Original Research Article

# Antifungal Topical Nanoemulgel Containing Miconazole Nitrate

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## ABSTRACT

Nanomulgel have emerged as one of the most interesting topical drug delivery system as it has dual release control system i.e. nanoemulsion and gel. Also the stability of nanoemulsion is increased when it is incorporated in gel. Miconazole nitrate is an antifungal medication topically administered to treat skin infections such as athlete's foot, jock itch and ringworm. The aim of the present research work was to investigate the potential of nanoemulgel in enhancing the topical delivery of hydrophobic drug. MCZ nanoemulsions were prepared using span 80, tween 80, propylene glycol and different conc. of sunflower oil by High pressure homogenization technique. The prepared nanoemulsions were evaluated for pH, drug content, centrifugation, globule size and zeta potential. F2 showed highest drug content 91.26%.The globule size are found to be satisfactory range of nanoemulsion. The drug release kinetics is in the order of F2>F3>F4>F5>F1.And Nanoemulgel is prepared by using Carbopol 934 as gelling agent The release kinetics of nanoemulgel was found to obey zero order kinetics. The nanoemulgel was found to be stable with respect to physical appearance, pH, rheological properties spreadability and drug content at all temperature and conditions for two months. Hence, in the present study it can be concluded that Miconazole Nitrate nanoemulgel formulation is a promising system for the topical drug delivery and also an alternative method to deliver the hydrophobic drugs in water soluble gel bases.

*Key Words:* Hydrophobic drugs, Nanoemulgel, Miconazole nitrate, Topical drug delivery.

## INTRODUCTION

For decades, human skin has provided a unique location for the delivery of a variety of medicines, both systemically and locally. The direct accessibility of the skin as a target organ for diagnostic and therapy is a unique characteristic of dermatological pharmacology.

The use of translucent gels in cosmetics and medicinal preparations has increased within the primary category of semisolid preparations. Gels are a more recent type of dosage form that is made by encasing significant volumes of aqueous or hydroalcoholic liquid in a network of colloidal solid particles. When opposed to an ointment or cream base, they contain a larger aqueous component, which allows for better drug solubility and easy drug migration via a vehicle that is virtually a liquid. In terms of ease of use and patient acceptance, these are far superior. Despite the many benefits of gels, hydrophobic drug delivery is a major limitation. To get around this limitation, nanoemulgels are created and used, allowing even a hydrophobic therapeutic moiety to benefit from gels' unique properties. [3, 5].

Nanoemulgels are dosage formulations that mix gels with nanoemulsions. The main goal of nanoemulgel drug delivery is to distribute

hydrophobic medicines so that they can benefit from the benefits of gel formulation as well. Because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension while simultaneously increasing the viscosity of the aqueous phase, there has been a lot of interest in using novel polymers with complex functions as emulsifiers and thickeners in recent years. Nanomulsions are elegant and easy to remove. They can also penetrate the skin quite well. [12,]

Miconazole nitrate comes as creams and lotions that may be purchased commercially. The low spreading coefficient, sticky character, and lack of stability are all disadvantages of these formulations. Topical nanoemulgel formulations have been offered as a way to get around these drawbacks. As a result, Nanomulgels have shown to be a great boon in the administration of hydrophobic medicines topically while also offering gel formulation benefits. The aim of the present research work is to design, develop and evaluate miconazole nitrate nanoemulgel for topical fungal disease.

## MATERIALS AND METHODS
### MATERIALS

Antifungal drug i.e., Miconazole nitrate from yarrow chemicals, Mumbai, india. Carbopol 93 Yarrow chemicals., Sunflower oil from local company. Tween 80; Span 80, Methanol; Hi-Media laboratory Pvt. Ltd, Mumbai, India. Propylene glycol from Loba cheme laboratory., Methyl paraben from SD Fine Chem limited, Mumbai. propyl paraben was purchased from Loba cheme laboratory. Distilled water was used for all experiments. All chemicals were of pharmaceutical grade and used without further modification.

### Methodology

High pressure homogenization method used for the formulation,
There are 3 steps involved,
1. Preparation of nanoemulsion
2. Preparation of gel
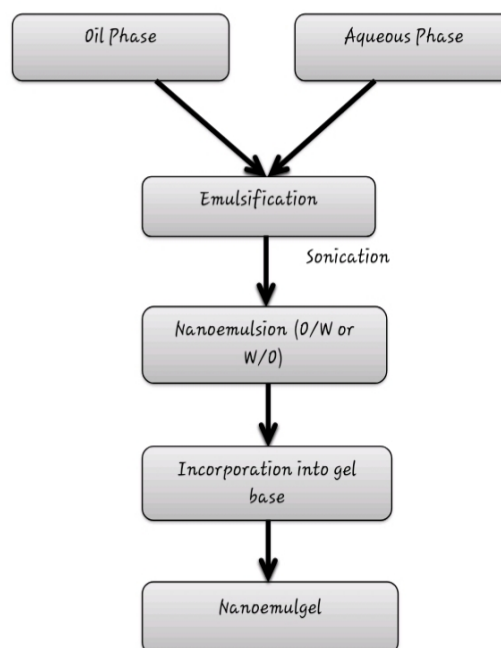3. Incorporation of nanoemulsion into gel



**Fig.no 01: Flow chart of preparation**

### Preparation of nanoemulsion

High pressure homogenization was used to make a miconazole nitrate nanoemulsion. The nanoemulsion's oil phase was made by dissolving span 80 in sunflower oil, while the aqueous phase was made by dissolving tween 80 in filtered water. The drug was dissolved in methanol, while the methyl and propyl parabens were dissolved in propylene glycol, and both solutions were combined with the oil phase. Both the oily and aqueous phases were heated to 70-80 °C separately, then the oily phase was introduced to the aqueous phase and homogenised for 1 hour before cooling to room temperature.

**Tab no.01: Composition of nanoemulsion**

| Ingredients/formulation code | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Miconazole nitrate (w/w) | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 |
| Sunflower oil (v/v) | 5 | 4.5 | 4 | 3.5 | 3 |
| Tween 80 (v/v) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Span 80 (v/v) | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 |
| Propylene glycol (v/v) | 4 | 4 | 4 | 4 | 4 |
| Methanol (v/v) | 2 | 2 | 2 | 2 | 2 |
| Methyl paraben (w/w) | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Propyl paraben (w/w) | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| Water (v/v) | 25 | 25 | 25 | 25 | 25 |

## Characterization of Nanoemulsion

### 1. Physical examination[35]

The visual appearance, phase separation, homogeneity, and consistency of the produced nanoemulsion formulations were all screened.

### 2. Centrifugation stability study[35]

Distilled water was used to dilute nanoemulsions. The nanoemulsions were then centrifuged at 1000 rpm for 15 minutes at 30°C to check for changes in homogeneity.

### 3. Measurement of pH[35]

A digital pH metre was used to determine the pH of nanoemulsion formulations. pH was measured by dissolving 1 mL of nanoemulsion in 100 mL of pure water.

### 4. Drug content determination[55]

A UV visible spectroscopic method was used to determine the drug content of a nanoemulsion formulation. Nanoemulsion formulation with methanol yielded a 2g/ml aliquot. At λ max, the samples were measured. Three copies of the results were taken.

### 5. Globule size determination[54]

Malvernzeta sizer was used to determine the nanoemulsion's globule size. With the help of a plastic syringe or micropipette, the nanoemulsion (1-1.5 ml) was transferred to a disposable polystyrene cuvette, and the droplet size of the nanoemulsion was determined using a combination of laser doppler velocimetry and phase analysis light scattering (PALS) at a 90°angle at 25°C.

### 6. Zeta potential[54]

Zetasizer was used to calculate the zeta potential. Because electrical charges on particles impact the rate of flocculation, the zeta potential is primarily helpful for evaluating flocculation.

### 7. In-vitro Drug Release Study

The drug release tests were conducted using a Franz diffusion cell (effective diffusion area 3.14 cm2 and cell volume 110 ml). In a cellophane membrane, nanoemulsion (5ml) is taken. Between the donor and receptor chambers of the diffusion cell, a cellophane membrane was clamped. To solubilize the drug, the receptor chamber was filled with a 25ML solution of newly produced phosphate buffer (pH 5.5) and methanol (80:20) solution. A magnetic stirrer was used to agitate the receptor chamber. After proper dilutions, the samples were collected at appropriate time intervals and tested for drug content using a UV visible spectrophotometer at λ -max.

### 8. Drug release kinetic studies[30]

The release data were fitted to zero order, first order, Higuchi model, and korsmeyer's peppas models to evaluate the mechanism of drug release from the topical nanoemulsion.

### Preparation of gel

Preparation of carbopol 934 Gel[24]

The carbopol gel formulations were made by dispersing Carbopol 934 in filtered water while stirring constantly at a moderate speed, and then adjusting the pH to 6 to 6.5 using Tri ethanol amine (TEA).

To make the MCZ nanoemulgel, nanoemulsion was combined with the gel in a 1:1 ratio with moderate stirring.

**Tab no.02: composition of nanoemulgel**

| Ingredients/ Formulation code | GF1 | GF2 | GF3 | GF4 | GF5 |
|---|---|---|---|---|---|
| MCZ Nanoemulsion (w/v) | 25ml | 25ml | 25ml | 25ml | 25ml |
| Carbopol 934 (w/w) | 1 | 1 | 1 | 1 | 1 |
| Glutaradehyde (v/v) | 0.02ml | 0.02ml | 0.02ml | 0.02ml | 0.02ml |
| Triethanolamine (v/v) | 0.05ml | 0.05ml | 0.05ml | 0.05ml | 0.05ml |
| Distilled water (qs) (v/v) | 50ml | 50ml | 50ml | 50ml | 50ml |

## CHARACTERIZATION OF NANOEMULGEL

Prepared nanoemulgel of Miconazole Nitrate were evaluated for the following parameters.

