CENTRAL COMPOSITE DESIGNED APREMILAST LOADED NANOSTRUCTURED LIPID CARRIERS FOR PSORIASIS TREATMENT

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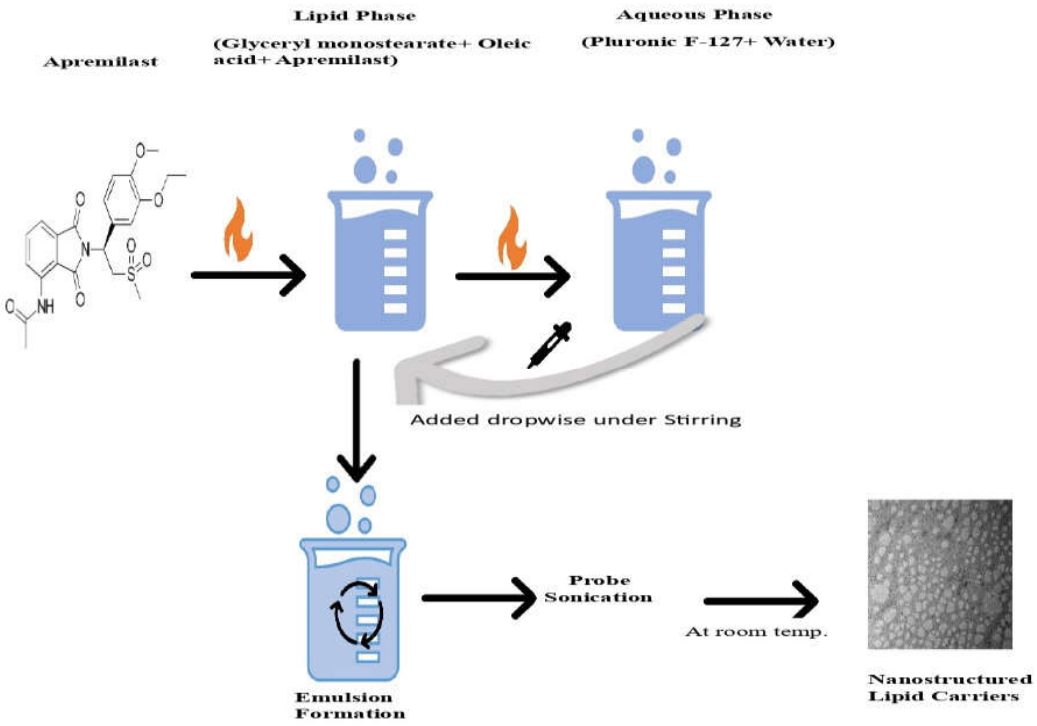
Graphical Abstract



ABSTRACT

Psoriasis is an inflammatory autoimmune disorder of the skin possesses reddened plaques and silvery-scaley patches. Apremilast is phosphodiesterase-4 inhibitor used for psoriasis and psoriasis arthritis. There are solubility constraints which limits its therapeutic effect such as Apremilast cannot be absorbed easily or nor does it dissolve well in water. It's solubility and bioavailability are quite low. To solve this problem NLCs have been prepared by Glyceryl monostearate solid lipid, Oleic acid liquid lipid, Pluronic F-127 as a surfactant using melt emulsification with probe sonication method. Central Composite Design has been used for optimization of critical formulation variables. Effect of two independent variables such as Glyceryl monostearate and Pluronic F-127 was studied on particle size and entrapment efficiency. The particle size was ranged between 179.3 and 242.1 nm while entrapment efficiency ranged from 74.21% to 86%. Two optimized formulations were selected; NLC7 for high entrapment efficiency and NLC8 smaller particle size. FTIR confirmed drug-excipient compatibility and DSC showed drug was well encapsulated in lipid matrix. Zeta potential of both optimized formulation was found to be –16.5mV and be –19.7mV and indicate good stability of the nanostructured lipid carriers due to sufficient repulsive forces preventing aggregation. *In vitro* drug release in pH 6.8 buffer for 24 hr showed sustained release NLC7- 86%, NLC8- 87%, respectively represented prolonged drug availability. For estimation of mechanism of drug release data was fitted to various kinetic models and revealed Higuchi model (r^2 0.9915) indicating diffusion-controlled release of drug from NLCs. TEM images showed smooth surface spherical particles with no aggregation. Overall, Optimized NLCs stable, nanosized and promising for topical delivery of Apremilast in psoriasis treatment.

Keywords: Psoriasis, Apremilast, Central Composite Design, NLCs

INTRODUCTION

Psoriasis is a skin condition characterized by reddened plaques, silvery-scaley patches.[1] It is common among all age group people and it can affect any area, including the knees, scalp, groin, elbows, palms, or the entire body. The exact cause of psoriasis is not known skin cell that grow and excessively quickly are assumed to be the reason but some the known cause of psoriasis are abnormal growth skin cells, immune system problems and genetics. Based on the scales visible on the skin, psoriasis can be divided into different types.[2,9] There are many medications available to treat psoriasis. But none of them is entirely safe and effective in treating the condition without endangering patient compliance. Topical treatment associated with some drawbacks, such as poor drug penetration, higher dose frequency, severe toxicity, and poor patient compliance.[9] Phototherapy and systemic drugs employed in psoriasis treatment is often associated with side effects like hepatic toxicity, nephrotoxic, skin cancers and high blood pressure.[6] Systemic treatments involve drugs such as methotrexate, cyclosporine, and retinoids, but their side effects and long-term toxicity have limited their use. Biological therapies have revolutionized psoriasis treatment, including immune mediators like TNF-α inhibitors, IL-17 inhibitors, and IL-23 inhibitors.[10-12] These drugs are effective but are very expensive and may not be available to every patient. These obstacles restrict the use of existing psoriasis therapies. Old treatments for a psoriasis are not working well at present, so new treatments are needed. When a drug is made through nanotechnology, its solubility, bioavailability and targeting ability are significantly improved. The major focus of nanotechnology is to enhance the drug`s stability, provide slow allowing for continuous release and enhance the drug penetration and absorption in the body. In conventional dosage forms like tablets and capsules the drug does not reach the blood circulation directly or is completely absorbed but nanocarriers helped to resolve this limitations.[13-24]

