



Formulation and *in vitro* evaluation of topical drug delivery system for emulgel to treat acne

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Abstract

This study presents a novel emulgel formulation combining turmeric and neem for the topical treatment of acne. Both ingredients are known for their strong anti-inflammatory, antibacterial, and antioxidant properties, making them effective against acne-causing bacteria and skin inflammation. By utilizing an emulgel a hybrid of gel and emulsion the formulation enhances skin penetration and stability, thus addressing common limitations of traditional topical acne treatments. Emulgel formulation (F1-F4) was developed using a concentration of carbopol 940 the formulation assessed their physical-chemical properties including appearance, pH, spreadability, viscosity, and microscopic study. Then we conduct a formulation where F3 and F4 have low spreadability and F1 has less consistency but the F2 formulation passes all the tests and consistency including pH measurement, viscosity, spreadability, and microscopic examination. Results showed that the emulgel has a pH level compatible with the skin, excellent spreadability, and optimal viscosity, making it easy to apply. Microscopic analysis confirmed the uniform dispersion of active ingredients within the gel matrix, ensuring even application and absorption.

Keywords: Topical drug, carbopol 940, emulgel, drug release

Introduction

Acne is a long-term inflammatory skin condition caused by increased sebum production, changes in skin cell formation, inflammation, and the presence of *Propionibacterium acnes* bacteria in hair follicles on the face, neck, chest, and back. The main causes of acne include increased keratinocyte proliferation, incomplete separation of corneocytes, androgen-mediated sebum production increase, *Propionibacterium acnes* colonization, and inflammation. While acne is often seen as a condition that resolves during the teenage years, it can persist into adulthood. Almost 90% of teenagers experience acne, and about half of them continue to have issues as adults. By the age of 40, approximately 1% of men and 5% of women still experience acne-related skin problems. Due to its potential to last for many years and require prolonged treatment, there is a movement to redefine acne as a chronic condition. Acne significantly impacts mental well-being and can lead to lasting scars on the skin. The skin has tiny pores connected to oil glands, and when these follicles become clogged, pimples form due to the accumulation of oil under the skin. Pores clogged by oil, dirt, or bacteria can develop pimples or "zits." This blockage leads to oil buildup, rapid bacterial growth, redness, and swelling, which can lead to acne, causing pain during severe outbreaks.

Types of acne

A comedo, which is a basic acne lesion, occurs when a hair follicle becomes clogged with oil and dead skin cells. Comedones (plural of comedo) can develop into whiteheads and blackheads.

Noninflammatory

1. Blackhead: This is a mild type of acne. Blackheads are visible on the skin's surface and are clogged with dead skin cells and abundant oil. The black color is caused by the uneven light reflection from obstructed hair follicles, not dirt.

2. Whitehead: This is also a mild type of acne. When a pore becomes clogged by sebum and dead skin cells, whiteheads can form. Unlike blackheads, the top of the pore closes, creating a small lump on the skin.

Inflammatory

1. Pimple: This is a moderate type of acne. Papules are topped by white or yellow pus-filled lesions that may be red at the base.

2. Pustules: This is also a moderate type of acne. When the walls around your pores break down due to acute inflammation, papules form. The pores become hard and plugged, and the skin around them is normally pink and painful to touch.

3. Nodule: This is a moderate to severe type of acne. Nodules are hard, inflammatory lumps that develop deep beneath the skin. They lack a visible head and can lead to skin issues such as dark patches or scars.

4. Cyst: This is a severe type of acne. Cysts are huge, painful, red or white tumors located deep beneath the skin. Unlike nodules, cysts are filled with pus and are usually soft to the touch. Cysts are the most severe type of acne lesion and can cause scarring if not treated properly. In severe cases, surgery may be required.