### 1. Physical Examination[30]

The colour, homogeneity, consistency, and phase separation of the produced nanoemulgel formulations were visually examined.

### 2. Measurement of pH[30]

A digital pH metre was used to determine the pH of nanoemulgel compositions. 1 g of gel was dissolved in 100 mL distilled water, left for 2 hours, and the pH was measured.

### 3. Rheological Study[30]

A Brookfield Viscometer with spindle 64 was used to determine the viscosity of the prepared batches. The viscosity of the formulation to be determined was added to the beaker. The spindle was lowered perpendicular to the nanoemulgel's centre, taking care not to contact the adapter's bottom, and cycled at a speed of 100 rpm.

### 4. Spreadability[57]

Two glass slides (14*5cm) of identical length were used to test the gel formulation's spreadability. 1gm gel was applied to one of the glass slides, the other slide was placed over it, and weights (125g) were placed on it, and the time it took for the glass slide to slip away from the first glass slide was measured in seconds. Better spreadability is indicated by a shorter interval. Spreadability was calculated by using the formula,
$$S = M*L/T$$

Where, S = spreadability, M = Weight tied to upper slide, L = Length of glass slides, T = Time taken to separate the slides completely from each other.

### 5. Drug Content Determination[57]

By dissolving 1g of nanoemulgel in 100ml of solvent, the drug concentration in Gellified nanoemulsion was determined (methanol). In a UV/VIS spectrophotometer, absorbance was measured after a sufficient dilution at $\lambda$ - max.

### 6. *In-vitro* drug release study[56]

The drug release tests were conducted using a Franz diffusion cell (effective diffusion area 3.14 cm2 and cell volume 110 ml). Nanoemulgel (1g) was placed to the cellophane membrane's surface. Between the donor and receptor chambers of the diffusion cell, a cellophane membrane was clamped. To solubilize the drug, the receptor chamber was filled with a 25ML solution of freshly prepared phosphate buffer (pH 5.5) and methanol (80:20) solution. A magnetic stirrer was used to agitate the receptor chamber. After proper dilutions, the samples were collected at appropriate time intervals and tested for drug content using a UV visible spectrophotometer at $\lambda$-max.

### 7. Drug release kinetic studies[30]

The release data was fitted to Zero order, First order kinetics, Higuchi's, and Korsmeyers peppa's equations to investigate the mechanism of drug release from the topical gel.

### 8. Accelerated stability studies[35, 58]

The best formulations were submitted to two months of stability testing at 402oC and 75% RH. At two-month intervals, parameters such as appearance, drug content, phase separation, and in-vitro release were evaluated.

## RESULTS & DISCUSSION
### Preformulation studies of miconazole nitrate

Tab.No.5: Preformulation studies of MCZ

| Properties | | Reported | Observed |
|---|---|---|---|
| Appearance | | White crystalline powder | White crystalline powder |
| Odour | | Odourless | Odourless |
| Melting point($^0$C) | | 179-182ºC | 179ºC ±1.52 |
| Solubility | Methanol | 13mg/ml | 10mg/ml |
| | PBS pH 5.5 | 0.3mg/ml | 0.1mg/ml |
| | Propylene glycol | 43 mg/ml | 40mg/ml |
| Identification (UV) | | 272nm | 272nm |

## Spectrum measurement
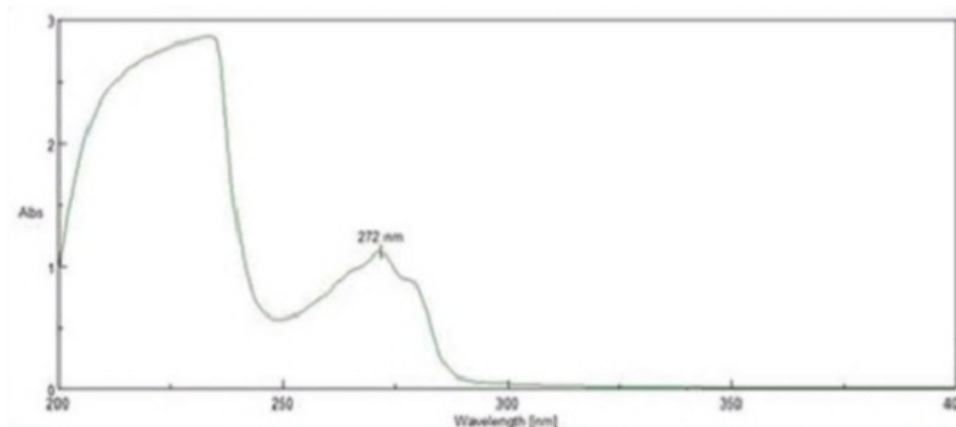


Fig.No. 5: λ-max of Miconazole Nitrate in methanol

Prior to that, preformulation experiments for the medication were conducted, followed by formulation production and assessment. The following are the outcomes of the following experiment.

### 1. Organoleptic characteristics:
MCZ's organoleptic characteristics, such as general description, colour, smell, and taste, were studied. MCZ was discovered to be a white crystalline powder that is somewhat bitter, odourless, and falls within the published literature limitations. Table No.05 displays the results observed.

### 2. Melting point:
Miconazole Nitrate has a melting point of 1790°C, which is within the pharmacopoeia's range of 179-1820°C with decomposition, confirming purity of the medicinal sample. Table No. 05 shows the result observed.

### 3. Solubility:
Miconazole Nitrate is soluble in methanol, propylene glycol, and phosphate buffer, according to the Indian pharmacopoeia's solubility profile. Table No. 05 shows the data obtained.

### 4. Spectrum measurement:
Between 200 and 400 nm, the absorption spectra of pure Miconazole Nitrate was scanned. In methanol, the λ-max of pure MCZ was determined to be 272 nm. Figure No. 05 depicts the results achieved.

### Standard calibration curve of Miconazole Nitrate

Tab.No.6: Standard calibration curve of MCZ

| Sl No. | Concentration of Miconazole Nitrate (μg/ml) | Absorbance |
|---|---|---|
| 01. | 0 | 0±0 |
| 02. | 5 | 0.05±0.01 |
| 03. | 10 | 0.11±0.01 |
| 04. | 15 | 0.16±0.01 |
| 05. | 20 | 0.21±0.02 |
| 06. | 25 | 0.25±0.01 |
| 07. | 30 | 0.3±0.05 |
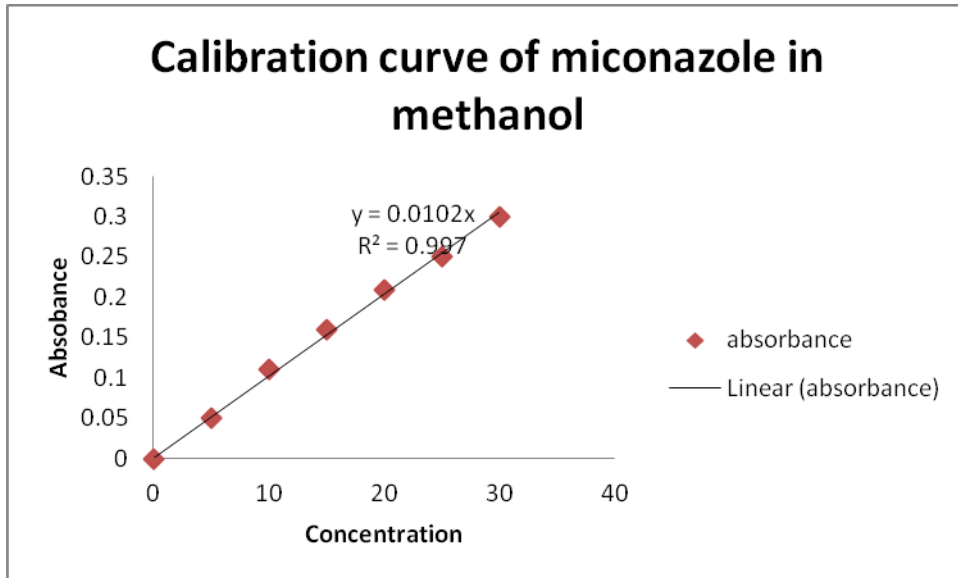
**Fig.No.05: Standard calibration curve of Miconazole Nitrate**

Miconazole Nitrate calibration curve was obtained at a wavelength of 272 nm in the concentration range of 5-30 g/ml. It exhibits high linearity, as illustrated in fig. 06, with a regression coefficient of 0.997 (r2 value).

