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Formulation, Development and Preformulation Studies of Eukalyptol & Thymol Containing organogels for Topical Delivery System

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***Abstract*:** There are many benefits to using a topical application as opposed to the more traditional methods of administering drugs systemically. The stratum corneum serves as an important defence mechanism against the introduction of potentially harmful foreign molecules; however, this barrier prevents most medications from penetrating the skin via the skin's surface. Penetration enhancers, which come in a variety of forms, have been shown to successfully circumvent this barrier and facilitate the efficient transport of medicines through the skin. Some skin penetration enhancers are connected with unpleasant and harmful consequences, despite the fact that the pharmaceutical industry already uses them in commercially available transdermal medications. This highlights the importance of finding novel skin penetration enhancers that are both safe and effective. Natural penetration enhancers are more widely utilised than their synthetic equivalents because they may be produced in large quantities using a renewable resource, and they can be cheaper to extract depending on the method used. The purpose of this article is to provide a synopsis of the findings from scientific studies of natural skin penetration enhancers.

Keywords: *Transdermal medication, Hydrophilic, Organogels, Eudragit, Topical permeation ect.*

1. Introduction

The medication is carried throughout the body via the circulatory system in a topical drug delivery system. Ophthalmic, rectal, vaginal, and cutaneous routes are all available for topical medication administration. [1] The skin has been identified as a significant channel in the topical drug delivery system, making it an essential and

extensively accessible organ for topical administration. The potential benefits of applying drugs topically include delivering the medication directly to the place of activity and extending the medication's effect period [2]. By avoiding the liver's metabolism of the drug and keeping the drug from irritating the gastrointestinal tract, topical preparation improves the drug's bioavailability [3]. In order to maximize the local effect while minimizing the systemic one, or to guarantee adequate absorption, efforts are being made to use sedate carriers that provide satisfactory limitation or penetration of the drug within or through the skin as part of a topical dosage form [4].

