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# Impact of Particle Size on *In Vitro* Release from Long-Acting Injectable Suspensions

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## INTRODUCTION

- Long-acting injectable (LAI) aqueous suspensions (*e.g.*, Depo-SubQ Provera104®) are administered intramuscularly or subcutaneously to achieve a depot with extended drug release from weeks to several months, which reduces dosing frequency and hence improves patient compliance or adherence.
- LAI suspensions achieve extended release through the formation of drug depots from which poorly soluble drugs gradually undergo dissolution followed by absorption into the systemic circulation. Active pharmaceutical ingredients (APIs) in LAI suspensions are generally in the form of micro or nano sized crystals dispersed in the injection media.
- The particle size of the drug crystals is critical to the *in vitro* as well as the *in vivo* performance. Accordingly, the impact of particle size on the *in vitro* release from LAI suspensions was investigated.

## MATERIALS & METHODS

- Medroxyprogesterone acetate (Micronized, USP grade) was purchased from Spectrum Chemical Manufacturing Corp.
- Three qualitatively (Q1) and quantitatively (Q2) equivalent medroxyprogesterone acetate suspensions formulations were prepared. Each formulation used APIs with different particle sizes.
- Formulation 1 was prepared using the API as received. Formulations 2 was prepared using the API recrystallized *via* the antisolvent method (acetone:water=1:1). Formulation 3 was prepared using the API recrystallized *via* the solvent evaporation method (tetrahydrofuran (THF)).
- The particle size distribution (*i.e.*, D50 and SPAN=(D90-D10)/D50) were determined using laser diffraction. Physicochemical characterization (e.g., distribution, drug content, morphology, *etc*.) was performed.
- An *in vitro* release testing method was developed and optimized: pH 7.4 phosphate buffered saline (PBS) with 1% w/v sodium dodecyl sulfate at 37°C using USP apparatus 2 with enhancer cells (exposed area: 4 $cm^2$). The release testing was performed under sink conditions. The samples were withdrawn at predetermined time intervals and replenished with fresh media.

