



REVIEW ARTICLE

**Emulsion Based Gel Technique: Novel Approach for Enhancing Topical Drug
Delivery of Hydrophobic Drugs**

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ABSTRACT

These modern days there is an upsurge in topical formulations such that it can be prepared by varying physico-chemical properties and providing better localized action. The patient adherence to topical formulations is significant in relation to chronic skin diseases, like fungal infections, acne, psoriasis. Emulgel is one of the recent technology in NDDS used topically having characteristics of dual control release i.e. emulsion as well as gel. Despite of many advantages of gels there is a major limitation of delivering the hydrophobic drug. Henceforth emulgel has been emerged as an auspicious topical drug delivery system for hydrophobic drugs and proves a boon for dermal care and cosmetology. It is prepared by different polymers which work as an emulsifier and thickener because the gelling capacity of these compounds give rise to stable emulsions and creams by decreasing surface and interfacial tension while at the same time increasing the viscosity of the aqueous phase. Emulgel are having major advantages on novel vesicular systems as well as on conventional systems considering various aspects. Numerous permeation enhancers can potentiate the effect of decreasing skin barrier resistance on the other hand promoting solubility of the drug in vehicle is also feasible. The use of emulgels can be considered well in analgesics and antifungal drugs.

KEYWORDS

Emulgel, Cosmetology, Hydrophobic Drug, Polymer, Chronic Skin Diseases

INTRODUCTION

Skin is one of the most readily accessible parts of human body for topical administration and molecules penetrate in the skin mainly by three routes: through intact stratum corneum, through sweat ducts, and through the sebaceous follicle. Topical drug delivery is used for localized action on the body through ophthalmic, rectal, vaginal and skin as topical routes. The topical drug delivery system such as emulgel (gellified emulsion) generally used where the other systems of drug administration fails to directly

treat cutaneous disorders such as fungal infections, acne, psoriasis etc¹. Since the mid 1980's, emulsion gels have been of growing importance in the field of pharmaceutical semisolid dosage forms.

In cosmetics, such as hydrophilic systems have already been known for a longer period and their wide utilization as pharmaceutical dosage form comes from the wide utilization as pharmaceutical dosage form comes from wide utilization of emulsions systems particularly for dermatological formulae². Emulgel is defined as the emulsion either o/w or w/o type, which is gelled by mixing it with gelling agent like (HPMC or Carbomer).

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Skin composed of both hydrophobic intercellular materials within the hydrophobic cornified cells. Thus emulgel is most preferred topical delivery for hydrophobic drugs³. Gel is composed of high cross-linkage networks based on organic or inorganic phase systems, containing higher amount of water i.e. hydrophilic by nature, thus it has drawback for incorporating highly hydrophobic drugs⁴. Emulsions are either o/w or w/o type which provides stability and better bioavailability for hydrophobic drugs.

Also avoids first pass metabolic effects and also they are easily washed off whenever desired. O/W emulsion is most useful as water washable drug bases while w/o emulsion are employed for the treatment of drug skin and for emollient action⁵. Thus mixing of both emulsion and gel systems results into an enhanced and improved formulation as emulgel. The viscosity due to gel and breaking of emulsion can be moderated by changing the interaction between oil droplets and gel matrix⁶. Now a days, polymers having dual properties as thickness and emulsifiers at a same time are preferred. Thus, the incorporation of gelling agent into the water phase converts the emulsion into an emulgel formulation⁷.

Advantages of Emulgel

- Avoidance of systemic adverse effects of drug i.e. first pass metabolism in the body.
- Systemic circulation is minimized or prevented.
- Improve patient compliance and acceptability.
- Suitable for self-medication.
- Provide target drug delivery on the body.
- Ability to easily terminate medication.
- Can easily pass through skin having dual behavior i.e. hydrophobic as well as hydrophilic.
- They are convenient to apply on hairy skin due to absence of greasiness and lack of residues upon application.