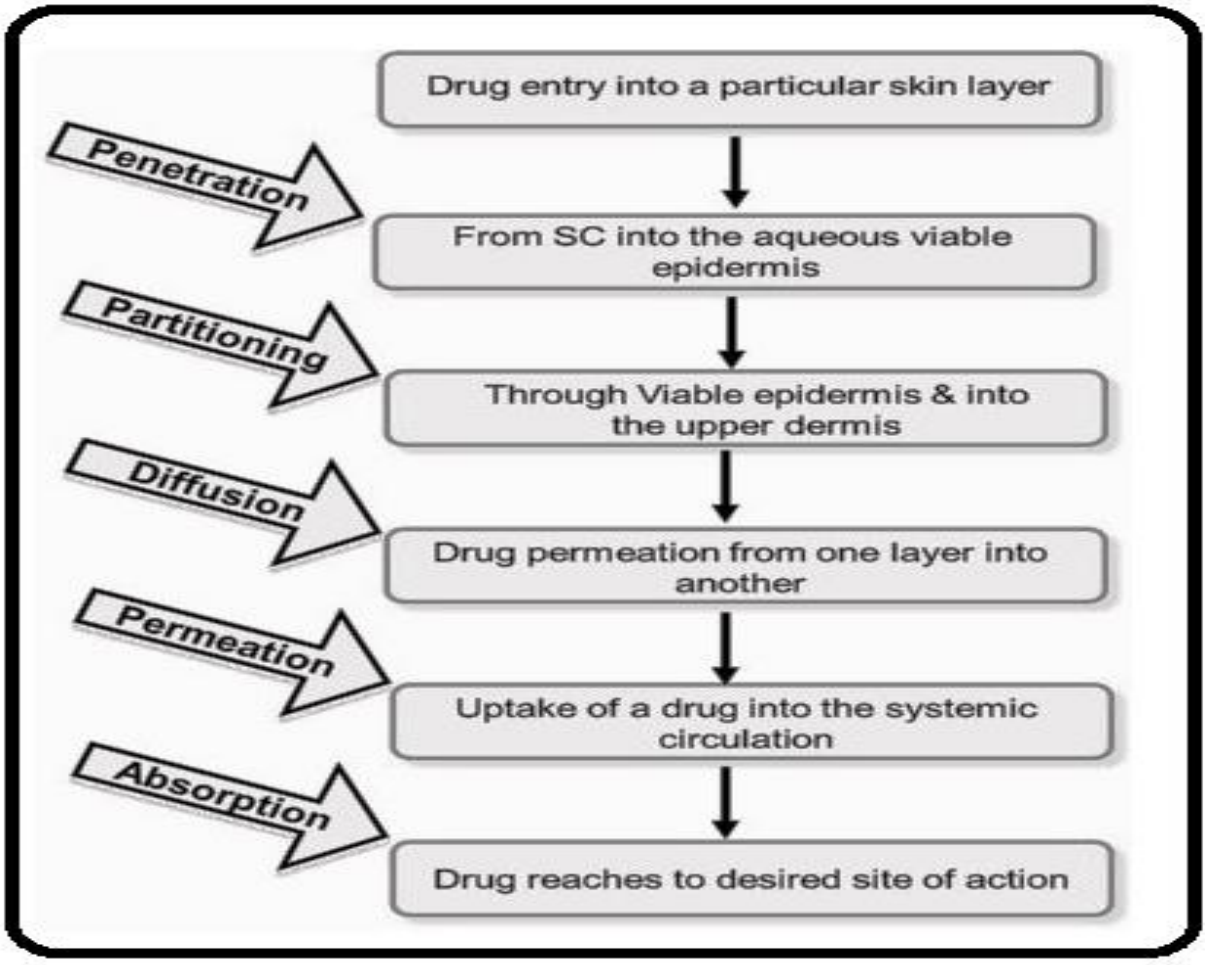


Fig.1 Various route of drug penetration to the skin layer[5]

Advancement of topical drug delivery system

Ophthalmic, rectal, vaginal, and cutaneous administration are all examples of topical medication administration, which is a localised drug delivery mechanism. alternative for the treatment of skin conditions[6]. When applied to the skin, topical medicines can have either a superficial, local, or systemic effect. The base's medicinal characteristics, such as emollient, calming, or protecting activity, might make it useful even when used alone [7]. Therapeutically active chemicals are often distributed or dissolved in the base of many topical treatments. Therapeutically active ingredients can be combined with a variety of bases to create a wide variety of topical preparations suitable for a wide variety of drug delivery and therapy methods. These bases can be categorized according to their physical properties (suspension), their intended use (liniments), or their composition (hydrophiliccreams).

2. Anatomy of human skin

There are tremendous opportunities for medication delivery because of its large surface area in direct touch with the environment [8]. The skin is a complex organ consisting of various layers of protecting tissue. The epidermis, dermis, and hypodermis are the three primary layers of skin. Semisolid preparations need to be very penetrative in order to be absorbed by the skin [9]. Gelation happens when a polar solvent is added to a solution containing lecithin, which causes the polar portion of the lecithin to expand, forming a cylindrical network. The non-polar solvent aids in the product's ability to permeate the skin.

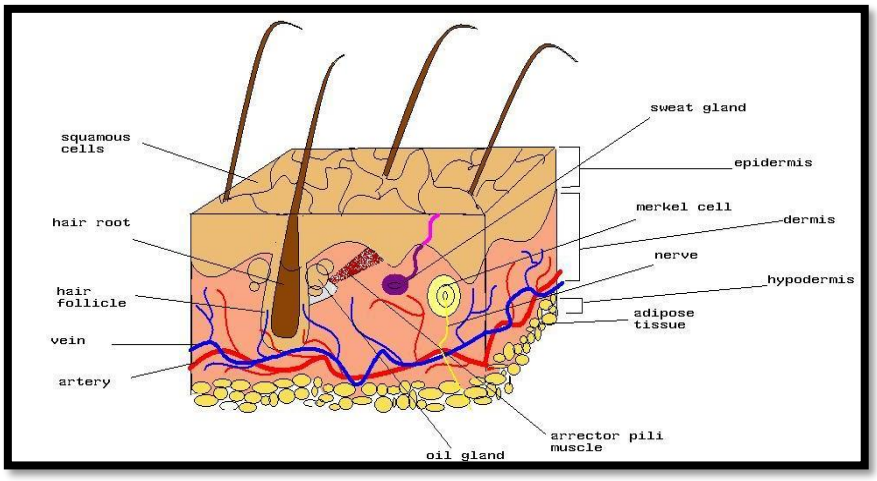


Fig. 2 Structure of Human Skin

3. Principles of topical permeation[11,12]

The stratum corneum, the skin's permeability barrier, must be breached before a topically administered medication can exert its local or systemic effects. Substances are absorbed via percutaneous absorption when they diffuse passively through the skin. It is possible for substances to penetrate the skin by absorption via the epidermis (trans-epidermal absorption) or diffusion via shunts, such as the ones provided by the hair follicles and sweat glands, which are located all over the body[13]. The drug molecules may enter the body through the follicular epithelium and the sebaceous glands after passing through the skin via transitory diffusion. Once the topical permeation has reached steady state, the predominant channel is diffusion via the intact stratum corneum. There is more than one stage involved in the release of a therapeutic drug from a topical formulation and its subsequent transport to the systemic circulation after being applied to the skin[14].

4. Types of organogels

I. Lecithin Organogels

Lecithin Recently, organogels have gained attention as a promising carrier system. An exterior or continuous phase of nonpolar organic solvent, a polar agent (often water), and a surfactant (lecithin) serve as the three primary components of an organogel matrix[15]. When non-aqueous lecithin is mixed with trace amounts of water or other polar compounds like glycerol, ethylene glycol, or formamide, an organogel is produced. Naturally occurring unsaturated lecithin is the only type of lecithin for which the transition into a jelly-like condition has been demonstrated. Most of the latter come from processing soy beans and egg yolks[16].

