

## **DEVELOPMENT AND OPTIMIZATION OF FENUGREEK EXTRACT LOADED NANOEMUGEL FOR THE TREATMENT ANTI- INFLAMMATORY ACTIVITY**

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### **ABSTRACT**

The bright green clover-like leaves of fenugreek (*Trigonella foenum graceum*) have a pleasantly bitter-sweet flavour. These seeds are quite hard and are usually ground into a powder. Their flavour is typically compared to maple syrup. The seeds have a flavour that is remarkably similar to the leaves. For transdermal distribution of *Trigonella foenum graceum* extract, a nanoemulsion system was designed with Tween 80 as the surfactant, IPA as the co-surfactant, and Isopropyl myristate as the oil phase. In the pseudo-ternary phase diagram generated at various Tween 80, a region of nanoemulsion was discovered. Water (16.6%), Smix (75%), and Oil (8.3%) The gelling agent carbapol 934 was used to make a nanoemulsion-based gel. Quercetin absorption through the skin was shown to be faster in this nanoemulsion than in aqueous solution. The results imply that the W/O nanoemulsion is a suitable anti-inflammatory gel because nanoemugel improves drug bioavailability.

**Key words:** Nanoemulsion, Nanoemugel, *Trigonella foenum graceum* extract.

### **1. INTRODUCTION**

Natural origin substances and their formulations have been known for their biological activity and health effects since ancient times. Plants' physiologically active components, such as tannins, flavonoids, and terpenoids, are mostly polar. They are, on the other hand, ineffective. Because of their huge molecular size, which prevents passive diffusion, and their pitiable lipid solubility, they have a pitiable bioavailability (Krishna and Gejjalagere 2018). Nanoemulsions are colloidal particulate systems with submicron size particles that act as medication carriers. Their diameter ranges from 10 to 1,000 nanometers. These carriers are solid spheres with an amorphous, lipophilic, and negatively charged surface. To improve site specificity, magnetic nanoparticles can be utilised. As a medication delivery system, they improve the drug's therapeutic efficacy while reducing side effects and hazardous reactions. Treatment of reticule endothelial system (RES) infection and enzyme replacement therapy are two major applications.. in the liver, cancer treatment, and vaccines An emulsion is a biphasic system in which one phase is dispersed in minute droplets with diameters varying from 0.1 to 100 lm in the other phase. It's a thermodynamically unstable system that could blow up at any time. The addition of an emulsifying ingredient will help to keep the mixture stable (emulgent or emulsifier). The dispersed phase is also known as the internal phase or the discontinuous phase, whereas the dispersion medium, external phase, or continuous phase is the outer phase. It's also known as the emulsifying agent. as a transitional or inter phase state A nanoemulsion is a fine oil/water or water/oil dispersion stabilised by an interfacial coating of surfactant molecules with droplet sizes ranging from 20 to 600 nanometers. Nanoemulsions are characterised by their microscopic size. Transparent. There are three types of nanoemulsions that can be created: (a) oil in water nanoemulsions in which oil is dispersed in a continuous aqueous phase, (b) water in oil nanoemulsions in which water droplets are dispersed in a continuous oil phase, and (c) bi-continuous nanoemulsions in which water droplets are dispersed in a continuous oil phase.

### **2. MATERIALS AND METHODS**

Near Shirpur, India, a *Trigonella foenum graceum* seeds was received and extract was prepared in Lab. Loba Chemie, Mumbai, India, provided Tween 80, IPA, isopropyl myristate, and methanol. All of the other reagents were of analytical quality. Extract solubility and oil and surfactant screening for nanoemulsion: The equilibrium solubility experiment was carried out by adding an excess of *Trigonella foenum graceum* extract in 2 mL of various oils (soybean oil, sunflower oil, coconut oil, olive oil, isopropyl myristate), surfactants (Tween 80, Tween 20, span 80, SLS, Transcutol), and Cosurfactants (IPA, ethanol, n-amyl alcohol) in 5 mL capacity vials each vortexed separately using a Cyclo mixer REMI (INDIA), CM 101]. (Rachmawati et al., 2015 Eid et al., 2013).

