World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

Check for updates

Formulation and development of herbal ingredients loaded Emulgel

Surendra Ahirwar * and Dharmendra Jain

Department of Pharmaceutical sciences, Dr. Harisingh Gour University, Sagar, Madhya Pradesh, India.

World Journal of Biology Pharmacy and Health Sciences, 2023, 13(02), 147–156

Publication history: Received on 01 January 2023; revised on 07 February 2023; accepted on 09 February 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.13.2.0091

Abstract

The present study aims to develop and evaluate an emulgel that contains curcumin, clove oil, and basil oil for the treatment of mouth ulcers. Emulgels have become a potentially effective method of delivering hydrophobic medications. Menthol was used as a penetration enhancer, which also provides cooling effect to ulcers, whereas clove oil also acts as a penetration enhancer. The herbal medicines such as clove oil, tulsi (basil) oil, curcumin, and menthol have very good antiulcer activity. Clove oil has analgesic and antioxidant activity whereas, basil oil obtained from ocimum basilicum plants has antimicrobial and analgesic activity. Curcumin is obtained from curcuma longa which acts as anti-inflammatory and as antiseptic, whereas menthol provides cooling to the ulcers or oral sore. Five formulations were prepared and evaluated for viscosity, spreadability, extrudability, diffusion tests, and short-term stability. At the end of the five-hour investigation, the optimised formulation (E3G3S5T2) had showed drugs (clove, basil, and curcumin) release of 79 ± 3.2%, 72.22 ± 3.1%, and 72.07 ± 4.8% respectively. From the study, it can be suggested that the emulgel can be delivered and used topically and has better penetrating capabilities.

Keywords: Mouth ulcers; Oral sore; Herbal Medicine; Volatile oils; Emulgel

1. Introduction

Oral ulceration is one of the most common conditions that affect the oral mucosa. When the epithelium and lamina propria are damaged, the condition is referred to as an ulcer [1]. Oral ulcers can be a symptom of many systemic illnesses, including inflammatory bowel disease, and a number of contributing factors have been identified like systemic illness, including its nature, site, duration, and frequency, causes oral ulcers [2]. Patients and medical professionals believe that the peroral route is the most convenient way to administer medication [3]. The environment of oral cavity has 37°C temperature, pH range from 5.75 to 7.05, which act as buffer in oral cavity and composition of oral fluid is water (99.5%), organic compounds and inorganic elements are respectively (0.3%) and (0.2%) [4, 5]. There are many commercially available products that can be used to treat aphthous ulcers, including vitamin B_{12} tablets, benzydamine hydrochloride mouthwash or spray, steroid lozenges, and local anaesthetics.[6] There are some limitations of commercially available dosage forms such as tablets take more time to give its action, mouthwashes rinse very fast so they are unable to give full effect of drugs [7]. In case of spray the wastage of formulation occur and lozenges also take the time for action as compared to emulgel [8].

Emulgel are a mixture of an emulsion and a gel, as their name suggests. Drugs are delivered to the skin via emulsions of water-in-oil and oil-in-water types. They are highly capable of penetrating the skin.[9] According to the BCS classification systems, emulgel is a preferable option for class II drugs with weak solubility and high permeability[10]. In the present study the herbal medicines such as clove oil, basil oil and curcumin were used to prepare emulgel formulation. Clove oil obtained from *syzygium aromaticum* plants have potent analgesic/pain reducing activity by inhibiting the capsaicin receptors. [11] Whereas tulsi (basil) oil was obtained from *ocimum basilicum* plants. It has antimicrobial, anti-inflammatory and analgesic activity [12]. Curcumin is obtained from *curcuma longa* which acts as

* Corresponding author: SURENDRA AHIRWAR

anti-inflammatory and antiseptic by inhibiting the synthesis of prostaglandin, whereas menthol was obtained from *mentha piperita* plants, it provides cooling to the ulcers or oral sore [13, 14]. A crosslinked polyacrylic acid polymer, carbopol 940 was used for preparation of gel phase. It is a highly effective rheology modifier that may produce high viscosity and clear gels or hydro-alcoholic gels and creams that sparkle [15, 16].

The purpose of the present study was to develop, optimize and characterize, the emulgel of essential oils and herbal ingredients for the treatment of mouth ulcers with reducing the drawbacks of marketed formulations i.e. mouthwashes, sprays and lozenges.