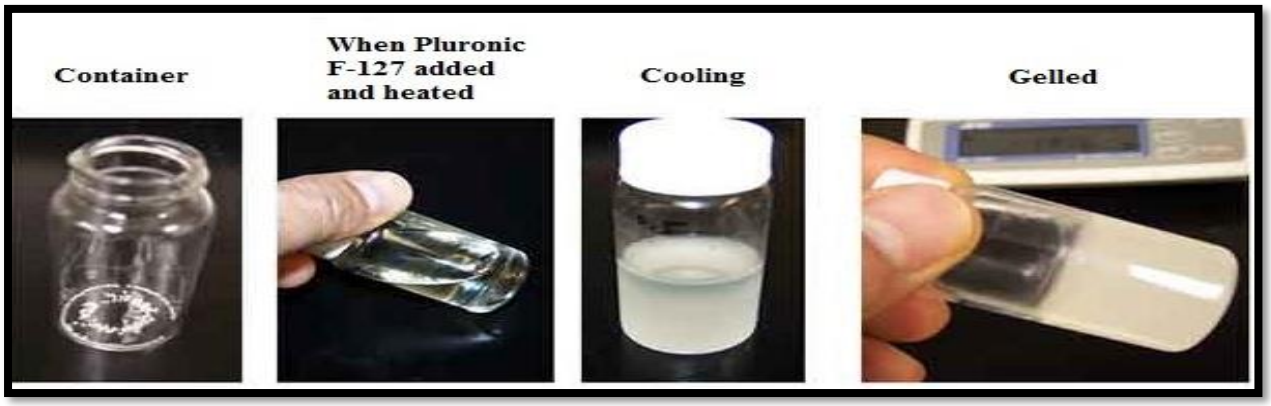


Fig.3 Formation of Organogels

II. Sorbitan monostearate Organogels[17]

Many organic solvents can be gelled at low concentrations with a mixture of Span 60 (sorbitan monostearate) and Span 40 (sorbitan monopalmitate).

III. Nano-emulsion based Organogels[18]

Microemulsions are a type of liquid system consisting of water, oil, and surfactants, often in conjunction with suitable co-surfactants, that is thermodynamically stable and clear, with a single optical isotropy. It is well-known that microemulsions improve the topical and systemic bioavailability of medicines.

IV. Poly (ethylene) Organogels

Only a few number of polymeric organogels have been developed with the intention of being used in medicine. Only two of these systems, poly (ethylene) organogels, have undergone extensive testing for potential drug delivery applications[19]. It was found that PO patches caused little irritation and had minimal sensitising effects.

V. Supramolecular Organogels[20]

Despite the discovery of a low molecular mass gelator in the early nineteenth century, little attention was paid to these materials until the late twentieth century as scientists struggled to better understand their supramolecular nature. Gels, with their wide variety of structural topologies, have been used as templates to create novel inorganic superstructures with potential catalytic and separation applications.

VI. Eudragit Organogels[21]

High concentrations of Eudragit (up to 30 or 40% w/w) are combined with polyhydric alcohols such glycerol, propylene glycol, and liquid polyethylene glycol to form Eudragit organogels. Increasing Eudragit concentrations were shown to enhance gel viscosities, while increasing medication content was found to decrease gel viscosities.

VII. Pluronic lecithin organogel (PLO)

PLO is a low-temperature Pluronic F127 (also known as Polaxomer (407)) solution in isopropyl palmitate or isopropyl myristate, water, and soy lecithin. Poloxamer is a heat-sensitive material that becomes viscous when heated. Both stages of PLO may or may not include the preservative sorbic acid. It often appears as a yellowish gel that is odourless and transparent, and it is rapidly absorbed by the skin. Similar to the tubular reverse micelle structures found in lecithin organogels, PLO can be thought of as having temporal three-dimensional structures.

6. Materials, Chemicals, and Reagents for Making Organogels

All of the following study components were either of pharmaceutical grade quality or of the highest quality Laboratory Reagent (LR) available from the supplier.

Table No.1 Organogel's reagents and compounds list

Sl. No	Reagent & compounds	Company
1	Eucalyptol	Yarrow chemicals, Mumbai
2	Thymol	Yarrow chemicals, Mumbai
3	Sodium Alginate	Otto chemical reagents
4	Guar gum	Yarrow chemicals, Mumbai
5	Xanthan gum	Merck ltd
6	Methyl paraben	Nice Chemicals Pvt. Ltd., Kerala
7	Pluronic F127	Yarrow chemicals, Mumbai
8	Methanol	Karnataka fine chem., Bangalore

Table No.2 List of Instruments used for evaluation of Organogel

Sl. No	Instruments	Manufacturer
1	FT-IR	IR-Affinity-1-FTIR Spectrophotometer, Shimadzu, Japan.
2	UV-Visible Spectrophotometer	UV-1800 Shimadzu UV Spectrophotometer, Shimadzu Corporation, Japan.
3	Electronic Balance	Citizen scales Pvt. Ltd, Mumbai.
4	Hot Air Oven	Servewell Instruments Pvt Ltd.
5	Pen type pH meter	Equinox Electronics Ltd, Bengaluru.