Fenugreek, scientifically known as *Trigonella foenum graecum* L., is a Fabaceae family leguminous herb. The seeds of this plant are widely used as an element in normal diets in Asia, the Mediterranean, and Africa, as well as for medicine and fragrances, as well as in cosmetics, drinks, and industrial applications The yellow and firm embryo of the fenugreek seed is covered by a bigger and corneous layer of semi-transparent white endosperm. Various

photochemicals, such as steroid sapogenins, are found in fenugreek. The embryo of an oily Diosgenin, a well-known steroid precursor, is found in fenugreek. The endosperm contains saponin and protein, and the husk has more total polyphenols. Several coumarin chemicals, as well as a number of alkaloids, have been discovered in fenugreek seeds (e.g., trigonelline, gentianine, carpaine). The most important bioactive component in Polyphenolic compounds such as rhamnolipid and isovitexin are thought to be present in fenugreek seeds. In fenugreek seeds, a tiny amount of volatile and fixed oils have been discovered. Diacetin, for example, is an essential chemical found in the volatile oil of fenugreek. 1-Octene-3-one, sotolon, acetic acid; eugenol, butanoic acid, caproic acid isovaleric acid, isovaleric acid, isovaleric acid, isovaleric acid, isovaleric acid 3-isobutyl-2-methoxypyrazine, 3-iso Linalool, (Z)-1, 3-amino-4,5-dimethyl-3, 4-dihydro-2(5H)-octadiene-3-one and 5-octadiene-3-one Furanone Fenugreek seeds contain a number of important phytoconstituents. This plant is said to have antiviral, antimicrobial, carminative, anticholesterolemic, and other pharmacological properties. Anticarcinogenic, anti-inflammatory, antioxidant, hypotensive, febrifuge, restorative, laxative, expectorant, galactogogue, uterine tonic, anticarcinogenic, anti-inflammatory, antioxidant, hypotensive, etc. Fenugreek seeds have long been used in traditional medicine as an anti-diabetic, gastric stimulant, and anorexia treatment. Many health benefits of fenugreek seeds have been clinically and preclinically validated in recent decades.

Pseudo-ternary phase diagrams were created using the oil titration method at room temperature to determine the concentration range of components for nanoemulsion (25°C). IPM is based on the solubility studies. As the oil phase, was chosen. Tween 80 was chosen as the surfactant and TPA was chosen as the Cosurfactants. As an aqueous phase, distilled water was used. Surfactant and Cosurfactants (Smix) were mixed in various mass ratios, including 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9. 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9. For a detailed study of the phase diagrams, these ratios were chosen in decreasing concentrations of surfactant relative to co surfactant. At different mass ratios, oil and Smix at a specific ratio were thoroughly mixed for each phase diagram. In various glass vials, the ratios range from 1:1 to 2:1. Different combinations of oil and Smix were created so that maximum ratios could be covered for the study in order to precisely define the phases' limits in phase diagrams. Phase using the aqueous titration method, pseudo-Ternary diagrams of oil, Smix, and aqueous phase were created. For each mass ratio of oil and Smix, a slow titration with aqueous phase was performed, and visual observations were made for a transparent and easily flowable o/w nanoemulsion. To make the phase diagrams easier to read, "water dilution lines" were drawn to represent increasing water content and decreasing surfactant-co surfactant levels. The water was titrated by drawing dilution lines from the surfactant-co surfactant side of the triangle to the opposite oil side. The value of the line intersection with the oil scale was arbitrarily assigned to the line (e.g., 20:80, 30:70). The samples were considered biphasic if turbidity appeared followed by phase separation. If everything is in order, After stirring, transparent mixtures were observed, and the samples were determined to be monophasic. On the phase diagram, the samples were labelled as points. The nanoemulsion region of existence was defined as the area covered by these points (Rachmawati et al., 2015 Eid et al., 2013, Ghosh et al., 2013). Herbal nanoemulsion formulation development: The phase diagram shows the surfactant/Cosurfactants ratio of 2:1, which is suitable for nanoemulsion simulation. The liquid nanoemulsion was made by dissolving extract in double distilled water (0.5-1 percent), then adding the Tween 80 mixture drop by drop to the resulting solution (38.10 percent), With continuous stirring on a vortex mixer, make IPA (19.04%) and then IPM (28.57%). During the formulation process, no heat is applied. The resulting nanoemulsion was tightly sealed and stored at room temperature, and its physical stability was determined by monitoring for phase separation on a regular basis; the nanoemulsion was also characterised. Nanoemulsion Characterization: A small amount of nanoemulsion was placed on a clean glass slide for a dilution test. A drop of water was added to the nanoemulsion and mixed with the help of a glass rod to determine their transparency. The emulsion will remain stable if it is diluted with water because water is the dispersion medium; however, if it is diluted with oil, the emulsion will break because oil and water are not compatible. Drug content of nanoemulsion: A UV spectrophotometer was used to determine the drug content of the optimised formulation. In 10 ml of methanol, 10 mg equivalent of extract containing nanoemulsion was dissolved. The solution's concentration was discovered to have a concentration of 100 g/ml Using the UV-Visible spectrophotometer UV-1700, the mono amino Trigonella foenum graceum content was calculated at 248nm. Diffusion studies in vitro: The Franz diffusion cell was used to perform in vitro diffusion of nanoemulsion and aqueous extract solution. The container has a diameter of 3.0 cm and a capacity of 25 ml. As a diffusion membrane, a dialysis membrane (Hi-media) with a molecular weight cut off range of 12000–14000 kDa was used. Prior to the experiment, the dialysis membrane was soaked in phosphate buffer pH 5.8 for 24 hours. The dialysis membrane was mounted on the diffusion cell, which was filled with phosphate buffer pH 5.8. The temperature has risen to a high level. The temperature was kept at 32.5°C. The nanoemulsion and aqueous solution containing extract equivalent to 10 mg were placed in the donor chamber after a 20-minute pre-incubation period. Samples were taken out of the

