Impact of Polyethylene Glycol Polymer in the Development of Long-Acting Injectable Suspensions

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M1030-06-39

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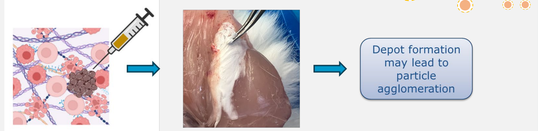
PURPOSE

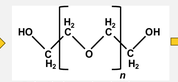
Long-acting suspensions

Administered at SC/IM site



The rate and extent of dissolution of dispersed solid is primarily considered to be governed by particle size following the Noyes Whitney theory with smaller particles undergoing dissolution at a faster rate

Depot formation could be controlled by dispersing agent such as polyethylene glycol



Polyethylene glycol polymer

- Could affect depot formation
- Different sources could affect particle-polymer interaction
- Could result in different agglomeration state

METHODS

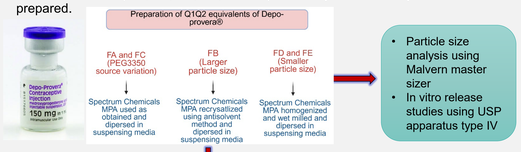
1. Characterization of PEG3350 polymer

PEG3350 polymer from Spectrum Chemical and BASF PEG3350 were characterized for thermogravimetric analysis (TGA), molecular fraction analysis, and molecular weight analysis

BASF We create chemistry | spectrum CHEMICAL MFG CORP → • TGA analysis • LC/MS analysis • GPC analysis

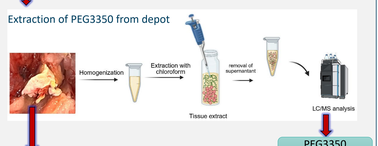
2. Characterization of Q1Q2 equivalents of Depo Provera ® (medroxyprogesterone acetate, MPA)

Five formulations (FA, FB, FC, FD, and FE) Q1Q2 equivalent to Depo Provera® were prepared.



Female NewZealand White Rabbit

Injection of MPA suspensions



RESULTS

The mean particle size Depo Provera® and its Q1Q2 equivalents: FA~11 µm, FB~25 µm, FC~11 µm, FD~ 5µm, FE~ 5 µm, Depo Provera® ~13 µm

TGA analysis

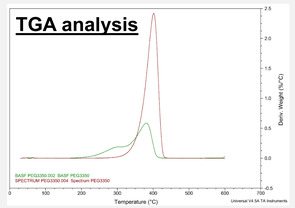


Figure 2: Graphical representation of thermogravimetric derivative curves of Spectrum Chemical and BASF PEG3350

Thermal analysis revealed a broad derivative peak for BASF PEG3350 and a narrower peak for Spectrum Chemical PEG3350, indicating greater heterogeneity in the BASF polymer likely due to variations in chain length or the presence of residual monomers.

Molecular fraction analysis

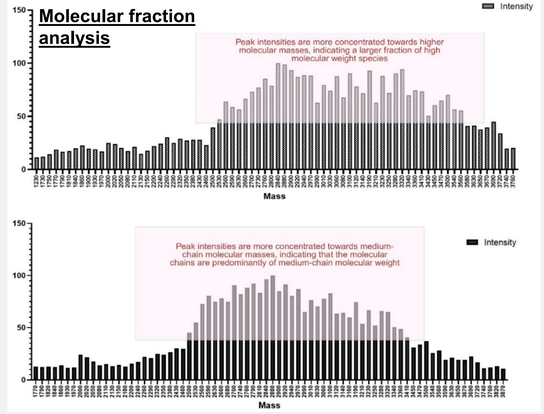


Figure 3: LCMS molecular fraction analysis of PEG3350 polymer from Spectrum Chemical (top panel) and BASF (bottom panel). Data generated using UNIDEC deconvolution tool.

GPC analysis

Polymer	Mn	Mw
Spectrum Chemical PEG3350	3111	3558
BASF PEG3350	3010	3113

Mn= number average molecular weight
Mw= weighted average molecular weight

- Gel permeation chromatography (GPC) showed differences in the weight-average molecular weight (Mw) between the two PEG3350 sources
- Liquid chromatography-mass spectrometry (LC-MS) analysis revealed that BASF PEG3350 contained a lower proportion of high molecular weight polymeric chains compared to the Spectrum PEG3350

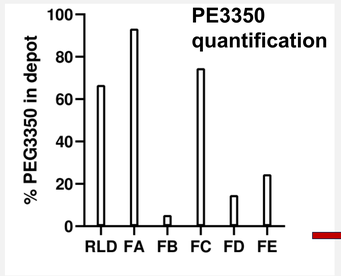


Figure 6: Percentage of PEG3350 remaining in depots removed 14-days post intramuscular injection

- FA and FC retained ~95% and ~78% of, indicating good particle polymer association.
- FB could have lower retention due to larger particles and reduced surface area.
- FD and FE could have lower retention as particle–particle interactions may outweigh particle–polymer interactions despite their smaller size.

