M0930-08-50

# Design, development, and evaluation of novel extended-release liposomal topical cream formulation of Pregabalin using microemulsion technique for the treatment of local neuropathic pain

Author: Chetan Chure
CONTACT INFORMATION: cchure@cplltd.com
Author Affiliation/Company: CPL, Canada

## PURPOSE

- Neuropathic pain (NP) is defined as a painful condition caused by neurological lesions or diseases. Pregabalin (PG) is the most prescribed drug by physicians for NPS treatment and it is only available in oral dosage forms like tablets, capsules, and solutions.

- To prepare a topical extended-release cream formulation of PG with an advanced liposome approach using a prominent nano-emulsion technique to benefit patients having difficulty in taking oral medication.

## OBJECTIVE

- To identify the processing variable required for achieving a stable liposomal topical formulation by using W/O, O/W, or W/O/W techniques.

- To prepare the liposomes containing topical formulations using available microemulsion techniques (W/O, O/W, or W/O/W) where the PG loaded in the liposomal bilayers (Oil phase) acting as an extended-release source and dissolved PG also in the continuous phase acting as an immediate-release mechanism.

- To evaluate the formulated batches for physical and chemical efficiency.

## METHOD

PG liposomal cream was prepared by using different emulsion techniques and selecting raw materials to form the liposome bilayers. The solubility trials of the PG in different solvent systems such as isopropyl myristate, propylene glycol, glycerin, diethylene glycol, and water were conducted to choose the correct solvent. L-α-phosphatidylcholine (95%) (soy) was used as a phospholipid and cholesterol as a stabilizing agent for the lipids. The cream base forming agents like cetyl alcohol and cetostearyl alcohol was used as a matrix. The different emulsifiers like Myrj S40, Span 80, and Tween 80 were selected for the water in oil (W/O), oil in water (O/W), and water in oil in water (W/O/W) emulsions respectively. Benzyl alcohol was used as a preservative. In all the batches, the oil phase and aqueous phase ingredients were heated to 70-80°C separately, PG was added to the oil and aqueous phase and mixed until dissolved. An emulsifier was added to the oil phase to create a W/OW or O/W emulsion. Both phases were emulsified for the required amount of time and then cooled down under mixing to room temperature (20-25°C). The first batch (F0) and the third batch (F2) were prepared with W/O/W and O/W emulsion techniques respectively, using SILVERSON® L5M-A homogenizer at 10000 RPM. The second batch (F1) was prepared using the W/O/W emulsion technique using MICROFLUIDICS™ M 110P HIGH PRESSURE MICROFLUIDIZER® at 25000 psi pressure and high temperature (50-60°C).

## RESULT(S)

**Table 1 :Critical Quality Attributes (CQAs) of the test experiments**

| Parameters | Batch # F0 | Batch # F1 | Batch # F2 |
|---|---|---|---|
| **Description** | uniform, smooth, and a homogenous white color cream | uniform, smooth, and a homogenous white color cream | uniform, smooth, and a homogenous white color cream |
| **pH** | 6.49 | 6.55 | 6.60 |
| **Morphology** | Round spherical liposomes | Round spherical liposomes | Round spherical liposomes |
| **PG assay** | 102.2% | 93.2% | 100.1% |

**Figure-1: (A-D )The phase separation study photographic images.Figure-1: (E-M). The macromolecular structure of the liposomes was observed using Nikon Eclipse microscope using 10x, 40x, and 100x objective lenses.**

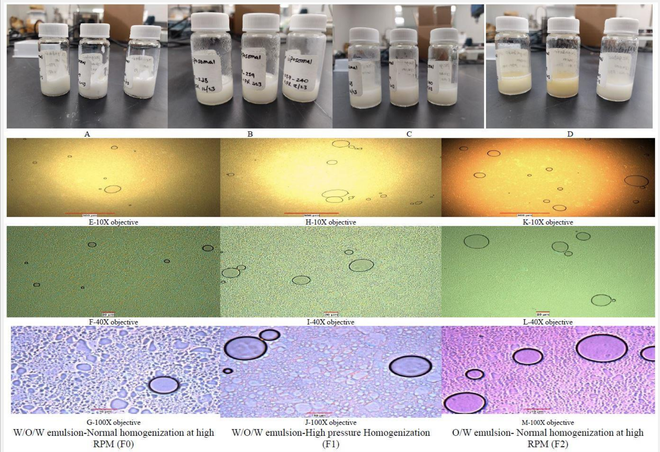



**Figure-2: (N-V). Images observed under the SEM - Quattro S ESEM by Thermoscientific equipment by using Peltier Cold Stage, a wet method at 2-5°C & Pressures between 200-400Pa**