receptor compartment for 6 hours at a time and replaced with the same amount of fresh phosphate buffer solution, then measured at 248 nm with a spectrophotometer. Nanoemulsions are being developed After complete dispersion, the 1 g of Carbapol 934 was dispersed in a sufficient quantity of distilled water (100ml) to make the gel base. The carbapol 934 solution was kept for 24 hours until the swelling was complete. Then, under magnetic stirring, the *Trigonella foenum graceum* extract loaded nanoemulsion was slowly added to the above prepared gel base for the development of nanoemulsion based gel (Modi JD, Patel JK 2011) Gel Physicochemical Evaluation: After the gel had been set in the container, they were tested for their appearance of homogeneity by visual inspection.

Carrageenan-induced rat paw edema was used in an in-vitro pharmacodynamics study. Anti-inflammatory properties: The inhibition of carrageenan-induced hind paw edema was used to evaluate it. The rats (180-200) were divided into four groups, one for each sex. containing a total of six animals The rats were fasted for 12 hours before being given water to induce edema. The rats are given 5ml of water via stomach tube to ensure uniform hydration. Thirty minutes later, the rats' left hind paws were injected with 0.1 ml of freshly prepared 1 percent suspension of carrageenan in normal saline via subplanter injection. One hour before and one hour after the carrageenan challenge the NEIG formulation (0.25g) or base was applied topically to the paw of each rat in the test group with gentle rubbing. The gel base and standard marketed for mulation diclofenac gel BP were applied in the same way as a reference standard to the rats in the control groups. The volume of the paws was measured at 0, 2, 4, 8, 12 hour Using a Vernier Calliper . In test groups, the percentage inhibition of paw volume was compared to the control group (Nadia Hisamuddin 2019) Edema inhibition percentage = 100 (1  $V_t/V_c$ ) Where  $V_t$  represents the inflammatory increase in paw volume in test groups and  $V_c$  represents the inflammatory increase in paw volume in normal control rats. The anti-inflammatory activity is proportional to the percentage inhibition of edema. Antimicrobial Research: Dilution of the broth macro Assay: Broth dilution is a technique for testing a bacterium suspension at a specific concentration against various antimicrobial concentrations. Agent. Because nanoemulsions o/w will break if mixed directly with broth media prepared in water, the 1% and 2% nanoemulsions were dissolved in DMSO to give final concentrations of 2.5mg/ml and 5mg/ml, respectively. DMSO was used to prepare mg/ml. In the test tubes above, a suspension of various bacteria and fungi was poured. The tubes containing bacterial suspension were kept at 37°C for 24 hours and the tubes containing fungal culture were kept at 300°C for 48 hours. Following incubation, check for growth or turbidity (Das K et al., 2010).

