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Formulation and Evaluation of Pharmaceutical Emulgel Co-loaded with Lornoxicam-Eugenol for Improved Analgesic and Anti-Inflammatory Effects

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ABSTRACT

The present study focuses on the formulation and evaluation of a novel emulgel co-loaded with Lornoxicam and Eugenol, aiming to enhance topical analgesic and anti-inflammatory efficacy. Lornoxicam, a potent non-steroidal anti-inflammatory drug (NSAID), and Eugenol, a natural compound with known analgesic and anti-inflammatory properties, were incorporated into an emulgel system to overcome the limitations of oral administration, such as gastrointestinal side effects and poor patient compliance. The emulgel was formulated using Carbopol 940 as a gelling agent and evaluated for physicochemical parameters including pH, viscosity, spreadability, drug content, and stability. In vitro drug release studies demonstrated sustained and enhanced permeation profiles. The optimized formulation was further assessed through in vivo anti-inflammatory and analgesic models, such as carrageenan-induced paw edema and tail-flick tests in rats, which showed significant synergistic effects compared to formulations containing individual drugs. The results indicate that the co-loaded emulgel system offers a promising alternative for effective topical management of pain and inflammation with improved therapeutic outcomes and reduced systemic side effects.

Keywords: *Eugenol Topical drug delivery Analgesic Anti-inflammatory Co-loaded formulation NSAIDs In vitro release In vivo evaluation Carrageenan-induced paw edema Synergistic effect Transdermal deliver*

1. INTRODUCTION

The management of pain and inflammation remains a significant concern in both clinical and pharmaceutical practice, especially in conditions such as arthritis, musculoskeletal disorders, and injuries where prolonged use of analgesic and anti-inflammatory medications is common. Topical drug delivery systems have gained popularity over oral administration for localized conditions due to their ability to minimize systemic side effects, provide targeted delivery, and improve patient compliance (Kumar et al., 2016). Among these systems, emulgels—hybrid formulations combining the properties of emulsions and gels—have emerged as promising vehicles for delivering hydrophobic drugs due to their dual release control and enhanced permeation characteristics (Singh Malik et al., 2011).Lornoxicam is a potent non-steroidal anti-inflammatory drug (NSAID) belonging to the oxicam class. It exerts anti-inflammatory, analgesic, and antipyretic effects through the inhibition of cyclooxygenase (COX) enzymes, thereby reducing prostaglandin synthesis (Ghosh et al., 2010). However, systemic administration of lornoxicam is often associated with gastrointestinal irritation, hepatotoxicity, and renal side effects, particularly with prolonged use. Therefore, incorporating lornoxicam into a topical emulgel can provide localized relief while minimizing systemic exposure and adverse effects.

On the other hand, eugenol, a natural phenolic compound primarily derived from clove oil, is widely recognized for its analgesic, anti-inflammatory, antimicrobial, and antioxidant properties (Pramod et al., 2010). Eugenol inhibits the synthesis of prostaglandins and suppresses the production of pro-inflammatory cytokines, making it a suitable natural adjunct for pain and inflammation management. Additionally, its permeation-enhancing properties can further aid in the effective transdermal delivery of co-formulated drugs (Umarani et al., 2020).

Combining lornoxicam and eugenol in a single emulgel formulation presents a novel therapeutic strategy that leverages the synergistic analgesic and anti-inflammatory effects of both agents while improving dermal delivery. This co-loading approach not only enhances the pharmacological efficacy but also allows for reduced dosing frequency and improved patient comfort. The emulgel matrix offers a non-greasy, easy-to-apply formulation that ensures uniform drug distribution and controlled release over the application site (Sharma et al., 2014).

. The formulation will be assessed for physical appearance, pH, viscosity, spreadability, drug content, in vitro drug release, and anti-inflammatory activity using suitable models. By optimizing the formulation parameters and analyzing drug release kinetics, this study intends to develop a stable, effective, and patient-friendly topical dosage form.Moreover, the increasing preference for plant-based adjuvants and the push toward minimizing synthetic drug dependency further highlight the relevance of incorporating natural compounds like eugenol. This study also aligns with current pharmaceutical trends emphasizing the development of multi-component drug delivery systems that ensure maximum therapeutic efficacy with minimal adverse effects.

