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The Effect of PLGA Molecular Weight on Drug Release from Microspheres

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PURPOSE

- Poly (lactide-co-glycolide) (PLGA) microspheres are one of the most successful complex parenteral drug products.
- However, to date, there are no generic microsphere drug products available. Generic drug products must be bioequivalent with the reference listed drug (RLD) product. Accordingly, it is important to investigate critical factors (such as molecular weight (Mw) and weight range) that can have an impact on the bioequivalence of such complex products.
- Hence, the objective of the present work was to understand the effect of differences in PLGA Mw on drug release characteristics from PLGA microspheres.

METHODS

- Four types of polymers (lactide/glycolide:75/25, ester end capped) , the same as in the RLD product (Risperdal Consta®) with respect to lactide/glycolide ratio[1] and end groups[2], but with different Mw (**Table 1**) were purchased from three different vendors. Risperidone was purchased from AK Scientific.
- Using the four PLGA polymers, four microsphere formulations were prepared via a single emulsion solvent evaporation method.
- Critical quality attributes (*e.g.,* drug loading, particle size, morphology, Mw) of the prepared microspheres were determined. Differences in the *in vitro* release profiles of the prepared microsphere formulations, if any, were investigated using a previously developed USP apparatus 4 method[3]. In addition, *in vitro* degradation studies of the prepared microsphere formulations were conducted. Briefly, microspheres were incubated under the same conditions as used in the *in vitro* release testing studies, and investigated for changes in morphology, Mw, and glass transition temperature (Tg) at predefined time points.

Table 1 Physicochemical properties of polymers (n = 3, mean ± SD).

Polymer	Mw (kDa)	Polydispersity	Inherent Viscosity (dL/g)	Tg (ºC)
1	70.1 ± 0.3	1.4 ± 0.0	0.64 ± 0.12	49.4 ± 1.0
2	56.5 ± 0.2	1.4 ± 0.0	0.49 ± 0.06	48.8 ± 0.3
3	86.1 ± 1.1	1.7 ± 0.0	0.78 ± 0.08	46.0 ± 2.8
4	103.7 ± 10.3	1.5 ± 0.1	0.91 ± 0.03	45.3 ± 0.9

Fig.1. Appearance of the polymers.

References

[1] Risperdal Consta drug labeling, [2]Garner J. et al., *Int. J. Pharm*, 2015, 495, 87-92
[3] Shen J., *J. Control. Release*, 2015, 218, 2-12, [4] Li J, *et al., J Am Chem Soc*, 2012, 134(39): 16352-9.

RESULTS

• *Physicochemical properties of PLGA polymers*

Table 2 Physicochemical properties of prepared formulations (n = 3, mean ± SD).

Sample	Polymer	Drug Loading (%, w/w)	Particle size (Population, µm)	Particle size (Volume, µm)
Formulation_1	1	35.8 ± 0.4	67.6 ± 0.8	111.0 ± 3.8
Formulation_2	2	34.7 ± 0.8	64.1 ± 1.2	89.9 ± 3.6
Formulation_3	3	35.6 ± 2.0	65.6 ± 1.9	121.4 ± 12.2
Formulation_4	4	37.4 ± 0.6	73.4 ± 1.2	129.7 ± 7.9

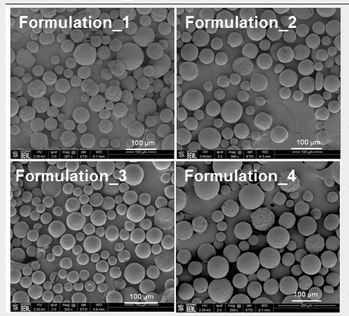


Table 3 Porosity of the prepared formulations.

Sample	Porosity %	average pore diameter (nm)
Formulation_1	57.5	0.12
Formulation_2	65.9	0.15
Formulation_3	73.2	0.17
Formulation_4	58.5	0.16

Fig.2. Scanning electron microscope (SEM) images of risperidone microsphere formulations.