Disadvantages of Emulgel

- Skin irritation on contact dermatitis.
- Bubbles formed during emulgel formulation.
- Possibility of allergenic reactions.
- Drugs having large particle size (>400 daltons) are not easily absorb or cross through the skin barrier.

Rationale of Emulgel^{8,9}

Many widely used topical agents like ointment, cream, lotion have many disadvantages. They have very sticky causing uneasiness to the patient when applied due to some reasons. Moreover they also have lesser spreading coefficient and need to apply with rubbing which may cause dermatitis. And they exhibit the problem of stability also.

Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. A gel is colloid that is typically 99% wt liquid, which is immobilized by surface tension between it rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body.

These include others, gels and creams for vaginal yeast infections, topical creams for skin infections and creams to soothe arthritis pain. New technologies now allow other drugs to be absorbed through the skin (transdermal). These can be used to treat not just the affected areas (for example, the skin) but the whole body (systemic).these can be applied to hairy skin without any uneasiness caused by other topical formulations.

Physiology of Skin

The skin is the largest organ of the body, accounting for about 15% of the total adult body weight. It performs many vital functions¹⁰.

- Protection against physical, chemical and biological assailants.
- Prevention of excess water loss from the body.

- Vital role in thermoregulation.

The skin consists of three layers i.e. the epidermis, the dermis and the subcutaneous tissue. An average human skin surface is known to contain, on the average 40-70 hair follicles and 200-300 sweat ducts on every cm² of the skin.

The pH of the skin varies from 4-5.6 the skin of an average adult body covers a surface area approximately 2m² and receives about one third of the blood circulating through the body.

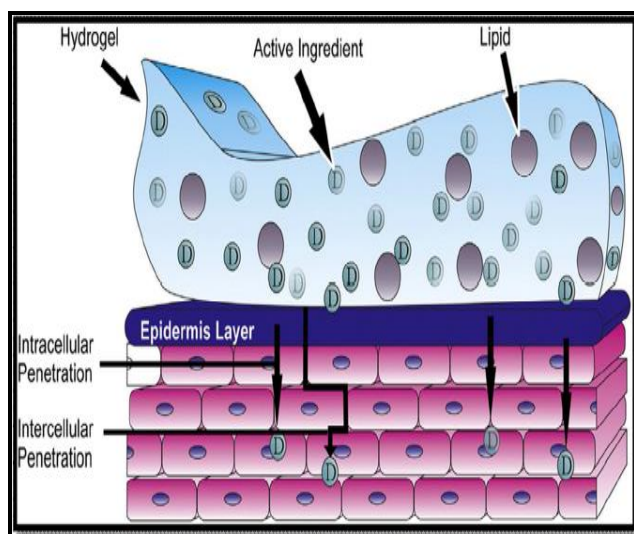


Figure 1: Drug delivery through the skin epidermis by gel formulation

The Epidermis

This is a stratified squamous epithelium layer i.e. composed primarily of two types of cells: keratinocytes and dendritic cells. Epidermis layer harbour a number of other cells such as melanocytes, Langerhans cells and Merkel cells. But the keratinocytes cells types comprises the majority of the cells by far. The layers of epithelium are -

- Stratum germinativum (growing layer or basal layer): It contains column-shaped keratinocytes that attach to the basement membrane zone with their long-axis perpendicular to dermis.
- Stratum spinosum (prickly cell layer or squamous cell layer) : Its thickness varies from 5-10 cells. Intercellular spaces between spinous cells are bridged by abundant

desmosomes (adhering spot) that promote coupling between cells of the epidermis and provide resistance to physical stresses.

- Stratum granulosum (granular layer) : It contains living cells, these are responsible for further synthesis and modification of proteins involved in keratinization. It is 1-3 cells layer in thickness.
- Stratum corneum (horny layer): the corneocytes are rich in protein and low in lipid content (hydrophilic nature) are surrounded by a continuous extracellular lipid matrix.
- Malpighian layer (pigment layer): the layer whose protoplasm has not yet change into horny material.
- Stratum lucidum

The Dermal-Epidermal

It act as a support for the epidermis, establishes cell polarity and direction of growth, directs the organization of the cytoskeleton in basal cells, provide developmental signals and function as a semi-permeable barrier between layer.

