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EMULGEL: AS A TROPICAL DOSAGE FORM

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Abstract

Emulgel is the name given to the dosage form created by combining gel and emulsion. Emulgels, which contain a dual release control mechanism that includes both a gel and an emulsion, have become one of the most innovative topical delivery systems. The main goal of this formulation is to transfer hydrophobic medications to systemic circulation through the skin. In fact, a classical emulsion becomes an emulgel when a gelling agent is present in the water phase. The emulgel for dermatological application has a number of advantageous qualities, including being thixotropic, greaseless, readily spreadable, easily removable, emollient, nonstaining, watersoluble, prolonged shelf life, biofriendly, clear, and appealing in appearance. The impact can be potentiated by a number of penetration enhancers. Therefore, this can be employed as a better topical medication delivery system than the currently available traditional techniques.

Key Words:- Emulgel, Tropical delivery, Hydrophobic Drugs, Penetration enhancers,

Introduction:-

Drugs have been administered to the human body by a variety of methods throughout the past few decades, including oral, sublingual, rectal, parental, etc., to cure illnesses. When conventional systems of drug administration fail or when a local skin illness, such as a fungal infection, occurs, the topical drug delivery system is typically used. The application of a medication-containing formulation to the skin to treat cutaneous disorders directly is known as topical drug delivery. [1,2]. Dermatological products used on the skin come in a variety of formulations and have a range of textures from liquid to powder, but semisolid preparations are the most widely used. Transparent gels are now used more frequently in pharmaceutical and cosmetic preparations, which is a key subgroup of semisolid preparations. Large volumes of aqueous or hydroalcoholic liquid are trapped in a network of colloidal solid particles to generate gels, a more recent family of dosage forms.Compared to creams and ointments, gel formulations typically offer faster medication release. Gels have a lot of benefits, but one significant drawback is that hydrophobic medications can't be delivered using gels. Emulgels are created as a solution to this problem, enabling even hydrophobic drugs to take use of gels distinctive features. dose forms are what are used when gels and emulsions are mixed. In reality, a traditional emulsion becomes an emulgel when a gelling ingredient is present in the water phase. Lipophilic pharmaceuticals are encapsulated using the direct (oil-in-water) system, whereas hydrophilic drugs are encapsulated using the reverse (water-in-oil) system.[3] Emulsions are easily removed whenever wanted and have a certain level of elegance. Additionally, they have a strong capacity for skin penetration. Emulgels for dermatological usage are thixotropic,

greaseless, readily spreadable, easily removed, emollient, nonstaining, watersoluble, prolonged shelf life, biofriendly, transparent, and have a beautiful look.[4]

Tropical delivery includes two types of products[5]

- To cover the affected area, external topicals are applied to the cutaneous tissues by spreading, spraying, or other means of dispersal.
- Internal topicals used for local activity on tissues of the mucous membrane when given orally, vaginally, or on the rectal area.

Table 1

Experimental data on gels & emulgel [6-17]

Sr.no.	Drug	Type	Polymer	Enhancer	Purpose
1	Chlorphenisn	Emulgel	Carbopol934,HPMC	Polyethylene glycol	Effect of gelling agent on release
2	Nimuselide	Gel	HPMC,Carbopol 940,Natural polymer	Dimethyl sulfoxide	Effect of gelling agent on release
3	Fluconazole	Liposomal gel	Carbopol 934	Cholesterol,steari acid	Increase permeation and decomposion
4	Diclofenac	Gel & Emulgel	Carbopol934,940,HPMC	Transcutol,Myrj52 Cineol	Effect of penetration enhancers
5	Ketoprofen	Gel	Polaxamer407 Carbopol934, Sod. CMC	Oleic acid	Effect of oleic acid on release
6	Meloxicam	Gel	Carbopol934P	PEG400 Menthol,azone	Effect of penetration enhancers
7	Miconazole	Emulgel	Carbopol940,934	Propylene glycol	Controlled delivery
8	Mefanamic acid	Emulgel	Carbobol934,HPMCK4M	Cloveoil, mentha oil	Release study and Pharmacologic action
9	Itraconazole	Emulgel	Carbopol934,940	Propylene glycol	More selective, safe
10	Aceclofenac	Gel	Carbopol, HPMC, Sod. CMC	Propylene glycol	Carbopol gel show superior release