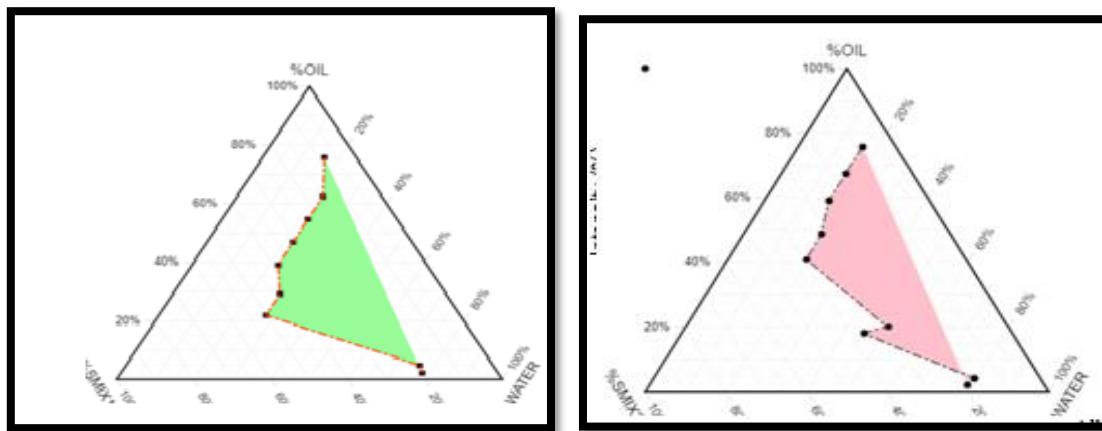
### **3. RESULTS AND DISCUSSION**

The physicochemical properties of drugs influence the development of nanoemulsion formulations. The drug's solubility, as well as the nanoemulsion's ability to keep the drug solubilized, is the most important factor. Lipophilic drugs' oil solubility and hydrophilic drugs' oil solubility The presence of drugs in the aqueous phase is an important criterion for choosing between oils and water. Quercetin is a hydrophilic substance. The solubility of Quercetin in various oils was determined because Quercetin's solubility was higher in the aqueous phase. For transdermal delivery of Quercetin, a w/o nanoemulsion was developed as opposed to an oil phase. The best oils and surfactants for good solubilizing of *Trigonella foenum graceum* herbal extract in various oils and surfactants were determined. In the development of nanoemulsions, medium and long chain triglyceride oils with varying degrees of saturation were used. Soybean oil, sunflower oil, coconut oil, and olive oil were among the oils tested. Isopropyl myristate (IPM), oil, etc. Tween 80, Tween 20, span 80, SLS, and Transcutol were used as surfactants, while IPA, ethanol, and n-amyl alcohol were used as co-surfactants. In different oils, the solubility of *Trigonella foenum graceum* was determined. *Trigonella foenum graceum* was found to have the highest solubility in isopropyl myristate (195.710.911 mg 2 mL-The poorly soluble drugs' polarity favours their solubilisation in small/medium molar volume oils. Due to their rancidity, edible oils are unable to depict large micro emulsion regions. Because of its well-known permeation-enhancing property and biocompatibility, IPM was chosen for the preparation of nanoemulsion. When administered transdermal, large amounts of surfactants can cause skin irritation. It is therefore critical to accurately determine the surfactant concentration and use the lowest concentration possible when developing nanoemulsions for simulation (Alam et al., 2010). Tween 80 performed the other surfactants tested When various co-surfactants were tested for solubility and miscibility with surfactant, it was discovered that isopropyl alcohol IPA has a higher solubilisation capacity and forms a transparent system. Because no surfactant or co-surfactant can dissolve all types of oil phase, screening surfactants and co-surfactants on the basis of solubility is difficult. The surfactant chosen must be able to reduce the interfacial tension to a very low value in order to aid the dispersion process during nanoemulsion preparation and provide a flexible film that can easily deform around the nanoemulsion. Droplets. The first phase is aqueous, the second is oil, and the third is a fixed mass ratio mixture of surfactant and Cosurfactants. Figure 1 shows the pseudo ternary phase diagrams for nanoemulsion systems, as well as the surfactant ratios.