7. Preformulation Studies[22]

I. Melting point determination of Eucalyptol and Thymol[23]

Thiele's tube method was used to determine the melting point of eucalyptol and thymol by placing a little amount of the medication in a capillary tube with a closed end, placing the tube in a Thiele tube with liquid petroleum, and recording the temperature at which the drug melted. We did this three times to ensure accuracy and provide the mean value.

II. Solubility of Eucalyptol and Thymol[24]

Researchers looked at how well eucalyptol and thymol dissolved in water, ethanol, and methanol, among others. Adding 5 ml of each solvent to a clean, dry test tube containing exactly 1 ml (or 1 mg) of the drug and shaking vigorously allowed for visual confirmation of solubility.

III. Infrared spectral studies [25]

Method: This method entails thoroughly combining approximately 1 mg of Eucalyptol and Thymol with approximately 100 mg of KBr (which is transparent to IR) in a mortar at a ratio of 1:100. The compound was manually compacted in a pellet die before being inserted into a Shimadzu FTIR spectrophotometer.

Preparation of standard graph of Eucalyptol and Thymol

Procedure

Preparation of Standard solution (Methanol)

The first stock was created by putting 100 mg each of eucalyptol and thymol to a 100 ml volumetric flask and dissolving them in a modest amount of methanol, then topping off the volume to 100 ml with more methanol (1000 g/ml).

The second stock was made by pipetting one millilitre of the identical solution into a second 100-milliliter volumetric flask, and then filling it to the top with methanol (10 milligrammes per millilitre).

Pipetting 0.5 ml, 1 ml, 1.5 ml, 2.0 ml, 2.5 ml, and 3.0 ml from the 2nd stock standard solution into 100 ml volumetric flasks. Methanol was used to make up the volume to the desired concentrations (5 g/ml, 10 g/ml, 15 g/ml, 20 g/ml, 25 g/ml, and 30 g/ml). The UV-Visible spectrophotometer was used to take a look at this solution's spectrum from 200 to 400 nm. Lambda max for Eucalyptol was measured at 310 nm, while that for Thymol was measured at 274 nm. Using methanol as a blank, we determined the absorbance at 310nm and 274nm for each concentration. We did this three times to ensure accuracy and provide the mean value.Preparation of Standard solution (phosphate buffer pH-6.8).

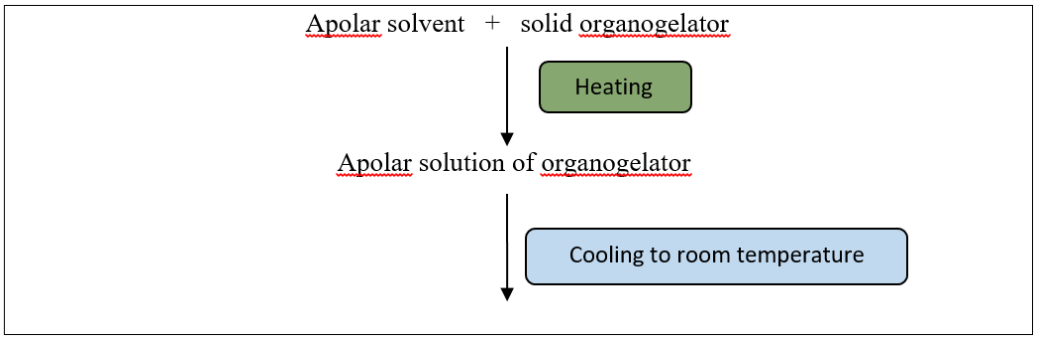
IV. Drug-Polymer compatibility[26]

A. FTIR spectrophotometer

Using an FTIR spectrophotometer, we examined the drug and polymer compatibility. Using a mortar and pestle, 1mg of the material was finely mashed alongside 100mg of potassium bromide (KBr) (1:100 ratio). A little amount of the mixtures was squeezed at 7 Kg/cm^2 for 2 minutes in a hydraulic press, and the resulting translucent pellet was examined under a microscope. Shimadzu FT-IR spectrophotometer was used to scan the pellet from 4000 cm-1 to 400 cm-1. Drug (Eucalyptol and Thymol) and polymer (Sodium Alginate, Guar Gum, and Xanthan Gum) samples, as well as physical mixtures of the drug and polymers, were created. Functional group peaks were examined across spectra and interpreted.

