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# Formulation, Evaluation of Naproxen and Dexpanthenol Emulgel for Transdermal Drug Delivery

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**Abstract**

**Objective:** The aim of this study was to formulate emulgel of naproxen and dexpanthenol, a NSAID and complex of B vitamin, utilizing Carbapol 940 as a gelling agent. Mineral oil and clove oil were used as penetration enhancers.

**Methodology:** In the first step emulsion was developed and it was added in gel base. Formulations were assessed for pH, viscosity, spread ability, conductivity, Homogeneity, drug content, FTIR, XRD, SEM, in-vitro drug release and stability studies were conducted**.**

**Results:** The formulations characteristics showed improved and stable results. F6 showed higher released rate as compared to others formulations, FTIR and XRD confirmed compatibility and stable physical states, while SEM revealed a uniform surface. In-vitro studies indicated a sustained drug release profile suitable for transdermal delivery.

**Conclusion:** It can be concluded that the naproxen-dexpanthenol emulgel demonstrated likely as an effective transdermal drug delivery system. Its stability, enhanced release, and possible physicochemical characteristics showed a promising option for treating inflammatory skin conditions**.**

**Keywords:** Emulgel, Naproxen, Dexpanthenol, Transdermal Drug delivery, NSAIDs.

## Introduction

The transdermal drug delivery system offers an alternative to oral administration by providing therapeutic drug through the skin directly into the systemic circulation [1]. It increases patient compliance while reducing gastrointestinal side effects, hence making it a popular route for managing chronic disease [2].. Controlled as well as sustained release is obtained by TDDS, which drugs that need long term administration. Emulgels are coming to the forefront as a suitable formulation for transdermal delivery since they encompass the properties of emulsions and gels, thereby increasing the solubility and stability of drugs along with easy application [3].

## Naproxen

Naproxen is an non-steroidal anti-inflammatory medicine (drug), which is generally used for arthritis, musculoskeletal disorders, and pain conditions [4]. Naproxen is analgesic, anti-inflammatory, and antipyretic in action [5]. Oral route of administration is associated with gastrointestinal discomfort, ulcers, and bleeding side effects [6]. The transdermal delivery route

of naproxen minimizes systemic side effects by targeting local inflammation sites through the skin itself [7].

**Dexpanthenol**

Dexpanthenol, the alcohol form of pantothenic acid (vitamin B5), is known for its skin healing properties [8]. It promotes wound healing, enhances skin barrier function, and has anti-inflammatory effects [9]. When combined with naproxen, dexpanthenol can provide synergistic effects, improving the healing of damaged skin while reducing inflammation and pain. Dexpanthenol is also largely used in topical formulations as it is considered to be safe and is advantageous for skin health [10].

**Emulgel Formulation**

Emulgel is the type of formulation that has the emulsion incorporated within a gel; it benefits both the characteristics of an emulsion that allows lipophilic drugs to be dissolved and the release and skin penetration characteristics of the gel [11]. The emulsion forms a continuous phase in the formulation, facilitating enhanced drug solubility, while the gel base helps to retain the drug on the skin for prolonged release, enhancing drug absorption. The combination of naproxen and dexpanthenol in an emulgel matrix can thus offer a promising solution for efficient transdermal drug delivery [12].

The purpose of this research work was to develop emulgel of naproxen and dexpanthenol, a NSAID and complex of B vitamin, utilizing Carbapol 940 as a gelling agent. Mineral oil and clove oil were utilized as penetration enhancers. Emulsion was developed and it was added in gel base. Formulations were assessed for pH, viscosity, spread ability, conductivity, Homogeneity, drug content, FTIR, XRD, SEM, in-vitro drug release and stability studies were also conducted**.**

## Materials and Methods

### Materials

Naproxen (active pharmaceutical ingredient) and Dexpanthenol were provided by (Martindow Marker). Carbopol 934, methylparaben, Tween 20 and Span 80, propylparaben were obtained from Pharmacy Lab, UOB. Dialysis cellulose membrane provided by Islamia University Bahawalpure, Pakistan. All other chemicals were utilized of analytical-grade.

### Preparation of Emulgel

Preparation of Emulsion: Oil phase, comprising of Span 20 in liquid paraffin while aqueous phase was prepared by mixing span 80 in purified water. Propyl and Methyl parabens were used mixed in propyl glycol, naproxen and dexpanthenol was dissolved in ethanol. Both the solutions were sheared with the aqueous phase. Mineral oil and clove oil were dissolved in phases.

