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A new method for improved topical drug delivery, Emulgel

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Abstract

Emulgel is used to treat injuries and diseases such as arthritis, headaches, muscle aches, backaches, and those brought on by colds. Patient compliance with topical formulations is crucial in the treatment of chronic dermatosis such psoriasis, acne, and fungal infections. Emulgel, a more recent NDDS technology used topically, combines the characteristics of an emulsion with a gel to provide a dual control release. Emulgels have emerged as one of the most exciting topical delivery methods because of their dual release control mechanism, which combines a gel with an emulsion. Gels have many benefits, but one significant drawback is that hydrophobic medication delivery is hampered. An emulsion-based approach is being developed to circumvent this limitation and enable even a hydrophobic medicinal component to take use of the unique properties of gels. Emulgel is the name given to the dosage form created by combining gel with emulsion. Emulgels can be added to analgesics and antifungal medications. In several aspects, these emulgels are superior to both cutting-edge vesicular systems and traditional systems.

Keywords: Emulgel; Topical medicine administration; Skin conditions (Dermatitis); Agents of gelling

1. Introduction

Localized drug distribution through the skin, vagina, rectal, and ocular cavities is known as topical drug administration. They treat their healthy or damaged skin using a variety of cosmetic and dermatological remedies. (1) Drug substances are typically provided in conjunction with one or more non-medicated compounds that have different and specific pharmacological functions as part of a formulation rather than on their own. Drugs are applied topically for local or systemic effects, depending on the drug's intended use. (2) The topical delivery system's primary benefit is avoiding first pass metabolism. Faster stomach emptying has the added benefit of avoiding the dangers and disadvantages of intravenous treatment as well as the numerous conditions for absorption, such as pH changes and the presence of enzymes. When other drug administration techniques fail, the topical pharmaceutical delivery mechanism is frequently used. Additionally, the study is being carried out to minimise the risks and drawbacks of intravenous therapy as well as the varied absorption circumstances, such as pH changes, the presence of enzymes, and stomach emptying time. (3) Most pharmacological preparations used topically are created with a local impact in mind and are intended to maintain a sustained local contact with a minimal amount of systemic drug absorption.(4) The human skin is a uniquely created organ that controls heat and water loss from the body and prevents the entry of dangerous chemicals or microorganisms, hence extending life on land. Thus, the human body's biggest organ occupies an average area of 1.7 m2 and accounts for around 10% of the average person's total body weight. (2) Despite appearing to offer good and many locations to administer therapeutic chemicals for both local and systemic activities, the human skin is a very effective self-repairing barrier created to keep the insides in and the outsides out. (5) Molecules can enter the skin in three major ways: through the intact stratum corneum, sweat ducts, or sebaceous follicles. The stratum corneum's surface makes

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up more than 99% of the total skin surface that can be exploited for percutaneous drug absorption. The rate-limiting step in percutaneous absorption is the passing through this top layer. The primary phases in percutaneous absorption are the establishment of a concentration gradient, which provides the force necessary for the drug to traverse the skin, the release of the drug from the vehicle (partition coefficient), and drug diffusion through the layers of skin (diffusion coefficient). The production of gels, a more modern family of dosage forms, involves encasing large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles. These particles might be organic polymers that are either natural or manmade, or they could be inorganic, like salts of aluminium. They have a bigger aqueous component than ointment or cream bases, which increases the drug's solubility and makes it easier for the medication to move through a vehicle that is essentially a liquid. (7) These are better in terms of user-friendliness and patient acceptability. Gels offer several advantages, but hydrophobic drug delivery is a severe disadvantage. Emulgels are developed to circumvent this constraint, enabling even a hydrophobic medicinal component to take use of the unique properties of gels. In actuality, the presence of a gelling component in the aqueous phase transforms a conventional emulsion into an emulgel. (8)

