

# Nanoemulgel Formulation of Tetrahydrocurcumin with Efficient Anti-inflammatory Effect for the Treatment of Skin Disorders

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## ABSTRACT

**Introduction:** Tetrahydrocurcumin (THC) is a partially reduced white metabolite of curcumin which does not impart yellowish colour on skin due to which it seemed to be a promising topical agent compared to curcumin which discoloured the skin with long lasting visible mark. **Objectives:** The research work was intended to formulate THC loaded Nano Lipid-based (TNL) Carbopol Gum Gel (TNLCG) also called tetrahydro curcumin nanoemulgel and to investigate its therapeutic efficacy against inflammation using animal model. **Materials and Methods:** TNLCG was prepared based on pseudoternary phase-diagram with solubilizing capacity of tocopheryl acetate (10% w/w) and emulsifying combination of tween 80: polyethylene-glycol 400 (2:1 in 35% w/w) in 45% w/w aqueous phase with Carbopol 934 gel base. Selected formulations were evaluated for various parameters using in-house developed HPLC analytical method (at 280nm). **Results:** Nanoemulgel was found to be a stable formulation which significantly improved cellular absorbency with tocopheryl acetate with high concentration of THC for treating skin inflammation. Significant increase in the steady state flux ( $J_{ss}$ ) of  $41\mu\text{g}/\text{cm}^2/\text{h}$ , permeability coefficient ( $K_p$ ) of 1.08 and Enhancement ratio ( $E_r$ ) of 3.7 were observed. The TNLCG demonstrated 77.36% *in vitro* drug release, significant skin permeability and optimal properties including spherical shape with 129nm nanosize, adequate zeta potential (-21.45mV), and PDI value of 0.18. **Conclusion:** This study revealed encouraging outcomes for TNLCG formulation as a novel tool for safe delivery of THC. According to the findings of the preceding research, it can be an effective therapeutic formulation which offers significant inflammation reducing activity with good moisturising quality.

**Keywords:** Tetrahydro-curcumin, Anti-inflammatory, Nanoemulgel, Permeation, Topical-delivery.

**Key messages:** Tetrahydro-Curcumin (THC) loaded Nano Lipid-based (TNL) Carbopol Gum Gel (TNLCG) also called tetrahydro curcumin nanoemulgel was prepared using tocopheryl acetate (10% w/w), tween 80: polyethylene-glycol 400 (2:1 in 35% w/w) in 45% w/w aqueous phase with Carbopol 934 gel base. The prepared formulation was tested for all parameters to check its safety and efficiency.

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## INTRODUCTION

Skin disorders are generally accompanied by chronic inflammatory problems with a complicated pathogenesis and a strong hereditary basis. Some of them are having an immune-mediated systemic illness condition with skin cutaneous component involvement like psoriasis, eczema etc, which affects around 11.43 percent of the general people globally creating it a critical worldwide challenge with around 100 million people affecting globally.<sup>1,2</sup> These disorders can have an adverse effect

on the patient's condition with its development and can cause psychosocial strain. For example, psoriasis is categorized as minor, moderate, or severe. Mild psoriasis causes rashes, and as it progresses to severe, the skin becomes scaly.<sup>3</sup> Because psoriasis is not currently curable, it is critical to regulate and restrict the symptoms of the disease to provide patients with long-term protection, resulting in a normal/usual skin surface.

The expectations and requirements of each individual patient also influences the treatment selection. Mild skin inflammation is usually treated with topical creams and accounts for the majority of sufferers. Phototherapy, systemic therapies, or biological agents such as monoclonal antibodies are often used to treat moderate to severe conditions. According to studies, patients currently do not receive appropriate medicines and are dissatisfied with the usefulness of available drug formulations, as evidenced by



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a higher prevalence of endurance. Since skin inflammatory disorders repeatedly necessitates long-term therapy therefore it should be safe, beneficial, and effective with high aesthetic acceptability. However, there are major gaps in topical therapy in terms of effectiveness and safety.<sup>4</sup> To fill these gaps, we conducted a rigorous study of the literature and find several challenges in the topical administration of medicines. Like the percutaneous permeation can be inconsistent according to the site of the disease, patient's age, severity of inflammation and so on.

Individuals with mild-to-moderate inflammatory diseases, topical therapy is the first-line therapeutic option. It includes cortico-steroids, tar-compounds, anthralins, calciferol, tazarotene, and salicylic acid are common treatments<sup>5</sup> for skin problems, but these are exceedingly hazardous, causing hepatotoxicity, nephrotoxicity and teratogenicity and even skin cancers. Progress is being going on to research new biologics that can successfully treat such skin conditions. One of such natural component is Tetrahydrocurcumin (THC) popularly known as "white curcumin", which is a colourless, stable curcumin hydrogenated compound (as shown in Figure 1) with outstanding antioxidant and anti-inflammatory activities with exceptional stability at biological pH (7.4) and in blood.<sup>6,7</sup> Furthermore, THC has been shown to be more water soluble (logp 2.73) than curcumin and it is an underutilised chemical for its use in topical illnesses, despite a few findings indicating its usage in cosmetic preparations as a depigmenting agent.

One of the utmost prominent novel dosage form for topical delivery is nanoemulgel drug delivery system, which is a formulation associated intervention aimed at improving lipophilic medication systemic transport in the skin. It is a hybrid of two systems, nanoemulsion-containing medication with a gel base, due to which it gets benefit from the combination of both due to presence of finely dispersed droplets in the nanoemulsion phase, lipophilic medicines easily get integrated, and the skin permeability of the medications also increases. Due to this, target drug pharmacokinetic as well as pharmacodynamic characteristics can be greatly improved.<sup>8</sup> When a nanoemulsion gel comes in touch with the skin surface, the lipophilic part get released from the gel system. These oil globules then penetrate the skin and provide the appropriate amount of medicine. This serves as a medication pool for topical distribution and helps to regulate drug delivery. The improved pharmacokinetic profile of pharmaceuticals supplied by the nano emulgel formulation is attributable to reduced drug deficit via the git route due to inadequate absorption and prevention from presystemic metabolism or elimination.<sup>9</sup> As a result, when compared to alternative formulations, topical nanoemulgel produced a greater pharmacological response. Modification of the thickness of the nanoemulgel with various types of gels can also regulate the drug's pharmacokinetic behaviour. In contrast, because gels are aqueous

in nature, they dissolve quickly, allowing for faster release than other topical preparations.<sup>10</sup> The current study uses successful optimization approaches to discover the optimal potential component and composition for developing a THC-loaded nanoemulgel.

## MATERIALS AND METHODS

### Chemicals and reagents

Tetrahydrocurcumin were procured from Novel Nutrient. Pvt. Ltd., HPLC grade solvents were used; Span 40, span 40 to 80, tween 40 to 80, Carbopol 934 and PEG (Polyethylene glycol) 200, 400, oleic acid, olive oil, corn oil, mineral oil, tocopheryl acetate, labrasol, transcutool, propylene glycol, glycerin, triethanolamine, carrageenan was obtained from CDH chemicals. Other chemicals used in the preparation and analysis of the formulation were of analytical quality.

### Animals

Male ICR mice's (7 weeks olds) weighing 19–23 g was obtained from KIET School of Pharmacy animal centre. The investigational protocol was approved by the Animal Ethics Committee through IAEC/KSOP/E/20/13, KIET School of Pharmacy, Ghaziabad, Uttar Pradesh.