Nanostructured Lipid Carriers (NLCs) provide targeted delivery of the drug and reduces side effects and increases the effect of the drug. These are modern nanotechnology-based drug delivery system made up of lipid materials and designed to improve bioavailability, drug solubility and targeted delivery. These are used for dermatological treatment like psoriasis, eczema, fungal infections. NLCs preparations consists of two types of lipids - solid lipid and liquid lipid and offered size range of 100-300 nm, this is so small that the drug can be taken into tiers of the skin bypassing the outermost layer of the epidermis. Advantage of the NLCs are better drug loading capacity, improving skin penetration. NLCs are safe with human skin, providing prolonged effect reduces side effect. [15] Apremilast is USFDA approved

phosphodiesterase inhibitor (PDE4) that is used in the medication of moderate-to-severe psoriasis. This drug does not cause any adverse reaction like other anti-psoriasis drugs and apremilast is expected to bring about a change in conditions like psoriasis. Currently, Apremilast is supplied exclusively as an oral tablet branded as Otezla, in doses of 10mg, 20mg, and 30 mg, respectively.[24]

MATERIAL & METHODS

Apremilast was obtained from Glenmark Life Sciences, Gujarat. Glyceryl monostearate and oleic acid acting as the respective solid and liquid lipid components, were obtain from Loba Chemie and Hi Media Laboratories, Mumbai. Pluronic F-127 used as the surfactant was purchased from Sigma-Aldrich, Germany.

EXPERIMENTAL DESIGN

Central Composite Design (CCD) is an experimental design specifically used to find the best combination or optimization of a process. The experiments were carried out using Design Expert software, version 13, developed by Stat-Ease Inc., based in Minneapolis, Minnesota. In this investigation, an experimental design was utilized in which two factors (X_1) Glyceryl monostearate (GMS) and (X_2) Pluronic F-127 were used to find out the effect of both on average particle size and entrapment efficiency. In this design, a polynomial equation and quadratic model were generated (in which $\alpha = 1.414$) to determine the effect of formulation factors, glyceryl monostearate (X1) and Pluronic F-127 (X2), on the particle size and drug entrapment. Total thirteen formulations were prepared (NLC-1-NLC-13).

PREPARATION OF APREMILAST LOADED-NLCs

Apremilast loaded NLCs were designed with CCD and total of 13 formulations were prepared based on the design matrix provided in Table 1. This formulation was developed using the melt emulsification with probe sonication process. Initially solid lipid (GMS) and liquid lipid (Oleic acid) were melted by heating to around 65-70°C then Apremilast (1% w/w) was added and thoroughly mixed (Lipid phase). In a separate beaker the Pluronic F-127 surfactant was dissolved in distilled water and heated up to the same temperature (Aqueous phase). It is critical step to maintain the same temperature of both the phases and then aqueous component was poured slowly to the lipid layer and first high-speed homogenization at 8000 rpm for 5 minutes was done then probe sonication was performed for 10 minutes to reduce the particle size. The prepared NLCs were cooled to room temperature allowed to solidify. [1]

Table 1: Formulations Composition as per Central Composite Design (NLC1-NLC13)

Formulation Code	Glyceryl monostearate (mg) (X_1)	Pluronic F-127 (mg) (X_2)
NLC-1	(-1) 200	(-1) 200
NLC-2	(+1) 300	(-1) 200
NLC-3	(-1) 200	(+1) 500
NLC-4	(+1) 300	(+1) 500
NLC-5	(−α) 179.28	(0) 350
NLC-6	(+α) 320.71	(0) 350
NLC-7	(0) 250	(−α) 137.86
NLC-8	(0) 250	(+α) 562.13
NLC-9	(0) 250	(0) 350
NLC-10	(0) 250	(0) 350
NLC-11	(0) 250	(0) 350
NLC-12	(0) 250	(0) 350
NLC-13	(0) 250	(0) 350

CHARACTERIZATION OF NLCs

Particle Size

Zeta sizer (Nano-ZS90, Malvern Instruments, UK) is used to assess particle size of the developed formulations. This equipment measures the size and size distribution of freshly prepared NLCs. A small portion of the NLCs is dispersed in distilled water to make them easily scannable. Polystyrene cuvette is a special glass/plastic container used ad each sample is scanned in triplicate for accuracy. Z-average value is noted this is an average of the particle sizes based on intensity obtained by the DLS technique.[16]

Entrapment Efficiency

The drug incorporation to NLCs was quantified through the addition of a specific amount of NLCs to methanol to released drug from the lipid matrix. The amount of drug released is checked by UV-spectrophotometer at λ max of Apremilast. After that entrapment efficiency is calculated using equation 1.[17]