11	Ibuprofen	Gel	Chitosan	Menthol, glycerol	Study of topical and systemic effect
12	Veldecoxib	Gel	Carbopol934,HPMC	Propylene glycol Ethanol	Effect of PG and ethanol on release

Advantages [18,19]

1. Avoidance of first pass metabolism.
2. Avoidance of gastrointestinal incompatibility.
3. More selective to a specific site.
4. Improve patient compliance.
5. Suitability for self medication.
6. Providing utilization of drug with short biological half life and narrow therapeutic window.
7. Ability to easily terminate medication when needed.

Disadvantages [20-22]

1. Skin irri-tation on contact dermatitis.
2. Possibility of allergenic reactions.
3. Poor permeability of some drug through skin.
4. Drug of large particle size not easy to absorb through the skin.

Rational behind formulation of emulgel as a tropical drug delivery

Numerous medicinal products are applied to the skin or mucous membranes, either to improve or restore a basic skin function or to pharmacologically alter an action in the tissues highlighted. Topical or dermatological products are the terms used to describe such items. Many commonly used topical medications, such as creams, lotions, and ointments, have a number of drawbacks. Such as When applied, they are uncomfortable for the patient because they are sticky, have a low spreading coefficient, and must be rubbed in. They also have a stability issue. The usage of transparent gels in pharmaceutical and cosmetic preparations has increased as a result of all these elements within the main category of semisolid preparations. Gels have a lot of benefits, but one significant drawback is that hydrophobic medications can't be delivered using gels. Since a hydrophobic medicinal moiety cannot be successfully integrated and supplied by gels, this constraint must be overcome. To do this, an emulsion-based technique is being developed.

Pathophysiology of Skin [23-24]

The majority of topical medicines are intended for skin application. Therefore, it is crucial to have a fundamental understanding of how the skin functions physiologically while creating topicals. A typical adult's skin has a surface area of around $2m^2$, and it gets about one third of the blood that circulates through the body. Every square centimeter

of human skin has an average of 4070 hair follicles and 200300 sweat ducts, according to research. The skin's pH ranges from 4 to 5.6. The pH of the skin's surface is influenced by sweat and fatty acids released by sebum.

1. Nonviable epidermis

2. Viable epidermis

3. Viable dermis

4. Subcutaneous connective tissue

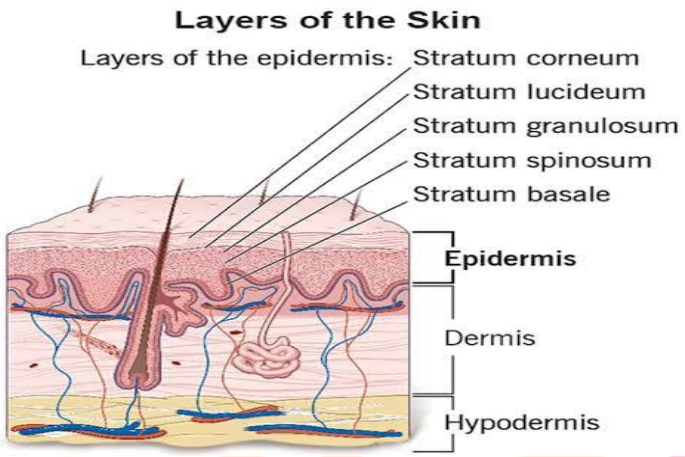


Fig 1. Cross Section of Skin

1. Non-viable epidermis

The stratum corneum, the skin's outermost layer, serves as a physical barrier to the majority of substances that come into contact with the skin. Over the majority of the body, the stratum corneum is 10 to 20 cell layers thick. Each cell is a flat, plate-like structure that is stacked up to one another in a brick-like pattern and is 3444 metres long, 2536 metres wide, and 0.5 to 0.20 metres thick. The stratum corneum is made up of protein (7585%), primarily keratin, and lipid (515%), including phospholipids, glycosphingolipids, cholesterol sulphate, and neutral lipid.