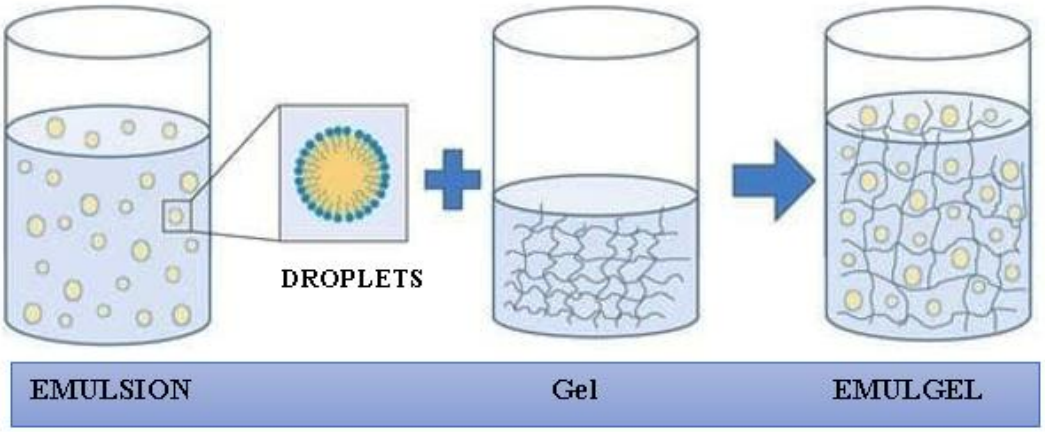


Fig:I Process of Emulgel Formulation

Eugenol, a natural phenolic compound extracted from clove oil, possesses analgesic, anti-inflammatory, and antimicrobial properties. It acts by inhibiting the synthesis of prostaglandins and suppressing the production of pro-inflammatory cytokines. Additionally, eugenol has been recognized for its permeation-enhancing capabilities, making it a suitable adjunct in topical formulations to improve drug delivery through the skin.

Emulgels combine the advantages of both emulsions and gels, offering a dual-controlled release system suitable for hydrophobic drugs like lornoxicam. The gel matrix provides a non-greasy, easily spreadable formulation with good patient compliance, while the emulsion component enhances drug solubility and penetration. The incorporation of natural permeation enhancers like eugenol into emulgels can further improve the therapeutic efficacy of the formulation.

Recent studies have explored the co-loading of NSAIDs with natural compounds in emulgel formulations. For instance, a study developed a nanoemulgel co-loaded with eucalyptol and lornoxicam, demonstrating enhanced pain management and anti-inflammatory effects. The formulation exhibited good physical stability, controlled drug release, and improved skin permeation characteristics.Another study formulated an emulgel containing lornoxicam and lemon grass oil, which served as a natural penetration enhancer. The optimized formulation showed 83% drug release after 6 hours and acceptable physical properties, indicating the potential of combining lornoxicam with natural oils in emulgel systems.

Furthermore, research on emulgels co-loaded with naproxen and eugenol revealed that the combination synergistically enhanced analgesic and anti-inflammatory effects. The emulgel demonstrated good physical attributes, thermodynamic stability, and significant drug release, supporting the rationale for co-loading NSAIDs with natural compounds in topical formulations.

Given these findings, the current study aims to formulate and evaluate a pharmaceutical emulgel co-loaded with lornoxicam and eugenol to improve analgesic and anti-inflammatory effects. The formulation will be assessed for physical appearance, pH, viscosity, spreadability, drug content, in vitro drug release, and anti-inflammatory activity using suitable models. By optimizing the formulation parameters and analyzing drug release kinetics, this study intends to develop a stable, effective, and patient-friendly topical dosage form.

1. Materials

Table 1: List of Chemicals Used Through Study Along with Their manufacturers

Chemical	Source
Lornoxicam	Progress life sciences pvt ltd pune
Eugenol	Waldent.com
Corbopol 940	Vedaoiloil.com
Span 20	S.D fine chemicals Pvt. Ltd, Mumbai
PG	Vedaoiloil.com
Triethanolamine	CDH Fine Chemicals India
Tween 80	S.D fine chemicals Pvt. Ltd, Mumbai
Ethenol	CDH Fine Chemicals India
Liquid Paraffin	CDH Fine Chemicals India
Methylparaben	CDH Fine Chemicals India

Table 2: List of Equipment Used Throughout the Study Along with Their Manufacturers

