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(REVIEW ARTICLE)

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Eucalyptus emulgel: A novel formulation with analgesic properties

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Abstract

Emulgels have emerged as a promising topical drug delivery system for the delivery of hydrophobic drug via skin. The objective of the study was to prepare eucalyptus emulgel. When we are preparing a emulsion individually shows stability problems during manufacturing and storage that effects on drug release pattern. In order to increase the drug stability, we incorporate it as emulgel. Emulgel is a thermodynamically stable formulation with low interfacial tension that is made by combining a surfactant and a co-surfactant and has several properties such as increased permeability and good thermodynamic stability. Emulgel has a dual control and a sustained release pattern. Emulgel improves bioavailability as well as patient compliance. This emulgel prepared as an analgesic, which satisfies all the testing parameters. The emulgel was produced in various batches of which F3 if found to be effective one.

Keywords: Emulgel; Emulsion; Eucalyptus; Phyto-constituent; Topical Drug delivery system

1. Introduction

Human health has been impacted by numerous sorts of diseases throughout history. The efforts have been made to administer newer pharmacological molecules using a variety of administration techniques for a variety of routes. The method of treatment chosen will depend on the type of disease, the urgency of treatment, the location of the disease, the severity of the condition, and other factors. Each form of medication delivery and route of administering drugs has benefits and drawbacks. Topical route refers to the delivery of a medicine through the skin with local effects as a cream, gel, lotion, emulsion, or suspension. Approximately 10-15% of the weight of the human body is made up of skin, which is considered to be the biggest portion of the body. The four layers of the human skin each have a unique cell makeup and structure. Topical route refers to the drug's formulation when it is administered to the skin for local action. However, the transdermal route is used when a drug's molecule is included in formulations that are applied to the skin for systemic effects. The administration of formulations is simple on the human skin. Stratum corneum, sweat ducts, and sebaceous glands are three pathways by which the medicine can enter the skin after being applied to it, depending on the skin's permeability [(1)(2)].

1.1. Topical drug delivery

The term **"topical drug delivery system"** refers to a pharmaceutical product that contains an active molecule and is applied to the diseased surface of the skin to treat local cutaneous disorders or the cutaneous manifestation of a general disease with the aim of limiting the pharmacological or other effects of the drug to the surface of the skin or within the skin. Topical medications are applied to the mucosal surface to provide localized effects at the location of application [(3)(4)].

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1.2. Skin physiology

The largest organ in the body is the skin, which covers an average area of 1.7 m2 and accounts for around 15% of the adult body weight. The primary function of is to shield the internal organs from harmful radiation, temperature changes, and other environmental factors. Additionally, the skin regulates the body's water balances and heat transfer. The skin is composed of three sheets comprised of various materials. The outermost layer is known as the epidermis, the middle layer as the dermis, and the innermost layer as the hypodermis. [5]

