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Development and characterization of composition-equivalent formulations to the one-month Lupron Depot®

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PURPOSE

- 1-month Lupron Depot® (LD) is a poly(lactic-co-glycolic acid) (PLGA) microsphere product with 10% water-soluble leuprolide acetate (LUP).
- No generic product is approved in the US despite patent expiration, likely due to the complexity of manufacturing processes by solvent evaporation.

➢ To facilitate generic LD development, we sought to:

- Develop composition-equivalent formulations to the LD as a function of manufacturing variables
- Determine effect of these variables on product attributes and release

METHODS

- Double emulsion-solvent evaporation method:

PLGA (lactic: glycolic ratio = 75:25, molecular weight = ~13 kDa) in methylene chloride (DCM) + Leuprolide + type B gelatin in water (60°C)

1st Homogenization ↓

0.25% polyvinyl alcohol (PVA) solution + Primary emulsion

2nd Homogenization ↓

Secondary emulsion → In-water drying (3 h)

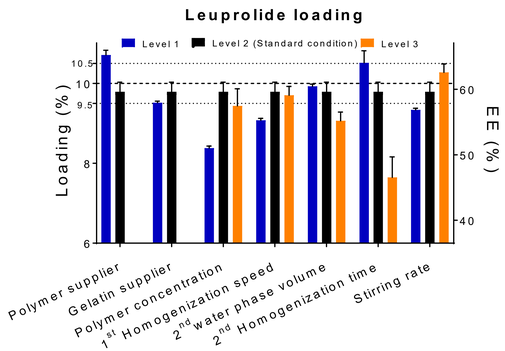
- Formulations prepared by changing one variable a time from the **standard condition** at constant theoretical loading of 16.4% LUP:

Parameters	Level 1	**Level 2 (Standard condition)**	Level 3
Polymer supplier	Resomer	**Wako**	-
Gelatin supplier/ bloom number	Sigma 225	**Nitta 300**	-
Concentration of PLGA (mg/mL)	400	**500**	600
1st homogenization speed (rpm)	8000	**10000**	12000
2nd water phase volume (mL)	1	**2**	4
2nd homogenization time (s)	10	**30**	45
Stir rate (rpm)	450	**750**	900

- Loading of leuprolide and gelatin were determined by UPLC and AAA, respectively.
- In vitro release kinetics was determined in PBST (10 mM PBS + 0.02% Tween 80 + 0.02% NaN_3, pH 7.4) at 37 °C by UPLC.
- All data indicate mean ± SEM (n=3).

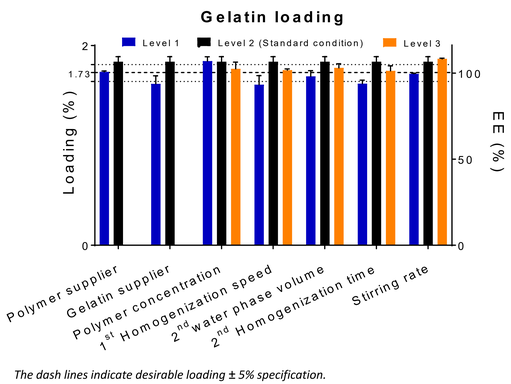
RESULTS

Effect of manufacturing parameters on the loading of leuprolide and gelatin



The dash lines indicate desirable loading ± 5% specification.

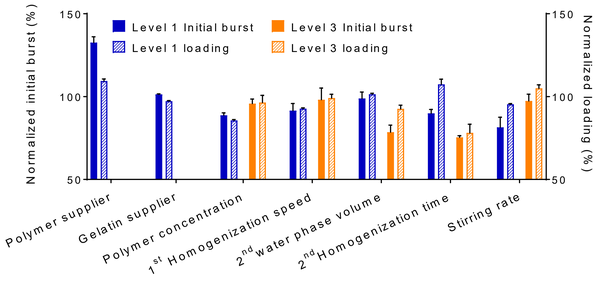
- Several formulations fell within a desired 10% loading ± 5% specification.
- Desirable conditions of 2nd homogenization time (30 s (standard condition)), volume of 2nd water phase (2 ml) and stir rate (750 rpm) are key to achieving high EE of LUP.



The dash lines indicate desirable loading ± 5% specification.

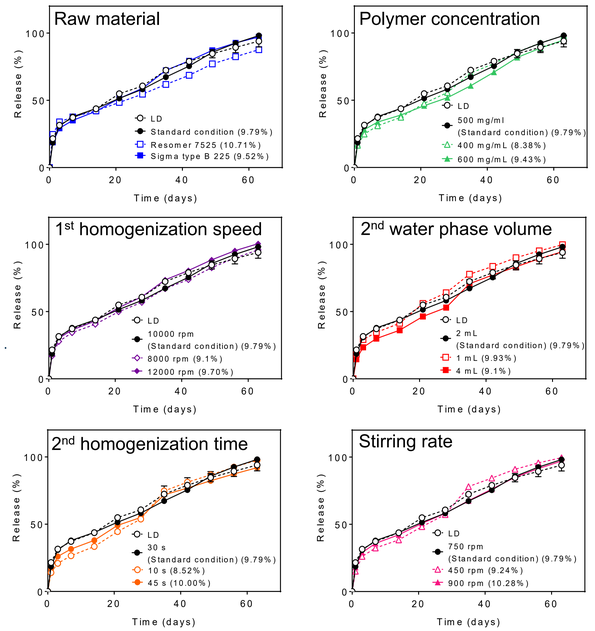
- The EE of gelatin (96.7 ± 1.5%) was observed to be much higher than that of LUP (~60%).

Effect of loading on initial burst release



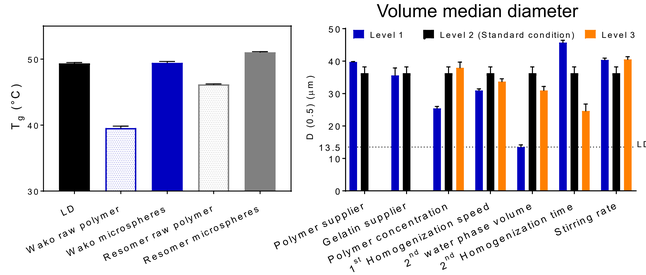
- The loading and initial burst of prepared formulations were normalized to the standard condition formulation.
- Higher loading corresponded to higher initial burst.

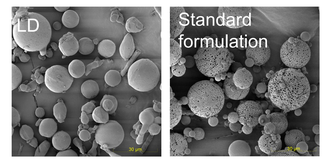
Effect of manufacturing parameters on release kinetics



- Release kinetics was not strongly affected by manufacturing variables, but ring-opening Evonik PLGA released peptide slightly slower than polycondensation Wako PLGA.

Product physicochemical attributes





- The formulations exhibited higher surface porosity and larger particle size compared to the LD.
- T_g of LD matched formulations prepared by Wako polymer.

CONCLUSIONS

- The composition, Tg, and in vitro release kinetics of the LD microspheres can be largely replicated on the bench scale.
- The substitution of ring-opening polymerized PLGA in place of polycondensation PLGA slightly reduces release rate.
- The loading efficiency of leuprolide is reduced relative to gelatin
- Changing manufacturing variables centered at a standard formulation did not strongly affect release behavior.
- Changes in Initial burst release mirrored changes in drug loading/encapsulation efficiency.

DISCLAIMER/ FUNDING

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