Preparation of Gel:

The gel phase was prepared by dissolving the Carbopol 934 in purified water with constant stirring and the pH was maintained to 6–6.5 with tri ethanol amine (TEA). Emulsion was properly mixed with the gel in ratio 1:1 with gentle stirring to obtain the emulgel [13, 14]. Various compositions of formulations have been discussed in Table 1.

Table 1: Formulation batches of different composition % W/W

| Components | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Naproxen | 1 | 1 | 1 | 1 | 1 | 1 |
| Dexpanthenol | 5 | 5 | 5 | 5 | 5 | 5 |
| Carbopol 934 | 1 | 1 | 1 | 1 | 1 | 1 |
| Liquid paraffin | 5 | 5 | 5 | 5 | 5 | 5 |
| Span 20 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Tween20 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Propylene glycol** | **5** | **5** | **5** | **5** | **5** | **5** |
| **Ethanol** | **3.0** | **3.0** | **3.0** | **3.0** | **3.0** | **3.0** |
| **Propyl paraben** | **0.05** | **0.05** | **0.05** | **0.05** | **0.05** | **0.05** |
| **Methyl paraben** | **0.02** | **0.02** | **0.02** | **0.02** | **0.02** | **0.02** |
| **Mineral oil** | **1** | **2** | **3** | **-** | **-** | **-** |
| **Clove oil** | | | | **1** | **2** | **3** |
| **Purified water** | **q.s** | **q.s** | **q.s** | **q.s** | **q.s** | **q.s** |

**Calibration Curve**

To prepare the naproxen standard curve, a stock solution was prepared by dissolving 10 mg of naproxen powder in 50 mL of distilled water, followed by shaking for a few minutes. The solution was then diluted to 100 mL using phosphate buffer (pH 7.4). From this stock, serial dilutions were prepared at concentrations of 0.005, 0.01, 0.015, 0.02, 0.025, 0.03, 0.035 and 0.04 mg/mL. The absorbance of each dilution was measured at 233 nm using a UV-Visible spectrophotometer Naproxen Calibration Curve (Shimadzu UV-1601, Japan) [13]. The graph for linearity is delineated in Figure 1.

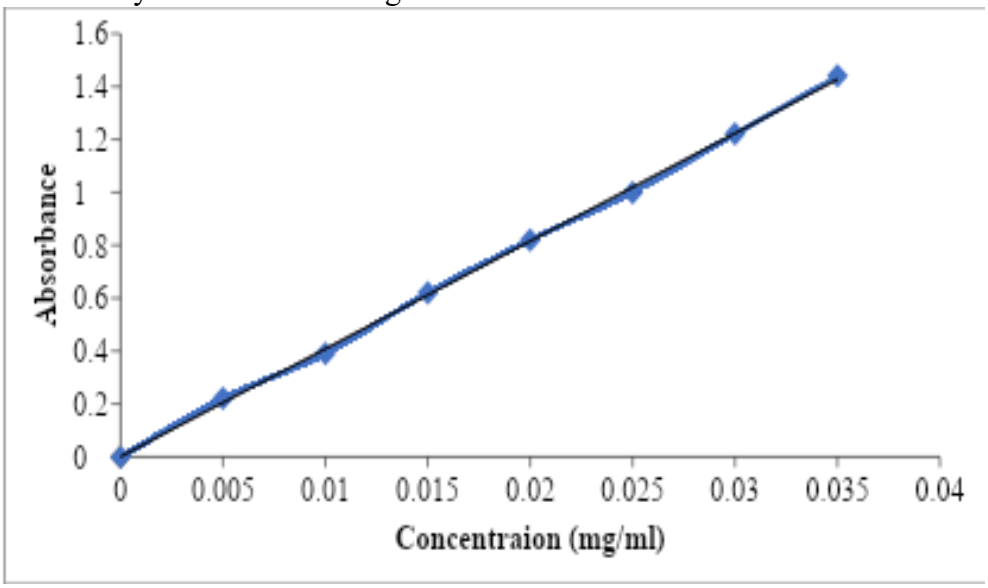



**Fig:1 Calibration curve of Naproxen**

**Physicochemical Characterization**

All the formulation was inspected physically for their color and appearance and other Physicochemical Characterization discussed in table 2.

