Long-Acting PLGA–Phospholipid Hybrid Oleogel *In Situ* Forming Implant for Once-Monthly Co-Delivery of Donepezil and Memantine

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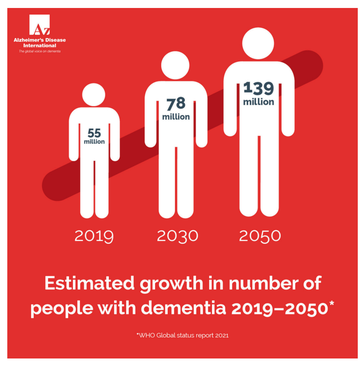
Introduction

- Alzheimer's disease (AD) is a continuous deterioration of cognitive function and memory [1]
- "Senile dementia"
- ~70% due to AD.
- Average survival: ~8 years after symptoms.

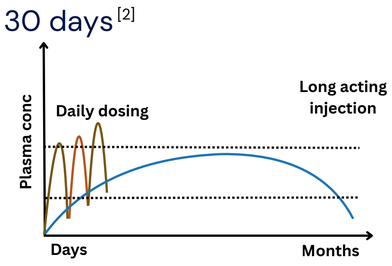


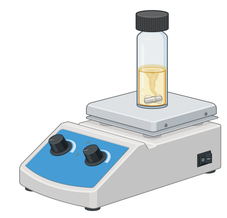
Research gap

- Multiple dosing
- Fluctuations in plasma concentration
- First pass metabolism along with side effects
- Difficulty in swallowing tablets or capsules by elderly patients

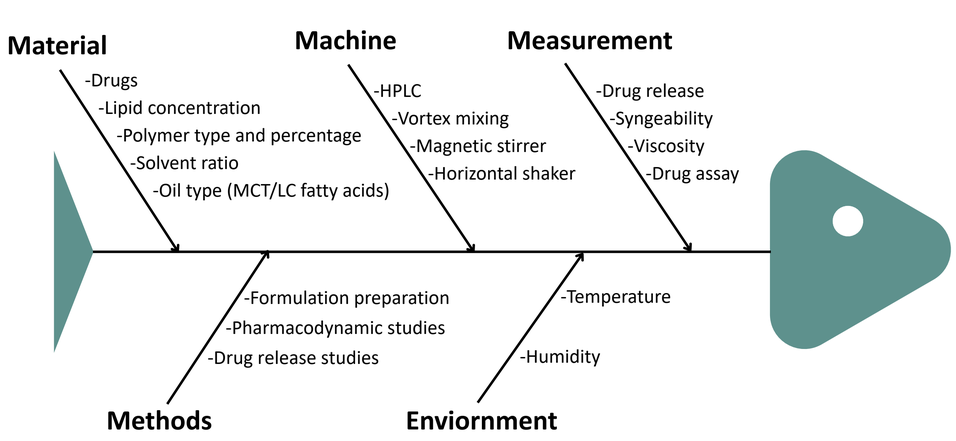
Aim & Hypothesis

To develop and characterize a biocompatible *in-situ* gel formulation capable of forming a stable depot after injection and providing sustained drug release for at least 30 days [2]





Methodology



Preparation of ISFI

- Different oils, lipids, polymers, and solvents were screened.
- The formulation showed no color change, no change in consistency, and no pH or odour change over time.

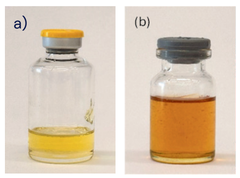


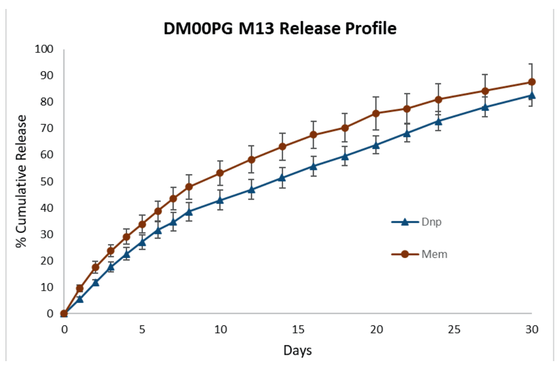
Fig: Visual appearance of the optimized (DM00PG-M13) in situ forming implant (a) blank matrix, and (b) matrix co-loaded with donepezil and memantine.

Component	Function
Donepezil	API
Memantine	API
Lipoid S100	Phospholipid Matrix Core
PLGA 50:50	Release Modifier / Polymer
Sesame oil	Oleogel Base Modifier
α-Tocopherol	Antioxidant Additive
NMP	Hydrophilic Co-solvent
Benzyl benzoate (BB)	Hydrophobic Co-solvent

Results & Discussion

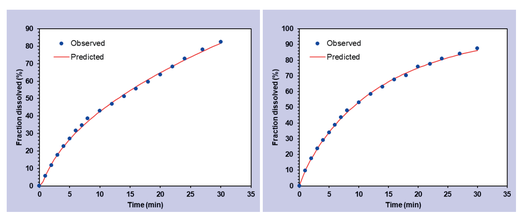
In vitro release studies & Mathematical modeling

- Minimal initial burst release: 5.69 % (Dnp) and 9.59 % (Mem)
- Sustained release over 30 days: 82.58 % (Dnp) and 87.61 % (Mem)
- Minimal burst and sustained release for 30 days