2. Material and methods

2.1. Materials

Carbopol 940 was received from the chemical store of Department of pharmaceutical sciences, Dr. Harisingh Gour University, Sagar. Basil pure and natural therapeutic grade essential oil was purchased from Himanshu store, 100-Shivshakti Nagar, Meerut. Clove oil was purchased from Kedarnath Pharmacy damdama, Siandrarao, Hathras. Curcumin was purchased from Trinath Ayurveda and Herbal (OPC) private limited, Domalguda, Hyderabad. Menthol crystals 100% pure were purchased from Turfy private limited, Joshi colony I.P. Extension Delhi. Tween80, Span80, Propylene glycol, Methyl paraben and propyl paraben were received from chemical store of Department of pharmaceutical sciences, Dr. Harisingh Gour University, Sagar. Honey was purchased from Patanjali. Distilled water received from distillation plant of Department of pharmaceutical sciences, Dr. Harisingh Gour University, Sagar.

2.2. Pre-formulation studies

2.2.1. Physical identification

The organoleptic and physical properties i.e., physical state, color, odor, melting point, boiling point, and acid value were determined and identified the purity of drugs i.e., clove oil, basil oil, and curcumin.

2.2.2. GC-MS

Gas chromatography-mass spectroscopy (GC-MS) was performed for the identification of active constituents of essential oils i.e., clove oil, basil oil. The identification of active constituents of clove oil and basil oil by GC-MS were done at 252 °C and 215 °C respectively [17].

2.2.3. Differential Scanning Calorimetry of Curcumin

Differential scanning calorimetry (DSC) analysis of curcumin was performed to examine the phase behaviour of pure curcumin. Curcumin powder was placed into the DSC pan. In a nitrogen gas atmosphere, the sample was heated from 50 to 300 °C at a rate of 10 °C/min to calculate the melting enthalpy (Hm) and melting point (Tm) of curcumin. Utilizing a thermal analysis device (Ta Instruments NETZSCH STA 449 F_1 Jupiter, India), the curcumin thermogravimetric analysis (TGA) curve of curcumin was recorded [18].

2.2.4. Solubility studies

The choice of excipients to be incorporated in the formulation was determined by solubility studies. It was qualitatively assessed whether drugs were soluble in liquid paraffin, propylene glycol, span 80, tween 80, methanol, and distilled water.

2.2.5. Drug excipients compatibility study by FTIR spectroscopy

The compatibility of the drugs with the excipients was determined using FT-IR spectroscopy. The existence of common peaks were confirmed by comparing the spectra of each drug with the final formulation containing excipients.

2.3. Formulation of emulgel

2.3.1. Preparation of the gel

The gel phase of emulgel formulation was prepared by dispersing Carbopol 940 in purified water with stirring by mechanical stirrer at 200 rpm. After that the pH of gel was adjusted between 6.0 – 6.8 using triethanolamine.

2.3.2. Preparation of emulsion

The emulsion was prepared by taking the oil phase i.e. liquid paraffin as a solvent for basil oil (5% w/w), clove oil (8% w/w) curcumin (0.2% w/w), menthol (5% w/w) and span80 in a beaker and in another beaker propylene glycol, methyl paraben and propyl paraben were taken. Then the required amount of water with honey was added in a beaker and tween80 was added in this water. Then both oil phase and aqueous phase were heated at 60-70°C and mixed together with continuous stirring by mechanical stirrer at 200 rpm at room temperature, till the emulsion was formed. (Table 1)

2.3.3. Preparation of Emulgel

The emulgel was prepared by mixing the emulsion with gel in 1:1 ratio with continuous stirring by a mechanical stirrer at 200 rpm for 60 minutes. pH was adjusted by using triethanolamine.

Table 1 Composition of different emulgel formulations (%w/w)

Ingredients	**E1**	**E2**	**E3**	**E3G1**	**E3G2**	**E3G3**	**E3G4**	**E3G5**
Liquid paraffin	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Carbopol 940	-	-	-	0.25	0.5	0.75	1	1.5
Span 80	1	2	3	3	3	3	3	3
Tween 80	0.5	1	1.5	1.5	1.5	1.5	1.5	1.5
Propylene glycol	5	5	5	5	5	5	5	5
Methyl paraben	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Propyl paraben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Honey	10	10	10	10	10	10	10	10
Triethanolamine	-	-	-	QS	QS	QS	QS	QS
Purified water	100 QS	100 QS	100 QS	100 QS	100 QS	100 QS	100 QS	100 QS

2.4. Optimization

2.4.1. Optimization of Emulsion

The optimization of the emulsion was performed by optimizing the quantity of emulsifying agent i.e., span 80 and tween 80 with respect to viscosity and stability.