## DRUG – POLYMER COMPATABILITY STUDIES
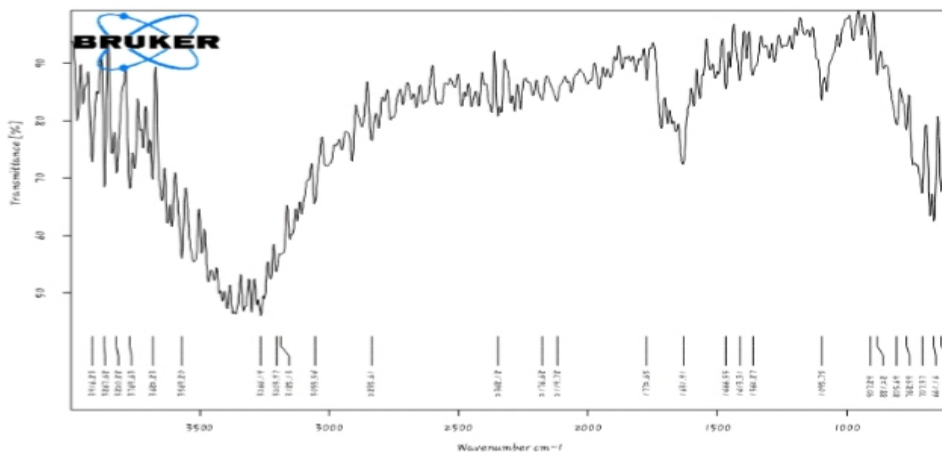


**Fig.No.06: FT-IR spectrum of Miconazole Nitrate**
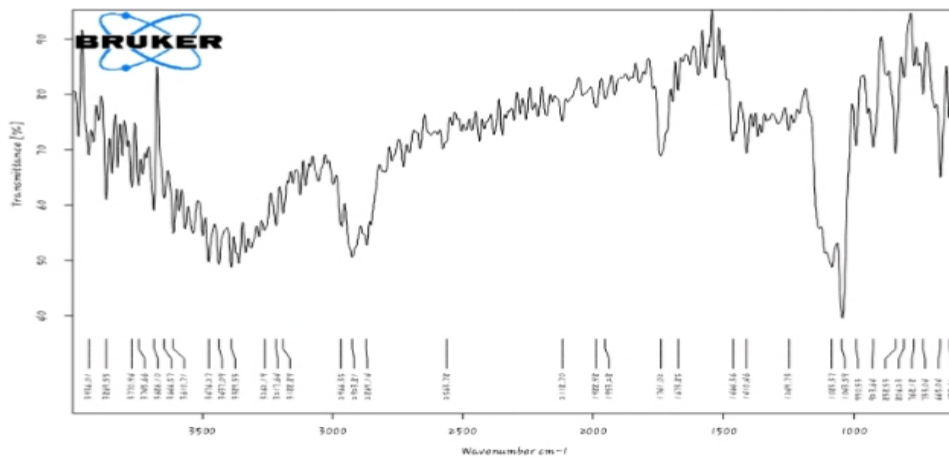


**Fig.No.07: FT-IR spectrum of MCZ + POLYMERS**

**Tab No.07 : Comparison of FT – IR spectra of MCZ & Polymers**

| SI No | Functional Group | Reported Frequency(cm⁻¹) | Observed frequency | |
|---|---|---|---|---|
| | | | Drug | Drug+Polymers |
| 1 | C=N | 1640 | 1631.91 | 1464.36 |
| 2 | C-H(aliphatic) | 2960 | 2835.61 | 2923.81 |
| 3 | C-H(aromatic) | 3048 | 3055.54 | 2966.35 |
| 4 | C=O | 1635 | 1631.91 | 1464.36 |

The IR spectra of the drug-polymer combinations and optimal formulation were compared to the standard spectrum of the pure medication Miconazole Nitrate, and the distinctive peaks associated with particular functional groups and the bonds of the molecules were recorded in table no.07.

The peak ranges from C=N 1631.91 to 1464.36cm⁻¹,C-H aliphatic 2835.61 to 2923.8cm⁻¹,C-H aromatic 3055.54-2966.35cm⁻¹,C=O 1631.91 to 1464.36cm⁻¹.

The ranges of peak values were found to be same, suggesting that Miconazole Nitrate did not interact with various polymers, indicating the drug's stability in the formulation.

## PSEUDO TERNARY PHASE STUDY

**Tab No.08: Pseudo ternary phase studies**

| SI. No | ml of Oil | Surfactant mixture(ml) | Water(ml) | Type of emulsion |
|---|---|---|---|---|
| 1 | 1 | 1 | 0 | No Emulsion |
| 2 | 1 | 1 | 1 | Gel |
| 3 | 1 | 7 | 2 | Gel |
| 4 | 1 | 6 | 3 | Nanoemulsion |
| 5 | 1 | 5 | 4 | Nanoemulsion |
| 6 | 1 | 4 | 5 | Emulsion |
| 7 | 1 | 3 | 6 | Gel |
| 8 | 1 | 2 | 7 | Emulsion |
| 9 | 1 | 1 | 8 | Emulsion |

From the pseudo ternary phase system, The S/Co S Mixture ratio is found out as 3:2, indicated that the best nanoemulsion formation region. The region is noted in Tab no.08.



**Fig no.08 :  Different concentrations of Prepared S/Co-S mixtures**

## EVALUATION OF NANOEMULSION
## 1. Physical examination

**Tab.No.9: Physical examination of various formulations of nanoemulsion**

| Formulation code | Appearance | Phase Separation | Homogenity | Consistency |
|---|---|---|---|---|
| F1 | Milky white | None | Good | Good |
| F2 | Milky white | None | Excellent | Excellent |
| F3 | Milky white | None | Good | Excellent |
| F4 | Milky white | None | Good | Good |
| F5 | Milky white | None | Excellent | Good |

## 1. Physical examination

Miconazole Nitrate emulsions were produced in a milky white colour with a smooth, homogeneous appearance and outstanding consistency. The formulations showed no signs of phase separation. The outcomes were shown in table No.9. Figure 09 depicts the prepared nanoemulsion.



**Fig.No.09: Prepared Miconazole nitrate nanoemulsion**

## 2. Centrifugation stability, pH, Drug content

**Tab.No.10: Centrifugation stability, pH & Drug content of various formulations of nanoemulsion**

| Formulation code | Centrifugation study | pH | Drug content % |
|---|---|---|---|
| F1 | No phase separation | 6.30 ±0.01 | 79.13 ± 0.39 |
| F2 | No phase separation | 6.27 ±0.01 | 91.26 ± 0.02 |
| F3 | No phase separation | 6.24 ± 0.01 | 88.55± 0.25 |
| F4 | No phase separation | 6.13 ± 0.01 | 86.12 ± 0.12 |
| F5 | No phase separation | 6.07 ± 0.01 | 81.46 ± 0.16 |

There was no phase separation, indicating that all of the produced nanoemulsions were stable. All formulations had pH values ranging from 6.07 to 6.30, which are deemed suitable for avoiding skin irritation when applied to the skin. The drug content of nanoemulsions was determined by spectrophotometry at 272 nm, with drug concentrations ranging from 79.13 to 91.26 percent. The highest drug content was found with F2 (91.26 %). The results were shown in the table No.10.

**Tab no.,11 : Globule size determination of various formulations**

| Formulation code | Globule size(d.nm) |
|---|---|
| F1 | 26.82 |
| F2 | 7.9 |
| F3 | 41.6 |
| F4 | 9.4 |
| F5 | 27.72 |

The mean globule size of nanoemulsion F2 was determined to be 7.9d.nm, which is within the literature limits, demonstrating nanoemulsion homogeneity. Table No.11 and Figure No.11-15 show the results.

## 3. Globule size determination
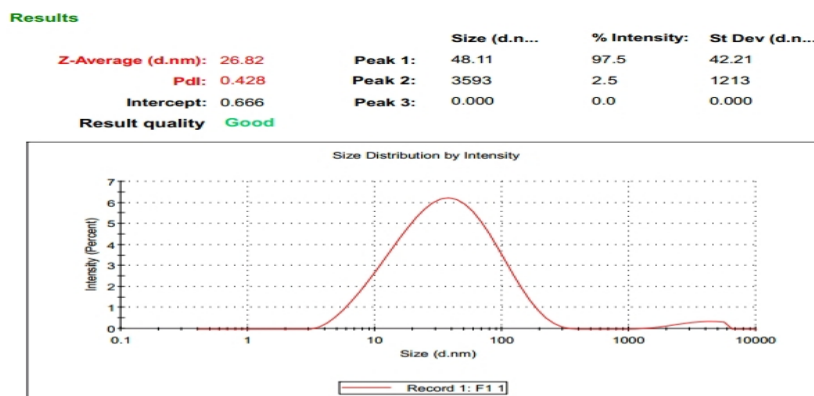


**Fig no.11 : Globule size distribution of Nanoemulsion F1**

**Results**

| | | | Size (d.n... | % Intensity: | St Dev (d.n... |
|---|---|---|---|---|---|
| Z-Average (d.nm): | 7.989 | Peak 1: | 12.82 | 100.0 | 10.43 |
| PdI: | 0.328 | Peak 2: | 0.000 | 0.0 | 0.000 |
| Intercept: | 0.647 | Peak 3: | 0.000 | 0.0 | 0.000 |
| Result quality | Good | | | | |
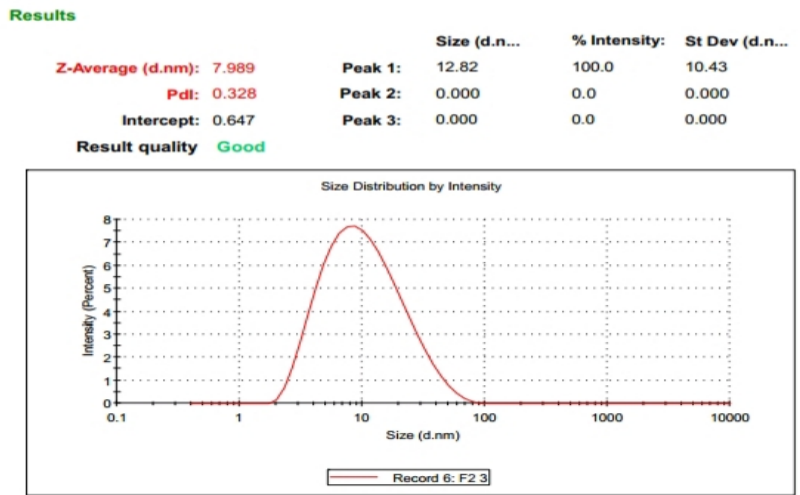