	Parameters	Adjusted R^2	AIC	n
Drug A	Zero-order	0.8798	138.5931	
	First Order	0.9912	89.0264	
	Higuchi	0.9701	112.1796	
	Korsmeyer-Peppas	0.9957	76.0550	0.637
	Hixson-Crowell	0.9773	106.8918	
	Peppas-Sahlin	0.9984	58.2455	
	Weibull-lag	0.9940	83.4055	
	Makoid–Banakar	0.9966	72.4593	
	Hopfenberg	0.9906	91.0640	
	Baker–Lonsdale	0.9312	128.0001	
Drug B	Zero-order	0.7473	155.3722	
	First Order	0.9902	93.6105	
	Higuchi	0.9882	97.1755	
	Korsmeyer-Peppas	0.9905	93.9177	0.540
	Hixson-Crowell	0.9604	120.1433	
	Peppas-Sahlin	0.9988	55.2201	
	Weibull with lag	0.9991	50.2995	
	Makoid–Banakar	0.9989	52.9465	
	Hopfenberg	0.9896	95.6356	
	Baker–Lonsdale	0.9605	120.0861	

- For Dnp, the best-fit model was Peppas-Sahlin[3]
- For Mem, the best fit model was Weibull-lag[4]



Ex Vivo Release studies

- The day 1 release showed 6.7% (Dnp) and 8.6% (Mem).
- The cumulative release from the tissue was approx 16% and 25% for Dnp and Mem, respectively.

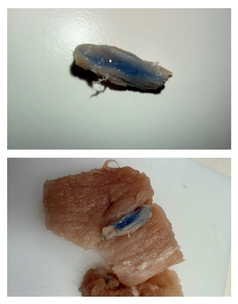
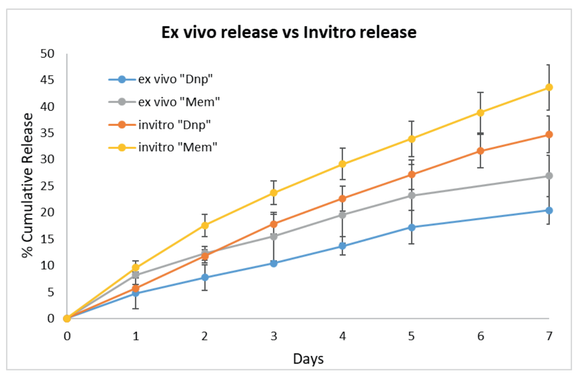


Fig: Visual appearance of depot formation of the optimized (DM00PG-M13) in Porcine muscle

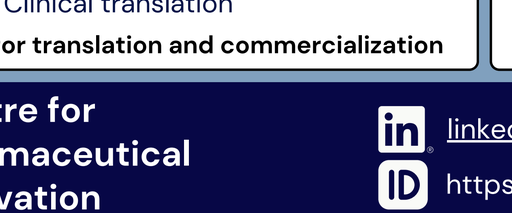


Syringeability

- The injection force: <11 N.
- Using 22 G: optimal injectability for IM administration.

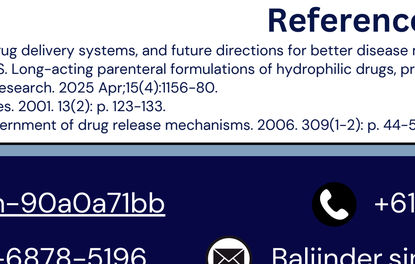
Viscosity

- Constant viscosity (0.20–0.22 Pa·s) across shear rates (100–1000 s^{-1}) at 20 °C from 22 G needle.



Cell Cytotoxicity Assay

- Cell viability above 70.0% (ISO 10993-5 regulatory guidelines)
- DM00PG-M13 depot possesses excellent biocompatibility and safety profiles.



Invitro exvivo correlation

- Correlation for Dnp release showed R^2 = 0.9924
- Correlation for Mem release showed R^2 = 0.9887

Provisional Patent filled

2026904410: Compositions with lipid component for in situ implant formation

Invention title	Compositions with lipid component for in situ implant formation
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Agent name	FPA Patent Attorneys Pty Ltd
Address for legal service	Level 19, South Tower 80 Collins Street Melbourne VIC 3000 Australia
Filing date	07-May-2026

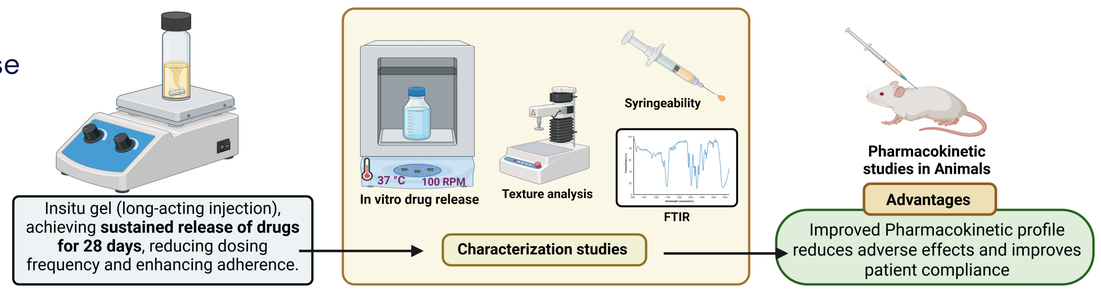
Future directions

Pharmacokinetic evaluation
Preclinical efficacy studies
Scale-up and GMP manufacturing
Clinical translation

Seeking industry and academic partners for translation and commercialization

Conclusions

- ✓ Injectable in situ gel platform
- ✓ Minimal burst release
- ✓ 30-day sustained delivery
- ✓ Improved patient compliance



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2. Nakmode DD, Singh B, Abdella S, Song Y, Garg S. Long-acting parenteral formulations of hydrophilic drugs, proteins, and peptide therapeutics: mechanisms, challenges, and therapeutic benefits with a focus on technologies. Drug Delivery and Translational Research. 2025 Apr;15(4):1156-80.
3. Modeling and comparison of dissolution profiles. 2001. 13(2): p. 123-133.
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