## MATERIALS & METHODS (CONT'D)

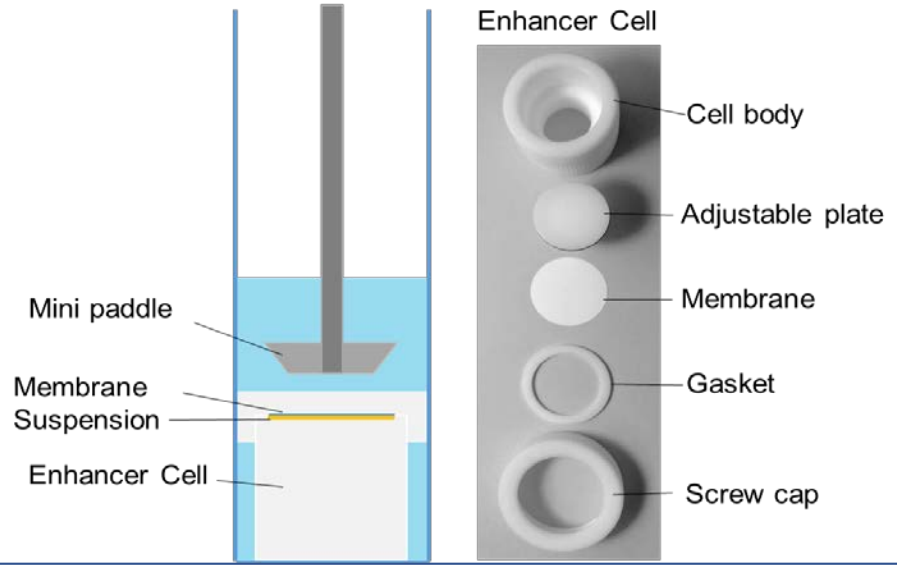


**Figure 1.** Graphic demonstration of USP apparatus 2 with enhancer cells.

## RESULTS

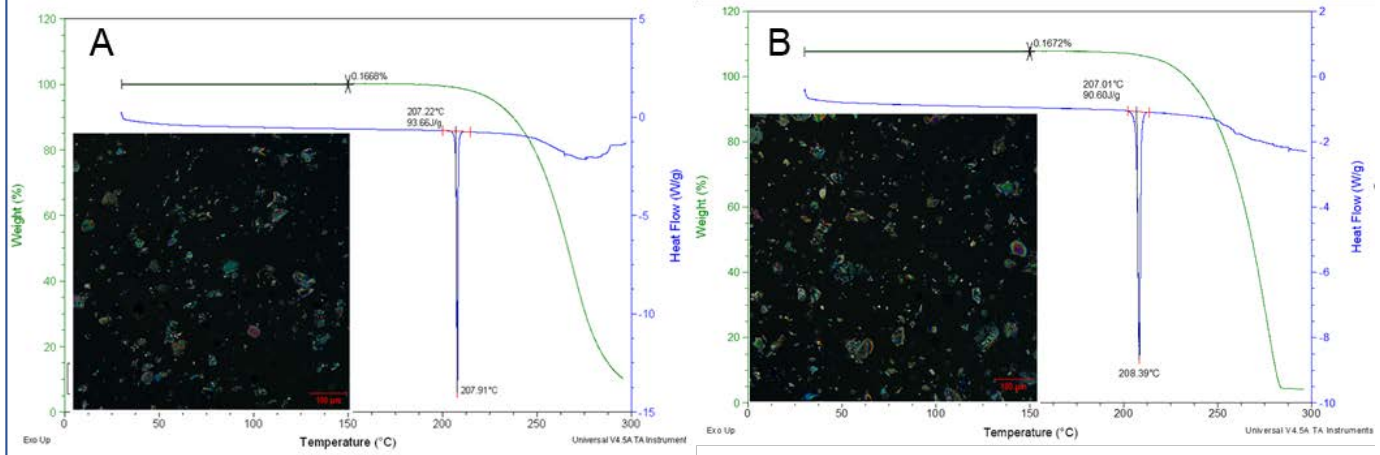


**Figure 1.** Differential scanning calorimetry, thermogravimetric profiles and polarized light microscopic (PLM) images (scale bar: 100 µm, 200-fold magnification) of the recrystallized API using: **A)** antisolvent (acetone:water=1:1); and **B)** solvent (THF) evaporation method.

- Three Q1/Q2 equivalent LAI suspensions were prepared using API of different particle sizes with the target drug content.

**Table 1.** Particle size distribution of the prepared LAI suspensions using AccuSizer (n=3, mean ± SD)

| | Dv10 (µm) | Dv50 (µm) | Dv90 (µm) | SPAN |
|---|---|---|---|---|
| F1 | 8.53 ± 0.21 | 15.07 ± 0.44 | 22.67 ± 0.94 | 0.94 ± 0.02 |
| F2 | 8.56 ± 0.99 | 19.10 ± 1.60 | 34.80 ± 1.17 | 1.38 ± 0.11 |
| F3 | 4.83 ± 0.77 | 9.59 ± 0.87 | 14.31 ± 0.84 | 0.99 ± 0.08 |