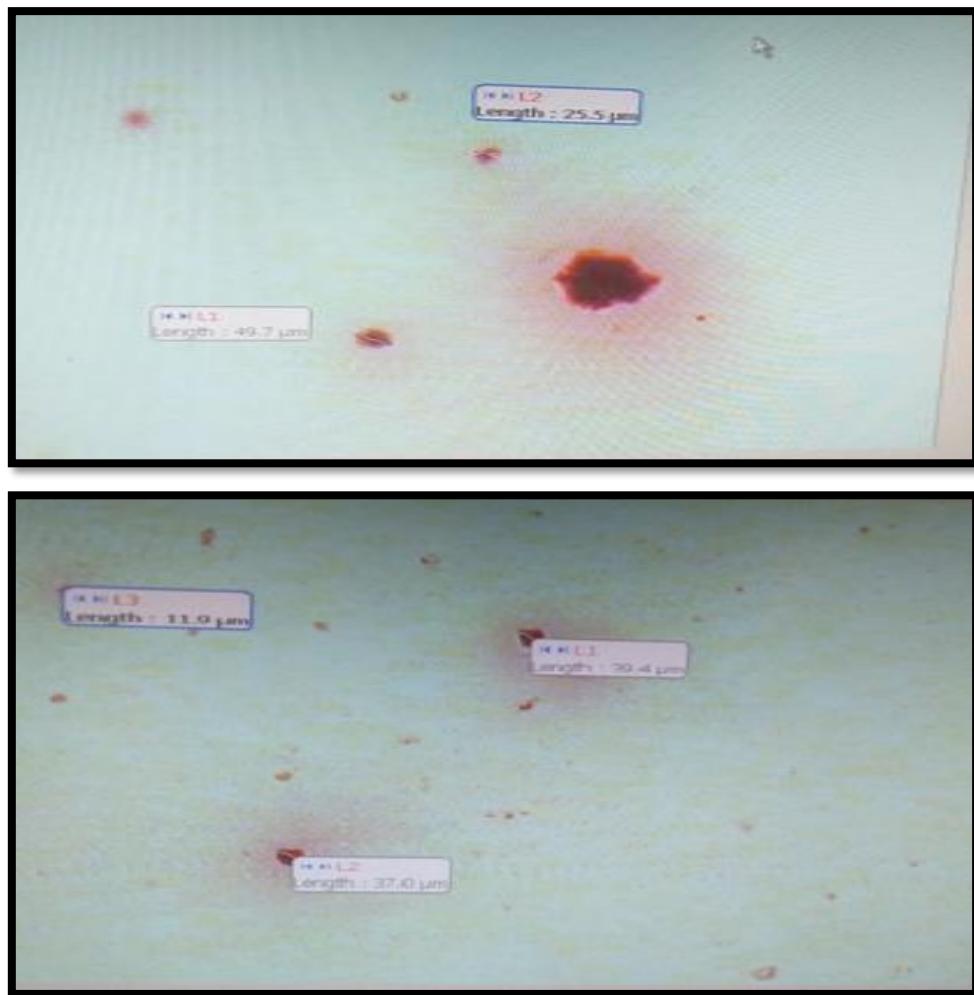
**Table no-01**

<b>Table no-01 Formulation composition of Nanoemulsion</b>		<b>Batch -1</b>
<b>Ingredient</b>	<b>Ratio</b>	
	2:1	1:1
Distilled Water	20	3.0
IPA	30.0	25
	10	1.0
IPM	60.0	25
Tween 80		

represent the surfactant and cosurfactant ratios as 1:1 and 2:1 in the pseudo ternary phase diagrams for nanoemulsion systems. The ternary phase diagram clearly shows how the ratio of surfactant to co-surfactant changes the area of the nanoemulsion region. The ratio of surfactant to water was changed from 1:1 to 2:1. Because of the high concentration of surfactant, the nanoemulsion region increased when the ratio of surfactant to cosurfactant was 2:1. Nanoemulsions are thermodynamically stable systems that form at a specific oil, surfactant, and water concentration, with no phase separation, creaming, or cracking. Different stress levels were applied to selected formulations from the phase diagram. Heating and cooling cycles, centrifugation, and freeze-thaw cycles are all examples of stability testing. Some formulations became turbid during physical stability testing, and phase separation occurred in others. The Ostwald ripening, in which molecules move as a monomer and small droplets coalesce, resulting in the formation of large droplets by diffusion processes driven by the gain in surface free energy, could be one reason for the instability in nanoemulsions.. Another reason could be that when temperature quench occurs during stress stability testing, nanoemulsion instability occurs due to oil phase separation, and droplet distribution of smaller sizes is favoured by the change in curvature free energy. Only those formulations, which showed no phase separation, creaming, cracking, coalescence, and phase inversion during stress stability tests, were selected for further studies (Osanloo et al., 2018). Novel nanoemulsion of *Trigonella foenum graceum* extract was prepared by the spontaneous emulsification method (oil phase titration method), Isopropyl myristate was used as oil phase components. Isopropyl alcohol (19.04%) and isopropyl myristate (19.04%) (28.57 percent ). The resulting nanoemulsion was clear and transparent. The system was w/o type with pH 5.590.01, 5.78 0.005 based on dilution and dye test results.



