Preparation and Evaluation of Herbal Nanoemulgel for Treatment of Sinusitis

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Abstract

Nanoemulgel have become a promising method for delivering hydrophobic drugs through the skin. The purpose of this study was to prepare an Nanoemulgel containing Curcumin and Eucalyptol. When Nanoemulsions are made separately, they often face stability issues during both production and storage, which can affect how the drug is released. To improve the drug's stability, it was incorporated into a gel. Nanoemulgel are formulations that are thermodynamically stable, have low interfacial tension, and are made by combining a surfactant with a co-surfactant. They possess several beneficial properties like enhanced permeability and good thermodynamic stability. Nanoemulgel offer dual control and a sustained release of the drug. They also improve the bioavailability of the drug and make it easier for patients to adhere to the treatment. The nanoemulgel developed in this study acted as an Anti-inflammatory and met all the required testing standards. It was prepared in multiple batches, and batch CU+EUNE5 was found to be the most effective one.

Keywords: Sinusitis; Nanoemulgel; Anti-inflammatory; Curcumin; Eucalyptol; Kinetic Drug Release; Spreadability; Extrudability.

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1. Introduction

Topical delivery defined as the application of a drug containing dosage form to the skin. It is used mainly to directly treat cutaneous disorders such as acne or the cutaneous manifestations of a universal disease such as Sinusitis. The main motto of this delivery is confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Various formulations such as foams, sprays, medicated powders, solution or others forms are widely used by topical route[1].

Topical drug administration is simplest and easiest route of localized drug delivery anywhere in the body by routes as ophthalmic, rectal, vaginal and skin. These are applied as a wide spectrum of preparations in case of both cosmeceutical and dermatological, to the healthy or diseased skin. The formulations are available in different forms like from solid through semisolid to liquid. Drugs are administered topically for their action at the site of application or for systemic effects. Drug absorption is enhanced through the skin if the drug substance is in solution, if it has a favorable lipid/water partition coefficient and if it is a non-electrolyte. The main benefit of the topical delivery system is to bypass first pass metabolism. Skip of the risk and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, the presence of enzymes, gastric emptying time are another advantage of the topical drug delivery system is generally used where the others system of drug administration fails. The study is also carried out for the avoidance of the risks and inconvenience of intravenous therapy and of the varied conditions of absorption, like pH changes, the presence of enzymes and gastric emptying time[2].

A big problem with using topical medicines is how well the drug dissolves and spreads through the skin, especially for drugs that don't mix well with water. For drugs that do mix with water, getting them through the outer layer of the skin is also tricky. Because of this, Nanoemulgel are used. Nanoemulgel are made using two kinds of mixtures: one where oil is mixed into water and another where water is mixed into oil. These mixtures help deliver both water-loving and water-hating drugs through the skin. They also help dissolve drugs better and let them get through the skin more easily. When oil is mixed into water, the resulting formula is easier to wash off with water. This study focuses on making an Nanoemulgel that includes Curcumin and Eucalyptol along with other ingredients. Curcumin is a type of medicine that helps reduce inflammation, pain, and fever [3]and Eucalyptol having anti-inflammatory and antimicrobial activity.

2. Materials and Methods

2.1 Materials

Curcumin, Eucalyptol, Olive Oil, PEG400 and Tween 80 were purchase from Yucca Enterprises An top Hill, Mumbai, (Maharashtra). All other chemicals used were of analytical grade and were used without any further chemical modification.

2.1 Preparation of Nanoemulgel

A clean beaker was taken, and Olive oil and PEG 400 were added. The mixture was stirred properly using a magnetic stirrer or a glass rod until it became uniform. The oil phase was then heated for one hour at 60–70 °C. It was kept to cool, and after cooling down to room temperature, Eucalyptol was added.

In a second beaker, Tween 80 was taken, and distilled water was added. The aqueous phase was heated for one hour at 60–70 °C. Curcumin dissolved in ethanol was then

added to the aqueous phase. The aqueous phase was added slowly, drop-wise, to the oil phase with continuous stirring for about 20–30 minutes. A translucent or slightly milky nano-emulsion was formed for the eucalyptol, and a yellow color was produced for the Curcumin. The resulting pre-emulsion was then subjected to high-speed homogenization at 12,000 rpm for 5–10 minutes using a high-speed homogenizer. This helped reduce droplet size and improved stability. In another beaker, Carbopol was dispersed into a small amount of distilled water. The mixture was stirred gently and allowed to hydrate for 30–60 minutes. Add triethanolamine dropwise with stirring the pH increases and gel formation occur. Add the nanoemulsion slowly into the Carbopol gel base. Stir gently until a homogeneous nanoemulgel forms. Avoid vigorous mixing to prevent air bubbles.

3. Characterization of Nanoemulgel

3.1 Determination of Organoleptic properties

The prepared Curcumin–eucalyptol Nanoemulgel formulations were inspected visually for their color, appearance and consistency[4].

3.2 Determination of pH

The pH of Curcumin–eucalyptol Nanoemulgel formulations were measure by using pH digital meter and the pH meter electrode was cleaned with pure water before putting it into the formulation[5].

3.3 Spreadability study

The spreadability of the Curcumin–eucalyptol Nanoemulgel was assessed 72 hours post-formulation by analyzing the spread diameter of the gel between two glass plates for duration of 1 minute. Initially, a sample of Curcumin-eucalyptol nanoemulgel was carefully weighed and placed on a glass plate featuring a pre-marked 1 cm circle. Following this, a second glass plate was positioned over the sample. As pressure increased on the upper plate, subsequent expansion of the Nanoemulgel diameter was observed and quantified using the provided equation[6].

3.4 Determination of Viscosity and Rheological study

The viscosity of the optimized Curcumin–eucalyptol Nanoemulgel formulations were measured with a Brookfield viscometer at room temperature. The spindle 4 was adjusted to 60 rpm, and the sample was placed in the beaker .[7,8]

3.5 Extrudability

The exctrudability test was conducted using a hardness tester. A portion of the Curcumin–eucalyptol Nanoemulgel was loaded into aluminum collapsible tubes, and a plunger was employed to secure the tube in place9. Subsequently, pressure equivalent to 1 g/cm² was applied to the tube for duration of 30 seconds. The amount of Nanoemulgel extruded from the tube under this pressure was measured. This cycle was repeated three times to ensure the reliability and consistency of results, allowing for a comprehensive assessment of the gel's extrudability characteristics[10].

