Characterizing Long-acting Injectable Through Innovative Dissolution Testing Methods

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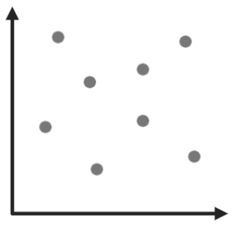
BACKGROUND

CHALLENGES IN LONG-ACTING INJECTABLES DISSOLUTION

Figure 1. Membrane clogging[1]

Typically evaluated with a dialysis setup, **membrane clogging** results in **restricted drug diffusion** and **compromised reproducibility**[2]



Difficulty in establishing IVIVC/IVIVR due to complex drug release kinetics[3]

MITIGATIONS

Modified dissolution platforms have been developed to overcome the challenges

	Dispersion Releaser [2,4,5] 	BioJect™ System [6,7] 
Primary Compendial System	USP Apparatus II	USP Apparatus IV
Underlying Mechanism	**Dialysis-based**, with stirring	**Perfusion-based flow** through a customizable physical biomatrix
Key Advantages	• Controlled shear forces via internal and external paddle stirrers • Provides **enhanced membrane transport** and **improved reproducibility** • Focused on colloidal/liquid dispersion mechanics	• Continuous laminar flow rates • **Mimics subcutaneous tissue** and **mechanical tissue resistance** through customizable biomatrix • Offers biorelevant dissolution conditions to enhance biopredictiveness

OBJECTIVES

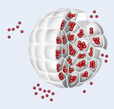
Evaluate and Compare Advanced Dissolution Systems

Assess the **technical capabilities** of the Dispersion Releaser and BioJect™ System in overcoming conventional artifact limits, parallel to their **analytical sensitivity** and **formulation-discriminating power**

MATERIALS & METHODS

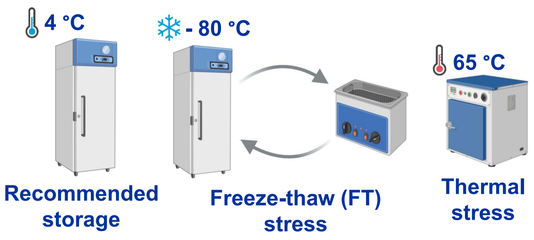
MODEL DRUG PRODUCT

EXPAREL®



A **long-acting** non-opioid **multivesicular liposomal (MVL)** bupivacaine formulation designed for prolonged analgesia effect of up to 72 hours post-surgery, often administered subcutaneously[8,9]

24 H SAMPLE INCUBATION



A vial of EXPAREL® was incubated under each specified storage conditions for 24 hours before characterization

CHARACTERIZATION

Dissolution

USP Apparatus II

300 kDa MWCO cellulose ester membrane

USP Apparatus IV

3 % (w/w) agarose biomatrix

Microscopy

Performed immediately following 24 h sample incubation

Particle Size Distribution

Measured at selected timepoints using a wet module

RESULTS & DISCUSSION

MICROSCOPY

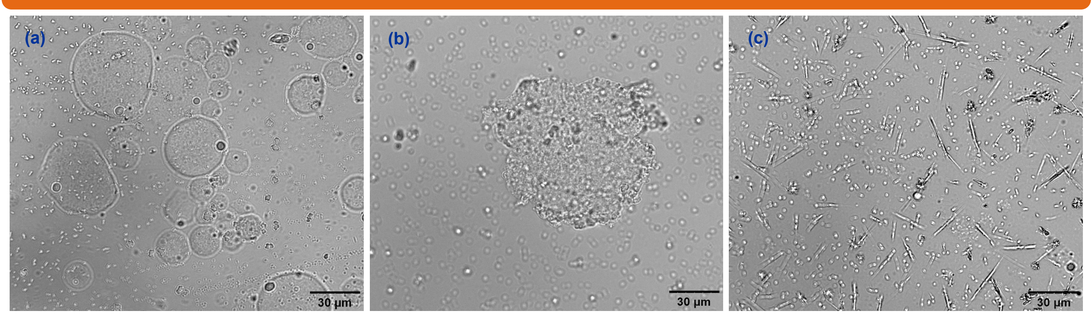


Figure 2. Impact of thermal and physical stress on the structural integrity of EXPAREL® MVLs.

(a) 4 °C formulation (b) 65 °C formulation (c) FT formulation

- **Control Group (4 °C):** Maintained a **well-defined, largely intact** liposomal morphology over 24 hours under recommended storage conditions
- **Thermal Stress:** Significant **liposomal rupture** followed by **aggregation** observed
- **Freeze-thaw Stress:** Extensive structural disruption, yielding **fractured liposomal fragments**, alongside observation of **drug recrystallisation**

PARTICLE SIZE DISTRIBUTION

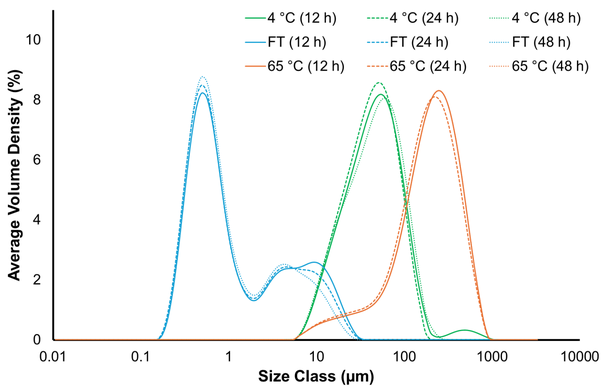


Figure 3. Particle size distribution (PSD) of EXPAREL® following exposure to the different stress conditions.