2. Viable epidermis

This skin layer has a thickness that ranges from 50 to 100 m and is located between the stratum corneum and the dermis. Similar to other live tissues, the structure of the cells of the viable epidermis is physiochemical. Tonofibrils keep cells bound together. Compared to water, this area has a density that is not significantly different. 90% or so of the substance is water.

3. Dermis

The dermis lies just below the viable epidermis. It is a structural fibrin, and histologically, very few cells in normal tissue resemble it. The dermis is made up of a matrix of loose connective tissue made of fibrous protein embedded in an amphorphose ground material and ranges in thickness from 2000 to 3000 m.

4. Subcutaneous connective tissue

The subcutaneous tissue, also known as the hypodermis, is not actually thought to be a true component of the structured connective tissue, which is made up of loose-textured, white, fibrous connective tissue that houses cutaneous nerves, secretary pores of the sweat glands, and blood and lymph vessels. Most researchers believe that

before a drug reaches the hypodermis by skin penetration, it enters the circulatory system, however the fatty tissue may act as a drug storage.

Factors affecting tropical Absorption of drug [25,26]

A. Physiological Factors

1. Thickness of skin
2. Lipid content.
3. Density of hair follicles.
4. Density of sweat glands.
5. pH of Skin
6. Blood flow to skin
7. Hydration of skin.
8. Inflammation of skin.

B. Physicochemical factors (Drug related factors)

1. Partition coefficient of drug molecule.
2. Molecular weight of drug (<400 dalton).
3. Degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles.

Factors to be consider when choosing a tropical preparation [27,28]

1. Effect of the vehicle e.g. an occlusive vehicle enhances penetration of the active ingredient and improves efficacy. The vehicle may have a cooling, drying, emollient, or protective action.
2. Match the type of preparation with the type of lesions. For example, avoid greasy ointments for acute weepy dermatitis.
3. Match the type of preparation with the site (e.g., gel or lotion for hairy areas).
4. Irritation or sensitization potential.

Factors to be consider when choosing Drug for Emulgel [45,46]

Properties	Criteria
Effective concentration	less than 10 mg
t1/2	≤10 hr.
Molecular mass	. 800 Dalton or less;
log p value	0.8to5

Skin permeability coefficient	≥0.5x10-3cm/hr.
Irritation to skin	Nonirritating
Polarity	Less
Molecular size	Small
pKa	Higher

Ideal properties of excipient candidate [45,46]

Properties	Criterion
Skin reaction	No-irritant and non-allergic
Effects on final preparation	Little or no deleterious effect on activity and stability
Regulatory status	IIGlisted,GRASlistedorbiologicallysafe
Concentration	Under regulatory limit
Compatibility	Compatible with API and the other excipients etc.