3.6 Swelling index

The swelling index of the prepared Curcumin–eucalyptol Nanoemulgel was assessed through a systematic procedure. Initially, 1 g of the gel was placed on porous aluminum foil and then individually positioned in 50 ml beakers containing 10 ml of 0.1 N NaOH solution. Subsequently, the samples underwent a swelling process within the NaOH solution for varying time intervals. After each designated interval, the samples were carefully retrieved from the beakers and allowed to dry thoroughly. Upon complete drying, the samples were reweighed to ascertain their final weight post-swelling[11]. The swelling index was determined through the following equation.

$$\text{Swelling Index } (SW)\ \% = \frac{[(Wt - Wo)]}{Wo} \times 100$$

3.7 Drug content

A specified quantity of the Curcumin–eucalyptol Nanoemulgel was accurately weighed and transferred into a suitable volumetric flask. An appropriate quantity of methanol was added as the extraction solvent. The mixture was sonicated for 15–30 minutes to ensure complete extraction of Curcumin and eucalyptol from the gel matrix. The volume was made up with methanol and mixed thoroughly to obtain a uniform solution.

The prepared solution was then filtered through a suitable membrane filter to remove insoluble excipients and polymeric components. The clear filtrate was diluted appropriately with methanol to obtain the required concentration for analysis. The prepared sample was analysed using a UV-visible spectrophotometer for the quantitative determination of Curcumin and eucalyptol. The concentrations of Curcumin and eucalyptol were determined separately using their respective calibration curves. The percentage drug content of each drug was calculated with respect to its theoretical amount in the formulation. The analysis was performed in triplicate, and the results were expressed as mean ± standard deviation.

3.8 In-vitro Release Study

The dialysis membrane was soaked in distilled water overnight for approximately 12 hours and equilibrated in phosphate-buffered saline for 30 minutes before use. The receptor compartment of the Franz diffusion cell was filled with 15–20 mL of phosphate-buffered saline , and the temperature was maintained at 37 ± 0.5 °C with continuous stirring at 400 rpm. The hydrated dialysis membrane was then mounted between the donor and receptor compartments, ensuring that no air bubbles were trapped beneath the membrane. One gram of the Curcumin–eucalyptol Nanoemulgel was accurately weighed and uniformly spread on the membrane in the donor compartment, which was subsequently covered to minimize the evaporation of eucalyptol during the study. The diffusion study was initiated, and the experimental conditions were maintained throughout the process. Samples of 1 mL were withdrawn from the receptor compartment at predetermined time intervals of 1, 2, 4, 6, 8, and 12 hours. The withdrawn volume was immediately replaced with an equal amount of fresh, pre-warmed PBS (37 ± 0.5 °C) to maintain sink conditions and a constant receptor volume. The collected samples were filtered through a 0.45 µm syringe filter and protected from light until analysis. Finally, the concentration of the released drugs was determined using a UV–Visible spectrophotometer.

3.9 Drug Release Kinetics

The drug release pattern of the selective formulation evaluated for model such as zero order release kinetics, first order release kinetics, higuchi model and Hixson-crosswell model. The release values were fitted into each model, and the correlation coefficients (R^2 values) were determined[12,13,14,15].

3.10 Stability of Nanoemulgel

After the centrifugation test, none of the Nanoemulgel formulations showed signs of creaming or phase separation as a form of physical instability.

3.11 Particle size and PDI

The Curcumin-Eucalyptol Nanoemulgel was evaluated for particle size and PDI analysis using nanoPartica SZ-100 equipment (HORIBA Scientific, Kyoto, Japan) via photon correlation spectroscopy. Measurements were taken at a controlled temperature of 25°C in disposable polystyrene cells [16].

3.12 Zeta potential of Nanoemulgel

The zeta potential of the prepared Nanoemulgel was measured using photon correlation spectroscopy with a nanoPartica SZ-100 Series Nanoparticle Analyzer (HORIBA Scientific, Kyoto, Japan). The measurements were carried out at a constant temperature of 25°C using omega cuvettes[17].

3.13 In Vivo Study

3.13.1 Experimental animals procured

Adult wistar rats of male 9 to 11 week age, weighing 160–180g were procured from Mahaveera enterprises, Hyderabad. Animals were housed in standard laboratory conditions at 25°c with 12 hr light-dark cycle with free access to chow and water ad libitum. The research protocol was approved by Dr Nitin Mahurkar.

3.13.2 Formalin-Induced rats Paw Oedema

The formalin-induced inflammation test was conducted based on the method of Turner. Edema was induced in the left hind paw of rats in all groups with sub planter injection of 20 µL of freshly prepared 2% formalin in the hind paw. The right hind paw was maintained as a negative control. The anti- inflammatory activity was compared with control and treated groups using the plethysmograph method. To all groups of rats, on both hind paws to ensure constant paw volume. In all groups, the left and right paw volume was measured at zero time (normal paw volume) and at 1, 2, 3, 5,12 and 24h after induction of inflammation[18,19].

The percent inhibition of edema was calculated as follow:

$$\% \text{ Edema Inhibition} = \frac{(V_L - V_R)_{control} - (V_L - V_R)_{treated}}{(V_L - V_R)_{control}} \times 100$$

Whereas,

VL: Represents the mean of the left paw displacement volume and

VR: Represents the mean of the right paw displacement volume.

Group-I: Control
Group-II: Formalin-induced
Group-III: Curcumin
Group-IV: Eucalyptol
Group-V: Curcumin and Eucalyptol Nanoemulgel

Table 1. Formulation of Curcumin and Eucalyptol Nanoemulgel

Ingredients	Formulation Code								
	CU+EU NE1	CU+EU NE2	CU+EU NE3	CU+EU NE4	CU+EU NE5	CU+EU NE6	CU+EU NE7	CU+EU NE8	CU+EU NE9
Eucalyptol (mg)	100	100	100	100	100	100	100	100	100
Curcumin (mg)	100	100	100	100	100	100	100	100	100
Olive Oil (ml)	1	1	1	1	1	1	1	1	1
Tween 80 (ml)	1.5	2.5	1.5	2	2.5	2.5	2	1.5	2
PEG 400 (mg)	100	100	100	100	100	100	100	100	100
Carbapol (gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Triethanolamine (gm)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Distilled Water q.s 10 ml	10	10	10	10	10	10	10	10	10

4. RESULT AND DISCUSSION

4.1 FTIR:

In comparison with pure drug (Fig:1&2), the absorption peak of the spectra of Curcumin and Eucalyptol in combination with different Excipients (Fig:4) showed no shift and no disappearance of characteristic peaks suggesting that there is no interaction between drug and the excipients used.