The particle size of the optimised nanoemulsion varied as drug loading increased by 0.51%, ranging from 104.2 nm to 185.3 nm, but it was mostly within the range. The smaller particle size of the emulsion droplets has been reported to lead to faster absorption and improved bioavailability. Polydispersity is defined as the ratio of standard deviation to mean droplet size, which indicates dispersity uniformity. The polydispersity index (PDI) is a scale that ranges from 0.0 to 1.0 in terms of particle homogeneity. The PDI 0.186-0.451 found it to be closer to zero, so The particles are more homogeneous. The term polydispersity refers to the consistency of droplet size within a formulation. The formulations' polydispersity value was very low (0.4), indicating droplet size uniformity within the formulation. the greater The greater the net charge of droplets and the more stable the emulsion, the lower the zeta potential. Lower zeta potentials (below -30 mv) indicate a high degree of physical stability in the zeta potential. -9.5 to -13.8 potential was discovered. With an increase in extract concentration, it shows little change, but all of the values are within range, and the nanoemulsion was found to be stable in a thermodynamic stability study.



**Droplet size of nanoemulsion by Motic Electron Microscopy 10X**

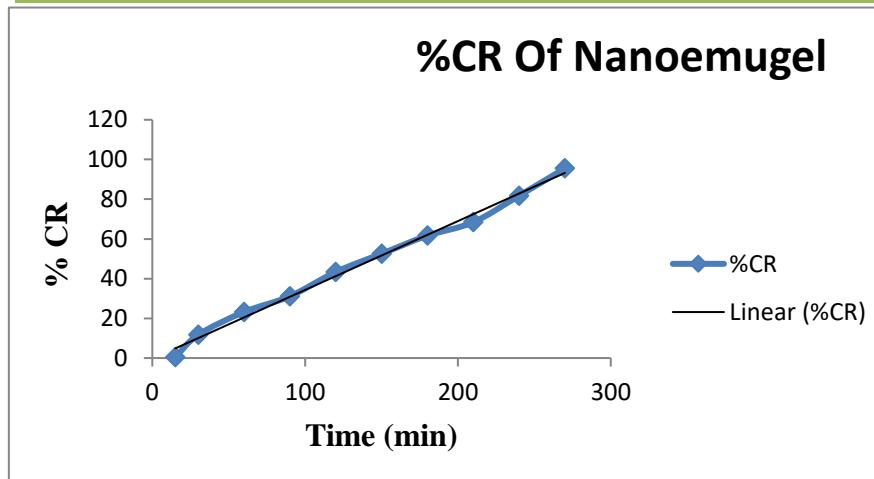
**Table No. 2 The Influence of mixture component on characterisation of prepared Nanoemulsion Batch-1**

Parameter	FA1	FB2	FC3
Zeta	217.5	199.2	169.4
PDI	0.135	0.167	0.161
Partical size	-14.3	189.5	-15.0

The extract was centrifuged, but all of the values were within range, and the nanoemulsion was found to be stable after a thermodynamic stability study. The viscosity of the nanoemulsion was 67.43 0.15cP at room temperature. The liquid's viscosity was found to be high in general. The extract was centrifuged, but all of the values were within range, and a thermodynamic stability study revealed that the nanoemulsion was stable. At room temperature, the nanoemulsion had a viscosity of 67.43 0.15cP. The viscosity of the liquid was found to be high in general. Physicochemical variables were used to assess its efficacy. The w/o nanoemulsion was found to be thermodynamically stable, and drug concentration had no or little effect on it. The formulation can be applied to the skin safely. The formulation is shown diffusing through a dialysis membrane in vitro. After 3.5 hours, the drug release from the Extract in Carbopol Gel was 40percent, while the drug release from the extract was 95.30 percent. The percentage of aqueous solution was 33.17 percent. This is significantly less when compared to NE. Because of their nano range size, the rate of diffusion of nanoemulsions was found to be improved. It's possible that the average droplet size is responsible for the significant difference in permeation between nanoemulsion formulations and aqueous solution. The results of an ex vivo permeation study on rat skin show that drug permeation through skin in 210 minutes (3.5 hours) is 92.26 percent, but only 33.61 percent through an aqueous solution of extract.