### Characterization and optimization of tetrahydro curcumin

The THC was characterized using HPLC FT-IR, UV-Visible spectroscopy and DSC. Tetrahydrocurcumin solubility in various oils (oleic acid, olive oil, corn oil, mineral oil and tocopheryl acetate) was investigated by checking the presence of any drug precipitates. Firstly oil was mixed with 100 mg of THC to prepare the concentration of 1 mg / 10  $\mu$ L, shaking at 25 $\pm$ 1°C, for 48 hr to attain the equilibrium. The maximal THC solubility was determined by centrifuging 10 min the samples at 3000 rpm, and the supernatant samples were then makeup with methanol.<sup>11</sup> The content of Tetrahydrocurcumin in oil was determined using by HPLC with  $\lambda_{\text{max}}$  of 280 nm. Various surface active agents (tween 40 to 80, span 40 to 80 and cremophor) were tested for optimal emulsifying capacity. To determine the emulsifying capacity, 5  $\mu$ L oil phase was mixed with 1 mL of 10% surfactant dilution to find the amount of single-phase isotropic system development. The oil phase was added again till the solution turned turbid. For the single-phase isotropic system, samples were made to equilibrate for 1 day before being visually examined.<sup>12</sup> Cosurfactants were then mixed to create a nano emulsion system with a low levels of surfactants, so that lower interfacial tension can be achieved with enhanced interface stability. Different co-surfactants, such as PEG 200 and 400, labrasol, transcutool and propylene glycol, were entirely solubilized as a single system in the surface active phase at a constant ratio of 1:1 for optimization.<sup>13</sup>

## Construction of pseudo ternary phase diagram

The phase diagrams of ternary (oil phase, surfactant phase, and water phase) and pseudoternary (oil phase,  $S_{\text{mix}}$  phase, and aqueous phase) systems were prepared using aqueous method of titration. Surfactant/ $S_{\text{mix}}$  was solubilized in oil phase at the following ratios: 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:2 and so on at room temperature. The % constitution of each ternary/pseudoternary system was established, and observations were displayed on triangle coordinates. In addition, the influence of a surfactant-cosurfactant mass ratio (Km) on the nanoemulsion region generated from the phase diagram was examined at ratios of 1:2, 1:3, 1:4, 2:1, 3:1, and 4:1. The calibration plot approach was used to estimate the area of the nanoemulsification zone in the produced phase diagram.<sup>14</sup>

## RP-HPLC Analytical method development

Quantification of THC in different preparations was executed by RP-HPLC system (Waters) consisting of Spherisorb reversed phase  $C_{18}$  column with dimensions of 250mm, 4.6 mm and 5  $\mu\text{m}$  particle size. Chromatographic separation was performed using mobile phase consisting of methanol and water in the ratio of 77:33 v/v at pH of 3. The injecting volume for sample was 20  $\mu\text{L}$  and the column was held at 25°C with a flow rate of 1 mL/min with UV absorbance at  $\lambda_{\text{max}}$  of 280 nm. The developed method was validated for system suitability, robustness, sensitivity, specificity through forced degradation studies, linearity, precision and accuracy.<sup>15</sup> The estimation was done at retention time of 4.4 min with a linearity in the range of 1–10  $\mu\text{g/mL}$  ( $r^2 = 0.999$ ). The LOD value comes out to be 0.092  $\mu\text{g/mL}$  and the LOQ value comes out to be 0.28  $\mu\text{g/mL}$  respectively. The samples were kept for some time to precipitate and then centrifuged at 4500 rpm for about 5 min and the obtained supernatant was examined using the HPLC. The percentage recovery of Tetrahydro curcumin was determined by spiking different concentrations of drug (2.5, 5 and 7.5  $\mu\text{g}$ ), completely mixed by vortexing (2 min).<sup>16</sup>

## Preparation and characterization of THC nano emulsion

TNL was created utilising ultrasonic emulsification approach that involved dissolving THC (10mg) in small amount of ethanol and then homogeneous mixing of chosen oil and  $S_{\text{mix}}$  phase through a vortex mixer in the best possible ratio, as determined by the Pseudoternary phase diagram creation. Purified water added after adequate mixing of oil and  $S_{\text{mix}}$  phase as a continuous phase, and instantly sonicated under ultra-sonicator for 30 min, until a clean, transparent, isotropic system was achieved.<sup>17</sup> Characterization of THC nanoemulsion was done by drug content, droplet size and thermodynamic stability studies by exposing the samples through centrifugation (8000 and 6000 rpm), freeze thaw cycles and heating-cooling cycles between 4°C and 45°C for not less than 48 hr at each condition.<sup>18</sup>

## Preparation and characterization of THC nanoemulgel (TLNCG)

Carbopol 934 (1%) was solubilised in distil water and was left for 8 hr to ensure entire swelling of the carbopol. The necessary quantity of 0.5% glycerine was included as a humectant and to generate a smooth surface. The triethanolamine in sufficient amount (1-1.5% w/w) was applied to counteract the system, resulting in the creation of the gel.<sup>19</sup> Finally, the obtained mixture was homogenized with THC Nanoemulsion (TNL) to get TLNCG, which was then estimated for drug content, pH, particle size, size distribution (Polydispersity index, PDI), and zeta potential. SEM and TEM was used to analyse the morphological properties of TLNCGs.<sup>20</sup> FTIR, microscopy, DSC and viscosity evaluation was done using Brookfield LVT DV-II Viscometer.<sup>21</sup>

The spreadability of developed nanoemulgels was assessed 48 hr after formation by determining the nanoemulgel spreading radius among two glass plates after 1 min. A mass of 500 mg of nanoemulgel was loaded on a glass plate with a 1 cm diameter circle which was before marked on it, over which a second glass plate was mounted. The expansion in diameter caused by the addition of weights resulted in gel spreading.<sup>22</sup>  $S = (m.l)/t$  is the formula for calculating spreadability. Where S is the spreadability, m is the weight placed on the upper slide, l is the length of the upper slide, and t is the time taken.

## In vitro occlusion test and extrudability

A beaker with 50 mL water was sealed with filter paper and TLNCG (250 mg) was uniformly placed on the cover of the filter paper to produce a fine-layer. In an incubator, the sample was held at 32°C with 60  $\pm$  5% RH for 2 days. Another similar beaker without drug acted as a comparison standard. The weight of the beaker was taken at a predetermined time period to assess the loss due to evaporation.<sup>23</sup> The occlusion factor ( $F_{\text{OF}}$ ) was determined by calculating the proportion of water loss all the way through filter paper using the given equation:

$$F_{\text{OF}} = 100 \times [(W_A - W_B)/W_A]$$

$$W_A = \text{Water loss from standard beaker}$$

$$W_B = \text{Water loss from test}$$

A collapsible tube holding the gel preparation was pressed hard at the folded portion to test extrudability properties. To estimate the extrudability properties of developed TLNCG formulations, the force essential to extrude a tiny ribbon length of gel in a defined period was measured.<sup>24</sup>

## In vitro drug release studies

A preliminary *in vitro* drug diffusion studies were assessed utilizing a diffusion cell equipment for the selected TLNCG formulation. Before being applied among the donor and receptor

compartments, a dialysis membrane with a molecular mass of 12000-14000 Da was hydrated with the receptor medium for 12 hr. The donor compartment contained 1 g of TNLCG formulation, whereas the receptor compartment had 20 mL of phosphate buffer (pH 7.4) at body temperature. At pre-set time intervals, a 1 mL aliquot was removed and immediately exchanged with an equivalent volume of new buffer.<sup>25</sup>

### Ex vivo skin permeation and retention studies

The skin of Wistar mice was removed and superfluous fat with connective tissue was also taken off. The skin was placed on a Franz diffusion cell assembly with a 4.91 cm<sup>2</sup> applicable diffusion area. The diffusion cell's receptor compartment was occupied with 20 mL of pH 7.4 phosphate buffer. The complete system was mounted on a magnetic stirrer, and the solution was stirred at 100 rpm (37 ± 0.5°C). The formulation (1 g) was spread over the membrane<sup>26</sup> and at appropriate time intervals, an aliquot of 1 mL sample was taken and immediately exchanged with an equal volume of new diffusion medium.

