ISSN: 0975-3583,0976-2833 VOL14, ISSUE 07, 2023

FORMULATION DEVELOPMENT AND EVALUATION OF OIL AND EMULGEL OF *VITEX NEGUNDO* FOR ANTI-INFLAMMATORY ACTIVITY

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Abstract

The essential oils contain *Vitex negundo Linn*. Used to treat eye disease, toothache, inflammation, vitiligo, splenomegaly, skin ulcers, catarrhal fever, rheumatoid arthritis, gonorrhea and bronchitis. It is also used as a tonic, anthelmintic, emulsifier, menstrual aid, antibacterial, antipyretic, and antihistamine. Preparations from parts of the *V. negundo* plant cure various diseases such as rheumatic diseases, arthritis, gout, cervicitis, inflammatory diseases of the musculoskeletal system, hemorrhoids (heaps), rheumatic pain, sprains and toothaches. It is used commercially in various Ayurvedic medicines and ointments to wounds, burns, and fungal skin infections. We conclude from in vitro drug diffusion studies that emulgels made of HPMC polymers can help control drug release over long periods, avoid greater fluctuations, and reduce treatment costs. As Emulgels helps improve spreadability, adhesion, viscosity, and extrusion, this new drug delivery is becoming popular, making topical application of hydrophobic drugs a worthy choice for both local and systemic effects.

Key words:- *Vitex negundo Linn*., Emulgels, skin ulcers

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Introduction:

Nowadays on the whole all pharmaceutical agencies, pharmacists, maximum popular R&D's and Researchers are increasingly turning their attention to people remedy, higher drugs towards microbial infections coupled with antibiotic resistance exhibited with the aid of pathogenic microbial infectious sellers has caused the screening of numerous medicinal negundo (*Verbenaceae*) typically known as Nirgundi. it's miles a big, fragrant shrub, on occasion a small slender tree discovered during the greater a part of India. essential oil includes *Vitex negundo Linn*. is used for the treatment of eye-disease, toothache, inflammation, leukoderma, growth of the spleen, skin ulcers, in catarrhal fever, rheumatoid arthritis, gonorrhea, and bronchitis. it's also used as tonics, vermifuge, lactagogue, emmenagogue, antibacterial, antipyretic and antihistaminic retailers. Oil organized with it, is applied to sinuses and scrofulous sores. Its extract has also shown anticancer pastime in opposition to Ehrlich ascites tumor cells.

Preparations from parts of the *V. negundo* plant cure various diseases such as rheumatic diseases, arthritis, gout, cervicitis, inflammatory diseases of the musculoskeletal system, hemorrhoids (cuticles), rheumatic pain, sprains and toothaches. It is used commercially in various Ayurvedic medicines and ointments to, wounds, burns, and fungal infections of the skin.

Materials and Method:

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Nirgundi Oil is prepared and Tween 20 and 80, Span 20 and 80, Polyethylene Glycol 200, 400, 600 and 800, Propylene Glycol, Poloxamer 188 and 407, Ethanol, Methanol, Acetone, Disodium was compounded. Hydrogen phosphate, gums, HPMC, gellan gum, etc.

Table: 1 List of chemical

Sr.No.	Compound Name
1	**DRUG**
	Nirgundi oil
2	**OIL**
	Nirgundi oil
3	**SURFACTANT**
	Tween-20 and 80, Span-20
	Poloxamer-188 and 407
4	**CO-SURFACTANT**
	Propylene Glycol
	Polyethylene Glycol-200,400,600
	Ethanol
5	**GUM**
	HPMC
	Gellan Gum
	Xanthan Gum
	Alginate
6	**SOLVENT**
	Distill Water
	Ethanol, Methanol, Acetone, Acetonitrile
	OTHER MATERIAL
	Nacl, $CaCl_2$, KCl

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7	Disodium Hydrogen Phosphate
	Sodium Dihydrogen Phosphate
	Sodium Lactate,Citric Acid

Experimental:

Extraction of oil from leaves:

Preparation of ethanol extract from *Vitex negundo*. In the present study, fresh leaves were carefully selected and washed to remove impurities. Approximately 100 g of fresh leaf material was extracted by hot extraction using a Soxhlet apparatus with 60% alcohol as solvent. Extraction was continued until the solvent in the thimble became clear, then a few drops of solvent were collected in a test tube at the completion of the cycle and chemical testing of the solvent was performed. After each extraction, the extracts were evaporated to dryness on a rotary vacuum evaporator. Additionally, a portion of the extract was saved for preliminary phytochemical screening to detect various botanical constituents, and the remaining extract was used to formulate a batch of gels.)

