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# FORMULATION AND EVALUATION OF CLOBETASOL PROPIONATE LOADED NANOEMULSION GEL CONTAINING BABCHI OIL FOR PSORIASIS

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**ABSTRACT**

Worldwide prevalence of the psoriasis is 2 – 3 %. Clobetasol propionate (CP) is a super potent corticosteroid having immunosuppressive, anti-inflammatory and antiproliferative activity. This study was intended to formulate and evaluate babchi oil nanoemulsion (NE) loadedgel containing CP and Salicylic acid (SA) for psoriasis. CP having a poor permeability to skin so, to enhance its permeability it was incorporated into the oil and formulated and evaluated a nanoemulsion gel.Another important objective regarding this research is to selection of natural oil having anti-psoriatic activity with this drug may be substantially reduce the side effects of CP and enhance anti-psoriatic activity in parallel ways with the CP. Aqueous phase titration method was used to formulate a nanoemulsion using oil phase, surfactant, co-surfactant, & aqueous phase as Babchi Oil (BO), Tween 80, Transcutol P, and distilled water respectively. Pseudo ternary phase diagram was constructed and different formulation composition were selected from phase diagram. Selected formulations were subjected to in vitro permeation studies, globule size distribution average globule size and zeta potential, pH, viscosity, refractive index (RI), conductivity and transmission electron microscopy (TEM). Optimized nanoemulsion loaded into HPMC hydrogel and salicylic acid was incorporated.The optimized nanoemulsion formulation (NE14) exhibited in vitro permeation (44.05 %), globule size distribution (0.124), average globule size (236.67 nm), zeta potential (-20 mV), pH (5.68 ± 0.124), viscosity (14.86 ± 1.05 cP), RI (1.417 ± 0.012), conductivity (53 ± 5.38 µs/cm) and TEM (). Optimized NE loaded into the HPMC gel containing 5% SA. Further, gel evaluation carried out for pH, viscosity, spreadability extrudability and permeation study, compared with in vitro permeation of nanoemulsion. The results were found to be pH (6.29 ± 0.173), viscosity (4438.69 ± 53.17 cP), spreadability (1.23 times more spreadable than marketed formulation), extrudability (almost similar to marketed formulation) and in vitro permeation (97.59 % permeation found in comparison to NE14). On behalf of above mentioned results it was concluded that optimized CP

loaded nanoemulsion gel might be an alternative approach for the topical delivery.

**Keywords:** Clobetasol propionate (CP), psoriasis, nanoemulsion, babchi oil, topical delivery.

## Introduction

Psoriasis is a long-term skin chronic autoimmune disorder which is due to hyperproliferation and keratinocyte differentiation. The development and progression of psoriasis is mostly dependent on skin-resident immune cells and important signal transduction pathways, among them tumor necrosis factor-α, interleukin (IL)-23p19, as well as the IL-17A axis, as shown by advances in biological therapy(Yamanaka et. al., 2021). This causes thick, red, scaly patches to appear on the skin's surface; these are frequently accompanied by discomfort, irritation, and itching. Everybody has psoriasis differently; moderate cases are limited to small portions of the body, while severe ones affect large areas of the body. Psoriasis symptoms might worsen due to triggers like stress, infections, certain drugs, and skin injury. Less than 3% of the body is affects in mild, moderate affects 3-10% of the body, and severe psoriasis affects >10% of the body (Langley et. al., 2005). Psoriasis is a long-term skin condition that typically has onset of mild or no symptoms, followed by periods of more severe symptoms.

Prevalence - The frequency of psoriasis varies greatly worldwide across various populations and geographical areas. Based on estimates,2-3% of the world population suffers with psoriasis (Sewerin et. al., 2019). The prevalence of psoriasis in various nations has been reported to vary between 0.09% and 11.4%. The majority of developed nations have a prevalence of 1.5–5% (Parisi et. al., 2013 & Danielsen et. al., 2013).

Risk factors - Psoriasis is a complicated autoimmune skin illness caused by a mix of genetic, immunological, and environmental factors. The tendency to acquire psoriasis is frequently inherited, indicating a strong genetic component.

Psoriasis treatment seeks to minimize inflammation, hinder skin cell proliferation, and reduce symptoms including itching and scaling. The possibilities for treatment are determined on the nature and extent of psoriasis, as well as specific factors such as overall health, age, and preferences. There are three main treatment options for psoriasis: topical dermatologic therapy, phototherapy, and systemic therapy.

Topical therapy is essential in the treatment of psoriasis, especially for mild to moderate scenarios and localized lesions. Medication is applied directly to the damaged skin to treat inflammation and abnormal skin cell proliferation. Corticosteroids, which reduce inflammation and itching, vitamin D analogs, which regulate skin cell growth, retinoids, which encourage normal skin cell growth, and calcineurin inhibitors, which suppress the immune system, are among the most used topical treatments (Elmets et. al., 2021). These drugs come in a variety of forms, including creams, ointments, gels, and foams, providing for flexibility in application while also responding to individual tastes and skin types. While topical treatment works well for many individuals, it may require persistent and long-term use to keep symptoms under control. The topical drugs that are used in the treatment of psoriasis as shown in table 1 (Ramanunny et. al., 2020).

Use of natural compounds is also a very common and effective method for the management of psoriasis from ancient to present scenarios. For a number of reasons, the use of herbs in medicine has grown significantly. It is now clear that synthetic medications have adverse effects. This has caused calls for managing or treating illnesses by going back to nature.

