Enabling Formulation Development of LAIs Thorough Understanding Critical Formulation Parameters

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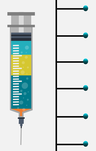
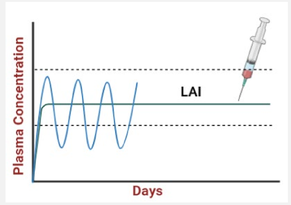
PURPOSE

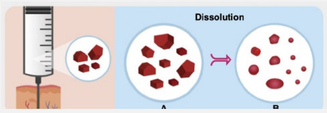
LONG-ACTING SUSPENSION



- Aqueous suspension
- Lipophilic active pharmaceutical ingredient (API)
- Poor dissolution
- Particle size and surface area
- Surfactants and stabilizers
- Reduced dosing frequency
- Intramuscular (IM)/Subcutaneous (SC) route

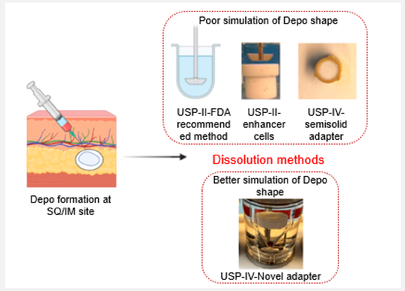
Dissolution method is one of the major challenges in product development





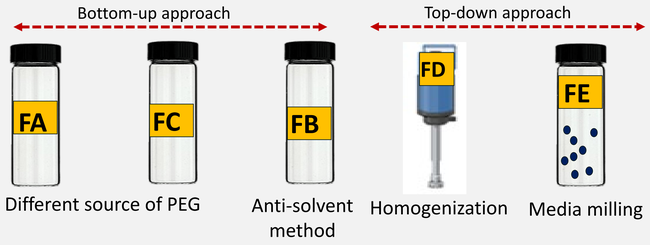
OBJECTIVE(S)

- To understand the critical formulation parameters that could have a significant impact on the *in vitro* drug release
- To develop a longer duration *in vitro* release method in comparison with the commonly used method such as use of semisolid adapters in USP-IV apparatus
- To develop an *in vitro* release method that can closely represent *in vivo* drug release in terms of general mechanism and duration



METHODS

1. Preparation of Q1/Q2 formulations of reference listed drug (RLD), Depo Provera® (medroxyprogesterone acetate) 150 mg/mL.
2. Design and optimization for novel adapter



3. Physicochemical characterization such as particle size, SPAN value, sedimentation value
4. *In vitro* release

RESULTS

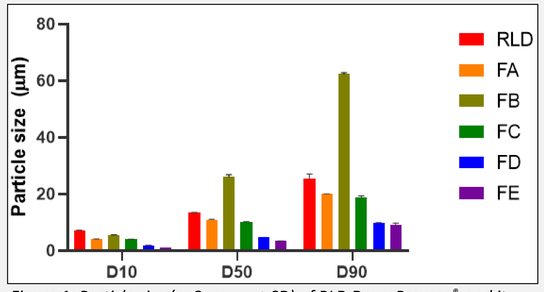


Figure 1: Particle size (n=3, mean ± SD) of RLD Depo-Provera® and its Q1Q2 formulations

The polymer source did not affect the particle size. Formulation FB prepared by antisolvent method showed larger particle size. FD and FE had similar particle size and were smallest amongst all the formulations.

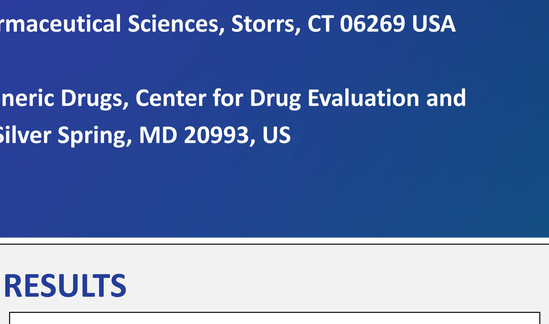


Figure 2: Particle size distribution (n=3, mean ± SD)

