Formulation Insights into Long-Acting Hormonal Contraceptives for Advancing Generic Product Development

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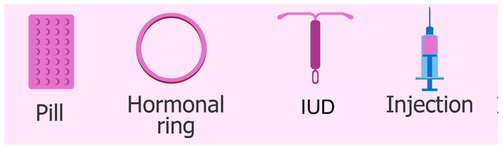
BACKGROUND

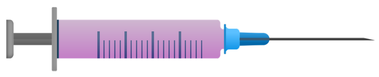
Contraception Statistics

According to a survey by the National Campaign

- 1 in 4 women (nearly 23%) find it difficult to afford contraceptives
- Those below the poverty line and those without insurance are affected more



Different methods of contraception



Long-acting injectable (LAI) suspensions- controlled delivery for prolonged periods

Advantages of generics

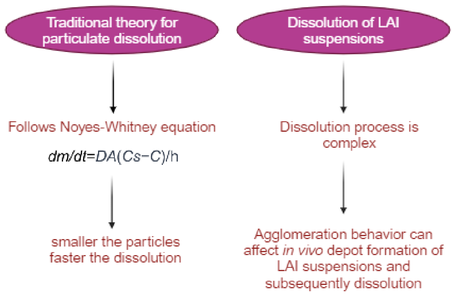
- Increase competition
- More choices available
- Increased adherence

- ✓ Patient compliance
- ✓ Improved safety
- ✓ Reduced pill burden
- ✓ Reduced risk of failure

OBJECTIVES

The purpose of this study was to investigate:

- ✓ Factors affecting agglomeration behavior
- ✓ Techniques to understand agglomeration behavior
- ✓ Impact of agglomeration behavior on *in vitro* drug release



METHODS

Five formulations (FA, FB, FC, FD, FE) Q1Q2 equivalent to Depo-Provera® Medroxyprogesterone acetate 150 mg/mL injection (depot) , the reference listed drug (RLD), were prepared as follows:

FA: MPA as obtained from Spectrum Chemicals and PEG3350 from Spectrum chemicals

FB: Particle size of Spectrum Chemicals MPA was changed using antisolvent method

FC: MPA as obtained from Spectrum Chemicals PEG3350 from BASF chemicals

FD: Spectrum Chemicals MPA Particle size reduced by High shear homogenization

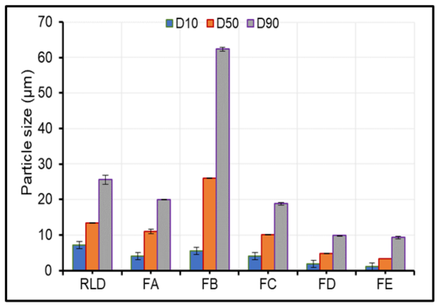
FE: Spectrum Chemicals MPA Particle size reduced by wet media milling

*MPA= Medroxyprogesterone acetate

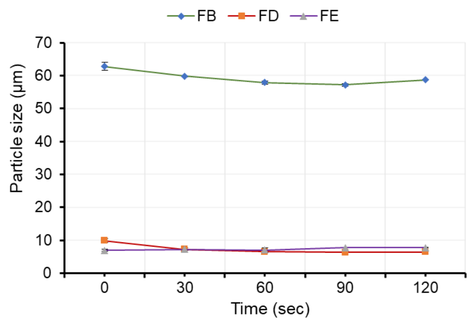
These formulations along with Depo-Provera® were characterized for:

- ✓ Particle size
- ✓ Sedimentation value
- ✓ Impact of low energy sonication
- ✓ *In vitro* dissolution
- ✓ Impact of shear
- ✓ Impact of stirring

RESULTS

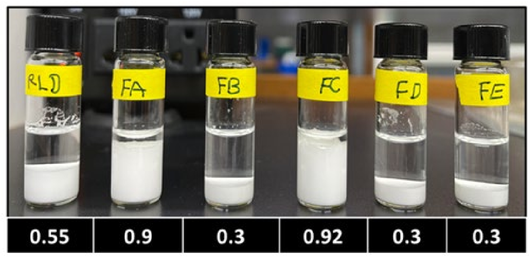


Rank order of particle size: FB>RLD>FA~FC>FD~FE

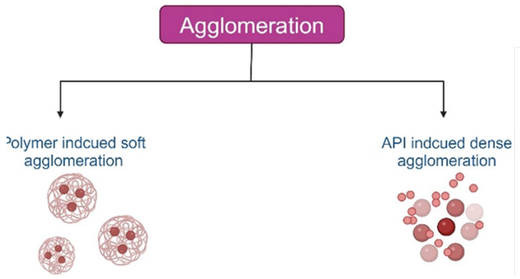


FB showed slight reduction in particle size whereas particle size of FD and FE remained unchanged (mean ± SD, n = 3)

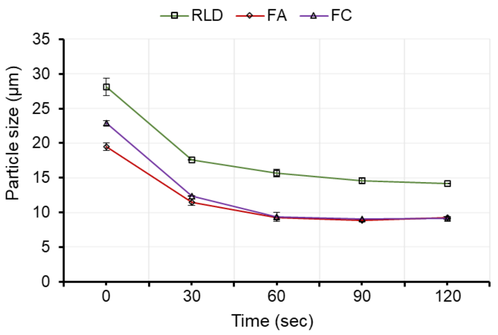
Sedimentation value



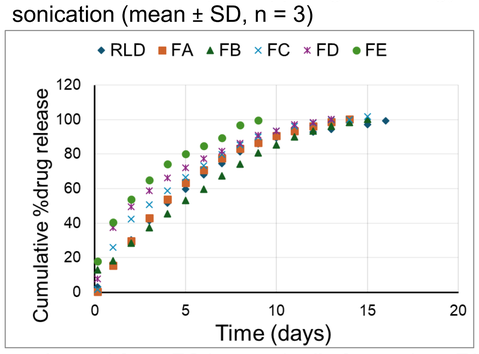
What is the state of particles? To understand this, particle size was determined with low energy sonication