### Anti-inflammatory effect

The carrageenan generated mice hind paw oedema technique was used to assess the anti-inflammatory efficacy of THC included nanoemulgel. Thirty five mice were randomly distributed into seven sets, each with five mice. Group I is normal control and in rest of the groups paw edema was induced in mice 1 hr before medication administration by intraperitoneal injection of 0.5 percent carrageenan in saline in the left hind paw.<sup>27</sup> Group II was positive control (caused inflammation without receiving any treatment), Group III was placebo (induced with inflammation, treated with nanoemulgel without THC), Group IV was the treatment group (induced with inflammation, treated with THC-loaded nanoemulsion), Group V was the treatment group (induced with inflammation, treated with THC-loaded nanoemulgel), Group VI was the treatment group (induced inflammation treated with standard hydrocortisone ointment 1%) and Group VII was treated with marketed formulation (Diclofenac sodium gel 1%). Changes in paw thickness were assessed utilizing a digital plethysmometer at time intervals of 0, 1, 2, 3, 4, 6, and 12 hr.

### Acute dermal irritation studies

A skin irritation assessment was performed on the removed hair dorsal side of the mice. Each mixture was applied to the skin by distributing it across the examined region. After 7 days of application, the skin's surface was examined and graded for any sensitive reaction like rating of 0, 1, 2, or 3, indicating no sensitivity reaction, modest erythema, sufficient erythema, and high erythema with or without oedema.<sup>28</sup>

### Stability study

Thermodynamic and temperature variation stability studies were done to study the prepared formulation. For thermodynamic study the nanoemulgel was centrifuged for 30 min at 3500 rpm in the event of freeze/thaw cycles and temperature stress tests were performed on the composition by keeping it at different temperature. Every composition was placed in tightly closed containers in freezer (4°C), room temperature (25°C), and at high temperature (40°C) for three months period. Sampling was done at intervals of 0, 1, 7, 14, 21, 30, 45, 60, and 90 days. The compounds were tested for physiological changes (like transparency, phase separation, drug precipitation, and changes in colour) as well as drug content and pH.<sup>29</sup>

### Release kinetics

The profile of an *in vitro* release research data was utilised to examine the correlation coefficient ( $r^2$ ) as well as release kinetics of THC-loaded preparations. *Ex vivo* permeation values were also fitted in several release models to investigate their release behaviour. The obtained values were put into various models like of zero order, first order, Higuchi, Korsmeyer and Peppas to determine the specify the release pattern of the drug, and to determine the exponent n value through the slope of the graph.<sup>30</sup>

### Statistical Analysis

Mean ± SD ( $n=6$ ) was used to express all the measured values. One-way ANOVA was used to analyse the data, and then post hoc Tukey-Kramer tests were performed using GraphPad Prism version 8. The values of  $p < 0.05$  were regarded appropriate.

## RESULTS

### Characterisation of Tetrahydro-Curcumin (THC)

THC estimated log p value (standard value 2.73) and solubility in water (around 0.009 mg/mL) of THC (at room temperature 25 ± 2°C) were 2.8 and 0.01 mg/mL, showing its high permeability potential. These obtained results were in conformity with earlier studies. THC has maximum solubility (shown in Figure 2) in tocopheryl acetate and it also enhances the stability of nanoemulsion by hampering the Ostwald ripening. Ng and Ko has also showed the anti-inflammatory potential of tocopheryl acetate through inhibition of NF-κB.<sup>31</sup> So, tocopheryl acetate was carefully chosen as the oil phase for preparation of nanoemulsion, Tween 80 was preferred as surfactant because it was having maximum emulsification capacity in comparison to the other surfactant. PEG 400 was included as co-surfactant owing to highest solubility within THC. Pseudo ternary phase diagram of surfactant (Tween 80) co-surfactant (PEG 400) in a variety of proportions 1:1, 1:2 and 2:1 illustrated in Figure 3. Pseudo ternary phase diagram of  $S_{mix}$  ratio (2:1) has major nanoemulsion area hence, it has been carefully chosen as per the selection criteria studies done by Belgodere *et al.*<sup>32</sup>



## Phase behaviour and optimization of nanoemulsion

The 2:1 ratio of surfactant: cosurfactant was chosen as the optimal ratio for usage in the preparation of nanoemulsion, from that several quantities of constituents (i.e. oil, surfactant co-surfactant combination, and water) used in the formation of nanoemulsion were combined at random as shown in Figure 3. The selection may be ascribed as done by Zeng *et al.*<sup>33</sup> to optimize various nanoemulsion parameters, so due to decreased oil phase size and usage of cosurfactant; higher penetration of the oil portion in the lipophilic area of the surfactant molecules was obtained. The THC concentration employed to prepare the nanoemulsion was 1.5 percent w/w.

## RP-HPLC Analytical method

An easy, specific, sensitive, and stability-indicating RP-HPLC technique was developed using Waters ODS2 column (4.6mm 250mm, 5µm particle size) utilizing the mobile phase consisting of methanol-water (77:33 v/v) at pH of 3 and with a flow rate of 1mL/min taking the UV absorbance under 280 nm wavelength. The Tetrahydro curcumin detector response was linear across the specified range of 0.5 to 9 µg/mL, with retention time of 4.4 min and a correlation value of 0.999. The precision ranged between 99.27 and 101.97 percent as shown in Table 1. The precision (R.S.D.) was 1.27 percent for the six sample preparations. LOD and LOQ values are 0.096 and 0.213 µg/mL. THC recovered at a rate of around 99.89%, which is quite suitable for the method development as shown by Sharma K.<sup>34</sup>

## Nanoemulsion preparation and characterization

Multiple formulas were chosen on the basis of NE area of every phase diagram, and the Table 2 shows the constitution of the chosen nanoemulsion systems having codes NF1 to NF9. Using a central composite design-based response surface technique,

the conditions for producing nanoemulsion were adjusted based on particle size and PDI.<sup>35</sup> Nanoemulsion was prepared by taking THC (10 mg) and tocopheryl acetate (10 -12%) were mixed in a measuring cylinder at 1500 rpm for 10 min to make an oily solution. The homogeneous water phase, consisting of  $S_{mix}$  (30-40%) and adequate distilled water, was made and then progressively disseminated into the organic portion using the high-speed ultrasonic homogenizer for 20 min.