**Table no-03**

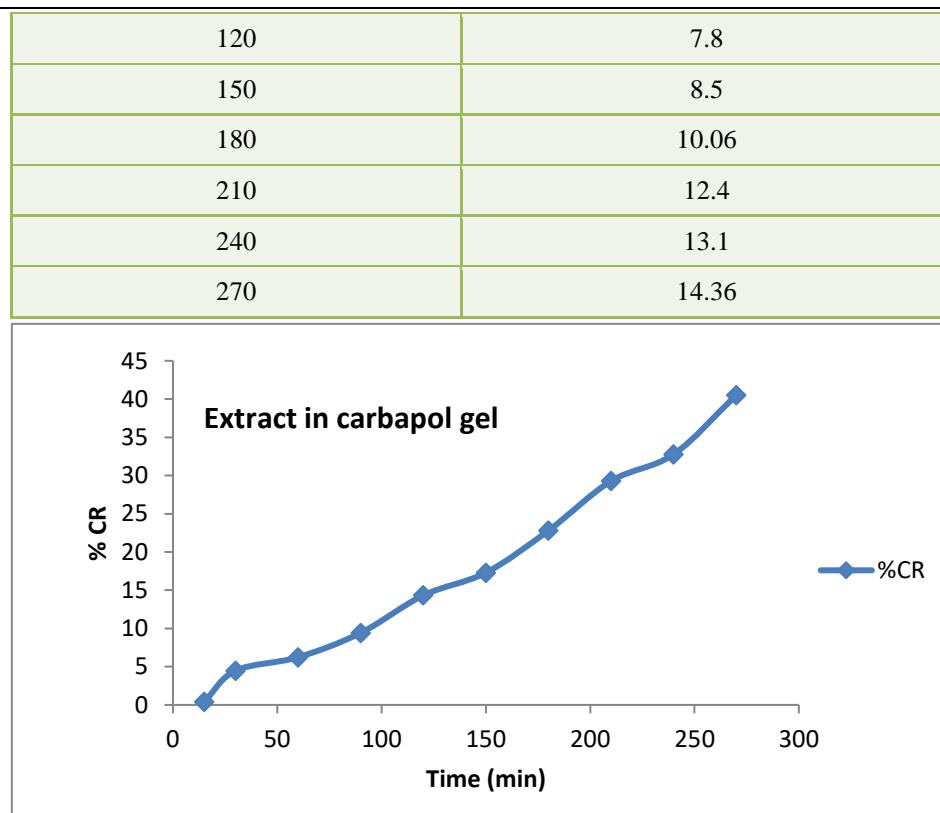
Time (min)	%CR
15	0.4
30	4.488889
60	6.233333
90	9.422222
120	14.32889
150	17.29556
180	22.80667
210	29.28
240	32.77556
270	40.52



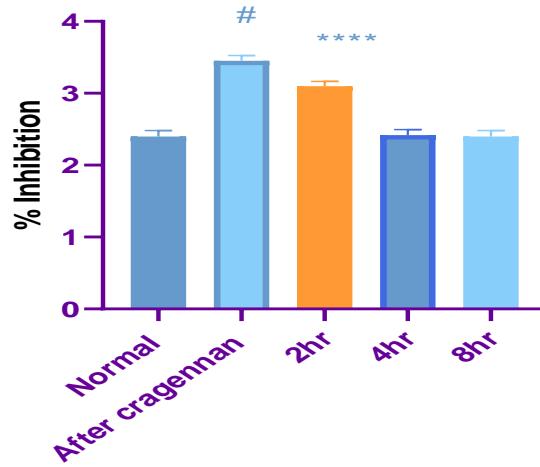
Drug release from Nanoemugel was 99% after 3.5 hours, while drug release from extract in gel base was 36.54 percent, which is significantly less than Nanoemugel the permeation of GG extract from Nanoemugel was found to be increased. It was discovered that incorporating nanoemulsion into Carbopol gel improves its permeation over nanoemulsion alone.. The nanoemulsion particles are thermodynamically compelled to bind to lipid-rich organisms. When enough nanoparticles bind to pathogens, a portion of the energy trapped in the emulsion is released. such as increase in paw volume at various time intervals and percent inhibition after topical administration of Diclofenac gel, NEIG, and Extract in gel, with all values expressed as mean SEM. n=6 (percent inhibition). The data was analysed using one-way ANOVA and the Dunnet test \*\* P0.05,\*\*\* P 0.001 Statistical analysis revealed When compared to the control group, the topical preparation inhibits carrageenan-induced rat paw edema significantly. The percent inhibition of edema by NEIG was also found to be higher than that of standard diclofenac gel and Extract in gel base. *Trigonella foenum graceum* extract has anti-inflammatory activity, which reduces paw edema, but when we use NEIG, the activity increases twofold, possibly due to increased MAG permeation through the skin. It was concluded that the nanosize of the extract in NEIG is responsible for better absorption, increasing its bioavailability and therapeutic effect (Mahboobian 2017, Rai et al., 2018)