2. Rationale

Despite being widely used, topical treatments like ointments, creams, and lotions have a number of disadvantages. They are quite sticky when delivered, which is irritating for the patient. They also require rubbing application since they have a reduced spreading coefficient. They exhibit the stability problem as well. All these factors within the primary category of semisolid preparations have led to a rise in the use of transparent gels in medicinal and cosmetic preparations. A colloid, which is typically 99 percent liquid by weight, is immobilised by the surface tension between the colloid and a macromolecular network of fibres made from a little amount of a gelating substance. Gels offer several advantages, but hydrophobic drug delivery is a severe disadvantage. By employing an emulsion-based strategy, it is possible to efficiently integrate and distribute a hydrophobic medicinal component via gels, circumventing this limitation. (9)

2.1. Advantages (10) (11)

- Refraining from first-pass metabolism.
- Avoiding stomach-related incompatibility
- Providing a medication with a limited therapeutic window and short biological half-life.
- The capability to quickly stop taking medication when necessary.
- Practical and simple to use.
- The use of hydrophobic medicines
- More concentrated on a certain area.
- Boost patient compliance.
- Suitability for self-care.
- Enhanced capacity for loading
- Greater steadiness
- Production viability and affordable setup costs
- Careful release
- There is no extensive sonication

2.2. Disadvantages

- 1. An inflammation of the skin due to contact dermatitis.
- 2. The possibility of allergic reactions.
- 3. Some drugs only partially penetrate the skin.
- 4. Drugs with large particles are challenging to absorb via the skin.
- 5. A bubble that appears while making emulgel.

Factors Affecting Topical Absorption of Drug. (12)(13)

- Weight of Skin.
- Lipidic substance.
- Hair follicle density
- Sweat gland density
- Body pH
- A flow of blood
- Skincare hydration

- Bruising of the skin

Physiochemical Factors

- Coefficient of division
- Mass of molecules
- Measurement of ions (only unionised drugs).
- A vehicle's impact

2.3. Physiology of skin (14)(15)

Almost all topical medications are used topically. Therefore, it is crucial to have a fundamental understanding of how the skin works physiologically when creating a dose form. Around one-third of the blood that circulates through the body passes through the skin of an average adult, which has a surface area of roughly 2 m2. Between 40 and 70 hair follicles and 200 to 300 sweat ducts are found on every square centimetre of human skin. The pH of the skin is between 4 and 5.6. Sweat and the fatty acids that sebum releases affect the pH of the skin's surface. The skin is made up of four different layers of tissue.

2.3.1. Non-viable epidermis

Most things that come into touch with skin are physically separated from it by the stratum corneum, the skin's top layer. The stratum corneum covers the majority of the body and is 10 to 20 cell layers thick. The cells are arranged in a brick-like pattern and are each a flat, plate-like structure with dimensions of 34–44 mm in length, 25–36 mm in width, and 0.5-0.20 mm in thickness. Protein (75–85%), predominantly keratin, neutral lipid (5–15%), phospholipids, glycosphingolipids, and cholesterol sulphate make up the stratum corneum.

2.3.2. Viable Epidermis

This layer of skin lies between the stratum corneum and the dermis and ranges in thickness from 50 to 100 m. Physically and chemically, the architecture of the live epidermis' cells is similar to that of other living tissues. Tonofibrils act as a cell's glue. The density of this region is quite close to that of water. It is mostly made up of water.

2.3.3. Dermis

Just underneath the healthy epidermis is the dermis. Few cells in healthy tissue histologically resemble this structural fibrin; it is one. The dermis ranges in thickness from 2000 to 3000 m and is composed of a matrix of loose connective tissue formed of fibrous protein embedded in an amphorphose base substance.

2.3.4. Subcutaneous connective tissue

The subcutaneous tissue, also known as the hypodermis, is not really considered to be a legitimate part of the organised connective tissue, despite the fact that it includes blood and lymphatic arteries, sweat gland secretary pores, and cutaneous nerves. Even while adipose tissue could serve as a drug storage area, the majority of researchers think that medications enter the circulatory system through the skin before they reach the hypodermis.

