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DEVELOPMENT AND EVALUATION OF DICLOFENAC GEL CONTAINING NIGELLA SATIVA

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Abstract:

The aim of this study is in pharmaceitocal dosage form which is better to relieve the pain due to this study we research about how to promote the activity of the pain relief gel by using the diclofenac diethylamine and nigella sativa. The diclofenac have the analgesic effect and nigella sativa have the anti-inflammatory activity . Diclofenac gel was prepared for pain relief for especially, arthritic pain, tooth aches, and other musculoskeletal disorders. Here we are discuss about the diclofenac and nigella sativa in this study we determine that the topical administration of diclofenac is better than other administration it was majorly used to pain relief it have analgesic, antipyretic, anti-inflammatory activity it was penetrate in to synovial fluid.

Keywords: *Diclofenac diethylamine, nigella sativa, anti-inflammatory, analgesic, topical agent.*

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INTRODUCTION:

Gels are uniform, semi-solid mixtures created by dispersing or solving one or more medications in appropriate hydrophilic or hydrophobic bases. They are typically made with the use of appropriate gelling agent. They are meant to be administered to the skin or specific mucous membranes for therapeutic, preventive, or protective reasons. Topical gels are semi-solid, homogenous formulations used for both skin condition treatment and prevention. Gels' hydrophilic properties allowed the medication or active ingredient to be released fast. Three-dimensional material with a large enough liquid content to form a stiff enough network to immobilize the liquid continuous phase. To form the structural network of gel, both inorganic particles and organic macromolecules are used. Its deeper penetration of the skin enhances absorption. There is no discernible advantage between topical application and traditional dose forms. They are usually considered safer and more effective than conventional formulations due to the bilayer composition and structure. It increases the medication's bioavailability by reducing GI irritation and preventing the liver from metabolizing the drug. Compared to other semi-solid formulations, gels are typically utilize better drug release and smoother, more elegant, non-greasy, and have a cooling effect. Compared to ointments, gels have greater potential as a vehicle for tropically administered drugs because they are stable, non-stick, and visually appealing they also require less energy during formulation. Gels may include appropriate extra ingredients such as stabilizers, antioxidants, and antibacterial preservative. Diclofenac diethylamine has been utilized in the production of diclofenac gel it was an ideal base. Diclofenac gel contains a minimum of 90.0% and a maximum of 110.0% of the specified equivalent amount of diclofenac diethylamine[5].

Diclofenac diethylamine along with the equivalent quantity of diclofenac sodium. The non-steroidal anti-inflammatory medicine (NSAID) diclofenac is commonly prescribed to symptomatically reduce pain and swelling brought on by illness including dysmenorrhea, arthritic pain, tooth aches, and other musculoskeletal disorders. Extended first pass metabolism and possible gastrointestinal irritations, bleeding, ulceration and perforation of the stomach have been associated to the consumption of oral diclofenac. While administrated through intramuscular injection of a diclofenac it cause skin lesion. Compared with oral and intramuscular administration the transdermal (tropical) administration it can improve the bioavailability with reduction of side effects and it enhance the therapeutic efficacy. The tropically applying diclofenac is more protective than other route of administration. An NSAID that has been clinically shown to be both efficacious and well-tolerated in both acute and chronic diseases is topical diclofenac diethylamine 1.16% gel. Synovial fluid, muscles, and joints are all accessible to diclofenac when it is given topically since it crosses the skin barrier [6].

Regarding drug distribution through the skin and vehicle release, there have been issues with conventional topical dose forms such lotions, creams, ointments, and powders Because creams and lotions are quickly removed from the skin and release the medication from their base poorly, they frequently have poor bioavailability. The mechanism of action involves the inhibition of cyclooxygenase (COX) and lipoxygenase enzymes, which leads to a strong suppression of prostaglandin and thromboxane formation.