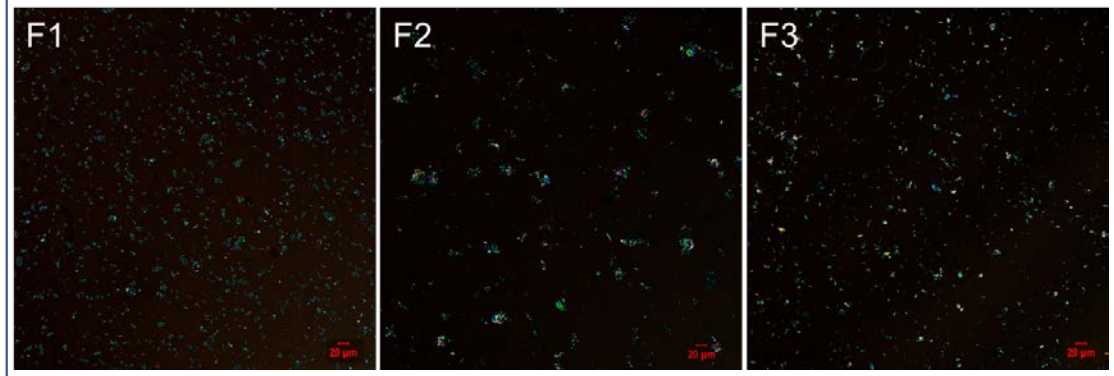


**Figure 3.** PLM images of LAI suspensions (scale bar: 20 µm, 200-fold magnification)

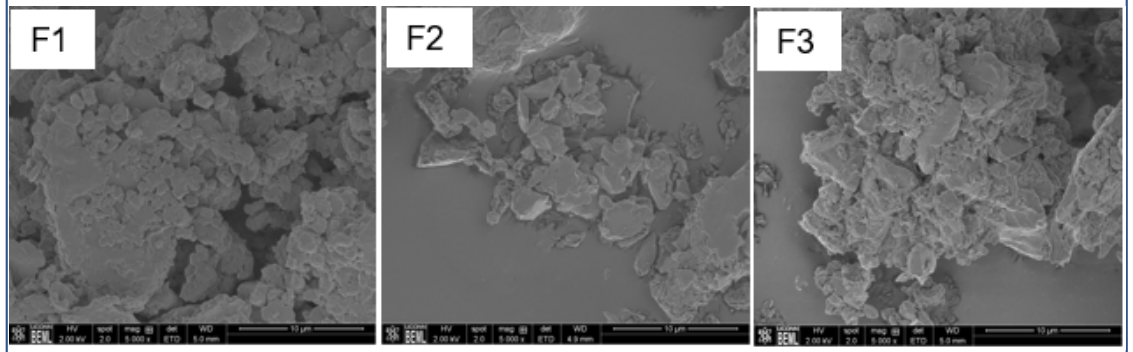


**Figure 4.** Scanning electron microscopic images of LAI suspensions (scale bar: 10 µm, 5000-fold magnification)

## RESULTS (CONT'D)

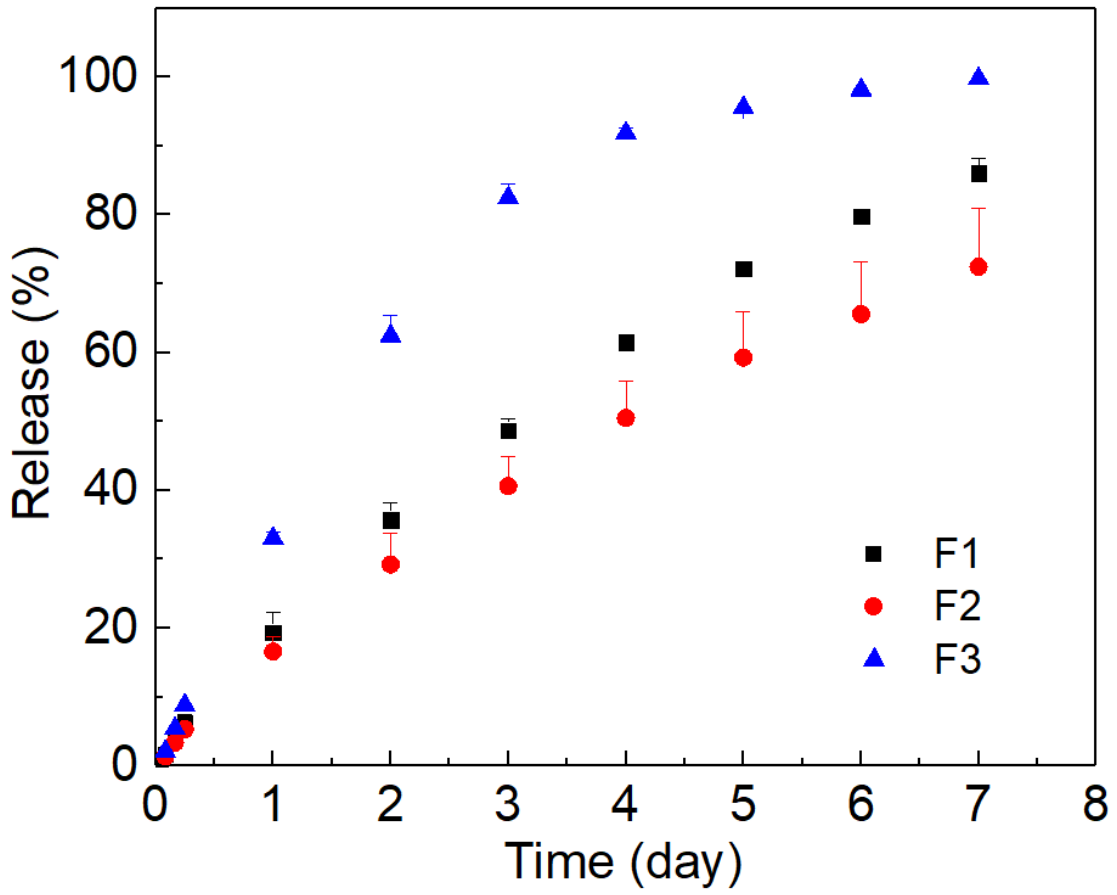


**Figure 2.** *In vitro* release profiles of Q1/Q2 equivalent LAI suspensions with difference in drug particle size (n=2, mean ± SD) using USP apparatus 2 with enhancer cells.

## CONCLUSION

- Particle size distribution has a significant impact on drug release from the LAI suspensions. Higher particle size yields to slower drug release rate and vice versa.
- The *in vitro* release testing method has good discriminatory ability for the Q1/Q2 equivalent formulations.
- *In vitro* release from the LAI suspensions followed first order release kinetics.

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