8. Preparation of Eucalyptol and Thymol Organogels E1-E6[27,28]

Components (mg)	**E1**	**E2**	**E3**	**E4**	**E5**	**E6**
Eucalyptol(ml)	10	10	10	10	10	10
Thymol	30	70	70	30	70	70
Sodium Alginate	30	30	70	-	-	-
Guar Gum	-	-	-	20	40	60
Xanthan Gum	-	-	-	-	-	-
Pluronic F-127	30	30	30	30	30	30
Methyl Paraben	20	20	20	20	20	20
Methanol(ml)	15	15	15	15	15	15
Water	QS	QS	QS	QS	QS	QS



Fibres of organogelators precipitate out, interacting with one another physically to produce a three-dimensional networked structure that immobilises the polar solvent.

9. Preformulation tests of Eucalyptol[29]

A. Determination of solubility

The solubility of eucalyptol and thymol in cold water was found to be low, while that of methanol was found to be even lower.

B. IR Spectroscopy

The IR spectra of pure drug was carried out and the graph is shown in Fig.4 and the peak are shown in table no.3

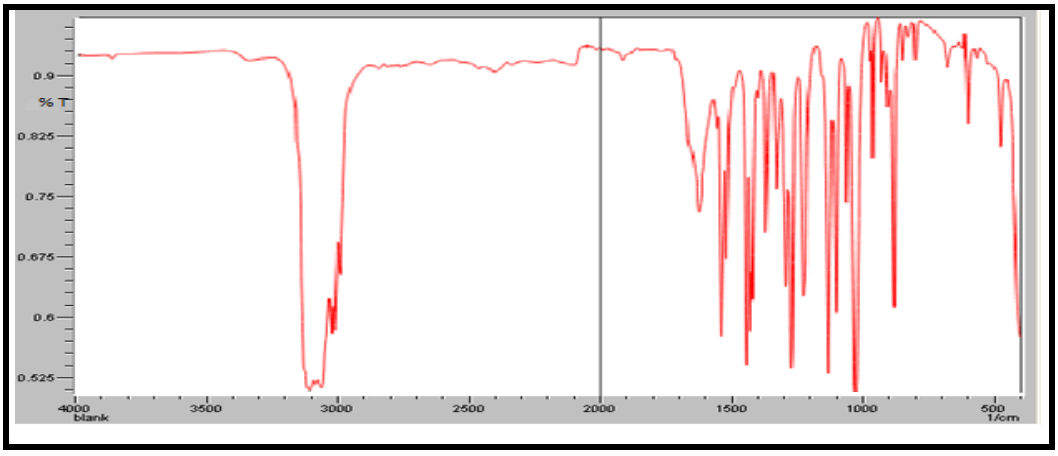


Fig.No.4 IR Spectra of Eucalyptol

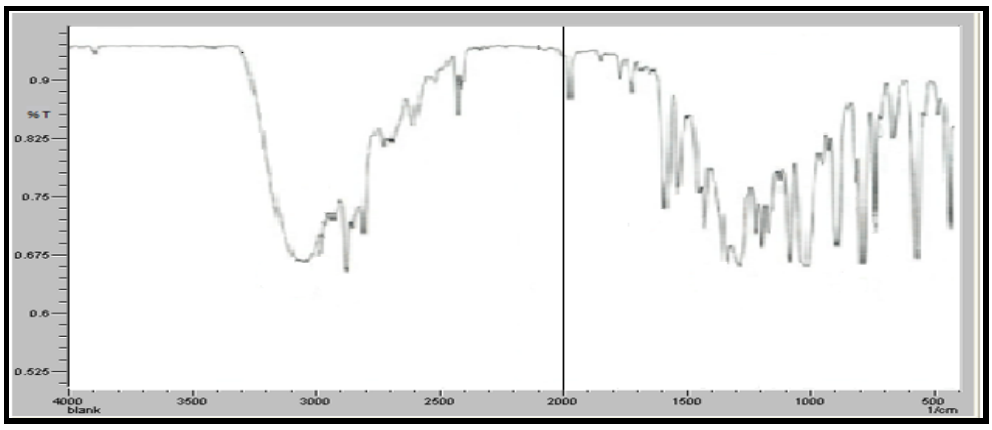


Fig.No. 5 IR Spectra of Thymol

Table no.3 IR Spectra Data of Eucalyptol and Thymol

Name of component	Functional group	Range of standard	Peak obtained
Eucalyptol	C-H Stretch	3,350 cm-1	3110 cm-1
	O-H Stretch		
Thymol	C-H Stretch	3,350 cm-1	3261 cm--1
	O-H Stretch		