Formulation and Development of Gel:

During the formulation, gelling agents were used at different concentrations to generate four different batches of leaf extract gels, for a total of four batches. In this case, HPMC K 100 M type gelator was used. Gelling agents were used as follows. HPMC K 100M (1% and 1.5% concentration) After trial and error, the gel formulation was perfected. And the finished configuration is listed here. All batches were manufactured according to the test plan.

Preparation of Gel by using cold method:

HPMC (1%w/w) and purified water taken in a beaker

↓

Soak for 24 hr

↓

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Stirring by mechanical stirrer at 400 to 650 rpm

↓

Add oil of *vitex negundo* firstly dispered in alcohol

↓

Maintain the pH with sufficient quantity of triethanolamine/ Disodium edetate

↓

Propylene glycol 400 as penetration enhancer, methyl paraben and propyl paraben as preservative

↓

Added slowly with continuous stirring

↓

Until homogeneous gel was formed

In-Vitro Drug Release Studies:

All gel formulations were subjected to in vitro diffusion studies. This study was performed using a Franz diffusion cell apparatus. HPMC and oil concentrations were varied in all formulations. G2 at 36°C. G3. The G4 formulation was stable but not very good in consistency, whereas the G1 formulation had optimal viscosity and consistency.

Optimization:

Batches were optimized for pH, viscosity, spreading, and extrusion of each batch of formulation by examining testing and physical evaluations. By examining the evaluation parameters of all batches.

Preparation of Emulgel:

Table: 2 List of oil, surfactant, co-surfactant used for solubility study.

Sr.No.	Vehicles	Sr.No.	Vehicles
1	Nirgundi oil	5	Propylene Glycol
2	Isopropyl Myristate	6	Polyethylene Glycol-600
3	Tween-80	6	Span-20
4	Tween-20	8	Ethanol

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Drug - excipients compatibility study:

Physical and chemical compatibility of water-insoluble drugs with oils, surfactants and co-surfactants should be used in the oil, surfactant and co-surfactant selection process. Physical compatibility includes phase separation and color change of the surfactant drug solution under study. Chemical compatibility is primarily considered to be the drug's chemical stability with oils, surfactants, and co-surfactants. Oils, surfactants and co-surfactants were considered for further development only if they were physically and chemically compatible with the drug. Following studies, drug excipient compatibility studies should be considered.

Formulation of Emulgel:

Table: 3 Different volumes of surfactant and co-surfactant taken to make a stock Smix ratio

Sr.No.	Volume of surfactant (mL)	Volume of co-surfactant (mL)	Ratio of Smix
1	65	25	3:1

In this method, the surfactant was mixed with the co-surfactant in a fixed weight ratio. The H. Emulgel formulation is 3:1. An aliquot of each surfactant/co-surfactant mixture (Smix) was then mixed with oil in a vial at ambient temperature. Drugs were then added to these oil blend mixtures. In each phase diagram, the ratio of oil to smix is 9:1, 8:2, 6:3, 6:4, 5:5, 4:6, 3:6, 2:8, 1:9. I changed (% of /v). Distilled water was added dropwise to each oil mix mixture with vigorous stirring. Add the gelling agent HPMC at the appropriate concentration to the above formulation. After equilibration, samples were visually inspected and determined to be clear emulgels, emulsions, or gels.

***In-Vitro* Drug Release Studies**

In vitro drug release studies were performed using a modified vertical Franz diffusion cell (effective diffusion area of 1.44 cm2 and cell volume of 15.5 ml). The formulation was applied to a 0.45 µm nylon membrane (previously soaked in phosphate buffer, pH 6.4 for 24 hours).