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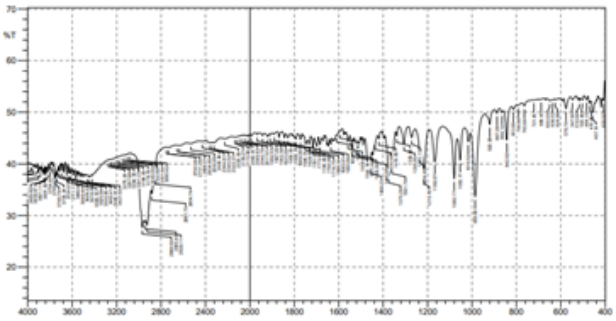

Figure 1. FTIR Spectra of Eucalyptol

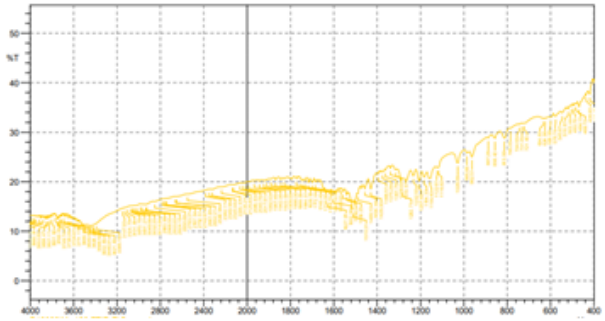

Figure 2. FTIR Spectra of Curcumin

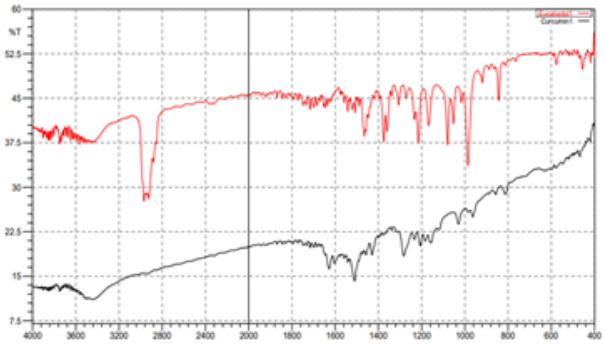

Figure 3. FTIR Spectra of Eucalyptol + Curcumin

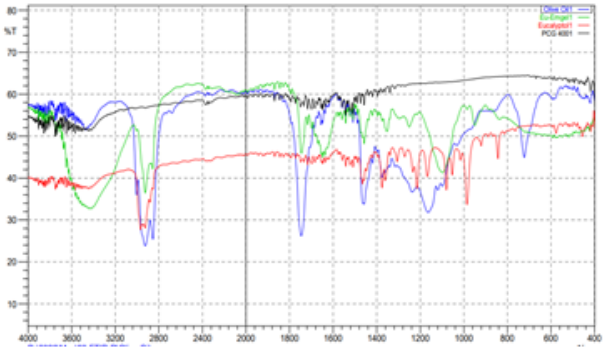

Figure 4. FTIR Spectra Drug and Excipients Mixture

4.2 Spectrophotometric Estimation of Crude Drug

The UV spectrum of Curcumin in buffer 6.8 exhibited wavelength of absorbance maximum at 433 nm and Eucalyptol showed at 260nm.

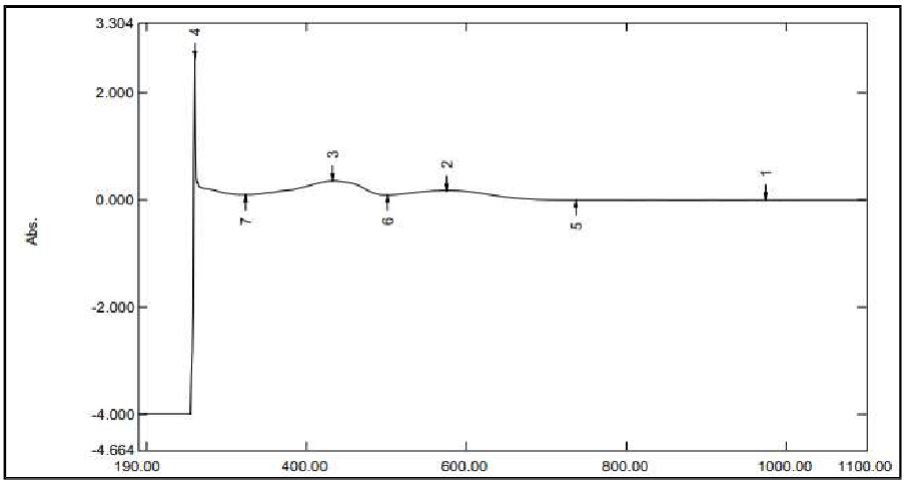

Fig 05- λ max of Curcumin and Eucalyptol

4.3 Construction of Calibration curve

4.3.1 Calibration curve of Curcumin in buffer 6.8

The UV absorption spectrum of showed peak at 433 nm for Curcumin. The standard calibration curve of Curcumin was obtained by plotting the absorbance of the standard solution against its concentration measured at 433 nm respectively.

4.3.2 Calibration curve of Eucalyptol in buffer 6.8

The UV absorption spectrum of showed peak at 260 nm for Eucalyptol. The standard calibration curve of Eucalyptol was obtained by plotting the absorbance of the standard solution against its concentration measured at 260 nm respectively.

