Riegelman method) are shown in **Figures 3A** and **3B**. Overall, the *in vivo* release profiles of the risperidone microspheres correlated well with their *in vitro* release profiles (**Figure 2**). A one-to-one linear relationship (Level A) between the fraction released *in vitro* and fraction released/absorbed *in vivo* was obtained ($R^2 > 0.98$) (**Figures 3C**).

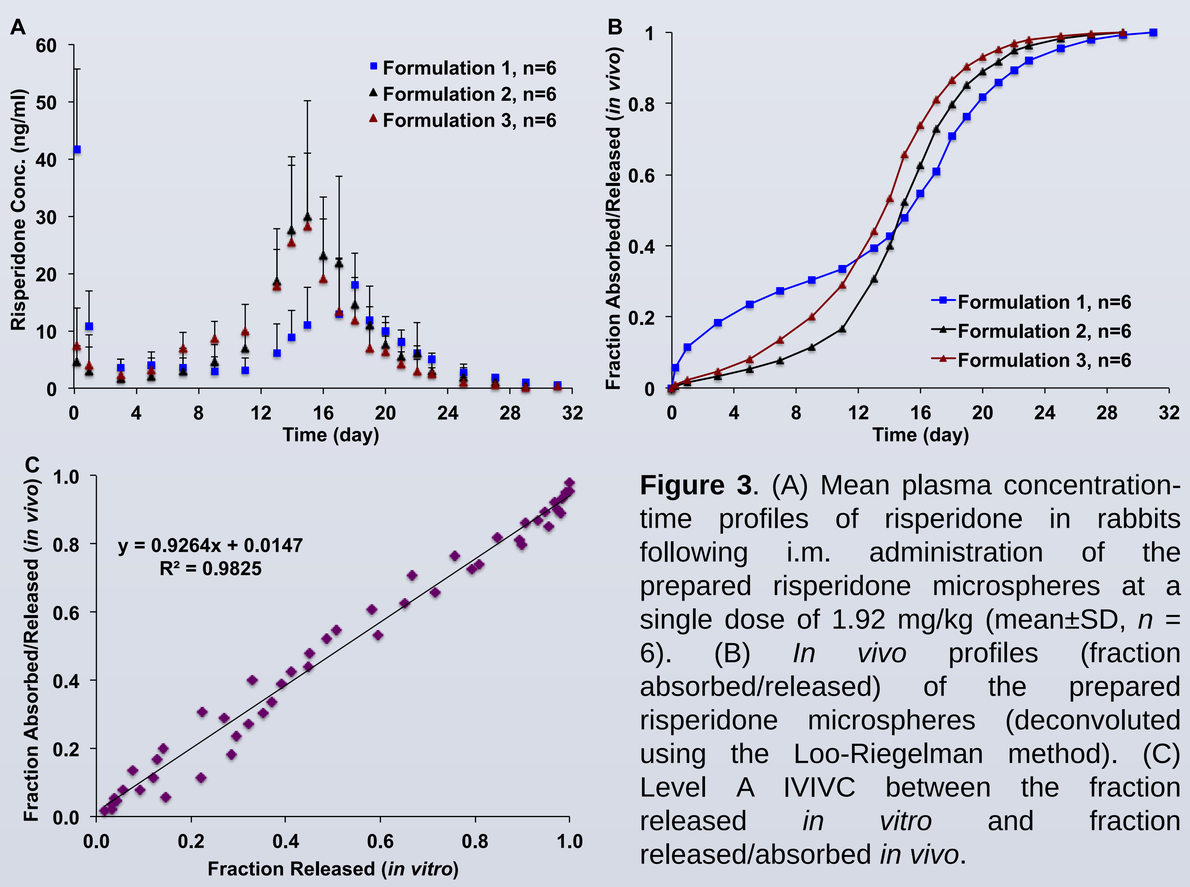


Figure 3. (A) Mean plasma concentration-time profiles of risperidone in rabbits following i.m. administration of the prepared risperidone microspheres at a single dose of 1.92 mg/kg (mean±SD, n = 6). (B) *In vivo* profiles (fraction absorbed/released) of the prepared risperidone microspheres (deconvoluted using the Loo-Riegelman method). (C) Level A IVIVC between the fraction released *in vitro* and fraction released/absorbed *in vivo*.

CONCLUSIONS

The critical physicochemical properties of risperidone microspheres were very sensitive to manufacturing differences. Even with the sameness in formulation composition and components, the prepared risperidone microsphere formulations with manufacturing differences showed different *in vitro* and *in vivo* release characteristics. The developed *in vitro* release testing method using USP apparatus 4 can differentiate compositionally equivalent risperidone microsphere formulations with manufacturing differences and most importantly, predict the *in vivo* performance of these microspheres.

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