Nanoemulsion is a kind of emulsion that is formed by combiningimmiscible liquids, such as water & oil, then stabilizing them with an emulsifying agent. The main feature of nanoemulsion is that the dispersed phase (either oil or water) has droplet sizes in the nanoscale range. This study was aim to formulate and evaluate babchi oil nanoemulsion loaded gel containing clobetasol propionate and salicylic acid for psoriasis.

**Materials and Methods**

CP was obtained as a gift sample from Mankind Pharma, India. Pure babchioil was purchased from deve herbes. PEG 200, Tween 80 (polysorbate 20), Tween 20, HPMC & Tween 60 was purchased from Merck (Merck, India).Labrasol,Transcutol Pand PlurolOleique were purchased from Gattefosse. All other chemicals were of analytical grade.

**Screening of Excipients**

When determining which components to test for enhanced drug loading and stability in nanoemulsions, thesolubility or miscibility of all components is a crucial factor to be considered. Using a vortex mixer (Shanti, Mumbai),excess amount of CP was added tostoppered vial in order to determine the solubility of CP in Babchi Oil. After that, the vial was stored for 72 hours at $37^0$C. After the samples had stabilized, they were taken out of the shaker and centrifuged for 15 minutes at 2000 rpm then the supernatant was extracted and filtered. Babchi Oil's CP concentration was measured at 253 nm using a UV spectrophotometer (Labomed, USA). Babchi Oil was miscible in a 1:1 ratio (oil: surfactant/co-surfactant) with a various surfactant, including Tween 20 (polysorbate 20), Tween 80, Labrasol, and Tween 60, and co-surfactants, including Ethyl acohol, Transcutol P, and PlurolOleique. Visual observations were made on miscibility. The combinations that were transparent or clear in a 1:1 ratio was taken into consideration for more research(Azeem et al., 2009).

**Phase Studies**

Babchi Oilchosen as the oil phase, Tween-80, and Transcutol-P (co-surfactant) based on solubility and miscibility experiments. To keep surface-active contaminants out of the aqueous phase,distilled water was utilized. Co-surfactant and surfactantcombined (Smix) in varying weight ratios (2:0, 1:1, 2:2, 2:1, 3:1, and 4:1, 5:1), with the proportion of surfactant to co-surfactant increasing. There were sixteen distinct oil and Smix combinations made (1:9, 1:8, 1:7, 1:6, 1:5 1:4, 1:3.5, 1:3, 3:7, 1:2, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1) in order to cover the maximum ratio necessary for the study in order to properly define the area of the phases formed in the phase diagrams. Using the aqueous phase titration approach, pseudoternary phase diagrams have been developed to determine the nanoemulsion's current zone. For everyratio of oil andSmix, a slow titration using the aqueous phase was carried out, and for clear oil-in-water (o/w) nanoemulsions, visual observations were taken. A pseudo three component phase diagram was used to depict the physical condition of nanoemulsion.

**Formulation of drug-loaded nanoemulsion**

Numerous formulations covering the whole range of nanoemulsion existence in the phase diagrams with lowest surfactant and highest water concentration were chosen fromthe pseudoternary phase diagrams displaying maximum nanoemulsion area. Preparation of drug-loaded nanoemulsions, on the basis of saturation solubility of drug in oil were dissolved. Then required amount of surfactant and co-surfactant was added and mixed properly, finally drop by drop water added in above mixture to get clear, transparent mixture (Alam MS et al., 2016).

**Stress testing (thermodynamic stability) of drug loaded nanoemulsions**

For the stress stability testing, the prepared nanoemulsion were subjected for the study mentioned below. After testing, it was observed that some formulations became unstable due to cracking, creaming or phase separation in the formulation (Alam MS et al., 2013).

**Freeze thaw cycle**

For freeze – thaw cycle, formulations first kept at -5 $^0$ C (in freezer) for 24 hrs. After that, they were removed out from freezer and kept at room temperature. After 2-3 minutes, nanoemulsions were returned to its original form considered to be stable (Azeem et al., 2009).

**Centrifugation studies**
For this study, prepared nanoemulsions were centrifuged for 30 minutes at 2000 rpm and stability was observed by phase separation & turbidity.

**Heating cooling cycle**
There were six cycles carried out, each lasting 48 hours of storage, between thetemperature 4 $^0$C and 40 $^0$C. More research was done on the formulations that proved stable at this temperature.

**EVALUATION OF NANOEMULSION**
**In-vitropermeation studies (Using Franz diffusion cell)**
For this study, Franz diffusion cells were used. It consists of water jacket, sampling unit, receptor compartment, donor compartment, inlet, and outlet. Dialysis membrane was used in this method. The dialysis membrane was placed in physiological buffer (pH 7.4) for 24 hours for the activation. After 24 hrs it was taken out and washed it.
Dialysis membrane was placed between both compartments and sample placed towards the side of donor compartment. Receptor compartment filled with buffer (40ml) and at each time interval like 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hour (h) one mL of diffusion medium (buffer) was taken and simultaneously one mL freshly prepared buffer added in receptor compartment to maintain sink condition. Filtered the taken sample, then dilute with phosphate buffer (7.4 pH) and UV, visible absorption spectrophotometer was used to determine the amount of drug permeated.

**CHARACTERIZATION OF NANOEMULSION**
**Globule size distribution, average globule size and zeta potential**
These were analysed by using a Malvern zeta-sizer instrument through dynamic light scattering (DLS) phenomena. The measurements were carried out at affixed scattering angle at 90 degrees, with appropriate dilutions and analysis was conducted at 25 $^0$C. Zete potential was calculated using an additional electrode on the same instrument.