**pH measurement**

The pH of the prepared formulation were determined at 25°C using a calibrated pH meter (WTW Inolab, Germany) [3,13,14]

**Viscosity**

Viscosity measurements for the different formulations were conducted, using a Brookfield RVDV Ultra Programmable Rheometer (Brookfield Engineering Laboratories, Middleboro, MA) fitted with a CP41 spindle. The measurements were taken at various rotational speeds at a controlled temperature of 25°C. Each sample was tested in triplicate, and the mean value was calculate [3, 13, 14}

**Consistency**

The consistency of the naproxen and dexpanthenol gel was assessed using the dropping cone method. In this technique, a cone attached to a weighted rod is positioned centrally within a gel-filled container, equidistant from the container's edges, with an initial vertical separation of 10 cm. The depth of penetration into the gel after 50 seconds was used as an indicator of the formulation's consistency [3, 13, 14}

**Homogeneity**

A sample containing naproxen and dexpanthenol gel was evaluated visually for homogeneity. To look for lumps, thin, transparent glass tubes filled with gel are examined under a light [3, 13]

**Spreadability**

The Spreadability of each formulation was determined in the diameter label by weighing the formulations after they were placed on a 10g microscopic slide and then pack in on another 10g microscopic slide. Consolidation between two slides was then used to measure the diameter, and a formulation circle was created. The spread of a 0.5 g preparation following the contrast of two 10-g microscope slides was used to assess the Spreadability of each formulation [3,13]

**Conductivity measurement**

Conductivity measurements for both blank and drug-loaded microemulsions were carried out at 25°C using a WTW Cond 1971 conductometer (Weilheim, Germany) on three individual gel samples[3,13]

**Centrifugation**

A centrifuge machine was used to hold 5g of formulation in tubes, which were then circulated at 3000 rpm for 30 minutes in order to determine the phase separation test. The formulation tubes' phase separation was examined at 25°C after a specific amount of time[3,13]

**Drug Content**

To quantify the naproxen content in the formulated gel, a 10 mg sample was dispersed in 100 mL of hydrochloric acid (HCl) and stirred thoroughly. The resulting solution was filtered via a 0.2-µm membrane filter. Naproxen concentration was then analyzed using a calibrated UV-Visible spectrophotometer, and the percentage content was subsequently determined [3,13]

**Table 2**: **Physicochemical Characteristics of Formulations Containing Naproxen and Dexpanthenol**

| Formulation | color | pH | Homogeneity | Consistency | Spreadability (g.cm/s) | Phase separation | Drug content (%) |
|---|---|---|---|---|---|---|---|
| F1 | White | 5.6 | Good | Good | 5.61 | None | 98.12 |
| F2 | White | 5.4 | Good | Good | 5.82 | None | 97.00 |
| F3 | White | 5.5 | Good | Good | 5.93 | None | 98.30 |
| F4 | Light yellow | 5.7 | Good | Good | 6.14 | None | 97.11 |
| F5 | Light yellow | 5.8 | Good | Good | 6.22 | None | 97.21 |
| F6 | Light yellow | 6.3 | Good | Good | 6.23 | None | 97.76 |

**In-vitro Drug Release Study**

An in vitro drug release study was performed utilizing a Franz diffusion cell apparatus (PermeGear, USA)A synthetic cellulose membrane was securely placed between the compartments of the Franz cell, receptor compartment was filled with phosphate buffer up to 12 mL and ethanol mixture (75:25), which served as the receptor medium. A 1 g portion of the microemulsion-based gel was applied to the donor compartment, of the Franz cell. Receptor

compartment was maintained at a constant temperature of 37°C during the experiment. At predetermined time intervals (0.5, 1, 2, 3, 4, 5, 6, and 12 ), 1 mL aliquots were taken from the receptor medium and immediately filled with an equal volume of fresh medium pre-equilibrated at temperature of 37°C. Sample analysis was carried out using UV-Visible spectrophotometry at 333 nm for naproxen and 205 nm for dexpanthenol, following the method described by [15].To ensure reproducibility and account for variability across the six Franz diffusion cells, each test were performed in triplicate.

**In Vitro Release Kinetics of Naproxen and Dexpanthenol Microemulsion-Based Gel"**

The amount of substance impregnated was determined and identified using the spectroscopic technique. The drug dosage (mg) in the receptor sample was collected and measured at specific time intervals between 0 and 24 hours." For each formula, the linearity regression research and the drug impregnation release threshold were assessed. To determine whether the drug release followed zero-order, first-order, Higuchi, Korsmeyer-Peppas, or Hixon-Crowell diffusion models, the correlation coefficient (r) was calculated [13]It is carried out for every formula. Complete computations were performed using a verified software application, DDSolver for Microsoft Excel 2007 [3], in relation to the following kinetics equations.