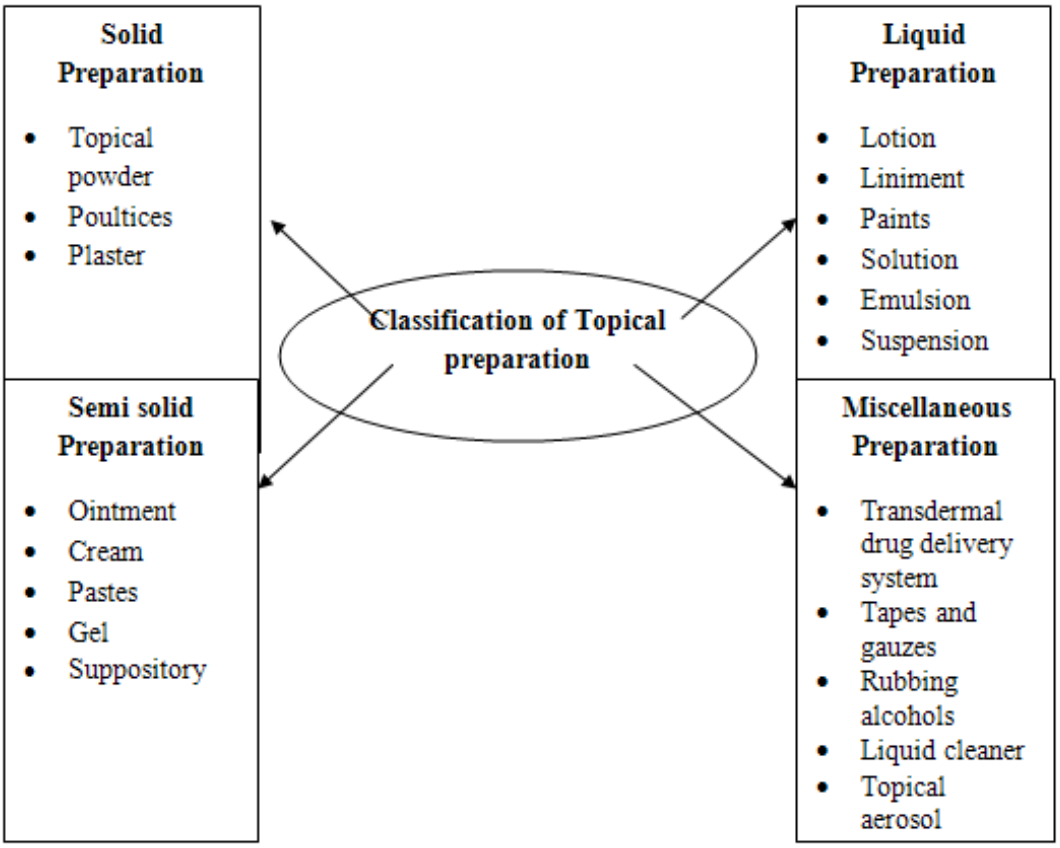
IIG: Inactive ingredients guideline;

GRAS: Generally referred as safe;

API: Active pharmaceutical ingredient

Methods for Drug Penetration Enhancement [29]

1. Chemical enhancement
2. Biochemical enhancement
3. Physical enhancement
4. Super saturation enhancement



Various Approaches Used For Tropical Drug Delivery [30]

Formulation of Emulgel

1. Vehicle

The vehicle has the following features.

- Efficiently and evenly distribute the medication over the skin.
- Allow the medicine to be released so that it can move freely to the area of action. Deliver the medication to the desired location.
- Maintain a therapeutic drug concentration in the target tissue for long enough to have a pharmacologic effect.
- Formulated properly for the anatomic site being treated.
- Acceptable in terms of appearance to the patent.

The amount of topical medication that penetrates the stratum corneum is typically low due to the effectiveness of the epidermal barrier. Rate and degree of absorption varies based on the active agent itself as well as the vehicle's properties.[31]

A) Aqueous Phase

The emulsion's aqueous phase is formed by this. Agents like water and alcohols are frequently utilised.

B) Oil Phase

These substances create the emulsion's oily phase. Mineral oils, either alone or in combination with soft or hard paraffin, are frequently utilised for topically applied emulsions because of their occlusive and sensory properties as well as their usage as a medication delivery system. Nonbiodegradable mineral and castor oils, which have a local laxative action, fish liver oils, or other fixed oils of vegetable origin (such as arachis, cottonseed, and maize oils) are commonly used in oral formulations. Oils used in formulation of emulsion are given in Table 2.[32]

Table 2

Oils used in formulation of emulgel

Oil (Chemicals)	Quantity Used	Dosage Form
Light Liquid paraffin	7.5%	Emulsion & Emulgel
Isopropylmyristate	7-7.5%	Emulsion
Isopropyl state	7-7.5%	Emulsion
Isopropyl palmitate	7-7.5%	Emulsion
Propylene glycol	3-5%	Gel

2. Emulsifiers

Emulsifying agents are used to control stability during a shelf life that can range from days for emulsions that are created on the spot to months or years for commercial preparations, such as butter. Stearic acid, Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Polyethylene glycol 40 stearate, and Sodium stearate. [33]