TNLCG was characterised using particle size, Polydispersity Index (PDI), and Zeta potential. The results revealed that the particle size of TNLCG ranged from 123 to 136 nm, with a batch NF8 having the size of  $129.65 \pm 0.63$  nm, the PDI value was  $0.181 \pm 0.82$ , indicating that particles in NLC are monodisperse. It was discovered that system with 15% tocopheryl acetate created nanoemulsion with higher particle sizes than those with 10% tocopheryl acetate, indicating that the average droplet size increased with increasing oil content. These results were in line with earlier studies conducted that shown that adding more oil causes the vesicles in the nanoemulsion to enlarge, which causes the  $S_{mix}$  proportion to simultaneously decrease. As a result, the mean droplet size increases dramatically. As, the particle homogeneity increases the PDI approaches zero. The chosen batch's zeta potential was found to be  $-21.56 \pm 1.35$  mv, indicating a negative charge on the prepared nanoemulsion. The findings confirm the homogeneity of distribution of droplet sizes. Additionally, Jiang and Charcosset reported that the amount of the surface charge will have a significant impact on nanoemulsion stability. When increasingly widespread repulsive forces emerge across NE nanoparticles, coalescence was shown to be inhibited.<sup>36</sup>

## Nanoemulsion characterization

The amount of drug in the Nanoemulsion preparation (NF8) was determined as 98.11% ( $n = 3$ ). About  $90.73 \pm 1.59$  percent

**Table 1: Method development and validation data of THC on HPLC.**

Chromatographic parameters	Mobile phase	pH	Flow rate	Detection	Linearity range	r <sup>2</sup>
	Methanol-water (77:33)	3±0.3	1mL/min	280nm	0.5 to 9 µg/mL	0.999
Analytical parameters	Retention time	Tailing factor ± SD	Theoretical plates ± SD	Limit of detection	Limit of quantitation	Recovery
	4.6	1.13±0.63	12438±0.787	0.096 µg/mL	0.213 µg/mL	99.89%
Precision	Intra-day (µg/mL)			Inter-day (µg/mL)		
	2.5	5	7.5	2.5	5	7.5
	2.45 ± 0.76	4.87 ± 0.73	7.35 ± 0.66	2.51 ± 0.21	4.69 ± 0.83	7.48 ± 0.62
Robustness (% recovery ± SD)	2.5 µg/mL	5 µg/mL	7.5 µg/mL	2.5 µg/mL	5 µg/mL	7.5 µg/mL
HPLC-2	98 ± 0.76	99 ± 0.38	98 ± 0.62	97 ± 0.34	98 ± 0.43	98 ± 0.77
Mobile phase ± 0.5%	97 ± 0.72	98 ± 0.25	98 ± 0.63	98 ± 0.36	97 ± 0.38	97 ± 0.62
Flow rate ± 0.1mL/min	99 ± 0.15	99 ± 0.43	98 ± 0.26	100 ± 0.12	99 ± 0.25	99 ± 0.54

**Table 2: Selected formulations composition with their used codes and ratio of all components.**

$S_{mix}$ ratio	Formulation code	Ingredients (%w/w)			
		Tocopheryl acetate	$S_{mix}$	THC	Water
1:1	NF1	5	30	10	55
	NF2	10	35	10	45
	NF3	15	40	10	35
1:2	NF4	5	30	10	55
	NF5	10	35	10	45
	NF6	15	40	10	35
2:1	NF7	5	30	10	55
	NF8	10	35	10	45
	NF9	15	40	10	35

**Table 3: Permeation parameters of different formulations prepared.**

Formulation	CADP (mg/cm <sup>2</sup> )	Flux (mg/cm <sup>2</sup> /h)	Lag time (h)	Drug retained (mg)
NF1	0.61 ± 0.04	0.036 ± 0.003	0.54 ± 0.01	1.02 ± 0.02
NF2	0.68 ± 0.02	0.023 ± 0.002	0.62 ± 0.02	0.98 ± 0.03
NF3	0.72 ± 0.03	0.034 ± 0.004	0.73 ± 0.01	1.12 ± 0.02
NF4	0.73 ± 0.02	0.032 ± 0.004	0.48 ± 0.04	0.95 ± 0.04
NF5	0.75 ± 0.03	0.036 ± 0.002	0.76 ± 0.04	0.89 ± 0.03
NF6	0.79 ± 0.01	0.038 ± 0.003	0.79 ± 0.03	1.56 ± 0.03
NF7	0.87 ± 0.03	0.035 ± 0.004	0.49 ± 0.03	0.96 ± 0.04
NF8	0.98 ± 0.02	0.041 ± 0.002	0.42 ± 0.04	0.81 ± 0.01
NF9	0.89 ± 0.04	0.033 ± 0.003	0.51 ± 0.03	0.87 ± 0.03

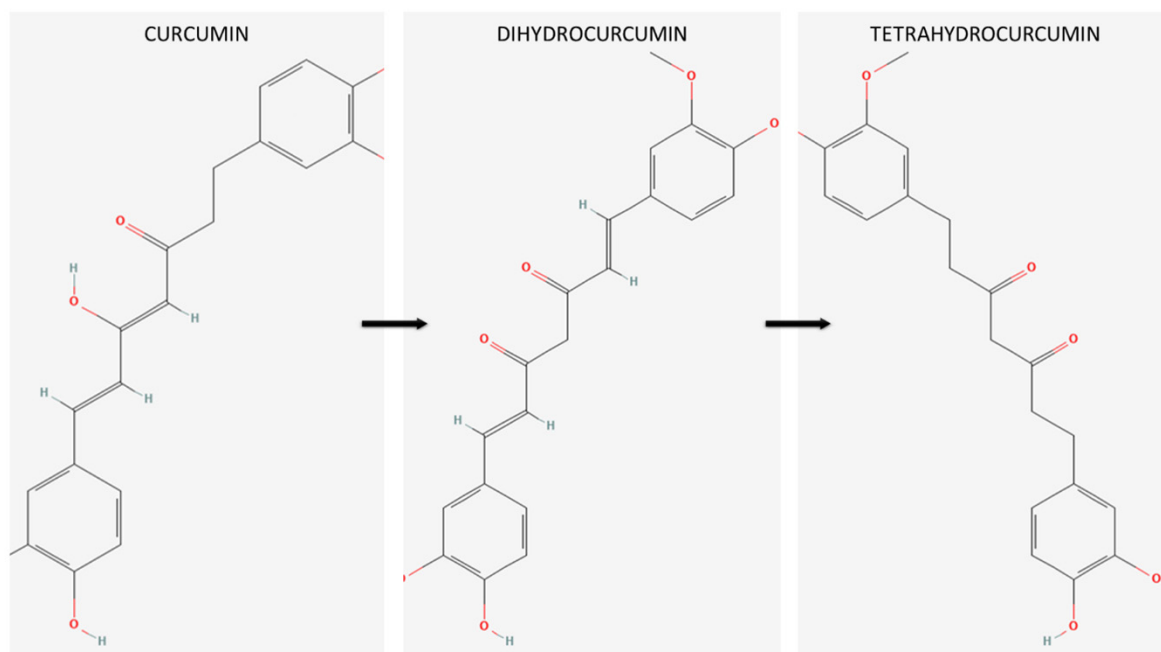
( $n = 3$ ) of the medication was contained in the lipid phase and  $7.38 \pm 1.65$  percent ( $n = 3$ ) in the aqueous phase, indicating high lipid loading capability. The nanoemulsion's droplet size and PDI value was come out to be  $101.25 \pm 0.76$  nm and 0.243 0.32, respectively. The generated nanoemulsion's zeta potential was measured to be  $-17.610 \pm 1.35$  mV. Nanoemulsions are thus found to be thermodynamically stable having no stability issues. Even after 48 hr of heat and/or cool cycles, the nanoemulsion did not destabilise. The formulations did not show any significant physical changes (such as haziness, phase separation, drug precipitation, and colour change), drug content and pH. Safaya and Rotliwala reported that stable nanoemulsion formulations tends to provide increased bioavailability of lipid soluble drugs.<sup>37</sup>