Table 2 Optimization of emulsifying agent concentration based on viscosity and stability

Formulation	**Span80:Tween80 (%w/w)**	**Viscosity (cps)**	**Stability**	
			Phase separation	**Creaming**
E1	1:0.5	117 ± 2.64	Phase separate	Not observed
E2	2:1	121 ± 2.00	No separation	Creaming observed
E3	3:1.5	119 ± 1.00	No separation	Not observed

The E3 formulation contains 3:1.5 ratio of span80: tween80 showed 119 ± 1.00 cps viscosity, and no phase separation, and no creaming was observed, so formulation E3 was chosen as an optimized formulation.

2.4.2. Optimization of Emulgel formulation

The prepared emulgels were optimized by determining quantity of the polymer (Carbopol 940) and optimum processing variables (stirring speed and stirring time) based on viscosity, spreadability, phase separation, and homogenicity.

Table 3 Optimization of polymer concentration based on viscosity and spreadability

Formulation	Carbopol 940 concentration (% w/w)	Viscosity (cps)	Spreadability (cm)
E3G1	0.25	16830 ± 30.55	48.00 ± 0.69
E3G2	0.5	19470 ± 20.16	46.66 ± 1.34
E3G3	0.75	27690 ± 25.0	43.33 ± 0.38
E3G4	1.00	29400 ± 60.33	40.00 ± 0.33
E3G5	1.5	32340 ± 70.00	36.00 ± 0.19

The formulation E3G3 shows optimum viscosity and good spreadability, so the concentration 0.75 % w/w of Carbopol 940 was selected or optimized formulation for further studies.

2.4.3. Optimization of Process variables

During formulation of emulgels the stirring speed 200 rpm for 60 minutes was considered as optimum, because formulation E3G3S5 was shown optimum viscosity, excellent homogenicity and phase separation was not observed.

Table 4 Optimization of stirring speed based on viscosity, phase separation and homogenicity

Formulation	Stirring Speed (rpm) for 60 minutes.	Viscosity (cps)	Phase separation	Homogenicity
E3G3S1	80	29540 ± 20.66	Not observed	Poor
E3G3S2	100	29020 ± 15.00	Not observed	Poor
E3G3S3	120	28350 ± 25.55	Observed	Good
E3G3S4	150	27700 ± 30.16	Not observed	Good
E3G3S5	200	27000 ± 10.00	Not observed	Excellent

Table 5 Optimization of stirring time based on viscosity, phase separation and homogenicity

Formulation	Stirring Time (minutes) at 200 rpm	Viscosity (cps)	Phase separation	Homogenicity
E3G3S5T1	30	28270 ± 20.00	Not observed	Good
E3G3S5T2	60	27500 ± 30.55	Not observed	Excellent
E3G3S5T3	90	26850 ± 30.00	Observed	Good
E3G3S5T4	120	26200 ± 25.16	Observed	Poor
E3G3S5T5	150	25900 ± 10.00	Observed	Poor

During formulation of emulgels the stirring time 60 minutes at 200 rpm was chosen as optimum, because formulation E3G3S5T2 had showed optimum viscosity, excellent homogenicity and phase separation not observed.

2.5. Evaluation of emulgel

2.5.1. Physical parameters of emulgel

All prepared formulations were visually checked for the color, appearance, phase separation and homogenicity and pH using digital pH meter.

2.5.2. Viscosity

At room temperature, Brookefield digital viscometer was used to measure the viscosity of prepared formulations with spindle no. – 64s at 20rpm till 10 minutes.

2.5.3. Spreadability

Two glass slides were used to test the spreadability of emulgel formulations. One slide was covered with the formulation whose spreadability was to be assessed, and the other slide was placed on top, sandwiching the gel between the two. The sticking gel was removed after the slides were pushed together to remove any air that might have been present. 20 g weight was securely fastened to the upper slide. The time taken by the upper slide to completely detach from the lower slide was noted [9].