**pH**
pH of nanoemulsion was measured by using a digital pH meter. pH mater was calibrated using phosphate buffer (pH 7.4). Then, transfer a nanoemulsion into the beaker and immersed probe into it. Readings were taken from the display and readings were performed in triplicates.

**Viscosity**
The viscosity of nanoemulsion formulations was measured in triplicate using a Brookfield viscometer (Brookfield Engineering Lab), followed standard condition for evaluation.

**Refractive Index**
Abbes refractometer was used to measure the refractive index (RI) of nanoemulsion. Readings were taken in triplicates for accurate result.

**Conductivity**
Nanoemulsion was taken into the beaker and probe was dipped into it, readings were noted down. This procedure was followed in triplicates and the instrument used during this experiment was conductometer (Spectronics, India).

**Transmission electron microscopy (TEM)**
TEM was used for the determination of individual particle size following method as mentioned in Alam MS et al., 2012.

## FORMULATION OF NANOEMULSION GEL CONTAINING SALICYLIC ACID

Topical usage is not suited for nanoemulsions due to their typically very low viscosity. By adding thickening agents, which also alter the formulation appearance and typically affect drug release, the viscosity can be enhanced. These days,various gelling agent like: carbopol 934, carpool 940, ethyl cellulose, xanthum gum&HPMC have been used to prepared the nanoemulsion based gel for improving the viscosity of nanoemulsion (Peltola et al., 2003). In this research work, HPMC was selected for gel preparation.

## EVALUATION OF NANOEMULSION GEL

### pH

pH of nanoemulsion gel was measured by using a digital pH meter. For analysis, dissolved 1 g of gel in 25 ml of water then, immersed a probe in beaker and readings were noted down. Readings were performed in triplicates.

### Viscosity

After putting 100 to 200 mg of the prepared gelon the sample holder, the spindle was lowered for five to ten minutes to allowed for equilibration. Viscosity was measured when the spindle rotated at 10 rpm and 10/s shear rate at room temperature. Viscosity of nanoemulsion gel was measured in triplicate using a Brookfield DV III ultra (Brookfield Engineering Lab), followed standard condition for evaluation.

### Spreadability

Set of petri dishes was used to measure the spreading ability of gels in centimetres as aweight applied in order to evaluate spreadability. The procedure involved compressing a sample that had been previously weighed under many plastic petri dishes with specified weights at predetermined intervals. The spreading diameter of sample was measured and contrasted.

### Extrudability

Extrudability of the formulated gel was observed as gel is ejected from syringe in uniform quantity. 15 g of gel formulation was packed into plastic syringe and firmly applied a pressure on plunger to extrude the gel until the pressure was dissipated (Kumar et al., 2013).

### In vitro permeation of nanoemulsion gel

The in vitro permeation was determined by the same procedure which was followed in permeation study of nanoemulsion using Franz diffusion cell. After in vitro permeation of gel was obtained, then it was compared with the permeation profile of nanoemulsion.

## RESULTS AND DISCUSSIONS

### Criteria for excipients selection

The selected excipients have to be approved by pharmaceutical companies, fall under the GRAS (generally regarded as safe) category, and not irritate or sensitize the skin. An additional crucial condition was higher drug solubility in the oil phase, which would aid in keeping the medication in a solubilized form within the nanoemulsion. Since many surfactants can irritate skin, safety is a key consideration when we selecting a surfactant. For this reason, non-ionic surfactants are thought to be less hazardous than ionic surfactants. The requirement that the hydrophilic lipophilic balance (HLB) value needed to generate the o/w nanoemulsion be more than 10 is a crucial factor for selecting the surfactants. An effective combination of high and low HLB surfactants produces a stable nanoemulsion composition. Cosurfactant reduces the bending stress at the interface and gives the interfacial film the flexibility it needs to take on the various curvatures needed to create nanoemulsions throughout a broad compositional range.

**Screening of excipients**

The development of nanoemulsion systems for poorly soluble pharmaceuticals depends on the drug's solubility in the oil phase, and one of the most important design factors is the amount of drug loading per formulation. Given the extremely low amount of CP, the solubility of CP in babchi oil was determined and it was 19.67 mg/mL, which is excellent for topical application. Butoil emulsification is quite challenging since babchi oil contains other fatty acids. A favourable nanoemulsion area in the ternary phase diagram depends on how oil is miscible with surfactant and cosurfactant. For that, test the miscibility of oil with various surfactants and cosurfactants were used(table 1).

**Table 1: Miscibility of BabchiOil with surfactants and co-surfactants.**

| **Miscibility of Babchi Oil** | | | | |
|---|---|---|---|---|
| **S. No.** | **With Surfactant (1:1)** | **Observation** | **With Co-surfactant** | **Observation** |
| 1 | Tween 20 | Turbid | Ethanol | Turbid |
| 2 | Labrasol | Clear | PlurolOleique | Turbid |
| 3 | Tween 80 | Turbid | PEG 200 | Turbid |
| 4 | Tween 60 | Turbid | Transcutol P | Clear |