### Tetrahydro Curcumin Nanoemulgel (TNLCG) formulation

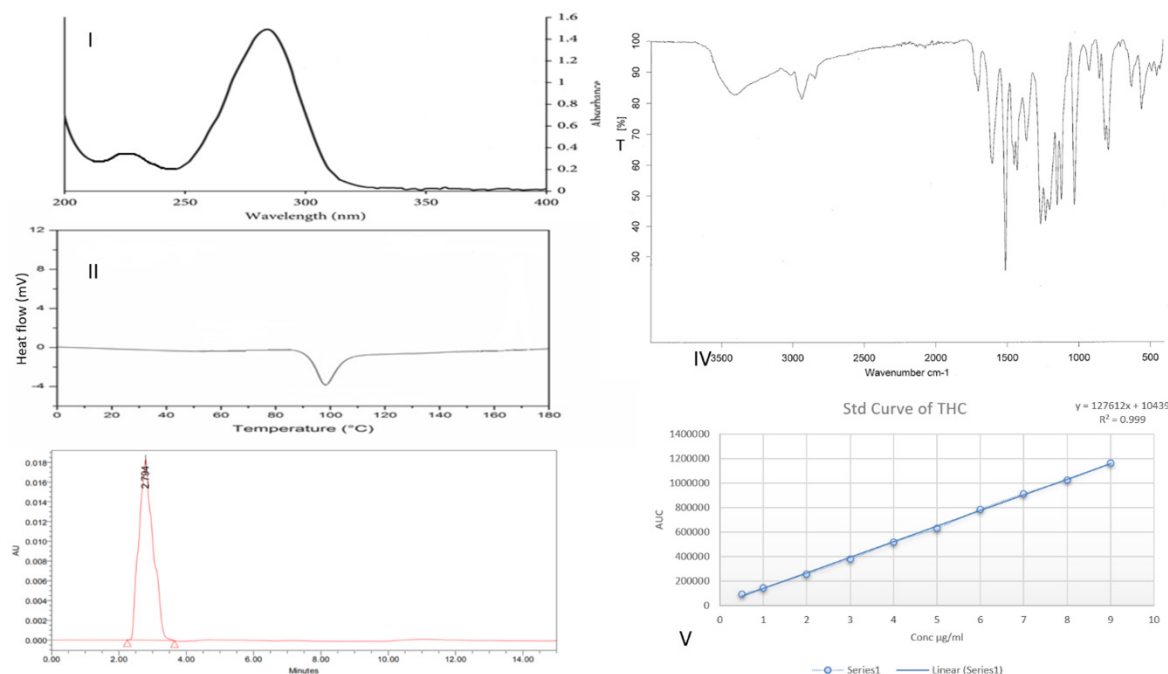
To create THC loaded nano-emulgel organic phase, THC (10%) and Tocopheryl acetate (10%) were mixed at 1500 rpm for 10 min. The water phase, consisting of  $S_{mix}$  (35%) and adequate distilled water (22%), was made discretely in a glass container. The homogeneous aqueous portion was then progressively disseminated into the organic portion using the high-speed ultrasonic homogenizer for 20 min. Verma and Easwari reported that 1% Carbopol hydrogel interconnected pores with different

sizes that can be quite helpful in drug loading and faster drug release.<sup>38</sup> Thus the gel part of formulation was made using the left-out water (22%) with 1% w/v of Carbopol 934 as the gelling agent. TNL was integrated with the gel base by 10 min mixing. The medication content of the nanoemulgel formulation ranged from  $98.60 \pm 0.78$  to  $99.87 \pm 0.65$  percent. The outcomes demonstrated that the medication was disseminated equally all over the formulation and that loss of drug was minimal during nanoemulgel creation<sup>39</sup> At 25°C, pH of the nanoemulsion and nanoemulsion gel were determined to be  $5.78 \pm 0.87$  and  $5.96 \pm 0.81$ , respectively. The pH of the produced gel was come out to be within the human skin pH range (4.5–6.0).

THC indicated a melting endotherm at 97°C that relates to an enthalpy of 131.23 J/g. TNLCG displayed a wide endotherm at a low temperature ranging from 65°C to 73.8°C (enthalpy of 65.56 J/g), demonstrating THC entrapment into lipophilic nano structures since no crest subsequent to THC was identified. The FTIR spectra of nanoemulgel did not show any significant interaction of drug with excipients. The scanning electron microscope produced a positive picture of a black globules surrounded by light surrounds. The TEM and SEM image showed sphere-shaped formation with and all preparations were in nano size range with low PDI indicative of homogeneity of droplet size



**Figure 1:** Structural changes in conversion of Curcumin to Tetrahydro-curcumin (reproduced from ref no. [7]).

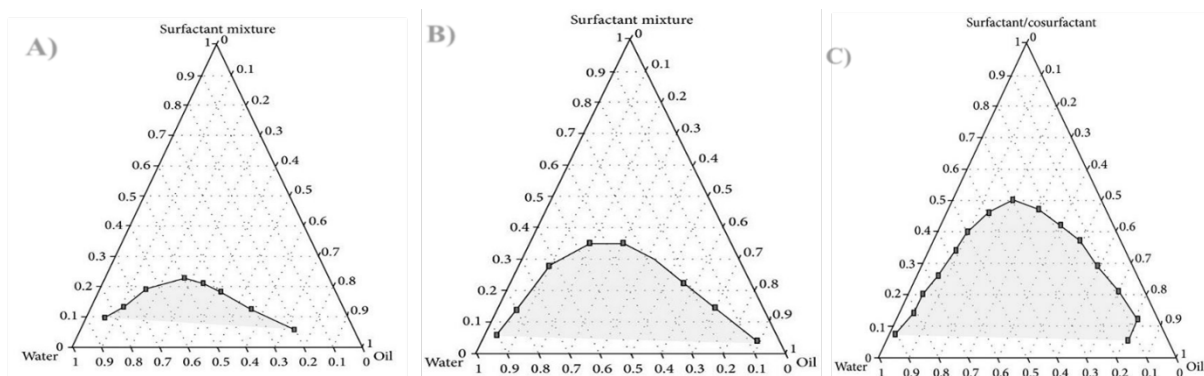


**Figure 2:** (I) UV-Visible spectra (II) DSC cure (III) HPLC chromatogram (IV) FTIR Spectra and (V) Calibration plot of THC (Tetrahydro-curcumin) for its characterization.