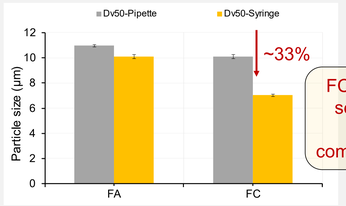


Figure 4: mean particle size after introducing suspensions into the particle sizing well using pipette or syringe. (All data are presented as mean ± SD, n = 3).

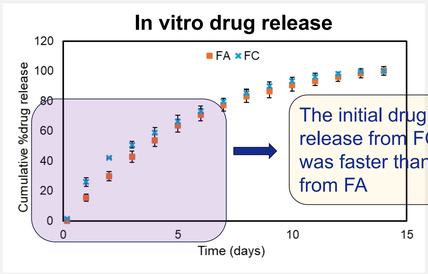


Figure 5: In vitro drug release for formulation FA and FC performed using a novel adapter with USP apparatus type-IV. (All data are presented as mean ± SD, n = 3).

Gross examination

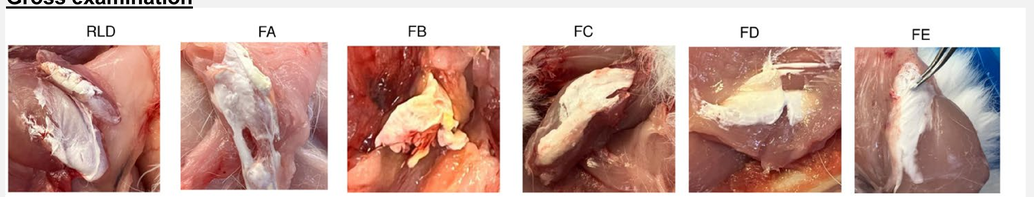


Figure 7: Gross appearance of depots retrieved from rabbit quadriceps muscles 14 days post-injection

Histopathology

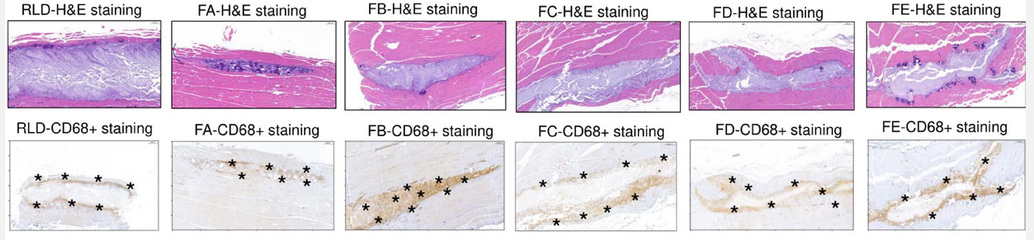


Figure 8: H&E and CD68+ stain of tissue exposed to Depo Provera® and its Q1Q2 equivalents, (*) indicates the area of macrophages recruitment

Histological evaluation indicated that

- FA and FC, containing higher PEG levels, could have promoted osmotic water retention, resulting in a hydrated, gel-like matrix. This structure probably slowed immune cell migration into the depot, confining the inflammatory response to the surface. FD and FE, with smaller particle sizes, also exhibited surface-localized inflammatory infiltration, which could be attributed to a compact depot structure that restricted immune cell entry.
- FB, which contained larger MPA particles, showed inflammatory cell presence both at the surface and within the core of the depot.

CONCLUSION

This study demonstrates that

- PEG polymers are a critical material attribute in the formulation development of LAI suspensions
- Manufacturing differences can lead to variations in the molecular composition of PEG, which in turn may influence particle–polymer interactions and result in subtle differences in *in vitro* drug release.
- Particle characteristics appear to affect PEG retention at the depot site, which may subsequently influence depot morphology and the extent of the local inflammatory response

FUNDING

The project was funded by a contract from the U.S. Food and Drug Administration (Contract # 75F40121C00133). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.

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