2.3.5. Diagram of Physiology of skin

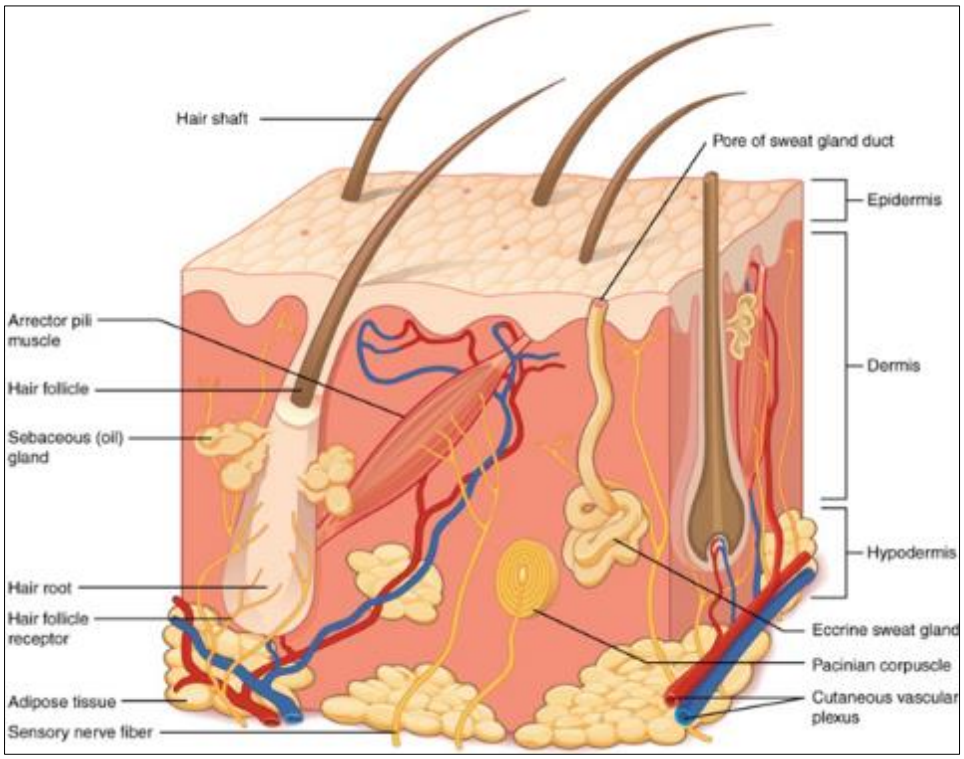

Figure 1 Structure of Skin

Considerations to Make When Selecting a Topical Preparation (16) (17)

- The impact of the vehicle, such as how an occlusive vehicle improves the penetration and efficacy of the active component The vehicle itself may function as a coolant, drier, emollient, or protector.
- Match the type of preparation to the type of lesions. Avoid using oily ointments, for example, if you have acute weepy dermatitis.
- Match the preparation strategy to the locale.
  (Example: For areas with hair, use gel or lotion.)
- Ointments and creams without alcohol often cause less irritation than gels in terms of risk for itchiness or hypersensitivity. Ointments are devoid of emulsifiers and preservatives if you have a preservative allergy.

How to Improve Drug Absorption and Penetration. (18)

- Chemical augmentation
- Physiological improvement
- Biological improvement
- Supersaturation augmentation.