The Dermis

It is on integrated system of fibrous, filamentous and amorphous connective tissue that accommodates stimulus induced entry by nerve, vascular-networks, appendages, fibroblasts, mast cells. Its thickness ranges from 2000-3000µm. The principal component of the dermis is collagen and represents 70% of the skin's dry weight.

Sub-cutaneous (Connective Tissue)

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue which is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves.

Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

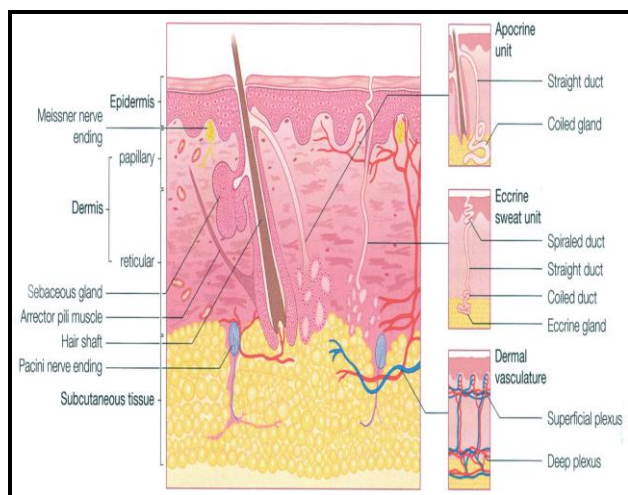


Figure 1: Cross-section of skin

Factors Affecting Topical Absorption of Drug¹¹

Physiological Factors

1. Skin thickness – varies from epidermis to subcutaneous layer. Epidermis has high thickness about 100-150 μ m. Skin on the sole and palm has a high rate of diffusion.
2. Lipid content - it is an effective water barrier, percutaneous penetration increases when lipid weight in stratum corneum is low.
3. Density of hair follicles – hair follicle infundibulum has a large storage capacity about 10 times more than the stratum corneum.
4. Density of sweat glands
5. Skin pH – sweat and fatty acid secreted from sebum influence the pH of the skin surface.
6. Hydration of skin – can enhance permeation of drug.
7. Inflammation of skin – that disrupts the continuity of stratum corneum increases permeability.
8. Skin temperature – increase in temperature gives rise to increase in rate of skin permeation.
9. Blood flow

Physicochemical Factors

1. Partition coefficient – more the value of log p more easily will be the percutaneous absorption of the drug.
2. Molecular weight (< 400 dalton)
3. Degree of ionization – only unionized drug molecules get absorbed well.
4. Effect of vehicles – hydroalcoholic gel provides the most efficient absorption through skin.

Drug Delivery across the Skin

There are two important layers in the skin: the epidermis and dermis. Blood vessels are distributed profusely beneath the skin in subcutaneous layer. There are three primary mechanisms for drug absorption through the skin: intercellular, transcellular and follicular. The next most common route of delivery is through the pilosebaceous route permeation tends to occur through intercellular matrix, but through transcellular pathway it has been shown to provide a faster alternative route of highly polar molecules. In normal intact skin it has been established that the keratinized corneocytes and the largely non-polar lipid intercellular cement of the horny layer are the major factors involved in the maintenance of efficient barrier for drugs¹². The drug penetration for skin can be enhanced by using organic solvents such as propylene glycol, surfactants and DMSO. The permeation enhancers altered the barrier properties of the stratum corneum by types of mechanism including enhancing solubility, partitioning the stratum corneum, fluidizing the crystalline structure of the stratum corneum¹³. Creams and gels that are rubbed onto the skin have been used for years for effective treatment against infections and pain by medication. New technologies now allow other drugs to be absorbed through the skin. These can be used to treat not just the affected areas of the skin but the whole body by systemic route¹⁴.

