wjpmr, 2025, 11(1), 234-247

SJIF Impact Factor: 6.842

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

NANO-EMULGEL AS CARRIER FOR TOPICAL DRUG DELIVERY OF ETORICOXIB-FORMULATION AND EVALUATION

Yashaswini M.R.* and Sudha B.S.

Department of Pharmaceutics, Nargund College of pharmacy, Banglore-85, Karnataka.

***Corresponding Author: Yashaswini M.R.**

Department of Pharmaceutics, Nargund College of pharmacy, Banglore-85, Karnataka.

Article Received on 27/10/2024 **Article Revised on 17/11/2024** **Article Accepted on 08/12/2024**

ABSTRACT

The present study aimed to formulate and evaluate Etoricoxib nanoemulgel for topical treatment of pain associated with rheumatoid arthritis. Etoricoxib nanoemulsion was prepared by using a high-energy method. Optimized Etoricoxib nanoemulsion was off-white with particle size, PDI, zeta potential, and drug content values of 98.3±0.3 nm, 0.45±0.01, 29.7±0.85 mV, and 97.9±0.35%, respectively. F9 exhibits the highest drug release of 99.63% after 12 hours compared to other nanoemulsion. 1% Carbopol 940 gel was selected best due to low viscosity and high spreadability. Prepare and evaluate Optimized nanoemulsion, was incorporated into an optimized gel in a 1:1 ratio. The *invitro* drug release studies of nanoemulgel show the highest drug release compared to marketed products and follow zero-order kinetics, with drug release mechanism swelling and diffusion (anomalous transport non-Fickian mechanism). The results indicate that the developed Etoricoxib nanoemulgel is a promising topical delivery system for treating pain associated with rheumatoid arthritis.

KEYWORDS: Etoricoxib, Nanoemulsion, Nanoemulgel, Tween 80, Ethanol, Carbopol 940.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that primarily impacts joints, causing pain, stiffness, and inflammation, particularly in the hands and feet. This disease involves the activation of pro-inflammatory mediators such as IL-1β and TNF-α, leading to progressive joint damage.[1] Global prevalence is estimated between 0.4% and 1.3%, affecting women two to three times more often than men, especially those over 50.[2]

Current RA treatments include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs), biologics, etc.[3] In this experiment, we used Etoricoxib, a potential cyclooxygenase-2 (COX-2) inhibitor, which has very less adverse effect as compare to other popular NSAIDs such as diclofenac etc. Etoricoxib, is a highly analgesic activity and does not inhibit the production of prostaglandin in the stomach and hence causes 40% lower relative risk of gastrointestinal adverse effect compared to other selective NSAIDs such as celecoxib, rofecoxib and valdecoxib et. Oral Etoricoxib administration are a major issue gastrointestinal ulcer. Therefore, using ETB in a topical form could improve its pain-relieving and anti-inflammatory effects while lowering the risk of gastrointestinal side effects.[4]

Topical delivery systems offer an alternative approach to minimize these complications by bypassing first-pass metabolism, avoiding gastrointestinal adverse effects, and reducing dosing frequency.[5] Among these, nano-emulgel systems, which combine Nanoemulsion with hydrogels, provide enhanced stability, skin retention, and permeability, making them promising for localized drug delivery. This study aims to develop an Etoricoxib-loaded nano-emulgel for to attenuate the GI related toxicities associated with oral administration.

MATERIALS AND METHODS

Etoricoxib were gift samples from Alembic pharmaceuticals limited Vadodara, India. Oleic acid Thomas baker pvt ltd. Mumbai, eucalyptus oil Ganesh Eucalyptus oil Oatacamund. Isopropyl myristate sisco research laboratories pvt ltd Maharashtra. Tween 80 Merck limited, Mumbai. Ethanol Karnataka Chemicals. Methanol Karnataka Chemicals, Bangalore. Carbopol 940 Sisco Research laboratories, Maharashtra. Triethanolamine T.V. Industrial estate, Mumbai.

Methods

Identification of pure drug[6]

Identification of Etoricoxib was carried out by FT-IR spectrophotometry.

Determination of λ max[7]
Absorption maximum for Etoricoxib was determined using UV spectrophotometer by scanning the solution of drug in phosphate buffer pH 7.4 between 200-400 nm.

Calibration curve of Etoricoxib[7]
Calibration curve for Etoricoxib drug were prepared using phosphate buffer pH 7.4. Absorbance of serially diluted 2-14 µg/ml solution were measured using spectrophotometer at 235 nm.

Drug-Excipient compatibility studies[8]
Weighed amount of drug and other excipients were mixed with IR grade Potassium Bromide (1:10) and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet.
The pellet was scanned by IR spectrophotometer over a range of 4000cm $^{-1}$ to 400 cm^{-1}.

Preparation of nanoemulgel[9]
Step 1: Preparation of Etoricoxib nanoemulsion.
Step 2: preparation of gel base
Step 3: Preparation of nano-emulgel by incorporating nano emulsion into hydrogel base

Preparation of nanoemulsion[10]
Etoricoxib loaded nanoemulsion were developed by high-speed stirrer and high-speed homogenization technique as reported with slight modification. The oil phase of nanoemulsion were prepared by using oil and 1%w/v drug. Aqueous phase was constituted by dissolving Tween 80 and ethanol in distilled water. Both phases were maintained at temperature of 60 ± 5 ºC. Then oil phases were added dropwise to the aqueous phase with continuous stirring for 20 minutes at 5000 rpm till emulsion was formed. After emulsion cooled down a high-speed homogenizer was used for 20 min at 5000 rpm.

Table 1: Composition of blank nanoemulsion.

F.C	Oleic acid (%v/v)	Eucalyptus oil (%v/v)	Isopropyl myristate (%v/v)	Smix (%v/v)	Ratio	Water (%v/v)	Stirring speed (Rpm)	Time
B1	20	-	-	25	1:1	55%	5000	20
B2	20	-	-	25	1:2	55%	5000	20
B3	-	20	-	25	1:1	55%	5000	20
B4	-	20	-	25	1:2	55%	5000	20
B5	-	-	20	25	1:1	55%	5000	20
B6	-	-	20	25	1:2	55%	5000	20

Table 2: Composition of drug loaded nanoemulsion.

F.C	Drug (%w/v)	Eucalyptus oil (%v/v)	Smix (%v/v)	ratio	Water (%v/v)	Stirring speed rpm	Homogenization time (min)
F1	1	10	25	1:1	65	5000	20
F2	1	15	25	1:1	60	5000	20
F3	1	20	25	1:1	55	5000	20
F4	1	25	25	1:1	50	5000	20
F5	1	10	20	1:1	70	5000	20
F6	1	10	30	1:1	60	5000	20
F7	1	10	30	1:1	60	4000	20
F8	1	10	30	1:1	60	6000	20
F9	1	10	30	1:1	60	6000	30
F10	1	10	30	1:1	60	6000	10

Characterization of nanoemulsion
Physical appearance[11]
Visual examination of the prepared nanoemulsion formulations was done to check for colour, phase separation, and homogeneity.

Particle size, PDI and Zeta potential[12]
The particle size, PDI and zeta potential was determined by using Horiba Scientific (Nano- Particle) SZ-100. 1ml of sample was diluted to 10ml double distilled water and the sample was vortexed for 5min. Sample were transferred into the polystyrene cuvette and kept inside the instrument, and particle size, PDI and zeta potential was measured.

pH[13]
The pH of nanoemulsion formulation was determined by using digital pH meter

Drug content[14]
1ml of the nanoemulsion sample was dissolved in 10ml of methanol and kept the sample is centrifuged for 15 mins at 7000 rpm. After that 1ml of supernatant was diluted with 10 ml of pH 7.4 phosphate buffer solution to get the concentration in the standard graph range and the drug content was determined by using UV-Spectrophotometry at 235nm.