Entrapment Efficiency % = (Entrapped drug / Total drug added) × 100 ……Equation 1

Zeta Potential

A Zeta sizer (Nano-ZS90, Malvern Instruments, UK) was employed to evaluate the zeta potential of the optimized Apremilast loaded-NLCs formulation (NLC-7 and NLC-8) (Zeta potential indicates how stable the formulation is, because it serves as a measure of the electrostatic forces preventing particle aggregation. For measurement, a specific quantity of NLCs was dispersed in distilled water and the zeta potential value was measured via electrophoretic mobility. [16]

Percentage Yield

To calculate the percentage yield of NLCs, the actual dry weight of the final NLCs is taken and divided by the weight of the total input, which is the drug and excipients used during formulation.[18] Process efficiency is evaluated using equation 2:

Percentage Yield = (Actual weight of NLCs obtained / Total weight of non-volatile materials used) × 100 …….. Equation 2

Fourier Transform Infrared Spectroscopy [FTIR]

FTIR is the effective analytical method for qualitative investigation of functional groups. FTIR Spectrophotometer ALPHA 2 Burker, Massachusetts, USA apparatus was used to record the FTIR spectrum of Apremilast, physical mixture and Apremilast loaded NLCs using KBR pellets. [19]

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) is the preferred technique for examining the physical state of drugs and excipients, particularly to assess the crystallinity or amorphous nature of the ingredients. The developed batches, physical mixture and Apremilast were subjected to DSC analysis using indium for calibration, the samples were sealed in

aluminium pans and heated from 30 °C to 300 °C under nitrogen flow (60 mL/min), with an empty pan as the reference.[22]

Transmission Electron Microscope [TEM]

The surface properties of NLCs (NLC-7 & NLC-8 Batch) were explored using the electron microscope JEM-100S (JEOL, Tokyo, Japan). NLCs were placed on a copper-coated carbon table before being set onto a wax sheet. After 30 minutes of desiccation, the sample was noted at a boosted voltage of 120 kB.[14]

***In vitro* Drug Release Studies**

In vitro drug release studies of the Apremilast-loaded NLCs were estimated utilizing the dialysis bag diffusion technique (molecular weight cut-off 12,000–14,000 Da; Sigma-Aldrich) Accurately weighed NLC formulations equivalent to 0.1% w/w Apremilast were placed in a dialysis membrane and the ends were tightly sealed. The dialysis bags were then immersed in 100 ml of phosphate buffer (pH 6.8) v/v maintained at 37 ± 1°C, and stirred at 100 rpm using a magnetic stirrer. At predetermined time intervals (0, 0.5, 1, 2, 4, 6, 8, 12 and 24 hrs), 5 ml aliquots were withdrawn from the release medium to keep sink conditions stable and replace with an equal volume of new medium right away. The samples were assessed with a UV-visible spectrophotometer set to 230 nm.[21]

Mechanism of Drug Released

To analyse the mechanism of Apremilast release from prepared NLCs formulations, the *in vitro* release data of the optimized batches NLC-7 and NLC-8 were fitted into mathematical kinetic models including zero-order, first-order, Higuchi square root, and Korsmeyer-Peppas models. The best-fit release kinetics were determined by comparing the correlation coefficients (R^2) from each model. The model with the highest R^2 value was selected as the best fit for the release mechanism of Apremilast from nanostructured lipid carriers.[26]

RESULTS & DISCUSSION

Apremilast loaded-NLCs were effectively developed using melt emulsification and probe sonication method. Both optimized formulations NLC-7 (highest entrapment efficiency) and NLC-8 (smallest particle size) were further evaluated.

Particle Size

The particle sizes of CCD-designed formulations (NLC-1 to NLC-13) are given in Table 2. The particle size ranges from 179.3 -242.1 nm (Figure 1). The smallest particle size (179.3

nm) was observed in batch NLC-8. Concentration of surfactant in this batch was highest; it means more surfactant means better emulsification leads to smaller particles. The effect of formulation variables on the particle size was estimated using contour plots and response surface plot (Figure 2 & 3 Figure 3, respectively) and a polynomial equation (Equation 3)