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

Where M is the weight tied to upper slide, L is length of glass slide and T is time taken to separate the slide.

2.5.4. Swelling Index

1g emulgel formulations were taken into porous aluminium foil and kept in a 50 ml beaker with 10 ml of distilled water. The samples were removed from the beaker at various time intervals and left undisturbed in a dry area for a while so that the exterior liquid could be drained and then weighed. The swelling index were determined using the formula: [19]

$$\text{Swelling Index (SW)}\% = [\ (Wt - Wo)/Wo] \times 100$$

Where (SW) % = Equilibrium percent swelling,

Wt = Weight of swollen emulgel after time t,

Wo = Original weight of emulgel at zero time.

2.5.5. Extrudability

A closed, collapsible tube carrying emulgel formulations was forcibly pressed at the crimped end to ascertain emulgels extrudability. The formulations extruded until the pressure subsided after the cap was removed. It was calculated as the weight in grams. Needed to extrude a 0.5 cm ribbon of the formulation in 10 seconds [20].

2.5.6. Phase separation testing by centrifugation

6g of emulgel formulation was taken in centrifuge tubes and centrifuged at 4000 RPM for 10 min. After 10 minutes all formulations were observed for any phase separation occurrence [19].

2.5.7. Drug content

1g of emulgel was taken and dissolved in 10 ml methanol and filtered using Whatman filter paper. Then 1ml of filtrate was taken in a 10 ml of volumetric flask and diluted with methanol up to 10ml. After that, the absorbance was taken using UV-Visible Spectroscopy at 277nm, 307nm, and 416nm for determining clove oil basil oil and curcumin content respectively [21].

2.5.8. In vitro drug release study

In-vitro studies were done by using membrane diffusion technique. The dialysis membrane was then immersed for 24 hours in dissolution media i.e. phosphate buffer (pH 6.8) and methanol in 9:1 ratio. 1g formulation was precisely weighed and kept in dialysis membrane. The dialysis membrane bag was floated in 100 ml of dissolution media that was kept at a constant temperature 37±2°C and the membrane just contacting the surface of the receptor medium. Using Teflon-coated magnetic beads, the dissolution media was agitated at 100 rpm. To maintain sink conditions, 5ml volume of the samples were regularly withdrawn and replaced with an equivalent volume of the receptor media at intervals of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 hours. The samples were appropriately diluted with receptor media before being examined by UV-visible spectrophotometer at 277nm, 307nm, and 423nm for clove oil, basil oil, and curcumin respectively, whereas dissolution media was used as blank.

3. Results and discussion

3.1. Pre-formulation studies

3.1.1. Physical identification of drug

The drugs i.e. clove oil, basil oil, curcumin identification studies were done to focus on physio-chemical properties. Clove oil and basil oil were pale-yellow liquid and had sweet spicy and sweet pungent odor respectively. Curcumin was odorless yellow powder.

The melting point of curcumin powder was found to be 180 °C-182°C and boiling point of clove oil and basil oil were found to be 148°C- 250°C and 210°C- 212 °C respectively. Acid values of clove oil and basil oil were found to be 4.5 and 0.8 respectively.

3.1.2. GC-MS of clove oil and basil oil

The gas chromatography-mass spectroscopy of clove oil and basil oil was done and found following active constituents eugenol in clove oil and linalool, methyl chavicol and eugenol in basil oil which indicated the purity of oils.

3.1.3. Differential Scanning Calorimetry of Curcumin

The thermal behavior of curcumin was measured at temperatures ranging from 25 to 400 °C. The melting temperature of curcumin was 170 °C according to the DSC thermogram of curcumin. Curcumin was thermally stable at temperatures lower than 180 °C, as can be shown clearly in Figure 1.

