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Development and Optimization of a Patient-Friendly lidocaine Nanoemulgel for Enhanced Skin Permeation

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PURPOSE

The goal of this study was to develop a lidocaine nanoemulgel with enhanced topical delivery performance. Nanoemulgels combine the advantages of nanoemulsions, including improved drug solubilization and skin permeation, with the favorable properties of hydrogels, such as improved skin retention, ease of application, and patient acceptability. Three excipients—Labrasol® ALF, Capryol® 90, and Transcutol® P were selected to develop nanoemulgels given their emulsifying, solubilizing, and permeation-enhancing properties. The optimized nanoemulgels and nanoemulsions were characterized using *in vitro* release testing (IVRT), with a synthetic membrane (Strat-M®) to mimic drug transport across the skin and its release performance was compared with that of a marketed 5% lidocaine gel (Topicaine®).

METHOD(S)

Saturation solubility of lidocaine was determined in select liquid lipid excipients using a validated UHPLC method.

Nanoemulgel preparation: Phase I was prepared by gentle mixing of lipid excipients, Transcutol® P and lidocaine. Gel base (Phase II) was prepared by gradually dispersing Carbopol® 980 NF/ Poloxamer 407 in water using a Turbotest mixer with a four-blade attachment at 500–1000 RPM. Neutralization of Phase II with 5N NaOH was performed for gels with Carbopol 980 NF. Phase I was then slowly incorporated into Phase II under mixing until a homogeneous gel was obtained.

Nanoemulsion preparation: Nanoemulsion were prepared by gently mixing lipid excipients, Transcutol® P, lidocaine and water.

Nanoemulgel/ nanoemulsion characterization: The optimized nanoemulgel formulations (F1 and F2), their respective nanoemulsion formulations and Topicaine® were characterized for their *in vitro* drug release (IVRT) with Strat-M® membrane, as well as appearance.

IVRT testing: Vertical dry heat diffusion cells (Logan Instruments) were used with phosphate buffer saline (pH 7.4) as the receiver media. The study was performed with Strat® M membrane at 32°C using 6 replicates. Sample aliquots were taken at 1, 2, 3, 4, 5, 6, 24, 30, 48, 54, and 72 hours and analyzed using a UHPLC.

RESULT(S)

Capryol® 90, Labrasol® ALF, and Transcutol® P were selected based on the high solubility of lidocaine in it. Labrasol® ALF and Capryol® 90 are self-emulsifying excipients, while Transcutol® P is a well-established skin permeation enhancer (Table 1). A previously constructed ternary phase diagram by Espinoza *et al.* identifying excipient ratios that spontaneously form nanoemulsions upon dilution with water (Figure 1) was used as the basis for nanoemulgel formulation in the present study. Poloxamer 407 and Carbopol® 980 were evaluated as gelling agents. None of the formulations could be successfully gelled using Poloxamer 407, whereas Carbopol® 980 effectively converted most nanoemulsion compositions into stable nanoemulgels, highlighting that selection of an appropriate gelling agent is critical for successful nanoemulgel development. The formulation highlighted in red could not be gelled even with Carbopol® 980, demonstrating that nanoemulsion composition also plays an important role in gel formation. The formulations highlighted in yellow were successfully converted into nanoemulgels using Carbopol® 980. Table 2 summarizes the compositions of the literature formulation, F1 and F2.

Figure 1. Ternary diagram (Water: Capryol® 90: Labrasol® ALF, and Transcutol® P[1:2])

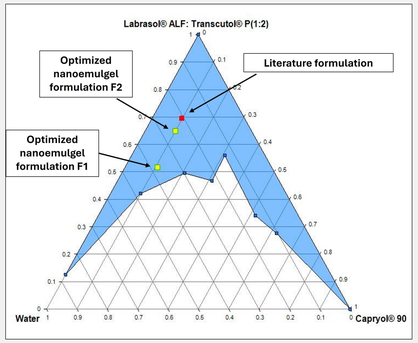


Table 1. Saturation solubility (Conducted at ~25˚C)

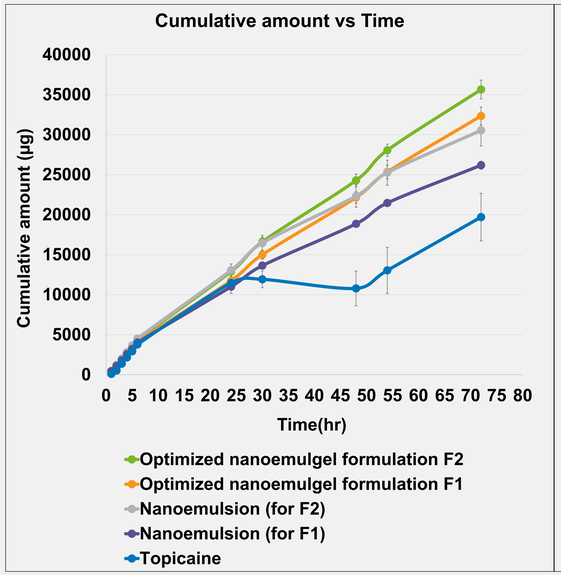
Excipient	Solubility (mg/g)
Capryol® 90	>552.83
Lauroglycol™ 90	471.67
Labrasol® ALF	286.67
Peceol™	388.17
Labrafac™ MC60	539.50
Labrafac™ WL 1349	229.50
Plurol® Oleique CC 497	234.67
Labrafac™ PG	270.00
Transcutol® P	>545.17
Water	4.00