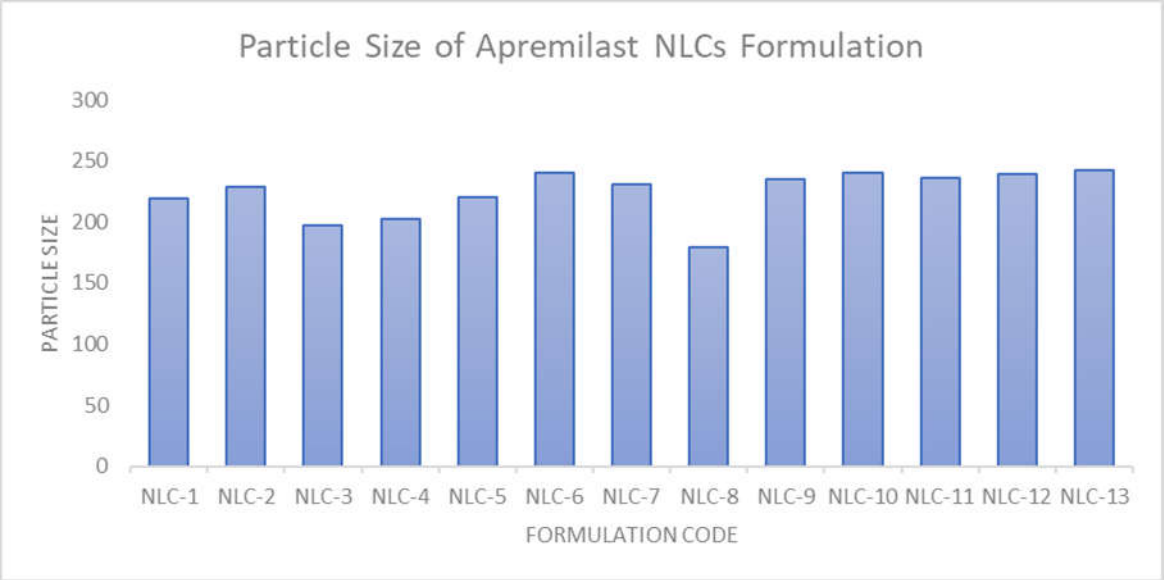


Figure 1: Particle Size of Apremilast Loaded NLCs Formulation

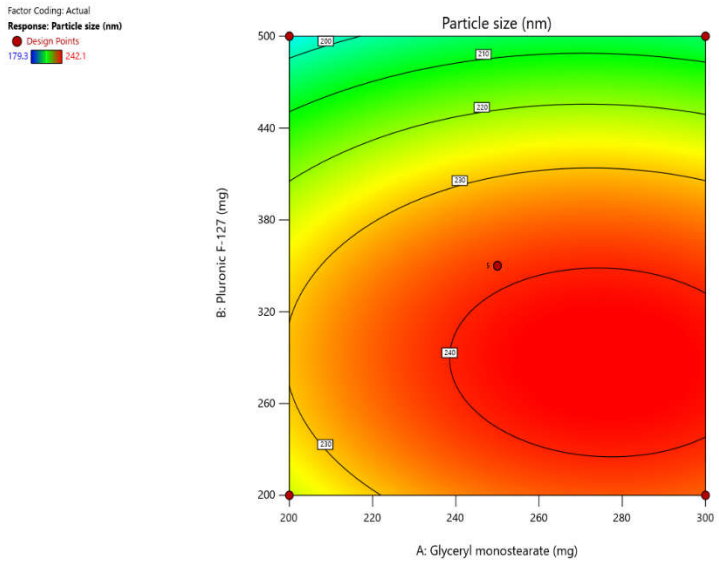


Figure 2: Contour plot of Particle Size

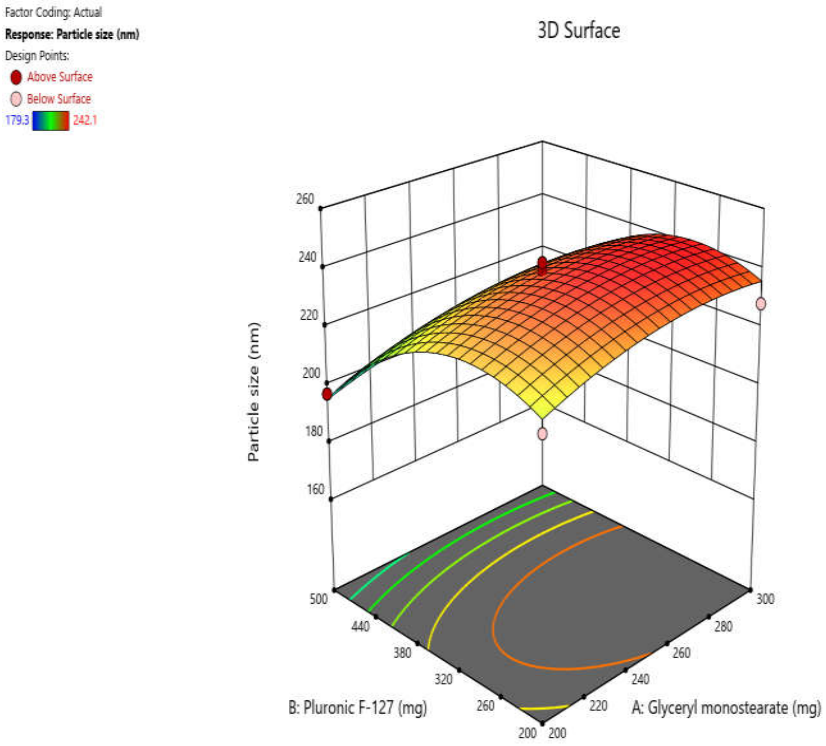


Figure:3 3D Response Surface Plot of Particle Size

The Polynomial equation of particle size:

Particle size = $238.56+5.36\ X_1 - 14.92X_2 - 0.875\ X_1\ X_2 - 5.54\ X_1^2 - 18.27\ X_2^2$…Equation 3

In this effect of Pluronic F-127 is negative it means that increasing Pluronic concentration decreases the particle size whereas Glyceryl Monostearate have positive impact on size. These coefficients indicate that Pluronic F-127 has the greatest effect on the response variables of the formulation, especially in both entrapment efficiency and particle size. Interaction and quadratic terms also make the model accurate.

Entrapment Efficiency

The entrapment efficiency of CCD-designed formulations (NLC-1 to NLC-13) are given in table 2 and Figure 4. Entrapment efficiency was found in the range of 74.21% to 86%. The data exhibited that high entrapment efficiency was observed at higher concentrations of GMS and lower concentrations of Pluronic F-127. This may be attributed to the fact that increased lipid content provides a more stable and extensive lipid matrix and offering better space for drug entrapment. The result of variables on the entrapment efficiency was estimated and

shown in Figure 5 (Contour plot) & Figure 6 (3D response surface) and mathematical equation (Equation 5).

