In situ forming implants: the effect of drug-polymer-solvent interplay on depot behavior

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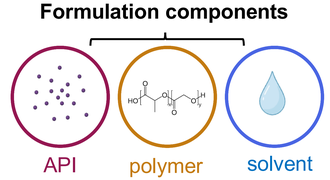
PURPOSE

Few studies have explored the critical interplay between drug, polymer, and solvent in shaping *in situ* forming implant (ISFI) behavior. This relationship is difficult to characterize due to the complex formation and release mechanisms of ISFIs. In this work, we highlight how this interplay influences implant performance using risperidone and paliperidone as model APIs. Their nearly identical structures—differing only by an added hydroxyl group in paliperidone—enable a unique comparison, as risperidone lacks hydrogen bond donors while paliperidone has one.

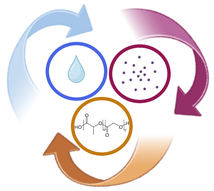
OBJECTIVE

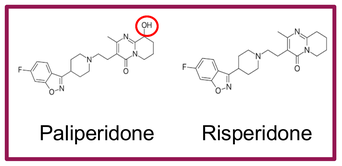
- To investigate the role of **API–polymer–solvent interplay** on implant behavior, focusing on **degradation and erosion** patterns over time, **Tg** changes and visualizing **API-polymer-solvent interactions**.

Formulation components



N-methyl pyrrolidone (NMP)





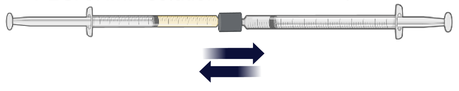
How do formulation interactions impact formulation behavior?

METHODS

Formulation preparation:

Syringe 1: PLGA/NMP solution

Syringe 2: API powder



Mixing: push contents back and forth to obtain homogeneous suspension.

- Reversed phase high performance chromatography (HPLC)
- Gel permeation chromatography (GPC)
- Scanning electron microscopy (SEM)
- Polarized light microscopy (PLM)
- Laser scanning confocal microscopy (LSCM)
- Differential scanning calorimetry (DSC)

RESULTS

Distinct particle morphology

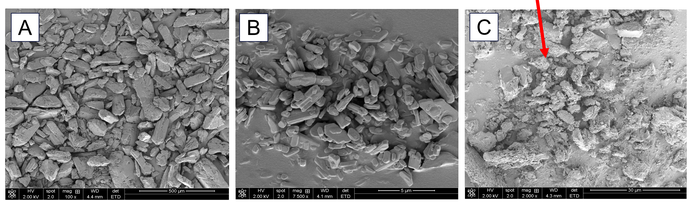


Figure 1: *SEM images of raw risperidone (A), milled risperidone (B) and raw paliperidone (C).*

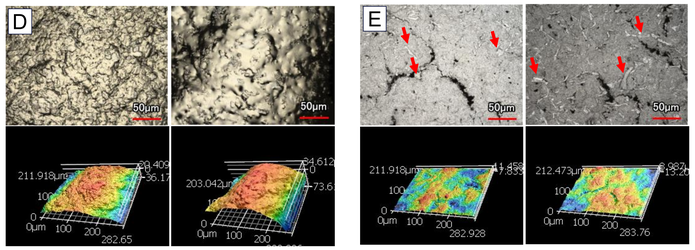


Figure 2*: Laser surface scans of paliperidone implants from Day 1 (D) and Day 20 (E), where paliperidone appears to become integrated into the PLGA matrix (red arrows).*

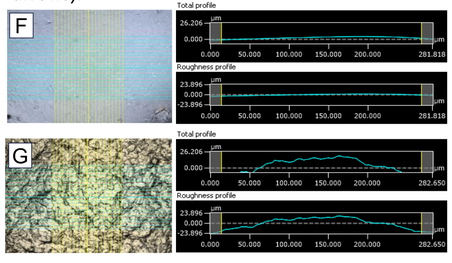


Figure 3*: Implants surface roughness analysis of paliperidone implant reveals a distinct bumpy morphology (F) as compared to risperidone loaded implants and non-drug loaded implants (G).*

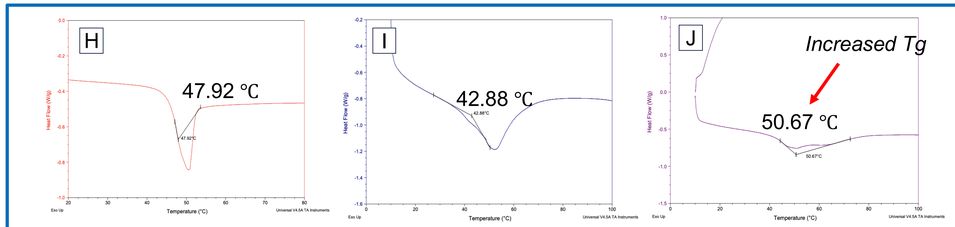


Figure 4: *DSC thermograms and Tg onset temperatures for raw PLGA (H), risperidone loaded implant (Day 20) (I), and paliperidone loaded implant (Day 20) (J), (from left to right).*

Water uptake remains same overtime

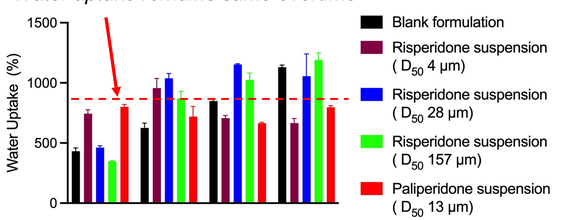


Figure 5*: Implant water uptake % (Day 1- Day 30).*

Degradation behavior is ~ to blank implant

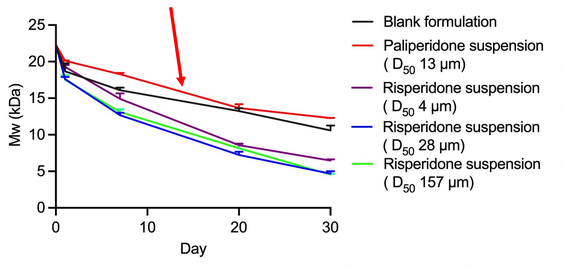


Figure 6*: Implant PLGA degradation % (Day 1- Day 30).*

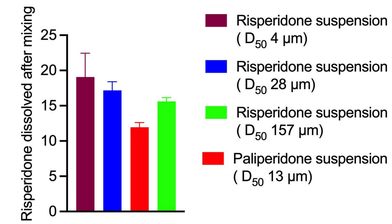


Figure 7*: % of risperidone/paliperidone dissolved after mixing.*

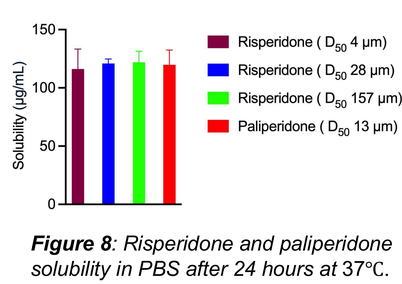


Figure 8*: Risperidone and paliperidone solubility in PBS after 24 hours at 37°C.*

CONCLUSIONS

- Paliperidone **had comparable PLGA degradation to the blank implant** as compared to **risperidone which accelerated it**.
- Paliperidone-polymer interactions increased the **Tg of the implant,** whereas **risperidone decreased the Tg.**
- These findings align with previous work demonstrating that **APIs with more hydrogen bond donor/acceptor groups** result in slower ISFI release rates.
- Laser scanning confocal microscopy (LSCM) enabled visualization of API-Polymer interactions.

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