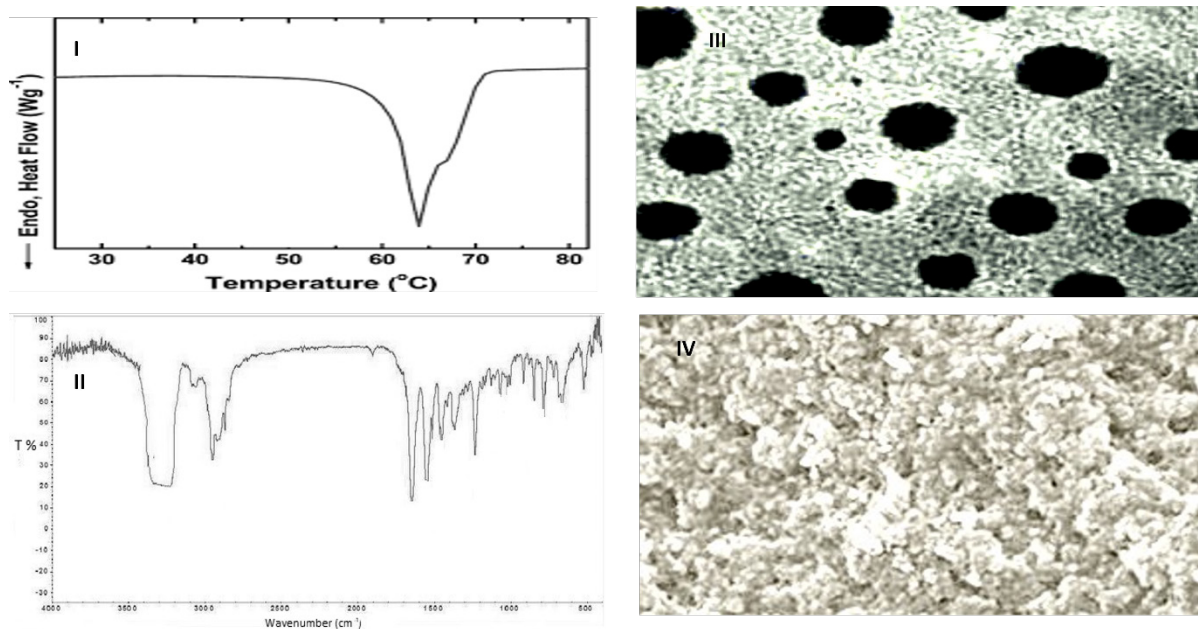
in preparation (as shown in Figure 4). These findings revealed that the droplets were in the nano size range, and so the formulation was nanoemulgel.

The viscosity of the formulations improved as the oil content rose from 5% weight percent to 10% weight percent. The viscosity of the nanoemulsion and nanoemulgel was determined to be  $1.978 \pm 1.05$  cps and  $3263.45 \pm 79.37$  cps, indicating that the generated gel is viscous sufficiently to follow non-newtonian

flow. It was intended to demonstrate the drug's lengthy residence period at the application site and gradual release. As according to Ramezanizadeh *et al.* the dynamic viscosity of nanoemulsion is one of the most critical characteristics influencing their thermal behaviour and drug delivering capabilities.<sup>40</sup> The formulation NF8 Farrow's constant (N) was found to be 1.28.  $N > 1$  denotes pseudoplastic flow thus the findings validated the nanoemulgel's pseudoplastic nature. This property is caused by the colloid nature



**Figure 3:** Pseudo ternary Phase diagram of nanoemulsion comprised of Oil phase, water, and various proportion of  $S_{mix}$  (Tween 20:PEG 400) A) 1:1 B) 1:2 C) 2:1.



**Figure 4:** (I) DCS curve, (II) FTIR Spectra, (III) TEM image and (IV) SEM image of selected TNLCG formulation (NF8).

gel network organization, which arrange itself in the direction of force applied, lowering the viscosity with increase in shear rate.<sup>41</sup> The pseudoplastic behaviour explains the designed system need for some expulsion force. Spreadability was discovered to be in the range of  $4.23 \pm 0.93$  to  $5.87 \pm 0.17$  gcmS<sup>-1</sup> indicating strong spread ability.

### **In vitro occlusion test and extrudability**

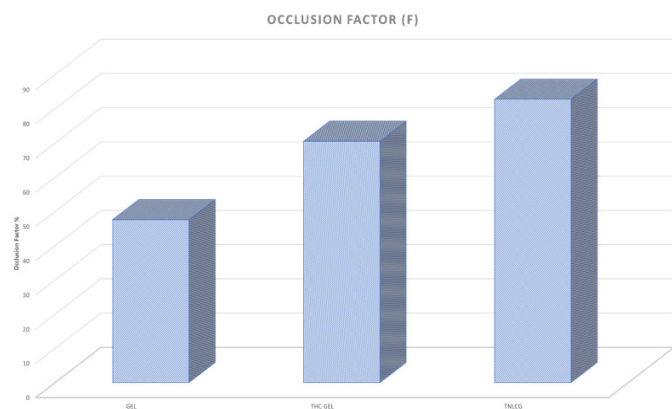
The results of an occlusion study were studied after 48 hr, the occlusion factor of FN8 had a F value of  $82.74 \pm 2.17$  percent, THC scattered gel was  $70.48 \pm 0.93\%$ , Diclofenac sodium gel was  $79.87 \pm 1.12$  and carbopol gel was  $47.56 \pm 0.43$  percent (as shown in Figure 5). It is recognised that THC nanoemulgel demonstrated superior occlusivity when compared to THC dispersed gel, diclofenac sodium gel (1%) and carbopol gel. TNLCG gel demonstrated high gel strength with a small work of shear, and the strength of extrusion was discovered to be

appropriate, indicating the easiness of extrudability from the tube,<sup>42</sup> which is a desirable property for a topical dosage form. Extrudability of all formulations was found to be 5.2 (NF1), 6.6 (NF2), 7.1 (NF3), 5.4 (NF4), 7.2 (NF5), 6.9 (NF6), 6.8 (NF7), 7.0 (NF8) and 7.5 (NF9) Newton.

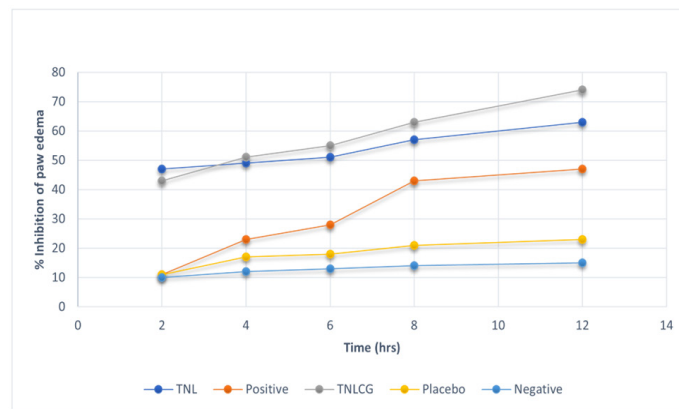
### **In vitro drug release studies**

The augmented drug permeation, appropriate droplet size, suitable viscosity, and appropriate polydispersity index of formulation NF8 make it a preferred formulation for *in-vitro* release. Figure 6 depicts the results of an evaluation produced from THC-loaded nanoemulgel preparations in phosphate buffer pH 7.4. According to the *in vitro* study, the proportion of THC released were found to be 77.36 percent from the formulation NF8 nanoemulgel, which surpassed the THC release from all other formulations (including marketed formulation) over a 300 min period. There is clearly a big distinction among the amount