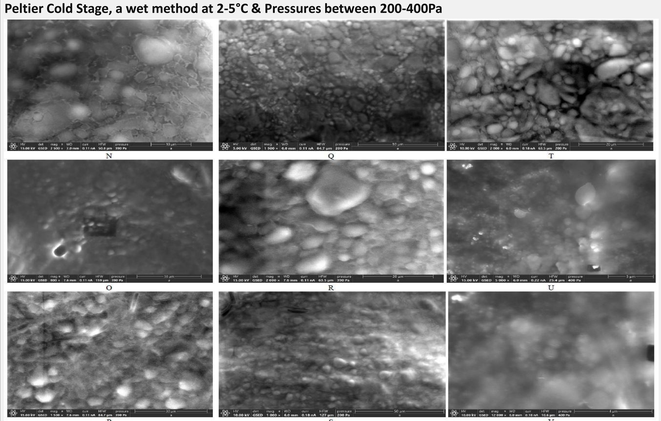



**Table2: IVRT study data of the amount of Active Released per Unit Surface Area(µg/cm²)**

| Vessel# / Time$^{0.5}$ | Amount of Active Released per Unit Surface Area (µg/cm²) | | |
|---|---|---|---|
| | F0 | F1 | F2 |
| **5.48** | 203.88 | 251.07 | 180.51 |
| **7.75** | 311.12 | 378.06 | 277.96 |
| **9.49** | 400.11 | 489.44 | 353.28 |
| **10.95** | 485.33 | 581.93 | 428.37 |
| **13.42** | 609.50 | 706.98 | 563.19 |
| **15.49** | 716.18 | 837.16 | 679.21 |
| **Slope (µg/cm²/time$^{0.5}$)** | 51.64 | 58.42 | 50.06 |
| **$R^2$** | 0.997 | 0.999 | 0.996 |

**Fig 3: IVRT study graph representing the amount of Active Released per Unit Surface Area(µg/cm²)**

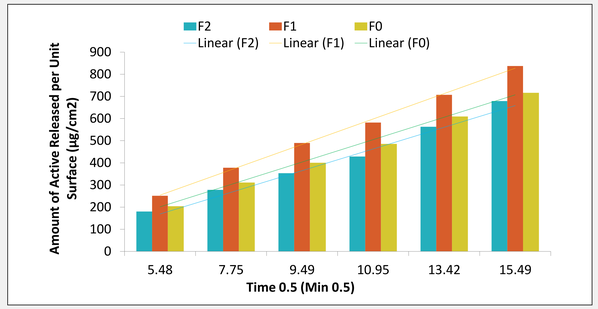
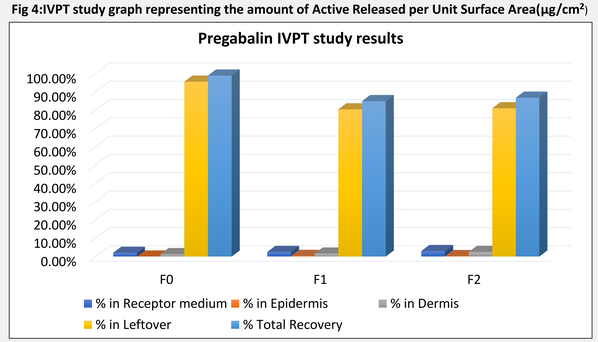



**Table 3: IVPT study data – The amount of Active Released per Unit Surface Area(µg/cm²)**

| % Distribution by Pregabalin | | | |
|---|---|---|---|
| **Analyte** | **Pregabalin** | | |
| **Batch No.** | **F0** | **F1** | **F2** |
| **% in Receptor medium** | 2.03% | 2.51% | 3.01% |
| **% in Epidermis** | 0.00% | 0.35% | 0.24% |
| **% in Dermis** | 1.33% | 1.64% | 2.51% |
| **% in Leftover** | 95.59% | 80.49% | 81.08% |
| **% Total Recovery** | 98.95% | 84.98% | 86.84% |

**Fig 4:IVPT study graph representing the amount of Active Released per Unit Surface Area(µg/cm²)**




## CONCLUSION(S)

- F1 formulation prepared using a microfluidizer showed better IVRT results than the F0 & F2 of Silverson homogenizer.
- F1 formulation IVPT result showed comparatively better skin distribution than F0 & F2 formulations.
- The prepared formulations were optimized with physicochemical characteristics and maintained stability for 5 days under stress conditions.
- IVRT and IVPT results indicate a successful novel – extended-release PG liposomal topical cream formulation.

This study entails a promising alternative to the oral formulations of PG for reducing NP treatment in adults.

## REFERENCES

1] Mitsikostas D, Moka E, Orrillo E, et al. (2022). Neuropathic Pain in Neurologic Disorders: A Narrative Review. Cureus 14(2): e22419. doi:10.7759/cureus.22419

[2] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

[3] Wang, J., Zhang, L., Chi, H., & Wang, S. (2016). An alternative choice of lidocaine-loaded liposomes: lidocaine-loaded lipid-polymer hybrid nanoparticles for local anesthetic therapy. Drug delivery, 23(4), 1254–1260.

[4] J. Wang, A. Shi, D. Agyei and Q. Wang, (2017). Formulation of water-in-oil-in-water (W/O/W) emulsions containing trans-resveratrol. RSC Adv., 7, 35917. DOI: 10.1039/C7RA05945K

## ACKNOWLEDGEMENTS:

We want to thank McMaster University, Canada for providing access to the ESEM in support of this project.