**Fig no.12 : Globule size distribution of Nanoemulsion F2**

**Results**

| | | | Size (d.n... | % Intensity: | St Dev (d.n... |
|---|---|---|---|---|---|
| Z-Average (d.nm): | 41.60 | Peak 1: | 62.76 | 100.0 | 41.13 |
| PdI: | 0.316 | Peak 2: | 0.000 | 0.0 | 0.000 |
| Intercept: | 0.677 | Peak 3: | 0.000 | 0.0 | 0.000 |
| Result quality | Good | | | | |
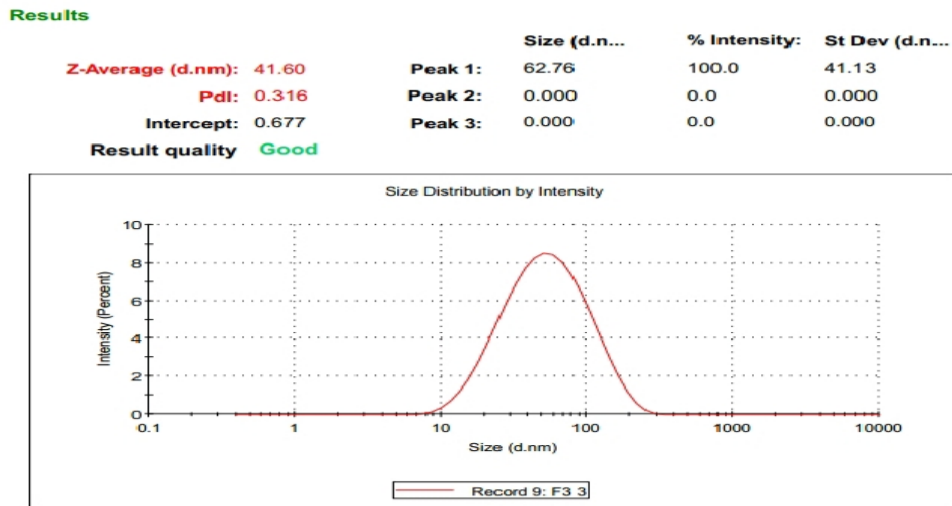


**Fig no.13 : Globule size distribution of Nanoemulsion F3**

**Results**

| | | | Size (d.n... | % Intensity: | St Dev (d.n... |
|---|---|---|---|---|---|
| Z-Average (d.nm): | 9.441 | Peak 1: | 14.72 | 94.8 | 10.79 |
| PdI: | 0.355 | Peak 2: | 1.273 | 2.7 | 0.3867 |
| Intercept: | 0.650 | Peak 3: | 3016 | 2.5 | 1341 |
| Result quality | Good | | | | |
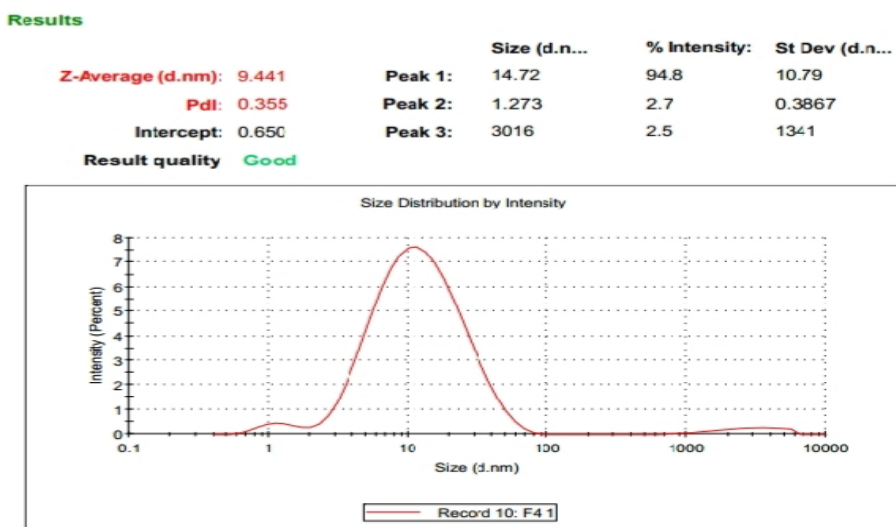


**Fig no.14 : Globule size distribution of Nanoemulsion F4**

**Results**

|  | | Size (d.n... | % Intensity: | St Dev (d.n... |
|---|---|---|---|---|
| Z-Average (d.nm): 27.72 | Peak 1: | 42.70 | 100.0 | 28.11 |
| Pdl: 0.332 | Peak 2: | 0.000 | 0.0 | 0.000 |
| Intercept: 0.661 | Peak 3: | 0.000 | 0.0 | 0.000 |
| Result quality  Good | | | | |
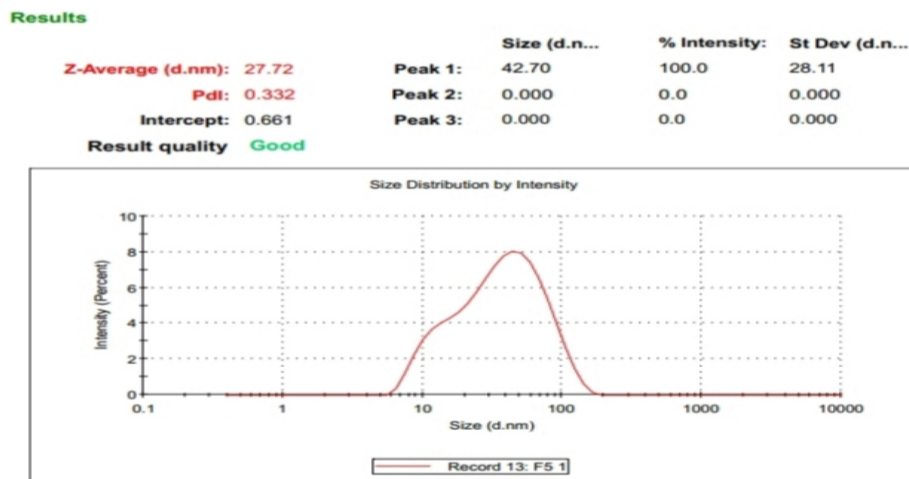
**Fig no.15 : Globule size distribution of Nanoemulsion F5**

## 4. Zeta potential of MCZ Nanoemulsion

**Tab.No.12:  Zeta potential of MCZ nanoemulsion F2**

| Formulation code | Zetapotential |
|---|---|
| F2 | -32.4 |

**Results**

|  | | Mean (mV) | Area (%) | Width (mV) |
|---|---|---|---|---|
| Zeta Potential (mV): -32.4 | Peak 1: | -32.4 | 100.0 | 8.75 |
| Zeta Deviation (mV): 8.75 | Peak 2: | 0.00 | 0.0 | 0.00 |
| Conductivity (mS/cm): 0.0207 | Peak 3: | 0.00 | 0.0 | 0.00 |
| Result quality : Good | | | | |
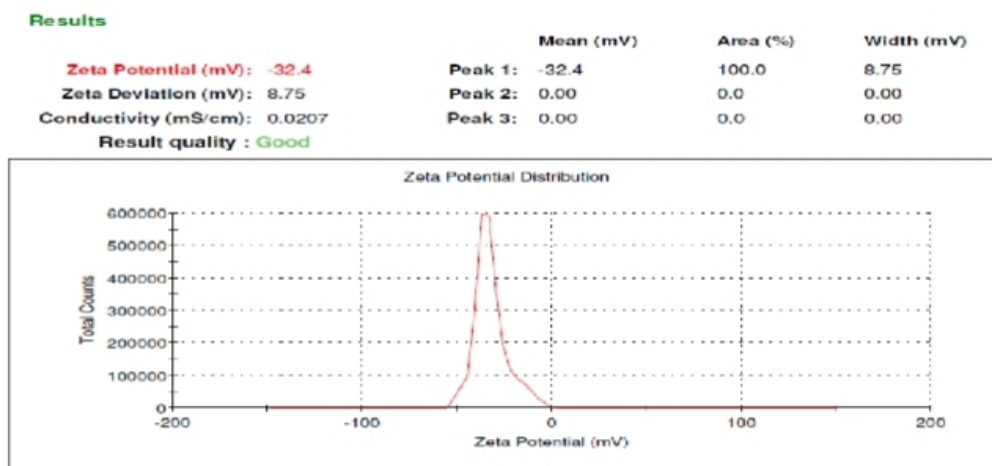
**Fig.No.16: Zeta potential graph**

Formulation F2's zeta potential was determined to be -32.4 mV. The negative zeta potential means that the nanoemulsion droplets have no charge and that the system is stable since there is no flocculation.

## 5. IN-VITRO DRUG RELEASE STUDY

**Tab no.13: In-vitro drug release study of nanoemulsion**

| Time in hr | Percentage Cumulative Drug Release* | | | | |
|---|---|---|---|---|---|
|  | F1 | F2 | F3 | F4 | F5 |
| 0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 |
| 1 | 3.03±0.015 | 6.01±0.02 | 8.01±0.02 | 4.04±0.01 | 7.95±0.05 |
| 2 | 4.8±0.02 | 8.3±0.04 | 10.1±0.03 | 4.89±0.04 | 11.93±0.015 |
| 3 | 6.58±0.01 | 10.02±0.04 | 13.5±0.02 | 5.9±0.02 | 14.32±0.02 |
| 4 | 8.4±0.05 | 12.5±0.02 | 17.9±0.01 | 7.4±0.02 | 18.27±0.03 |
| 6 | 13.24±0.03 | 16.89±0.01 | 23.46±0.016 | 13.63±0.01 | 24.8±0.03 |
| 7 | 17.05±0.01 | 21.5±0.05 | 29.54±0.02 | 19.4±0.015 | 26.25±0.05 |
| 8 | 20.95±0.02 | 28.07±0.016 | 32.01±0.04 | 23.3±0.02 | 34.95±0.02 |
| 12 | 36.2±0.017 | 42.01±0.02 | 46.8±0.03 | 40.08±0.04 | 48.1±0.04 |
| 24 | 72.5±0.04 | 92.3±0.01 | 90.6±0.02 | 88.2±0.01 | 88.91±0.01 |
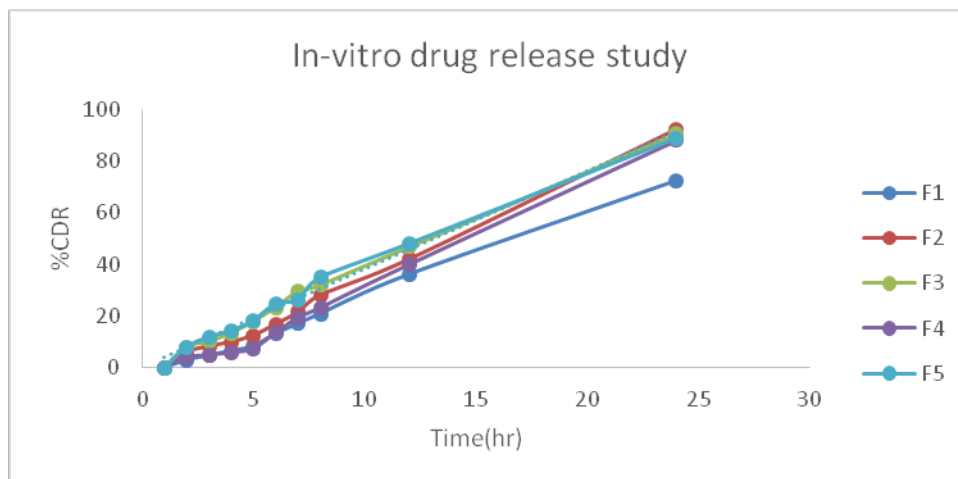
**Fig No.17 : In-vitro drug release of various formulations**