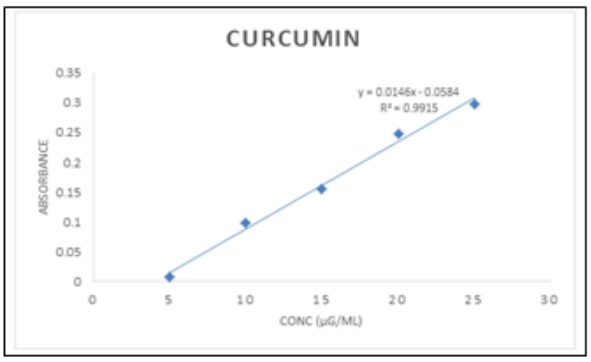

Fig 06- Calibration curve of Curcumin in buffer 6.8

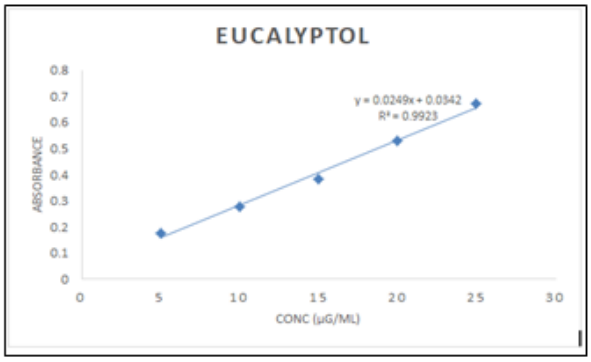

Fig 07- Calibration curve of Eucalyptol in buffer 6.8

Table 02- Calibration curve of Curcumin in buffer 6.8

Sr.no	Concentration (µg/ml)	Absorbance
1	5	0.0079
2	10	0.0972
3	15	0.1545
4	20	0.2484
5	25	0.2984

Table 03- Calibration curve of Eucalyptol in buffer 6.8

Sr.no	Conc (µg/mL)	Absorbance
1	5	0.176
2	10	0.278
3	15	0.384
4	20	0.528
5	25	0.674

4.4 Organoleptic Properties

Table 04- Organoleptic properties

Formulation code	Colour	Odour	Result
CU+EUNE1	Yellow	Aromatic	confirm
CU+EUNE2	Yellow	Aromatic	confirm
CU+EUNE3	Yellow	Aromatic	confirm
CU+EUNE4	Yellow	Aromatic	confirm
CU+EUNE5	Yellow	Aromatic	confirm
CU+EUNE6	Yellow	Aromatic	Confirm
CU+EUNE7	Yellow	Aromatic	confirm
CU+EUNE8	Yellow	Aromatic	confirm
CU+EUNE9	Yellow	Aromatic	Confirm

4.5 Skin Irritation Test

Skin irritation test as performed on the male wistar rats for all the developed formulations and there was no redness or swelling observed during the 24 hr test period.

Table 05- Determination of physical properties of formulation

Formulation	pH	Viscosity (CPS)	Spreadability (g.cm/sec)	Swilling index	Extrudability
CU+EUNE1	5.8	3988	8.9	18	0.8
CU+EUNE2	6.9	3802	8.2	18	0.8
CU+EUNE3	6.0	3911	9.1	19	0.7
CU+EUNE4	6.1	3939	9.3	19	0.7
CU+EUNE5	6.1	3926	9.1	20	0.7
CU+EUNE6	6.0	3942	9.1	20	0.7
CU+EUNE7	5.8	3902	8.9	19	0.8
CU+EUNE8	6.0	3993	8.9	19	0.9
CU+EUNE9	6.1	3915	9.2	20	0.8

4.6 Drug Content

Table 06- Drug Content of Percentage Value

Formulation	Curcumin Content (mg/unit)	Eucalyptol Content (mg/unit)	Uniformity (%)
CU+EUNE1	190 ± 5	198 ± 3	~95%
CU+EUNE2	194 ± 4	199 ± 2	~97%
CU+EUNE3	191 ± 5	198 ± 3	~95%
CU+EUNE4	196 ± 3	200 ± 1	~98%
CU+EUNE5	198 ± 2	200 ± 0	~99%
CU+EUNE6	197 ± 3	200 ± 1	~98%
CU+EUNE7	193 ± 4	199 ± 2	~96%
CU+EUNE8	192 ± 4	199 ± 2	~96%
CU+EUNE9	195 ± 3	200 ± 1	~98%

4.7 In-vitro drug Release Study

07- Cumulative % Drug Release Curcumin and Eucalyptol

Time (Hr)	CU+EUN 1		CU+EUN 2		CU+EUN 3		CU+EUN 4		CU+EUN 5		CU+EUN 6		CU+EUN 7		CU+EUN 8		CU+EUN 9	
	CRM	EUC	CRM	EUC	CRM	EUC	CRM	EUC	CRM	EUC	CRM	EUC	CRM	EUC	CRM	EUC	CRM	EUC
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	11.8	43.5	16.2	56.4	12.1	44.2	18.4	62.7	22.7	72.4	19.3	61.8	14.8	50.6	14.2	48.4	16.8	56.2
2	21.5	62.8	28.5	76.8	22.0	63.5	32.6	82.4	39.4	88.6	33.8	81.5	26.2	71.2	25.1	68.7	29.5	76.9
4	38.2	83.4	48.7	92.5	39.1	84.1	54.8	95.8	62.8	97.8	56.4	95.2	45.3	89.8	43.6	88.6	50.2	93.8
6	51.6	91.2	62.3	96.8	52.4	91.8	68.9	98.6	76.5	99.5	70.2	98.4	58.9	95.4	57.3	94.8	64.8	97.6
8	61.8	94.7	72.1	98.2	62.5	95.1	78.2	99.4	85.1	99.9	79.6	99.2	69.4	97.6	67.8	97.2	74.6	98.9
10	69.7	96.3	79.4	98.9	70.3	96.8	84.6	99.8	90.4	100.0	86.1	99.6	77.2	98.5	75.9	98.4	81.7	99.4
12	75.9	97.1	84.6	99.3	76.4	97.5	89.3	99.9	94.2	100.0	90.8	99.8	83.1	99.1	82.4	99.0	86.9	99.7

4.8 Drug Release Kinetics

Table 08- Drug release kinetic (Curcumin)