3. Transdermal drug delivery

The two crucial skin layers are the epidermis and dermis. Numerous blood arteries can be seen in the subcutaneous layer just below the skin. The three primary pathways for medication absorption via the skin are intercellular, transcellular, and follicular. The second most common form of dispersion is by the pilosebaceous route. Although highly polar substances have been shown to move more quickly through the transcellular channel, penetration frequently occurs through the intercellular matrix. It is well recognised that in healthy, undamaged skin, the keratinized corneocytes and the mostly non-polar lipid intercellular cement of the horny layer are essential for maintaining an effective barrier for medications (19). . DMSO, surfactants, and propylene glycol are examples of organic solvents that can be used to increase drug penetration through skin. Numerous methods, including boosting solubility, dividing the stratum corneum, and fluidizing its crystalline structure, alter the stratum corneum's barrier properties (20). Creams and gels that are applied to the skin are used to deliver pharmaceuticals that can successfully cure infections and

discomfort since many years ago. Thanks to breakthrough technology, several drugs can now be absorbed via the skin. These can be given systemically to treat both the affected parts of the skin and the complete body. (21)

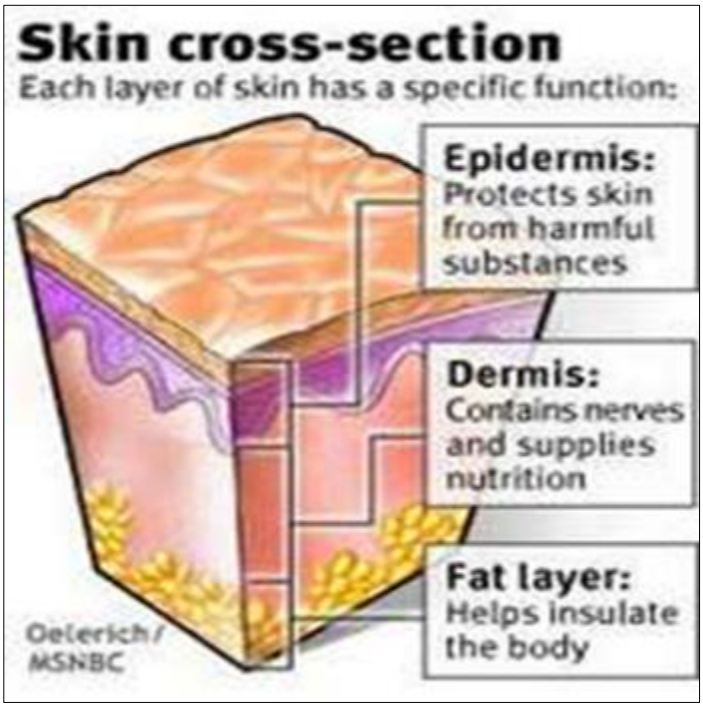

Figure 2 Cross Section of skin

3.1. Important Constituents of Emulgel Preparation

Oils: The oily phase of the emulsion is formed by the combination of these components. Because of their occlusive and sensory qualities as well as their utility as a medicine delivery method, mineral oils, either alone or in conjunction with soft or hard paraffin, are commonly used in topically administered emulsions. Oral formulations frequently make use of fixed oils of vegetable origin, such as Arachis, cottonseed, and maize oils, as well as non-biodegradable mineral and castor oils with local laxative effects, fish liver oils, and others. (22)(23)

Table 1 Use of oils

Chemical	Quantity	Dosage form
Light Liquid Paraffin	7.5%	Emulsion and Emulgel
Isopropylmyristate	7-7.5%	Emulsion
Isopropyl stearate	7-7.5%	Emulsion
Isopropyl palmitate	7-7.5%	Emulsion
Propylene glycol	3-5%	Gel

Emulsifiers: Emulsifying agents are used to regulate stability over a shelf life that might range from a few days for spontaneous emulsions to months or years for prepared goods. At the time of creation, they are also employed to improve emulsification. sorbitan monooleate (span 80) (25), polyoxyethylene sorbitan monooleate (tween 80) (25), sodium stearate (27), polyethylene glycol 40 stearate (24), and stearic acid (27). (26). (28).