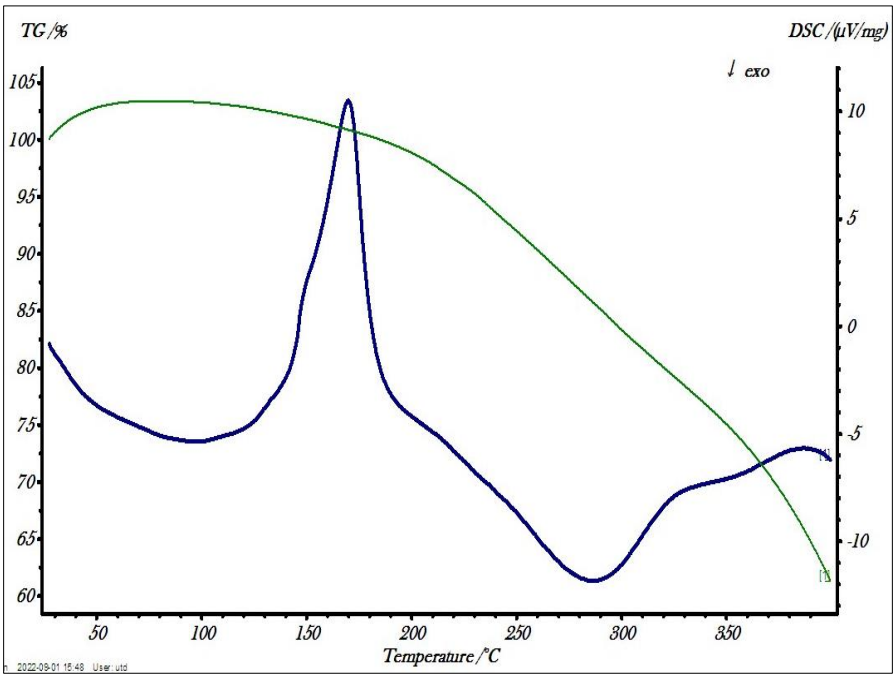

Figure 1 Differential Scanning Calorimetry of Curcumin

3.1.4. Solubility studies

Liquid paraffin and span80 were used as oil phase for preparation of emulgel because drugs were soluble and miscible in these solvents.

Table 6 Solubility and miscibility of drugs i.e. curcumin, clove oil and basil oil

Solvents	Curcumin	Clove oil	Basil oil
Liquid paraffin	Soluble	Miscible	Miscible
Methanol	Soluble	Miscible	Miscible
Tween 80	Insoluble	Miscible	Miscible
Span 80	Soluble	Miscible	Miscible
Propylene glycol	Insoluble	Immiscible	Immiscible
Distilled Water	Insoluble	Immiscible	Immiscible

3.1.5. Compatibility studies by FTIR

Figure 2 shows the infrared spectra of curcumin, clove oil, basil oil, carbopol 940 and emulgel formulation, respectively.