- **Control Group (4 °C):** Maintained a median particle diameter (d_{50}) of **45 µm** under recommended conditions
- **FT Stress:** Exhibited extensive structural breakdown, with a marked reduction of the median particle size down to **0.773 µm**
- **Thermal Stress:** Induced severe particle agglomeration, increasing the d_{50} value to **198 µm**

DISSOLUTION

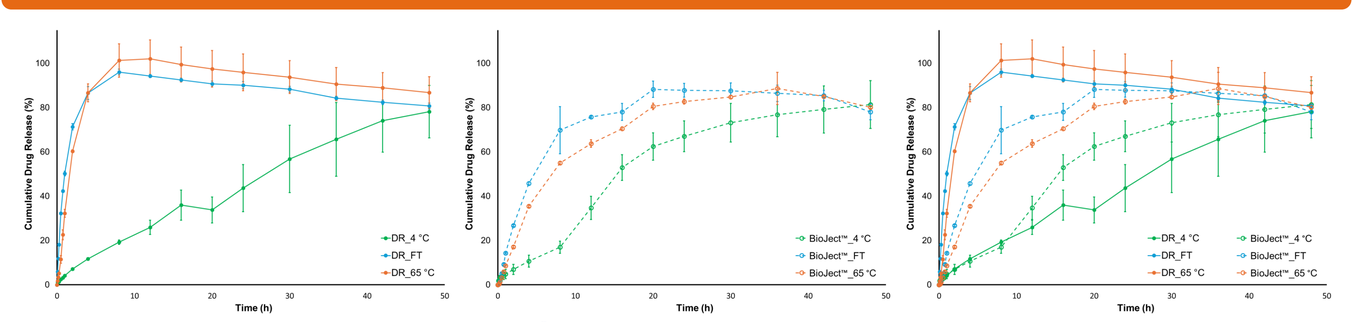


Figure 4. In vitro release profiles of EXPAREL® under distinct stress conditions across different testing platforms (n=3).

Formulation release kinetics of EXPAREL® using (a) the Dispersion Releaser and (b) the BioJect™ system. (c) Comparative drug release profiles of Dispersion Releaser and BioJect™.

- **Baseline Stability:** Under 4 °C, the formulation exhibited **controlled, sustained release** over 48 hours
- **Stress-induced Destabilization:** FT cycling and thermal stress induced an **immediate, accelerated burst release**
- **Kinetic Discrimination:** Both systems **successfully differentiated distinct drug release kinetics** between intact and compromised formulations

Comparing Dispersion Releaser (DR) and BioJect™				
Reference (DR)	**Test (BioJect™)**	**Difference Factor (f_1)**	**Similarity Factor (f_2)**	**Verdict**
4 °C		26.42	47.24	Dissolution profiles are **statistically dissimilar** across all incubation conditions between the two tested platforms
FT		67.62	26.09	
65 °C		67.82	29.20	

Accelerated release in DR suggests the formulation is **sensitive to environmental fluid dynamics**, with dissolution **primarily driven by mechanical shear and matrix erosion** rather than passive diffusion

Comparing Between Incubation Conditions				
DR				
Reference	**Test**	**f_1**	**f_2**	**Verdict**
4 °C	**FT**	892.07	18.38	**Statistically dissimilar** profiles, with an anomalous f_1 (>100)
4 °C	**65 °C**	596.34	22.87	
BioJect™				
Reference	**Test**	**f_1**	**f_2**	**Verdict**
4 °C	**FT**	108.03	30.04	**Statistically dissimilar** profiles across all incubation conditions
4 °C	**65 °C**	51.27	36.57	

4 °C vs FT/65 °C

FT/65 °C exposure **compromised liposomal structures**, causing **immediate dose-dumping** and statistical dissimilarity to 4 °C controls

SUMMARY

KEY FINDINGS

- **Structure-Function Correlation:** Liposomal structural integrity directly dictates in vitro dissolution kinetics, as corroborated by morphological and particle size distribution data
- **Analytical Capability:** Both the Dispersion Releaser and BioJect™ platforms can effectively differentiate intact from compromised formulations
  - Dispersion Releaser offers accelerated, time-efficient formulation discrimination
  - BioJect™ system provides higher resolution analytical discrimination between formulations

LIMITATIONS

- **Batch Limitations:** Evaluation restricted to a single EXPAREL® lot, overlooking potential inter-batch variability
- **System Specificity:** MVL mechanisms are not extrapolative to alternative drug delivery systems (e.g., polymeric matrices)
- **Temporal Gaps:** Microscopy was performed only at T_0, failing to account for any morphological changes over the course of dissolution

FUTURE WORK

- **Batch Expansion:** Evaluate multiple independent production lots of EXPAREL® to heighten statistical robustness
- **Matrix Diversification:** Investigate Dispersion Releaser and BioJect™ across a wider array of complex drug delivery systems matrices
- **Temporal Imaging:** Perform time-resolved microscopy at selected timepoints aligned with PSD timepoints, allowing for monitoring of MVL structural transitions over the dissolution period

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