When diclofenac was applied topically as opposed to orally, the synovial fluid's C-max AUC values were noticeably higher. When transdermal diclofenac diethylamine is used instead of diclofenac sodium, the percentage of adverse gastrointestinal events is significantly lower. Each gram of 11.6mg of diclofenac diethylamine is equivalent to 10mg of diclofenac sodium. Nigella sativa, often known as N. sativa (Family Ranunculaceae), is gaining popularity among therapeutic plants due to its wide range of pharmacological potential and rich religious and historical past.N. sativa is frequently referred to as black seed. Native to Southwest Asia, North Africa, and Southern Europe, N. sativa is grown throughout the world, including the Middle East and Mediterranean region, South Europe, India, Pakistan, Syria, Turkey, and Saudi Arabia.

This nigella sativa have a anti-inflammatory activity so it helps to heal the swelling and it act as a pain relief there are many herbal plants are there but we choose this nigella sativa because it is easily available and low cost compare to some other plants.

The nigella sativa is also denote as black cumin seeds and black seeds in tamil they called as (karuseragam).

Recent studies in ethnopharmacology have shown that both contemporary and traditional medicine often use Nigella species. Given that it has been used, Nigella sativa is perhaps the most well-known species in the genus as an alternative medicine in numerous parts of the globe.

Narcissus sativa has been traditionally associated with several medicinal properties, including analgesic, liver tonic, diuretic, appetite stimulant, and digestive.

A number of studies have demonstrated the oil numerous properties, including those of an antioxidant, antitumor, antibacterial, anti-inflammatory, and many more .

Most of this plant medicinal qualities are a result of thymoquinone (TQ), a significant active ingredient in the essential oil. Because one of the Prophetic hadiths states that black seed is the cure for all ailments save death, Muslims view it as one of the best types of medicinal treatment available.

It is typically obtained by cold pressing seeds. An illness of the lungs that impedes breathing (Chronic Obstructive Pulmonary Disease, or COPD) is cured when black seed oil helps taken orally to enhance breathe easier.

Route of drug administration:

- Topical diclofenac is absorbed through the skin and penetrates sub dermal tissues, including synovial tissue, to act directly at the site of pain and inflammation
- Synovial fluid, muscles, and joints are all accessible to diclofenac when it is given topically since it crosses the skin barrier
- When diclofenac was applied topically as opposed to orally, the synovial fluid's c-max AUC values were noticeably higher.

Ideal properties of nigella sativa:

Physical Properties	Biological Properaties
Yellowish brown	Anti-inflammatory
Aromatic odar	Anti-oxidant
Agreable taste	Anti-bacterial

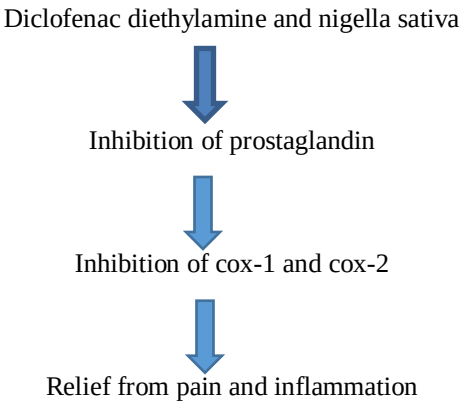
Ideal properties of diclofenac diethylamine:

Physical Properties	Biological Properties
Odourless	Analgesic
White / off white crystalline	Antipyretic
Slightly hygroscopic powder	Anti-inflammatory

Uses:

- Dysmenorrhea
- Arthritic pain
- Inflammatory disorders
- Rheumatoid arthritis
- Osteoarthritis
- Tooth aches
- Musculoskeletal disorders

Mechanism of action:



METHODS AND MATERIAL:

Material:

1.Diclofenac Diethylamine
2. Propylene Glycol
3. Isopropyl Alcohol
4. Ethanol
5. Carbopol-934
6. sodium benzoate
7. Methyl paraben
8. Triethanolamine
9. Water
10. Nigella sativa

Methods:

S.NO	DRUGS	Study 1	Study 2	Study 3	Study 4
1	Diclofenac diethylamine	12.18g	12.18g	12.18g	12.18g
2	Propylene glycol	150ml	150ml	150ml	150ml
3	Isopropyl alcohol	55ml	55ml	55ml	55ml
4	Ethanol	15ml	15ml	15ml	15ml
5	Carbopol-934	17g	17g	17g	17g
6	Sodium benzoate	30g	30g	30g	30g
7	Methyl paraben	10g	10g	10g	10g
8	Triethanolamine	40ml	40ml	40ml	40ml
9	Water	671ml	651ml	621ml	571ml
10	Nigella sativa	NIL	20ml(2%)	50ml(5%)	100ml(10%)

Procedure:

Step 1 for 100gm:

i. 25 ml of water should be taken
ii. Add carbopol 934 1.7 gm
iii. Add sodium benzoate 3gm
iv. Add Methyl paraben 1gm

Steps 2 for 100gm:

i. Triethanolamine 4 ml
ii. Add Water 10 ml
iii. Mixed together

Steps 3 for 100gm:

i. Heat the 5 ml propylene glycol at 60ºc
ii. Add 1.218 gm diclofenac diethylamine
iii. Add 3 ml isopropyl alcohol
iv. Add 1.5 ml ethanol

Steps 4 for 100gm:

i. Take a mixture of carbopol 934 (sodium benzoate, methyl paraben,water)
ii. Add mixture of triethanolamine with water
iii. Add mixture of propylene glycol (diclofenac diethylamine, isopropyl alcohol, ethanol)
iv. Add nigella sativa oil extract(black cumin seed oil)

EVALUATION:

pH:-

- The pH is determined by the following procedure
- The pH is measured by using the instrument – Digital pH meter
- The pH meter is calibrated by using the buffer solution of pH4.0
- Then the probe is washed with distilled water
- Then the required quantity of gel is taken and mixed with that same volume of distilled water (for ex:- 25gm of gel mixed with 25ml of distilled water)
- Then the probe is placed in the solution with gel
- Then the pH was determined and noted
- Following the same procedure for measure the different quantity of the gel

S.NO	QUANTITY OF PREPARED GEL		QUANTITY OF WATER ADDED	pH FOR THE CONCENTRATION		
				5g	10g	15g
1	For 100 g	5g	50ml	7.64	7.68	7.70
		10g	100ml	7.64	7.68	7.70
		15g	150ml	7.64	7.68	7.70
2	For 500g	5g	50ml	7.62	7.70	7.74
		10g	100ml	7.62	7.70	7.74
		15g	150ml	7.62	7.70	7.74
3	For 1000g	5g	50ml	7.64	7.73	7.78
		10g	100ml	7.64	7.73	7.78
		15g	150ml	7.64	7.73	7.78

Spreadability:

- Spreadability was determined by fallowing procedure
- It was determined by glass slide apparatus
- Required amount of prepared gel was place in lower slide
- Place the upper slide on gel placed lower slide
- Place the weight up to 1000g on the upper slide for 5min.
- After the 5min. separate the two slides
- Measure the time for removing the slides separately
- It is calculated by using this formula

$$S = \frac{M \times L}{T}$$

Where,

M – weight tied to upper slide
L – length of glass slides
T – time taken to separate the slides

S.NO	QUANTITY OF PREPARED GEL	T1 (SEC)	T2 (SEC)	T3 (SEC)	AVERAGE TIME (SEC)	SPRADABILITY S = M×L / T
1	2g	6	6	5	5.6	644g cm/sec
2	4g	6	7	7	6.6	546g cm/sec
3	5g	7	8	8	8.3	515g cm/sec
4	6g	8	9	6	7	435g cm/sec
5	10g	21	20	21	20.6	175g cm/sec
6	15g	22	23	23	22.6	159g cm/sec

Weight tied on upper slide is =190 g*

Viscosity:

- Viscosity is determined by following procedure
- The ostwald viscometer is taken on washed with distilled water
- 100 ml beaker is taken and washed with distilled water
- Then the preparation gel is taken and required quantity is weighed and transfer into beaker
- The distilled water is taken according to weighed quantity
- Then it is transfer into Ostwald viscometer
- The standard viscosity procedure is carried out
- It is calculated by using this formula

$$ny = nw \frac{dy \times ty}{dw \times tw}$$

S.NO	DEUG CONTENT	T1 (SEC)	T2 (SEC)	T3(SEC)	AVERAGE TIME(SEC)	DENSITY	VISCOSITY
1	5g	1.16	1.23	1.51	1.30	0.05	0.06 $kg.m^{-1}.s^{-1}$
2	10g	5.32	5.51	5.60	5.47	0.1	0.52 $kg.m^{-1}.s^{-1}$
3	15g	9.11	9.15	9.15	9.14	0.15	1.3 $kg.m^{-1}.s^{-1}$
4	20g	11.5	11.54	11.63	11.56	0.20	2.2 $kg.m^{-1}.s^{-1}$

Water density = 1 g/cm^3
Water flow rate = 1.5 sec

Homogenisity:
Homogeneity measurement were carried out on gel preparation that had been made before and after being given storage condition. It is carried out by means gel preparation applied to a piece of gels or other suitable transparent material then homogeneity is observed.

- Homogeneity is determined by following procedure
- A small slide taken and washed with distilled water
- The required quantity gel is weighed and taken
- The weigh gel is taken to glass slide
- Homogeneity is tested

S.NO	QUANTITY TAKEN	HOMOGENEITY
1	5	Clear
2	10	Clear
3	15	Clear

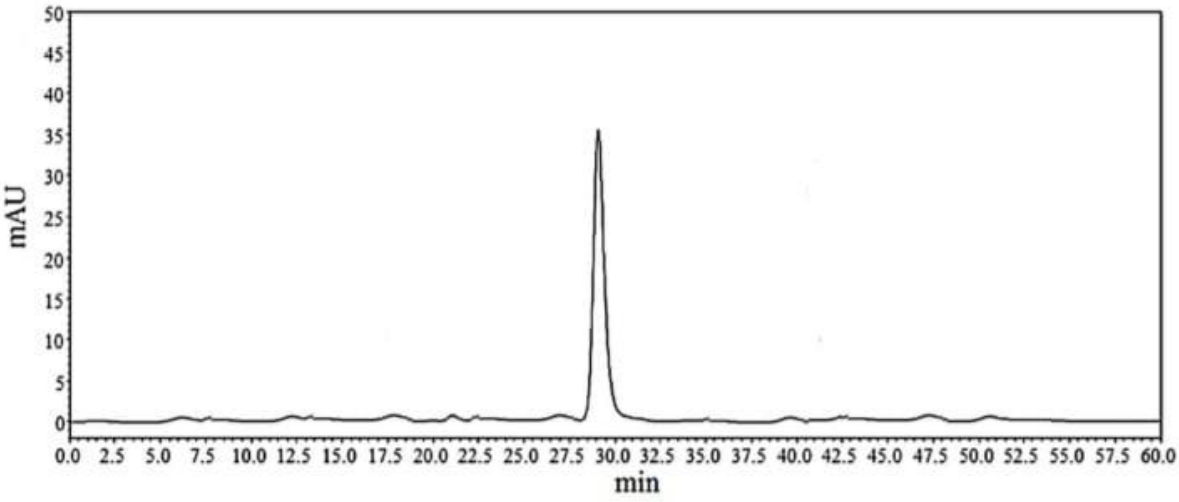
Assay:
Hplc:
Instrumentation:
Chromatography was performed on Acquity® (UPLC) system, column heater, photodiode array (PDA) eλ detector and BEH C18 column (2.1 × 50 mm, 1.7 µm). Separation employed reverse-phase isocratic elution using a mobile phase consisting of 0.05 M acetate buffer (pH, 2.5) and acetonitrile (50:50, v/v) run at flow rate of 0.5 ml/min and injection volume 1 µl. PDA Detector was set to acquire 3D data from 210 to 280 nm. The column temperature was kept at 50 °C while sample temperature was kept at 10 °C.

System suitability:
System suitability was determined before sample analysis from injections of the standard solution containing 1.2 mg/mL of diclofenac diethylamine. The acceptance criteria were less than 2% relative standard deviation (RSD) for peak areas, USP plate count (N) more than 5000, capacity factor (K) more than 2 and resolution (Rs) more than 1.5 for DS peaks from standard solution.