1. $Qt = Qo + K_o t$ (Zero order)
2. $\ln Qt = \ln Qo + K_1 t$ (First Order)
3. $Qt = K^H\sqrt{t}$ (Higuchi Model)
4. $Mt/M\infty = Kt^n$ (Korsmeyer-Peppas Model)
5. $Qt / Qo = K_k t^n$ [13].( Hixson–Crowell Model)

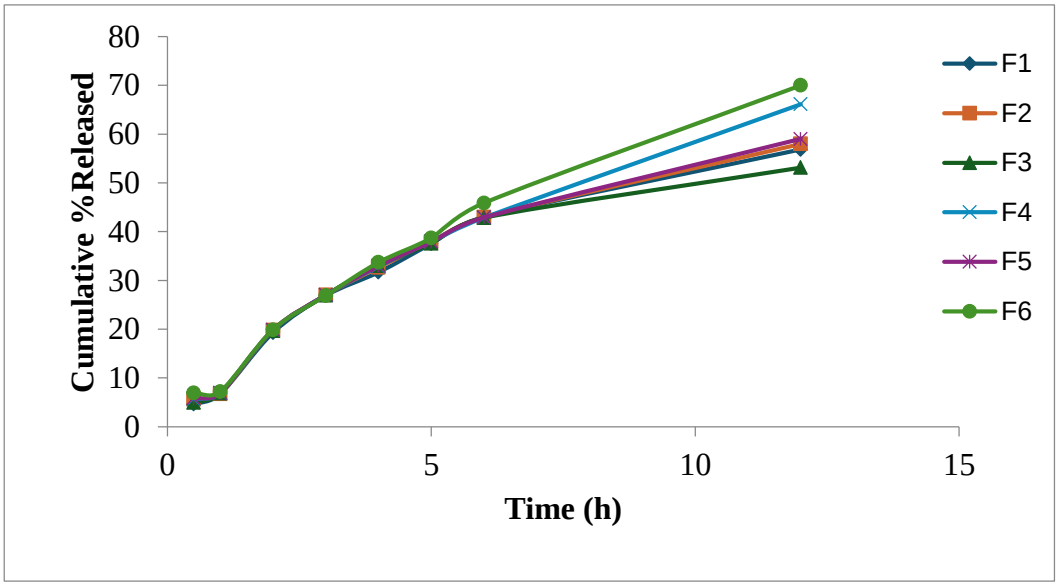



**Fig.2 Release of Naproxen gel 5% (W /V) via cellulose membrane.**

**FTIR**

FTIR analysis was performed to evaluate the compatibility between the drugs and excipients in the formulation.. FTIR spectra were measured in the range of 4000–400 $cm^{-1}$ using a FTIR (Perkin-Elmer, USA). The samples were prepared by mixing the components in their solid state and analyzed under the same conditions as the pure drug and excipient formulations [16].

**X-ray Diffraction**

The transparent nature of naproxen and dexpanthenol in the emulgel was evaluated using X-ray Diffraction analysis. An X-ray diffractometer (X'Pert Pro, PANalytical, Netherlands) was used to obtain the X-ray diffraction patterns of the test materials. The 2θ range was between 5° and 40° [17].

**Scanning Electron Microscopy**

Scanning Electron Microscopy (SEM) was used to analyzed the surface morphology of the emulgel formulation. A small quantity of the formulation was applied to a stub and gold-coated

using a sputter coater. The samples were subsequently analyzed under an SEM (JEOL JSM-6390, Japan) at different [18].

**Stability Studies**

Stability data of the naproxen formulations was assessed at various storage conditions. Samples were stored for three months in (freezer), at 0 ± 1°C in (refrigerator) at 8 ± 0.1°C in (incubator) at 25 ± 0.1°C and in at (incubator) 40 ± 0.1°C Throughout this period, formulations were examined for alterations in physical form, homogeneity, consistency, and pH [19,20].

**Statistical Analysis**

Kinetic data analysis was conducted using DD Solver, an add-in for Microsoft Excel 2007 [11,12,13]. An ANOVA calculation was performed using SPSS software (version 18.0, IBM, USA) [21]. The data would be adjusted with kinetic models.