• *Real-time in vitro release testing*

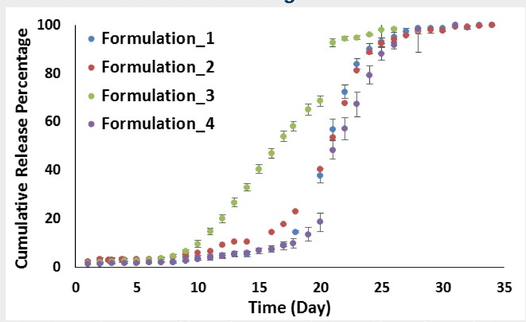


Fig.3. *In vitro* release profiles of prepared risperidone formulations (Mean±SD) using the USP apparatus 4 at 37ºC, 10 mM PBS (pH7.4) with 0.01% (*w/v*) sodium azide.

• *In vitro degradation studies*

Mw (gel permeation chromatography)

Since risperidone is an amine drug and catalyzes PLGA hydrolysis, an initial rapid polymer Mw decrease was observed for all polymers. Consequently, the Mw differences between the four polymers is rapidly mitigated.

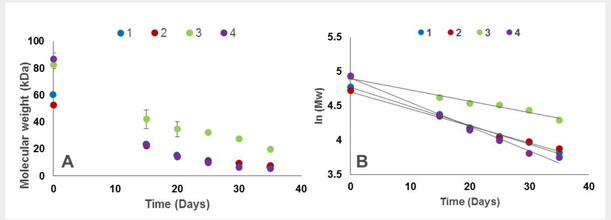
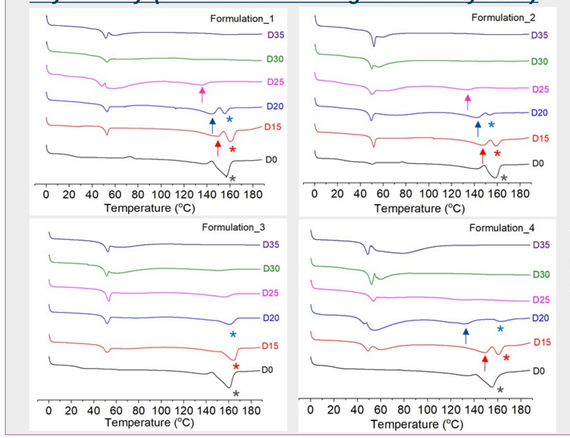


Fig.4. A) Changes in the Mw of risperidone microsphere formulations after exposure to 10 mM HEPES (pH 7.4) at 37˚C; and **B)** the same results as A in semi-logarithmic plots.

Crystallinity (differential scanning calorimetry DSC)



Morphology (SEM)

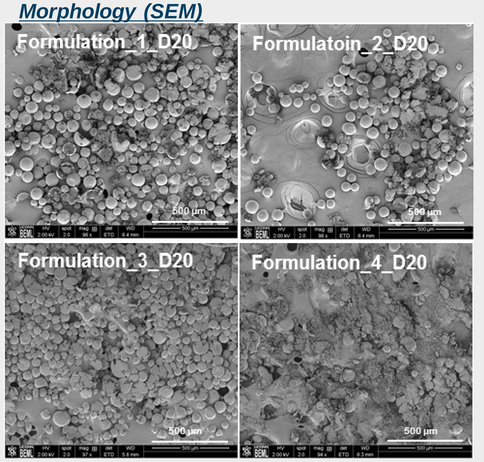


Fig.5. SEM images of prepared formulations with different molecular weight polymers after exposure to 10 mM HEPES (pH 7.4) for 20 days: scale bar 500 µm.

The higher porosity of Formulation 3 may cause rapid release of the acidic degradation products, reducing their autocatalytic effect. Note that the the degradation product peak is missing for Formulation 3 in Fig. 6.

Fig.6. DSC thermograms (1st cycle) after exposure to 10 mM HEPES (pH 7.4) over a period of 35 days. The arrow indicates the crystallization of degradation products trapped in the microspheres. The star indicates the melting of risperidone.

CONCLUSIONS

- These results indicate that there is not necessarily a correlation between PLGA Mw and risperidone release characteristics from the microspheres.
- Other physicochemical characteristics such as microsphere porosity as well as polymer manufacturing differences/source variations should also be taken into consideration when investigating risperidone release properties. This knowledge may help to establish specifications for PLGA polymers to be used in the development of bioequivalent risperidone-microsphere products.

ACKNOWLEDGEMENT

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