**Construction of pseudo ternary phase diagrams**

One of the first phases and the foundation of the nanoemulsion drug delivery system is the construction of a phase diagram, especially when the goal is to precisely define a phase boundary. Careful observations are undertaken to distinguish metastable systems from the phase boundary; despite the extremely low free energy needed to make a nanoemulsion, the formation is thermodynamically stable. A phase diagram was able to determine the relationship between a mixture's phase behaviour and composition. To thoroughly examined the phase diagrams, Babchi oil, Tween 80 (surfactant), and Transcutol P (co surfactant) were utilized. The visual clarity and flow capabilities of the compositions were observed. The ones that did not exhibit a shift in the meniscus upon being tilted to a 90° angle were categorized as metastable nanoemulsion gel and were not chosen. Following observation, pseudo-ternary phase diagrams were developed using the titration observations noted. Phase diagrams were constructed independently for every prepared ratio of Smix in order to identify the o/w nanoemulsion zones.In ternary phase diagrams (Figure) only o/w nanoemulsion region for Smix (1:1) was shown because the area of nanoemulsion was greatest in case of Smix (1:1) with respect to all other Smix. Following the construction of the nanoemulsion delivery system's framework, various formulations were chosen at various phases of the phase diagram.

Whether a large or very small nanoemulsion area forms depends on how well the specific surfactant or blend of surfactants can dissolve the oil phase. A larger region with more of a clear, uniform solution is produced depending on the degree of solubilization. It was observed that the oil phase was less solubilized when the surfactant (Tween80) was used alone. This suggests that the surfactant was unable to sufficiently lower the interfacial tension of the lipid phase and, as a result, could not lower the system's free energy to the ultra-low level required to create nanoemulsions.The addition of a cosurfactant resulted in a significantly lower interfacial tension and very little free energy, which helped the phase diagram show a larger nanoemulsion area (Ali et al., 2014).

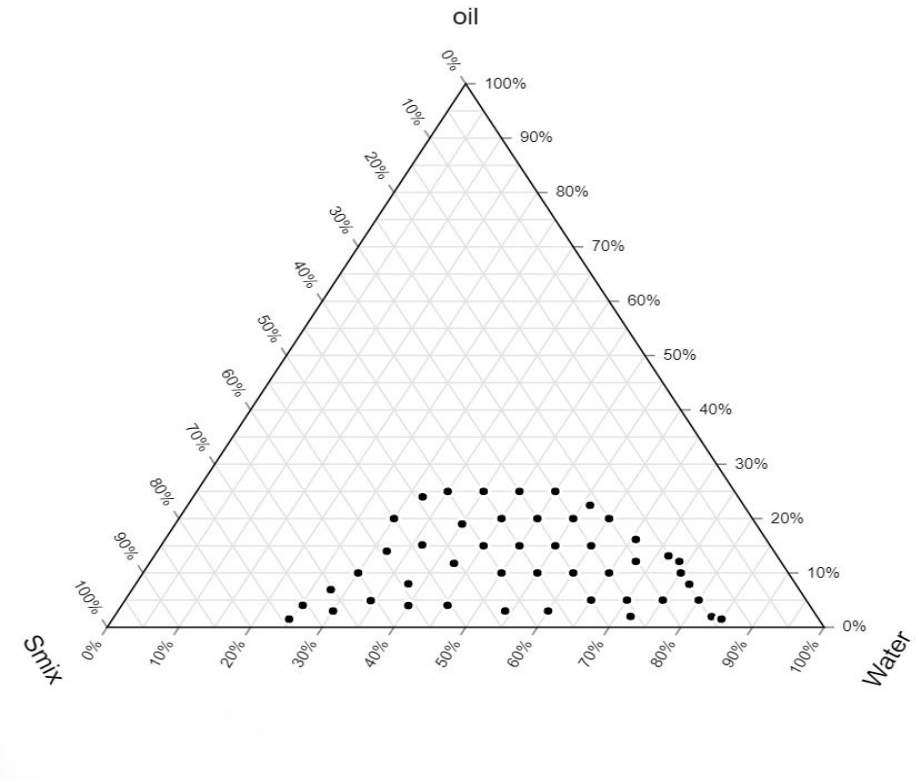


**Figure 1: Phase diagram of Smix 1:1**

## FORMULATION OF NANOEMULSION

### Selection of drug-loaded formulation from phase diagram of Smix 1:1

Many formulations were selected randomly within the nanoemulsion zone formed in pseudo-ternary phase diagram which was mentioned in above figure. The percentage composition of different formulations listed below in(table 2). For formulation of nanoemulsion, oil was taken which contains drug dissolved in there. The drug quantity dissolved in oil as per solubility mentioned previously in solubility study i.e. 19.67 mg/mL.

**Table 2: Selected drug loaded formulations from pseudoternary phase diagram**

| Formulation Code | % v/v ratio of oil, $S_{mix}$ and aqueous phase | | |
|---|---|---|---|
| | Oil | Smix | Aqueous phase |
| NE1 | 3 | 17 | 80 |
| NE2 | 5 | 25 | 70 |
| NE3 | 5 | 50 | 45 |
| NE4 | 5 | 65 | 30 |
| NE5 | 8 | 17 | 75 |
| NE6 | 8 | 21 | 71 |
| NE7 | 8 | 38 | 54 |
| NE8 | 10 | 16 | 74 |
| NE9 | 10 | 20 | 70 |
| NE10 | 10 | 54 | 36 |
| NE11 | 11 | 33 | 56 |
| NE12 | 12 | 28 | 60 |
| NE13 | 15 | 20 | 65 |
| NE14 | 15 | 31 | 54 |

| | | | |
|---|---|---|---|
| NE15 | 15 | 37 | 48 |
| NE16 | 15 | 40 | 45 |
| NE17 | 17 | 22 | 61 |
| NE18 | 17 | 49 | 34 |
| NE19 | 18 | 22 | 60 |
| NE20 | 20 | 38 | 42 |

**Stress testing (thermodynamic stability) of drug-loaded nanoemulsions**

For the stress stability testing, the prepared nanoemulsion were subjected for the thermodynamic studies (freeze/thaw, centrifugation, and heating-cooling) mentioned below. After testing, it was observed that some formulations became unstable due to cracking, creaming or phase separation in the formulation.

