# Effect of Manufacturing Processes on Burst Release of Risperidone Microspheres

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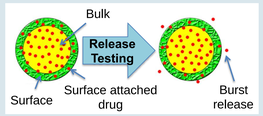
2017 AAPS ANNUAL MEETING & EXPOSITION

## PURPOSE

Microspheres reduce dose related toxicity by controlled release of small amount of drug over the longer period of time.

- Burst release – Initial fast release of drug
- Burst release is highly variable and may affect microspheres performance adversely.




- Minor manufacturing changes that may affect drug solubility, drug diffusion and hence, homogenous drug distribution in the polymeric matrix, may in turn affect the burst phase kinetics of compositionally equivalent microspheres.
- The purpose of the study is to investigate the burst release phase of compositionally equivalent polymer microspheres prepared using five different solvent compositions and two post manufacturing size separation methods.

## OBJECTIVES

1. Prepare compositionally equivalent risperidone microspheres with minor changes in manufacturing processes.
2. Characterize differences in the burst release phase along with various critical quality attributes of prepared microspheres such as drug loading, particle size and morphology.

## METHODS

**Model Drug:** Risperidone

**Polymer:** Poly(lactic-co-glycolic acid) (PLGA) with similar molecular weight to that of the commercially available risperidone microsphere product (Risperdal® Consta®, one Month formulation).

**Preparation Method:** PLGA microspheres were prepared *via* a single emulsion-solvent extraction/evaporation method.

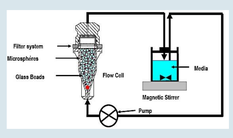
**Process variables:** Solvent systems (type and composition), sieving method.

**Characterization of microspheres:**

**1. Critical quality attributes:** Drug loading, particle size, size distribution, and morphology

***2. In Vitro* Release Testing**:

- Method: Developed USP apparatus 4 method
- Cell Preparation: Briefly, ~ 10 mg of microspheres mixed with glass beads were put into flow through cells
- Medium: 10 mM phosphate buffer with 0.01% w/v sodium azide, pH 7.4
- Testing Temperature: 37°C
- Flow Rate: 8 mL/min





## RESULTS

**Table 1.** Physicochemical properties of the prepared risperidone microspheres

| Formulations | Solvent systems/Sieving Method | Drug Loading (%W/W) | Population Distribution (Mean ± SD) | Volume Distribution (Mean ± SD) |
|---|---|---|---|---|
| F1 | DCM_Dry Sieving | 36.77±1.44 | 6.14±0.37 | 108.40±1.16 |
| F2 | DCM_Wet Sieving | 37.67±0.94 | 63.94±4.39 | 103.89±2.66 |
| F3 | DCM/MeOH | 37.68±0.52 | 60.95±3.07 | 96.03±0.61 |
| F4 | DCM/BA | 36.69±2.89 | 57.54±3.61 | 89.66±1.52 |
| F5 | DCM/EA (0.7/0.5 w/w) | 38.20±0.89 | 51.75±3.80 | 102.84±1.84 |
| F6 | DCM/EA (0.8/0.6 w/w) | 38.18±1.09 | 5.69±0.06 | 82.65±9.62 |

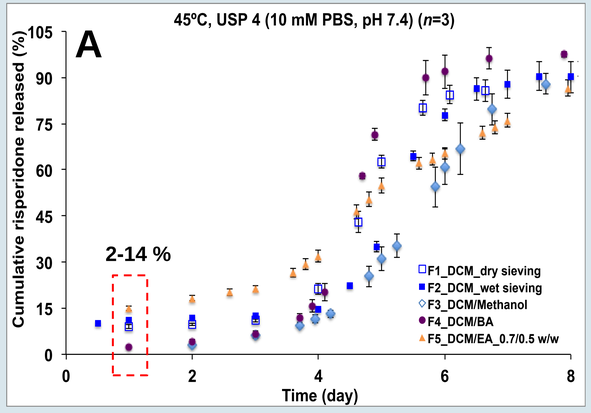
DCM: Dichloromethane, BA: Benzyl Alcohol, EA; Ethyl Acetate

- Dry Sieving: Post drying sieving of microspheres for separation of particles.
- Wet Sieving: Post drying sieving of microspheres for separation of particles.
- Difference in sieving stage may affect the size distribution with more number of smaller particles in dry sieving method, resulting in higher surface area and higher burst release.

➢ In terms of population distribution, those formulations prepared using the dry sieving procedure (F1) had smaller particle size (D50: ~6 µm) than the formulations prepared using the wet sieving procedure (F2, D50: ~50 µm)[1].

- Solvent systems were selected based on the differences in the drug solubility.

➢ Despite the use of different solvent systems, all the microsphere formulations had similar drug loading (36%, w/w).



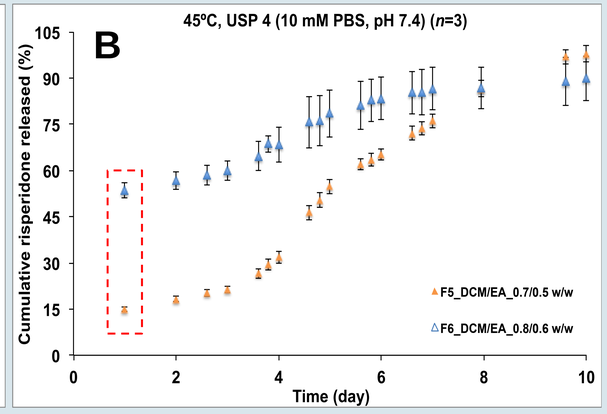




**Figure 1**. Effect of solvent system and sieving method (A); and cosolvent ratio (B) on the burst release phase of *in vitro* release profiles of risperidone microspheres

- Formulations 2 and 3 showed the lowest burst release as a result of the least surface associated drug, which may be due to better drug solubility and more uniform drug distribution inside the bulk of the microspheres.
- While Formulation 6 had the highest burst release percentage. This may be due to poor drug solubility leading to drug precipitation and hence, more surface distribution of drug.
- Moreover, the burst release percentage of microspheres was also affected by the cosolvent ratios used for the microspheres prepared using the same solvent system (**Figure 1B**) due to significant reduction in drug solubility.
- The developed USP apparatus 4 *in vitro* release testing method was able to discriminate variations in the burst release phase of risperidone microsphere formulations (**Figure 1**).

## CONCLUSIONS

✓ The burst release phase of risperidone microspheres appeared to be sensitive to manufacturing changes such as the solvent system.

✓ The developed USP apparatus 4 *in vitro* release testing method was capable of discriminating variations in the burst release phase of the risperidone microsphere formulations prepared with manufacturing differences.

## REFERENCE:

**1**. Shen J. *et al*. J Control Release, 2015, 218: 2-12.

## ACKNOWLEDGEMENTS

- This work was supported by the FDA/CDER, Office of Generic Drugs/Office of Research and Standards (1U01FD004931-02).
- Support from Sotax Corporation for instrumentation and instrument maintenance is highly appreciated.

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