***In-vitro* drug release studies**[15]

In vitro drug release of Etoricoxib loaded Nanoemulsion was performed by using membrane bag diffusion technique. Etoricoxib nanoemulsion suspension equivalent to 10mg (1ml) was taken in dialysis bag and the bag dipped in 100ml of dissolution medium (pH 7.4 phosphate buffer) at 100rpm. The sample were analysed by UV spectrophotometer at 235nm.

MORPHOLOGICAL STUDY

Binocular microscopy[16]

The morphology of the synthesized nanoemulsion was studied by using binocular microscope at 45X resolution with a measuring shape. One drop of synthesised nanoemulsion was dropped on clean glass slide and was gently covered with a glass coverslip for analysis under microscope.

Scanning Electron Microscopy[17]

The surface morphology was analysed using scanning electron microscopy (SEM), which provides a 3D image of globules. To visualize the nanoemulsion, a drop of it was placed on a clear glass stub, air dried, and coated with gold before being examined under SEM

Preparation of gel[18]

Gel was prepared using two different types of gelling agent and two different concentration specified quantity of gelling agent was weighed and placed in a beaker contain purified water and allowed to soak for 24h our (overnight) and neutralized by adding triethanolamine.

Table 3: Composition of blank gel.

F.C	Carbopol 940 (%w/v)	HPMC K100M (%w/v)	Methyl paraben	Water	Triethanolamine
G1	2	-	0.01%	Qs	Qs
G2	-	2	0.01%	Qs	Qs
G3	1.5	-	0.01%	Qs	Qs
G4	1	-	0.01%	Qs	Qs

Characterization of gel

Physical appearance[19]

The colour, homogeneity, and consistency of the prepared gel formulations were visually assessed.

Viscosity[20]

Viscosity of the gel was determined using Brookfield viscometer. Accurately weighed 25g of gel was transferred to 50 ml glass beaker. Spindle no 63 was selected and immersed into gel. The viscometer was operated at100 rpm until the reading gets stabilized and reading was noted in centipoises.

Spreadability[21]

The most common method for measuring the spreadability is the parallel-plate method. 1g of prepared sample was placed between two glass plates. A weight of 100 g was placed on top for 1 minute. Then the diameter of sample between the plates was measured.

$$S = M \times L / T$$

S = Spreadability
M = weight tied to the upper slide
L = length of the slides
T = time(sec) taken to travel the distance

Preparation of nanoemulgel[22]

Optimized Nanoemulsion and optimized gel was mixed at 1:1 ratio with stirring for 10min at 500 rpm using a magnetic stirrer prepare nanoemulgel.

Characterization of gel and nanoemulgel

Physical appearance[23]

The colour and homogeneity of the prepared Nanoemulgel formulations were visually assessed.

pH: The pH of nanoemulgel was measured by using digital pH meter.[23]

Viscosity[20]

Viscosity of the nanoemulgel was measured by using Brookfield viscometer. Accurately weighed 25g of Etoricoxib nanoemulgel was transferred to 50 ml glass beaker. Spindle no 63 was selected and immersed into nanoemulgel. The viscometer was operated at10 rpm until the reading gets stabilized and reading was noted in centipoises.

Spreadability[21]

The most common method for determined the spreadability is the parallel-plate method. 1g of the sample was placed between two glass plates. A weight of 100 g was placed on top for 1 minute. Then the diameter of sample between the plates was measured.

$$S = M \times L / T$$

Drug content[22]

The drug content was determined by dissolving the nanoemulgel equivalent to 10 mg of drug in methanol followed by phosphate buffer pH 7.4. the solution was then filtered and diluted with phosphate buffer pH 7.4 and analysed under UV spectrophotometer at 235 nm.

***In vitro* diffusion studies**[23]

In-vitro diffusion study was carried out in a Franz diffusion cell using dialysis membrane which was soaked overnight in pH 7.4 phosphate buffer. The membrane was tied to the donor compartment and mounted on the reservoir compartment of Franz diffusion cell containing 135 ml of pH 7.4 phosphate buffer. 1g of Nanoemulgel was placed over the dialysis membrane on donor

compartment. Whole set was placed on the magnetic stirrer. The study was carried out at 37±0.5 ºC and 100 rpm. Samples were withdrawn from the sampling port of respecter compartment at regular intervals and same volume was replaced. Absorbance was measured at 235 nm.

Kinetics of drug release and mechanism of drug release[24]

The drug release kinetics from the nanoemulsion and nanoemulgel were evaluated using four distinct models: zero-order, first-order, the Hixson–Crowell model, and the Higuchi model. Each of these models interprets the release profile based on specific inherent properties. Additionally, the drug release mechanism was analysed using the Peppas equation.

Stability studies[24]

Stability testing of pharmaceutical products is a complex set of procedures involving considerable cost, time consumption and scientific expertise in order to build in quality, efficacy and safety in a drug formulation. The formulations were stored at room temperature (25^{o}C± 74%) for 3months. The formulations were evaluated by measuring, physical appearance, homogeneity, drug content, viscosity spreadability, invitro drug release

RESULTS AND DISCUSIONS

Identification of pure Drug[25]

The IR spectrum of pure drug was found to be similar to the standard spectrum of Etoricoxib.

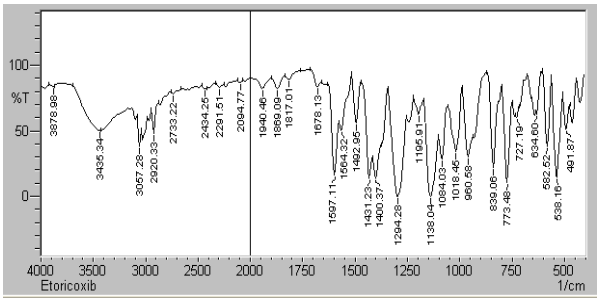

Fig. 1: IR spectrum of etoricoxib.

Determination of λ max of Etoricoxib[26]

Standard solution was scanned in UV spectrophotometer with wavelength range of 200-400nm. The absorption maximum was found to be at 235 nm.

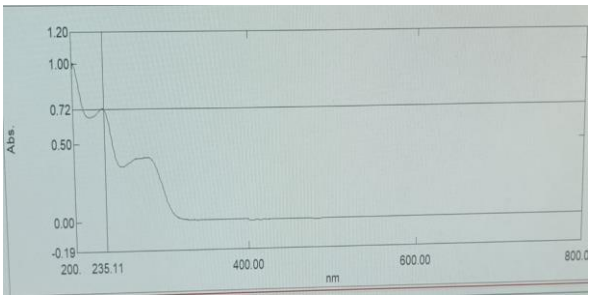

Fig. 2: Absorption maxima of Etoricoxib.

Calibration curve of Etoricoxib in pH 7.4 phosphate buffer[26]

The standard calibration curve of etoricoxib was developed at the λ max of 235nm.The calibration curve was linear between the concentration ranges of 2-14µg/ml.

Table 4: Standard calibration curves of etoricoxib.