3. Gelling Agents

These substances can also be employed as thickeners to improve the consistency of any dose form. Various gelling agents given in table 3[34]

Table 3

Gelling Agents

Gelling agent	Concentation In (%)	Dosage Form
Carbopol-934	1%	Emulgel
Carbopol-940	1%	Emulgel
HPMC-2910	2.5%	Emulgel
HPMC	3.5%	Gel
Sodium CMC	1%	Gel

4. Penetration Enhancers

Drug delivery vehicles frequently contain penetration-enhancing components that temporarily disrupt the skin barrier, fluidize the lipid channels between corneocytes, change how the drug is partitioned into skin structures, or improve skin delivery in other ways. Examples of some important penetration enhancers are given in Table 4[35]

Properties of Penetration Enhancers [35]

- They have to be non-allergenic, non-irritating, and non-toxic.
- They should preferably act quickly, with predictable and repeatable activity and duration of impact.
- They should not bind to receptor sites and should not have any pharmacological effect in the body.
- In order to allow therapeutic drugs to enter the body while avoiding the loss of endogenous material from the body, the penetration enhancers must function unidirectionally.
- The penetration enhancers must to be suitable for incorporation into different topical treatments, making them compatible with excipients and medications alike.
- They ought to have appropriate skin "feel" and acceptable cosmetic appearance.

Table 4
Examples of Penetration Enhancers

Penetration Enhancers	Quantity	Dosage Form
Olic acid	1%	Gel
Lecithine	5%	Gel
Urea	10%	Gel
Isopropyl myristate	5%	Gel
Linoleic acid	5%	Gel
Clove oil	8%	Emulgel
Menthol	5%	Emulgel

Mechanism of action of Penetration Enhancers

The three basic processes by which penetration enhancers work include:

1. A breakdown in the stratum corneum lipid's highly organised structure.
2. Coordination with intercellular proteins
3. Improved stratum corneum stratum corneum partitioning of the medication, co enhancer, or solvent

By changing one of three pathways, the enhancers work. Inducing protein conformational changes or solvent swelling is the key to changing the polar route. The mobility of the stratum corneum's lipid and protein component was improved by the fatty acid enhancers. Some enhancers change the multi-laminate pathway for penetration to function on both polar and nonpolar pathways. Through skin proteins, enhancers can make drugs more diffusible. On the development and design of the enhancer, the type that is used has a considerable bearing.[36]

