*Journal of Applied Pharmaceutical Research*
*Volume 12 Issue 2, Year of Publication 2024, Page 42 – 50*
*DOI: 10.18231/j.joapr.2024.12.2.42.50*

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**Research Article**

*JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH* | *JOAPR*
*www.japtronline.com* *ISSN: 2348 – 0335*

# *FORMULATION, DEVELOPMENT, AND CHARACTERIZATION OF LORATADINE EMULGEL*

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***Article Information***
Received: 13th January 2024
Revised: 26th March 2024
Accepted: 9th April 2024
Published: 30th April 2024

**Keywords**
*Emulsion, gel, emulgel, loratadine, in-vitro, entrapment efficiency*

***ABSTRACT***
***Background:*** This study was to develop loratadine (LTD) emulgels to treat localized skin allergies. ***Method:*** Initially, the oil-in-water emulsion was prepared by 3 different types of surfactants & finally, gelling agent carbopol 940 was incorporated into the emulsion to produce emulgel (i.e., standard conventional method). ***Results:*** The developed formulations were characterized using various parameters, including particle size (PS), zeta potential (ZP), polydispersity index (PDI), entrapment efficacy (EE), pH, extrusion efficiency, physical stability, *in-vitro* drug release studies, and scanning electron microscopy (SEM). PS, EE, PDI, ZP and *In-vitro* studies range between 186.25 ± 6.42 mm (LE-F4) to 395.24 ± 8.64 mm (LE-F1), 62.38 ± 0.36 % (LE-F2) to 76.48 ± 0.69 % (LE-F4), 0.276 ± 0.02 (LE-F4) to 0.652 ± 0.02 (LE-F1), 16.45 ± 2.13 mV (LE-F1) to 29.46 ± 2.78 mV (LE-F3) and 21.90 ± 0.3 % (LE-F1) to 68.30±0.9 % (LE-F4) respectively. ***Conclusion:*** Based on all physicochemical properties, LE-F4 formulation was considered to be optimized with minimum PS (186.25±6.42 nm), PDI (0.276±0.02), satisfactory positive surface charge (23.15 ± 1.89 mV) and maximum EE (76.48±0.69 %). FTIR studies were confirmed that there is no physical interaction between drug and excipients and SEM studies revealed that vesicle size was spherical with smooth texture. A significantly greater rate of drug release (i.e., 68.30 ± 0.90%) was seen in the LTD emulgels that were made with anionic surfactant (i.e., LE-F4) and found to be good spreadability and extrudability.

## *INTRODUCTION*

Local administration (i.e., ophthalmic, rectal, vaginal) delivers drugs to the target site, which enhances drugs bioavailability and minimizes the side effects [1-3]. Topical administration is a common method for administering many different types of drugs, such as corticosteroids, antivirals, antibiotics, antiseptics, local anesthetics, and anti-neoplastics [4-6]. Now, the topical delivery system is ahead a massive consideration for researchers due to its capability to calm products on both local and systemic illnesses [7]. Compared to other dosage forms, it offers several benefits such as to prevent first pass metabolism, prevents gastro intestinal (GI) issues linked to oral dosage forms and enhances

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patient adherence [8]. Topical administration is common for local skin infections, wounds, and allergies [9]. It's beneficial when other methods are ineffective or have substantial systemic adverse effects [10-11]. Topical creams, ointments, gels, lotions, etc. are available [12]. However, both hydrophilic and hydrophobic drugs may be incorporated into emulgel system. It shows better stability by preventing the rancidity of oils in emulsion [13]. Additionally, as it is a non-invasive technique, emulgel can be easily applied by the patients without any need of skilled professionals. It has better loading capacity with controlled release [14-15]. Second-generation antihistamines treat allergic rhinitis, urticaria, discomfort, small cuts, insect bites, burns, rashes, and atopic dermatitis [16-18]. Gels are dosage form that trap large volumes of aqueous or hydroalcoholic liquid in a network of inorganic or organic polymer colloidal solid particles [19]. Compared to ointments and cream bases, they have a higher aqueous component that allows drugs to dissolve and migrate through a liquid carrier [20]. These are more user-friendly and patient-friendly. Gels have several benefits, but hydrophobic drug delivery is a drawback. Emulgels are employed to administer hydrophobic therapeutic moieties [21]. Thixotropy, greaselessness, spreadability, emollience, non-staining, longevity, transparency, environmental friendliness, and aesthetic appeal are some of the desirable features of dermatological emulgels [22].

