Beyond Particle Size: Impact of Milling Techniques on Agglomeration Behavior and *In Vitro* Performance of Long-Acting Injectable Suspensions

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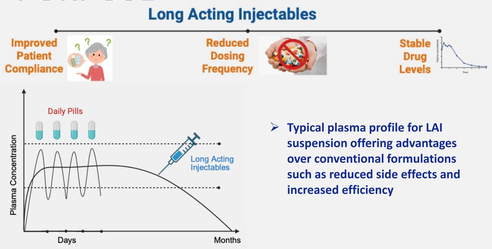
PURPOSE



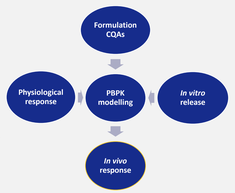
➢ Typical plasma profile for LAI suspension offering advantages over conventional formulations such as reduced side effects and increased efficiency

But formulation remains a challenge!!

- Complex formulation parameters, *e.g.,* particle size and agglomeration
- *In vitro in vivo* mismatch due to complex depot pharmacokinetics
- Lack of standardization in QC tests, such as particle size characterization and *in vitro* release testing
- Complex interplay of processing, size and morphology

OBJECTIVES

- ✓ To evaluate the influence of different particle size reduction techniques on the agglomeration behavior and *in vitro* release of medroxyprogesterone acetate (MPA) suspensions
- ✓ To investigate the effect of different processing methods on in vitro performance of similarly sized particles.



METHODS

Particle size reduction

In-house Q1/Q2 equivalent formulations of Depo Provera® (Medroxyprogesterone Acetate) 150 mg/mL injectable suspension

Characterization

- ➢ Particle size characterization: polarized light microscopy & MasterSizer
- ➢ Physicochemical characterization: Differential scanning calorimetry, Thermogravimetric analysis, X-ray diffraction
- ➢ Brunauer–Emmett–Teller (BET surface area analysis
- ➢ Viscosity analysis
- ➢ Impact of stirring, sonication and stress: to understand agglomeration

In Vitro Release

In vitro release was performed using USP apparatus IV in combination with customized adaptor using 1% SDS as release media

RESULTS

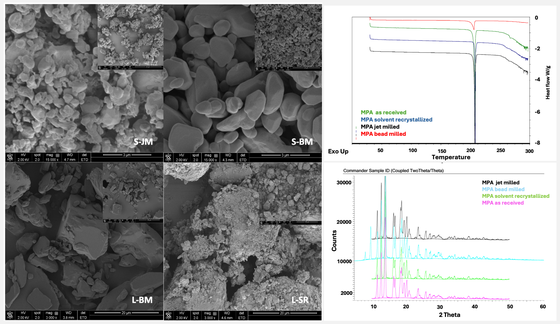


Fig 1: Physicochemical characterization of processed API.

Scanning electron microscopy images show morphological differences, with S-JM exhibiting agglomerated structures composed of smaller primary particles, while L-SR displays porous, tightly bound agglomerates. DSC and PXRD analyses confirm the crystalline nature of MPA with no polymorphic changes across processing techniques.

Formulations	Surface area (m^2/g)	Formulations	Surface area (m^2/g)
S-BM	0.7746	L-BM	0.02
S-JM	**1.8606**	**L-SR**	**0.3292**
S-SR	0.799		

Table 2: Surface area analysis

The S-JM formulation exhibited a higher surface area compared to S-BM and S-SR. Similarly, L-SR showed a greater surface area than L-BM, which was consistent with its faster release profile and the presence of an agglomerated particle structure.

Formulation	Processing method	Observed mean particle size (D_{50} ± SD) µm (N=3)
S-JM	Jet Milling	15.8 ±0.08
S-SR	Solvent Recrystallization	3.98±0.05
S-BM	Bead Milling	3.75±0.04
L-SR	Solvent Recrystallization	19.5±0.22
L-BM	Bead Milling	20.1±0.34

➢ Table 1: Summary of in-house Q1/Q2 equivalent formulations prepared using different processing techniques and observed mean particle sizes

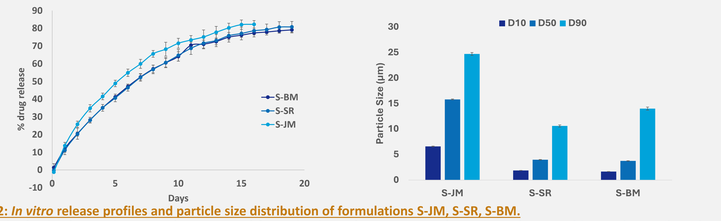


Fig 2: *In vitro* release profiles and particle size distribution of formulations S-JM, S-SR, S-BM.