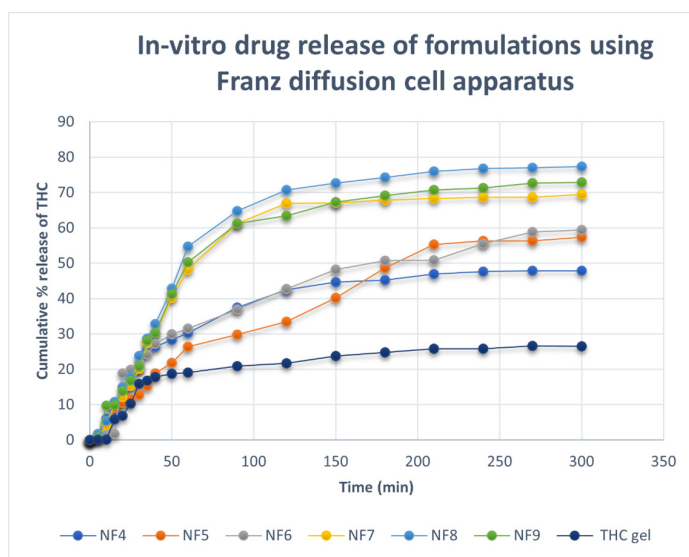




**Figure 5:** Occlusion factor of without drug carbopol gel, THC incorporated gel and THC nanoemulgel.



**Figure 7:** Effects of THC-loaded formulations on carrageenan-induced paw edema in rats along with placebo and negative control.

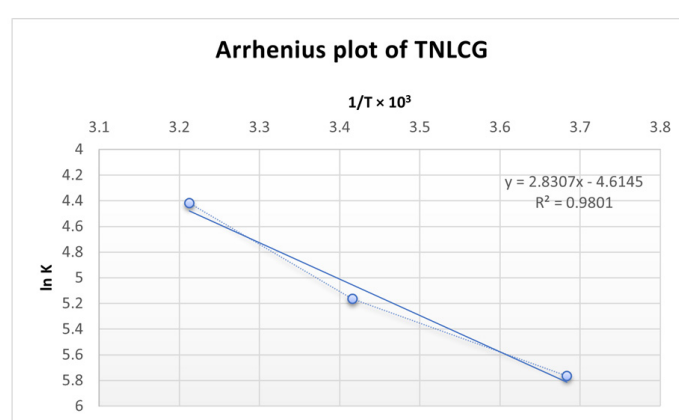


**Figure 6:** In vitro release of THC from different selected formulations using Franz diffusion cell apparatus.

of THC released from all preparations and the percentage of THC released from the NF8. The greater viscosity of nanoemulgel and decreased water content with the existence of oil; the dispersion of the drug entrapped demonstrates the significantly reduced THC release initially from nanoemulgel.<sup>43</sup>

### Ex vivo skin permeation studies

When compared to standard formulations, nanoemulgel was reported to improve penetration rates (as shown in Table 3) deep inside layers of the skin with reduce lag time. With respect to time, a gradual rise in the drug levels was seen in the receptor compartment. By the end of the 12 hr after treatment, there was no discernible variation in the amount of medicine that had seeped through the skin. The findings showed that the penetration rate and coefficient of TNLCG formulation NF8 through mice skin are considerably greater ( $p < 0.05$ ) than the others. The amount of transdermal flux (0.041 mg/cm<sup>2</sup>/h) for the NF8 formula was quite high than the other formulations (0.023-0.038 mg/cm<sup>2</sup>/h),



**Figure 8:** Arrhenius plot of selected nanoemulgel formulation.

showing that the constituents of the formulae had a substantial effect on the penetration properties of THC from nanoemulgel. Because all the nanoemulgel formulations included the same drug load, it is possible to conclude that the concentration gradient is not the controlling aspect in the permeation progression. The microscopic nanodroplets that settle down into intimate contact with the skin may also be the cause of this high permeability, offering a wider surface area for drug absorption and delivering higher drug levels on the area affected as reported in earlier studies.<sup>44</sup>

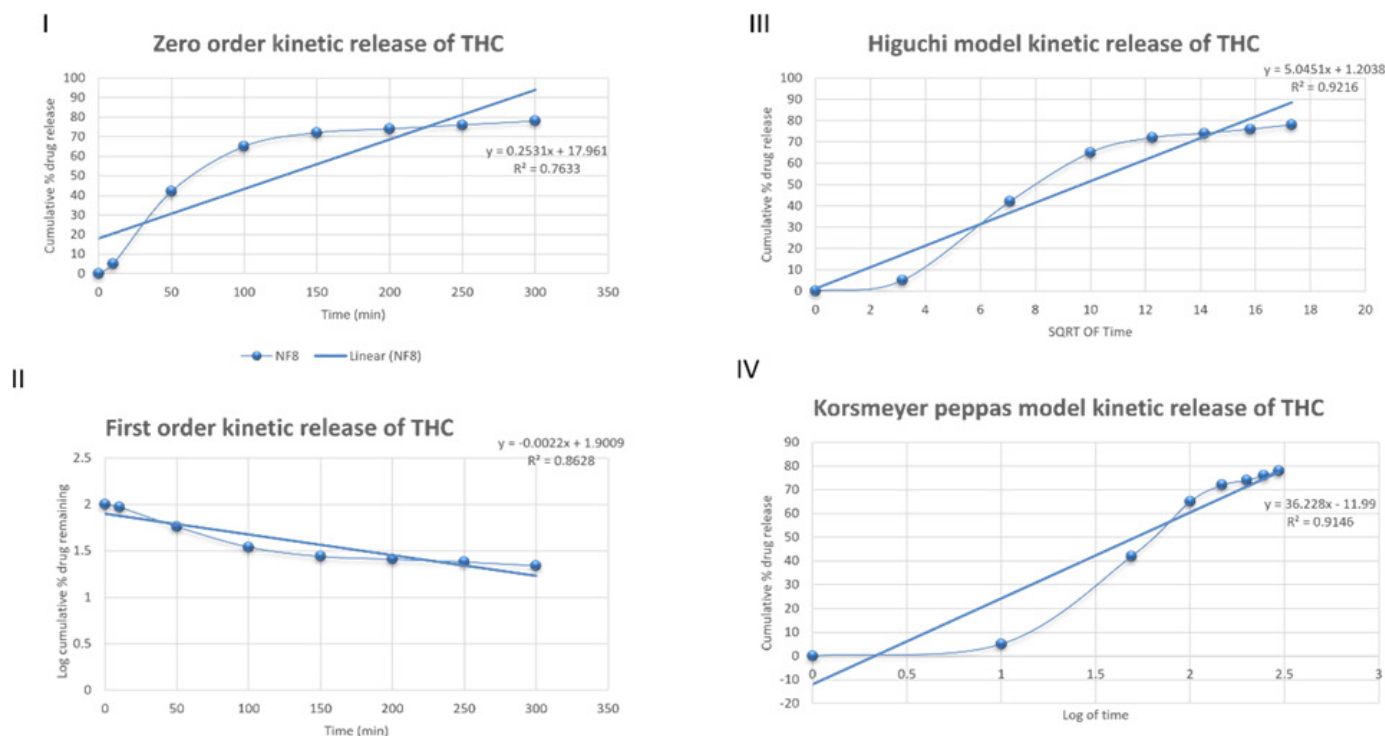
### Acute anti-inflammatory studies

Carrageenan injection resulted in substantial growth ( $p < 0.05$ ) in the swelling or tenderness of the negative control group, which was obtained after 1 hr (100 percent) compared to the without inflammation hind paw. When compared to the other groups under examination, animals treated with THC-loaded nanoemulsion formulations had a considerably reduced proportion of inflammation of about 63.25% ( $p < 0.05$ ) (as shown in Figure 7). Excitingly, the TNLCG treated group had the greatest amount reduction in inflammation (74.37%), 12 hr after the topical application. Figure 7 showed the anti-inflammatory activities of the prepared formulations, as Zhang *et al.* reported