C. Maximum absorbance of Eucalyptol[30]

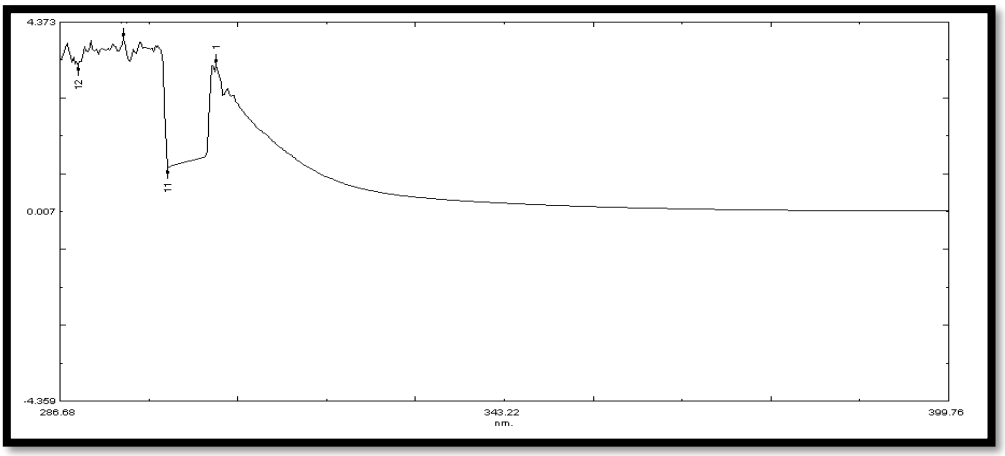


Fig.6 UV spectrum of Eucalyptol from 200-400 nm

D. Calibration curve of Thymol

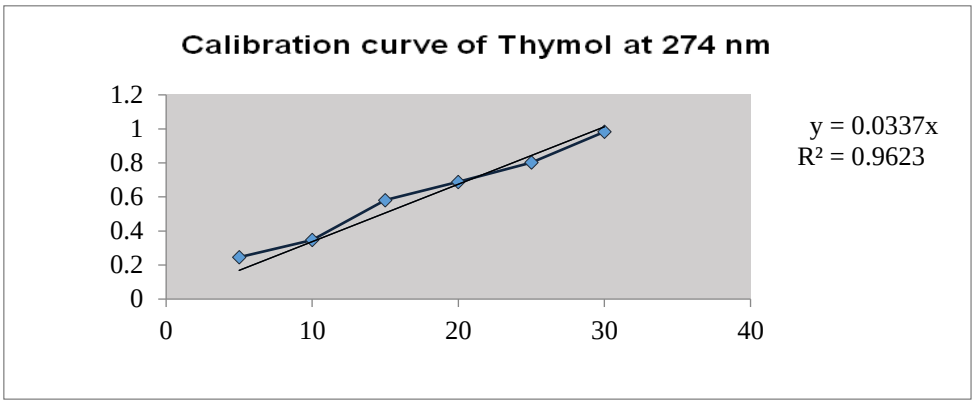


Fig.7 Calibaration curve of Thymol

E. Calibration curve of Eucalyptol.

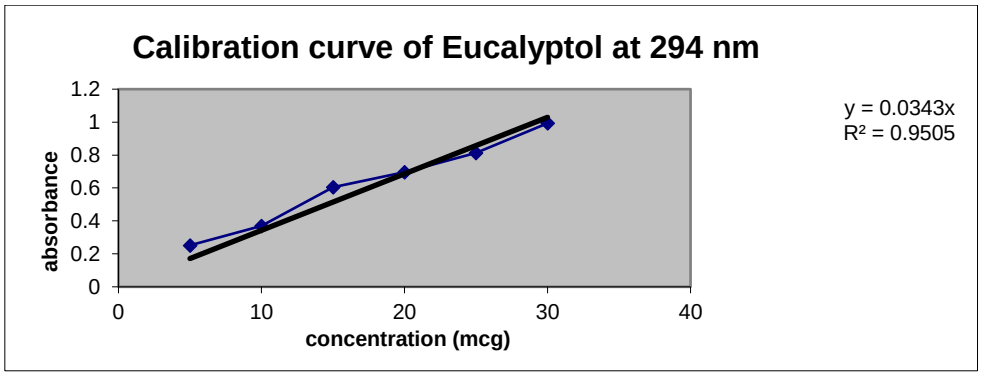


Fig.8 Calibration Curve of Eucalyptol

10. Evaluation studies of organogel[31,32]

1. Physical appearance

Appearance of Organogel observed visually

Formulation	Colour
F1	Pale White
F2	Pale White
F3	Pale white
F4	Cream
F5	Cream
F6	Cream
F7	Yellowish White
F8	Yellowish White
F9	Yellowish white

2. Spreadabililty[33]

The Spreadability of the prepared gel were carried out and the results are shown in table no.4

Table 4. Spreadability of the organogel

Formulation	Spreadability (Mean cm ±SD)*
F1	1.7±0.23
F2	2.4±0.11
F3	2.8±0.16
F4	2.5±0.12
F5	3.2±0.22

F6	3.9±0.36
F7	2.1±0.52
F8	2.4±0.23
F9	2.9±0.56
F10	3.6±0.56
F11	3.3±0.29
F12	3.1±0.28

3. Viscosity:

The viscosity of the optimized formulation of Organogel was shown in table no.5.10. Viscosity of F6 and was found to be 27000 cp.