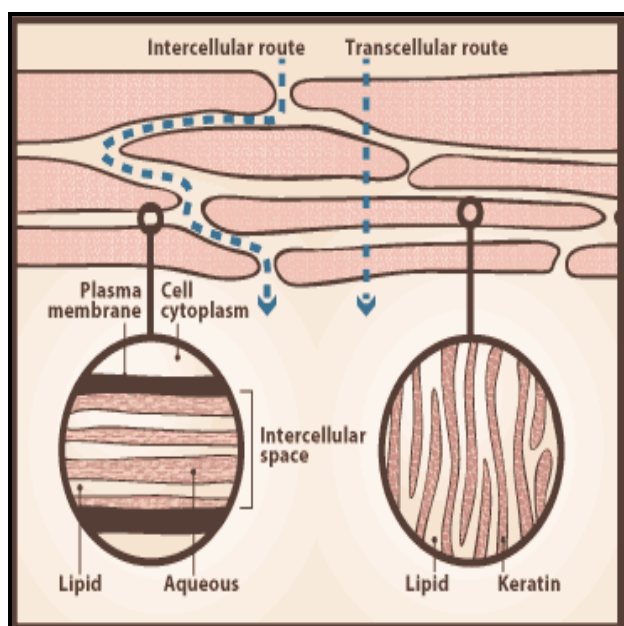


Figure 2: Drug penetration pathways across skin

Strategies to Enhance Drug Penetration and Absorption¹⁵

A suitable data is given below for this section

Table 1: Types of method to enhance drug penetration through skin

Chemical	Bio-Chemical	Physical
<ul style="list-style-type: none"> Water Solvents Surfactant 	<ul style="list-style-type: none"> Peptides Metabolic-inhibitors 	<ul style="list-style-type: none"> Stripping Iontophoresis Electroporation Ultrasound (thermal) Ultrasound (cavitation) Thermal ablation Mechanical abrasion Microneedles

Advantages of using Emulgel as a Drug Delivery System¹⁶

- **Hydrophobic drugs can be easily incorporated into gels using d/o/w emulsions**

Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in an aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.

- **Better stability**

Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.

- **Better loading capacity**

Other novel approaches like niosomes and liposomes are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.

- **Production feasibility and low preparation cost**

Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.

- **No intensive sonication**

Production of vesicular molecules needs intensive sonication which may result in drug degradation and leakage. But this

problem is not seen during the production of emulgels as no sonication is needed.

Controlled release

Emulgels can be used to prolong the effect of drugs having shorter $t_{1/2}$.

Patient compliance

They are less greasy and easy to apply.