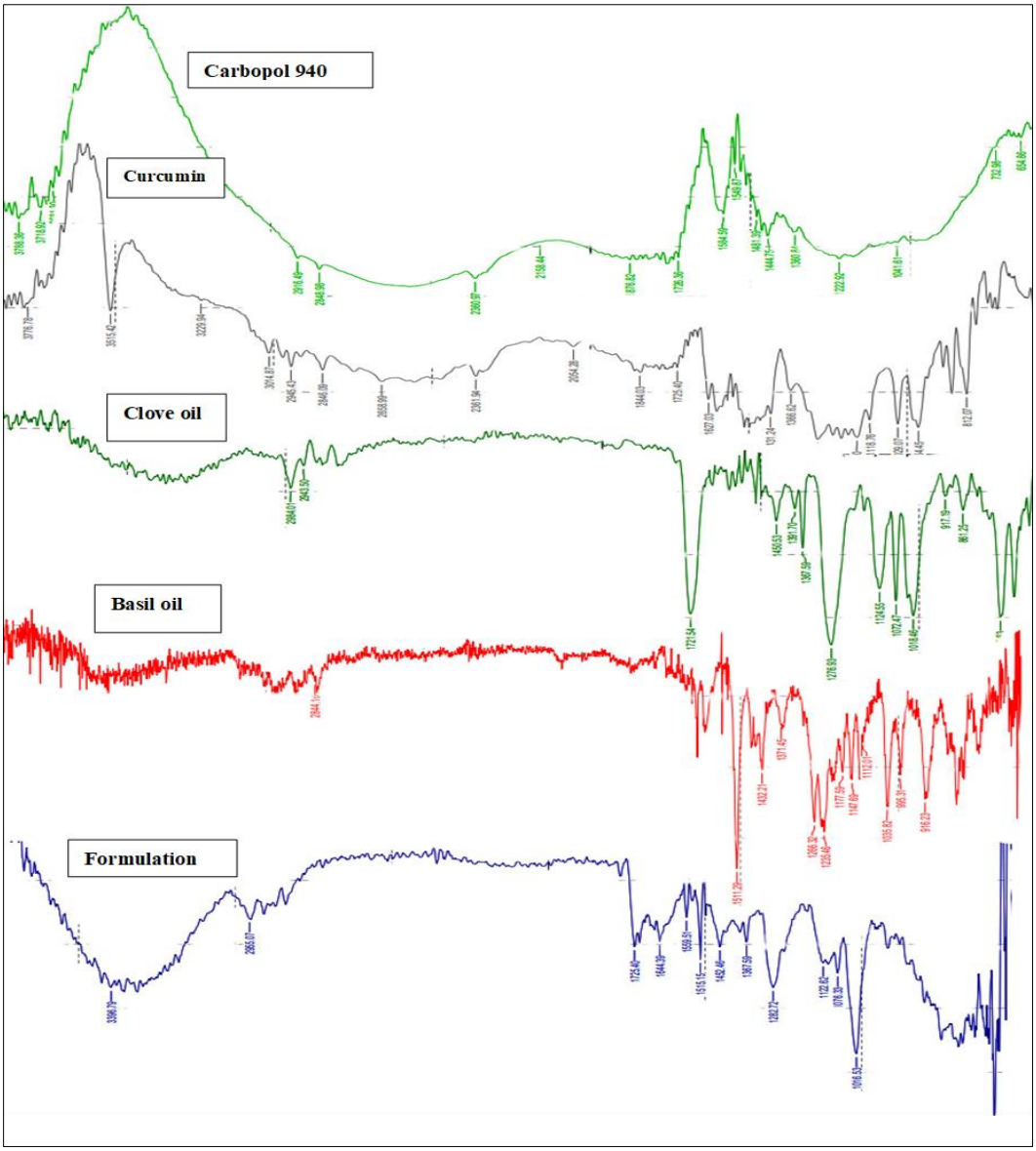

Figure 2 FTIR spectrum of curcumin, clove oil, basil oil, carbopol 940 and emulgel formulation

The IR spectra of curcumin shows stretching vibrations of alkene (c=c) and carbonyl goup (c=o) due to overlapping at 1627 cm-1. Cucumin IR spectra also gives stretching vibrations of O-H and aromatic C=C groups at 3200-3500 and 1431 cm-1 respectively. It also showed bending virations of C-O group in phenol at 1282 cm-1 [22]. The IR spectra of clove oil eugenol displayed significant peaks of aliphatic and aromatic C=C at 720-1250 and 1721-1400 cm-1 respectively [23]. The basil oil IR spectra showed peaks at 2844.16 cm-1, 1640cm-1, 1740cm-1 due to the presence of –CH2 group, C=C group, C=O group respectively. The stretching vibrations of C-O group shown at 1240-1100 cm-1 and bending vibrations at 1450-990cm-1 [24]. The major peaks in FTIR spectra of Carbopol 940 were shown at 1726.36 (due to C=O), 1444.75, 1360.84, 1222.92 (due to C-O group), 1041.61, 732 cm-1 [23]. The FTIR spectra of formulation shown significant peaks of eugenol in clove oil between 1650-1500cm-1, stretching vibrations of basil oil at 2850-3300cm-1 and bending vibrations at 1500-500cm-1 and the peaks of Carbopol 940 in between 1750-1125cm-1.

The characteristic peaks of carbopol 940 and drugs were shown in FTIR spactra of formulation. Hence FTIR study concluded that the drugs and excipients were compatible.

3.2. Evaluation of emulgel

3.2.1. Physical parameters of emulgel

The optimized formulations were homogenous yellowish emulgel with excellent consistency, viscous creamy preparation, and absence of grittiness.

3.2.2. pH

The pH values of optimized formulation E3G3S5T2 was found to be 6.7, which is regarded as adequate to prevent the risk of irritation when applied to the oral mucosa as the pH of oral cavity is 6.5 to 6.8.

3.2.3. Viscosity

Formulations E3G1 to E3G5 had shown the lowest and highest viscosities respectively. The lowest viscosity was found in emulgels containing 0.25% w/w Carbopol 940, while the highest viscosity was found in those containing 1.5% w/w Carbopol 940. When other variables are maintained constant, formulations viscosity increases as polymer concentration rises. The viscosity of optimized formulation E3G3S5T2 was found to be 27500 ± 55.67cps.