The most often prescribed drug for allergic diseases such rhinitis, urticaria, and atopic dermatitis is loratadine (LTD) (Molecular weight = 382.88 g/mol.), a second-generation histamine H1 receptor antagonist. According to recent research, loratadine is safe and effective in emergency treatment of granulocyte-colony stimulating factors (G-CSF)-induced bone pain [23]. The goal of the study was to develop and characterize the loratadine emulgel. Investigating the ideal ratios between penetration enhancers and gelling materials was the first step in the procedure; emulgels were then produced utilizing these ratios and characterize the prepared LTD emulgels.

## *MATERIALS AND METHODS*

### Materials

Loratadine was received as a gift sample from Hetero Labs Ltd, Hyderabad, India. Hydrochloric acid (HCl) was purchased from central scientific supplies Co. Ltd., Hyderabad and remaining all reagents and chemicals purchased form S.D. fine chem. limited, Mumbai.

### Methodology

#### *Pre-formulation studies*

All the pre-formulation studies were conducted at room temperature only.

**Solubility (Equilibrium method):** To make a saturated solution, an excess amount of the drug was dissolved at room temperature in the selected quantity of solvents ((i.e., Dimethyl sulfoxide (DMSO), dimethyl fumarate (DMF), ethanol, pH, 6.8 buffer, 0.1N hydrochloric acid (HCl), citro-phosphate buffer) in a glass beaker. To disperse the undissolved drug particles, the solution was shaken occasionally for 24 h. The resultant mixture was filtered and amount of drug in filtered solution was extracted, diluted with corresponding solvents, and analyzed by UV-spectrophotometer at 270 nm [24].

#### *Melting point*

**Capillary method (n=3):** The drug was injected into dry capillaries to a depth of 6 mm. A thermometer with a heating rate of 1 °C/min provided the melting point apparatus. The thermometer's temperature was noted when the drug was modified into a liquid state [25].

**Determination of maximum wavelength:** 100 mg of loratadine transferred into 100 ml volumetric flask by dissolving with pH 5.0 citrate-phosphate buffer (i.e., 1 mg/ml or 1000 µg/ml) [26].

**Construction of calibration curve:** Using 10 ml volumetric flask by above stock prepare 2, 4, 6, 8 and 10 µg/ml with pH 5.0 citrate phosphate buffer then record the absorbance using UV–visible spectrophotometer (Elico, SL210, Hyderabad) at 270 nm [27].

#### *Compatibility studies*

**Fourier Transform Infrared (FTIR) Spectroscopy:** The FT-IR spectrometer (Shimadzu, Tokyo, Japan), equipped with a diamond horizontal attenuated total reflectance (ATR) sampling attachment, was used (i.e., 5 mg) to analyze both the pure drug and ideal loaded emulgel formulations. The samples were scanned at a resolution of 4 $cm^{-1}$ from 400 to 4000 $cm^{-1}$. [28-29].

### Formulation development of emulgel

Table 1 enlists the excipient amounts for various emulgel formulations and based on literature various excipient were selected for the study. The gel constituent was prepared by dissolving carbopol-940 in water and stir moderately to produce a homogeneous mixture. Triethanolamine (TEA) stabilized pH between 6.0 and 6.5. The oil phase was made by dissolving span 40 in liquid paraffin and the aqueous component by dissolving tween 20/SLS in distilled water. It was necessary to dissolve the

methylparaben in propylene glycol and the extract in ethanol before mixing them with the aqueous phase to maintain the emulsion. Separately, the oil and water phases were heated in water baths to 70°C. Once the aqueous and oil phases were combined, the homogenizer was run at 3000 rpm for 10 min while stirring continuously. Then the mixture was cooled to room temperature (i.e., 25 ± 2°C). Finally, emulsion and gel were mixed (i.e., 1:1) and gently stirred to make emulgel [30-32].