**Table 3: Stress stability testing of different selected nanoemulsions from Smix ratio 1:1**

| **Oil used: Babchi Oil, Surfactant used: Tween 80, Cosurfactant used: Transcutol P, Aqueous phase: Distilled water** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Formulation Code** | **Composition (% v/v)** | | | **Observations** | | | **Inference** |
| | **Oil** | **Smix** | **Water** | **Freeze Thaw** | **Centr** | **H/C** | |
| NE1 | 3 | 17 | 80 | X | √ | √ | Failed |
| NE2 | 5 | 25 | 70 | √ | √ | √ | Passed |
| NE3 | 5 | 50 | 45 | √ | X | √ | Failed |
| NE4 | 5 | 65 | 30 | √ | √ | X | Failed |
| NE5 | 8 | 17 | 75 | √ | √ | √ | Passed |
| NE6 | 8 | 21 | 71 | √ | √ | √ | Passed |
| NE7 | 8 | 38 | 54 | X | X | √ | Failed |
| NE8 | 10 | 16 | 74 | √ | √ | √ | Passed |
| NE9 | 10 | 20 | 70 | √ | √ | √ | Passed |
| NE10 | 10 | 54 | 36 | √ | √ | X | Failed |
| NE11 | 11 | 33 | 56 | X | X | √ | Failed |
| NE12 | 12 | 28 | 60 | √ | √ | √ | Passed |
| NE13 | 15 | 20 | 65 | √ | √ | X | Failed |
| NE14 | 15 | 31 | 54 | √ | √ | √ | Passed |
| NE15 | 15 | 37 | 48 | √ | √ | √ | Passed |
| NE16 | 15 | 40 | 45 | √ | X | √ | Failed |
| NE17 | 17 | 22 | 61 | √ | X | √ | Failed |
| NE18 | 17 | 49 | 34 | √ | √ | X | Failed |
| NE19 | 18 | 22 | 60 | X | X | X | Failed |
| NE20 | 20 | 38 | 42 | √ | X | √ | Failed |

**Stable nanoemulsions formulation after stability testing**

Certain formulations proved unstable when nanoemulsions were tested for thermodynamic stability(table 3). Nanoemulsions which remained stable after stability testing is mentioned in (table 4).Further, selection of stable nanoemulsion from the above table 4 on the basis of Smix and oil ratio. Because high amount of surfactant incorporated in nanoemulsion topically, leading cause of irritation to the skin (Mushtaq et al., 2023).On the behalf of above-mentioned reference, only three formulations respectively: NE8, NE9 and NE14 were selected from (table 5). Because, these formulations contain no more than 2 folds of Smix with respect to oil.Therefore, for further studies only above mentioned three formulations were selected for the permeation study.

**Table 4: Selected compositions of stable nanoemulsions**

| S. No. | Formulation Code | Percentage (v/v)composition of different formulations which were passed the thermodynamic stability test & consider for further studies. | | |
|---|---|---|---|---|
| | | Oil(µl) | Smix(µl) | Water(µl) |
| 1 | NE2 | 50 | 250 | 700 |
| 2 | NE5 | 80 | 170 | 750 |
| 3 | NE6 | 80 | 210 | 710 |
| 4 | NE8 | 100 | 160 | 740 |
| 5 | NE9 | 100 | 200 | 700 |
| 6 | NE12 | 120 | 280 | 600 |
| 7 | NE14 | 150 | 310 | 540 |
| 8 | NE15 | 150 | 370 | 480 |

**Table5: Selected compositions of stable nanoemulsions on the basis of Smix:Oil**

| S. No. | Formulation Code | Oil(µl) | Smix(µl) | Ratio (Smix: Oil) | Interference |
|---|---|---|---|---|---|
| 1 | NE2 | 50 | 250 | 5 | X |
| 2 | NE5 | 80 | 170 | 2.125 | X |
| 3 | NE6 | 80 | 210 | 2.625 | X |
| 4 | NE8 | 100 | 160 | 1.6 | √ |
| 5 | NE9 | 100 | 200 | 2 | √ |
| 6 | NE12 | 120 | 280 | 2.333 | X |
| 7 | NE14 | 150 | 310 | 2.066 | √ |
| 8 | NE15 | 150 | 370 | 2.466 | X |

**EVALUATION OF NANOEMULSION**

**In vitro permeation studies**

In vitro permeation study of nanoemulsion formulations (NE8, NE9 and NE 14) were carried out for 24 h using dialysis membrane in phosphate buffer solution (pH 7.4) by Franz diffusion cell. Figure 2 illustrated the progressive permeation of drug loaded nanoemulsion formulations (NE8, NE9 and NE14) at 37 $^{0}$C. Different formulations from the phase diagrams with maximum area were chosen

for in vitro permeation studies in order to evaluate nanoemulsions. In all these three formulations respectively: NE8, NE9 and NE14. The permeation of NE8 showed maximum permeability but in case of rest two formulations were also almost similar permeation (table 6, 7 &8).