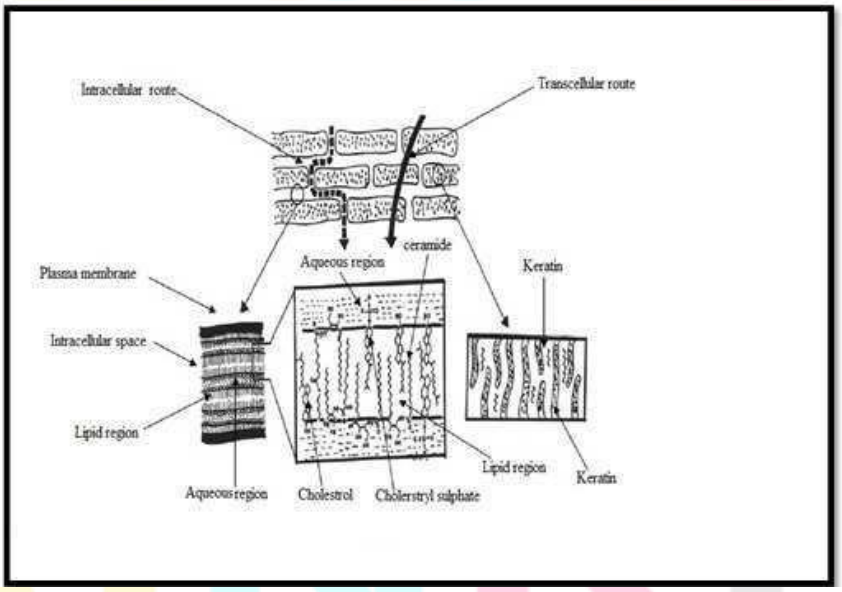


Fig 2 Mechanism of Penetration of Drug In to The Skin

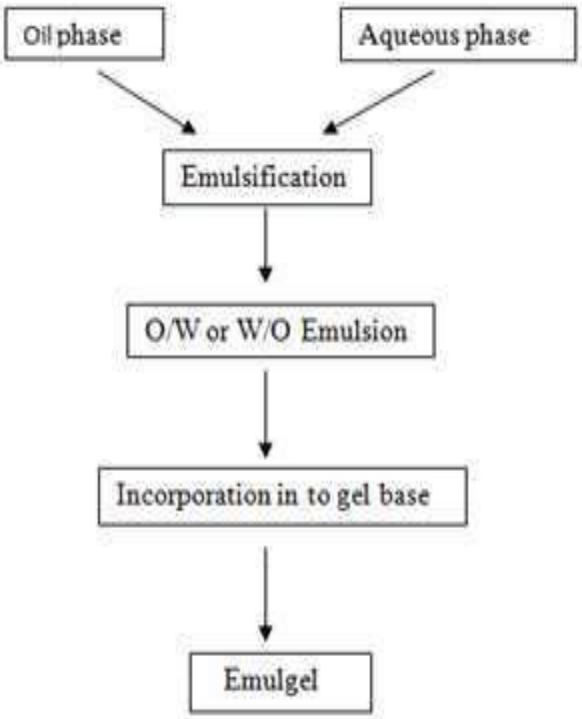


Fig 3 :- Flow chart of emulgel formulation

Pathway for Drug Penetration through Transdermal route

Diffusion is a method of permeation that includes:

1. Transdermal permeation through the stratum corneum.
2. Permeation of the stratum corneum into intercellular spaces.
3. Transappendaged permeation via sweat, sebum, and hair follicle glands. Most substances enter the skin through the intercellular micro channel, hence many boosting approaches try to interfere with or avoid the delicate molecular architecture.[36]

Method of Preparation

Step 1:- Formulation of O/W or W/O Emulsion

Step 2:- Formation of gel base (Concentrated solution of Polymers)

Step 3 :- Incorporation of emulsion & gel base with continuous stirring

Evaluation of Emulgel [4,37-47]

1. **Physical Examination**

The colour, homogeneity, consistency, and phase separation of the created emulgel formulations are visually examined.

2. **Rheological Examination**

Using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories) coupled to a thermostatically controlled circulating water bath, the viscosity of the various emulgel compositions is assessed at 25°C.

3. **Spreading coefficient**

Spreadibility is measured using Mutimer's (1956) recommended apparatus, which is appropriately adjusted in the lab and employed for the investigation. It is made up of a wooden block that has a pulley at one end. This method bases the measurement of spreadibility on the emulgels'"Slip" and "Drag" properties. On this block is fastened a ground glass slide. On this ground slide, extra emulgel (approximately 2 gm) is being studied.The emulgel is then placed in a sandwich between this glass slide and another glass slide with a hook and a fixed ground slide dimension. To remove air and create a consistent emulgel coating between the slides, a 1 kg weight is placed on top of the two slides for five minutes. The edges are scraped clean of extra emulgel. After that, an 80 gramme pull is applied to the top plate. With the use of a thread fastened to the hook, record the amount of time (in seconds) needed for the top slide to travel 7.5 cm. Better spreadibility is indicated by a shorter interval.[41]

4. **Extrudability study of Tropical Emulgel**

To determine the force necessary to extrude the material from the tube, an empirical test is typically used. The technique used to determine the amount of applied shear in the area of the rheogram where the yield value is exceeded and plug flow is as a result. The method used in the current study to assess an emulgel formulation's extrudability is based on the amount of emulgel and emulgel extruded from a lacquered aluminium collapsible tube on application of the weight in grammes required to extrude at least 0.5 cm of emulgel ribbon in 10 seconds. Extrudability is improved by greater extrusion volume. Each formulation's extrudability is measured three times, and the average results are given.The following equation is then used to compute the extrudability:

Extrudability = Applied weight to extrude emulgel from tube (in gm) / Area (in cm^2)

5. **Swealing Index:- [42]**

One grame of topical emulgel is taken and placed separately in a 50 ml beaker containing 10 ml of 0.1 N NaoH in order to measure the swelling index of the gel. After then, samples were taken out of the beakers at various intervals and placed on a dry surface for a while before being reweighed.