**Table 4: Shelf life of nanoemulgel formulation (pH 7.4) (n=6) at 40, 25 and 4°C.**

Formulation	Temp (°C)	T <sup>a</sup> (K)	1/T × 10 <sup>3</sup> (K <sup>-1</sup> )	K <sup>b</sup> (month <sup>-1</sup> )	ln k	t <sub>90</sub> <sup>c</sup> = 0.105/k (month)	t <sub>90</sub> (year)
FN8	40	313.15	3.212	0.039137	-4.416	2.545	0.212
	25	298.15	3.415	0.017234	-5.164	11.792	0.982
	4	277.15	3.683	0.002537	-5.764	45.703	4.018

<sup>a</sup> Temperature in degree Kelvin. <sup>b</sup> Degradation constant (k) from slopes of the first order degradation kinetic plots. <sup>c</sup> Shelf life of the nanoemulgel formulation (pH 7.4).

**Figure 9:** Graphical representation of (I) Zero order, (II) First order, (III) Higuchi model and (IV) Korsmeyer peppas model for kinetic release of THC.

that THC is well known for its good inflammation reduction property but its lipophilic nature limits its bioavailability, but the prepared TNLCG formulation enhanced the anti-inflammatory activity of THC compared to the conventional formulations.<sup>45</sup>

### Acute dermal irritation and stability studies

When administered to the hairless skin of mice backside, all experimental formulations exhibited a sensitivity response of score 0. Three days of observation were spent on the administered area, and throughout the entire investigation there were no signs of erythema, edoema, or discomfort. In the current study, selected (NF8) formulations were held at 40, 25 and 4°C. The amount of undecomposed medication that remains in the nanoemulgel were 86.34 percent, 97.6 percent, and 99.12 percent left after ninety days of storage, respectively. Stability studies were done as per the ICH guidelines.<sup>46</sup> The sequence of degradation of THC as seen in the Figure 8, nanoemulgel was discovered to be 1<sup>st</sup> order as mapped against the natural log of the percentage of

medication remaining and period which resulted in the straight line<sup>47</sup> employing the following formula:

$$\ln C_t = \ln C_0 + kt^{0.5}$$

where  $C_t$  is the quantity of drug at given interval of time  $t$ ,  $C_0$  is the initial amount of drug and  $k$  is the reaction constant. The shelf life of the prepared formulation was estimated through the equation:

$$(t_{90})^{0.5} = (C_t - C_0) / \text{anti ln } kt_{90} = [(t_{90})^{0.5}]^2$$

Where  $t_{90}$  is the time required to decrease the original potency or content of the active ingredient by 10%. The shelf life of selected formulation was come out to be 0.212, 0.982 and 4.018 years (as shown in Table 4). The Arrhenius plot was prepared (as shown in Figure 8) by taking value of  $k$  on x-axis and reciprocal of absolute temperature on y-axis. The slope value taken from the graph of tetrahydro-curcumin in nanoemulgel formulation was found to be 3.267 kcal/mol, which provides information regarding the activation energy.

## Release kinetics

Release kinetics data of THC from all preparations were illustrated in Figure 9 using various kinetic models and the respective  $r^2$  (slope) values were come out to be 0.7633 (0.253) for zero order, 0.8628 (0.002) for first order, 0.9216 (5.045) for Higuchi model and 0.9146 (36.228) for Korsmeyer Peppas model. The release kinetics was acquired by graphing the quantity of drug released vs time, and by studying the graph it becomes clear that the release kinetics of all THC preparations were mostly suited to the Higuchi model as it presented a linear relationship between defined variables and the greatest  $r^2$  value for this particular model. This also demonstrated that the THC has been released from the matrix type and that ideal sink conditions in the surroundings are maintained indefinitely.<sup>48</sup>

## DISCUSSION

Numerous studies have demonstrated the potency of THC in alleviating skin inflammation and improving skin healing process. The poor solubility and bioavailability of THC, however, would restrict its potential for repairing the skin. This study is being conducted to investigate the efficiency of nanoemulgel to other traditional THC formulations of gel and emulgel in terms of alternative topical THC preparations for anti-inflammatory activity. In fact, the findings of this investigation demonstrated that THC nanoemulgel had the maximum drug release during the *in vitro* release investigation. However, in an *ex vivo* permeation analysis, both THC emulgel and nanoemulgel demonstrated high penetration when compared to commercial formulation. In conjunction to their colloidal features, the surfactant component of emulgel and nanoemulgel acts as a permeability enhancer, which may be the cause of the improved THC permeation action. The medicament does not degrade on storing, as per the data of stability testing of the THC formulations. Furthermore, no adverse consequences were noticed when THC gel, emulgel, or nanoemulgel was applied to animal skin. Thus, these findings showed that the THC emulgel and nanoemulgel under investigation had good formulations and skin tolerabilities, which are beneficial in improving patient acceptance of the therapy. Future research is required to assess the safety and efficacy profile of the proposed hydrogel system in an *in-vivo* model.

## CONCLUSION

Nano-encapsulation of Tetrahydrocurcumin with insufficient biopharmaceutical performance and instability produced formulation with improved permeability and storage stability. This increase in outcomes can be explained by the nanoemulgel system's improved solubilization capacity, as well as the nanosize dimension of the capsulating delivery system, which favours the penetration of tetrahydro curcumin into the skin layers via numerous mechanisms/routes of the epidermis. Thus, we can summarize that the nanoemulsion gel of tetrahydro-curcumin

was effectively formulated and it has passed all the desired characterization and evaluations required for the topical drug delivery method by enhancing bioavailability and permeability of tetrahydro-curcumin. *In vitro* and *in vivo* studies also demonstrated that TNLCG exhibited highest percentage of cumulative drug release in comparison with other formulations with good skin compatibility. Lastly, this study revealed promising outcomes regarding efficiently performing topical TNLCG nano-formulation in safe and effective way.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**THC:** Tetrahydrocurcumin; **TNL:** THC loaded nano lipid-based; **TNLCG:** TNL in carbopol gum gel; **LOD:** Limit of detection; **LOQ:** Limit of quantitation.

## SUMMARY

- Ultrasonication was used to produce the nano size formulation.
- THC loaded nanoemulsion and nanoemulgel were developed and characterized by HPLC.
- TNLCG texture was found to be suitable for topical use after rheological studies.
- *In vivo* anti-inflammatory studies revealed that TNLCG gel was more effective than free TNL.
- The nanoemulgel was the most suitable for the topical delivery of THC with enhanced bioavailability.
- Nano-gel (NF8) was stable at 40°C for longer period as supported by accelerated stability studies.

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