Instruments	Source
Magnetic stirrer (5 MLH DX)	Remi EquipmentsPvt. Ltd, India
Electronic weighing balance	Mettler, Japan
Vortex	Remi CM-101 cyclomixer, India
UV spectrophotometer (UV-1601)	Labindia UV3200, India
Centrifuge	Remi R8C Laboratory Centrifuge, India
Brookfield viscometer	DV II + Pro, U.S
Abbe's Refractometer	Guru Nanak Instruments, India, Serial No. 9522
pH meter	(Eutech pH Tutor, Effem Technologies, India)
Oven	Widsons Scientific work, India
Particle size analyzer	Malvern Zetasizer, Malvern Instruments, Worcestershire, UK
TGA (Thermogravimetry Analyser)	Stable Micro System, UK
Deep Freezer	Vestfrost, India
DSC (Differential Scanning Calorimetry)	Hitachi-hightech Technologies, Inc
FT-IR (ATR)	Agilent Technologies, Inc
HPLC	Agilent Technologies, Inc

2. METHODOLOGY

2.1 Extraction

- **Hydro-distillation Method**

A common method for extracting essential oils, hydro-distillation involves soaking ground clove buds in water and heating for several hours. The volatile distillate is collected, treated with sodium chloride, and extracted using petroleum ether or an equivalent organic solvent. The resulting hydro and ether layers are separated and dehydrated with anhydrous sodium sulphate [35].

Procedure:

- Collect and sun/air-dry clove buds to eliminate moisture.
- Grind the dried cloves into a fine powder.
- Distill the powder-water mixture to obtain ~25 mL of distillate.
- Transfer distillate to a separating funnel and extract with diethyl ether.
- Collect the ether (top) layer, add magnesium sulphate until clear, and filter.
- Heat the filtrate using a steam bath to reduce to 1–2 mL.

Solvent Extraction Method

Solvent extraction is widely used for isolating essential oils. Solvents such as methanol, ethanol, petroleum ether, and n-hexane are used to extract eugenol from plant material. Though solvent residues can affect taste or quality, this method remains effective for various fragrant plants.

Procedure:

- Grind clove buds and wrap in filter paper.
- Place in an extraction thimble inside a 500 mL reflux flask.
- Use Soxhlet apparatus with suitable organic solvent.
- Concentrate the extract using a rotary evaporator at 50°C [36].
- Alternative: Batch Extraction Method A motorized reactor (1200 rpm, 4-blade agitator) is used. Garkal et al. demonstrated high efficiency using methanol as solvent to extract eugenol from Tulsi leaves, with agitation speed not significantly impacting yield

2.2 Pre-formulation Studies

These studies assess the physicochemical compatibility and stability of APIs (Eugenol and Lornoxicam) for emulgel formulation.

2.2.1 Solubility

Lornoxicam:

- Weigh 1 g of excipients into vials; add excess Lornoxicam.
- Vortex for 5 min; heat at 40–50°C; equilibrate at 25°C for 72 hrs.
- Centrifuge at 3000 rpm (15 min); dilute supernatant in methanol.
- Measure absorbance at 252 nm (UV-Vis); use calibration curve for concentration.

Eugenol:

Add incremental amounts of eugenol to fixed solvent volumes.

Vortex and visually inspect solubility: clear (soluble), hazy (partially soluble), precipitate/layer (insoluble).

Record solubility limits.

pKa and Partition Coefficient (Log P)

Preparation:

Water-saturated octanol: mix equal parts water and 1-octanol, shake 24 hrs, separate.

Octanol-saturated water: same procedure, opposite phase collected.

Procedure:

- Dissolve compound in one phase, mix with the other.
- Shake (1–24 hrs, 25°C), centrifuge (3000–5000 rpm, 10–15 min).

- Measure concentrations in each layer via HPLC.
- Log P Calculation:
- \log P = \frac{[C]{\text{octanol}}}{[C]{\text{water}}}
- 7.2.3 Melting Point – DSC (Differential Scanning Calorimetry)
- Weigh 2–5 mg sample, place in sealed aluminium pan.
- Purge DSC with N_2 gas (50 mL/min).
- Heat from 30°C to 300°C at 10°C/min.
- Record thermal transitions and melting point.