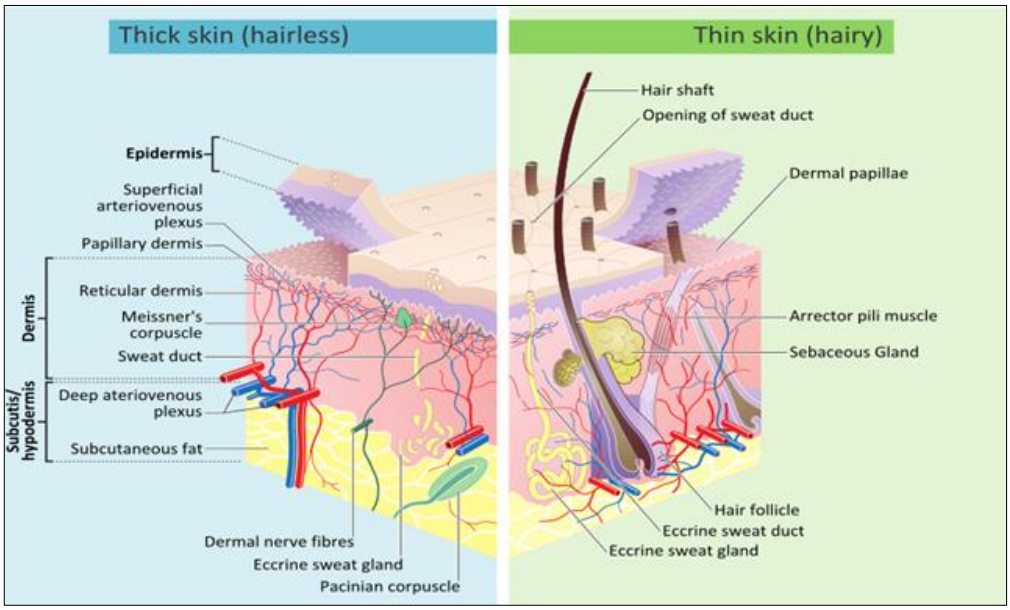

Figure 1 Skin Physiology

1.3. Emulgel

Emulgels are emulsions—either an oil phase distributed in a continuous phase of water or aqueous material, or a water/aqueous phase scattered in an oil phase—that are made into gels by combining with the right polymers. Emulgel is a very promising method for delivering hydrophobic medications. In other terms, the emulgel combines emulsion with gel [6][7][8].

2. Emulsions

Emulsions are a type of dispersion system made up of two immiscible fluids that are mixed together. Due to the biphasic nature of this system, emulsion instability increased. Using surfactants and emulsifiers improves the stability of the emulsion. Emulsions often combine an aqueous phase, which is made up of water or aqueous solvents like propylene glycol, glycerin, and polymethylene glycol, with an oil phase, which is made up of different oils and/or waxes. If the oil globules are distributed in every part of the aqueous, the emulsion is known as oil-in-water (o/w) emulsion. A biphasic system in which water/aqueous phase is distributed in every part the oil phase is known as water-in-oil emulsion [9] [10].

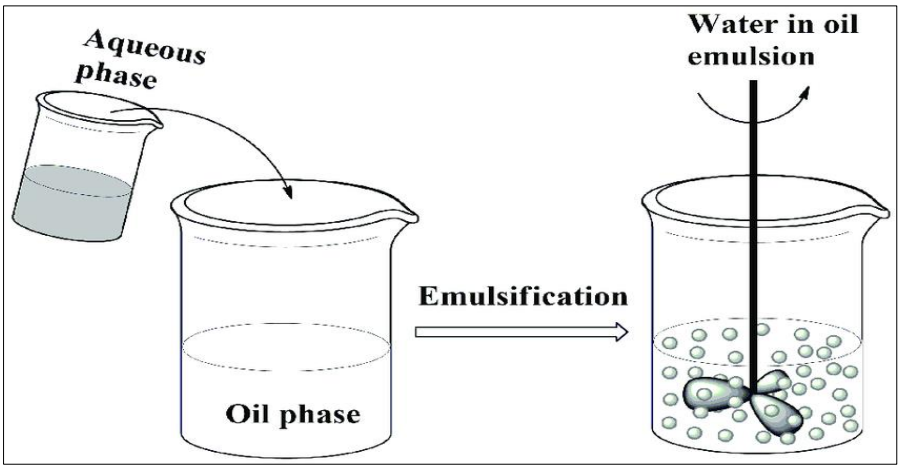

Figure 2 Emulsion

2.1. Theories of emulsification

The process of emulsifying chemicals or surfactants to create physically stable emulsions is known as emulsification hypothesis. This is an exterior surface phenomenon, or more specifically, an interface phenomenon between the aqueous and oil phases. Surfactants are crucial at the point where water and oil mix. There are numerous theories proposed to explain how surfactant/emulsifiers work to create stable emulsions [(11)].