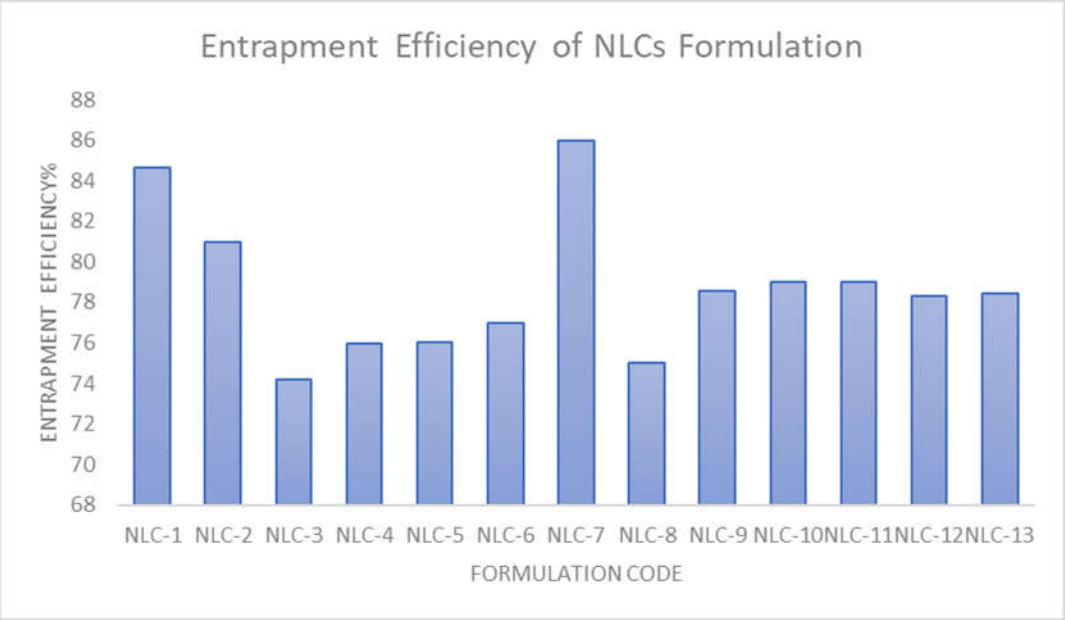


Figure 4: Entrapment Efficiency of Apremilast Loaded NLCs Formulation

The Polynomial equation for Entrapment Efficiency (EE):

$EE = 78.67 - 0.0645\ X_1 - 3.88\ X_2 + 1.36\ X_1 X_2 - 0.9694\ X_1^2 + 1.03\ X_2^2$ Equation 4

Equation depicts the negative effect of Pluronic F-127; it means that more Pluronic decreases drug entrapment efficiency and the effect of Glyceryl Monostearate is slightly less negative.

the response.