Time in Hours	cumulative % Drug Release	Cumulative % Drug Remain	Log % Drug Remain	Sq Root of Time	Log Time	Log of Dissolve Amount	Fraction Released (Mt/M∞)	Cube Root (%) Drug Remaining
0.00	0.0000	100.0000	2.0000	0.0000	0.0000	0.0000	0.0000	4.6416
1.00	22.7000	77.3000	1.8882	1.0000	0.0000	1.3560	0.2270	4.2598
2.00	39.4000	60.6000	1.7825	1.4142	0.3010	1.5955	0.3940	3.9279
4.00	62.8000	37.2000	1.5705	2.0000	0.6021	1.7980	0.6280	3.3382
6.00	76.5000	23.5000	1.3711	2.4495	0.7782	1.8837	0.7650	2.8643
8.00	85.1000	14.9000	1.1732	2.8284	0.9031	1.9299	0.8510	2.4607
10.00	90.4000	9.6000	0.9823	3.1623	1.0000	1.9562	0.9040	2.1253
12.00	94.2000	5.8000	0.7634	3.4641	1.0792	1.9741	0.9420	1.7967

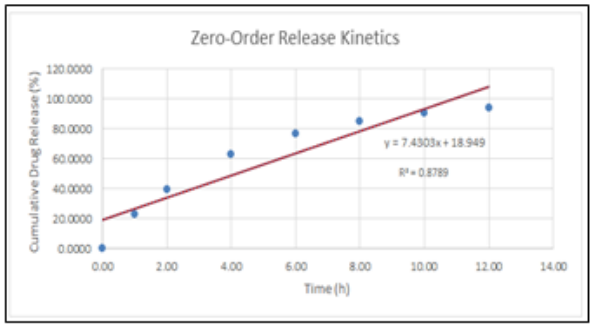

Fig 08- Zero order kinetic drug Release

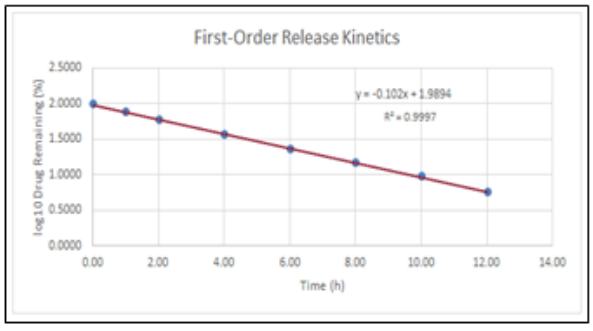

Fig 09- First order kinetic drug Release

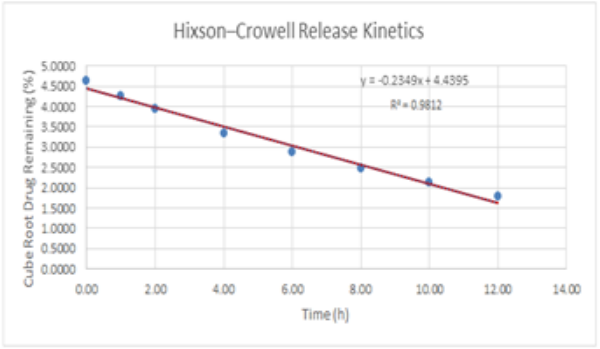

Fig 10- Hixson–Crowell Release

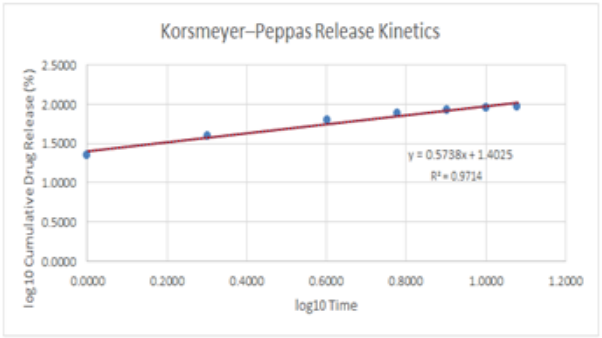

Fig 11- Korsmeyer–Peppas Release Kinetics

Table 09- Drug release kinetic (Eucalyptol)

Time in Hours	cumulative % Drug Release	Cumulative % Drug Remain	Log % Drug Remain	Sq Root of Time	Log Time	Log of Dissolve Amount	Fraction Released (Mt/M∞)	Cube Root (%) Drug Remaining
0.00	0.0000	100.0000	2.0000	0.0000	0.0000	0.0000	0.0000	4.6416
1.00	72.4000	27.6000	1.4409	1.0000	0.0000	1.8597	0.7240	3.0221
2.00	88.6000	11.4000	1.0569	1.4142	0.3010	1.9474	0.8860	2.2506
4.00	97.8000	2.2000	0.3424	2.0000	0.6021	1.9903	0.9780	1.3006
6.00	99.5000	0.5000	-0.3010	2.4495	0.7782	1.9978	0.9950	0.7937
8.00	99.9000	0.1000	-1.0000	2.8284	0.9031	1.9996	0.9990	0.4642
10.00	100.0000	0.0000	0.0000	3.1623	1.0000	2.0000	1.0000	0.0000
12.00	100.0000	0.0000	0.0000	3.4641	1.0792	2.0000	1.0000	0.0000

Fig 12- Zero order kinetic drug Release

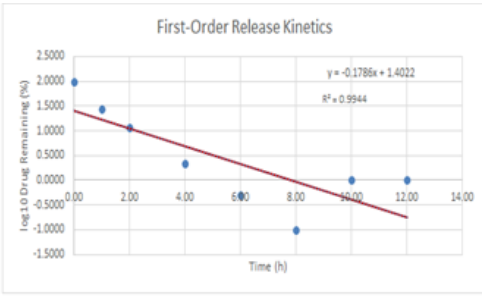

Fig 13- First order kinetic drug Release

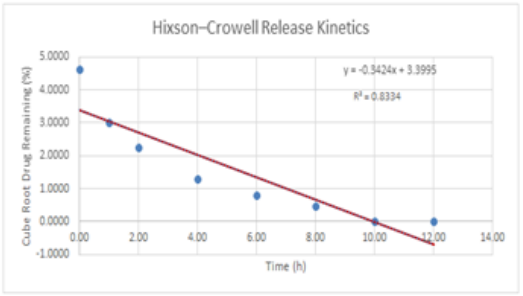

Fig 14- Hixson–Crowell Release

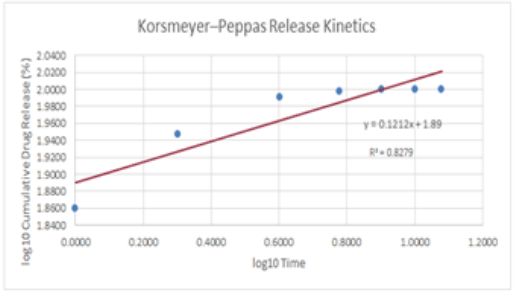

Fig 15- Korsmeyer–Peppas Release Kinetics

4.9 Surface Morphology

The surface morphology of Curcumin–eucalyptol Nanoemulgel was examined using scanning electron microscopy (SEM). Pictures of Curcumin & Eucalyptol Nanoemulgel are shown in Fig 16. Nanoemulgel stability was confirmed by scanning electron microscopy (SEM) analysis, which revealed almost spherical Curcumin & Eucalyptol Nanoemulgel free of droplet coalescence.