2.2. Types of Emulsions

- Macro Emulsions
- Micro Emulsions
- Nano Emulsions
- Double/Multiple Emulsions

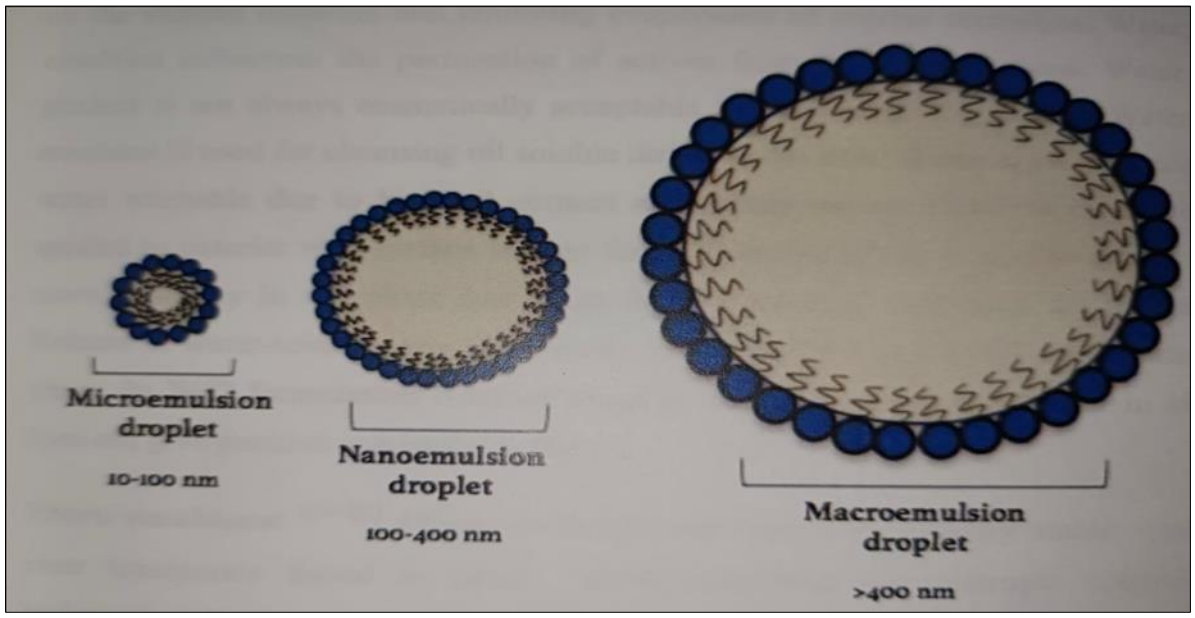

Figure 3 Types of Emulsions

2.2.1. Macro Emulsions

The most often utilized emulsions are macro emulsions, which are white to white-opaque in appearance. The macro emulsion has globules that are at least 400 nm in size. A digital microscope could be used to study the macro emulsion globules. The introduction of surface-active substances such as surfactants or emulsifiers could boost the stability of the macro emulsions.

2.3. Types of Macro emulsions

- **Oil-in-water emulsion** - (o/w) made up of different oils and waxes mixed with aqueous phase or aqueous solvents. The formulation is referred to as an o/w emulsion if the continuous phase is an aqueous phase and the oil phase is in a dispersed form. Wax, oil, or fat compositions in liquids can be used orally as active treatments or as lipophilic drug solvents. Lipophilic medicines are typically loaded in o/w emulsions. Because the oil is trapped in the non-greasy aqueous phase, oil in water emulsions is non-greasy. Because there is a significant volume of water in oil in water emulsion, the skin surface can be removed with ease. Oil in water emulsions are applied externally to the skin to impart a cooling sensation and block the taste of oils. The oil-in-water emulsion releases its active ingredients more quickly when they are more soluble in the watery phase. Oil-in-water emulsions have water as their exterior phase and perform well in conductivity tests when compared to water.
- **Water in oil emulsions** (w/o)- Because they have an occlusive effect on the stratum cornea and prevent eccrine secretions from evaporating, water-in-oil emulsions have a hydrating effect. The penetration of actives from w/o formulations is influenced by the water-in-oil emulsion. Because of its greasy character, water with oil products is not always desirable cosmetically. To remove oil soluble filth from the skin, use oil in water emulsion. Due to the high oil content and greasy nature of the oil emulsion, the water is not washable. To stop the skin from drying out, a water-in-oil emulsion is applied to the skin's surface on the outside. The medicine is released from formulations much more quickly when the actives are more soluble in the oil phase. Release of water-soluble drug form water in oil emulsion is retarded due to external oil phase. In w/o formulation external phase is oil phase, due to this water in oil phase does not give positive conductivity tests [12].