3.2.4. Spreadability

Spreadability shows how quickly the minimal amount of shear will spread the emulgel over the affected tissue. The Spreadability of optimized formulation E3G3S5T2 was found to be 43.33 ± 0.33 cm.

3.2.5. Swelling Index

The E3G5 emulgel with Carbopol 940 (1.5% w/w) showed the highest swelling index among all the formulations. The degree of water uptake and chain strength of the polymer may affect the swelling index value. The % swelling index of optimized formulation E3G3S5T2 found to be 65 ± 0.5%.

3.2.6. Extrudability

Excellent extrudability of optimized formulations E3G3S5T2 was observed, suggesting that emulgel have good flowability.

3.2.7. Phase separation testing by centrifugation

No phase separation was visible in the optimized formulation E3G3S5T2, indicating the product's stability under high shear rates.

3.2.8. Drug content of emulgel

The drug content of optimized formulations E3G3S5T2 was determined. The Percentage drug content of clove oil, basil oil, and curcumin contents were found to be 97.07 ± 2.1%, 95.91 ± 1.9%, and 96.22 ± 2.0% respectively. It means the drugs were uniformly distributed in the formulations.

3.2.9. In vitro drug release study

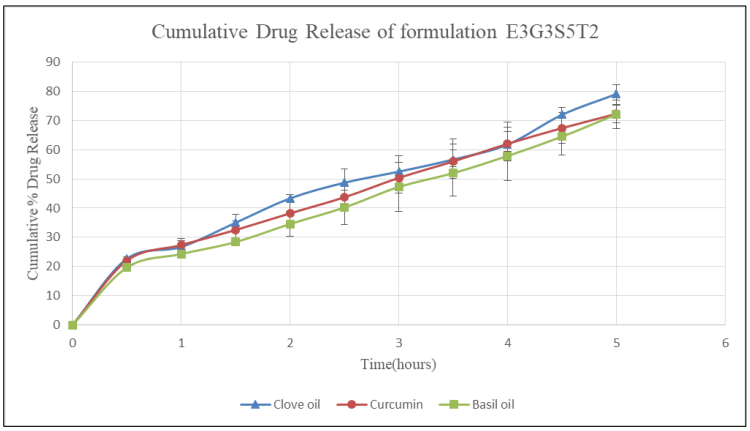

Figure 3 *In vitro* cumulative % drug release of formulation E3G3S5T2 of clove, curcumin, and basil

4. Conclusion

From the present study it can be concluded that eugenol containing clove oil, basil oil and curcumin, can be given topically as an emulgel in the local therapy of mouth ulcer. An additional benefit is that the topical emulgel demonstrated effective drug release and penetration characteristics. The ease of application to the oral mucosa is improved by clove oil, basil oil and curcumin inclusion in the gel dosage form. It needs more research on its clinical effectiveness, because of the drugs hydrophobic property, which is the biggest barrier to its formulation as a gel.

Compliance with ethical standards

Acknowledgments

All India Council of Technical Education (AICTE), New Delhi.

References

[1] Leão JC, Gomes VB, Porter S. Ulcerative lesions of the mouth: an update for the general medical practitioner. Clinics. 2007; 62:769-780.

[2] Challacombe SJ, Shirlaw PJ, Mestecky J, Lamm ME, Strober W, Bienenstock J, McGhee JR, Mayer L. Immunology of diseases of the oral cavity. Chapter 89. InLocal immune responses in tuberculosis 2005; 1517-1546.

[3] Scholz OA, Wolff A, Schumacher A, Giannola LI, Campisi G, Ciach T, Velten T. Drug delivery from the oral cavity: focus on a novel mechatronic delivery device. Drug Discov. Today. 2008 Mar 1;13(5-6):247-253.

[4] Pickel FD, Cort W, Starr N, Bilotti A, Pigman W. Evaluation of enamel-rehardening agents in saliva. J. Dent. Res. 1965 Sep;44(5):855-859.

[5] Mandel ID. Relation of saliva and plaque to caries. J. Dent. Res. 1974 Mar;53(2):246-266.