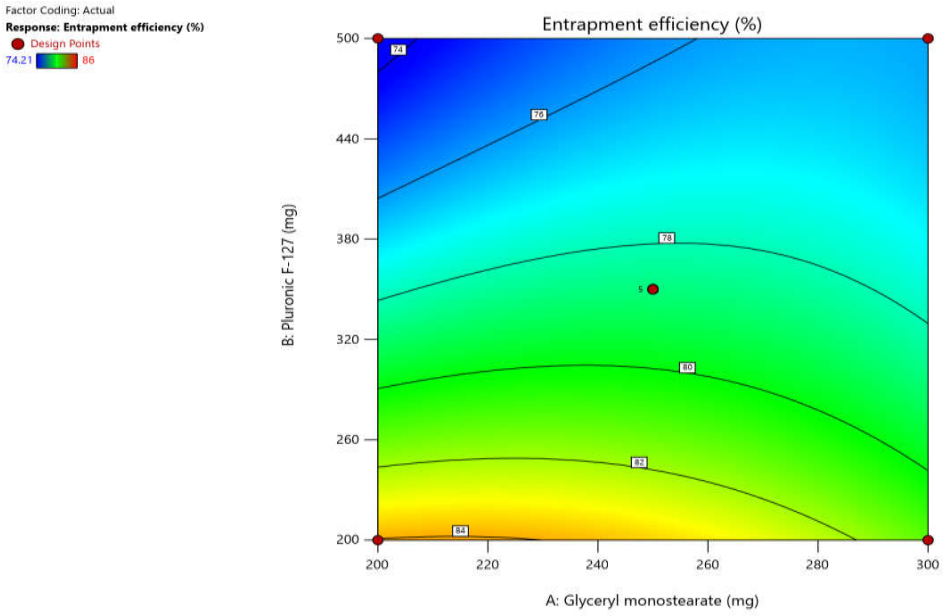


Figure 5: Contour Plot of Entrapment Efficiency

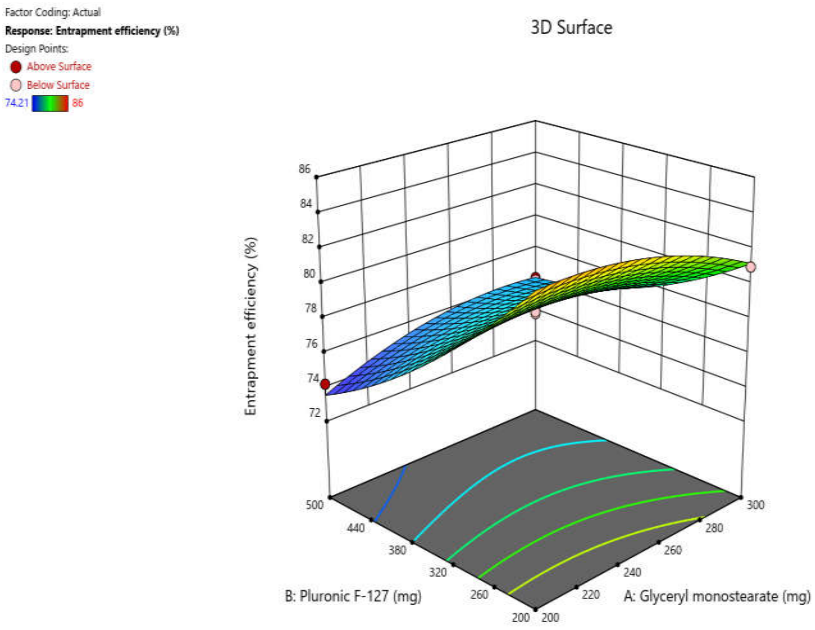


Figure 6: 3D Response Surface Plot of Entrapment Efficiency

Zeta Potential

Formulations NLC-7 and NLC-8 were investigated to zeta potential analysis to predict the stability of the formulated NLCs. Formulations NLC-7 and NLC-8 have negative zeta potential values of -16.5 mV and -19.7 mV, respectively. It indicates stable formulations

Percentage Yield (%)

All the developed formulations were analyzed for percentage yield. The lowest yield was 76.37% (NLC-3) and the highest was 92.30% (NLC-7). Overall, % yield was also good it means the process confirming the effectiveness of the preparation method.

Table 2: Characterization of Apremilast Loaded-NLCs

Formulation	Particle Size(nm)	Entrapment Efficiency (%)	Percentage Yield(%)
NLC-1	219.1	84.68	90.52±0.250
NLC-2	228.3	81.00	85.54±0.205
NLC-3	197.3	74.21	76.37±0.280
NLC-4	203.0	75.96	78.73±0.250
NLC-5	220.4	76.00	78.79±0.246
NLC-6	240.2	77.00	80.14±0.245
NLC-7	230.0	86.00	92.30±0.208
NLC-8	179.3	75.00	77.44±0.215
NLC-9	234.7	78.56	82.25±0.220

NLC-10	240.3	78.99	82.83±0.230
NLC-11	236.2	79.01	82.86±0.225
NLC-12	239.5	78.34	81.95±0.259
NLC-13	242.1	78.45	82.10±0.248

Fourier Transform Infrared Spectroscopy

Compatibility analysis was carried out to examine interactions between Apremilast and used excipients. FTIR peaks of Apremilast as well as Loaded NLCs were shown in table 3. A slight shift was observed in some peaks due to physical interaction with the lipid GMS, oleic acid and surfactant Pluronic F-127 but no peak was missing. This means that no chemical reaction between the drug and excipients and the formulation is completely compatible. This confirms that the drug has been successfully encapsulated in the lipid matrix of the NLCs.

Table 3: FTIR interpretation of drug excipient compatibility

IR Spectrum	**Stretching/Bending**	**Groups**	**Peaks cm^{-1}**
Pure Apremilast	Stretching	O-H	3719.41
	Stretching	O-H	3234.69
	Stretching	C=O	1762.11
	Stretching	C–H	3002.09
	Stretching	C=O	1687.76
	Stretching	C–O/C–O–C	1133.72
Apremilast Loaded-NLCs	Stretching	O–H	3345.80
	Stretching	C–H	3031.51
	Stretching	C–H	2955.92
	Stretching	C–H	2914.44
	Stretching	C=O	1762.11
	Stretching	C=O	1618.39
	Stretching	C–O/C–O–C	1134.68

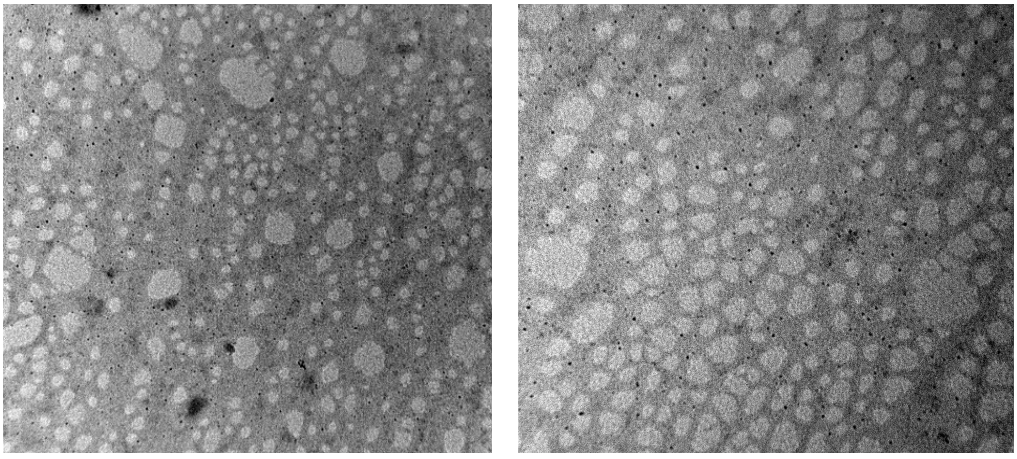
Differential Scanning Calorimetry

To study the thermal properties and compatibility between Apremilast and excipients, DSC investigation was done for pure drug, physical mixture and optimized NLC formulations. The DSC curve of pure Apremilast showed a clear endothermic peak at 155.56°C, which