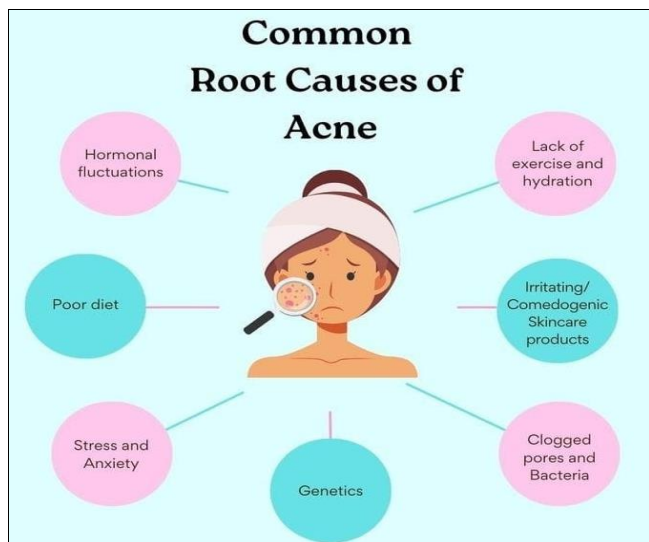


Fig 1: Causes of acne

Causes of acne

The causes of acne vulgaris can have a significant and long-lasting psychological impact. Diagnosis often involves a clinical examination, and patients should be questioned about their family history, symptoms, and indicators of hyperandrogenism or another endocrine disease, such as cortisol or growth hormone excess. Factors such as the consumption of excess oily foods and dairy products, as well as irregular sleep-wake cycles, can also increase the likelihood of acne formation. A history of irregular menstrual periods and hirsutism may indicate polycystic ovary syndrome (PCOS), while a sudden onset of acne may indicate a gonadal tumor.

Patients should also be asked about their use of acne-related drugs, such as phenytoin, lithium, glucocorticoids, and progestin-only contraceptives. Certain cosmetic ingredients, such as decyl oleate, isopropyl palmitate, isopropyl myristate, isopropyl isostearate, myristyl myristate, butyl stearate, isocetyl stearate, coconut oil, and cocoa butter, can be comedogenic. Additionally, exogenous androgens and whey protein supplements have been associated with exacerbating acne in some cases, particularly truncal acne. [1]

Emulgels

Emulgels are unique dermatological preparations that provide direct access to the skin for diagnosis and treatment. This sector is still developing for topical drug delivery and currently has few marketed products. Emulgels are a combination of gels and emulsions, forming a biphasic system comprising an internal emulsion within an aqueous gel base. This innovative approach is mainly used for transporting hydrophobic drugs. The hydrophobic drug is mixed in the oily phase, which is then incorporated into a gel base. Emulgels can be either oil in water or water in oil and are used as a vehicle to deliver drugs topically. They can be stabilized by using an emulsifying agent. Emulgels can be easily rinsed off through the skin and have excellent penetration abilities. A perfect emulsion is converted into an Emulgel by adding a gelling agent in an aqueous segment. Various drugs are transported to the systemic circulation through Emulgels. Emulgels are bio-friendly, thixotropic, greaseless, easily spreadable, easily removable, non-staining, have an extended shelf life, are transparent, and

have a good appearance. Nanoemulsions have attracted attention for the transportation of therapeutically potent agents, as approximately 40 percent of new chemical moieties are hydrophobic, making it a challenge to deliver poorly water-soluble drugs. Nanoemulsions refer to the dispersion of two isotropic immiscible liquids. Nanoemulsions differ from traditional emulsions in the size and shape of particles, with particle size in nanoemulsions ranging from 100 – 200 nm, whereas traditional emulsions range from 1 – 20 μm . Nanoemulsions have a large loading capacity and can be used to formulate both hydrophobic and hydrophilic drugs. These non-toxic, non-irritant systems are used for skin or mucous membranes and are made up of oil droplets scattered in an aqueous phase and strengthened by surfactant. The advantages of nanoemulsions include increased drug loading and boosted bioavailability. They can also be used for sustained and targeted drug delivery.

Herbal emulgels

The term "medicinal plant" encompasses various plants used in herbalism or herbal medicine. These plants' parts, such as roots, flowers, stems, seeds, bark, and other plant parts, have been used for medicinal purposes long before the prehistoric period. According to the World Health Organization (WHO), 80 percent of the world's communities rely on medicinal herbs.

The use of medicinal plants is believed to be very safe with little to no side effects.