Despite having larger size, S-JM demonstrated faster *in vitro* release compared to S-SR and S-BM. This may be attributed to the presence of agglomerates in S-JM containing smaller primary particles and loose flocculates as revealed by SEM (fig 1). (All data are presented as mean ± SD, n = 3)

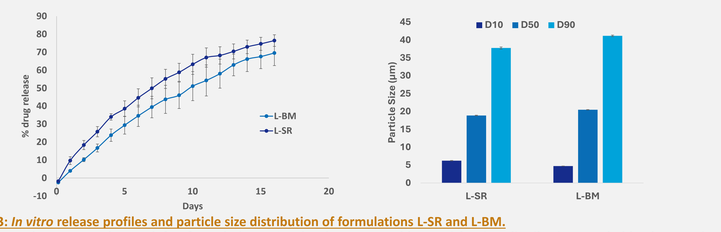


Fig 3: *In vitro* release profiles and particle size distribution of formulations L-SR and L-BM.

Faster release was observed for formulation L-SR despite comparable particle size distribution, probably due to the agglomerated state as evident in SEM analysis (fig 1). (All data are presented as mean ± SD, n = 3)

Understanding ~~the~~ agglomeration

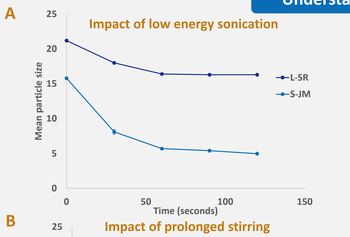


Fig 4: Impact of low energy sonication and prolonged stirring on agglomeration.

Low-energy sonication markedly reduced the particle size of S-JM (~60%) (A), indicating loose agglomerates, while prolonged stirring decreased L-SR particle size (~70%), suggesting relatively strong agglomerates (B). (All data are presented as mean ± SD, n = 3)

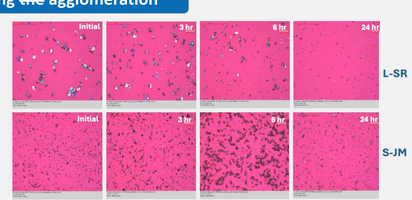


Fig 5: Polarized light microscopy (PLM) images of LAI formulation L-SR and S-JM.

24 hours of stirring show distinct agglomeration behaviors in formulations L-SR and S-JM. Continuous stirring led to a reduction in particle size for L-SR, indicating progressive deagglomeration.

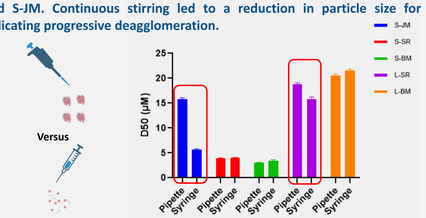


Fig 6: Impact of shear on agglomeration.

Higher shear generated during syringe injection (compared to pipette introduction in particle size analysis) disrupts agglomerates—reducing particle size and revealing agglomerate characteristics as observed in S-JM and L-SR. (All data are presented as mean ± SD, n = 3)

Impact of agglomeration on quality attributes of MPA LAI suspension

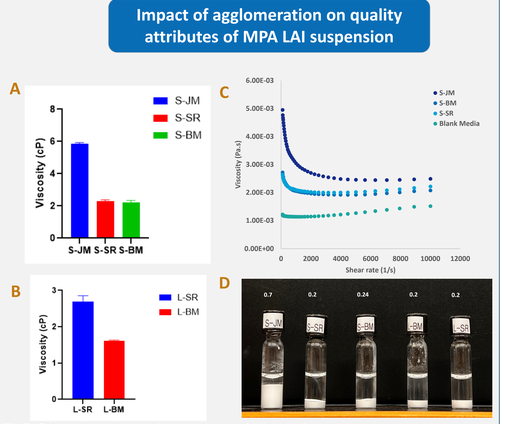
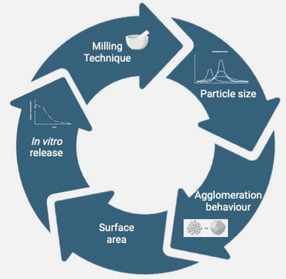


Fig 7: Effect of agglomeration on suspension behavior.

Viscosity analysis showed that formulation S-JM exhibited higher viscosity than S-SR and S-BM (A), while L-SR showed higher viscosity than L-BM (B), indicating greater agglomeration (All data are presented as mean ± SD, n = 3). These parameters provide insight into agglomeration behavior. Formulation S-JM also displayed the highest F value (D), consistent with its loose, flocculated agglomerate structure.

CONCLUSION

- ✓ Different size reduction methods can affect release and sedimentation profiles
- ✓ Agglomeration, not just mean particle size, critically influences *in vitro* performance of LAI MPA suspensions
- ✓ Faster drug release in S-JM and L-SR was likely due to agglomerates with smaller primary particles and higher surface area
- ✓ Techniques such as low-energy sonication and prolonged stirring can help in understanding agglomeration behavior
- ✓ Robust, harmonized particle characterization methods are essential for designing effective and predictable LAI formulations



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