The drug can be seen being released from all nanoemulsion formulations, and the nanoemulsion formulations may be ordered in the following order: F2>F3>F4>F5>F1 Tab no. 13 and Fig no. 17 illustrate the results.

## 6. DRUG RELEASE KINETIC STUDIES

**Tab no.14: Drug release kinetics of F1**

| Time | Log time | Square root of time | %cumulative release of F1 | Log % cumulative release of F1 | %Cumulative remaining | Log cumulative remaining |
|---|---|---|---|---|---|---|
| 0 | 0 | 1 | 0 | 0 | 100 | 2 |
| 1 | 0.30103 | 1.414214 | 3.03 | 0.481443 | 96.97 | 1.986637 |
| 2 | 0.477121 | 1.732051 | 4.8 | 0.681241 | 95.2 | 1.978637 |
| 3 | 0.60206 | 2 | 6.58 | 0.818226 | 93.42 | 1.97044 |
| 4 | 0.69897 | 2.236068 | 8.4 | 0.924279 | 91.6 | 1.961895 |
| 6 | 0.778151 | 2.44949 | 13.24 | 1.121888 | 86.76 | 1.93832 |
| 7 | 0.845098 | 2.645751 | 17.05 | 1.231724 | 82.95 | 1.918816 |
| 8 | 0.90309 | 2.828427 | 20.95 | 1.321184 | 79.05 | 1.897902 |
| 12 | 1.079181 | 3.464102 | 36.2 | 1.558709 | 63.8 | 1.804821 |
| 24 | 1.380211 | 4.898979 | 72.5 | 1.860338 | 27.5 | 1.439333 |

**Tab No.15:  Drug release kinetics of F2**

| Time | Log time | Square root of time | %Cumulative release of F2 | Log % cumulative release of F2 | %Cumulative remaining | Log cumulative remaining |
|---|---|---|---|---|---|---|
| 0 | 0 | 1 | 0 | 0 | 100 | 2 |
| 1 | 0.30103 | 1.414214 | 6.01 | 0.778874 | 93.99 | 1.973082 |
| 2 | 0.477121 | 1.732051 | 8.3 | 0.919078 | 91.7 | 1.962369 |
| 3 | 0.60206 | 2 | 10.02 | 1.000868 | 89.98 | 1.954146 |
| 4 | 0.69897 | 2.236068 | 12.5 | 1.09691 | 87.5 | 1.942008 |
| 6 | 0.778151 | 2.44949 | 16.89 | 1.22763 | 83.11 | 1.919653 |
| 7 | 0.845098 | 2.645751 | 21.5 | 1.332438 | 78.5 | 1.89487 |
| 8 | 0.90309 | 2.828427 | 28.07 | 1.448242 | 71.93 | 1.85691 |
| 12 | 1.079181 | 3.464102 | 42.01 | 1.623353 | 57.99 | 1.763353 |
| 24 | 1.380211 | 4.898979 | 92.3 | 1.965202 | 7.7 | 0.886491 |

**TabNo.16:  Drug release kinetics of F3**

| Time | Log time | Square root of time | %Cumulative release of F3 | Log % cumulative release of F3 | %Cumulative remaining | Log cumulative remaining |
|---|---|---|---|---|---|---|
| 0 | 0 | 1 | 0 | 0 | 100 | 2 |
| 1 | 0.30103 | 1.414214 | 8.01 | 0.903633 | 91.99 | 1.963741 |
| 2 | 0.477121 | 1.732051 | 10.1 | 1.004321 | 89.9 | 1.95376 |
| 3 | 0.60206 | 2 | 13.5 | 1.130334 | 86.5 | 1.937016 |
| 4 | 0.69897 | 2.236068 | 17.9 | 1.252853 | 82.1 | 1.914343 |
| 6 | 0.778151 | 2.44949 | 23.46 | 1.370328 | 76.54 | 1.883888 |
| 7 | 0.845098 | 2.645751 | 29.54 | 1.47041 | 70.46 | 1.847943 |
| 8 | 0.90309 | 2.828427 | 32.01 | 1.505286 | 67.99 | 1.832445 |
| 12 | 1.079181 | 3.464102 | 46.8 | 1.670246 | 53.2 | 1.725912 |
| 24 | 1.380211 | 4.898979 | 90.6 | 1.957128 | 9.4 | 0.973128 |

**Tab No.17: Drug release kinetics of F4**

| Time | Log time | Square root of time | % Cumulative release of F4 | Log % cumulative release of F4 | %Cumulative remaining | Log cumulative remaining |
|------|----------|---------------------|---------------------------|-------------------------------|----------------------|--------------------------|
| 0 | 0 | 1 | 0 | 0 | 100 | 2 |
| 1 | 0.30103 | 1.414214 | 4.04 | 0.606381 | 95.96 | 1.98209 |
| 2 | 0.477121 | 1.732051 | 4.89 | 0.689309 | 95.11 | 1.978226 |
| 3 | 0.60206 | 2 | 5.9 | 0.770852 | 94.1 | 1.97359 |
| 4 | 0.69897 | 2.236068 | 7.4 | 0.869232 | 92.6 | 1.966611 |
| 6 | 0.778151 | 2.44949 | 13.63 | 1.134496 | 86.37 | 1.936363 |
| 7 | 0.845098 | 2.645751 | 19.4 | 1.287802 | 80.6 | 1.906335 |
| 8 | 0.90309 | 2.828427 | 23.3 | 1.367356 | 76.7 | 1.884795 |
| 12 | 1.079181 | 3.464102 | 40.08 | 1.602928 | 59.92 | 1.777572 |
| 24 | 1.380211 | 4.898979 | 88.2 | 1.945469 | 11.8 | 1.071882 |

**Tab No.18: Drug release kinetics of F5**

| Time | Log time | Square root of time | %Cumulative release of F5 | Log % cumulative release of F5 | %Cumulative remaining | Log cumulative remaining |
|------|----------|---------------------|---------------------------|-------------------------------|----------------------|--------------------------|
| 0 | 0 | 1 | 0 | 0 | 100 | 2 |
| 1 | 0.30103 | 1.414214 | 7.95 | 0.900367 | 92.05 | 1.964024 |
| 2 | 0.477121 | 1.732051 | 11.93 | 1.07664 | 88.07 | 1.944828 |
| 3 | 0.60206 | 2 | 14.32 | 1.155943 | 85.68 | 1.932879 |
| 4 | 0.69897 | 2.236068 | 18.27 | 1.261739 | 81.73 | 1.912381 |
| 6 | 0.778151 | 2.44949 | 24.8 | 1.394452 | 75.2 | 1.876218 |
| 7 | 0.845098 | 2.645751 | 26.25 | 1.419129 | 73.75 | 1.867762 |
| 8 | 0.90309 | 2.828427 | 34.95 | 1.543447 | 65.05 | 1.813247 |
| 12 | 1.079181 | 3.464102 | 48.1 | 1.682145 | 51.9 | 1.715167 |
| 24 | 1.380211 | 4.898979 | 88.91 | 1.948951 | 11.09 | 1.044932 |
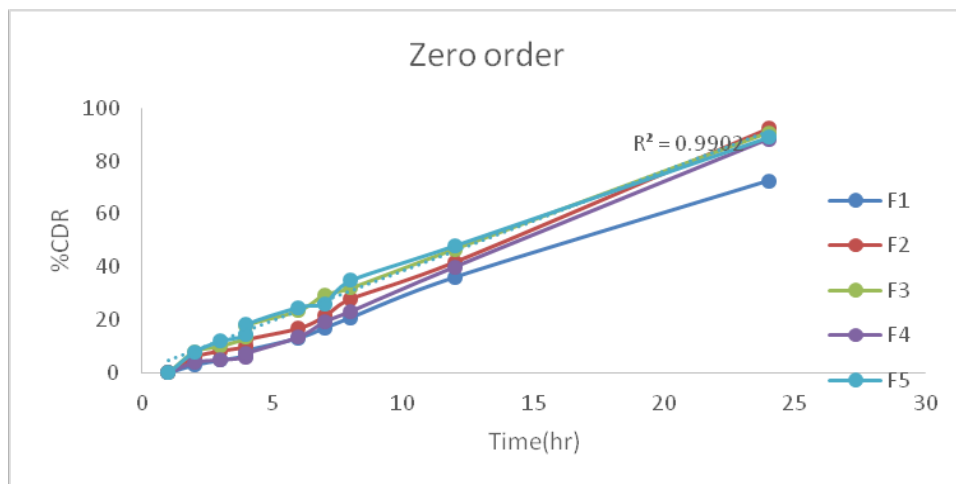