Herbal plants are considered a rich source of active constituents that can be used in new drug inventions including pharmacopeial, non-pharmacopeial, or synthetic drugs. Over the past era, there has been a significant increase in the practice of herbal medicinal preparations. Herbal drugs are easily obtainable, cheaper, traditional, and considered safer than man-made drugs. About half of the best-selling pharmaceuticals used today are derived from natural products. Herbal medicines consist of plant parts used to treat injuries, diseases, or illnesses and promote health and healing. Herbal medication is the oldest form of health care known to humanity. [2]

Advantages

- First-pass metabolism is bypassed.
- Target specific sites.
- Improves patient compliance.
- Suitable for hydrophobic drugs.
- High loading capacity.
- Enhanced penetration and stability.
- Low manufacturing cost.
- Simple application.

Disadvantages

- Dermal inflammation or contact dermatitis.
- Hypersensitivity.
- Poor absorption of certain drugs through the skin.
- The large molecule size of the drug may not be absorbed through the skin.
- Possibility of allergic reactions.

Topical drug delivery system

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal, and skin topical routes. Skin is one of the most readily accessible organs in the human body for topical

administration and is the main route of the topical drug delivery system. This review is concerned with detailed information regarding the rational approach to topical formulations, principles of topical permeation, and basic components of topical drug delivery systems.

Overall, the clinical evidence indicates that topical gel is a safe and effective treatment option for use in the management of skin-related disease. Topical preparations are applied to the skin for surface, local, or systemic effects. Sometimes, the base may be used alone for its therapeutic properties, such as emollient, soothing, or protective action. Many topical preparations, however, contain therapeutically active ingredients which are dispersed or dissolved in the base.

The combination of active ingredients and base provides the opportunity for a wide range of topical preparations, appropriate for many types of drug delivery and therapy terms used to classify the bases of topical preparations in which therapeutically active ingredients are incorporated, may be based on their physical properties (suspension) or their intended use (liniments) or their composition ((hydrophilic creams).^[3]

Turmeric

Turmeric, scientifically known as *Curcuma longa*, is a flowering plant in the ginger family. It is known for its culinary and medicinal uses. The active compound in turmeric is called curcumin, which is extracted from the rhizomes. This compound has antioxidant and anti-inflammatory properties. Turmeric is commonly used in traditional medicine and various culinary applications, not only for flavor but also for potential health benefits.



Fig 2: *Curcuma longa*

The herbal preparation of turmeric, derived from the rhizomes of the *Curcuma longa* plant, has a rich history rooted in traditional medicine and culinary practices. Turmeric, a member of the ginger family, has been a staple in various cultures for centuries. The key component responsible for turmeric's therapeutic properties is curcumin. Extracted from the rhizomes, curcumin is a polyphenol with potent antioxidant and anti-inflammatory effects. These qualities make turmeric a valuable ingredient in herbal remedies aimed at promoting overall health and well-being. In the traditional system, turmeric has been utilized for its effect in alleviating various ailments. It has been employed as an anti-inflammatory agent, aiding in the management of conditions such as arthritis. Additionally,

curcumin is believed to have anticancer properties and may contribute to cardiovascular health. Culturally, turmeric holds significance as a spice and coloring agent in culinary applications. Its warm, earthy flavor enhances a variety of dishes, and it is a fundamental ingredient in curry powder.

Description of turmeric

Turmeric (*Curcuma longa*) is a perennial herbaceous plant that belongs to the Zingiberaceae family, which also includes ginger. Here are some of its main characteristics:

- 1. Rhizomes:** Turmeric is mainly grown for its underground stems, or rhizomes, which are thick, tuberous, and orange-yellow. These rhizomes are the source of the spice and medicinal compound known as curcumin.
- 2. Leaves:** The plant has long, lance-shaped leaves with a central rib and a smooth texture. The leaves grow in a dense spiral arrangement from the base of the plant.
- 3. Flowers:** Turmeric plants produce spikes of yellow to pink flowers, with a central cylindrical spike called an inflorescence. The flowers are sterile, and the plant primarily reproduces through the propagation of rhizomes.
- 4. Height:** Mature turmeric plants can grow to be around 3 to 5 feet (1 to 1.5 meters) tall.
- 5. Habitat:** Turmeric is native to Southeast Asia and thrives in tropical and subtropical climates. It requires well-drained soil and warm temperatures for optimal growth.
- 6. Cultivation:** Turmeric is commonly cultivated as a crop, with the rhizomes being harvested for various purposes.