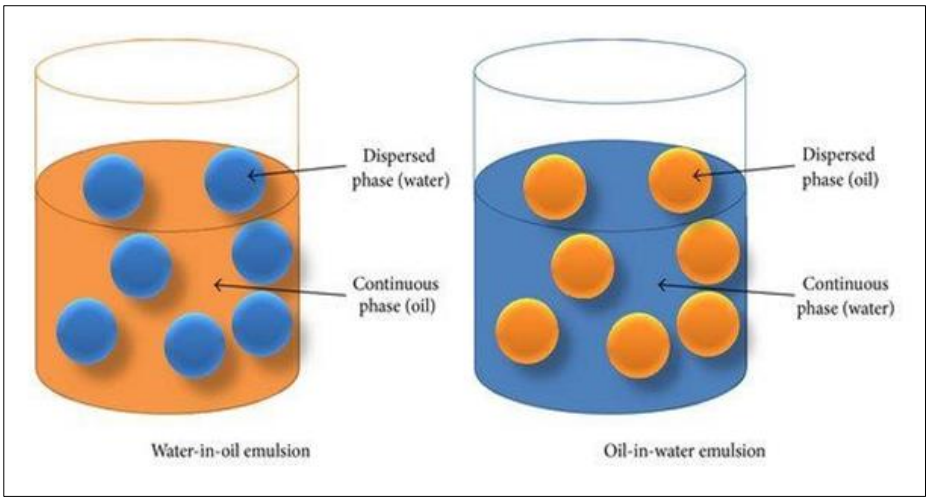

Figure 4 o/w & w/o emulsion

2.3.1. Micro Emulsions

Micro emulsions are clear, transparent liquids that are thermodynamically stable. Micro emulsions are isotropic dispersions of hydrocarbon liquids and aqueous phase that are kept together by an interfacial coating of emulsifier, surfactant, and coemulsifier molecules. Micro emulsions develop naturally without the use of outside energy. The diameter of the distributed, spherical micro droplets ranges from 20 nm to 200 nm[13] [14].

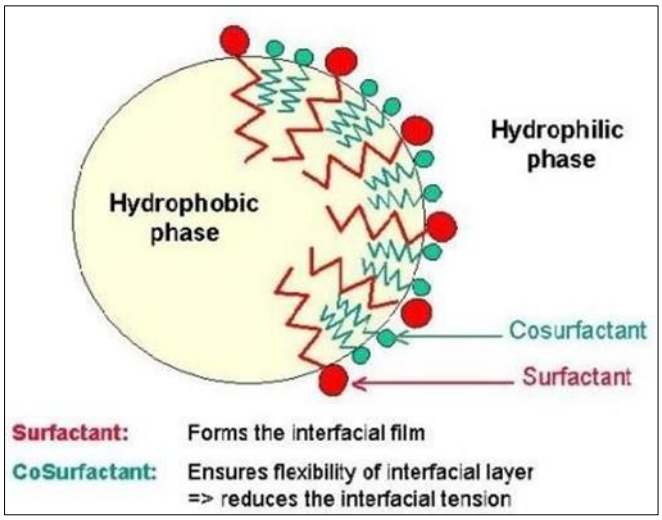

Figure 5 Micro Emulsion

2.3.2. Nano Emulsions

A surfactant, emulsifier, emulsifying agent, and co-surfactant, emulsifier, or coemulsifying agent form an interfacial coating that stabilizes the clear, transparent liquid or, in some cases, transparent dispersions of water phase and oil phase that are known as Nano emulsions. Nano emulsions are a system that is thermodynamically stable. Because Nano-emulsion compositions have globule sizes no larger than 100nm [15].

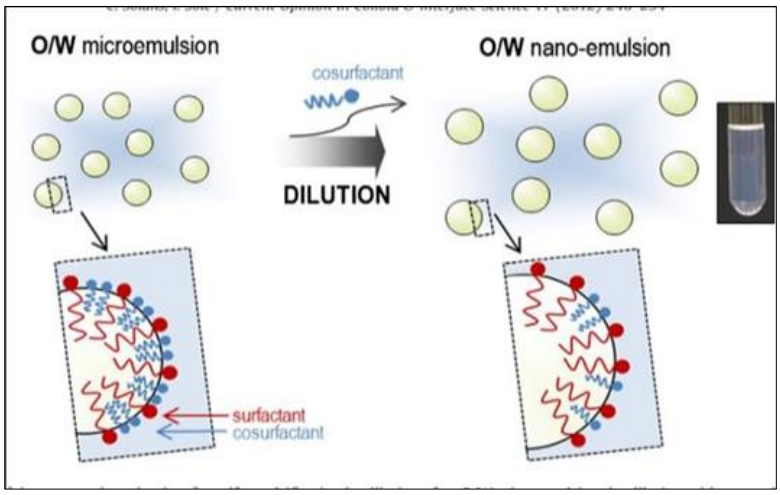

Figure 6 Nano-emulsion

2.3.3. Double/Multiple Emulsions

Small droplets of one phase (such as oil) are distributed in bigger droplets of a second phase (such as water), with the latter being the continuous medium and the latter being further dispersed in the first. Water/oil/water emulsions and oil/water/oil emulsions are the two varieties of multiple emulsions [16] [17].