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Sandwiched between the donor and acceptor compartments of the Franz diffusion cell. Phosphate buffer pH 6.4 + ethanol (80:20) was used as dissolution medium. The cell temperature was maintained at 36±0.2° C. by placing the cell in a water bath. This entire assembly was held with a magnetic stirrer and the solution was continuously stirred using magnetic beads at 50 rpm. Samples (1.0 ml aliquots) were taken at appropriate time intervals, diluted appropriately and then analyzed for drug content using a UV-Visible spectrophotometer at 321 nm.

Anti-Inflammatory evaluation:

The study was approved by the CPCSEA (Committee for the Control and Oversight of Animal Experimentation; Ref. ARTI/CPCSEA/0046-2013) Institutional Ethics Committee (Ref. 722/PO/a/ CPCSEA/IAEC/EXP-46). it was done. An ICR mouse, either male or female, was placed in a polypropylene cage at 24 ± 2 °C and he was allowed food and water ad libitum for 1 week. Prior to treatment, they fasted her for 19 hours and allowed her free access to water.

Selected plants are known for their pharmacological activity. The use of methanolic extracts of all four plants studied for pharmacological evaluation has been reported, with no reported toxicity.

Grouping of Mice:

Mice were divided into 10 groups of 6 each. The groups were as follows:

1. -ve control - treated with only vehicle (1% gum acacia in water)
2. +ve control - treated with Standard drug in 1% of gum acacia (in water).
3. 250mg/Kg Meth. extract of *L. aspera* in 1% of gum acacia (in water).
4. 500mg/kg Meth. extract of *L. aspera* in 1%of gum acacia (in water).
5. 250mg/Kg Meth. extract of *L. nodiflora* in 1%of gum acacia (in water).
6. 500mg/kg Meth. extract of *L. nodiflora* in 1% of gum acacia (in water).
7. 250mg/Kg Meth. extract of *M. alba* in 1% of gum acacia (in water).
8. 500mg/kg Meth. extract of *M. alba* in 1% of gum acacia (in water).

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9. 250mg/Kg Meth. extract of *N. indicum* in 1% of gum acacia (in water).
10. 500mg/kgMeth. extract of *N. indicum* in 1%of gum acacia in water Xylene-induced ear edema, were used.

Xylene induced ear edema Method (Dai et al., 1995, Kou et al., 2005)

It is a "Sub acute" Inflammatory model. Indomethacin (10mg/kg) was used as Standard drug. Protocol used was as follows.

- Mice were administered with drugs orally to respective groups.
- One hour later, each animal received 30µl of xylene using a micropipette on anterior and posterior surface of the left ear. The right ear is considered a control.
- Thickness of the ear is measured using a micrometer screw gauge after 1, 2, 3 & 4h intervals
- Percent ear edema was calculated using the following formula

$$\% \text{ EA} = \frac{\text{Thickness of LE - thickness of RE x 100}}{\text{Thickness of RE}}$$

EA = Ear Edema; LE = Left year; RE = Right ear

Formalin-induced paw edema/Arthritis **(**Brownlee et al., 1950, Gujral et al., 1959)

It is an "Acute" Inflammatory model. Aspirin (10mg/Kg) was used as standard. The protocol used was as follows.

- Mice are given the drug/test compound/vehicle orally
- After 24h, paw volume and joint diameter were measured. After 30 minutes mice were again given the test drug/compound.
- After 30 minutes, 20 µl of freshly prepared 2% formalin (FA) was injected to the right hind paw.
- Volume of the paw was measured with a lab made set up (Fig.3.1C) after 1, 2. 3 & 4 hours

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- Percent paw edema was calculated using the following formula

$$\% PE = \frac{PV \text{ after 1h of FA injection} - PV \text{ before 1h of FA injection}}{PV \text{ before 1h of the FA injection}} \times 100$$

PE = Paw edema; FA = Formaldehyde; PV =Paw Volume

Results and Discussion:

Table 4. Extraction of oil from Nirgundi leaves

Solvent	Plant part	Color	%yield	Alkal-oids	Glyco-ls Sides	Carbo-hydrates	Tannins % phenolic compounds	Flav-noids
Ethanol	leaf	grey	0.0466	+	-	-	+	+
Methan-ol	leaf	blackish grey	0.0762	-	+	-	+	+

HPLC CHROMATOGRAPH OF Vitex

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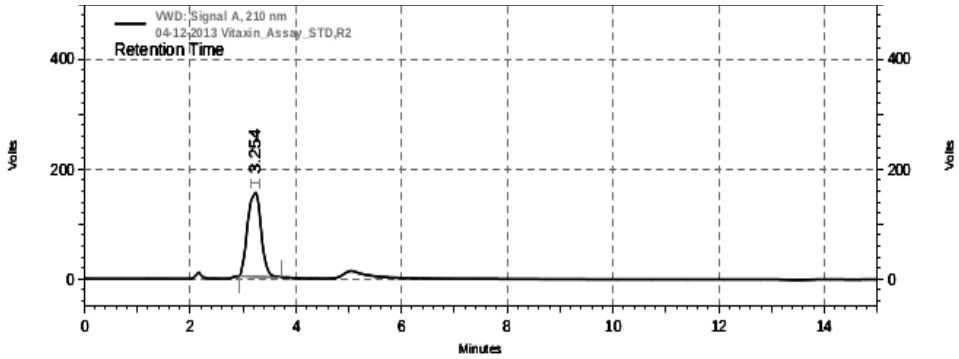

VWD: Signal A, 210 nm Results

Pk #	Name	Retention Time	Area	Area %
1	Vitexin	3.254	45541252	100.00

Fig 1: HPLC Chromatogram of Vitexin having mobile phase (methanol : water ; 70:30)

Preparation of Gel by using cold method

Table 5 Preparation of Gel by using cold method

Ingredient	**G1**	**G2**	**G3**	**G4**
Nirgundi oil	1ml	2ml	3ml	4ml
HPMC	0.25gm	0.25gm	0.30gm	0.40gm
Propylene glycol 400	2.5ml	2.5ml	2.5ml	2.5ml
Methyl paraben	0.15gm	0.15gm	0.15gm	0.15gm
Propyl paraben	0.15gm	0.15gm	0.15gm	0.15gm
Water	3ml	3ml	3ml	3ml

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Triethanolamine	QS	QS	QS	QS

***In-Vitro* Drug Release Studies**

Table 6 *In-Vitro* Drug Release of gel formulation

Sr. No.	Time (min)	Percentage drug release, Mean±SD, n=3			
		G1	G2	G3	G4
1	0	0	0	0	0
2	15	0.42±0.03	0.00	0.00	0.60±0.02
3	30	6.57±0.01	4.382±0.01	3.16±0.10	3.35±0.03
4	60	13.25±0.01	12.03±0.78	11.08±0.30	15.16±0.04
5	90	23.18±0.02	21.13±0.56	20.41±0.23	21.50±0.05
6	120	36.36±0.02	34.22±0.02	31.00±0.20	31.33±0.48
7	150	48.77±0.04	44.41±0.78	43.18±0.01	40.33±0.63
8	180	62.13±0.05	59.42±0.54	55.44±0.21	53.32±0.20
9	210	70.29±0.01	66.37±0.68	65.30±0.10	57.58±0.98
10	240	76.65±0.01	74.11±0.51	75.17±0.30	67.40±0.58
11	270	84.08±0.01	80.72±0.20	81.49±0.25	73.05±0.01
12	300	92.14±0.01	87.48±0.14	84.35±0.01	79.57±0.03