Turmeric is classified as follows

Kingdom: Plantae (plants)
Clade: Angiosperms (flowering plants)
Order: Zingiberales
Family: Zingiberaceae (ginger family)
Family: Turmeric
Species: *Curcuma Longa*

Benefits of turmeric

- Anti-inflammatory Activity
- Antioxidant Properties
- Anti-cancer Potential
- Antibacterial and Antiviral Effects
- Cardioprotective Effects
- Wound Healing
- Reduction of scars and stretch marks
- Moisturizing and hydration^[4]

Neem

Azadirachta indica, commonly known as neem, is native to India and has become naturalized in most tropical and subtropical countries. It is of great medicinal value and is widely distributed throughout the world. Neem contains many biologically active compounds, including alkaloids, flavonoids, triterpenoids, phenolic compounds, carotenoids, steroids, and ketones. The most biologically active

compound is azadirachtin, which is a mixture of seven isomeric compounds labeled as azadirachtin A-G, with azadirachtin E being the most effective. Other compounds with biological activity include salannin, volatile oils, meliantriol, and nimbin. The importance of the neem tree has been recognized by the US National Academy of Sciences, which published a report in 1992 entitled "Neem - A Tree for Solving Global Problems." Previous advancements in neem research have also been documented.



Fig 3: *Azadirachta indica*

Neem is classified as follows:

Kingdom: Plantae,
Order: Rutales,
Suborder: Rutinae,
Family: Meliaceae,
Subfamily: Melioideae,
Tribe: Melieae,
Genus: *Azadirachta*,
Species: *India*

Distribution of neem

The tree is native to East India and Burma, and it can be found in various regions of Southeast Asia, West Africa, the Caribbean, and South and Central America. In India, it naturally occurs in the Siwalik Hills, the dry forests of Andhra Pradesh, Tamil Nadu, and Karnataka, up to an altitude of about 700 meters. It is cultivated and commonly found in the drier regions of tropical and subtropical India, Pakistan, Sri Lanka, Thailand, and Indonesia. Additionally, it is grown and frequently found in Peninsular Malaysia, Singapore, the Philippines, Australia, Saudi Arabia, tropical Africa, the Caribbean, and Central and South America.

Botanical description

The tree grows to a height of 40-50 feet or higher, with a straight trunk and long spreading branches that form a broad round crown. Its rough, dark brown bark has wide longitudinal fissures separated by flat ridges. The leaves are compound and imparipinnate, each comprising 5-15 leaflets. The compound leaves alternate with one another. The tree bears many-flowered panicles, mostly in the leaf axils. Its flowers have ovate sepals and sweet-scented white oblong petals, and it produces yellow drupes that are ellipsoid and glabrous, 12-20 mm long. The fruits are green,

turning yellow when ripe, and they have an aromatic, garlic-like odor. Fresh leaves and flowers appear in March-April, and the fruits mature between April and August, depending on the locality.

Benefits of neem

- Analgesic
- Anthelmintic
- Antibacterial
- Anti yeast
- Antiulcer
- Antifertility
- Antifungal
- Antihyperglycemic
- Anti-inflammatory

Medicinal use

All parts of the neem tree have been used for centuries in traditional medicine. Its fruits, seeds, oil, leaves, roots, and bark have been utilized in Ayurvedic and Unani medicine for over 4000 years. These components are now finding applications in the pharmaceutical and cosmetic industries.

- Antiseptic properties: Neem preparations can be used to treat skin diseases, septic sores, and infected burns.
- Antiviral effects: Neem leaves can treat smallpox, chickenpox, and warts.
- Anti-inflammatory properties: Neem can help reduce acne and skin blemishes.
- Antifungal properties: Neem has properties that can help treat fungal infections.
- Detoxification: Neem can help detoxify the body internally and externally.
- Immunity: Neem has antimicrobial and antibacterial effects that can help increase immunity.
- Gastrointestinal diseases: Neem can help reduce inflammation of the gastrointestinal tract and treat diseases like constipation, stomach ulcers, and flatulence.
- Dandruff: Neem oil can help with dandruff and itching.^[5]

Materials

- Herbal drugs: turmeric and neem
- Oil phase: olive oil
- Gelatin: carbopol 934
- Emulsifying agent: tween 80
- Preservative: methylparaben
- To adjust the pH and viscosity: triethanolamine