**Fig No.18: Plot of %CDR v/s Time**
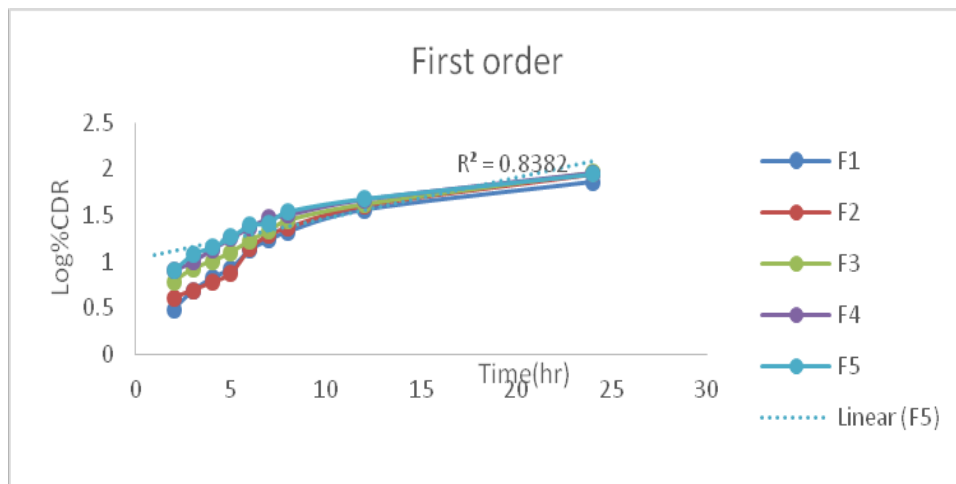


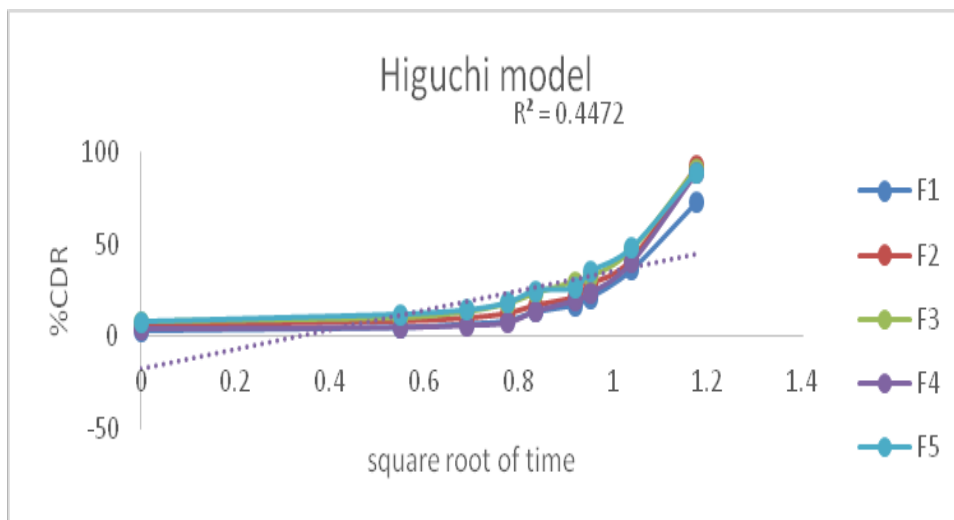**Fig No.19: Plot of log percentage CDR v/s Time**

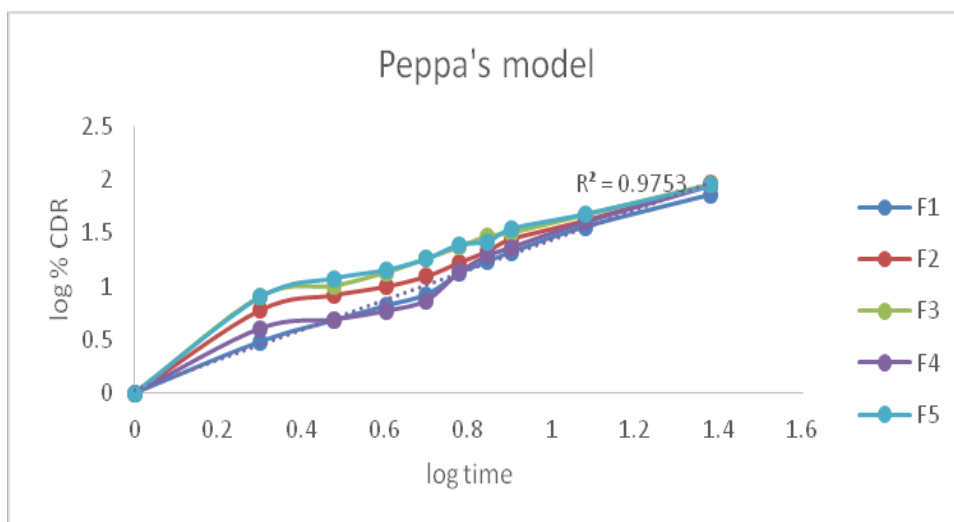**Fig No.20: Plot of percentage CDR v/s square root of time**



**Fig No.21: Plot of log percentage CDR v/s log time**

Various dissolving models were used to the in-vitro release profiles of the optimum formulation to explore the release mechanism of nanoemulsions. Zero order, first order, Higuchi, and Korsmeyer-Peppas equations were among the kinetic models used. The values of correlation-coefficient ($r2$) for all formulations were high enough to evaluate drug dissolving behaviour, as shown in tables 14 to 18. Because r2 values are larger than those of other release kinetics, kinetic findings indicated that all formulations followed Zero order kinetic release. Figures 18 through 21 depicted the results.

## EVALUATION OF NANOEMULGEL
## 1. Physical examination

**Tab.No.19: Physical examination of various formulations of nanoemulgel**

| Formulation code | Appearance | Phase Separation | Homogeneity | Consistency |
|---|---|---|---|---|
| GF1 | White | None | Excellent | Good |
| GF2 | White | None | Excellent | Excellent |
| GF3 | White | None | Good | Excellent |
| GF4 | White | None | Fair | Fair |
| GF5 | White | None | Excellent | Good |

There was no phase separation in any of the Miconazole Nitrate nanoemulgel formulations, which were white viscous preparations with a smooth and uniform appearance. Table No.19 shows the results of physical examinations. Figure No. 22 shows how to make nanoemulgel.



**Fig.No.22: Prepared Miconazole nitrate nanoemulgel**

## 2. Measurement of pH

**Tab.No.15: pH of various formulations of nanoemulgel**

| Formulation code | pH |
|---|---|
| GF1 | 6.5±0.01 |
| GF2 | 6.2±0.03 |
| GF3 | 6.1±0.10 |
| GF4 | 6.4±0.06 |
| GF5 | 6.3±0.10 |

All formulations had pH values ranging from 6.1 to 6.5, which are deemed suitable for avoiding skin irritation when applied to the skin. Table No.15 shows the pH of all of the formulations.

## 3. Rheological Study

**Tab.No.16: Viscosity of various formulations of nanoemulgel**

| Formulation code | Viscosity (g/cm2) |
|---|---|
| GF1 | 16.3 |
| GF2 | 24.3 |
| GF3 | 21.9 |
| GF4 | 19.8 |
| GF5 | 16.8 |

The viscosities of various formulations were measured using a Brookfield viscometer at 37°C and 100 rpm with spindle no. 64. Table No.21 shows the viscosities of all the formulas. The viscosity ranges from 16.3 to 24.3g/cm2

## 4. Spreadability

**Tab.No.17: Spreadability of various formulations of nanoemulgel**

| Formulation code | Spreadability (g cm/sec) |
|---|---|
| GF1 | 19.25±0.12 |
| GF2 | 26.33±0.15 |
| GF3 | 24.01±0.44 |
| GF4 | 22.37±0.10 |
| GF5 | 20.31±0.19 |

Table No.17 displays the spreadability values. The highest spreadability was achieved by GF2 (26.33g cm/sec), whereas the smallest spreadability was achieved by GF1 (16.3g cm/sec).

## 5. Drug Content Determination

**Tab.No.18: % Drug content of various formulations of Nanoemulgel**

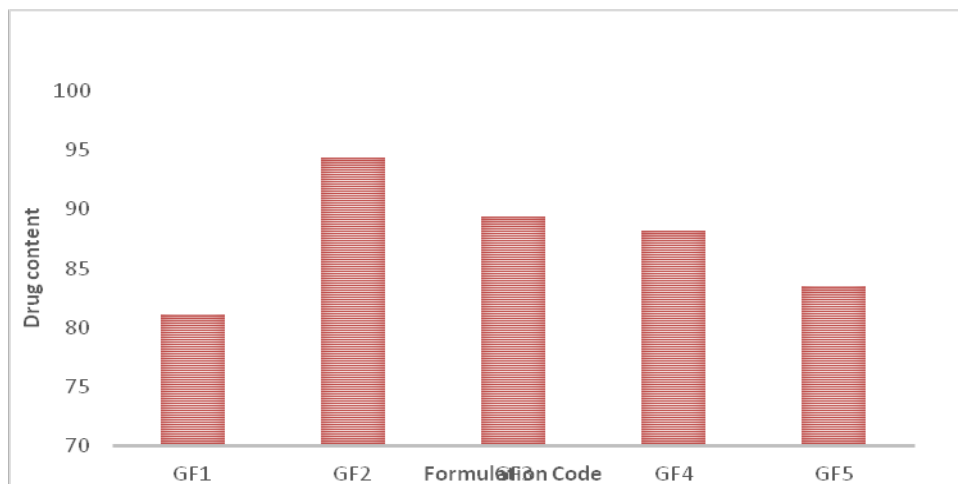| Formulation code | % Drug content |
|---|---|
| GF1 | 81.19±0.43 |
| GF2 | 94.45±0.01 |
| GF3 | 89.43±0.27 |
| GF4 | 88.18±0.14 |
| GF5 | 83.52±0.19 |

**Fig.No.23: Bar graph of % Drug content of various formulations of nanoemulgel**

The drug content of nanoemulgels was determined by spectrophotometry at 272 nm, with drug concentrations ranging from 81.19 to 94.45 percent. GF2 had the highest drug content (94.45 percent), whereas F1 had the lowest drug level (81.19 percent). Fig No.23 shows the findings.