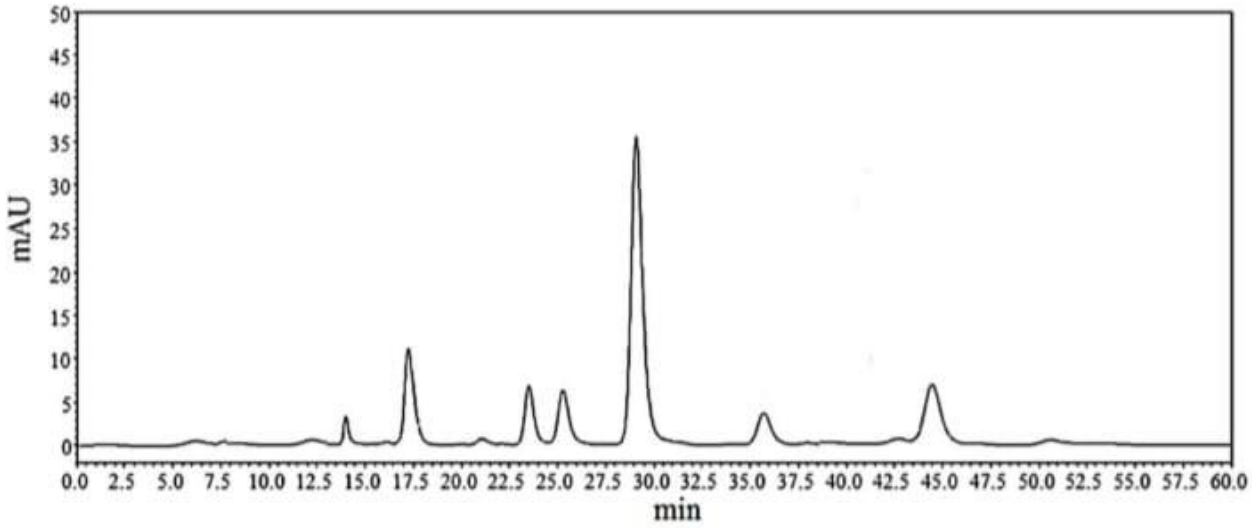
Standard solutions:
Diclofenac diethylamine gel stock solution was prepared in 0.2 M phosphate buffer; pH 6.8 to produce final concentration of 1000 µg/ml. Standard solutions were then diluted to concentration (1–1000 µg/ml).

Method validation:
Several performance parameters were designed to be tested via validation experiments including specificity, linearity, limit of detection (LOD), lower limit of quantitation (LLOQ), accuracy and precision according to FDA guidelines.

Specificity:
It is the ability of an analytical method to differentiate the analyte in the presence of other components in the sample and quantify it. Specificity was assessed to test the effect of gel for interference at the same retention time as well as to ensure the validity of the method to be further utilized as a stability-indicating assay. To evaluate the specificity of the method, drug free quality control zero samples were carried out through the assay procedure and the retention times of the gel formulation components were compared with that of standard.