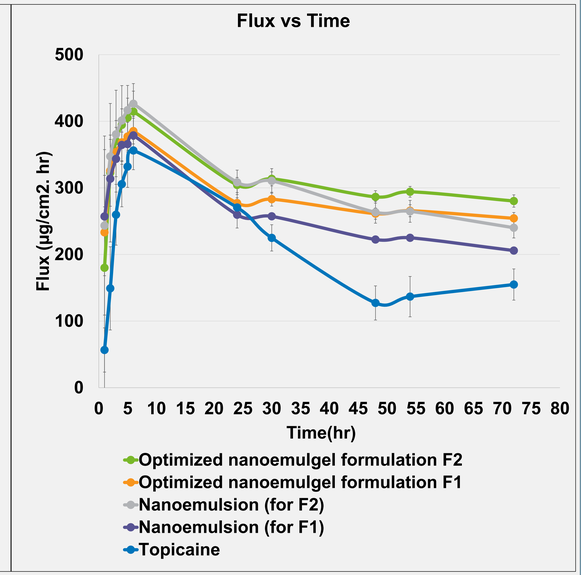
Table 2. Composition of nanoemulgel formulation

Phase	Components	% Composition (w/w)		
		Literature formulation*	Optimized nanoemulgel formulation-F1	Optimized nanoemulgel formulation-F2
I	Lidocaine	-	5.00	5.00
	Capryol® 90	8.00	10.15	9.30
	Labrasol® ALF	19.00	16.17	20.15
	Transcutol® P	38.00	32.34	40.30
II	Water	17.00	35.34	23.25
	Poloxamer 407/ Carbopol® 980 NF	18.00	0.50	1.00
	5N NaOH	-	0.50	1.00

*Literature formulation used Poloxamer 407

Figure 2. IVRT profiles for F1, F2, respective nanoemulsions and Topicaine® : (A) Cumulative amount released vs time (B) Flux vs time (5% lidocaine, n=6, Franz diffusion cells, Media : Phosphate buffer 7.4 pH, Strat-M® membrane, Temp: 32°C)





IVRT results (Figure 2) are presented as cumulative lidocaine release and flux over time. The cumulative release profiles showed comparable release among the formulations during the initial 6 hours. Thereafter, the optimized nanoemulgels and their corresponding nanoemulsions demonstrated greater cumulative lidocaine release than Topicaine®. Among the tested formulations, F2 exhibited the highest cumulative release at 72 hours, followed by F1. The nanoemulsions corresponding to F2 and F1, as well as Topicaine® showed the lowest cumulative release. The flux profiles showed an initial increase during the early time points, followed by a gradual decline for all formulations. After approximately 24 hours, both optimized nanoemulgels and their corresponding nanoemulsions maintained higher flux than Topicaine® through 72 hours.

CONCLUSION(S)

- During formulation optimization, excipient proportion was identified as a key factor influencing gel consistency.
- F2 represented the highest nanoemulsion loading that maintained the desired gel consistency, indicating a formulation threshold beyond which higher levels of Labrasol® ALF and Transcutol® P compromised gel viscosity. This highlights the need to balance excipient composition with appropriate gelling-agent.
- Both F1 and F2 nanoemulgels showed higher cumulative lidocaine release than Topicaine® after approximately 24 hours, with F2 demonstrating the highest overall release, potentially due to its higher nanoemulsion content.
- Both nanoemulgels showed release performance comparable to their corresponding nanoemulsions indicating that the nanoemulgel platform can preserve the release characteristics of the nanoemulsion while providing the additional benefits of a gel formulation.
- Overall, nanoemulgels demonstrated promising potential as a topical lidocaine delivery platform, with formulation composition and gel structure playing key roles in performance.

REFERENCE

Espinoza, L. C., Vera-García, R., Silva-Abreu, M., Domènech, Ò., Badia, J., Rodríguez-Lagunas, M. J., Clares, B., & Calpena, A. C. (2020). Topical Pioglitazone Nanoformulation for the Treatment of Atopic Dermatitis: Design, Characterization and Efficacy in Hairless Mouse Model. *Pharmaceutics*, *12*(3), 255. https://doi.org/10.3390/pharmaceutics12030255

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