The processing of API increases the SPAN value of suspension

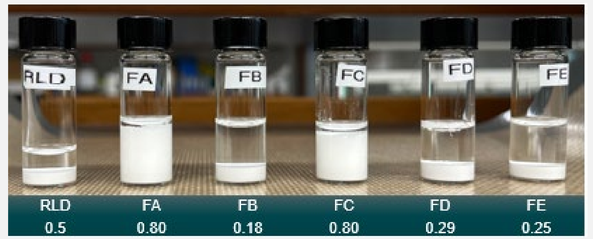


Figure 3: F-value of RLD Depo-Provera® and its Q1Q2 formulations

The sedimentation value data indicated that the formulations RLD, FA, and FC were in flocculated state, whereas FB, FD, and FE were in deflocculated state. To confirm this, particle size analysis was conducted while using ultrasonic energy.

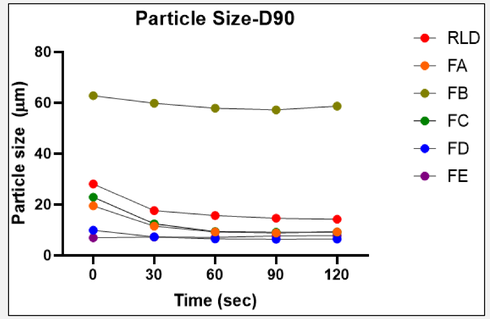


Figure 4: Particle Size (D90) (n=3, mean ± SD) at Different Time of Dissolution

On application of ultrasonic energy, formulations FA, FC, and RLD showed reduction in particle size suggesting the breaking of agglomerates whereas the particle size of FB, FD, and FE remained similar.

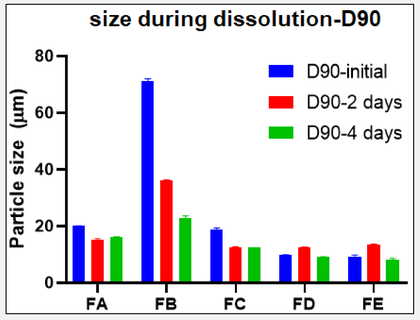


Figure 6: Particle size (n=3, mean ± SD) of RLD Depo-Provera® and its Q1Q2 formulations at different time of dissolution

The particle size exhibited distinct trends among the different formulations. FA and FC demonstrated a gradual decrease in particle size, while Formulation FB exhibited a rapid reduction in particle size. On the other hand, FD and FE displayed an increase in particle size.

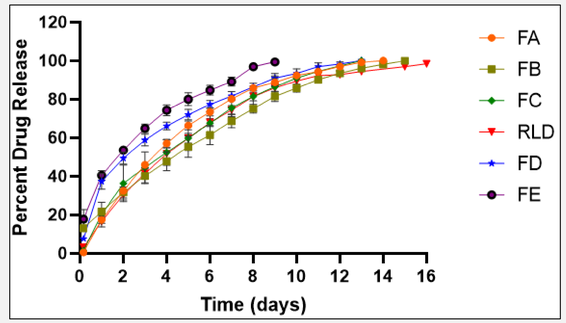


Figure 5: In vitro drug release of RLD Depo-Provera® and its Q1Q2 formulations

Although drug release followed the rank order of particle size, the release rate for FB was faster, while FD and FE exhibited a slower than expected release rate.

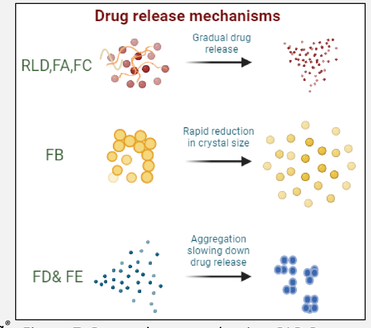


Figure 7: Drug release mechanism RLD Depo-Provera® and its Q1Q2 formulations

CONCLUSIONS

1. Particle size and distribution have a significant impact on the drug release.
2. Formulations FA and FC did not show any significant difference in the drug release given similar particle size/SPAN and flocculation state during in vitro release test (IVRT).
3. The larger-particle formulation FB, while exhibiting a slower drug release, did not experience a higher decrease in drug release rate, considering its particle size.
4. The formulations FD and FE showed aggregation during IVRT resulting in slower release than expected thereby suggesting instability of the particles.
5. The novel adapter developed for release testing showed drug release profile with low standard deviation and good discriminatory ability.

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