Methodology

Extraction: Twenty-five grams of turmeric and neem powder were placed in a separate glass container. Then, 70 ml of distilled water and 30 ml of ethanol (in a 70:30 ratio) were added to the powder to obtain a hydro-alcoholic extract of turmeric and neem. The glass container was properly sealed to prevent the evaporation of the solution and then was kept to stand for 7 days with frequent stirring at room temperature ($24 \pm 1^\circ\text{C}$). Afterward, the suspension was filtered to separate the powder from the liquid. After complete filtration, the liquid solution was stored in sealed test tubes and kept refrigerated.^[16]



Fig 4: Extraction

Formulation

Table 1: Formulation

Ingredients	F1	F2	F3	F4
Turmeric	2	2	2	2
Neem	2	2	2	2
Olive oil	2.25	2.25	2.25	2.25
Carbopol 934	1gm	1.5gm	2gm	2.5gm
Tween 80	0.8	0.8	0.8	0.8
Methylparaben	0.03gm	0.03gm	0.03gm	0.03gm
Triethanolamine	1-2 drop	1-2 drop	1-2 drop	1-2 drop
Water	qs	qs	qs	qs



Fig 5: Preparation

Methods

- Oil phase preparation:** Mix oil phase ingredients in a separate container.
- Water phase preparation:** Mix water phase ingredients in another container.
- Emulsification:** Slowly add the oil phase to the water phase or water phase to the oil phase with continuous stirring using a suitable emulsifying agent.
- Gel formation:** Take the required quantity of gelling agent and distilled water and add 1-2 drops of triethanolamine
- Mixing and homogenization:** Ensure uniform mixing and homogenization.^[9]

Use of ingredients

Turmeric

- Natural antiseptic.
- Natural analgesic.
- Speeds up wound healing.
- Improves digestion.
- Blood purifier.
- Strengthens ligaments.
- Helps alleviate coughing.

- Improves asthma.
- Anti-arthritis.
- Improves skin conditions (psoriasis, eczema).
- Reduces side effects of chemotherapy.

Neem

- Treating acne
- Reducing inflammation
- Hydrating
- Cleansing
- Controlling oil
- Treating fungal infections.
- Nourishing skin

Carbopol

- Is used as a gelling agent
- It is also used to stabilize, suspend, and control the release of pharmaceutical products.

Methylparaben

- To prevent the growth of mold and other harmful bacteria.

Triethanolamine

- Is used as a neutralizer and the pH of the gels.

Physical properties

- Colour:** The color of the formulations was checked by visual inspection.
- Odour:** The odor of the formulations was checked by mixing the gel with water and observing the smell.

Table 2: Physical properties

Sl no	Parameter	Evaluation
1	Color	Pale yellowish
2	Odor	Characteristic

The pH of emulgel

The pH values of all prepared emulgel formulations ranged from 5.76 to 5.94 as shown in the table. The range is acceptable as they minimize skin irritation. The standard range of pH of herbal emulgel is found to be 5.5-6.5 is good for the skin.

Table 3: pH

Formulation	F1	F2	F3	F4
pH	5.76	5.94	5.68	5.82

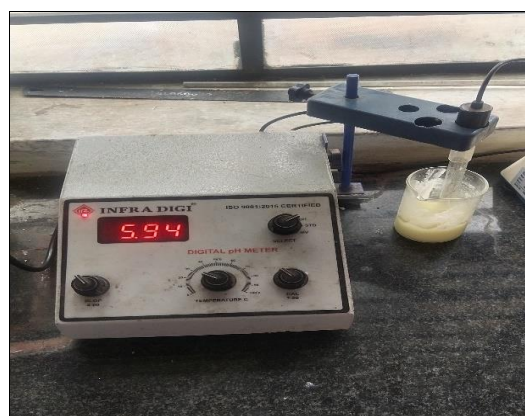


Fig 6: Digital pH

Spreadability

The spreadability of emulgel formulation was determined 48 hours after preparation by measuring the spreading diameter of 1 gm emulgel which is placed in the center of the slide and sandwiched between two slides. A weight of 100 g was allowed to rest on the upper side for 1 min. The increase in the diameter due to the spreading of the emulgel is noted.