Gelling agent: To enhance the consistency of any dosage form, a thickening agent may also be used with a gelling agent. (29)(30)

Table 2 Use of gelling agents

Gelling agent	Quantity	Dosage forms
Carbopol-934	0.5%-2%	Emulgel
Carbopol-940	0.5%-2%	Emulgel
HPMC-2910	2.5%	Emulgel
HPMC	3.5%	Gel
Sodium CMC	1%	Gel

Permeation Enhancers: Substances that temporarily and reversibly increase skin permeability are referred to as "permeation enhancers." These substances partition into and interact with skin cells (31).

Table 3 Use of penetration enhancers

Permeation enhancers	Quantity	Dosage form
Oleic acid	1%	Gel
Lecithine	5%	Gel
Urea	10%	Gel
Isopropyl myristate	5%	Gel
Linoleic acid	5%	Gel
Clove oil	8%	Emulgel
Menthol	5%	Emulgel
Cinnamon	8%	Emulgel

3.2. Emulgel preparation

Emulgel was created using the method outlined by Mohammad et al., with a few minor alterations (2004). To make the gel in the formulations, carbopol 934 and 940 were dissolved in purified water and swirled continuously at a moderate speed. The pH was then adjusted to 6 to 6.5 using triethanolamine (TEA) (TEA). The oil component of the emulsion was created by mixing Span 20 with light liquid paraffin, while the watery phase was created by dissolving Tween 20 in clear water. Methyl and Propyl paraben was dissolved in propylene glycol, whilst the medicine was dissolved in ethanol. The aqueous phase was then added to both solutions. . The oily phase was added while the combination was still heated to between 70 and 80 degrees Celsius after the aqueous and oily phases had each been heated independently and cooled to room temperature. Glutaraldehyde should be added when mixing the gel and emulsion in a 1:1 ratio to generate the emulgel. (32)

3.2.1. Evaulation of emulgel (33)(34)(35)

The major objectives of this work, which used Fourier transforms infrared spectroscopy (FTIR), were to locate a stable storage environment for the medicine in its solid state and to identify excipients that were compatible with the formulation.

- **Physical examination**: The produced emulgel formulations were visually inspected for colour, homogeneity, consistency, and phase separation.
- **pH measurement**: A digital pH metre was used to ascertain the formulation's pH. Before dipping the electrode of the pH metre into the liquid to test pH, it was cleaned three times with distilled water.
- **Viscosity measurement**: The produced batches' viscosities were determined using a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 63. The formulation whose viscosity was to be measured was added to the beaker, and before the measurement was taken, it was allowed to settle for 30 minutes at the test temperature (25 °C). Spindle rotated for 10 minutes at a speed of 50 rpm after being

dropped perpendicularly into the centre of the emulgel while being careful not to let it hit the jar's bottom. The viscosity measurement was noticed.

- **Spreadability**: The spreadability of the gel compositions was examined using two glass slides with standard diameters. The formulation whose spreadability was to be evaluated was put on one slide, and the other slide was positioned on top, sandwiching the gel between the two. The slides were pressed together to eliminate any possible air before the adhering gel was taken off. Only the bottom slide is securely held by the opposing teeth of the clamp, allowing the higher slide to fall off easily due to the force of the weight attached to it. The upper slide was firmly secured with a 20 g weight. The amount of time it took the upper slide to completely separate from the lower slide. A shorter interval is an indication of better spreadability. We calculated spreadability using the following formula:

$$S = M.L/T$$

S is the spreadability,
Weight fastened to top slide: M
L stands for glass slide length.
T is the amount of time it took to fully separate the slides from one another.

Distribution of globule size in preparation of emulgel: Malvern zeta sizing is used to determine the size and dispersion of globules in an emulgel. A 1.0 g sample is dissolved in filtered water and agitated to achieve homogeneous dispersion. The sample was placed into the zeta sizer's photocell. The mean globule diameter and dispersion are calculated.

- **Swelling Index:** The swelling index of the gel is determined individually using a 50 ml beaker containing 10 ml of 0.1 N NaoH and 1 g of generated topical emulgel. Following that, samples were periodically removed from the beakers and left on a dry surface before being weighed once again.