**Table 1: Formulation development of loratadine emulgels (Ingredients in %w/v)**

| Ingredients | LE-F1 | LE-F2 | LE-F3 | LE-F4 | LE-F5 |
|---|---|---|---|---|---|
| Loratadine (g) | 1 | 1 | 1 | 1 | 1 |
| Ethanol (ml) | 5 | 5 | 5 | 5 | 5 |
| Propylene glycol (g) | 5 | 5 | 5 | 5 | 5 |
| Methyl paraben (g) | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 |
| Span 40 (g) | 2.1 | - | - | - | 1.5 |
| Tween 20 (g) | 0.9 | - | 3 | - | 1.5 |
| SLS (g) | - | - | - | 3 | - |
| EDTA (g) | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| Liquid paraffin (g) | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 |
| Propyl paraben (g) | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| Carbopol 940 (g) | 1 | 1 | 1 | 1 | 1 |
| Distilled water (ml) | 20 | 20 | 20 | 20 | 20 |

SLS= Sodium lauryl sulphate, EDTA= ethylene diamine tetra acetic acid

## Characterization

### *Physical characterization*

The prepared loratadine emulgels were visually inspected for color, homogeneity, consistency, and phase separation [33].

**pH:** The pH was checked directly by dipping the electrode into the loratadine emulgel and allowing it to equilibrate for 2 h. Then, the pH was measured (n=3) by a calibrated pH meter maintained at 25°C [34].

**Particle size (PS):** PS and size distribution were measured by particle size/zeta potential analyzer. 5 mW He-Ne laser was used with a scattering angle of 90º and 25ºC at a wavelength of 632.80 nm. We used distilled water to dilute each freshly made sample to the correct concentration [35].

**Zeta potential (ZP) and polydispersity index (PDI):** To get the ideal (i.e., range of 50-200 for measurements) Kcps (kilo counts per second), 100 µL of the produced loratadine emulgel was diluted to 5 mL using double-distilled water. The Smolochowski equation was used to determine the Zeta potential directly [36-37].

$$\zeta = \varepsilon\mu/\eta$$

Where, ζ = ZP, µ - Electrophoretic mobility (EM); Ɛ= Electric permittivity of the liquid (EPL); η = Viscosity of the liquid (VL).

**Entrapment efficiency (EE):** RP-C-18 analytical column (250 mm, 4.6 mm i.d., 5 mm; Merck, Mumbai, India), SPD-20A UV-Visible variable wavelength detector with a deuterium lamp, and 1 mL/min. acetonitrile-water (80:20) mobile phase was utilized [38]. To dissolve the unloaded drug particles, 1 mL of prepared emulgel was mixed with 2 mL of diluent. Centrifuged at 8000 rpm for 20 min., the diluted sample was placed in the top chamber of the ultracentrifuge tube. The ingredients remain in the top of the chamber, while the free drug (i.e., aqueous phase) passed through the semi-permeable membrane into the bottom chamber. Using an auto sampler and a dual wavelength absorbance detector, HPLC was used to quantify the flow through in the lower chamber. The samples were dissolved in acetonitrile before being injected into a 20 µL sample loop. The loratadine-loaded emulsion had a retention time of 4.56 min. while maintaining a flow rate of 1 mL/min.

In preparation for future shelf stability testing, the emulsions were lyophilized and kept at 4°C. Using these equations, we were able to determine the EE [39]:

$$\%\, EE \;=\; \frac{Amount\ of\ drug\ in\ emulsion}{Total\ amount\ of\ drug\ added} \times 100$$

**In-vitro release studies**

**Diffusion technique:** After checking for leaks, the activated dialysis bag was suspended in a glass beaker with 100 mL citrate phosphate buffer and 1% SLS, acting as a receptor compartment at 37 ± 0.5 ºC, with a magnetic stirrer, collect 1mL aliquots from receptor compartment and replaced with fresh media at 1, 2, 3, 4 and 5 h. Testing was done using UV-visible spectrophotometer [40].

**Phase separation or creaming**

The prepared emulgels were centrifuged at ambient temperature under 6000 rpm for 10 min; later, the system was visually inspected [41].

**Extrudability**

Prepared emulgel formulations was filled into closed collapsible tubes, pushed firmly at the crimped end, and cramped to prevent rollback. The cap was removed to extrude the gel, and the

resulting extrudate was weighed. The % of gel extrusion was calculated and finally the extrudability was confirmed according to the following specifications. (>90% extrudability: great, >80%: acceptable, >70%: fair) [42]. The prepared LTD emulgels had good physical properties including a pH range of 6.0 to 6.5, great homogeneity, and thermodynamic stability (i.e., no phase separation). Viscosity, spreadability, and extrudability showed little variations as a function of temperature.

