AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Emulgel- Novel Strategy for Delivery of Hydrophobic Drugs

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ABSTRACT

When gels and emulsions are used in combined form the dosage form are referred as emulgel. Also there has been incredible interest for the utilization of novel polymers and drug molecules. A one of the feature of topical drug delivery is the immediate availability of the skin as target organ for diagnosis and treatment. Among the different group of semisolid planning, the utilization of gel has extended both in cosmetics and in the pharmaceuticals. Although Gel has many advantages, there is many limitation in delivery of hydrophobic drugs, so to overcome this limitation an emulsion base novel approach is being most used. That is emugel system used so that even a hydrophobic moiety can enjoy the unique properties of gels and having characteristics of dual control release i.e. emulsion as well as gel. The formulation is prepared by various polymer which behave as an emulsifer and thickening agent because of gelling capacity of these compounds give rise to stable emulsions and creams by diminishing surface and interfacial pressure while in the meantime expanding the thickness of the aqueous phase. In order to understand the potential of emulgel as delivery vehicles, this review gives an overview of the ideal properties, formation, and characterization of emulgels. So this can be use as analgesics and antifungal drugs, as superior topical drug delivery systems over present conventional systems available in market.

Keywords: Emulgel, Cosmetology, Hydrophobic Drug, Polymer, Chronic Skin Diseases.

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Received 14 January 2017 Accepted 27 Janaury 2017

Please cite this article as: Dalvi PB *et al*., Emulgel- Novel Strategy for Delivery of Hydrophobic Drugs. American Journal of PharmTech Research 2017.

INTRODUCTION

In the course of the most recent decades the treatment of illness has been expert by regulating medication to human body through different routes to be specific oral, sublingual, rectal, parental etc. The topical drug delivery system is generally used where these systems of drug administration fails or in local skin infection like fungal infection [1]

Skin is a standout amongst the most promptly available parts of human body for topical administration and molecule penetration in the skin predominantly by three courses:

- through intact stratum corneum,
- through sweat ducts, and
- through the sebaceous follicle.

Skin composed of both hydrophobic intercellular materials within the hydrophobic cornified cells. Thus emulgel is most preferred topical delivery for hydrophobic drugs.

Dermatological products applied to skin are diverse in formulation and range in consistency from liquid to powder but the most popular products are semisolid preparation. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Gels are relatively newer classes of dosage form created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles. Gel formulations generally provide faster drug release compared with ointments and creams.[2] Although Gel has many advantages, there is many limitation in delivery of hydrophobic drugs, so to overcome this limitation an emulsion base novel approach is being most used. That is emugel system used so that even a hydrophobic moiety can enjoy the unique properties of gels and having characteristics of dual control release i.e. emulsion as well as gel.

Emulgel is composed of two parts:

- Emulsion.
- Gel.

Emulgels are emulsions, either of the oil-in-water or water in oil type, which are gelled by mixing with gelling agent. which provides stability and better bioavailability for hydrophobic drugs. In fact, the presence of a gelling agent in water is responsible for conversion of classical emulsion into emugel . Direct (oil-in-water) system is used to entrap lipophilic drugs where as hydrophilic drugs are encapsulated in the reverse (water-inoil) system. 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 action.[3,4]

Advantages of Emulgel[6]

- Hydrophobic drug can be easily incorporated into hydroxyanisole(BHA), etc. gel using o/w emulsion.
- Better loading capacity.
- Control released.
- Suitable for self-medication.
- They are convenient to apply on hairy skin due to absence of greasiness and lack of residues upon application.
- Dual release of drug from emulsion and gel.
- Emulgels used even for cosmetic purposes.
- Avoidance of gastrointestinal incompatibility.

Disadvantages of Emulgel [7]

- Skin irritation on contact dermatitis.
- Possibility of allergenic reactions.
- Poor permeability of some drug through skin.
- Drug of large particle size not easy to absorb through the skin.

Rationale of Emulgel[8,9]

Many generally utilized topical agent like ointment, cream, lotion have many burdens. or limitation They have extremely sticky making uneasiness to the patient when applied. In addition they additionally have lesser spreading coefficient and need to apply with rubbing . What's more, they display the issue of stability also. Because of all these components inside the significant gathering of semisolid arrangements, the utilization of straightforward gels has extended both in cosmetic and in pharmaceutical. A gel is colloid in nature typically contain 99% wt liquid, which is immobilized by surface tension. In-spite of Gel has many advantages, there is many limitation in delivery of hydrophobic drugs, so to overcome this limitation an emulsion base novel approach is being most used.

Ideal Properties of Drug Candidate To Formulate As Emulgel[9]

- Drug dose should be low i.e. less than 10 mg.
- Drug should be non irritating and non-sensitizer having a less polarity.
- Molecular weight of drug should be 400 Dalton or less.