**Results and Discussion**

The naproxen formulation's color, pH, homogeneity, Spreadability, phase separation, drug content, and consistency were determined (Table 2). The liquefaction, colour, and other parameters of the formulations were all comparable, and the pH was also satisfied. The formulations' pH ranged from 5.82 to 6.7, which is comparable with the pH range used in earlier research on naproxen microemulsion-based gel topically in relation to the pH range of normal human skin (4.5 to 6.5) [19, 20]. Over the course of ninety days, consistency and Spreadability were investigated. Between 4.6 and 5.7 g/cm/s, the Spreadability varies slightly with shearing pressure. The lack of lumps assured homogeneity. The drug concentration of naproxen ranged from 97.0 0 to 99.69%, and the gel based on microemulsions demonstrated good homogeneity. Convenient outcomes for transdermal application are suggested by the total physical examined factors. The results obtained from conducting stability tests for three months at 25 ± 1°C and 40 ± 1°C were satisfactory and confirmed that the formulation is adequate at (25 ± 1°C) as the percentage of drug left over is not decreased over 10% [21]. The standard deviation findings at the end of three months also clearly show that the standard deviation was somewhat higher at 40°C and outside of normal and reasonable ranges, while the standard deviation was smaller at 25 ± 1°C and within a sufficient range. Therefore, it was determined that formulations predict the standards needed to generate the emulgel, which is the subject of interest in extent stability experiments, at 25 ± 1°C.In this investigation, 180 µm thick 0.025-µm cellulose membranes were used, and statistical analysis revealed that the membranes had good release. The highest amount released (69.993%) was displayed by formulation (F6). This result is similar with previous research by Gul et al. [21], who provided a thorough written description of the release of caffeine from water in alcoholic gels and oil emulsions. The first order permeation model was applied to the data from each formulation discussed in table 3. Figure 2 shows how naproxen is released from the transdermal preparation and through the cellulose membrane. The outcomes of the result showed that the amount of drug released through each formulation after 12 hours of investigation was recorded in the receptor solvent contained cellulose membrane (56.83–69.993%).

**Table 3: Naproxen Release from the Formulations Using a Cellulose Membrane**

| Formulation type | Zero (0) Order | First(1st) Order | Higuchi | KorsmeyerPeppass | Hixon-Crowell |
|---|---|---|---|---|---|
| **F1** | 0.9417 | 0.9830 | 0.9801 | 0.9821 | 0.9733 |
| **F2** | 0.9457 | 0.9853 | 0.9910 | 0.9840 | 0.9764 |
| **F3** | 0.9182 | 0.9959 | 0.9801 | 0.9726 | 0.9560 |
| **F4** | 0.9743 | 0.9968 | 0.9901 | 0.9939 | 0.9935 |

| | | | | | |
|---|---|---|---|---|---|
| **F5** | 0.9506 | 0.9879 | 0.9927 | 0.9861 | 0.9797 |
| **F6** | 0.9798 | 0.9978 | 0.9957 | 0.9949 | 0.9964 |

**FTIR Analysis**

No expressive interaction between the drug and excipient was noticed by FTIR for naproxen, dexpanthenol, and emulgel formulation. Naproxen was observed with retention of characteristic peaks at 1720 $cm^{-1}$ corresponding to C=O stretching while at 3300 $cm^{-1}$ with retention of N-H stretching peak in the spectrum for dexpanthenol; it thus, depicts their stability within the emulgel matrix

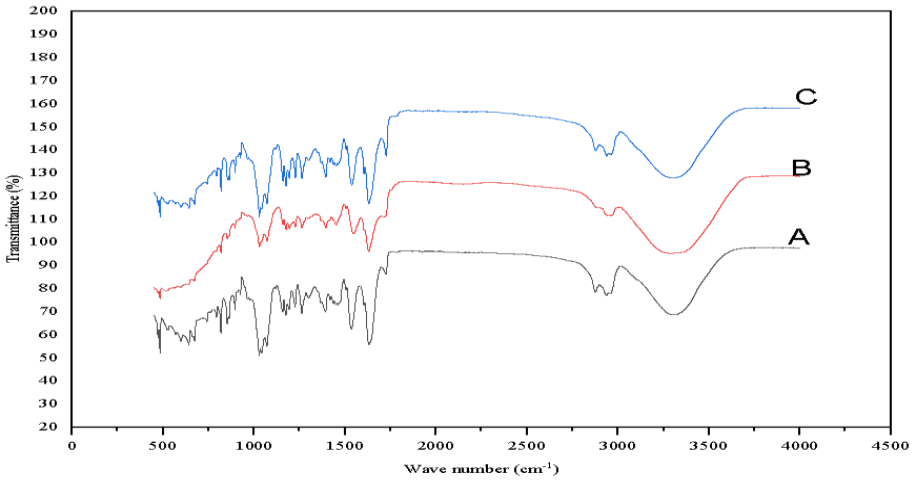



**Fig.3 FTIR spectra of naproxen drug A, Carbopol B, Formulation C**

**XRD Analysis**

The emulgel formulation shows a decrease in the crystallinity of naproxen and dexpanthenol through its XRD pattern, thus depicting an amorphous solid dispersion formed that can significantly enhance the drugs' solubility