Table no. 5 Viscosity of the optimized formulation of Organogel

RPM	**F-6**
8	**27000cp**

4. Drug Content:

The drug content in the formulation varied from 86.4-103 % which indicates that the drug was stable in each of the formulations.

Formulation	**Drug content (Mean % ±SD) ***
F1	78.63±0.17
F2	82.36±0.26
F3	86.27±0.49
F4	95.12±0.25
F5	99.0±0.39
F6	102.0±0.48
F7	90.21±0.45
F8	92.36±0.82
F9	93.18±0.24
F10	96.38±0.09
F11	98.26±0.27
F12	99.32±0.45

5. pH

pH was determined by utilising Digital pH metre of each compositions.

Formulation	pH (Mean ±SD) *
F1	6.2±0.6
F2	6.4±0.4
F3	6.5±0.3
F4	6.6±0.2
F5	6.9±0.1
F6	6.8±0.0
F7	7.1±0.3
F8	6.9±0.1
F9	6.7±0.1
F10	7.2±0.4
F11	7.1±0.3
F12	6.9±0.1

(n=3)

6. In-vitro Diffusion Studies of Organogels[34,35]

Table no. 6 In-vitro diffusion studies

Time	F1	F2	F3	F4	F5	F6
0.5	12.3±0.25	14.2±0.23	15.6±0.11	17.2±0.11	18.6±0.25	19.58±0.27
1	17.25±0.24	23.25±0.25	25.63±0.26	28.14±0.13	30.25±0.25	33.24±0.24
2	21.24±0.11	29.65±0.14	32.04±0.27	37.28±0.18	40.28±0.29	42.31±0.28
3	28.4±0.15	35.6±0.12	38.25±0.29	42.02±0.24	45.75±0.16	51.28±0.17
4	33.5±0.18	43.25±0.27	45.28±0.26	52.14±0.21	56.42±0.19	60.87±0.24
5	55.42±0.23	60.23±0.26	67.25±0.29	72.21±0.26	75.26±0.18	81.03±0.27
6	68.5±0.27	79.21±0.14	80.2±0.24	82.25±0.23	84.52±0.35	88.14±0.18
8	88.5±0.26	88.23±0.28	87.45±0.34	92.65±0.31	93.01±0.24	96.18±0.19

Table no.7 In vitro diffusion studies of Organogel

Time	F7	F8	F9	F10	F11	F12
0.5	21.3±0.25	24.2±0.23	25.6±0.11	27.2±0.11	28.6±0.25	29.58±0.27
1	34.25±0.24	35.25±0.25	36.63±0.26	38.14±0.13	39.25±0.25	40.24±0.24
2	41.24±0.11	42.65±0.14	43.04±0.27	45.28±0.18	47.28±0.29	49.31±0.28
3	50.4±0.15	52.6±0.12	53.25±0.29	55.02±0.24	57.75±0.16	55.28±0.17
4	61.05±0.18	63.25±0.27	65.280.26	67.14±0.21	69.42±0.19	70.87±0.24

5	72.42±0.23	74.23±0.26	76.25±0.29	77.21±0.26	79.26±0.18	81.03±0.27
6	83.5±0.27	85.21±0.14	87.2±0.24	89.25±0.23	90.12±0.35	92.18±0.18
8	90.5±0.26	90.23±0.28	92.45±0.34	93.65±0.31	94.01±0.24	95.18±0.19