Classification of Topical Drug Delivery System

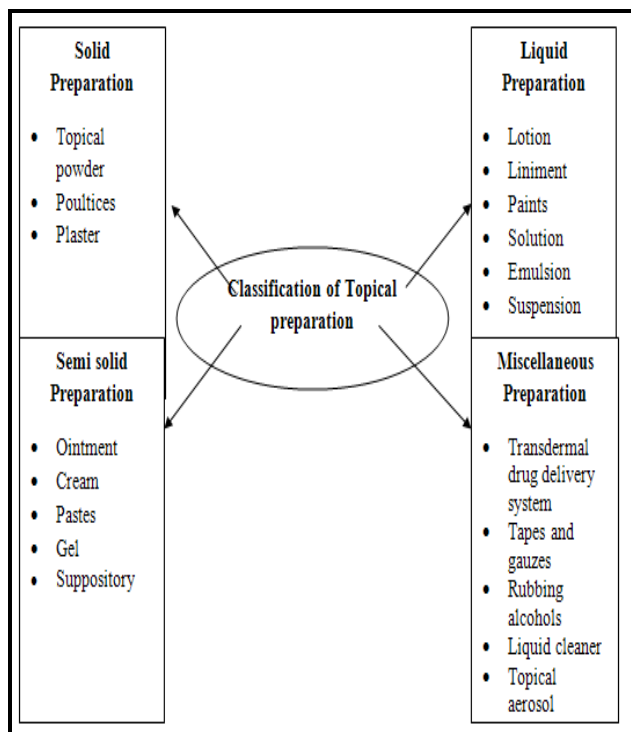


Figure 4: Classification of topical preparation

Important Constituents of Emulgel Preparation

Vehicle

The vehicle is an important link between drug potency and therapeutic effectiveness, since extensive pharmaceutical research has shown that the composition of the vehicle can profoundly influence the rate and extent of absorption (bioavailability). In the rational design of dermatologic vehicles that maximize bioavailability, two factors are of critical importance: solubilizing the drug in vehicle and maximizing movement (partitioning) of drug from vehicle to stratum corneum¹⁷.

These are of two types –

- Aqueous material: these form the aqueous phase of the emulsion mainly used are water, alcohol etc.
- Oils: These agent forms the oily phase of the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffin, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics¹⁸.

Table 2: uses of different types of oil with their quantity (in percentage)

Chemical	Quantity (%)	Dosage Form
Light liquid paraffin	7	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 both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations.eg Polyethylene glycol 40 stearate, Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate¹⁹.

Gelling Agent

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent listed below in the table²⁰. Gelling agents are the agents which increase the consistency of any dosage form by swelling in an aqueous phase and forming gelly like structure²¹.

Table 3: use of different gelling agent

Gelling agent	Quantity (%)	Uses
Carbopol-934	1	Emulgel
Carbopol-940	1	Emulgel
HPMC	3.5	Gel
Sodium CMC	1	Gel

Penetration Enhancers

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.

Table 4: use of different penetration enhancers

Penetration enhancer	Quantity (%)	Dosage form
Oleic acid	1	Gel
Lecithine	5	Gel
Urea	10	Gel
Clove oil	8	Emulgel
Isopropyl myristate	5	Gel
Menthol	5	Emulgel

Mechanism of Penetration Enhancer

These enhancers include compounds that interact with the lipid matrix of the stratum corneum to alter its nanostructure and thereby increase permeability²². The fatty acid enhancers increased the fluidity of the lipid protein portion of the stratum corneum. Some enhancers act on both polar and non-polar pathway by altering the multi laminate pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development of the product. Penetration enhancers may act by one or more of three main mechanisms:

- Disruption of the highly ordered structure of stratum corneum lipid.
- Interaction with intercellular protein.
- Improved partition of the drug, co- enhancer or solvent into the stratum corneum²³.

Re-organisation of lipid domain and barrier disruption is shown by the use of terpenes, which enhance the drug diffusion by extracting lipids from stratum corneum^{24, 25}.

Preparation of Emulgel

Emulgel was prepared by the method reported by²⁶ with minor modification. The Gel in formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed and Carbopol 940 in purified water with constant stirring at a moderate speed then the pH are adjusted to 6 to 6.5 using Tri ethanol amine (TEA). The oil phase of the emulsion were prepared by dissolving Span 80 in light liquid paraffin having drug in ethanol solution while the aqueous phase was prepared by dissolving Tween 80 in purified water. Methyl and Propyl paraben was dissolved in propylene glycol and was mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. And add glutaraldehyde in during of mixing of gel and emulsion in ratio 1:1 to obtain the emulgel.