**Table 6: In vitropermeation of CP in phosphate buffer (pH 7.4) usingFranz diffusion cell for nanoemulsion formulation(NE8)**

| S. No. | Time (h) | Absorbance | Concentration (µg/ml) | Cumulative amount of drug permeated (µg) | Cumulative percentage of drug permeated (%) | Cumulative amount of drug permeated/ area (µg/cm2) |
|---|---|---|---|---|---|---|
| 1. | 0.25 | 0.181 | 0.937 | 37.483 | 7.496 | 5.249 |
| 2. | 0.5 | 0.195 | 1.400 | 56.026 | 11.205 | 7.846 |
| 3. | 1 | 0.211 | 1.930 | 77.218 | 15.443 | 10.814 |
| 4. | 2 | 0.213 | 1.996 | 79.867 | 15.973 | 11.185 |
| 5. | 3 | 0.23 | 2.559 | 102.384 | 20.476 | 14.339 |
| 6. | 4 | 0.234 | 2.692 | 107.682 | 21.536 | 15.081 |
| 7. | 5 | 0.261 | 3.586 | 143.443 | 28.688 | 20.090 |
| 8. | 6 | 0.279 | 4.182 | 167.284 | 33.456 | 23.429 |
| 9. | 8 | 0.296 | 4.745 | 189.801 | 37.960 | 26.582 |
| 10. | 10 | 0.31 | 5.208 | 208.344 | 41.668 | 29.179 |
| 11. | 12 | 0.317 | 5.440 | 217.615 | 43.523 | 30.478 |
| 12. | 24 | 0.329 | 5.837 | 233.509 | 46.701 | 32.704 |

| Formulation Code | Flux (µg/cm$^2$/h) | Permeability constant (Kp) |
|---|---|---|
| NE8 | 1.362 | $2.724 \times 10^{-3}$ |

**Table 7: In vitropermeation of CP in phosphate buffer (pH 7.4) using Franz diffusion cell for nanoemulsion formulation(NE9)**

| S. No. | Time (h) | Absorbance | Concentration (µg/ml) | Cumulative amount of drug permeated (µg) | Cumulative percentage of drug permeated (%) | Cumulative amount of drug permeated/ area (µg/cm2) |
|---|---|---|---|---|---|---|
| 1. | 0.25 | 0.183 | 1.003 | 40.132 | 8.026 | 5.620 |
| 2. | 0.5 | 0.197 | 1.466 | 58.675 | 11.735 | 8.217 |
| 3. | 1 | 0.209 | 1.864 | 74.569 | 14.913 | 10.443 |
| 4. | 2 | 0.219 | 2.195 | 87.814 | 17.562 | 12.298 |
| 5. | 3 | 0.226 | 2.427 | 97.086 | 19.417 | 13.597 |
| 6. | 4 | 0.234 | 2.692 | 107.682 | 21.536 | 15.081 |
| 7. | 5 | 0.257 | 3.453 | 138.145 | 27.629 | 19.348 |
| 8. | 6 | 0.276 | 4.082 | 163.311 | 32.662 | 22.872 |
| 9. | 8 | 0.291 | 4.579 | 183.178 | 36.635 | 25.655 |
| 10. | 10 | 0.305 | 5.043 | 201.721 | 40.344 | 28.252 |
| 11. | 12 | 0.311 | 5.241 | 209.668 | 41.933 | 29.365 |
| 12. | 24 | 0.323 | 5.639 | 225.562 | 45.112 | 31.591 |

| Formulation Code | Flux (µg/cm$^2$/h) | Permeability constant (Kp) |
|---|---|---|
| NE9 | 1.316 | $2.632 \times 10^{-3}$ |

**Table 8: In vitropermeation of CP in phosphate buffer (pH 7.4) usingFranz diffusion cell for nanoemulsion formulation(NE14)**

| S. No. | Time (h) | Absorbance | Concentration (µg/ml) | Cumulative amount of drug permeated (µg) | Cumulative percentage of drug permeated (%) | Cumulative amount of drug permeated/ area (µg/cm2) |
|---|---|---|---|---|---|---|
| 1. | 0.25 | 0.18 | 0.903 | 36.158 | 7.231 | 5.064 |
| 2. | 0.5 | 0.193 | 1.334 | 53.377 | 10.675 | 7.475 |
| 3. | 1 | 0.204 | 1.698 | 67.947 | 13.589 | 9.516 |
| 4. | 2 | 0.216 | 2.096 | 83.841 | 16.768 | 11.742 |
| 5. | 3 | 0.222 | 2.294 | 91.788 | 18.357 | 12.855 |
| 6. | 4 | 0.23 | 2.559 | 102.384 | 20.476 | 14.339 |
| 7. | 5 | 0.252 | 3.288 | 131.523 | 26.304 | 18.420 |
| 8. | 6 | 0.272 | 3.950 | 158.013 | 31.602 | 22.130 |
| 9. | 8 | 0.286 | 4.413 | 176.556 | 35.311 | 24.727 |
| 10. | 10 | 0.301 | 4.910 | 196.423 | 39.284 | 27.510 |
| 11. | 12 | 0.307 | 5.109 | 204.370 | 40.874 | 28.623 |
| 12. | 24 | 0.319 | 5.506 | 220.264 | 44.052 | 30.849 |

| Formulation Code | Flux (µg/cm$^2$/h) | Permeability constant (Kp) |
|---|---|---|
| NE14 | 1.287 | $2.574 \times 10^{-3}$ |