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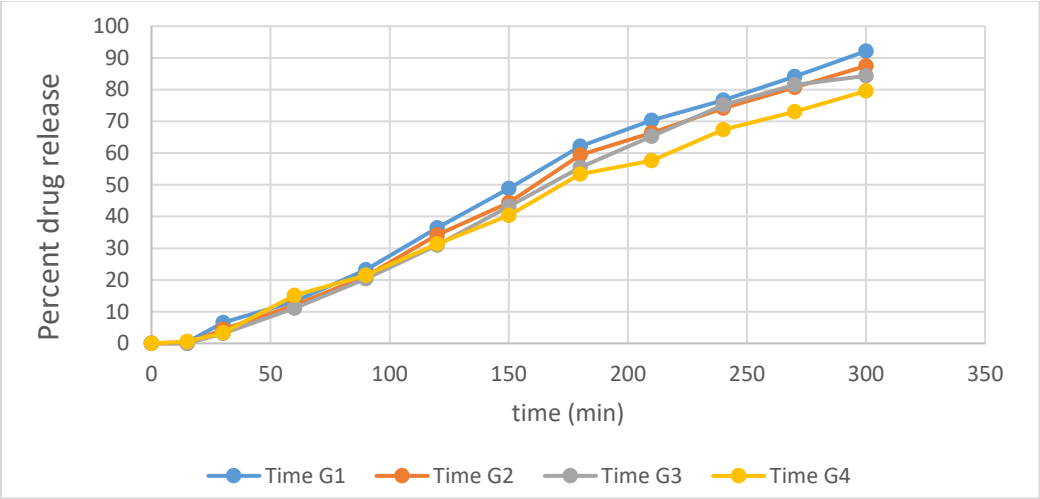

Figure: 2. *In-Vitro* Drug Release of gel formulation

All gel formulations were subjected to in vitro diffusion studies. This study was performed using a Franz diffusion cell apparatus. HPMC and oil concentrations were varied in all formulations. G2 at 37°C. G3. The G4 formulation was stable, but the consistency was not very good. However, the G1 formulation had optimal viscosity and consistency. The release of the G1 formulation was 92.14%, while the release of G2 was 87.48%, G3 84.35% and G4 79.57%. Therefore, the G1 formulation was selected for further study.

Formulation of Emulgel:

a) Formulation of 3:1 Smix ratio Emulgel:

Table 7 Composition of Nirgundi oil, Tween 80, PEG 400 and distilled water at 3:1 Smix ratio of Emulgel formulation

S.No.	Ratio (O:S) *	The volume of different components in the formulation			composition	Observation
		Oil (mL)	Smix (mL)	Water (mL)	HPMC	
1	1:9	0.25	2.25	1.4	0.25	Emulgel
2	2:8	0.5	2	2.5	0.25	Emulgel
3	3:7	0.75	1.75	3.5	0.25	Emulgel
4	4:6	1	1.50	5	0.25	Emulgel
5	5:5	1.25	1.25	5.5	0.25	Emulgel

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6	6:4	1.50	1	-	-	NO
7	7:3	1.75	0.75	-	-	NO
8	8:2	2	0.5	-	-	NO
9	9:1	2.25	0.25	-	-	NO

*O: S:-oil: Smix ratio (Smix ratio:-surfactant: co-surfactant)

***In-Vitro* Drug Release Studies:**

Table 8 In-*Vitro* Drug Release Studies of emulgel formulation:

Sr. No.	Time (min)	Percent drug release, Mean±SD, n=3				
		EG1	EG2	EG3	EG4	EG5
1.	0	0	0	0	0	0
2.	15	2.93±0.01	1.74±0.02	1.21±0.10	0	0.42±0.03
3.	30	10.14±0.02	7.05±0.02	3.70±0.12	3.202±0.04	6.57±0.01
4.	60	19.22±0.01	17.27±0.20	14.25±0.12	11.14±0.02	13.25±0.01
5.	90	32.67±0.01	28.11±0.01	22.34±0.10	20.18±0.03	23.18±0.02
6.	120	42.50±0.12	39.41±0.01	29.77±0.01	25.59±0.05	36.36±0.02
7.	150	51.99±0.21	46.01±0.10	43.12±0.02	37.92±0.01	48.77±0.04
8.	180	64.77±0.14	55.01±0.02	51.11±0.01	44.46±0.01	62.13±0.05
9.	210	74.89±0.15	62.81±0.03	60.97±0.02	53.53±0.02	70.29±0.01
10.	240	80.89±0.01	71.94±0.12	70.78±0.03	61.40±0.02	76.65±0.01
11.	270	90.43±0.01	79.00±0.48	75.48±0.01	69.68±0.03	84.08±0.01