Study on in vitro drug release: Diffusion cells were utilised in the in vitro drug release experiments for the Emulgel. This was firmly fastened to one end of the hollow glass tube of the dial-y-sis cell. Emulgel was used to treat the surface of the egg membrane dialysis membrane (1g). A freshly made PBS solution (pH 7.4) was introduced into the receptor chamber to solubilize the drug. The receptor chamber was stirred using a magnetic stirrer. Following the correct dilutions, samples (1 ml aliquots) were collected at spaced-out intervals and evaluated using a UV-visible spectrophotometer for drug content. Cumulative adjustments were made to establish the total quantity of medicine released at each time interval. Based on our calculations, we determined the total quantity of drug release across the egg membrane according to time. The cumulative% drug release was calculated using a common calibration curve.

- **Microbiological assay**: Utilizing the ditch plate method for microbiological analysis. It is a technique for figuring out whether a substance has bacteriostatic or fungal static activity. It is mostly utilised for semisolid formulations. Prior to this, Sabouraud's agar dried plates were created. Three grammes of the gellified emulsion are applied to the plate after a trench has been carved into it. From the ditch to the border of the plate, freshly produced culture loops are smeared at an angle over the agar.
- Skin irritancy test: The test item was then introduced under two layers of gauze to a skin area that was around 1" by 1" in size at each location (two sites per rabbit) (2.54 x 2.54 cm2). The Gellified Emulsion was applied to the fur of a rabbit. The animals were returned to their cages. A 24-hour exposure is followed by the removal of the gellified emulsion. The test sites were washed with tap water to remove any remaining test item residue. (36)
- **Stability studies**: Three-month stability tests were carried out on the created emulgels at 5 °C, 25 °C/60% RH, 30 °C/65% RH, and 40 °C/75% RH. The emulgels were then put in aluminium collapsible tubes (5 g). Samples were extracted and analysed for their physical traits, pH, rheological traits, drug content, and drug release patterns at intervals of 15 days. (37).

Applied weight to extrude emulgel from tube (in grammes) / Area is the formula for extrudability (in cm2)

- **Rheological Study**: The viscosity of the various emulgel formulations is measured at a temperature of 25 °C using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories) connected to a thermostatically controlled circulating water bath.
- **Swelling Index**: To determine the topical emulgel's swelling index, 1 gram of the gel is put on a piece of porous aluminium foil and then placed separately in a 50 ml beaker with 10 ml of 0.1 N NaOH. The samples were then periodically removed from the beakers and left on a dry surface before being reweighed. The swelling index is calculated using these procedures.

Swelling Index (SW)% is calculated as [(Wt - Wo)/Wo] x 100.

Where
(SW)% is the equilibrium swelling percentage,
Wo is the initial weight of the emulgel at time t.
Weight of the enlarged emulgel is Wt.

Measurement of the bioadhesive strength of ex-vivo topical emulgel: (MICES' SKIN IS SHAVED) The bioadhesive strength is determined using a modified method. Separately, two pieces of skin were fixed to two glass slides; one glass slide was fastened to a wooden piece, and the second glass slide was fastened to the balance on the right side. The fresh skin was cut into pieces and washed with 0.1 N NaOH. The right and left pans were balanced by putting additional weight on the left-hand pan. The left pan's extra weight is removed, 1 g of topical emulgel is placed between the two slides containing the hairless skin areas, and pressure is applied to remove any remaining air. The balance is kept in place for five minutes. At a rate of 200 mg/min, weight is gradually added to the left-hand pan until the patch breaks from the skin's surface. The mass (gramme force) required to remove the emulgel away from the skin's surface was used to calculate the bioadhesive strength. The bioadhesive strength is determined using the following formulas:

Weight needed (in gms) / Area = Bioadhesive Strength (cm2)