corresponded to the literature reported melting point of 156.1°C confirming its purity and crystalline nature. Pure GMS showed a distinct melting peak at 61.98°C, which also falls within the standard range of 58–65°C and confirming its high purity and crystalline state. In the physical mixture two peaks were observed at 60.61°C (GMS) and 120.60°C but Apremilast's sharp melting peak was missing. This indicates that the drug may be partially dispersed within the lipid matrix but no strong chemical interaction occurred only minor physical mixing or partial miscibility. The DSC graph of the optimized NLC formulations showed a broad endothermic peak around 60.61°C corresponding to GMS. This clearly suggests that Apremilast is no longer in its crystalline form and has been molecularly dispersed or converted into an amorphous state within the lipid matrix. Its significant no new or extra peaks were observed in the NLC thermogram, highlighting had no chemical interaction or incompatibility among the drug and excipients. Thus, DSC study confirms good thermal compatibility and successful encapsulation of Apremilast in the NLC system.

TEM

The morphology of both the optimized formulations NLC-7 AND NLC-8 was checked by TEM and showed that particles were spherical in form possessing a uniform texture and magnitude. No signs of aggregation were detected (Figure 7).



(a) **(b)**

Figure 8: TEM Images (a)NLC-7 and(b)NLC-8

***In Vitro* Drug Release Studies**

In-vitro drug release of two optimized batches (NLC-7 and NLC-8) was carried out in phosphate buffer (pH 6.8) at 37°C for 24 hours. The cumulative drug release at 24 hours was

observed to be 86% (NLC-7) and 87% (NLC-8), respectively as shown in Figure 8. The release was initially rapid due to the surface associated drug and the drug is encapsulated in the lipid matrix and resulting in a prolonged release profile. The diffused data was fitted to different mathematical models. NLC-7 Showed highest linearity First order (r^2 0.9307) and NLC-8 showed highest linearity with the Higuchi model (r^2 0.9915) indicating diffusion-controlled release.

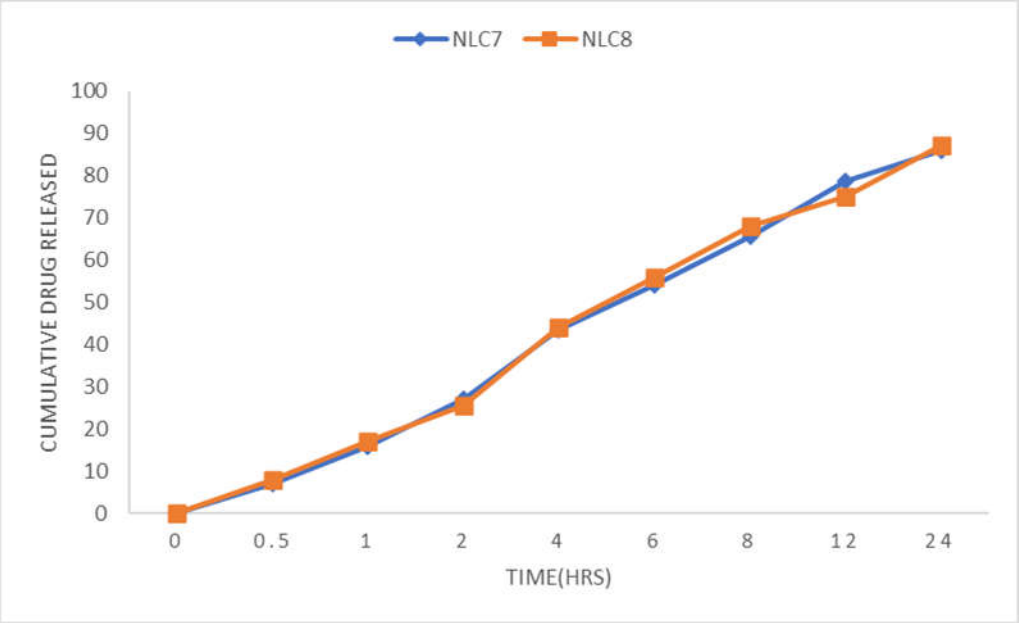


Figure 8: *In vitro* drug release of NLC-7 and NLC-8

CONCLUSION

Apremilast is a promising drug for the treatment of psoriasis but its low solubility and permeability limits its therapeutic effects. To improve bioavailability nanotechnology approach was utilized. In this study, Apremilast-loaded NLCs were prepared using melt emulsification-probe sonication method using solid lipid; liquid lipid and Pluronic F-127 as surfactant. Central Composite Design was employed for formulations optimization, after optimization, the best formulations were selected based on lowest particle size (179.3 nm) and highest entrapment efficiency (86%). Zeta sizer analysis confirmed that the fabrication of nano size particles with good stability. TEM analysis of the optimized formulations revealed spherical and uniformly distributed particles with smooth surfaces. *In vitro* drug release study showed that the formulation showed sustained release up to 24 hours and beneficial for long-term psoriasis management. It was also observed that the batch NLC-8 showed better release and entrapment. NLC-7 Showed highest linearity First order (r^2 0.9307) and NLC-8 showed highest linearity with the Higuchi model (r^2 0.9915) indicating diffusion-controlled release.

REFERENCES

[1] Armstrong and C. Read. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. *JAMA*, 323(19):1945–1960, 2020.

[2] American Academy of Dermatology Association. (2023). *Psoriasis: Types and treatments*. https://www.aad.org/public/diseases/psoriasis/types-treatment.