**Scanning electron microscopy (SEM)**

The morphology was studied by scanning electron microscope (Hitachi, Tokyo, Japan). Loratadine emulgel was suitably diluted with double distilled water (1 in 100). A high vacuum was used to observe the sample under various magnifications after placing a drop on the sample holder and letting it air dry. The accelerating voltage was set at 15,000 volts [43].

## *RESULTS AND DISCUSSIONS*

### Pre-formulation Studies

**Solubility:** The equilibrium solubility method was used to conduct solubility investigations in several solvents (i.e., shown in Table 2) using a cyclone mixer. The solubility of loratadine in citro-phosphate buffer (pH 5) was found to be 0.59±2.01mg/mL, whereas in DMSO, it was 48.56±3.25 mg/mL at 25°C, and solubility statistics are included in Table 2.

**Table 2: Solubility of loratadine in different solvents**

| Solvents | Solubility (mg/ml) |
|---|---|
| DMSO | 48.56±3.25 |
| DMF | 26.82±3.45 |
| Ethanol | 38.27±4.15 |
| pH 6.8 Buffer | 0.001±2.08 |
| 0.1N HCl (pH 1.2) | 4.52±3.27 |
| Citro-phosphate Buffer (pH 5) | 0.59±2.01 |

According to previous research and current findings, loratadine has an exceedingly poor water solubility; however, by incorporating a hydrophilic polymer that is water-miscible into each solvent, this solubility can be significantly enhanced.

**Melting point (n=3)**: Capillary fusion method used to find out drug's melting point and that was measured fell within the acceptable range. Melting point of loratadine by glass capillary method and melting point apparatus was found to 134±1.59°C, the observed melting point of loratadine was confirmed with the standard melting point of loratadine (134-136°C) reported in literature.

**Determination of $\lambda_{max}$:** Using phosphate buffer scan in UV-visible spectrophotometer between 200-400 nm and found maximum absorbance at 270 nm. This maximum wavelength is used for further studies.

**Construction of standard graph:** The absorbance values were analyzed for the above-prepared solutions (i.e., 4 to 20 µg/ml) at 270 nm, and a graph was plotted between concentrations versus absorbance values shown in Figure 1. The calibration curve showed good linearity with $R^2$ value of 0.996

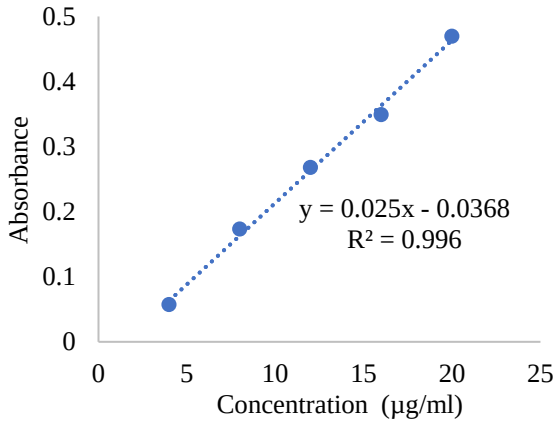


**Figure 1: Standard graph of loratadine**

All the above-mentioned pre-formulation studies was evident that the results may helpful in the formulation of Loratadine emulgels.

### Fourier Transform Infrared (FTIR) Spectroscopy

Loratadine has unique (C-H) transmittance bands in its Fourier transform infrared spectra. The stretching of carbon atoms includes 1702.28 C=O, 713.22 C-Cl, 3037.27 C-H, 1591.37 C=N, 2982.06 C-H, aromatic, 1579.60 C-C, skeletal, and 1355.68 C-N in tertiary amines. Figures 2 and 3 display the functional groups linked to peaks seen at various wave numbers. Similar to the loratadine functional group, the main peaks are also present. Therefore, loratadine was determined to be the sample, and the improved formulation showed the same peaks.

### Preparation of loratadine emulgels

According to table 1, several emulgel formulations were developed as per above mentioned procedure shown in figure 4.

### Characterization of loratadine emulgels

#### *Physical characterization of loratadine emulgels*

After 24 h, the prepared emulgels were tested for color (i.e., white to yellow white), physical appearance (i.e., stable) was semi solid, homogeneity and consistency was excellent. They

were white, homogeneous, and transparent to white opaque, viscous gel compositions with no phase separation and all the results shown in table 4.