SL. NO	Concentration (µg/ml)	Absorbance at 235nm (mean ± SD)
1	0	0
2	2	0.1643±0.0015
3	4	0.3023±0.0025
4	6	0.439±0.001
5	8	0.564±0.00115
6	10	0.722±0.0026
7	12	0.878±0.0145
8	14	1.005±0.0032

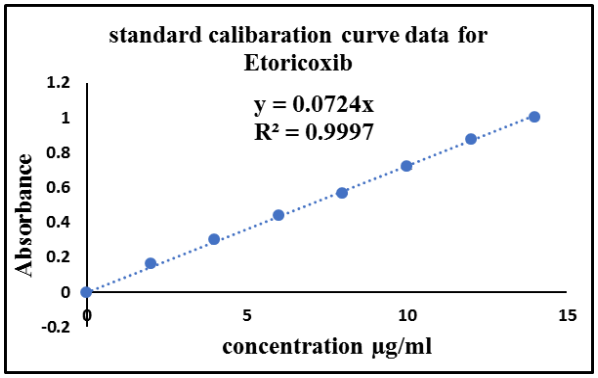

Fig. 3: Standard calibration curve data for Etoricoxib.

Drug -Excipient Compatibility studies[21]

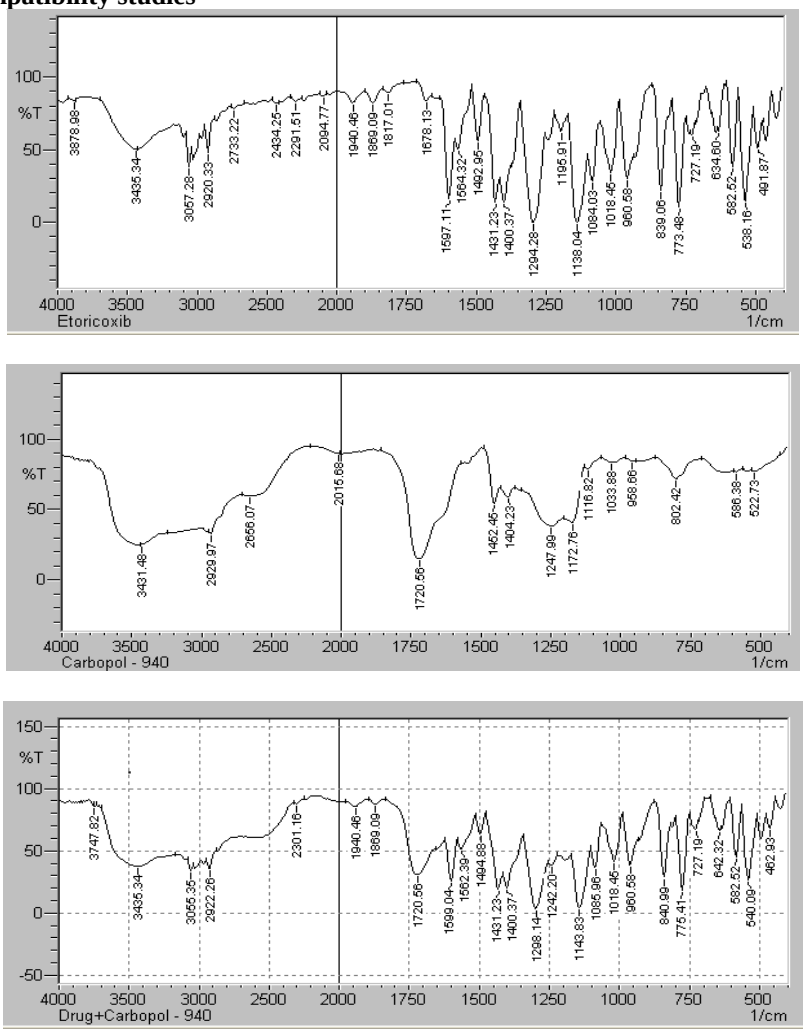

Fig. 4: Drug -Excipient Compatibility studies.

Table 5: FT-IR peak of Drug -Excipient Compatibility studies.

Sl.No	Functional group	Reported Frequency cm^{-1}	Observed Frequency cm^{-1} Drug	Observed Frequency cm^{-1} Carbopol-940	Observed Frequency cm^{-1} Drug +Carbopol-940
1	O-H stretching	3500-3400	3435.34	3431.48	3435.34
2	C=C Aromatic	1400-1600	1431.23	1452.45	1599.04
3	C-N stretching	1080-1360	1138.04	1247.99	1298.14
4	C-O stretching	1050-1150	1084.03	1116.82	1138.4
5	At ring Vibration	1000-600	773.48	958.66	775.41

Drug - excipient interactions play a vital role concerning the purity of drug from the formulation amongst others. FT-IR techniques have been used here to study the chemical and physical interaction between drug and excipients used. In the present study, it has been observed that there was no chemical interaction between drug and the polymers used as is shown in the (table 5). The main characteristic peaks of drug remain unchanged when it is mixed with excipients indicates that the drug has not interacted.

Formulation of nanoemulsion

Etoricoxib loaded nanoemulsion were successfully produced by high energy method. Different concentration oil, surfactant and cosurfactant, stirring speed and homogenization time were tried in order obtained the nanoemulsion.

Characterization of blank nanoemulsion

Nanoemulsion should have average particle size ranging from to 20 to200. A low PDI indicates a narrow size distribution and increase stability. High PDI values indicates broad distribution leading to physically instability and aggregation of nanoparticle. PDI valves of 0.2 or less indicates monodispersed system and stable droplet size. A PDI less than 0.5 is considered as excellent for topical delivery.[27] This facilitates rapid pore transport by providing a large surface area and

efficient drug transfer through the skin barrier. Zeta potential plays an important role in the stability, as it measures the surface charge of particles in a nanoemulsion. When zeta potential is more positive than +30mv or more negative -30mv, the particles repel each other, which enhance the stability of the nanoemulsion. Hower, when the zeta potential is closer to zero, the particles tend to aggregate and coalesce, leading to decreased stability.[27]The acceptable pH range for topical nanoemulsion for human application through the skin b/w 4-6.5. The acceptable range for drug content is 85-115 A/c to USP.

Table 6: Characterization parameter for blank nanoemulsion.

F.C	Appearance	Particle size (nm)	PDI	Zeta potential (mv)	pH
B1	Of white	215.3±0.32	0.56±0.026	-14.6±0.3	6.05±0.02
B2	Of white	228.2±0.15	0.58±0.043	-15.7±0.2	6.12±0.005
B3	Of white	187.9±0.2	0.65±0.026	-21.4±0.15	5.05±0.02
B4	Of white	192.9±0.36	0.7±0.026	-19.6±0.45	5.14±0.01
B5	Of white	250.2±0.3	0.74±0.025	-12.1±0.58	6.4±0.04
B6	Of white	292.9±0.15	0.77±0.037	-13.4±0.25	6.7±0.1

PDI and zeta potential of all the blank formulation were within the acceptable range for a stable nanoemulsion since particle size of B3 formulation was the least. Eucalyptus oil and surfactant and cosurfactant ratio 1:1 was considered as optimum for further studies.

Characterization drug loaded nanoemulsion

All the formulations containing drug(F1-F10) has shown Physical appearance, particle size polydispersity index, pH, Drug content with in the stated acceptable range.

Table 7: Characterization parameter of drug loaded nanoemulsion.