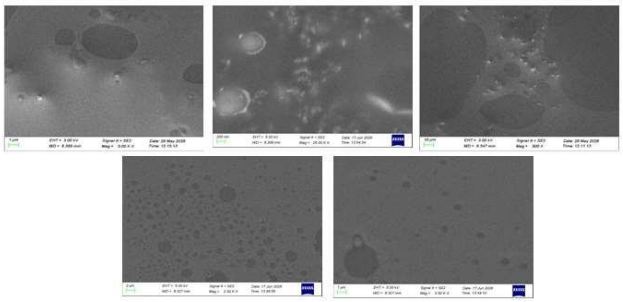

Fig 16- SEM Images of Nanoemulgel

4.10 Polydispersity Index and Zeta potential

Table 10- Polydispersity Index and Zeta potential

Code	Eucalyptol(100)+ Curcumin (100) (w/mgs)	Olive oil (W/ml)	Tween 80 (W/ml)	Homogenizer Time in min	PDI	Zeta Potential
CU+EUNE1	200	1	1.5	5	0.810	-35.84
CU+EUNE2	200	1	2.5	5	0.592	-33.24
CU+EUNE3	200	1	1.5	7.5	0.798	-35.41
CU+EUNE4	200	1	2	10	0.552	-31.74
CU+EUNE5	200	1	2.5	10	0.380	-26.1
CU+EUNE6	200	1	2.5	7.5	0.614	-30.41
CU+EUNE7	200	1	2	5	0.706	-34.05
CU+EUNE8	200	1	1.5	10	0.572	-32.21
CU+EUNE9	200	1	2	7.5	0.734	-32.3

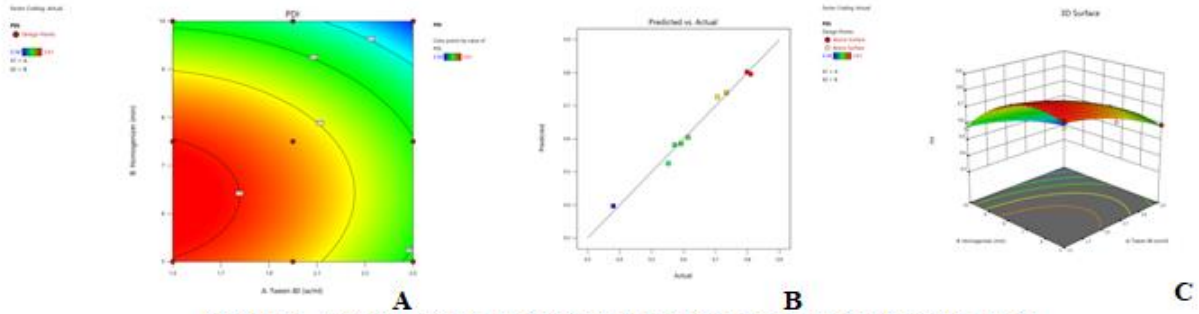

Figure 17- A:Contour Plot of PDI; B: Actual vs Predicted of PDI; C: RSM of PDI

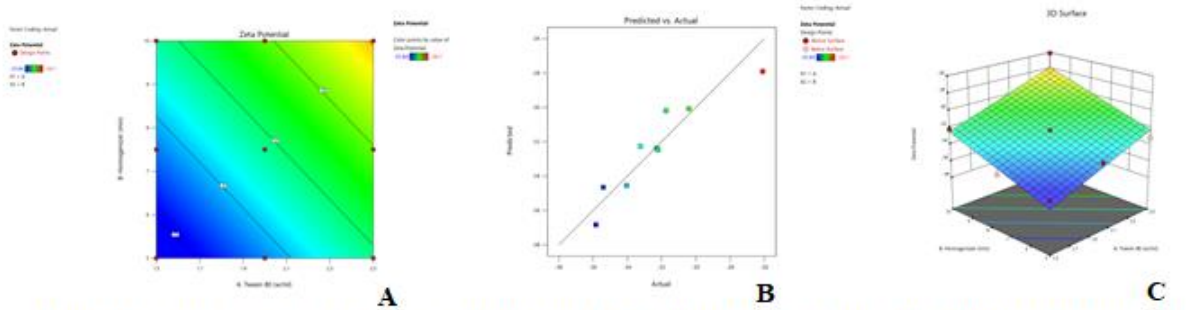

Figure 18- A: Contour Plot of Zeta Potential; B: Actual vs Predicted of Zeta Potential; C: RSM of Zeta Potential