## 6. Comparison *of In-vitro* release study of formulations with marketed product

**Tab no.24: Comparison *of In-vitro* release study of GF-Formulations and Marketed product Dk gel**

| Time in hr | Percentage cumulative drug release* | | | | | |
|---|---|---|---|---|---|---|
| | GF1 | GF2 | GF3 | GF4 | GF5 | Marketed product |
| 1 | 14.2±0.01 | 18.07±0.01 | 17.55±0.03 | 17.36±0.02 | 22.79±0.04 | 20.92±0.02 |
| 2 | 18.26±0.01 | 27.26±0.02 | 25.51±0.05 | 23.81±0.04 | 23.56±0.01 | 27.5±0.03 |
| 3 | 26.22±0.04 | 30.23±0,01 | 29.62±0.01 | 27.58±0.01 | 25.8±0.02 | 34.75±0.01 |
| 4 | 28.45±0.02 | 38.45±0.05 | 36.44±0.04 | 35.72±0.02 | 33.62±0.03 | 38.36±0.04 |
| 5 | 34.24±0.01 | 44.11±0.01 | 42.11±0.01 | 41.51±0.04 | 40.86±0.04 | 42.86±0.15 |
| 12 | 52.71±0.02 | 60.56±0.02 | 56.55±0.02 | 54.98±0.03 | 52.19±0.01 | 65.5±0.04 |
| 24 | 74.05±0.01 | 96.5±0.04 | 92.62±0.02 | 93.64±0.04 | 89.57±0.01 | 93.67±0.03 |
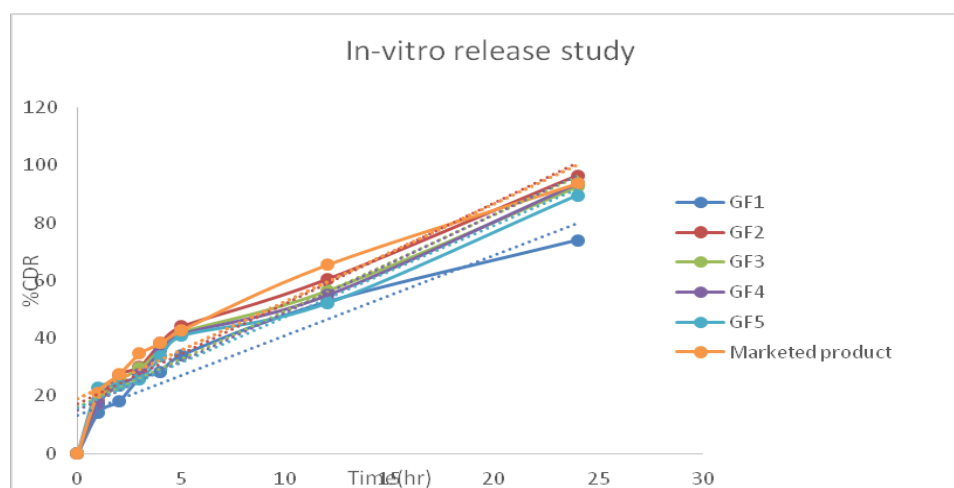


**Fig No.24: Plot of percentage CDR v/s Time**

The materials were examined spectrophotometrically at 272 nm after being incubated for 24 hours in phosphate buffer pH 5.5 and methanol (80:20) in a Franz diffusion cell. The GF2 has a superior outcome. Table No.24 displays the results.

## 7. Drug release kinetic studies

**Table no. 25: Drug release kinetics of GF1**

| Time | Log time | Square root of time | %cumulative release of GF1 | Log % cumulative release of GF1 | %Cumulative remaining | Log cumulative remaining |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 100 | 2 |
| 1 | 0 | 0 | 14.2 | 1.152288 | 85.8 | 1.933487 |
| 2 | 0.30103 | 0.548662 | 18.26 | 1.261501 | 81.74 | 1.912435 |
| 3 | 0.477121 | 0.69074 | 26.22 | 1.418633 | 73.78 | 1.867939 |
| 4 | 0.60206 | 0.775925 | 28.45 | 1.454082 | 71.55 | 1.85461 |
| 5 | 0.69897 | 0.836044 | 34.24 | 1.534534 | 65.76 | 1.817962 |
| 12 | 1.079181 | 1.038836 | 52.71 | 1.721893 | 47.29 | 1.674769 |
| 24 | 1.380211 | 1.174824 | 74.05 | 1.869525 | 25.95 | 1.414137 |

**Table no. 26: Drug release kinetics of GF2**

| Time | Log time | Square root of time | %cumulative release of GF2 | Log % cumulative release of GF2 | %Cumulative remaining | Log cumulative remaining |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 100 | 2 |
| 1 | 0 | 0 | 18.07 | 1.256958 | 81.93 | 1.913443 |
| 2 | 0.30103 | 0.548662 | 27.26 | 1.435526 | 72.74 | 1.861773 |
| 3 | 0.477121 | 0.69074 | 30.23 | 1.480438 | 69.77 | 1.843669 |
| 4 | 0.60206 | 0.775925 | 38.45 | 1.584896 | 61.55 | 1.789228 |
| 5 | 0.69897 | 0.836044 | 44.11 | 1.644537 | 55.89 | 1.747334 |
| 12 | 1.079181 | 1.038836 | 60.56 | 1.782186 | 39.44 | 1.595937 |
| 24 | 1.380211 | 1.174824 | 96.5 | 1.984527 | 3.5 | 0.544068 |

**Table no. 27: Drug release kinetics of GF3**

| Time | Log time | Square root of time | %cumulative release of GF3 | Log % cumulative release of GF3 | %Cumulative remaining | Log cumulative remaining |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 100 | 2 |
| 1 | 0 | 0 | 17.55 | 1.244277 | 82.45 | 1.916191 |
| 2 | 0.30103 | 0.548662 | 25.51 | 1.40671 | 74.49 | 1.872098 |
| 3 | 0.477121 | 0.69074 | 29.62 | 1.471585 | 70.38 | 1.847449 |
| 4 | 0.60206 | 0.775925 | 36.44 | 1.561578 | 63.56 | 1.803184 |
| 5 | 0.69897 | 0.836044 | 42.11 | 1.624385 | 57.89 | 1.762604 |
| 12 | 1.079181 | 1.038836 | 56.55 | 1.752433 | 43.45 | 1.63799 |
| 24 | 1.380211 | 1.174824 | 92.62 | 1.966705 | 7.38 | 0.868056 |

**Table no. 28: Drug release kinetics of GF4**

| Time | Log time | Square root of time | %cumulative release of GF4 | Log % cumulative release of GF4 | %Cumulative remaining | Log cumulative remaining |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 100 | 2 |
| 1 | 0 | 0 | 17.36 | 1.23955 | 82.64 | 1.91719 |
| 2 | 0.30103 | 0.548662 | 23.81 | 1.376759 | 76.19 | 1.881898 |
| 3 | 0.477121 | 0.69074 | 27.58 | 1.440594 | 72.42 | 1.859859 |
| 4 | 0.60206 | 0.775925 | 35.72 | 1.552911 | 64.28 | 1.808076 |
| 5 | 0.69897 | 0.836044 | 41.51 | 1.618153 | 58.49 | 1.767082 |
| 12 | 1.079181 | 1.038836 | 54.98 | 1.740205 | 45.02 | 1.653405 |
| 24 | 1.380211 | 1.174824 | 93.64 | 1.971461 | 6.36 | 0.803457 |

**Table no. 29: Drug release kinetics of GF5**

| Time | Log time | Square root of time | %cumulative release of GF5 | Log % cumulative release of GF5 | %Cumulative remaining | Log cumulative remaining |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 100 | 2 |
| 1 | 0 | 0 | 22.79 | 1.357744 | 77.21 | 1.887674 |
| 2 | 0.30103 | 0.548662 | 23.56 | 1.372175 | 76.44 | 1.883321 |
| 3 | 0.477121 | 0.69074 | 25.8 | 1.41162 | 74.2 | 1.870404 |
| 4 | 0.60206 | 0.775925 | 33.62 | 1.526598 | 66.38 | 1.822037 |
| 5 | 0.69897 | 0.836044 | 40.86 | 1.611298 | 59.14 | 1.771881 |
| 12 | 1.079181 | 1.038836 | 52.19 | 1.717587 | 47.81 | 1.679519 |
| 24 | 1.380211 | 1.174824 | 89.57 | 1.952163 | 10.43 | 1.018284 |

**Table no. 30:Drug release kinetics of Marketed Product formulation**

| Time | Log time | Square root of time | %cumulative release of marketed product | Log % cumulative release of marketed product | %Cumulative remaining | Log cumulative remaining |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 100 | 2 |
| 1 | 0 | 0 | 20.92 | 1.320562 | 79.08 | 1.898067 |
| 2 | 0.30103 | 0.548662 | 27.5 | 1.439333 | 72.5 | 1.860338 |
| 3 | 0.477121 | 0.69074 | 34.75 | 1.540955 | 65.25 | 1.814581 |
| 4 | 0.60206 | 0.775925 | 38.36 | 1.583879 | 61.64 | 1.789863 |
| 5 | 0.69897 | 0.836044 | 42.86 | 1.632052 | 57.14 | 1.75694 |
| 12 | 1.079181 | 1.038836 | 65.5 | 1.816241 | 34.5 | 1.537819 |
| 24 | 1.380211 | 1.174824 | 93.67 | 1.971601 | 6.33 | 0.801404 |