F.C	Appearance	Particle Size (nm)	PDI	Zeta Potential (mV)	pH	Drug Content (%)
F1	Of white	126.2±0.3	0.39±0.02	-23.9±0.3	5.37±0.00	87.4±0.25
F2	Of white	148.9±0.1	0.35±0.02	-17.8± 0.05	5.15±0.02	88.6±0.20
F3	Of white	169.3±0.2	0.35±0.01	-14.2±0.2	5.45±0.02	93.5±0.15
F4	Of white	195.9±0.2	0.39±0.02	-12.5±0.1	5.56±0.01	94.6±0.25
F5	Of white	131.9±0.2	0.49±0.02	-16.7± 0.05	5.55±0.02	91.5±0.3
F6	Of white	116.3±0.2	0.35±0.02	-24.5±0.1	5.27±.015	95.7±0.2
F7	Of white	124.8±0.1	0.4±0.01	-17.8±0.3	5.98±0.06	91.2±0.3
F8	Of white	105.0±0.2	0.45±0.03	-28.7±0.3	5.37±0.12	96.4±0.15
F9	Of white	98.3±0.3	0.45±0.01	-29.7± 0.85	5.65±0.02	97.9±0.3
F10	Of white	115.0±0.2	0.44±0.04	-18.7± 0.15	5.45±0.05	93.5±0.1

Physical appearance: All formulations were off white in appearance, no phase separation.

Particle size: Increasing the eucalyptus oil concentration resulted in larger particle sizes due to droplet aggregation,[6] while higher surfactant and cosurfactant concentration reduced particle size by lowering interfacial tension.[28] Faster stirring speeds during high-energy homogenization further decreased particle size by intensifying disruptive forces,[29] and longer homogenization times led to even smaller particles due to increased shear stress.[30]

PDI: PDI of all the formulations was less than 0.5 thus ensuring uniform particle size distribution.[8]

Zeta potential: Increasing the oil concentration in nanoemulsion tends to reduce the surface charge of the droplets, likely due to a resulting increase in particle size. This size increase can promote droplet aggregation and coalescence, ultimately reducing stability.[31] Conversely, higher concentrations of surfactants and cosurfactants enhance surface charge while decreasing particle size, which collectively supports improved stability.[32] Additionally, increasing stirring speed and homogenization time contributes to higher surface charge, likely due to reduced viscosity and particle size. These changes enhance repulsive forces between particles, preventing coalescence and aggregation and thereby further stabilizing the nanoemulsion.[33]

Drug content

A higher oil concentration increases the viscosity of the nanoemulsion, slows globule formation, and produces larger globules with higher drug content.[34] Similarly, increasing surfactant and co-surfactant levels, along with longer homogenization times, enhances drug content by improving solubilization and forming smaller particles with greater surface area.[35] Additionally, faster stirring boosts drug solubility, further increasing drug content in oil-in-water nanoemulsion.[30]

***Invitro* drug release**

Table 8: Invitro drug release of different oil concentration.

Time(hr)	Cumulative dug release (%)			
	F1	F2	F3	F4
0	0	0	0	0
0.5	9.68%±0.69	8.24%±1.12	7.13%±1.11	6.90%±0.84
1	16.29%±0.36	15.79%±3.19	13.76%3.45	12.66%±0.79
2	24.44%±1.26	20.34%±4.67	18..00%±3.47	17.95%±0.63
3	31.35%±2.30	27.62%±2.35	26.65%±2.35	23.48%±0.47
4	36.18%±3.4	35.17%±4.16	31.97%±1.41	30.89%±0.77
5	42.79%±3.73	40.60%±1.07	37.200%±0.76	36.35%±2.22
6	48.54%±6.09	46.45%±1.41	42.12%±1.20	41.16%±0.49
7	55.15%±3.25	53.49%±1.19	49.81%±2.63	46.72%±1.23
8	64.41%±3.34	60.33%±1.105	56.33%±3.57	51.51%±0.96
9	69.27%±8.11	67.12%±1.18	64.59%±5.49	58.60%±1.88
10	77.11%±4.35	75.06%±1.54	69.24%±4.48	64.91%±2.006
11	85.72%±2.28	82.59%±0.498	78.63%±4.45	72.92%±0.84
12	93.46%±1.52	90.88%±2.952	85.12%±1.71	80.06%±0.57

Table 9: Invitro drug release of different concentration surfactant and co surfactant.

Time	Cumulative dug release (%)		
	F1	F5	F6
0	0	0	0
0.5	9.68%±0.69	8.65%±1.07	10.81%±0.79
1	16.29%±0.36	15.83%±2.14	17.26%±1.45
2	24.44%±1.26	23.02%±1.55	25.19%±0.813
3	31.35%±2.30	30.29%±0.079	34.53%±1.827
4	36.18%±3.4	35.77%±0.99	40.00%±0.78
5	42.79%±3.73	41.11%±1.66	47.42%±0.88
6	48.54%±6.09	46.36%±1.73	51.88%±1.43
7	55.15%±3.25	53.31%±1.18	59.85%±1.01
8	64.41%±3.34	59.02%±0.94	65.51%±1.99
9	69.27%±8.11	67.81%±0.73	75.27%±1.51
10	77.11%±4.35	76.61%±1.38	81.03%±0.76
11	85.72%±2.28	84.80%±1.22	88.90%±1.38
12	93.46%±1.52	91.89%±3.05	95.32%±1.475

Table 10: Invitro drug release of influence of stirring speed.

Time(hr)	Cumulative dug release (%)		
	F6	F7	F8
0	0	0	0
0.5	10.81%±0.79	9.3%±2.10	11.27%±2.10
1	17.26%±1.45	16.98%±2.19	20.39%±1.05
2	25.19%±0.813	24.53%±2.79	26.56%±2.11
3	34.53%±1.827	32.41%±1.79	35.40%±2.95
4	40.00%±0.78	38.85%±3.10	41.66%±0.42
5	47.42%±0.88	44.106%±3.16	47.37%±2.03
6	51.88%±1.43	48.25%±2.06	53.17%±1.38
7	59.85%±1.01	52.30%±1.38	60.35%±1.76
8	65.51%±1.99	60.35%±1.13	66.62%±2.14
9	75.27%±1.51	65.101%±0.55	76.28%±2.32
10	81.03%±0.76	77.85%±0.76	84.57%±1.58
11	88.90%±1.38	85.58%±1.03	93.64%±3.94
12	95.32%±1.475	92.12%±1.51	97.28%±0.69

Table 11: Invitro drug release of influence of homogenization time.

Time (hr)	Cumulative dug release (%)		
	F8	F9	F10
0	0	0	0
0.5	11.27%±2.10	12.56%±2.89	9.48%±0.73
1	20.39%±1.05	22.00%±1.05	18.27%±2.38
2	26.56%±2.11	26.61%±0.84	24.72%±0.70
3	35.40%±2.95	36.58%±1.93	32.50%±3.37
4	41.66%±0.42	42.44%±1.51	39.64%±0.99
5	47.37%±2.03	47.74%±1.46	45.99%±2.59
6	53.17%±1.38	53.26%±0.84	51.61%±1.46
7	60.35%±1.76	63.029%±1.63	57.02%±1.45
8	66.62%±2.14	70.25%±1.41	65.69%±2.20
9	76.28%±2.32	79.% ±0.15	72.97%±0.71
10	84.57%±1.58	88.20%±2.27	79.18%±3.17
11	93.64%±3.94	95.67%±2.41	85.81%±0.44
12	97.28%±0.69	99.63%±0.70	92.86%±1.19