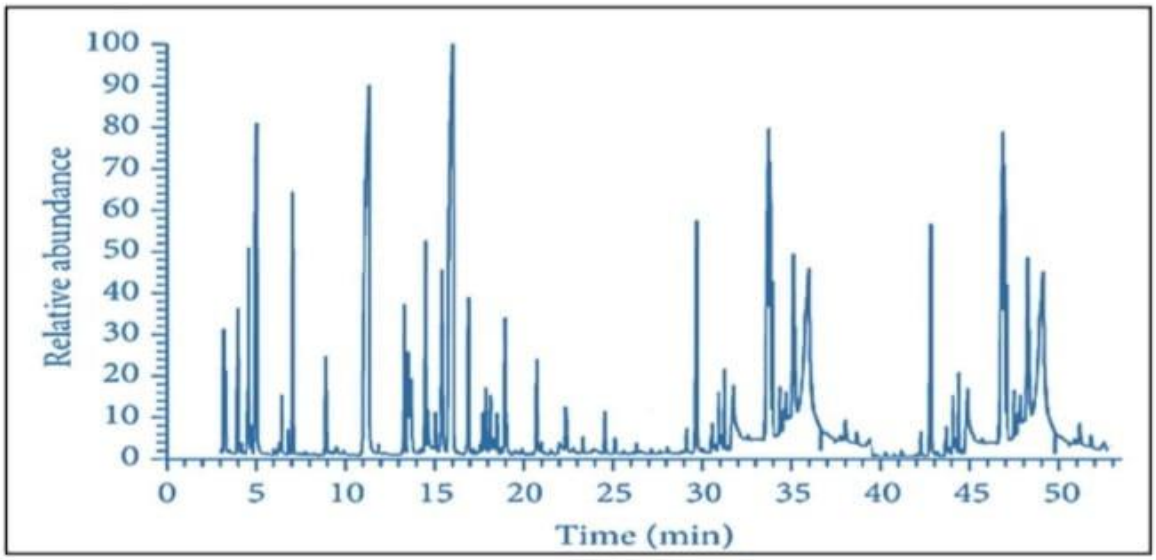
HPLC chromatogram of standard Diclofenac ethanylamine



HPLC chromatogram of Diclofenac diethylamine gel

GC-MS:

GC-MS analyses were conducted in a gas chromatograph. Trace GC Ultra gas chromatograph attached to a TSQ Quantum XLS triple quadruple mass spectrometer purchased from Thermo Scientific. All the analyses were performed with a fused silica DB-5-MS column (30 m × 0.25 mm × 0.25 ϧm). The temperature of the oven was raised to 220∘C from 70∘C at 4∘C/min and maintained isothermally for 15 min. The temperatures of the injector and detector temperatures were maintained at 220∘C and 240∘C, respectively, with the preparation of 10% of samples in acetonitrile. The split mode ratio of 1:15 was applied for the injection of a 0.5 ϧL sample. Carrier gas used was helium at 1 mL/min flow rate. EI at 70 eV provided the mass spectra with mass scanning done from 40 to 400 nm.



The major components for diclofenac diethylamine gel with nigella sativa oil were 1,3,8-pMenthatriene, thymoquinone, cyclohexen, 1,4-Cyclohexadiene, longifolene, ylangene, 3-allyl-6-methoxypphenol, caryophyllene, ascorbic acid, methyl sterate, butyl9,12-octa decadienoate, methyl tetraecanoate, diclofenac, (N-(2,6-dichlorophenyl)indolin-2-one), diethylamine and carvacrol.

RESULT AND DISCUSSION:

(a). pH:

As per BIS (Bureau of Indian Standards) specification skin preparation should have pH values in the range of 4 to 9. Ideally, any topical preparations are in the pH value of slightly acidic to neutral. Our result of study sample within considerable limits. From this all the preparations are in neutral pH range, confirms standard BIS and ideal requirements.

(b). Spreadability

All the values are with in certain limits indicates the prepared formulations have good spread ability

(c) Viscosity

Our study with Oswald viscometer to understand the flow property all the study samples shows more uniformity in flow

(d) Homogeneity

All the study samples shows good homogeneity indicates the concentration of two phases most probably in exact concentrations.

(e) Removal test

All the prepared formulation has easy washable character indicates better phase character

(f) Assay

The major components for diclofenac diethylamine gel with nigella sativa oil were 1,3,8-pMenthatriene, thymoquinone, cyclohexen, 1,4-Cyclohexadiene, longifolene, ylangene, 3-allyl-6-methoxypphenol, caryophyllene, ascorbic acid, methyl sterate, butyl9,12-octa decadienoate, methyl tetraecanoate, diclofenac, (N-(2,6-dichlorophenyl)indolin-2-one), diethylamine and carvacrol.

SUMMARY AND CONCLUSION:

The following conclusions can be drawn from the results obtained.

- Study on the spreadability, pH, homogeneity assay proves is an efficient study formulation.
- The results obtained from the above various trials clearly indicating that Study trial 1, 2, 3 has accurate results and provide as significant aid in further processing in-vivo studies and remaining tests of in-vitro

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