## Zero order release:



**Fig.No.25: Plot of percentage CDR v/s time (zero order)**

## First order release:



**Fig.No.26: Plot of log percentage CDR v/s time (first order)**

## Peppa's model:
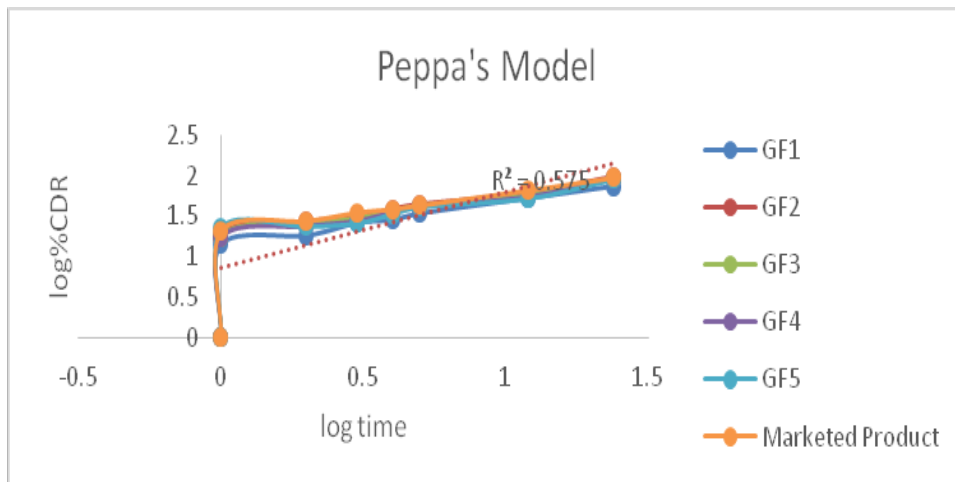


**Fig.No.27: Plot of log percentage CDR v/s log time (Peppa's model)**

## Higuchi's model:
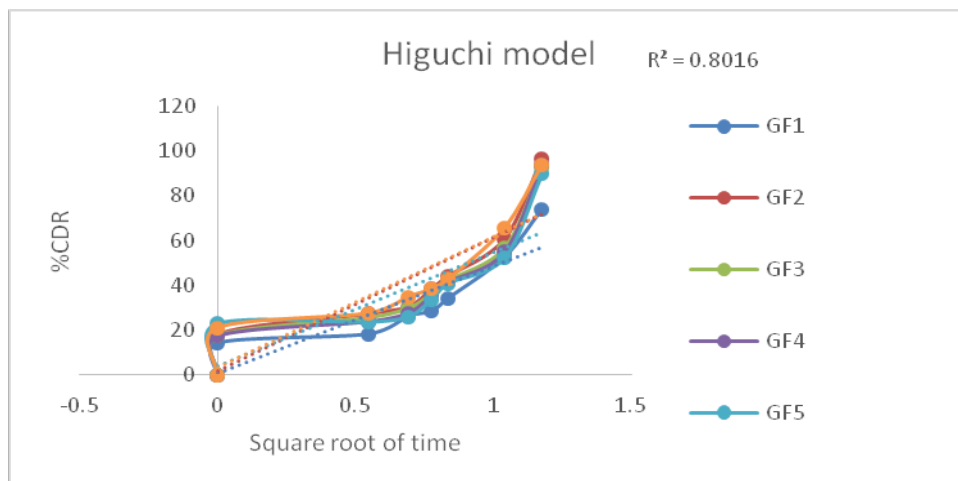


**Fig.No.28: Plot of percentage CDR v/s √ t (Higuchi's model)**

Various dissolving models were used to the in-vitro release profiles of formulations to explore the release mechanism of nanoemulgels. Zero order, first order, Higuchi, and Korsmeyer-Peppas equations were among the kinetic models used. The values of correlation-coefficient ($r^2$) for all formulations were high enough to evaluate drug dissolving behaviour, as shown in table no.20. Because $r^2$ values are larger than those of other release kinetics, kinetic findings indicated that all formulations followed Zero order kinetic release. Tables 25 to 30 and figures 25 to 28 illustrate the results.

## 8. Accelerated stability studies

**Tab.No.31: stability study of GF2**

| Evaluation Parameters | Time (days) Accelerated condition at 40±2ºC and 75±5% RH | | |
|---|---|---|---|
| | At 0 days | After 30 days | After 60 days |
| Colour | White | White | White |
| Phase separation | None | None | None |
| Drug content | 94.45 | 90.39 | 90.3 |

## 9. In-vitro drug release study

**Tab.No.32: *In-vitro* drug release of GF2 during stability study**

| Time (hrs) | % CDR Accelerated condition at 40±2ºC and 75±5% RH | | |
|---|---|---|---|
| | At 0 days | After 30th day | After 60th day |
| 0 | 0 | 0 | 0 |
| 1 | 18.07 | 17.98 | 17.62 |
| 2 | 27.26 | 26.26 | 26.02 |
| 3 | 30.23 | 30.03 | 29.96 |
| 4 | 38.45 | 37.72 | 37.04 |
| 5 | 44.11 | 43.94 | 43.72 |
| 12 | 60.56 | 60.01 | 59.98 |
| 24 | 96.5 | 95.94 | 95.88 |
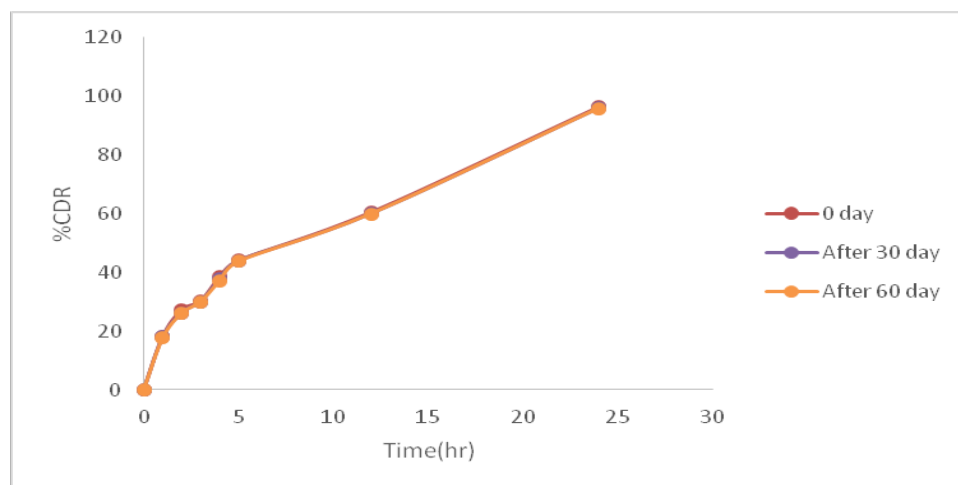


**Fig no.29: In-Vitro release of GF2 during stability Study.**

Stability tests were performed on chosen formulations F2 in accordance with ICH standards Q1C. The best formulas were kept for two months in sealed aluminium tubes at 40 degrees Celsius and 75% relative humidity. During the research, there was no change in colour, phase separation, or drug content. After two months, the percentage drug release in F2 after 24 hours was 95.88 percent, suggesting no major alterations and that nanoemulgels are stable in storage. The results are shown in table Nos. 31 and 32, as well as picture No. 29.

## SUMMARY AND CONCLUSION

The goal of this research was to design and develop a Miconazole nitrate nanoemulgel to treat fungal infections on the skin. Miconazole nitrate preformulation experiments were found to be within the published literature limitations. FTIR tests indicated no chemical interactions between the drug, the polymer, and the excipients, indicating that the drug is stable in the formulation. High-pressure homogenization was used to create nanoemulsions. Physical tests of the produced nanoemulsions revealed that they were milky white with a smooth and homogeneous appearance and good consistency, indicating that the nanoemulsions were stable. The pH, drug content, and centrifugation stability tests all reported back within acceptable limits. The drug content of all formulations was determined, and the F1, F2, F3, F4, and F5 values were 79.13, 91.56, 88.55, 86.12, and 81.46 percent, respectively. The formulations were determined to be stable and homogenous, and there was no coalescence in the nanoemulsion, according to globule size determination and zeta potential tests. The size distribution of globules varies from 7.9 to 41.6 d.nm. Nanoemulsion Formulation F2 was judged to be excellent based on assessment factors. The nanoemulgels were made by mixing o/w emulsion with carbopol 934, and all of the results were consistent and stable. The pH, viscosity, and spreadability tests were completed, and the findings were consistent and reproducible. The drug content of the formulations was analyzed, and it was determined that the drug content GF2 is satisfactory. The Franz diffusion cell was used to conduct in-vitro release experiments on all formulations for 24 hours. The greatest release was 96.5 percent for GF2, while the highest release was 93.69 percent for the marketed product. All formulations were subjected to kinetic drug release experiments, and all of them followed zero order kinetics. For the best formulations GF2, stability experiments were carried out for two months, and the findings of appearance, phase separation, and drug content were all within the literature limitations. In-vitro drug release tests revealed no significant alterations, leading to the conclusion that all formulations were stable during storage. The Nanoemulgels were shown to be stable and to release Miconazole nitrate effectively. The current investigation shown that carbopol 934 may be used to successfully produce Miconazole Nitrate nanoemulgel formulations. Nanoemulgels appear to be a reliable approach for topical administration of hydrophobic medicines in water soluble gel bases.

## ACKNOWLEDGMENT

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