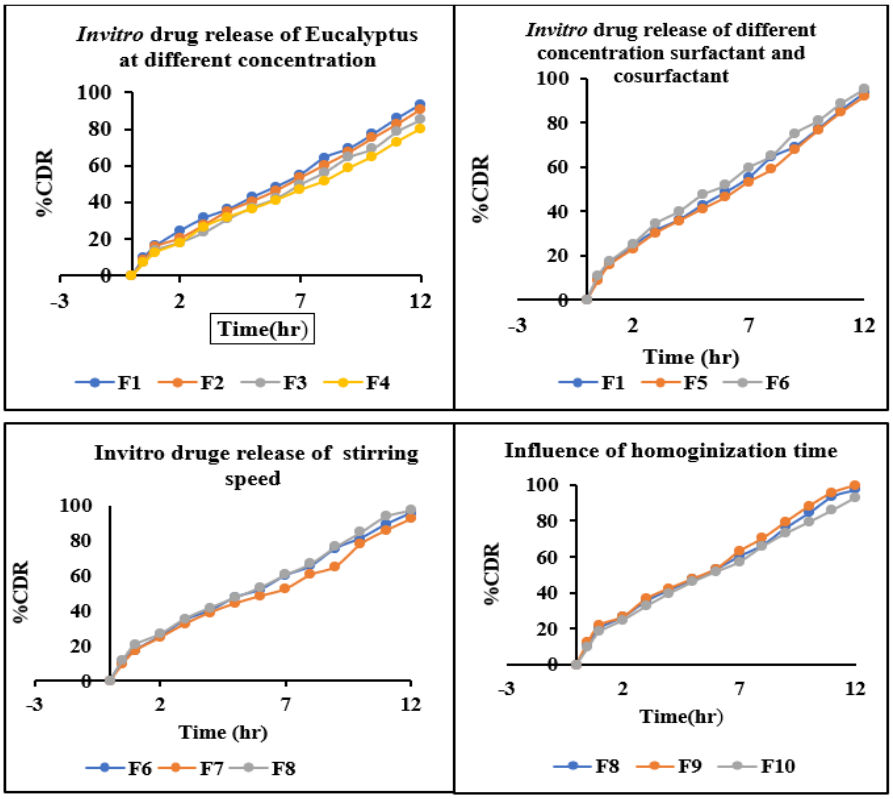

Fig. 5: Invitro drug release drug loaded nanoemulsion.

As concentration of oil increases, viscosity of nano emulation increases. As a result, particle size increases and effective surface area of globule decreases causing slower drug releases.[36]

As concentration of surfactant and cosurfactant increases, interfacial tension further decreases to cause further decreases in particle size. Thus, enhanced effective surface area results in enhanced drug release.[37]

As stirring speed increases the particle size decreases due to the higher energy applied in a limited volume and exhibited the highest drug release compared to the other two formulations. This is because smaller droplet sizes provide a larger surface area for drug diffusion. According to the Noyes-Whitney equation, a larger surface area enhances the dissolution rate.[38]

Increasing the homogenization time significantly enhances the dissolution rate of etoricoxib in the nanoemulsion formulation. Among the tested formulations, F9(30min) shows the highest drug release, likely due to improved mixing and particle dispersion, resulting in a more uniform distribution of the API and excipients, which can exhibit the highest drug release.[16]

Kinetics of drug release of nanoemulsion formulation

Table 12: Kinetics of drug release of nanoemulsion formulation.

Formulation Code	Zero order	First order	Higuchi plot	Korsmeryers peppas
	R2	R2	R2	n value
F1	0.993	0.85	0.981	0.671
F2	0.99	0.8646	0.976	0.66
F3	0.99	0.87	0.97	0.64
F4	0.99	0.85	0.98	0.638
F5	0.99	0.85	0.978	0.665
F6	0.992	0.85	0.986	0.6831
F7	0.99	0.85	0.98	0.670
F8	0.99	0.84	0.974	0.688
F9	0.99	0.85	0.98	0.678
F10	0.99	0.85	0.98	0.694

The drug release from the formulation followed by the zero-order kinetics which shows that the rate of drug release was at predictable and constant rate. The n-value of Korsemeyer-peppas equation was found to be 0.56 which showed that mechanism of drug release has by Anomalous transport non-Fickian mechanism (n>0.5).[39]

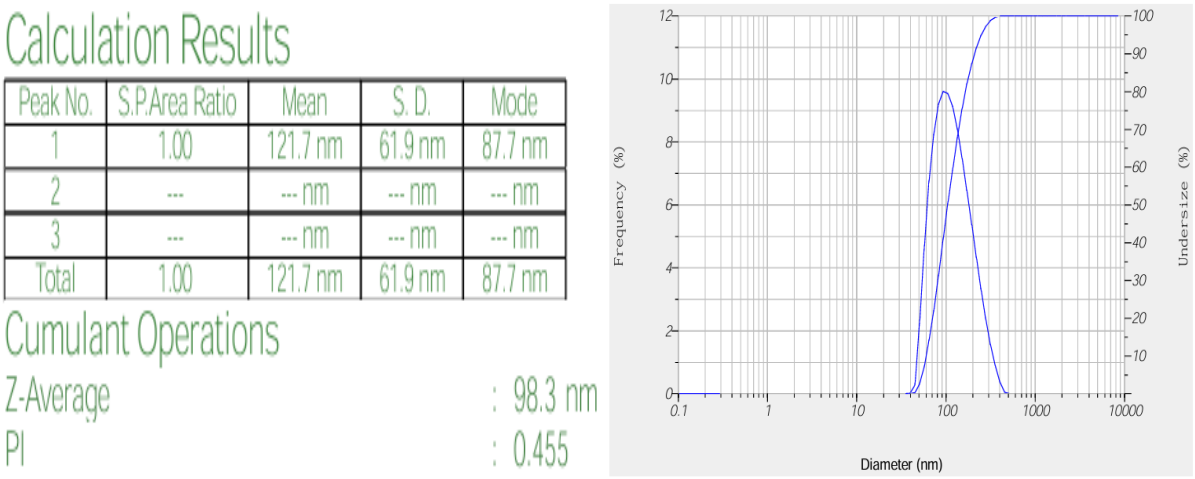

Fig. 6: Particle size distribution of F9 optimized nanoemulsion.

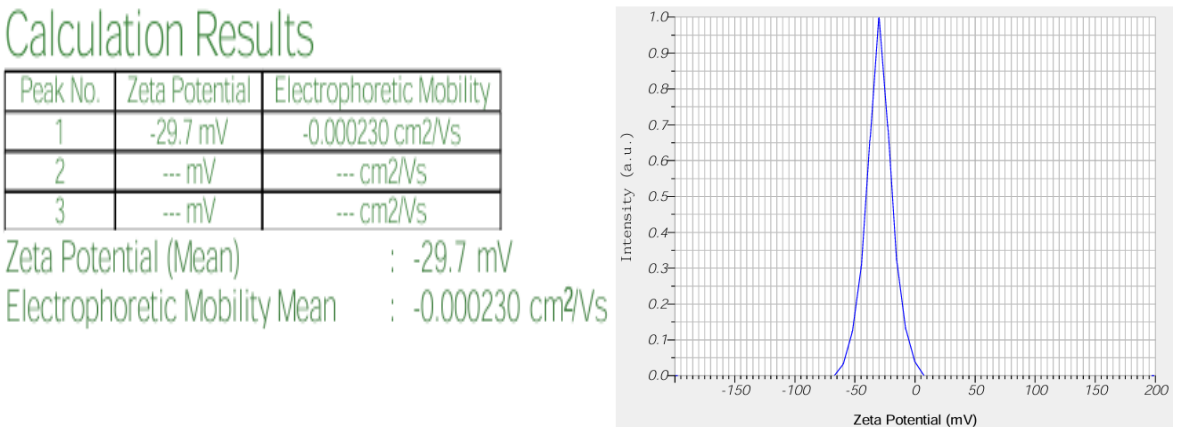

Fig. 7: Zeta potential of F9 optimized nanoemulsion.