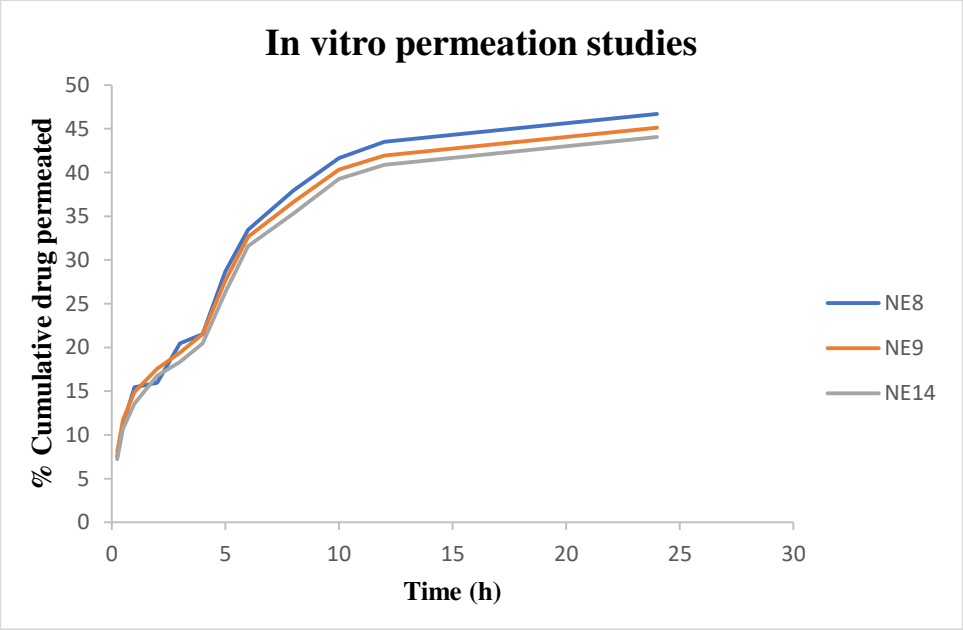


**Figure 2: In vitropermeation of CP nanoemulsions in phosphate buffer (pH 7.4)**

## CHARACTERIZATION OF NANOEMULSION

### Globule size distribution, average globule size, zeta potential

On the basis of above results, among all these three formulations only one formulation was selected for further studies on behalf of their uniformity in size distribution (Polydispersity Index) which was mentioned in (table 9).NE14 was selected for further studies because it was found that PDI value 0.128, it indicates uniformity of the size that corelates with better stability. Another important parameter i.e. zeta potential also noted within the ideal range ±30 mV ensures better stability of nanoemulsion (Ermawati et al., 2020).

**Table 9:Readings of different parameters.**

| Formulation code | Average globule size (nm) | Polydispersity index (PDI) | Zeta potential (mV) |
|---|---|---|---|
| NE8 | 205.35 | 0.437 | -30.81 mV |
| NE9 | 213.89 | 0.401 | -25.63 mV |
| NE14 | 225.1 | 0.128 | -20.14 mV |

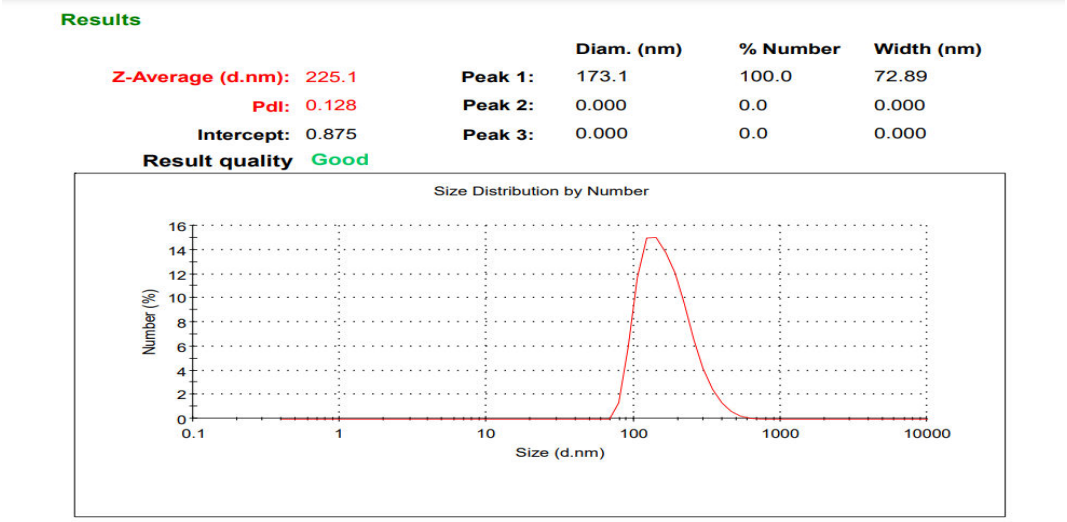


**Figure 3: Globule size distribution of nanoemulsion formulation (NE14).**

### pH of optimized nanoformulation (NE14)

The pH of nanoemulsion formulation (NE14) was found to be 5.68 ± 0.124 which was compatible for the topical application. pH of skin ranges in between 5.0 -7.0 (Dinshaw et al., 2021).

### Viscosity of optimized nanoemulsion (NE14)

Formulation (NE14) showed lower viscosity of14.86 ± 1.05cP, it may be due to less amount of oil and Smix but larger amount of water. Similar trend was reported in O/W nanoemulsion by Chime et al., 2014.