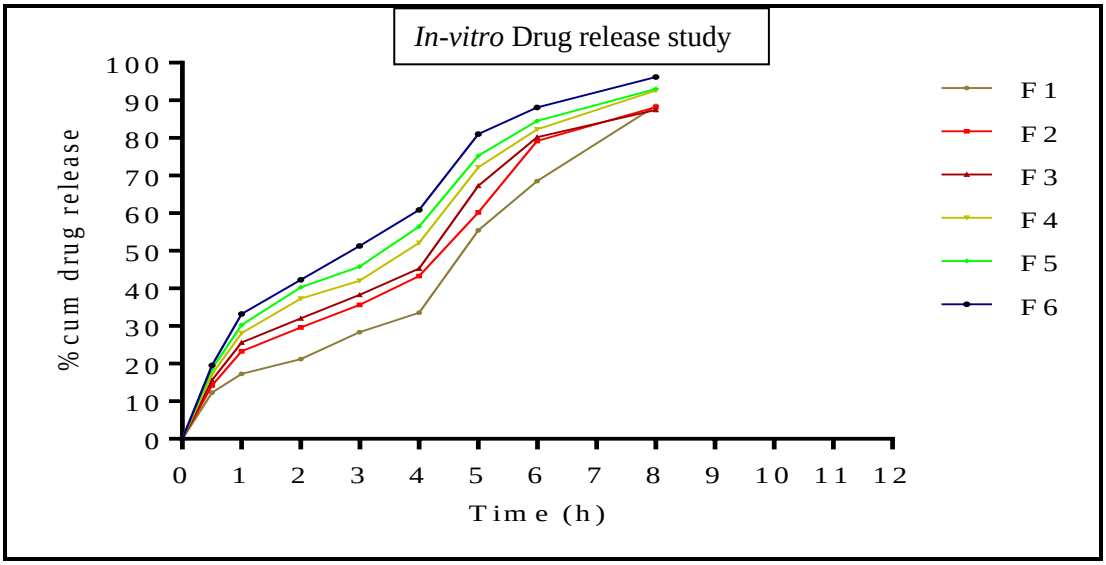


Fig.9 % cumulative drug release vs Time of Eucalyptol and Thymol organogel.

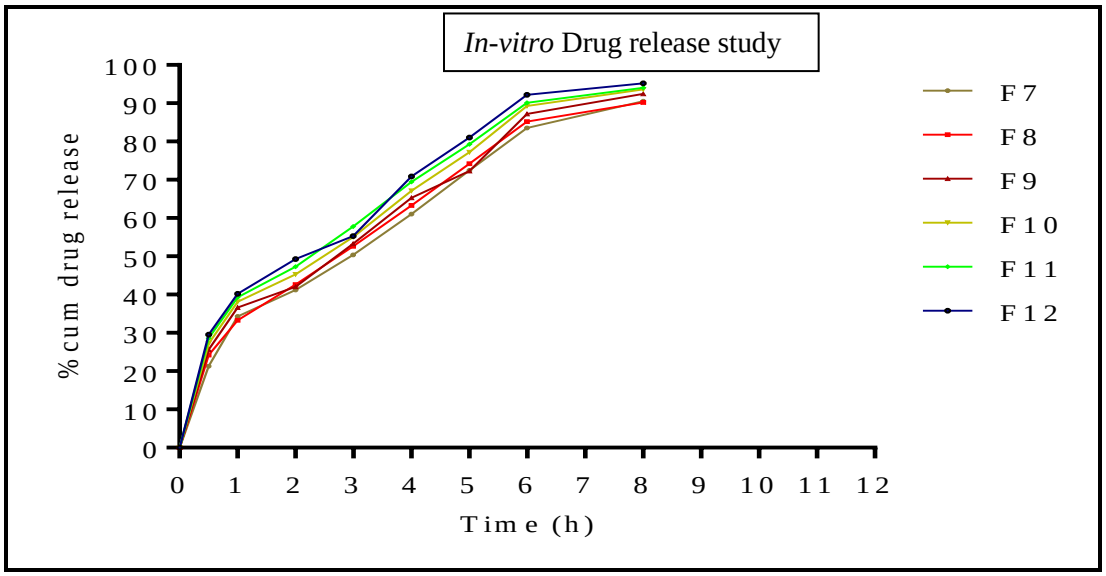


Fig.10 % cumulative drug release vs Time of Eucalyptol and Thymol Organogel.

7. Stability studies of Organogels[36]

No. of days	**Physical Appearance**	**pH evaluation**	**% drug content (Mean cm ±SD)***
Initial	++	6.8	96.18±0.02

30	++	6.8	96.18±0.03
60	+	6.5	94.25±0.16
90	+	6.4	93.56±0.24

*** Average of three trails**

(Table No.8 Data of stability study of formulation F6)

++ No change in color

\+ Slight change in color

11. Result and Discussion

Hydrophobic and acting as an anti-inflammatory, eucalyptol and thymol are found in volatile oils that have a relatively short biological half-life. Ingestion causes problems in the gastrointestinal tract, kidneys, and liver. Therefore, topical application of the medicine is necessary to counteract the aforementioned downside. Pre-formulation investigations compared the medication to the gold standard in terms of solubility and melting point. FTIR was used to test the compatibility of Eucalyptol and Thymol with a few different polymers, and the results were positive. Sodium alginate, guar gum, and xanthan gum were used in the formulation of organogel. The developed topical Organogel of Eucalyptol and thymol was put through a battery of physicochemical tests, including spreadability and in vitro release studies, to ensure its efficacy. Each formulation was determined to have a drug content of between 86% and 103%, and a pH of between 6-7. The Spreadability was excellent across all formulations. An ICH-required stability study was conducted on the final, improved formulation. Formulation F6 subjected to accelerated 40°C 2°C/70°F 5% RH testing. There was no discernible shift in colour, pH, or drug concentration. After all was said and done, it was determined that the Organogel formulation was an efficient drug delivery system. More research is needed to demonstrate the formulation's clinical efficacy.

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