[3] Beg, S., Sheikh, A. M., Barkat, M. A., & Hussain, T. (2020). Nanostructured lipid carrier (NLC) based topical gel of Apremilast: Formulation, optimization, and evaluation. *Journal of Drug Delivery Science and Technology, 59*, 101847. https://doi.org/10.1016/j.jddst.2020.101847

[4] Bhattacharya, S., & Tiwari, R. (2021). *Formulation and in vitro/in vivo evaluation of Nateglinide-loaded nanostructured lipid carriers*. *BioNanoScience, 15*, 148. https://doi.org/10.1007/s12668-024-01704-6

[5] Eaton, D. J. (2023). *Plaque Psoriasis – Common and localized presentation*. JAD International.

[6] Farmer, Z., & Smith, T. *Phototherapy, oral retinoids, methotrexate, and cyclosporine in psoriasis: drawbacks and monitoring needs. American Family Physician, 93*(9), 725–732. 2013.

[7] Mayo Clinic**.** (2023). *Psoriasis – Symptoms and causes*. Mayo Foundation for Medical Education and Research. https://www.mayoclinic.org/diseases-conditions/psoriasis/symptoms-causes/syc-20355840

[8] Mall, J., Naseem, N., Haider, M. F., Rahman, M. A., Khan, S., & Siddiqui, S. N. (2024). Nanostructured lipid carriers as a drug delivery system: A comprehensive review with therapeutic applications. *Intelligent Pharmacy*. https://doi.org/10.1016/j.ipha.2024.09.005Pharma Excipients

[9] N. Bhatia. Challenges with topical treatments in psoriasis. *HPLC Live*, 2020. National psoriasis Foundation. (2024). *Types of psoriasis*. https://www.psoriasis.org/types

[10] Griffiths CE, Armstrong AW, Gudjonsson JE, Barker JN. Psoriasis. Lancet. 2021;397(10281):1301-1315.

[11] Raychaudhuri, S. K., & Raychaudhuri, S. P. (2014). *Diagnosis and classification of psoriasis*. Autoimmunity Reviews. *(Pustular subtype prevalence/symptoms)* en.wikipedia.org+1ecronicon.net+1

[12] Rodriguez, E., & Jones, H. (2022). *Biologics for psoriasis: efficacy, cost, and access. Journal of Clinical Dermatology, 15*(4), 200–210.

[13] "Pustular psoriasis" entry. (2025, June 5). *Wikipedia*. Retrieved from https://en.wikipedia.org/wiki/Pustular_psoriasis

[14] Sindhoor, S. M., & Koland, M. (2021). *Topical Delivery of Apremilast Loaded*

Nanostructured Lipid Carrier Based Hydrogel for Psoriasis Therapy. *Journal of Pharmaceutical Research International, 33*(28B), 7–20. https://doi.org/10.9734/JPRI/2021/v33i28B31531

[15] Shende, P., & Wagh, R. (2023). *Role of lipid nanoparticle size in dermal drug delivery: a review. International Journal of Pharmaceutics, 558*, 120–134.

[16] Malvern Panalytical. (n.d.). *Malvern Zetasizer Nano ZS90: Particle size and zeta potential analysis using dynamic light scattering.* Shared Research Support Services. Retrieved June 2025, from research facility documentation.

[17] Ivanović, M., Škrinjar, M., & Filipović-Grčić, J. (2017). Formulation & Characterization of Nanostructured Lipid Carriers (NLCs): Entrapment Efficiency Determination. *Journal of Drug Delivery & Therapeutics, 6*(2), 4–13.

[18] LibreTexts. (n.d.). *Theoretical yield and percent yield*. In *Chemistry LibreTexts*. Retrieved June 2025, from Chemistry LibreTexts website.

[19] Esteve, D., Bachiller-Barrón, I., & Rodelas, J. (2023). Evaluation of nanostructured lipid carriers by FTIR spectroscopy: Application to cannabidiol-loaded NLCs. *Food Chemistry, 417*, 135754.

[20] Gaware, N. R., Talele, S., Bendale, A. R., Borse, L. B., & Jadhav, A. G. (2022). *A review on nanostructured lipid carrier*. International Journal of Research in Pharmacy and Pharmaceutical Sciences, 7(2), 61–72

[21] Kazi, K. R., Amran, M. T., & Islam, M. S. (2022). Dialysis bag method for evaluating in vitro drug release of drug-loaded NLCs in phosphate buffer pH 6.8: methanol. *International Journal of Drug Delivery, 14*(3), 213–222.

[22] TA Instruments. (2020). *Optimizing DSC accuracy: impact of aluminum sample pan & lid; DSC purge gas recommendations*. TA Instruments.

[23] Gómez-Lázaro, L., Martín-Sabroso, C., Aparicio-Blanco, J., & Torres-Suárez, A. I. (2024). *Assessment of in vitro release testing methods for colloidal drug carriers: A comparative protocol study*. Pharmaceutics, 16(1), Article 103. https://doi.org/10.3390/pharmaceutics16010103

[24] US Food & Drug Administration. (2014). *FDA approves Otezla (apremilast) for adult patients with plaque psoriasis and psoriatic arthritis.*

[25] Renuka M. Tone, Ganesh N. S., Gopinath E., Ranjitha K. S., & Vineeth Chandy. (2021). *Nanostructured lipid carriers, novel approach for drug delivery: A comprehensive review. International Journal of Pharmaceutical and Phytopharmacological Research, 20*(4), 319–338.

[26] Zhao, Y., & Li, Y. (2025). *Preparation and evaluation of nanostructured lipid carriers for α-tocopherol delivery: in vitro release kinetics. International Journal of Pharmaceutics, 606*, 120867.