Morphological study

The F9 optimized nanoemulsion was subjected to binocular microscope and SEM to determine the particle shape, the result obtained is showed in figure. it was observed that particles possess a nearly spherical in shape.[16-40]

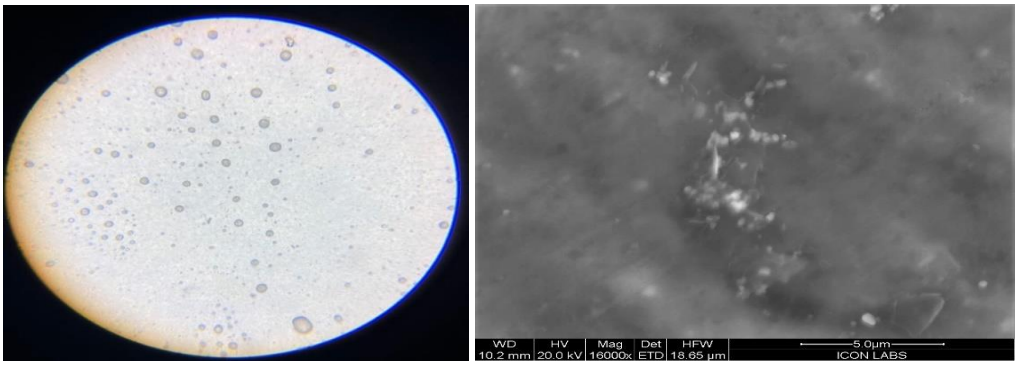

Fig 8: a) Microscopic F9 nanoemulsion. b) SCM image F9 nanoemulsion.

Table 13: Characterization of gel.

Formulation code	Appearance	Viscosity(cps)	Spreadability(mm)
G1	Opaque	3990±1.5	25±0.3
G2	Opaque	4568±3.6	20±0.25
G3	Opaque	3854±2.5	26.8±0.20
G4	Opaque	3754±1.15	27.2±0.15

All blank gel formulations were in Opaque appearance and shows good homogeneity.[40] Carbopol 940 has a lower viscosity compared to other gelling agent due to its polyelectrolyte nature. This leads to expansion of the polymer chains and reduction tin viscosity.[41] However, increasing the concentration of Carbopol reduce the surface tension, resulting in higher viscosity. As increased gelling agent concentration and decrease spreadability due to the higher viscosity.[40]

Table 14: Characterization for nanoemulgel.

Parameter	F9G4 optimized nanoemulgel	Marketed gel
Appearance	Off white	white
Homogeneity	homogenous	homogenous
Viscosity	3548±1.5cps	5822± 0.5cps
Spreadability	29.73±0.15mm	17±0.3mm
pH	5.39±0.21	6.4±0.34
Drug content	97.4±0.3%	95.3±0.15%

Viscosity of marketed product was lesser than that of formulation nanoemulgel. This could be the reason for enhanced spreadability of our product in comparison to the marketed product.[42] The increase spreadability of nanoemulgel compared to marketed formulations due to the lower viscosity compared to marketed product, making it easier to spread and apply the nanoemulgel to the skin.[43] The pH of both the formulations were within the acceptable range.[40] There is no significant difference in drug content.[10]

***Invitro* drug release**

Table 15: Comparison study of for F9G4 optimized nanoemulgel and marketed gel.

Time(hr)	F9G4 Optimized Nanoemulgel	Marketed
0	0	0
0.5	5.96±1.68	2.85±1.07
1	10.44±1.02	6.09±1.07
2	16.96±0.75	10.44±1.86
3	22.56±0.75	13.48±1.02
4	27.03±0.55	19.64±1.39
5	31.51±0.70	23.05±1.26
6	36.36±0.56	26.60±1.50
17	40.83±6.5	30.39±1.34
8	48.29±0.9	34.37±0.42
9	56.33±0.3	37.91±0.38
10	68.05±1.87	40.89±0.9
11	73.65±1.86	45.43±1.2
12	81.67±1.02	48.35±2.3

The change in cumulative % drug release may be attributed to the change in viscosity of the products.

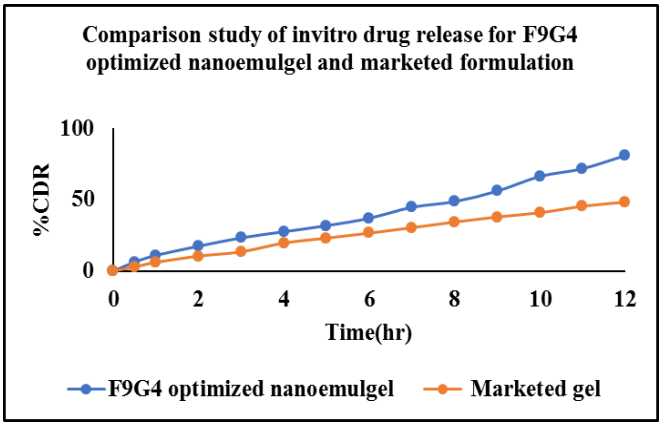

Fig. 9: comparison study of invitro drug release for F9G4 optimized nanoemulgel and marketed gel.

Table 16: Kinetic modelling of drug release.

Formulation	Zero order	First order	Higuchi plot	Korsemeyer-Peppas plot
	R2	R2	R2	n value
Optimized Nanoemulgel	0.99	0.88	0.95	0.627
Marketed gel	0.99	0.89	0.97	0.56

The drug release from the formulations followed zero-order kinetics, R^2 of which showed that the rate of drug release was at predictable and constant rate. The n-value of Korsemeyer-peppas equation was found to be which showed that mechanism of drug release followed swelling of polymer and diffusion of drug the swollen matrix (Anomalous transport non- Fickian mechanism).[44]

Stability studies[45]

Table 17: stability studies Invitro drug release of formulation F9G4.

Sl.no	Evaluation parameters	Short term stability studies	
		Initial (0 month)	After 3 months
1	Physical appearance	Off White	Off white
2	Homogeneity	Homogenous	Homogenous
3	Viscosity(cp)	3548±1.15	3234±2.5
4	Spreadability (mm)	29.73±0.3	29.98±0.15
5	Drug content	97.4%±0.35	96.4%±0.5

Table 18: Stability studies Invitro drug release of formulation F9G4.