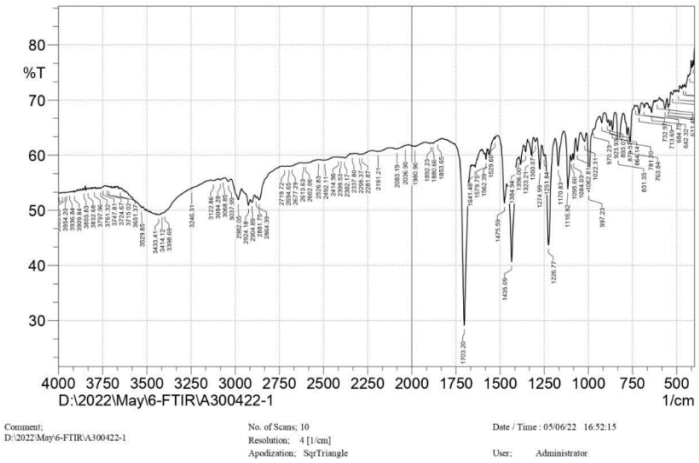


**Figure 2: FTIR spectrum of Pure API (i.e., loratadine)**

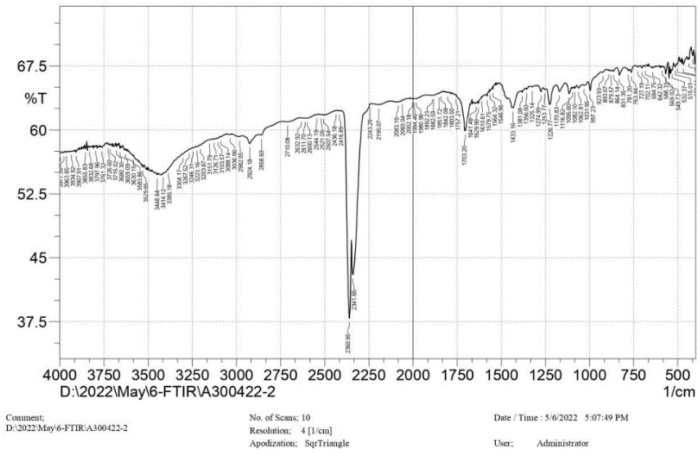


**Figure 3: FTIR spectrum of optimized formulation loratadine emulgel (i.e., LE-F4)**

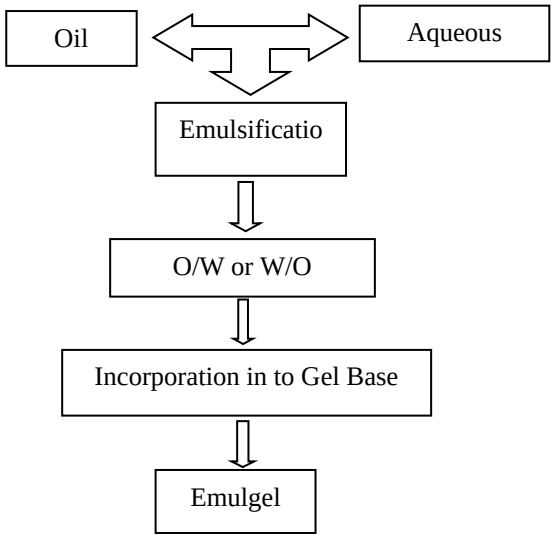


**Figure 4: Flow chart of preparation method**

**pH:** The emulgel compositions' pH ranged from 6.09±0.01 to 6.34±0.03 and would not irritate skin. All results included in table 4.

**PS and size distribution:** Table 3 and figure 5 displayed the findings of the experiments, which were given as the mean size ± standard deviation (SD).