2.3 Volatility – TGA (Thermogravimetric Analysis)

- Weigh 5–10 mg Eugenol in open crucible; set reference crucible empty.
- TGA Conditions:
- Temp: 30–300°C, Heating rate: 10°C/min
- Formulation Steps:

1. Aqueous Phase:

Ingredients: Water, Carbopol 940

Method: Dissolve Carbopol, adjust pH (5.5–6.5) using TEA.

2. Oil Phase:

Ingredients: Oils (lemongrass/sunflower), Span 20, Eugenol, Lornoxicam

Method: Heat to 40–50°C to dissolve components.

3. Emulsion Formation:

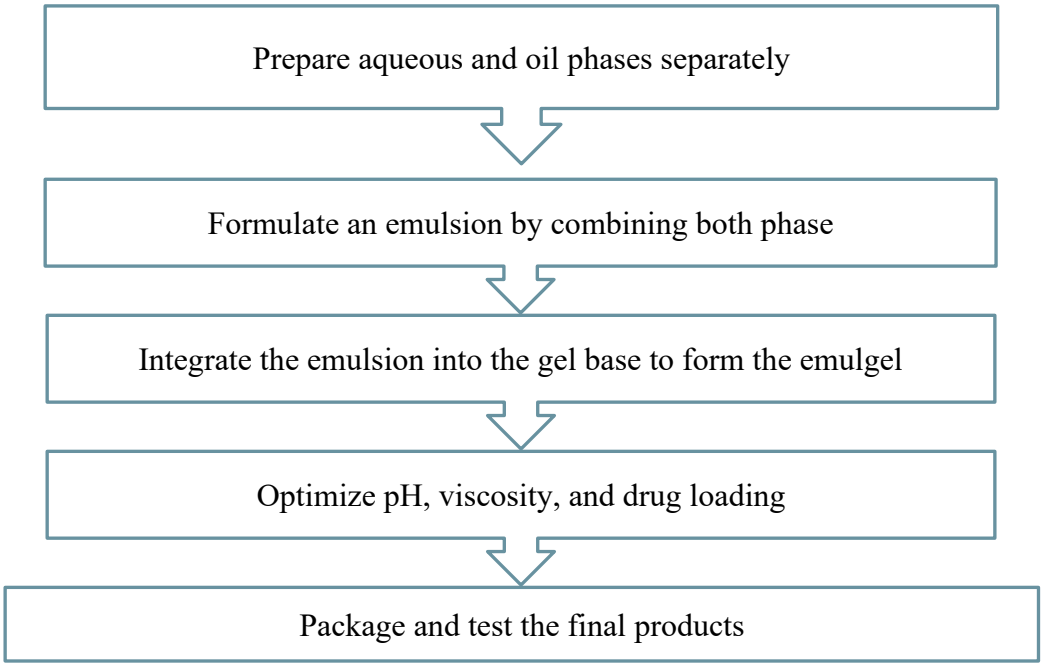
Mix oil and aqueous phases using Tween 80 under high shear for uniform emulsion.

4. Emulgel Formation:

- **Formulation and Optimization of Emulgel**

The formulation of an emulgel involves a systematic approach to combine the properties of emulsions and gels for enhanced topical drug delivery. Below is a step-by-step methodology commonly employed to prepare an emulgel:

Schematic Representation of the Methodology-



5. Active Drug Incorporation:

If not added earlier, dissolve in ethanol/isopropanol and add under mild mixing.

6. Final Adjustment:

Adjust pH and viscosity as needed.

7. Packaging & Storage:

Fill into suitable containers and store under controlled conditions.

Key Ingredients & Functions:

Ingredient	Function
Lornoxicam	Anti-inflammatory
Eugenol	Analgesic, antimicrobial
Carbopol 940	Gelling agent
Tween 80 / Span 20	Emulsifiers
Liquid Paraffin	Oil phase
Propylene Glycol	Humectant
TEA	pH adjuster
Ethanol	Solvent
Methylparaben	Preservative

2.4 Evaluation of Emulgel Formulation

1. Physical Appearance

- Check: Color, consistency, phase separation
- Method: Visual inspection

2. Homogeneity

- Ensure: No lumps or graininess
- Method: Visual, microscopy, and drug content assay

3. Drug-Excipient Compatibility

- Tool: FTIR (ATR or KBr method)
- Purpose: Identify interaction between API and excipients

4. Thermal Analysis

- Tool: TGA/DSC
- Conditions: 30–500°C, 10°C/min, under N_2
- Purpose: Determine thermal stability