Figure 3 Set up for bio-adhesive test

- **Drug Content Calculation**: The gelified emulsion's drug content was determined using a spectrophotometer. By sonicating a known amount of the emulsion into a solvent, the drug concentration of the gellified emulsion was ascertained (methanol). Using a UV/VIS spectrophotometer, absorbance was measured after the proper dilution (UV-1700 CE, Shimadzu Corporation, Japan). (38)
- **In Virto Release Study**: Franz diffusion cell, with a 3.14 cm2 effective diffusion area and a 15.5 ml cell capacity, was used for the in vitro release testing. The surface of the egg membrane was evenly coated with a gelatinized emulsion (200 mg). The egg membrane was constricted in the diffusion cell's donor and receptor chambers. A freshly prepared PBS solution (pH 5.5) was introduced to the receptor chamber in order to solubilize the drug. To agitate the receptor chamber, a magnetic stirrer was employed. The samples were taken in 1.0 ml aliquots at predetermined intervals. Using a UV visible spectrophotometer, samples were tested for drug content after the correct dilutions. Adjusted Cumulative data are used to calculate the overall amount of medicine used throughout each time period. The calculation of the total amount of drug delivered across the egg membrane was based on time. (39)
- **Microbiological assay**: Utilizing the ditch plate approach, a microbiological test was conducted. It is a technique for determining whether a substance has bacteriostatic or fungistatic properties. It is mostly utilised for semisolid formulations. Prior to this, Sabouraud's agar dried plates were created. A ditch is cut in the plate, and three gramme of the gellified emulsion are put to it. From the ditch to the border of the plate, freshly produced culture loops are spread at an angle over the agar. After 18 to 24 hours of incubation at 25°C, the fungal growth was checked, and the % inhibition was computed as follows.

% inhibition = 100 divided by L2

Where,
L1 stands for the streaking culture's overall length.
The length of inhibition is L2.

Accelerated stability testing for gelled emulsion: Stability tests were conducted in accordance with ICH guidelines. The formulations were stored in a hot air oven for three months at 37°, 45°, and 60°. Using a UV-visible spectrophotometer, samples were checked for drug content every two weeks. The pH change of gel was periodically measured as part of a stability investigation (40).

4. Results

- Homogeneity: All gel formulations demonstrated improved homogeneity with no lumps, and the gels were determined to be clear and free from the presence of particles, aggregates, foreign matter, and phase separation.
- Calculating pH: Depending on the polymer ratios of the medication in each formulation, the pH changes.
- Spreadability: The spreadability diameters of various formulae vary.
- Extrudability: For a suitable gel formulation, it should be easily extrudable from the container. All formulations had high extrudability, it was discovered.
- Drug content: The drug content of each formulation is very similar. Therefore, the impact of polymer ratios is less significant in this case.
- Viscosity: All Emulgel formulations were tested using a Brookfield viscometer, which measures viscosity (in cps) by releasing a cone-shaped holding rod from a distance of 10 cm such that it lands in the middle of a glass cup containing Emulgel.

5. Conclusion

To increase patient compliance, topical medication administration will be increasingly used in the next years. Emulgels will become a favoured drug delivery strategy due to its spreadability, adhesion, viscosity, and extrusion advantages. They will also be used as a way to incorporate hydrophobic medications into water-soluble gel bases

According to this outcome, Emulgel was effectively incorporated into the different topical gel formulations and is suitable for topical usage. The majority of medical gels sold now are either used as analgesics or as anti-inflammatory medications. Most of them have antibacterial properties. To treat bacterial or fungal skin conditions, antiseptic creams, ointments, or solutions are routinely employed; nevertheless, additional antimicrobial gels are projected to hit the market in the near future. We now have the opportunity to patent an increasing number of gels as a consequence. Transdermal prodrugs could potentially be made accessible in the following years. Due to the growing usage of cutting-edge technologies, indications of gels for the treatment of systemic illnesses are predicted.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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