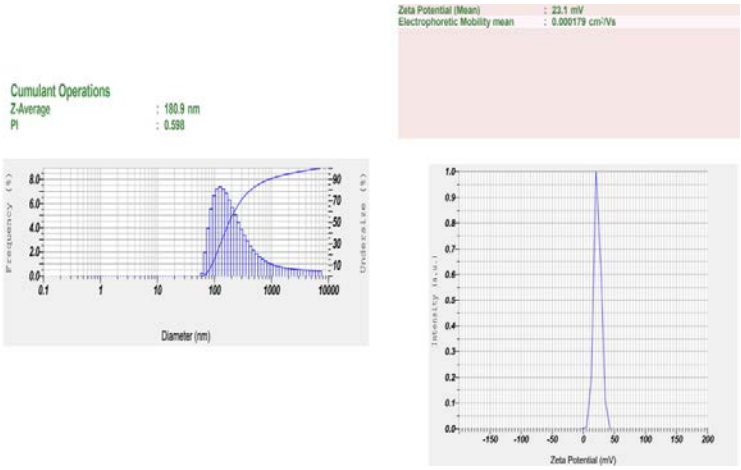


**Figure 5: Particle size, size distribution, and zeta potential of optimized formulation (i.e., LE-F4)**

**Table 3: Particle size, entrapment efficiency, polydispersity index, zeta potential results of all prepared loratadine emulgel formulations**

| F. Code | PS (nm) | EE (%) | PDI | ZP (mV) |
|---|---|---|---|---|
| LE-F1 | 395.24±8.64 | 65.31±0.42 | 0.652±0.02 | 16.45 ± 2.13 |
| LE-F2 | 254.36±5.63 | 62.38±0.36 | 0.592±0.04 | 23.16 ± 2.54 |
| LE-F3 | 326.74±4.38 | 67.35±0.85 | 0.462±0.03 | 29.46 ± 2.78 |
| LE-F4 | 186.25±6.42 | 76.48±0.69 | 0.276±0.02 | 23.15 ± 1.89 |
| LE-F5 | 257.31±2.39 | 65.35±0.41 | 0.358±0.01 | 19.86 ± 2.44 |

**Table 4: Evaluation parameters of prepared loratadine emulgels**

| | Color | pH | Extrudability | Phase separation |
|---|---|---|---|---|
| LE-F1 | Yellow | 6.09±0.01 | 90% | No |
| LE-F2 | White | 6.14±0.03 | 89% | No |
| LE-F3 | White | 6.21±0.02 | 95% | No |
| LE-F4 | Milky white | 6.18±0.02 | 96% | No |
| LE-F5 | Pale Yellow | 6.34±0.03 | 94% | No |

**ZP and PDI**

Table 3 and figure 5 show the results of directly determining the ZP from the equation using the Smolochowski equation, with the mean size ± standard deviation (SD) being indicated.

**EE**

In this investigation, the amount of loratadine that remained in the filtered emulsion relative to the amount that was initially added was used as a measure of the drug incorporation efficiency. Table 3 contains the outcomes of the EE.

**In-vitro drug release studies**

Drug release profiles of all prepared loratadine emulgel formulations shown in Figure 6. The order of drug release was LE-F4 > LE-F3 > LE-F5 > LE-F2 > LE-F1. LE-F4 formulation showed greater drug release (i.e., 68.30±0.9% in 5 h) when compare to other formulations. This happens because of difference in the HLB values of surfactants used in emulgel. HLB represents the balance between the hydrophilic and lipophilic properties of a surfactant. In emulsified liquid systems, the HLB value of the surfactant plays a crucial role in determining how efficiently drugs are released from various formulations and significantly influences drug release. Hence, from the findings it confirmed that LE-F4 formulation is best than other formulations, as LE-F4 contains SLS as surfactant with HLB 40 and other preparations contain Tween 20 and Span 40 as surfactant with HLB values 16.7 and 6.7 respectively. The higher HLB values tend to enhance the drug release from emulgels. The presence of these surfactant with higher HLB induces change in solid-liquid interface of emulgel from hydrophobic to hydrophilic leading to decline in contact angle with enhanced swelling rate and increases the dissolution rate of polymer matrix and enhances water ingress. As the HLB of surfactants in gel increased, release was shifted from non Fickian diffusion and/or partially erosion-controlled release to Fickian diffusion. Therefore, understanding the HLB of surfactants is essential for optimizing drug release in various formulations.

**Phase separation**

The prepared loratadine emulgels passed a centrifugation test for physical stability without phase separation or creaming and shown in table 4.

**Extrudability**

The gel compositions (i.e., LE-F1 to LE-F5) have exceptional extrudabilities, as shown in Table 4.

**Scanning electron microscopy (SEM)**

The SEM was used to investigate the morphology of emulgel, and the results showed that the particles were of the same size throughout both magnifications and were spaced quite far away from one another. All the morphological results are shown in Figure 7.