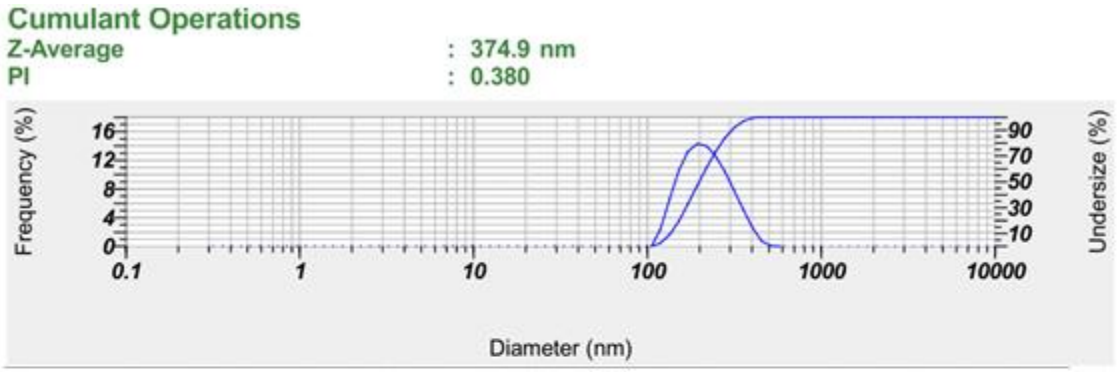

Figure 19- Particle size & PDI of Nanoemulgel

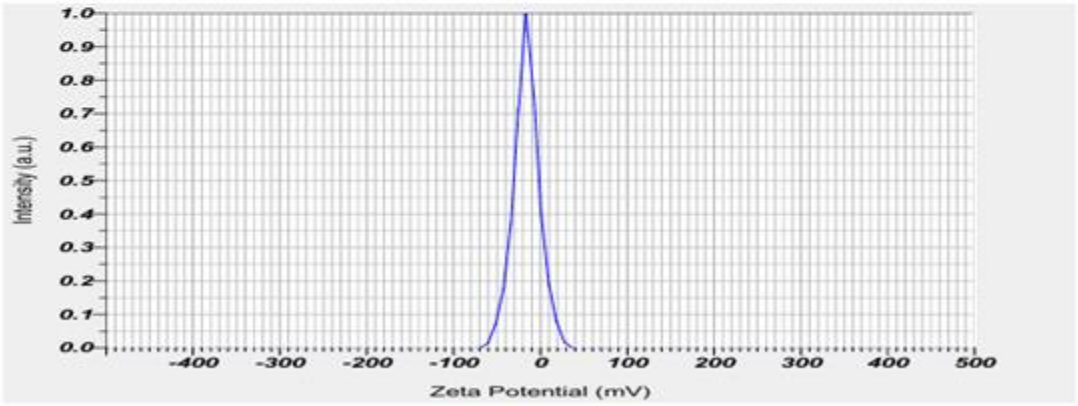

Figure 20- Zeta Potential of Nanoemulgel

4.11 Histopathological Analysis

Following the euthanasia of the rat, paw was extracted for histopathological analysis. The tissue samples were cut into 4 µm thick sections, fixed in 10% neutral buffered formalin, and embedded in paraffin wax. Each specimen was then treated with hematoxylin and eosin stain, toludine blue stain and Masson's trichome stain[20,21].

Treatment	0-hrs	1 hrs	2hrs	4hrs	6hrs	10hrs	12hrs
Control	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Formalin-induced	1.04±0.012	1.68±0.28***	2.15±0.48***	2.57±0.39***	2.82±0.44***	2.61±0.41***	2.50±0.46***
Curcumin	1.03±0.01	1.51± 0.22^{ns}	2.10±0.41 ^{ns}	2.12±0.27*	2.10±0.24**	2.01±0.29**	1.92±0.26**
Eucalyptol	1.03±0.02	1.53±0.21 ^{ns}	2.13±0.24 ^{ns}	2.15±0.23*	2.08±0.32**	1.96±0.31**	1.89±0.23***
Curcumin+ Eucalyptol Nanoemulgel	1.02±0.02	1.51±0.19**	1.94±0.18**	1.85±0.11**	1.80±0.12**	1.73±0.11***	1.71±0.11***
Diclofenac gel	1.02±0.02	1.51±0.19**	1.91±0.18**	1.84±0.11**	1.76±0.12**	1.71±0.11***	1.63±0.11***

One-way ANOVA followed by Tukey–Kramer multiple comparison test showed * p < 0.05 ** p < 0.01 and *** p < 0.00 as compared to the positive control group and the reference group.

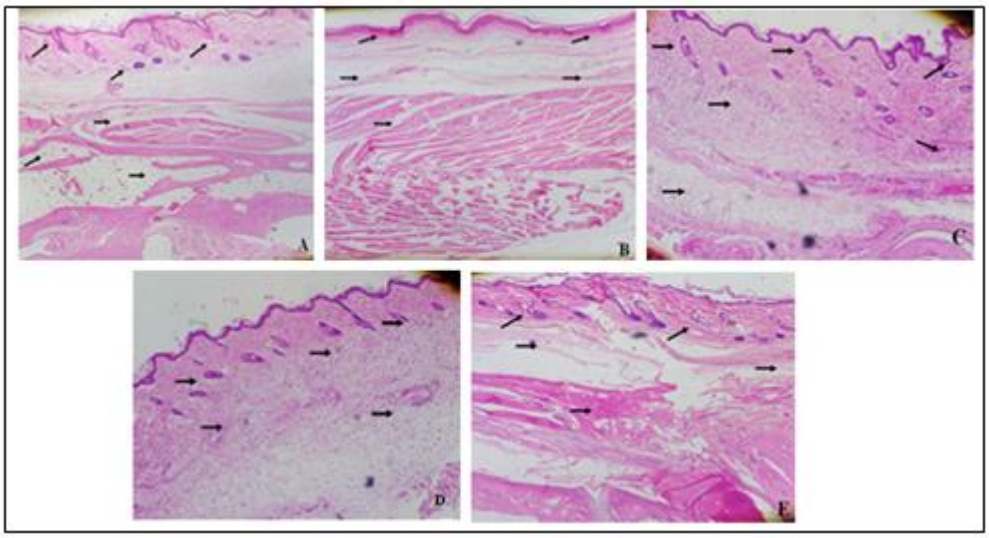

Figure 21- Histopathology of paw tissue using H & E stain: A: Control, B: Formalin induced group, C: Curcumin treatment Group, D: Eucalyptol treatment Group, E: Curcumin and Eucalyptol Nanoemulgel Group. Histopathology

a. Hematoxylin and eosin (HE) Staining: Curcumin and Eucalyptol nanoemulgel showing control group (A) Photomicrographs of H&E-stained sections from control rat group A displaying a histologically normal structure in the paw tissue. Formalin induced group (B) showed tissue disorganization, interstitial edema, marked inflammation with inflammatory exudation, vascular injury, were observed. Curcumin treatment Group (C) treated rat showing mild inflammation, mild infiltration and cartilage damage. Eucalyptol treatment Group (D) treated rat showing mild inflammation, mild infiltration and cartilage damage and Curcumin and Eucalyptol Nanoemulgel Group (E) treated rat exhibited significant reduction in interstitial edema and structural damage with absence of inflammatory infiltration in rat plantar tissue return to a normal histological structure.