Swealing Index calculated as follows

$$SW\% = \left[\frac{(Wt - Wo)}{Wo}\right] \times 100$$

SW % = Percentage Swelling

Wt = Weight of the emulgel after time t

Wo = Original weight of emulgel at time t = 0

6. Drug Content Determination:-

Take 1 gram of emulgel. Add a suitable solvent and combine. To get a clear solution, filter it. Utilize a UV spectrophotometer to ascertain its absorbance. The same solvent is used to prepare common drug plots. By using the absorbance value in the standard plot equation, concentration and drug content can be calculated using the same standard plot.

$$Drug\ Content = (\ Concentration\ \times Dilution\ Factor \times Volume\ taken) \times Conversion\ Factor$$

7. Skin irritation Test:-

The preparation is applied to a rat's properly shaven skin, and any unfavourable effects, such as a change in skin colour or morphology, should be monitored for up to 24 hours. The study can employ the entire set of 8 rats. The test is successful if there is no irritability. The trial should be repeated if the skin irritation symptom appears in more than two animals.

8. Ex - Vivo Bioadhesive Strength Measurement of Tropical Emulgel:-

The modified approach is utilised to gauge the bioadhesive strength. Cut into bits, the fresh skin is next rinsed with 0.1 N NaoH. One glass slide is fastened to the wooden piece, and the other piece is tied with the balance on the right side, two strips of skin were tied to the two glass slides independently. By placing additional weight on the left-hand pan, the right and left pans might be balanced. The two slides containing the hairless skin sections are sandwiched between 1 g of topical emulgel and some pressure is applied to remove any air bubbles. Additional weight from the left pan is then removed. This state of balance is maintained for For five minutes, the balance is held in this posture. Weight is gradually added to the left hand pan at a rate of 200mg/min until the patch separates from the skin's surface. The bioadhesive strength was determined by the mass (gramme force) needed to pull the emulgel away from the skin's surface. The formula below is used to calculate the bioadhesive strength. [43]

$$Bioadhesive\ Strength = \frac{Weight\ required(gm)}{Area\ (cm2)}$$

9. In Vitro Release/ Penetration Studies

Franz diffusion cells were used to conduct release investigations.

Drug Release Kinetic Study[44]

The release data were fitted to the following equations in order to examine the mechanism of drug release from the topical gel.

Zero Order Equation

$$Q = k^0\ t$$

Where k^0 is the zero-order release rate

Q is the amount of substance released at time t, respectively.

First Order Equation

k^1 is the first-order release rate constant,

Q is the percentage of drug release at time t.

$$\ln(100 - Q) = \ln 100 - k^{1t}$$

Higuchi Principles

$$Q = k2\sqrt{t}$$

K^2 is the diffusion rate constant,

Q is the percentage of drug release at time t.

10. Stability Study

The prepared emulgels were placed in aluminium collapsible tubes (5 g), and stability tests were conducted on them for three months at 5°C, 25°C/60 RH, 30°C/65 RH, and 40°C/75% RH. At 15-day intervals, samples were taken out and examined for their physical characteristics, pH levels, rheological characteristics, drug contents, and drug release patterns.

Conclusion

Due to improved patient compliance, topical medication administration has become widely used in recent years. The spreadability, adhesion, viscosity, and extrusion advantages of emulgel will make them a preferred drug delivery method. Additionally, they will serve as a means of incorporating hydrophobic pharmaceuticals into gel bases that are water soluble.

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