Time (hrs)	Cumulative % drug release	
	Initial (0 month)	After 3 months
0	0±0	0±0
0.5	5.96±1.68	5.71±1.4
1	10.44±1.02	8.19±0.6
2	16.96±0.75	13.73±1.5
3	22.56±0.75	20.57±1.6
4	27.03±0.55	24.79±1.34
5	31.51±0.70	28.52±1.34
6	36.36±0.56	34.74±0.4
7	40.83±6.5	39.65±0.5
8	48.29±0.9	46.92±2.1
9	56.33±0.3	54.56±1.5
10	68.05±1.87	64.88±1.59
11	73.65±1.86	70.23±2.1
12	81.67±1.02	78.31±1.8

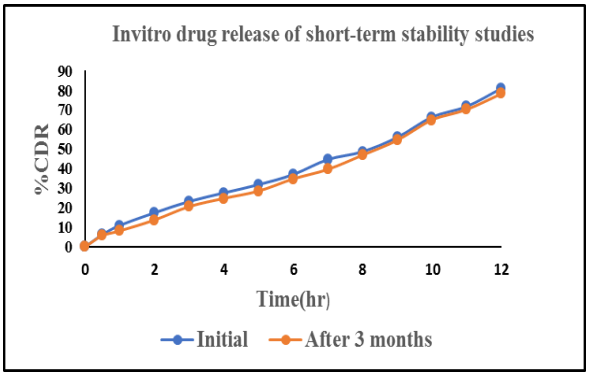

Fig. 10: Invitro drug release of short-term stability studies.

The formulation F9G4 was selected for short stability studies and kept in room condition (temperature 25°C± 74%) for 3months was analysed. There were no major changes observed in the homogeneity, pH, viscosity,

spreadability drug content and invitro drug release after 3 months when compared to initial studies which indicate the prepared nanoemulgel has a good stability.

CONCLUSION

The aim of the present study was to formulate and evaluate the Etoricoxib nanoemulgel for topical treatment of pain associated with rheumatoid arthritis. The pre-formulation studies were demonstrated the purity of the drug and its compatibility with excipients. The calibration curve of etoricoxib was linear between 2-14µg/ml, and the λ max was found to be 235 nm. The nanoemulsion was prepared by using high energy method i.e high-speed stirring speed and high-speed homogenization technique. The evaluation parameters physical appearance particle size, zeta potential, pH, drug content, invitro drug of blank nanoemulsion and drug-loaded nanoemulsion were within the acceptable range, indicating a stable and coalescence-free system. The particle size of F9 formulation was small with PDI, and high zeta potential and drug content. The invitro drug release profile of F9 exhibit highest drug release compared other nanoemulsion, so consider as optimized nanoemulsion. Optimized nanoemulsion later incorporated into 1% Carbopol 940 gel in 1:1 ratio. The evaluation parameters include physical appearance, viscosity, spreadability, drug content and invitro drug release. The invitro drug release studies of nanoemulgel shows highest drug release compared marketed product and followed zero-order kinetics, with drug release mechanism swelling and diffusion (Anomalous transport non-Fickian mechanism). The stability studies demonstrated that the prepared nanoemulgel has good stability after one months, with no considerable changes in homogeneity, pH, viscosity, spreadability, drug content, and invitro drug release and the Overall, results suggest that the developed Etoricoxib nanoemulgel formulation is a promising topical delivery system for treating pain associated with rheumatoid arthritis.

REFERENCES

1. Kwiatkowska B, Majdan M, Mastalerz-Migas A, Niewada M, Skrzydło-Radomańska B, Mamcarz A. Status of etoricoxib in the treatment of rheumatic diseases. Expert panel opinion. Reumatologia, 2017; 55(6): 290–7.
2. Radu AF, Bungau SG. Management of Rheumatoid Arthritis: An Overview. Cells, 2021; 10(11): 2857-89.
3. Anita C, Munira M, Mural Q, Shaily L. Topical nanocarriers for management of Rheumatoid Arthritis: A review. Biomedicine & Pharmacotherapy, 2021; 141: 111880-896.
4. Alhakamy NA, Kotta S, Ali J, Alam MS, Hosny KM, Shaik RA, et al. Formulation Development, Statistical Optimization, In Vitro and In Vivo Evaluation of Etoricoxib-Loaded Eucalyptus Oil-Based Nanoemulgel for Topical Delivery. Applied Sciences, 2021; 11(16): 7294-313.
5. Donthi MR, Munnangi SR, Krishna KV, Saha RN, Singhvi G, Dubey SK. Nanoemulgel: A Novel Nano Carrier as a Tool for Topical Drug Delivery. Pharmaceutics, 2023; 15(1): 164-92.
6. Chaudhari PM, Kuchekar MA. Development and evaluation of nanoemulsion as a carrier for topical delivery system by Box -Behnken design. Asian J Pharm Clin Res., 2018; 11(8): 286-93.
7. Aparna et al. - 2023 - Formulation and Evaluation of Etoricoxib Nanogel. Int J Pharm Sci Rev Res., 2023; 78(1): 113–8.
8. Bashir M, Ahmad J, Asif M, Khan SUD, Irfan M, Y Ibrahim A, et al. Nanoemulgel, an Innovative Carrier for Diflunisal Topical Delivery with Profound Anti-Inflammatory Effect: in vitro and in vivo Evaluation. IJN., 2021; 16: 1457–72.
9. Gadkari PN, Patil PB, Saudagar RB. Formulation, development and evaluation of topical nanoemulgel of tolnaftate. J Drug Delivery Ther., 2019; 9(2-s): 208–13.
10. Khan BA, Ahmad N, Alqahtani A, Baloch R, Rehman AU, Khan MK. Formulation development of pharmaceutical nanoemulgel for transdermal delivery of feboxostat: Physical characterization and in vivo evaluation. European Journal of Pharmaceutical Sciences, 2024; 195: 106665. -74
11. Adegbenro OO, Opeyemi OT. Development and estimation of Anti-inflammatory activity of topical Etoricoxib emulgel by carrageenan induced paw oedema method. Univ J Pharm Res., 2019; 3(4): 22-26.
12. Alhasso B, Ghori M, Rout S, Conway B. Development of a Nanoemulgel for the Topical Application of Mupirocin. Pharmaceutics, 2023; 15(10): 2387.
13. Burki IK, Khan MK, Khan BA, Uzair B, Braga VA, Jamil QA. Formulation Development, Characterization, and Evaluation of a Novel Dexibuprofen-Capsaicin Skin Emulgel with Improved In Vivo Anti-inflammatory and Analgesic Effects. AAPS PharmSciTech., 2020; 21(6): 211-24.
14. Fonseca VR, Jivaji Bhide P, Purushottam Joshi M. Formulation, Development and Evaluation of Etoricoxib Nanosize Microemulsion Based Gel for Topical Drug Delivery. IJPER, 2019; 53(4s): s571–9.
15. Siddiqui A, Jain P, Alex TS, Ali MA, Hassan N, Haneef J, et al. Investigation of a Minocycline-Loaded Nanoemulgel for the Treatment of Acne Rosacea. Pharmaceutics, 2022; 14(11): 2322-34.
16. Saxena V, Hasan A, Sharma S, Pandey LM. Edible oil nanoemulsion: An organic nanoantibiotic as a potential biomolecule delivery vehicle. International Journal of Polymeric Materials and Polymeric Biomaterials, 2018; 67(7): 410–9.
17. Babu VN, Rao GSNK, Budha RR, Alavala RR, Desu PK, Babu GK, et al. Development, characterization and optimization of solid lipid nanoparticles of alpha-mangostin by central