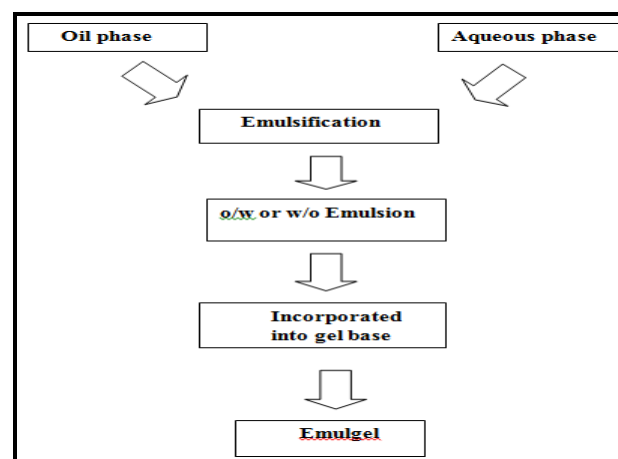


Figure 5. representing flow chart for preparation of emulgel

Characterization of Emulgel

Physical Appearance

The prepared Emulsion formulations were inspected visually for their color, homogeneity, consistency and pH as described by²⁷. The pH values of 1% aqueous solutions of the prepared Gellified Emulsion were measured by a pH meter (Digital pH meter, DPH 115 pm).

Spreadability

Spreadability is determined by apparatus suggested by²⁸ which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide is fixed on this block. An excess of emulgel (about 2gm) under study is placed on this ground slide. The emulgel is then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges. The top plate is then subjected to pull of 80gm. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5cm be noted. Lesser time indicates better spreadability. Spreadability was calculated by using the formula,

$$S = M.L/T$$

Where, S = Spreadability, M = Weight tied to upper slide,

L = Length of glass slide;

T = Time taken to separate the slides completely from each other.

Extrudability Study²⁹

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the

yield value and exhibiting consequent plug flow. In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in percentage of emulgel and emulgel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability. The measurement of extrudability of each formulation is in triplicate and the average values are presented. The extrudability is than calculated by using the following formula:

$$\text{Extrudability} = \frac{\text{Applied weight to extrude emulgel from tube (gm)}}{\text{Area (cm}^2\text{)}}$$

Swelling Index

To determine the swelling index of prepared topical emulgel, 1 gm of gel is taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaOH. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed³⁰. Swelling index is calculated as follows:

$$\text{Swelling index (SW) \%} = \frac{[(Wt - Wo) / Wo] \times 100}{100}$$

Where, (SW) % = Equilibrium percent swelling,

Wt = Weight of swollen emulgel after time t,

Wo = Original weight of emulgel at zero time

Drug Content Determination³¹

Take 1gm of emulgel. Mix it in suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. Standard plot of drug is prepared in same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance.

$$\text{Drug Content} = (\text{Concentration} \times \text{Dilution Factor} \times \text{Volume taken}) \times (\text{Conversion factor})$$

Rheological Study

The viscosity of the different emulgel formulations is determined at 25°C using a cone

and plate viscometer with spindle 52 (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath.

Ex-vivo Bioadhesive Strength Measurement of Topical Emulgel (MICE SHAVEN SKIN)^{32, 33}

The modified method is used for the measurement of bioadhesive strength. The fresh skin is cut into pieces and washed with 0.1 N NaOH. Two pieces of skin were tied to the two glass slide separately from that one glass slide is fixed on the wooden piece and other piece is tied with the balance on right hand side. The right and left pans were balanced by adding extra weight on the left-hand pan. 1 gm of topical emulgel is placed between these two slides containing hairless skin pieces, and extra weight from the left pan is removed to sandwich the two pieces of skin and some pressure is applied to remove the presence of air. The balance is kept in this position for 5 minutes. Weight is added slowly at 200 mg/ min to the left-hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the emulgel from the skin surface gave the measure of bioadhesive strength. The bioadhesive strength is calculated by using following:

$$\text{Bioadhesive Strength} = \frac{\text{Weight required (in gms)}}{\text{Area (cm}^2\text{)}}$$

In-vitro Release Permeation Studies

In vitro release studies were carried out using Franz diffusion cell. Franz diffusion cell (with effective diffusion area 3.14cm² and 15.5 ml cell volume) was used for the drug release studies. Gellified Emulsion (200 mg) was applied onto the surface of egg membrane evenly³⁴. The egg membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time interval. Samples were analyzed for drug content by UV

visible after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug released across the egg membrane was determined as a function of time.

Drug Release Kinetic Study

To analyze the mechanism of drug release from the topical gel, the release data were fitted to following eq.