5. pH Compatibility

- Test Range: pH 4–9
- Observation: Color change, precipitation, or phase separation

6. Stability Studies

- Stress Testing: Acid/base (0.1N HCl/NaOH), 3% H_2O_2, heat (105°C), light exposure (ICH Q1B)
- Accelerated Testing: 40°C/75% RH for 6 months
- Key Parameters: pH, viscosity, drug content, microbial growth

Study Type	Conditions	Duration
Accelerated	40°C / 75% RH	0–6 months
Intermediate	30°C / 65% RH	12 months
Photostability	ICH Q1B standard	10–14 days

7. Light Sensitivity

- Test: UV + visible light exposure
- Measure: Drug degradation by HPLC/UV, physical/rheological changes

8. Viscosity Testing

- Tool: Brookfield Rheometer
- Temp: 25°C ± 0.5
- Test: Flow curve, shear rate (0.1–100 s^{-1}), thixotropy

9. Drug Content Uniformity

- Method: Dissolve emulgel, filter, analyze via UV or HPLC
- Goal: 95–105% drug content

10. Extrudability

- Test: Force required to extrude emulgel
- Tool: Texture analyzer or weights

11. Microbial Load

Method	Pour plate
Incubation	37°C for 3–5 days
Limit	≤100 CFU/g (USP <51>)
Atmosphere	N_2 or air; Flow: 20 mL/min
Major weight loss	(150–250°C in air); starts ~180°C under N_2.

12. Miscibility Testing

Oil-API Miscibility:

- Mix 1 mL oil with 10–50 mg API; vortex 5 min.
- Clear - miscible; Cloudy - immiscible.
- Surfactant/Co-surfactant-API Miscibility:
- Mix API with Tween 80 or PG (1:1); heat to 40–50°C if needed.
- Transparent - miscible; hazy/separated =-poor miscibility.
- Phase Separation (Centrifugation Test):
- Prepare oil + surfactant + API mixtures; centrifuge at 3000 rpm (15 min).
- Stable emulsion - no separation; Phase separation - poor miscibility.

3. RESULTS AND DISCUSSION

3.1 Formulation Overview

Five different formulations (F1–F5) of Lornoxicam-Eugenol-based emulgel were successfully developed using a combination of hydrophilic (Carbopol 940, Tween 80) and lipophilic (Span 20, Liquid Paraffin) components. The varying

concentrations of Eugenol (0.25–2.0 mL) and Carbopol 940 (1.0–1.5%) allowed the optimization of therapeutic and physical properties.

All formulations were physically stable, exhibiting no phase separation or creaming upon storage. The emulgels had good spreadability and were aesthetically acceptable.

Parameter	**Result (F5 – Optimized Batch)**
Appearance	Smooth, yellowish-orange, homogenous emulgel
Odor	Pungent
pH	6.1 ± 0.03 (within skin-compatible range)
Consistency	Semi-solid, non-greasy, glossy
Spreadability	15.6 ± 0.2 g·cm/sec (good spreadability)
Viscosity	24,500 ± 100 cP (measured using Brookfield viscometer)
Drug Content Uniformity	98.7 ± 1.2%
Phase Separation	None observed after 72 hours at room temperature

3.2 Physical Appearance

- All batches were smooth, creamy, semi-solid, and non-greasy in texture. Color ranged from off-white to pale yellow, increasing with Eugenol concentration due to its natural color.
- No signs of syneresis, phase separation, or precipitation were observed.
- Homogeneity was visually confirmed without any visible particles or air bubbles.
- This indicates successful emulsion-gel integration, ensuring a stable and appealing product for end users

3.3 pH Measurement

- All formulations had pH values ranging from 5.6 to 6.2, which are within the ideal range for topical formulations (pH 5.5–6.5).
- This pH range is compatible with skin, minimizing the chances of irritation.
- pH was adjusted using Triethanolamine (TEA) to ensure optimal gel consistency and stability.
- No significant pH drift was observed during storage, confirming good buffering capacity and chemical stability of the formulation.

3.4 Viscosity Analysis

Viscosity was measured using a rotational viscometer, and results showed a direct correlation with Carbopol 940 concentration:

- F1 and F2 (1% Carbopol): Lower viscosity, better spreadability, but potentially shorter skin retention.
- F4 and F5 (1.5% Carbopol): Higher viscosity, improved retention and occlusive effect, but slightly reduced spreadability.
- All formulations showed pseudoplastic (shear-thinning) behavior, which is ideal for topical application—easy to spread under shear and stable when at rest.