The spreadability (g.cm.min⁻¹) was calculated by using the formula $S = M \cdot L / T$

S is spreadability M is the weight of the upper plate and rested on it (g). L is diameter of spreading emulgel (cm) and T is time taken (min)

$S = M \cdot L / T$

1] $F1 = 100 \cdot 4 / 60 = 6.6 \text{ cm/sec}$ 2] $F2 = 100 \cdot 3 / 60 = 5 \text{ cm/sec}$ 3] $F3 = 100 \cdot 2.5 / 60 = 4.166 \text{ cm/sec}$ 4] $F4 = 100 \cdot 2 / 60 = 3.33 \text{ cm/sec}$

The spreadability of emulgel formulation of the spreadability test was found to range from 3.33cm/sec to 6.6cm/sec, for the formulation of F1 to F4 and the data of the given table. By taking the data into consideration it was observed that the concentration of gelling agent makes the difference in spreadability.

The formulations F1 and F2 have a good range of spreadability compared to the standard value.

Table 4: Spreadability

Formulation	F1	F2	F3	F4
Spreadability (cm/sec)	6.6cm/sec	5cm/sec	4.166cm/sec	3.33cm/sec



Fig 7: Spreadability

Viscosity: The viscosity of the formulated emulgel was measured using a Brookfield RV viscometer at 20 RPM with spindle number S-03. According to the data from the table, formulations F1, F2, F3, and F4 demonstrate that an increase in polymer concentration leads to a corresponding increase in viscosity.

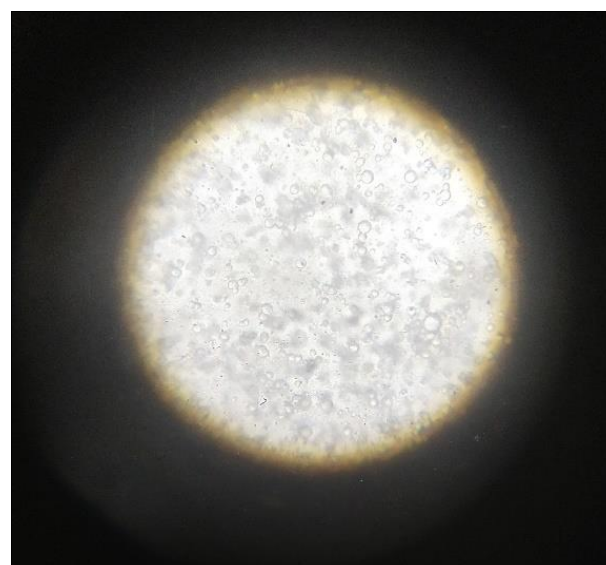
Table 5: Viscosity

Formulation	F1	F2	F3	F4
Viscosity	769cp	815cp	890cp	900cp

Microscopic study

Based on the tests conducted, we performed a microscopic study on the F1 and F2 formulations. The F1 formulation showed less dispersion of oil globules, while the F2

formulation exhibited spherical globules. This indicates a uniform dispersion of oil droplets within the gel matrix, resulting in the formation of an emulsion in the gel base.



F1: Microscopic view



F2: Microscopic view

Fig 8: Microscopic study

Conclusion

- The formulation and *in vitro* evaluation of an emulgel for acne treatment for topical drug delivery system. We conducted the four formulations F1, the formulation has good pH and spreadability but the formulation is not consistent F3 and F4 have good pH but spreadability is not accurate compared to standard values because of the high concentration of gelling agent but F2 passes all the tests like pH, viscosity, spreadability, and oils are uniformly dispersed.
- The formulation and *in vitro* evaluation of an emulgel for acne treatment demonstrates significant potential as a topical drug delivery system. The study focused on combining natural ingredients like turmeric and neem, known for their anti-inflammatory, antibacterial, and antioxidant properties, into an emulgel to target acne-related bacteria and skin inflammation. Key evaluations

showed that the emulgel displayed an optimal pH close to the skin's natural pH, excellent spreadability, stability, and a suitable viscosity, making it easy to apply and potentially more effective for acne skin.

- The microscopic analysis revealed uniform dispersion of the active ingredients, which ensures consistent application and absorption. Using natural ingredients also minimizes the likelihood of side effects, setting this formulation apart from conventional acne treatments that can cause skin irritation or resistance.
- Herbal cosmetics have a great demand in the market and are a priceless gift of nature. The herbal gel is much safer has fewer side effects and non toxic.
- From the above study, it can be concluded that herbal emulgel is safe to use as it is formulated from the herbal.

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