Zero – order equation: $Q = k_0 t$

Where, Q is the amount of drug released at time t, and k₀ is zero – order release rate.

First – order equation: $\ln(100 - Q) = \ln 100 - k_1 t$

Where, Q is the percent of drug release at time t, and k₁ is the first – order release rate constant.

Higuchi's equation: $Q = k_2 \sqrt{t}$

Where, Q is the percent of drug release at time t, and K₂ is the diffusion rate constant.

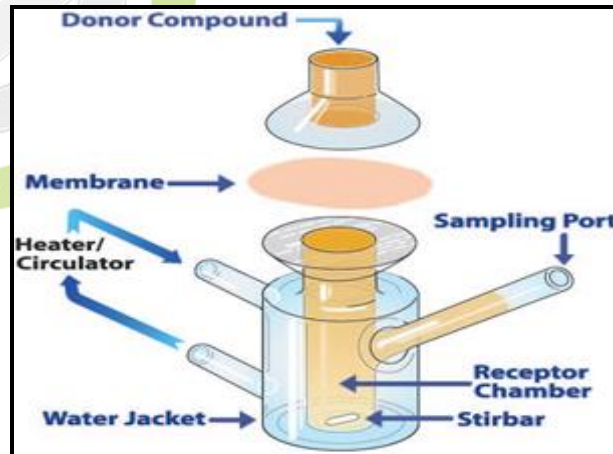


Figure 6: Franz diffusion cell

Skin Irritation Test

The preparation is applied on the properly shaven skin of rat and its adverse like change in color, change in skin morphology should be checked upto 24 hours. The total set of 8 rats can be used of the study. If no irritation occurs the test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated³⁵.

Marketed Formulations

Table 5: marketed formulations with their brand and company names

S.No.	Product name	Drug	Manufacturer
1.	Voltaren emulgel	Diclofenac-diethyl-ammonium	Novartis pharma
2.	Miconaz-H- emulgel	Miconazole nitrate, Hydrocortisone	Medical union pharmaceuticals
3.	Excec gel	Clindamycin, Adapalene	Zee Laboratories
4.	Pernox gel	Benzoyl peroxide	Cosme Remedies Ltd.
5.	Lupigyl gel	Metronidazole, Clindamycin	Lupin Pharma
6.	Clinagel	Clindamycin phosphate, Allantion	Stiefel Pharma
7.	Topinate gel	Clobetasol propionate	Systopic Pharma
8.	Kojivit gel	Kojic acid, Dipalmitate Arbuti	Micro Gratia Pharma
9.	Acent gel	Aceclofenac	Intra Labs India Pvt. Ltd.
10.	Avindo gel	Azithromycin	Cosme Pharma Lab.
11.	Cloben gel	Clotrimazole, Beclomethasone	Indoco Remedies
12.	Nadicin cream	Nadifloxacin	Psycho remedies
13.	Zorotene gel	Tezarotene	Elder Pharmaceuticals

Accelerated Stability Studies

Stability studies were performed according to ICH guidelines. The formulations were stored in hot air oven at $37 \pm 2^\circ$, $45 \pm 2^\circ$ and $60 \pm 2^\circ$ for a period of 3 months.

The samples were analyzed for drug content every two weeks by UV-visible spectrophotometer.

Stability study was carried out by measuring the change in pH of gel at regular interval of time.

CONCLUSION

In the recent years, topical drug delivery system will be used extensively due to better patient compliance. Emulgel is the recent technique for the topical drug delivery it is better suitable for hydrophobic drugs and obviously it is a very good technique for drug delivery of combination of both hydrophilic and hydrophobic drugs. Mainly the hydrophobic drug formulation can be developed with emulgel technique because it contain both oil and aqueous (i.e. gel base) on the other hand hydrogel are not suitable for

hydrophobic drugs. Since emulgel is enhancing spreadability, adhesion, viscosity and extrusion. This novel drug delivery becomes a popular formulation in future.

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