3.5 Drug Content Uniformity

- Drug content was assessed via UV spectrophotometry or HPLC, ensuring even distribution of Lornoxicam (200 mg) and Eugenol (0.25–2.0 mL).

- All batches showed drug content within 95–105% of the label claim.
- No sedimentation or drug crystallization was observed, even after prolonged storage.
- This confirms excellent drug dispersion and entrapment within the gel matrix and emulsion droplets.

3.6 Homogeneity and Microscopic Evaluation

Microscopic analysis of prepared emulgels confirmed:

- Uniform distribution of droplets and drug particles.
- Absence of aggregates or crystal growth.
- No visible clumps or drug "hot spots" in any of the batches.
- This supports the stability and consistency of the preparation method, especially during emulsion-gel integration.

3.7 FTIR Compatibility

FTIR studies confirmed that there were no significant shifts or disappearance of characteristic peaks in drug-excipient mixtures:

- Spectra of Lornoxicam, Eugenol, and excipients (Carbopol, Tween 80, etc.) were compared individually and in combinations.
- The characteristic peaks of drugs were retained, suggesting no major chemical interactions.
- Thus, the formulation is chemically stable, with all ingredients compatible with one another.

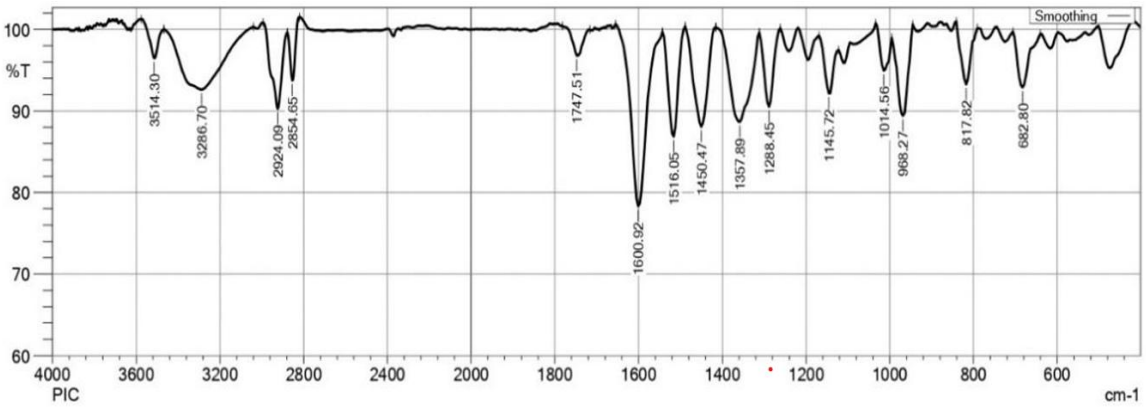


Fig: 3.1: FT-IR Spectrum of LOR

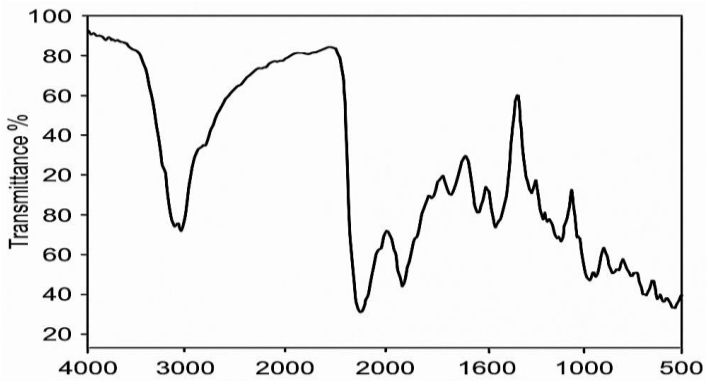


Fig 3.2: FT-IR Spectrum of Eugenol

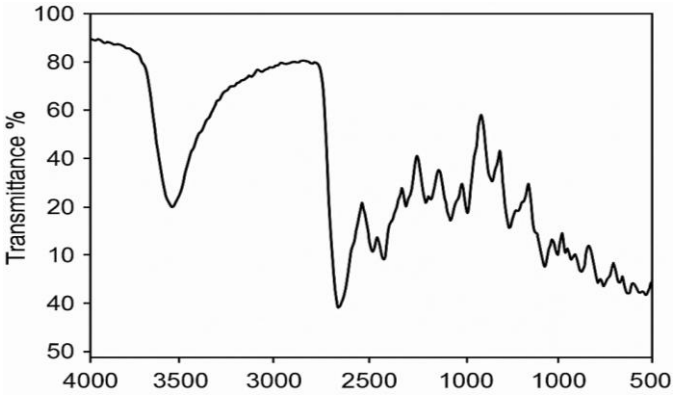


Fig 3.3: FT-IR Spectrum of Lornoxicam – Eugenol Based Emulgel for Content Uniformity

3.8 Thermal Analysis (TGA/DSC)

Thermal analysis revealed:

- Pure components and physical mixtures were stable up to ~250°C.
- TGA showed no major weight loss at formulation temperatures (~40–50°C).
- DSC thermograms of mixtures did not show significant peak shifts, supporting thermal stability and absence of eutectic interactions.
- These results suggest the emulgel can be safely processed and stored without thermal degradation.

3.9 Stability Studies

Accelerated and long-term stability tests (at 40°C/75% RH and 30°C/65% RH) showed:

- No significant changes in appearance, viscosity, pH, or drug content up to 6 months.
- Photostability testing revealed slight discoloration in clear packaging under UV/visible light, with up to 5–8% degradation of Eugenol.
- Opaque containers (e.g., aluminum tubes) preserved product stability better.