Particle size with low energy sonication suggests that particles in suspension could exist as weak agglomerates, strong agglomerates and/or primary particles



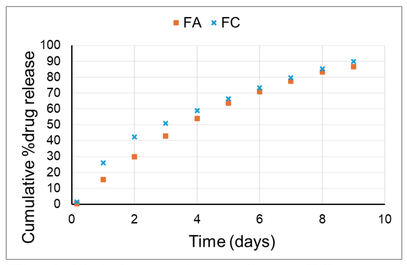
The particle size of RLD, FA, and FC were reduced significantly on applying low energy sonication (mean ± SD, n = 3)



Drug released from FC is marginally faster than FA. The drug released from FB is faster than expected. The drug released from FD and FE is slower than expected (mean ± SD, n = 3)

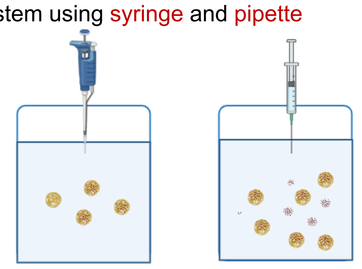
Impact of shear on the particle size

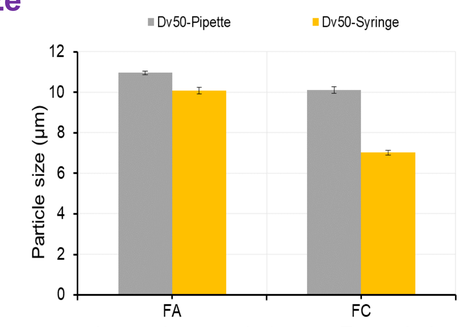
Zoomed in view of the drug release from formulation "FA" and "FC"



The initial drug release from "FC" was marginally faster than "FA" (mean ± SD, n = 3)

Suspension introduced into the particle sizing system using syringe and pipette

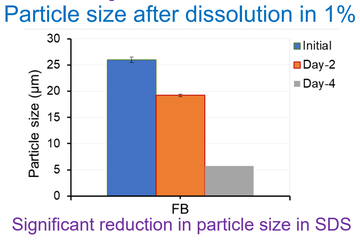




Suspension introduced into the particle sizing system using syringe and pipette- Formulation "FC" containing BASF polymer PEG3350 was more sensitive to shear (mean ± SD, n = 3)

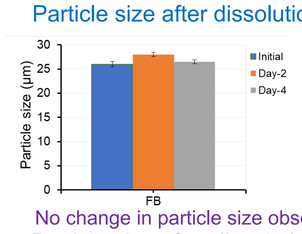
Impact of release media on the particle size

Particle size after dissolution in 1% SDS



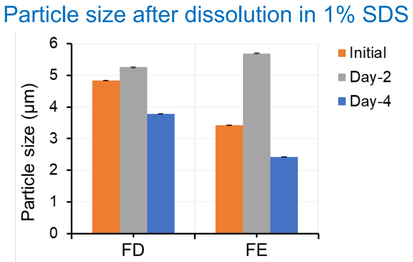
Significant reduction in particle size in SDS

Particle size after dissolution in PBS

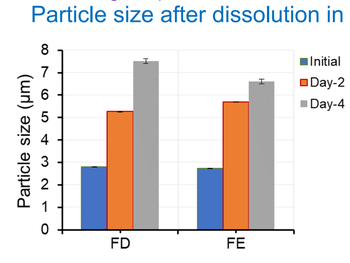


No change in particle size observed in PBS

Particle size after dissolution in 1% SDS

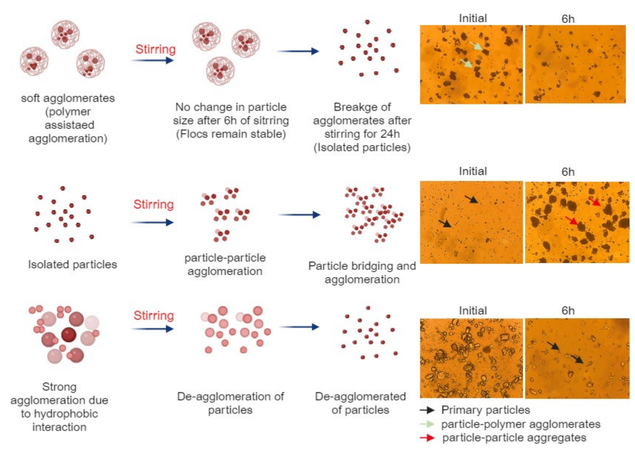


Particle size after dissolution in PBS



Extensive aggregation seen when dissolution was performed using PBS (All data are presented mean ± SD, n = 3)

Impact of stirring on the particle size



Overtime stirring can be performed to predict dissolution behavior (All data are presented as mean ± SD, n = 3).

CONCLUSIONS

- LAI suspensions were prepared with manufacturing and formulation differences
- A suitable dissolution method was developed for LAI suspensions
- Particles can be in the form of weak-flocculates, strong-flocculates, and/or primary particles
- Suspensions with polymers from different vendor sources can affect drug release
- Suspensions with different particle states can have unusual drug release behavior
- Real time particle size analysis during dissolution may be useful to understand particle behavior

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- Bao, Quanying, et al. "Impact of formulation parameters on in vitro release from long-acting injectable suspensions." *The AAPS journal* 23 (2021): 1-11.
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