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12.	300	96.55±0.01	90.78±0.40	81.90±0.01	76.35±0.02	92.14±0.01

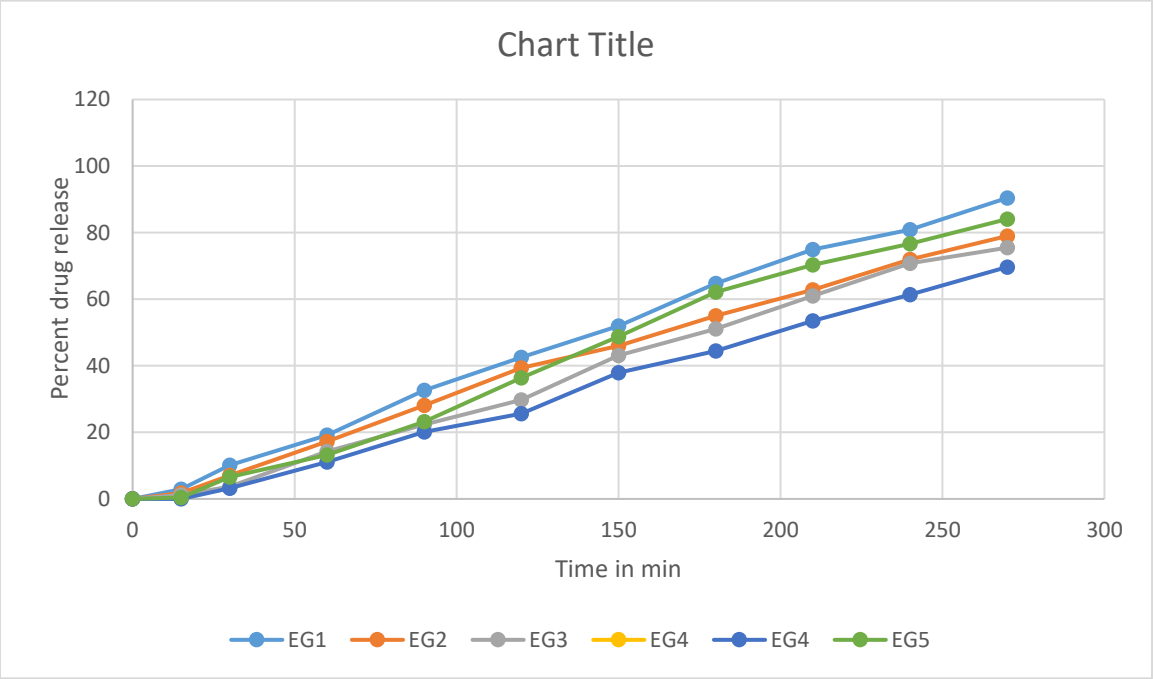

Figure: 3. In Vitro Drug Release Studies of Emulgel formulation

The in vitro release profiles of Nilgundi oil from various emulsified formulations are shown above. It was observed that all his Emulgel formulations exhibited superior drug release compared to standard gels formulated according to the United States Pharmacopoeia. was prepared and had a drug release of 55.67% at 6 hours. For Nirgundi-Emulgel-based formulations, drug release can be ranked in the following descending order: EG1 > EG2 > EG3 > EG4 > EG5, level of drug release after 6 hours. 96.55%, 90.78%, 81.90%, 76.35%, 92.14%, but drug release occurred for emulsion-based formulations.