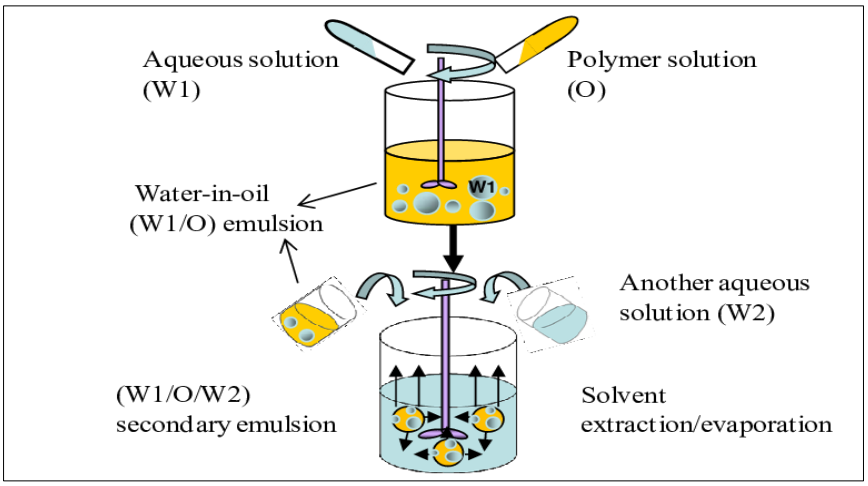

Figure 7 Double/Multiple Emulsion

2.3.4. Gel

Gel is a highly to minimally viscous semisolid formulation made up of a dispersion of ether big organic molecules or small inorganic particles, or of both, enclosed and interpenetrating by liquid phase. The diluted cross-linked polymer system prevents the gels from flowing in steady state. The gel is a highly liquid-rich system. When continuous structure is present, solid-like qualities result. A gel is made up of a natural or synthetic polymer that has been dispersed across a hydrophilic liquid or dispersion media to create a three-dimensional matrix. When a gel formulation is applied to the skin, the liquid vaporizes, leaving behind a thin film in which the medicine is trapped. Gel formulations physically cover the skin with a thin matrix. The stiffness of gel is provided by a dense network of polymers used in its formation. The type of form that links the particles together and the nature of those linkages influence the structure of the network and the characteristics of the gel.

2.4. Polymers Used in Gel Formulations

The different types of polymers are used to achieve the controlled drug delivery. The physicochemical characteristics of the drug and polymer determine how the drug is released. Gel Forming Polymers Are listed below

- **Natural Polymers** Proteins- Collagen, Gelatin, Polysaccharides- Agar, Tragacanth, Xanthun Gum
- **Semi: Synthetic Polymers-** Semi Synthetic-Cellulose Derivatives, Carboxymethyl Cellulose, Methyl Cellulose, Hydroxyethyl Cellulose.
- **Synthetic Polymers- Carbomer** E.G Carbopol 934, Carbopol940. Poloxamer Polyacrylamide Polyvinyl alcohol Polyethylene and Its Copolymers
- **Inorganic Substances**: E.G Aluminum Hydroxide, Bentonite
- **Surfactants**: E.G Cetosteryl Alcohol, Brij-96 [18].