### Refractive index of optimized nanoemulsion (NE14)

In this formulation, it was observed that minimal increase in the refractive index of nanoemulsion was 1.417 ± 0.012 in comparison to water (1.334). This might be due to the oil added in the formulation and decrease in the water concentration (Azeem et al., 2009).

### Conductivity

Nanoemulsion (NE14) showed a conductivity of 53 ± 5.38 µs/cm which indicates it was an oil-in-water nanoemulsion. Oil-in-water nanoemulsion have high electric conductivity which is ranges in between 10 – 100 µs/cm **(Khalid et al., 2023)**.

**Transmission Electron Microscopy (TEM)**

TEM image of the nanoemulsion formulation (NE14) shown the individual size of globules which was ranges between 150 – 270 nm.

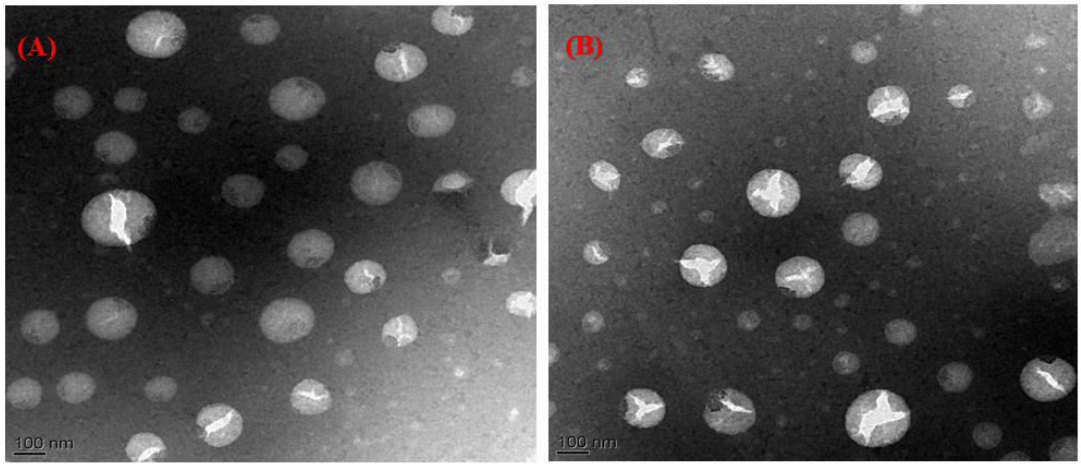


**Figure 4: TEM images nanoemulsion (NE14).**

**FORMULATION OF NANOEMULSION GEL CONTAINING SALICYLIC ACID**

For formulation of nanoemulsion gel, optimized amount 2 g of hydroxy propyl methyl cellulose (HPMC) and 5 g of salicylic acid added in 50 ml of the water and continuously stirred with magnetic stirred till homogenous mixture was obtained. Then dropwise already prepared nanoemulsion (NE14) of 16.93 ml was added in above prepared HPMC gel and continued mixing to get homogenous mixture. Finally, water was added to make it total volume up to 100 ml. The pH of the prepared gel was maintained in between 5.5 to 6.5 with the help of triethanolamine.

**EVALUATION OF NANOEMULSION GEL**

Nanoemulsion loaded gel (NE14) was evaluated and it was found that pH of the gel was 6.29 which is compatible to skin. Viscosity was found to be 4438.69 cP, it was very high in comparison to nanoemulsion formulation (NE14) because of gelling agent (HPMC). Spreadability of nanoemulsion loaded gel was found to be 1.23 times greater than marketed CP gel (Topinate gel). Extrudability was found almost similar to that of marketed formulation, it was easily extruded out from the syringe (table 10). In vitro permeation of gel was found to be 97.59 % in comparison to nanoemulsion, which indicated that there was a slight decrease in the permeation due to increased viscosity (table 11).

**Table 10: Evaluation of nanoemulsion gel (NE14).**

| S.NO | Parameters | Results |
|---|---|---|
| 1 | pH | 6.29 ± 0.173 |
| 2 | Viscosity | 4438.69 ± 53.17 |
| 3 | Spreadability | 1.23 times more spreadable than marketed CP-gel |
| 4 | Extrudability | Almost similar to than that of marketed preparation |
| 5 | In vitro permeation | Our NE14 nanoemulsion gel showed 97.59% cumulative drug permeation in comparison to NE14 nanoemulsion (table). |

**Table 11: Comparison of % cumulative drug release of NE14 nanoemulsion Vs NE14 nanoemulsion gel.**

| Formulation | % cumulative drug permeation at 24 hrs | Inference |
|---|---|---|
| NE14 nanoemulsion | 44.05 | (42.99/44.05) *100 = 97.59 % |
| NE14 nanoemulsion gel | 42.99 | |

## CONCLUSION

Nanoemulsion emerged as a promising drug delivery system that addresses the challenges associated with poorly water-soluble drugs. The nanoemulsion was designed to improve the penetration and bioavailability of the clobetasol propionate (CP) and nanoemulsion loaded in the HPMC gel to increased its viscosity which resulted in high viscosity. One of the key advantages of nanoemulsion gel is their ability to sustained and controlled the permeation rate of incorporated drug in oil phase. This research, demonstrated great potential as an advanced method of drug delivery for CP. Overall, the research demonstrated that the successful formulation and evaluation of nanoemulsion loaded gel.

## Future Prospective

The clinical utility of prepared nanoemulsion loaded gel containing CP and SA needs further investigation like animal study after that pre-clinical trial for therapeutic and toxicity effect.

## Conflict of Interest

The authors state no conflict of interest and have received no payment for this project.

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