Comparison of Gel and Emulgel formulation:

Table 9 Comparison of Gel and Emulgel formulation:

Parameter	pH	Viscosity	Spreadability	Extrudability	Drug content	In-diffusion

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						study
G1	5.12	42600	27	81.11	99.64±0.02	92.14±0.01
EG1	5.01	42500	30.21±03	-	103.62±0.01	96.55±0.01

Optimization of gels and emulgels from the above data by evaluating various parameters. In this gel formulation, G1 exhibits good pH, viscosity, spreadability, extrusion, drug loading and in vitro drug release. In this emulgel formulation, batch EG1 exhibits good pH, diffusivity, swelling index, viscosity, bioadhesive strength, drug content, and in vitro drug release. Comparison of optimized gel and emulgel formulations. Emulgel shows superior drug content (103.62 ± 0.01) compared to Gel (99.64 ± 0.02). The in vitro drug release of HPMC-based emulgel shows (96.55 ± 0.01) and the in vitro drug release of HPMC-based gel (92.14 ± 0.01) shows the maximum drug release at 6 h compared to the gel formulation . Emulgel provides maximum therapeutic effect in the shortest possible time compared to HPMC-based gel formulations.

Table 10 Anti-inflammatory activity of methanol extracts (Xylene ear edema method)

Treatment	**Dose**	**Ear edema in ml**			
		1h	**2h**	**3h**	**4h**
Control		0.485 ± 0.01118	0.44167 ± 0.00833	0.4 ± 0.01291	0.39167 ± 0.01537
Diclofenac	15 mg/kg	0.38333± 0.01054***	0.34167 ± 0.02007***	0.30833 ± 0.00833***	0.23167 ± 0.0174***
Vitex Negundo gel	250 mg/kg	0.39167 ± 0.01537***	0.325 ± 0.01118***	0.24167 ± 0.01537***	0.19333 ± 0.01453****
Vitex Negundo gel	500 mg/kg	0.34167 ± 0.02007***	0.31667± 0.02108***	0.25833 ± 0.02386***	0.18833 ± 0.01515***
Vitex Negundo emugel	250 mg/kg	0.38833± 0.00833***	0.37667 ± 0.00919***	0.36333 ± 0.01563	0.34667 ± 0.01333*

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Vitex Negundo emugel	500 mg/kg	0.3800 ± 0.01826***	0.375 ± 0.02739***	0.35833 ± 0.00833*	0.33333 ± 0.02108*

Values are mean ± SE, n = 6, *P< 0.05, **P<0.01, ***P<0.001 vs. control

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Table 11 Anti-inflammatory activity of methanolic extracts (Formaldehyde method):

Treatment	Dose	Paw edema in ml			
		1h	2h	3h	4h
Control	-	0.4125 ± 0.01250	0.3975 ± 0.0225	0.3925 ± 0.02175	0.39 ± 0.02273
Aspirin	10 mg/kg	0.375 ± 0.00289*	0.3375 ± 0.02394*	0.325 ± 0.01443**	0.25 ± 0.02041**
Vitex Negundo gel	250 mg/kg	0.3675 ± 0.01181*	0.335 ± 0.0119*	0.3425 ± 0.0075*	0.2625 ± 0.0427*
Vitex Negundo gel	500 mg/kg	0.345 ± 0.005*	0.3325 ± 0.0175*	0.32 ± 0.01225**	0.25 ± 0.02041**
Vitex Negundo emugel	250 mg/kg	0.365 ± 0.005*	0.3575± 0.0025*	0.3225 ± 0.01315**	0.275 ± 0.02887***
Vitex Negundo emugel	500 mg/kg	0.36 ± 0.00707*	0.35 ± 0.00408*	0.3125 ± 0.02394*	0.27 ± 0.01225*

Values are mean ± SE, n = 6, *P< 0.05, **P<0.01, ***P<0.001 vs. control

Summary and Conclusions:

A thorough investigation concluded that topical gels made from HPMC polymers possess excellent extensibility, extrudability, and bio adhesive strength. Excellent for making topical preparations. Emulgel (EG1) refers to topical gels made of natural polymers that swell more easily with a higher swelling index (96.67%) compared to other properties.

Emulgel shows superior potency (103.62 ± 0.01) compared to Gel (99.64%). The in vitro drug release of HPMC-based emulgel shows (96.55 ± 0.01) and the in vitro drug release of HPMC-based gel (92.14 ± 0.01) shows the maximum drug release at 6 h compared to the gel formulation. From the results it can also be concluded that Vitex Negundo's Emugel formulation showed a better anti-inflammatory effect than the gel formulation.

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