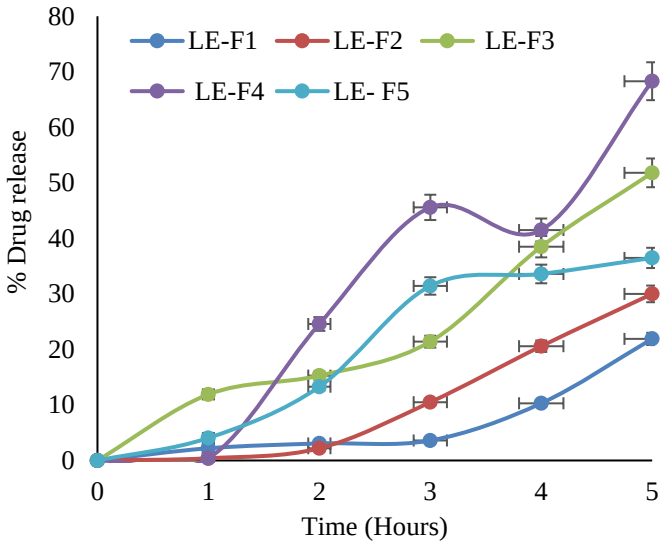


**Figure 6: In-vitro drug release study profiles of prepared loratadine emulgels**

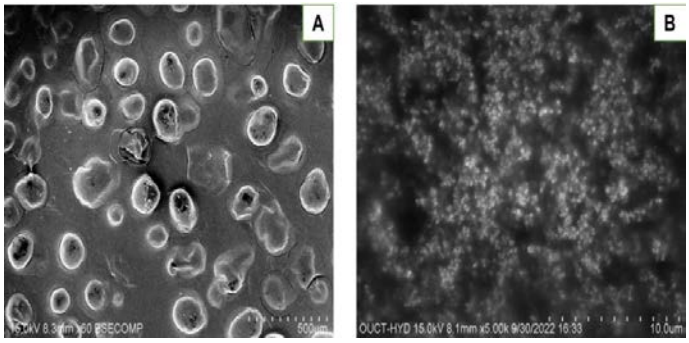


**Figure 7: Morphological structure of optimized (i.e., LE-F4) formulation with different magnifications**

In contemporary practice, comparative literature and findings offer a unique chance to explore concepts across boundaries.

***CONCLUSION***

In getting closer years, topical drug delivery will be widely employed to improve patient compliance. This new drug delivery is appealing since emulgel improves spreadability, viscosity, and extrusion. They will also load hydrophobic drug in water-soluble gel bases for long-term stability. Loratadine topical emulgels were also created and tested for rheology, spreading coefficient, and in-vitro release. The test formulations were released from emulgels in-vitro to measure drug release rate and duration. Based on the results obtained, LE-F4

preparation was indicated to be satisfactory with lower particle size and the least PDI of 186.25±6.42 and 0.276±0.02 respectively, showing the highest entrapment of drug of 76.48±0.69% with positive vesicle surface charge of 23.15 ± 1.89mV. In-vitro experiments indicated formulation LE-F4 released 68.30±0.9% in 5 h. Thus, loratadine emulgel can be administered as a topical anti-inflammatory analgesic. FTIR studies showed reproducible characteristic peaks in both the FTIR spectrum of the drug and optimized formulation; this reveals that the excipients used for the study were safe and compatible without physical interaction between the drug and excipients. SEM studies confirmed the vesicle morphology with smooth texture. The characteristics of the LTD emulgels were more extensive, indicating a firm gel with high consistency, good spreadability, and extrudability suitable for topical application. Overall, research findings indicate that LTD-loaded emulgels may be a viable option for treating allergic skin diseases topically and giving the scope for further ex vivo and in vivo evaluation studies to determine permeation and toxicity.

***FINANCIAL ASSISTANCE***
Nil

***CONFLICT OF INTEREST***
The authors declare no conflict of interest

***AUTHOR CONTRIBUTION***
Rajendra Kumar Jadi contributed to conceptualization and methodology. Chandana Setty Sharaff and Pranay Renukuntla conducted characterization and formal analysis. Himabindu Peddapalli wrote the original draft. Mounika Kuchukuntla and Vasudha Bakshi reviewed and edited the draft. All authors have read and agreed to the published version of the manuscript.

***ACKNOWLEDGMENT***
The authors are thankful to Anurag University, Hyderabad, and Telangana, India, for providing facilities and carrying out the work

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