3. Emulgel

It is the name of the formulation in which an oil-and-water emulsion is contained within a gel phase. A primary emulsion is first created with an appropriate ratio of oil to water, and this emulsion is then added to the thick gel phase. Aqueous phase, oils, gelling agents, penetration enhancers, and emulsifiers are all components of emulgel formulation, which is used to create emulsions. The emulsion in emulgel serves as a carrier for the medications it contains to dissolve. Most commonly used topical formulations like lotion, emulsion, suspension, ointment, and cream have a number of drawbacks. When applied to the skin, traditional topical formulations cause the patient to feel oily and uncomfortable. Traditional topical formulations need to be applied to the skin with rubbing since they have a lower spreading coefficient. The usage of translucent gel formulations has been expanded to pharmaceutical and cosmetic formulations due to the drawbacks of all conventional semisolid formulations. A gel formulation is a heavily saturated, dense, semisolid liquid stiff structure that is immobilized by the surface tension of the chains of a macromolecular network of fibers. Although gel formulation has more benefits than the typical topical formulation, it has a major drawback in the transport of hydrophobic actives. Therefore, to lessen the drawback of carrying for hydrophobic medicinal molecules, they can be combined in the formulation of emulgel and supplied more effectively via the skin.

3.1. Advantages of Emulgel

- **Better stability** - Lotions, emulsions, suspensions, ointments, and cream are considerably less stable than emulgel. The main drawbacks of the powdered dosage form are its hygroscopicity, the phase separation/inversion of cream formulations, and the greasy, oily, and rancidity susceptibility of ointments.
- Hydrophobic Drugs Can Be Easily Incorporated into Gels Using D/O/W Emulsions The gel base formulation's primary drawback is the delivery of hydrophobic or lipophilic medications. To create an o/w emulsion, hydrophobic or lipophilic drugs are first integrated into the oily phase and then disseminated throughout the aqueous phase. The gel is then combined with this emulsion and homogenized or stirred to create emulgel. Such a formulation, known as an emulgel, provides greater medication stability and release.
- Production Feasibility and Low Preparation Cost - Simple and quick procedures are used in the emulgel manufacturing process, increasing the viability of commercial production. Manufacturing requires no specialized equipment, and even the materials are less expensive and more readily available, lowering the cost of production.
- **Better Loading Capacity** - The vesicular form of liposome and noisome causes leakage and lower trapping efficiency, which raises the cost of manufacture. But because of their broad network and use of polymer chains, emulgel formulations have better drug loading and retention capabilities.
- **Controlled Release** - The emulgel formulation may be used to prolong medication release, hence reducing the issue of pharmaceuticals with shorter half-lives.

3.2. Formulation of emulgel

In the present study emulgel is prepared from modified emulsion solvent diffusion method.

- Step 1: In the first step accurately weighed quantity of drug is dissolved in distilled water.
- Step 2: The gel phase in the formulations was prepared by dispersing carbopol 934 in purified water with constant stirring at a moderate speed using mechanical shaker.
- Step 3: In this step the oil phase of the emulsion was prepared by dissolving span 20 in liquid paraffin. (oil phase)
- Step 4: In this step the aqueous phase was prepared by dissolving tween 20 in purified water. (aqueous phase)
- Step 5: In this step methyl paraben is dissolved in propylene glycol. The drug phase and propylene glycol solutions both are mixed with the aqueous phase.
- Step 6: The penetration enhancers' menthol and clove oil were mixed in oil phase. The prepared both the oily and aqueous phase separately heated to 70-80 c then the oily phase is added to the aqueous phase with continuous stirring until it gets cooled to room temperature.
- Step 7: PH was adjusted to 6 to 6.5 by using the triethanolamine and the obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel [18].

3.3. Formulation table

Table 1 Formulation Table

Ingredients	**F1**	**F2**	**F3**
Eucalyptus(ml)	0.25	0.5	1
Carbopol 934(mg)	1	1	1
Liquid Paraffin(ml)	10	10	10
Propylene Glycol(ml)	2	2	2
Tween 20(ml)	2	2	2
Span 20(ml)	2	2	2
Triethanolamine(ml)	Q.S	Q.S	Q.S
Methyl Paraben (gm)	0.01	0.01	0.01
Menthol(ml)	1.0	1.5	2.0
Water	Q.S	Q.S	Q.S

3.4. Evaluation

The prepared Emulgel were evaluated by following parameters.

- Physical properties [19]

All the formulations were evaluated visually for the colour, odour, homogeneity and consistency.

- pH: [20]

A digital pH meter was used to determine the pH of various Emulgel formulations.