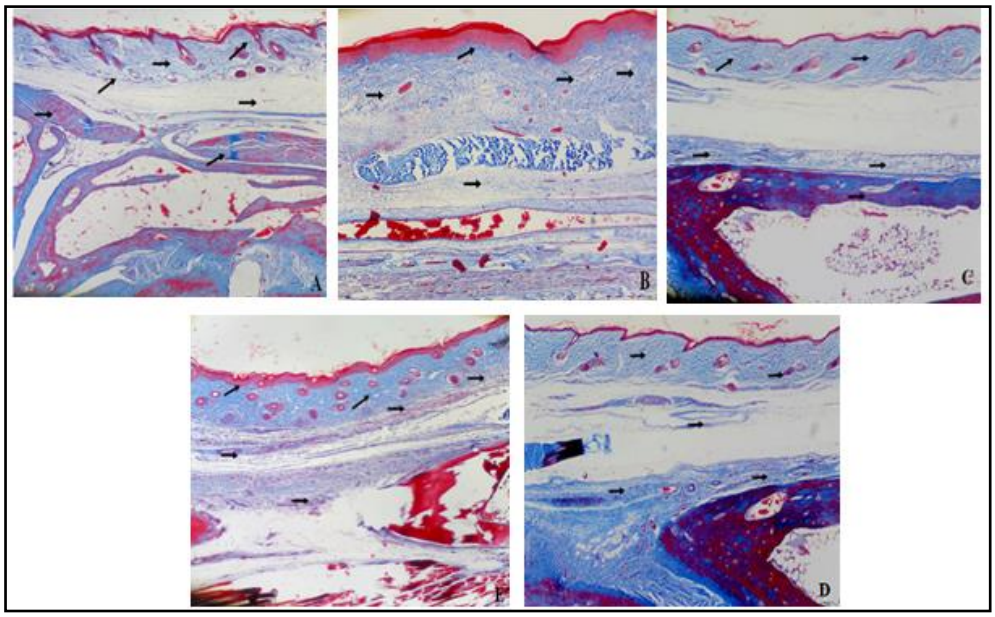

Figure 22- Histopathology of paw tissue using Masson's trichome stain A: Control, B: Formalin induced group, C: Curcumin treatment Group, D: Eucalyptol treatment Group, E: Curcumin and Eucalyptol Nanoemulgel Group.

b. Histopathology of paw stained Masson's trichrome Staining: Curcumin and Eucalyptol nanoemulgel showing control group (A) control rat A showing normal collagen deposition with dermal bundles of thin blue stained collagen fibers. Formalin induced Group (B) rat paw showed a focal increase in the collagen bundles revealing intense collagen deposition. Curcumin Group (C) treated rat showing mild to moderate collagen deposition Eucalyptol Group (D) treated rat showing mild to moderate collagen deposition and Curcumin and Eucalyptol Nanoemulgel Group (E) treated rat exhibiting protective role with mild collagen density resembling normal tissue.

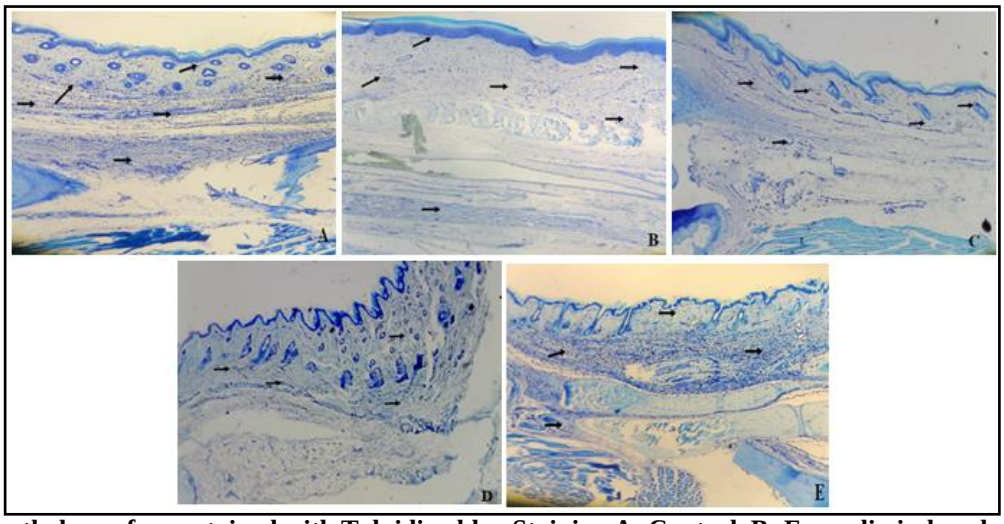

Figure 23- Histopathology of paw stained with Toluidine blue Staining A: Control, B: Formalin induced group, C: Curcumin treatment Group, D: Eucalyptol Group, E: Curcumin and Eucalyptol Nanoemulgel Group.

c. Histopathology of paw stained with Toluidine blue Staining: Curcumin and Eucalyptol Nanoemulgel Control group (A) displaying a histologically normal cell distribution with intact architectural appearance, normal mast cells density in the paw tissue. Formalin induced Group (B) showed tissue disorganization, marked inflammation, cellular infiltration and cartilage damage and dilated blood vessels and increase in mast cells around the vessels. Curcumin Group (C) treated rat showing showing mild to moderate inflammation, cellular infiltration, mild loss of toluidine blue staining with mild to moderate cartilage damage and presence of moderate mast cell. Eucalyptol Group (D) treated rat showing mild to moderate inflammation, cellular infiltration, mild loss of toluidine blue staining with mild to moderate cartilage damage and presence of moderate mast cell. Curcumin and Eucalyptol Nanoemulgel Group (E) treated rat exhibiting protective role with mild inflammatory cellular infiltration, normal mast cell density resembling normal tissue.

5. CONCLUSION

The optimized Curcumin and Eucalyptol Nanoemulgel batch CU+EUNE5 was developed successfully and subjected to physicochemical studies i.e. rheological studies, spreading, in vitro release study and in-vivo Study. It was concluded that Curcumin and Eucalyptol Nanoemulgel stable and effective in inflammation of sinusitis.

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