composite design approach. J Appl Pharm Sci., 2023; 12(6): 1455-65.
18. Morteza-Semnani K, Saeedi M, Akbari J, Eghbali M, Babaei A, Hashemi SMH, et al. Development of a novel nanoemulgel formulation containing cumin essential oil as skin permeation enhancer. Drug Deliv and Transl Res., 2022; 12(6): 1455–65.
19. Abdallah MH, Abu Lila AS, Unissa R, Elsewedy HS, Elghamry HA, Soliman MS. Preparation, characterization and evaluation of anti-inflammatory and anti-nociceptive effects of brucine-loaded nanoemulgel. Colloids and Surfaces B: Biointerfaces, 2021; 205: 111868-75.
20. Shafiq M, Khan BA, Rashid SA, Khan MK, Naseem F, Alqahtani AM, et al. Biodegradable Polymeric Pharmaceutical Nanoemulgel Coloaded with Eucalyptol-Lornoxicam: Fabrication and Characterizations for Possible Better Pain Management. Agrawal N, editor. BioMed Research International, 2023; 2023: 1–16.
21. Ahmed MM, Anwer MdK, Fatima F, Alali AS, Kalam MA, Zafar A, et al. Development of Apremilast Nanoemulsion-Loaded Chitosan Gels: In Vitro Evaluations and Anti-Inflammatory and Wound Healing Studies on a Rat Model. Gels, 2022; 8(5): 253-69.
22. Yeo E, Yew Chieng CJ, Choudhury H, Pandey M, Gorain B. Tocotrienols-rich naringenin nanoemulgel for the management of diabetic wound: Fabrication, characterization and comparative in vitro evaluations. Current Research in Pharmacology and Drug Discovery, 2021; 2(20221): 100019-28.
23. Bhattacharya S, Prajapati BG. Formulation and optimization of celecoxib nanoemulgel. Asian J Pharm Clin Res., 2017; 10(8): 353-65.
24. Laxmi M, Bhardwaj A, Mehta S, Mehta A. Development and characterization of nanoemulsion as carrier for the enhancement of bioavailability of artemether. Artificial Cells, Nanomedicine, and Biotechnology, 2015; 43(5): 334–44.
25. Aman RM, Abu Hashim II, Meshali MM. Novel Clove Essential Oil Nanoemulgel Tailored by Taguchi's Model and Scaffold-Based Nanofibers: Phytopharmaceuticals with Promising Potential as Cyclooxygenase-2 Inhibitors in External Inflammation. IJN, 2020; 15: 2171–95.
26. Sharma K, Rai JP, Somkuvar S, Singhai AK. Design, Optimization and Evaluation of Etoricoxib Castor Oil Emulgel for acute gout therapy. J Drug Delivery Ther., 2022; 12(4): 15–22.
27. Prasetyo BE, Karsono, Maruhawa SM, Laila L. Formulation and Physical Evaluation of Castor Oil based Nanoemulsion for Diclofenac Sodium Delivery System. Rese Jour of Pharm and Technol, 2018; 11(9): 3861-5.
28. Mehmood T, Ahmed A, Ahmad A, Ahmad MS, Sandhu M. Optimization of mixed surfactants-based β-carotene nanoemulsions using response surface methodology: An ultrasonic homogenization approach. Food Chemistry, 2018; 253: 179–84.
29. Qian C, McClements DJ. Formation of nanoemulsions stabilized by model food-grade emulsifiers using high-pressure homogenization: Factors affecting particle size. Food Hydrocolloids, 2011; 25(5): 1000–8.
30. Priyadarshini P, Karwa P, Syed A, Asha AN. Formulation and Evaluation of Nanoemulgels for the Topical Drug Delivery of Posaconazole. J Drug Delivery Ther., 2023; 13(1): 33–43.
31. Sharma A, Singh AP, Harikumar SL. Development and optimization of nanoemulsion based gel for enhanced transdermal delivery of nitrendipine using box-behnken statistical design. Drug Development and Industrial Pharmacy, 2020; 46(2): 329–42.
32. Akrawi SH, Gorain B, Nair AB, Choudhury H, Pandey M, Shah JN, et al. Development and Optimization of Naringenin-Loaded Chitosan-Coated Nanoemulsion for Topical Therapy in Wound Healing. Pharmaceutics, 2020; 12(9): 893-115.
33. Patil A, Dyawanapelly S, Dandekar P, Jain R. Fabrication and Characterization of Non-spherical Polymeric Particles. J Pharm Innov, 2021; 16(4): 747–58.
34. Abdallah MH, Abu Lila AS, El-Nahas HM, Ibrahim TM. Optimization of Potential Nanoemulgels for Boosting Transdermal Glimepiride Delivery and Upgrading Its Anti-Diabetic Activity. Gels, 2023; 9(6): 494-516.
35. Donthi MR, Saha RN, Singhvi G, Dubey SK. Dasatinib-Loaded Topical Nano-Emulgel for Rheumatoid Arthritis: Formulation Design and Optimization by QbD, In Vitro, Ex Vivo, and In Vivo Evaluation. Pharmaceutics, 2023; 15(3): 736-64.
36. Shehata TM, Elnahas HM, Elsewedy HS. Development, Characterization and Optimization of the Anti-Inflammatory Influence of Meloxicam Loaded into a Eucalyptus Oil-Based Nanoemulgel. Gels, Apr. 22, 2022; 8(5): 262-80.
37. Algahtani MS, Ahmad MZ, Shaikh IA, Abdel-Wahab BA, Nourein IH, Ahmad J. Thymoquinone Loaded Topical Nanoemulgel for Wound Healing: Formulation Design and In-Vivo Evaluation. Molecules, 2021; 26(13): 3863-79.
38. Kotta S, Khan AW, Ansari SH, Sharma RK, Ali J. Formulation of nanoemulsion: a comparison between phase inversion composition method and high-pressure homogenization method. Drug Delivery, 2015; 22(4): 455–66.
39. Younis MK, Khalil IA, Younis NS, Fakhr Eldeen RR, Abdelnaby RM, Aldeeb RA, et al. Aceclofenac/Citronellol Oil Nanoemulsion Repurposing Study: Formulation, In Vitro Characterization, and In Silico Evaluation of Their Antiproliferative and Pro-Apoptotic Activity against Melanoma Cell Line. Biomedicines, 2023; 11(9): 2531-50.
40. Morsy MA, Abdel-Latif RG, Nair AB, Venugopala KN, Ahmed AF, Elsewedy HS, et al. Preparation and Evaluation of Atorvastatin-Loaded Nanoemulgel on

Wound-Healing Efficacy. Pharmaceutics, 2019; 11(11): 609-23.
41. Özdemir S, Üner B, Karaküçük A, Çelik B, Sümer E, Taş Ç. Nanoemulsions as a Promising Carrier for Topical Delivery of Etodolac: Formulation Development and Characterization. Pharmaceutics, 2023; 15(10): 2510-30.
42. Khan BA, Ahmad S, Khan MK, Hosny KM, Bukhary DM, Iqbal H, et al. Fabrication and Characterizations of Pharmaceutical Emulgel Co-Loaded with Naproxen-Eugenol for Improved Analgesic and Anti-Inflammatory Effects. Gels., 2022; 8(10): 608-617.
43. Latif MS, Nawaz A, Asmari M, Uddin J, Ullah H, Ahmad S. Formulation Development and In Vitro/In Vivo Characterization of Methotrexate-Loaded Nanoemulsion Gel Formulations for Enhanced Topical Delivery. Gels, 2022; 9(1): 3-22.
44. Fonseca VR, Jivaji Bhide P, Purushottam Joshi M. Formulation, Development and Evaluation of Etoricoxib Nanosize Microemulsion Based Gel for Topical Drug Delivery. IJPER, 2019; 53(4s): 571–9.
45. Algahtani MS, Ahmad MZ, Ahmad J. Nanoemulgel for Improved Topical Delivery of Retinyl Palmitate: Formulation Design and Stability Evaluation. Nanomaterials, 2020; 10(5): 848-65.