- Partition coefficient i.e. Log p (Octanol-water) between 0.4-0.8
- Oral bioavailability and therapeutic index should be low.
- Half life of drug 10 hr or less.
- Having a skin –permeability coefficient more than 0.5 * 10^{-3} cm/hr

Physiology Of Skin

The layers of epidermis are:

- Stratum Germinativum (Growing Layer)
- Malpighion Layer (pigment Layer)
- Stratum Spinosum (Prickly cell Layer)
- Stratum Granulosum (Granular Layer)
- Stratum Lucidum
- Stratum Corneum (Horny Layer)

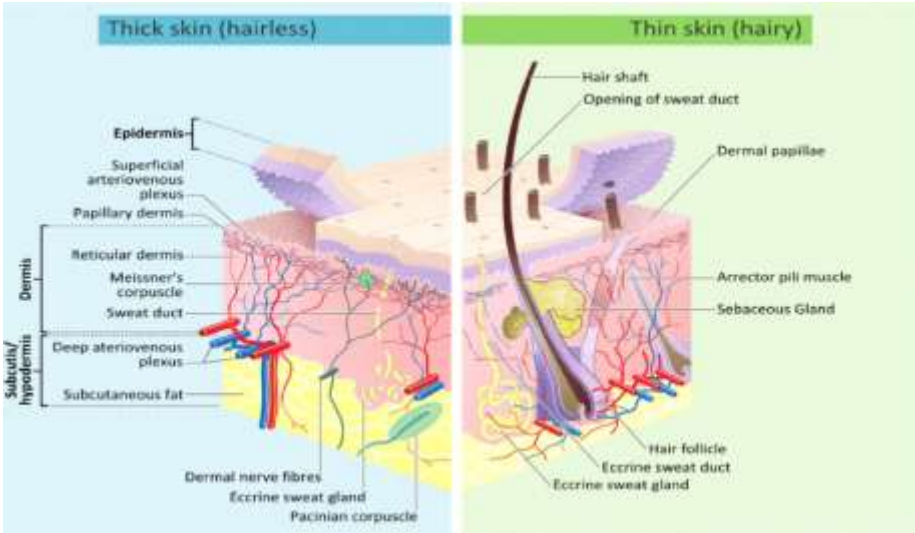

Figure 1: Layers of skin showing thick skin (hairless) and thin skin (hairy)[10]

Non-viable epidermis:

Outermost layer of skin is Stratum corneum. Which act as physical barrier during trans movement of the many substance across the layer.

The stratum corneum is 10 to 20 cell layer thick over most of the body.

Stratum corneum consists: lipid (5-15%) including phospholipids, glycosphingo lipid, cholesterol, sulfate and neutral. which is mainly keratin.

Viable epidermis:

Viable epidermis of the skin occurs between the stratum corneum and the dermis and has a thickness ranging from 50-100 µm. It resemble physiochemically to the structure of living tissues.

Dermis:

This layer found beneath the layer of Viable epidermis It is structural fibrin and very few cells are like it can be found histological in normal tissue. Dermis thickness ranges from 2000 to 3000µm.[11]

Subcutaneous 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, secretary pores of the sweat gland and cutaneous nerves.

Drug Delivery across The Skin[12]

The epidermis is the maximum superficial layer of the skin and consists of stratified keratinized squamous epithelium which varies in thickness in different components of the body.

it is thickest on with elastic fibres. the skin forms a pretty waterproof layer that protects the deeper and extra sensitive systems. blood vessels are distributed profusely under the pores and skin. specifically crucial is a continuous venous plexus this is furnished by influx of blood from the pores and skin capillaries.

inside the most exposed regions of the body is the arms feet, and ears blood is likewise provided to the plexus immediately from the small arteries through particularly muscular arteriovenous anastomoses. a unique factor of dermatological pharmacology is the direct accessibility of the skin as a goal organ for analysis and treatment. the pores and skin acts as a two-manner barrier to prevent absorption or loss of water and electrolytes.

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 corneum[13].

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 route.[14]

There are three primary mechanisms for drug absorption through the skin:

- intercellular,
- transcellular and
- follicular

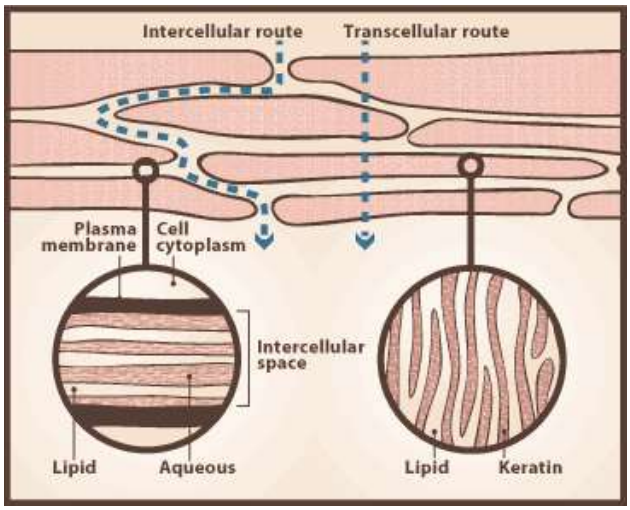

Figure 2: Drug penetration pathways across skin

METHOD TO ENHANCE DRUGPENETRATION:

1. Chemical enhancement:-

- Solvents
- Water
- Surfactant.