[6] Ahmed MG, Adinarayana S. Formulation design of hydrocortisone films for the treatment of aphthous ulcers. Turk. J. Pharm. Sci. 2019 Sep;16(3):348-355.

[7] Rahmani F, Moghadamnia AA, Kazemi S, Shirzad A, Motallebnejad M. Effect of 0.5% Chitosan mouthwash on recurrent aphthous stomatitis: A randomized double-blind crossover clinical trial. Electron. Physician. 2018 Jun;10(6):6912-6919.

[8] Motamedi MR, Golestannejad Z. Use of pure nicotine for the treatment of aphthous ulcers. Dent. Res. J. 2015 Apr 5;12(2):197-198.

[9] Yadav SK, Mishra MK, Tiwari A, Shukla A. Emulgel: a new approach for enhanced topical drug delivery. Int. J. Curr. Pharm. Res. 2016;9(1):15-19.

[10] Redkar MR, Patil SV, Rukari TG. Emulgel: A modern tool for topical drug delivery. World J. Pharm. Res. 2019 Jan 29;8(4):586-597.

[11] Guénette SA, Ross A, Marier JF, Beaudry F, Vachon P. Pharmacokinetics of eugenol and its effects on thermal hypersensitivity in rats. Eur. J. Pharmacol. 2007 May 7;562(1-2):60-67.

[12] Singh D, Chaudhuri PK. A review on phytochemical and pharmacological properties of basil (Ocimum sanctum L.). Ind. Crops. Prod. 2018 Aug 1; 118:367-382.

[13] Shahare N, Chouhan S, Darwhekar GN. Herbs used in treatment of mouth ulcer-a review. IJPC. 2021 Jul 29:68-74.

[14] Ale SI, Hostýnek JJ, Maibach HI. Menthol: a review of its sensitization potential. Exo. Derm. 2002;1(2):74-80.

[15] Sirivat A, Vayumhasuwan P. Viscoelastic properties of Carbopol 940 gels and their relationships to piroxicam diffusion coefficients in gel bases. Pharm. Res. 2005 Dec;22(12):2134-2140.

[16] R. Varges P, M. Costa C, S. Fonseca B, F. Naccache M, de Souza Mendes PR. Rheological characterization of carbopol® dispersions in water and in water/glycerol solutions. Fluids. 2019 Jan 4;4(1):3, 1-20.

[17] Mohammed NH, Ahmed MH, Hussien MO. Qualitative analysis of the essential oil of Syzygium aromaticum (L)(clove) using gas chromatography-mass spectrometry (GC-MS). IJRPC. 2015;5(2):350-354.

[18] Sayyar Z, Jafarizadeh-Malmiri H. Temperature effects on thermodynamic parameters and solubility of curcumin O/W nanodispersions using different thermodynamic models. Int. J. Food Eng. 2019 Feb 1;15:1-2.

[19] Sah SK, Badola A, Mukhopadhyay S. Development and evaluation of tioconazole loaded emulgel. Int. J. Appl. Pharm. 2017; 9:83-90.

[20] Khan AW, Kotta S, Ansari SH, Sharma RK, Kumar A, Ali J. Formulation development, optimization and evaluation of aloe vera gel for wound healing. Pharmacogn. Mag. 2013 Oct;9(Suppl 1): S6-S10.

[21] Varma VN, Maheshwari PV, Navya M, Reddy SC, Shivakumar HG, Gowda DV. Calcipotriol delivery into the skin as emulgel for effective permeation. Saudi Pharm. J. 2014 Dec 1;22(6):591-599.

[22] Ismail EH, Sabry DY, Mahdy H, Khalil MM. Synthesis and Characterization of some Ternary Metal Complexes of Curcumin with 1, 10-phenanthroline and their Anticancer Applications. J. Sci. Res. 2014 Aug 26;6(3):509-519

[23] Pramod K, Suneesh CV, Shanavas S, Ansari SH, Ali J. Unveiling the compatibility of eugenol with formulation excipients by systematic drug-excipient compatibility studies. J. Anal. Sci. Technol. 2015 Dec;6(1):1-4.

[24] Predoi D, Groza A, Iconaru SL, Predoi G, Barbuceanu F, Guegan R, Motelica-Heino MS, Cimpeanu C. Properties of basil and lavender essential oils adsorbed on the surface of hydroxyapatite. Materials. 2018 Apr 24;11(5):652; 1-17.