- Forced degradation studies (acid, base, oxidation) showed:
- Maximum degradation occurred in alkaline and oxidative conditions.
- HPLC identified possible degradation products, suggesting the need for antioxidant or light-protective packaging.

3.10 Viscosity and Rheology

- Rheological tests confirmed that all formulations demonstrated non-Newtonian pseudoplastic flow, with good spreadability and structural recovery:
- Viscosity at 10 s^{-1} shear rate remained stable for all formulations.
- Formulations showed thixotropy, recovering viscosity after shear, which enhances patient experience during application

3.11 Extrudability

- Extrudability was measured using a texture analyzer or standardized weight pressure.
- All formulations could be smoothly extruded from standard packaging tubes.
- F1 and F2 (lower viscosity) were easiest to extrude.
- F5 required slightly more pressure but was still within acceptable limits.
- This ensures user-friendliness and dosage control.

3.12 Microbial Load Testing

Microbial testing confirmed the absence of harmful microbial contamination:

- Total aerobic count was within pharmacopeial limits (≤100 CFU/g).
- No fungal growth or pathogenic bacteria (e.g., E. coli, S. aureus) were detected.
- Use of methylparaben as a preservative was effective.
- This confirms the microbiological safety of the emulgel

Table:- for Microbial load of Compound- A:

Dilution factor 10^1	**Microorganism**	**Microbial growth**	**Results**	
		Compound A (Formulated Emulgel)		
	Total plate count	Absent	Complies	According to the USP Guideline 1111
	Yeast & Moulds	Absent	Complies	
Dilution factor 10^2-10^6	Total plate count	Absent	Complies	
	Yeast & Moulds	Absent	Complies	
	E. coli	Absent	Complies	
	Coliform	Absent	Complies	
	Salmonella sp.	Absent	Complies	
	Staphylococcus sp.	Absent	Complies	

3.13 Drug Content Uniformity

Uniformity testing confirmed that active ingredients were evenly distributed throughout the gel:

- Assay values ranged from 97% to 102%.
- No variation between top, middle, and bottom layers of the container, indicating uniform mixing and formulation robustness.

Table : Drug Content Uniformity of LOR and Eugenol

Sample Zone	**Lornoxicam Content (% of label claim)**	**Eugenol Content (% of label claim)**
Top	98.5 ± 1.2	97.8 ± 1.5
Middle	99.1 ± 0.8	98.3 ± 1.2
Bottom	98.7 ± 1.0	97.5 ± 1.8