**Table no - 04**

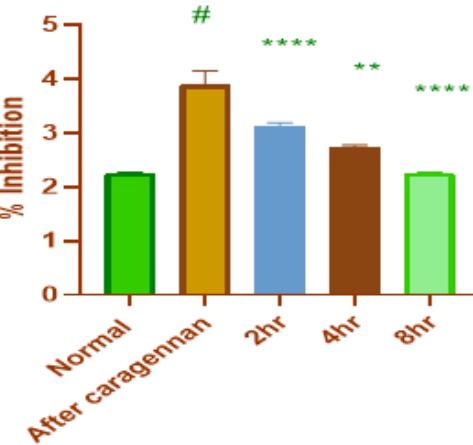
Time (min)	%CR
15	3.4
30	4.8
60	5.3
90	6.28



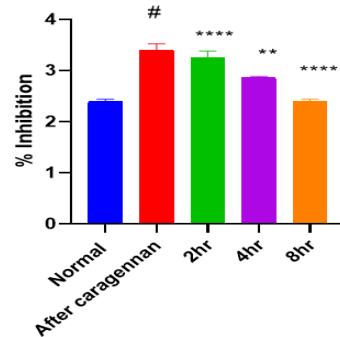
**% inhibition of paw edema Nanoemugel**



**% inhibition of paw edema (Dichlofenac gel)**



**% inhibition of paw edema (Extract in carbapol gel)**



In-vitro drug diffusion and ex-vivo permeation studies revealed that nanoemulsion permeation was faster than extract solution; Nanoemulsion was homogeneously incorporated into Carbapol 934 (NEIG). An in-vitro diffusion study revealed that incorporating nanoemulsion into Carbapol gel improves permeation over nanoemulsion alone. Due to the convenience of drug delivery through the skin to the systemic circulation for a variety of clinical conditions, there has been a lot of interest in this area. NEIG Because of the nanosize of the extract, it has a significant anti-inflammatory and antimicrobial effect, which is attributed to its rapid and complete absorption, which improves its therapeutic effect. The use of nanoemulsion in transdermal drug delivery is an important area of research in drug delivery because it improves therapeutic efficacy as well as drug bioavailability without causing any side effects. It's also thought to be a promising technique with a number of benefits, including high storage stability, low preparation costs, thermodynamic stability, and the absence of organic solvents. and a high likelihood of production

**Table no-05**

Treatment	Initial	2hr	4hr	8hr
<b>Group-I</b> <b>(Diclofenac gel)std</b>	2.2± 0.0001 (3.14)	2.3± 0.0052 (40.5)	2.3± 0.0511 (4.12)	2.3± 0.0001 (4.28)
<b>Group-II</b> <b>Test-1</b> <b>(Extract in carbapol gel)</b>	2.4± 0.0001 (3.67)	2.3± 0.3500 (3.32)	2.5± 0.004*** (3.5)	2.4± 0.0001 (3.15)
<b>Group-III</b> <b>Test-2</b> <b>(Nanoemugel)</b>	2.5± 0.0001 (3.38)	2.3± 0.0052 (3.4)	2.4± 0.0511 (3.52)	2.4± 0.0001 (3.51)



**Fig. 1** After carrageenan



**Fig. 2** Carrageenan injection



Fig. 3 Measured by vernier calliper,

Fig. 4 applying gel



Fig. 5 Measured by vernier calliper

#### 4. CONCLUSION

In-vitro drug diffusion and ex-vivo permeation studies revealed that nanoemulsion permeation was faster than extract solution; also, Nanoemulsion Carbopol 934 (NEIG) was also incorporated with good homogeneity. The nanoemulsion incorporated in Carbopol gel enhances its permeation, according to an in-vitro diffusion study. Alone. Due to the convenience of drug delivery through the skin to the systemic circulation for a variety of clinical conditions, there has been a lot of interest in this area. NEIG has significant anti-infl ammatory properties. The nanosize of the extract is responsible for its rapid and complete absorption, which improves its therapeutic effect. The use of nanoemulsion in transdermal drug delivery is an important area of research in drug delivery, as it improves the effectiveness of the drug. therapeutic efficacy and also the bioavailability of the drugs without any adverse effects. It is also regarded as a promising technique with many advantages including, high storage stability, low preparation cost, thermodynamic stability, absence of organic solvents, and good production feasibility.

#### ACKNOWLEDGMENTS

The project was supported by North Maharashtra University, Jalgaon. And thank full the Dr. S. J. Surana Providing the Facilities and authors are thankful to the Department of Pharmacognosy and Pharmaceutics, Pharmaceutical Chemistry. (R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur Disclosure: The authors report no conflict of interest in this work

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