Formulation Insights into Long-Acting Injectable Suspensions for Advancing Pharmaceutical Development

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Purpose
An accepted theory for particulate dissolution is that dissolution is dependent on particle size. However, in long-acting injectable (LAI) suspensions, additional factors such as micromeritic properties, agglomeration behavior and depot formation add complexity. The current study investigates the impact of formulation factors on the drug release behavior of LAI suspensions.

Methods
Depo-Provera 150® with medroxyprogesterone acetate (MPA) was the chosen model drug. Five formulations (F1, F2, F3, F4, F5), all Q1/Q2 to Depo-Provera 150®, were prepared. F2 utilized larger recrystallized MPA particles, while F4 and F5 employed homogenization and wet milling to achieve smaller particle sizes. Formulations F1, F2, F4 and F5 used a suspending medium containing PEG3350 polymer from Spectrum Chemicals. However, F3 employed PEG3350 from BASF. The formulations were characterized, and subsequently in vitro release studies were conducted.

Results
All formulations had mean particle size values from 5 to 35 microns. The sedimentation values suggested that formulations F2, F4 and F5 were in a deflocculated state whereas F1 and F3 were in the flocculated state. Although F1 and F3 showed particle size reduction upon low energy sonication, no change occurred in F2, F4, and F5, indicating either single particles or hard agglomerates. Particle size determination showed that the F2 particles were in the form of dense agglomerates that deagglomerated with long-term stirring (1,3, 6 and 24 h) due to the impact of the dense particles on each other. This is probably responsible for the faster-than-expected drug release of F2, underscoring the significance of dense API agglomerates in LAI formulation development. Conversely, the high system energy generated during long-term stirring induced agglomeration in F4 and F5 (small sized particles with high surface energy), resulting in slower-than-expected dissolution rates. These results highlight how particle size can alter API characteristics, such as surface energy, rendering different agglomeration behavior during depot formation which subsequently affects drug release.

Conclusion
In summary, this study shows that the particle size, surface energy and density of the API can impact the agglomeration behavior of LAIs, thereby influencing depot formation and subsequent drug release. This research underscores the importance of understanding agglomeration behavior in the development of LAI suspensions.

Keywords: Long-acting injectable suspensions, Depo-Provera 150®, Formulation and development, Agglomeration behavior, In vitro drug release