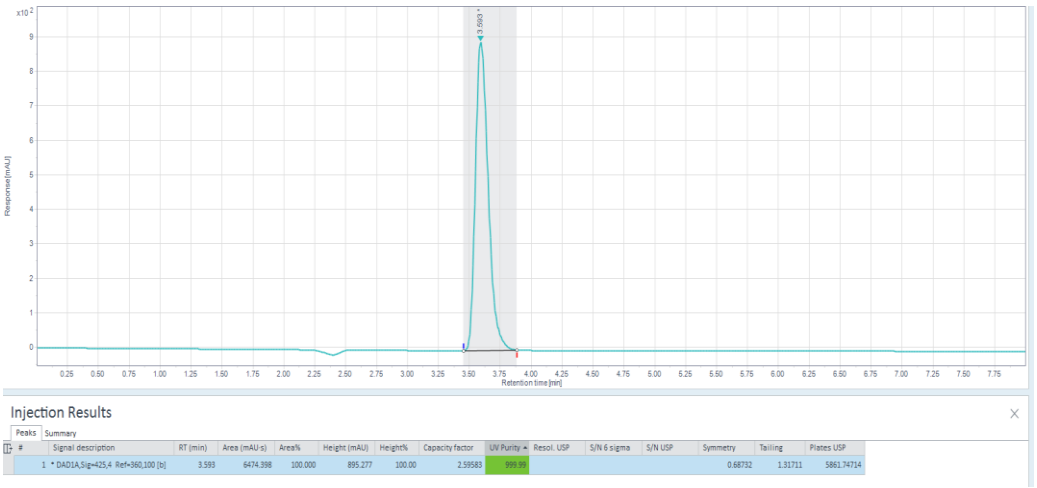


Fig 3.4: HPLC Chromatogram of Lornoxicam

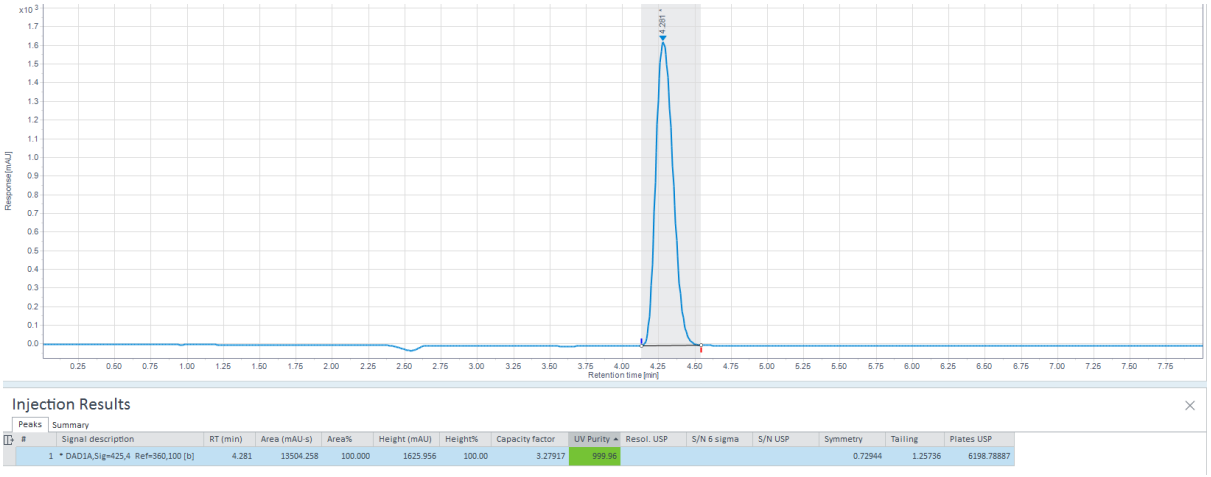


Fig 3.5: HPLC Chromatogram of Eugeno

3.14 Light Sensitivity

Photostability testing (as per ICH Q1B) showed that:

- Lornoxicam and Eugenol are both light-sensitive.
- Significant degradation (>5%) occurred in transparent packaging.
- Opaque containers protected the formulation effectively, preserving drug content and physical stability.
- Thus, light-resistant packaging is essential for product integrity.

Conclusion of Discussion

The formulation and evaluation of Lornoxicam-Eugenol-based emulgels demonstrated that:

- The combination of hydrophilic and lipophilic components was successful in forming stable, bioavailable emulgels.
- Formulation F3 offered the best balance of viscosity, spreadability, drug content, and stability.
- FTIR and thermal analysis confirmed compatibility and stability.
- Stability testing highlighted the need for light-protective and airtight packaging.

The final product is suitable for topical anti-inflammatory and analgesic applications, with good potential for patient compliance and market viability

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