- Viscosity:

The viscosity of the formulations (gel) was measured in cps at 25°C using a Brookfield viscometer with spindle no. S-96 spinning at 1rpm. Each formulation was measured three times and the average values were determined

- Spreadability:

This test was performed using the slide method. The gel was placed in between the two slides after some times Spreadability was observed.

$$S=M*L/T$$

Where,
M = Weight on Upper Slide
L = Length moved on glass slide
T = Time taken to separate the slide completely from each other.

- Drug content studies

Three Batches were wrapped in soft gelatin paper and allowed to stand in buffer solution. The above buffer solution with a pH range of 5 to 6 was prepared by mixing anhydrous acetic acid with sodium acetate. For an hour, aliquots of each Batch were obtained at 10-minute intervals.

4. Results

Batch F3 was found to be optimized batch.

Results of batch C are as follows

Figure 8 Prepared Gel

4.1. Physical Characters

Table 2 Physical Characters

Batch	Colour	Odour	Homogeneity	Consistency
F3	White	Odorless	Homogeneous	Smooth

4.2. Determination of pH

pH was determined by using pH meter and found to be 5.8 pH.

4.3. Determination of Viscosity

It was measured in cps at 25°C using a Brookfield viscometer with spindle no. S-96 spinning at 1rpm and found to be 3856 cps

4.4. Spreadability

$$S=M*L/T$$

Where,
M = Weight on Upper Slide = 5g
L = Length moved on glass slide = 4 cm
T = Time taken to separate the slide completely from each other =5 min

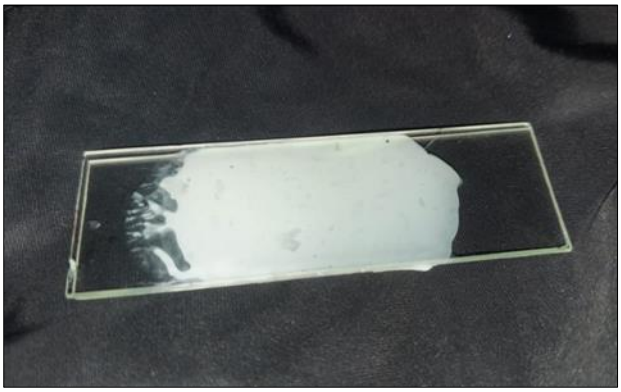

Figure 9 Spreadability

S = 20 g.cm/min

4.5. Drug Content Release

R^2 value was found to be 0.99

Figure 10 Release Mechanism

Table 3 Drug Release

Time (min)	Absorbance
10	12.8
20	19.55
30	27.77
40	36.01
50	47.67

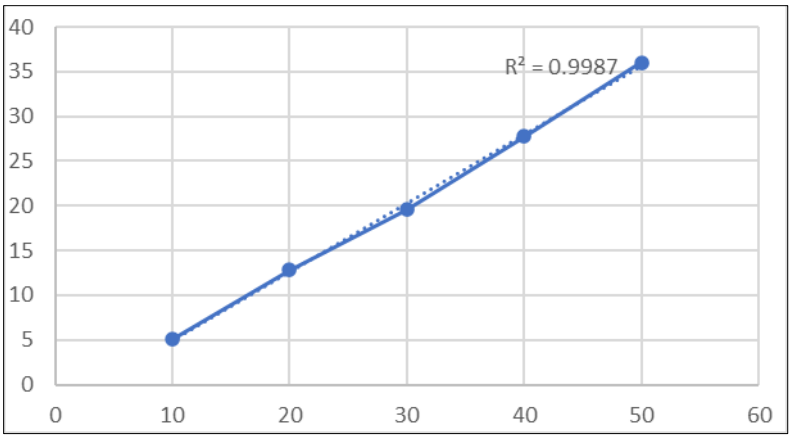

Figure 11 Permeation of Batch C

5. Conclusion

The formulation of Eucalyptus Emulgel represents a significant advancement in the development of topical analgesics. The novel combination of eucalyptus oil with a gel-based emulsion matrix has demonstrated promising analgesic properties, offering a potential alternative for pain relief. The emulgel formulation ensures enhanced penetration of the active ingredients, providing effective and sustained relief from pain. Additionally, the natural origin of eucalyptus oil reduces the risk of side effects associated with synthetic analgesics. Further clinical studies are warranted to fully establish the therapeutic efficacy and safety profile of Eucalyptus Emulgel, but the initial findings suggest a bright future for this innovative formulation in pain management

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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