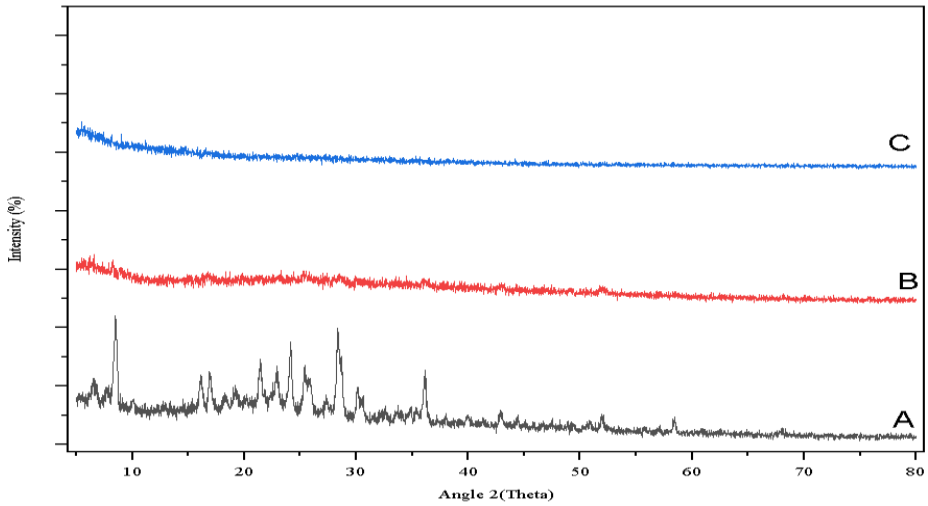
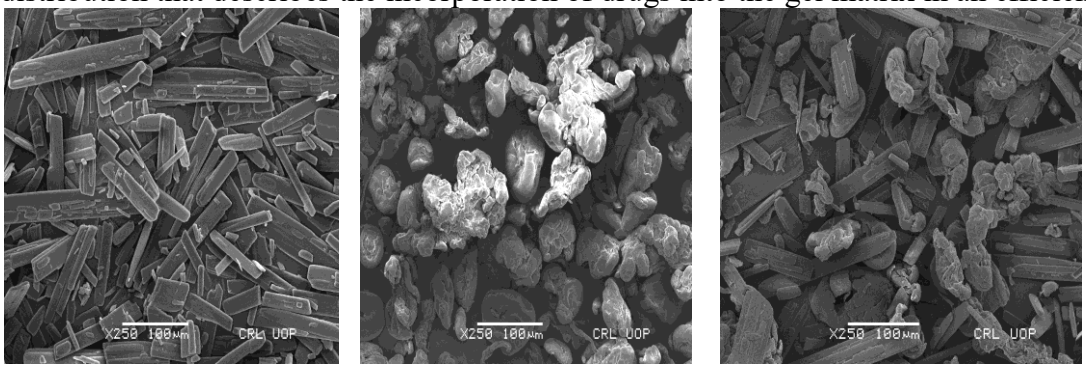



**Fig.4 X-ray diffractogram of naproxen drug A, Carbopol B, Formulation C**

**SEM Microscopy**

SEM images of the emulgel represented a smooth and non-granular surface as well as even distribution that describes the incorporation of drugs into the gel matrix in an efficient way




A B C

**Fig4. SEM of naproxen drug A, Carbopol B, Formulation C**

## CONCLUSION

Transdermal drug delivery would be utilized widely in future to impart best patient compliance; It will be a way out for the hydrophobic drugs in water soluble gel bases, for best stability. The prepared emulgel formulation showed satisfactory physicochemical properties and stability with a controlled release profile, which promises this formulation for the treatment of inflammatory skin disorders. The coexistence of the anti-inflammatory effects of naproxen and skin-healing action of dexpanthenol brings out a synergistic benefit for the transdermal drug delivery. Further clinical studies are advised to be done to assess the efficacy and safety of this preparation in human subjects.

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## CONFLICT OF INTEREST

No conflict of interests.

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