2. Biochemical enhancement:-

- Metabolic- inhibitors
- Peptides

3. **Physical enhancement:-**

- Microneedles
- Iontophoresis
- Stripping
- Electroporation
- Ultrasound (thermal)
- Ultrasound (cavitational)
- Thermal ablation
- Mechanical abrasion

Classification Of Topical Drug Delivery System

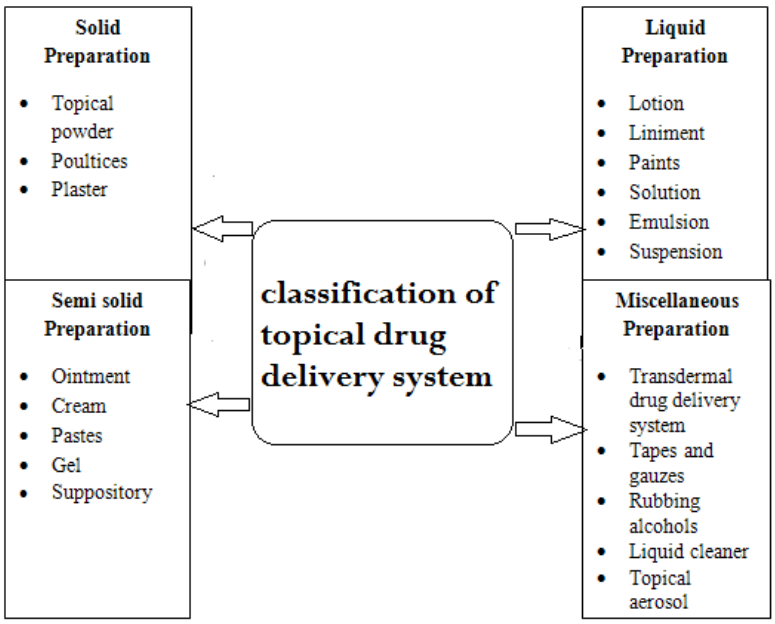

Figure 3: Classification of topical drug delivery

Factors Affecting Topical absorption Of Drug[16,17]

A) Physiological Factors

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

B Physiochemical Factors

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

IMPORTANT CONSTITUENTS OF EMULGEL PREPARATION[19-21]

Aqueous material:

This forms aqueous phase of the emulsion. Most commonly use, water and alcohols.

Oils:

These agents form the oily phase if 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 characteristics. Widely used oils in oral preparations are non-biodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils.

Table 1: Uses of different types of oil with their quantity (in percentage)[18]

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:

emulsification process and stability of emulsion totally depend on the type and quantity of emulsifer use. By incorporating an appropriate emulsifying agent stability of emulsion can be increased because these are thermodynamically unstable.

Polyethylene glycol 40 stearate, Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate.

Surfactants having HLB values greater than 8 such as the nonionic surfactant (spans, tweens) are used in the formulation of o/w emulsions whereas mineral oils such as liquid paraffin have HLB value less than 8 and therefore are used in the formulation of water in oil emulsions.

Permeation enhancer:[22]

In order to promote absorption of drugs, vehicles often include penetration enhancing ingredients that temporarily disrupts the skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into skin. So called penetration enhancers.

E.g. Clove oil 8% , Menthol 5%, Oleic acid ,lecithin , isopropyl, myristate , urea , eucalyptus oil , chenopodium oil, linoelic acid ,menthol.

Table 2: Quantity of permeation enhancers preparation of gels and emulgel

Chemical	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

Properties of Penetration Enhancers:

- They should be non-toxic, non-irritating and non- allergenic.
- They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body i.e. should not bind to receptor sites
- The penetration enhancers should work unidirectional i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
- The penetration enhancers should be appropriate for formulation into diverse topical preparations thus should be compatible with both excipients and drugs.
- They should be cosmetically acceptable with an appropriate skin 'feel'.

Preservatives:

e.g. Propyl paraben, methyl paraben, Benzalkonium chloride, Benzoic acid, Benzyl alcohol etc.

Antioxidants:

e.g. Butylated-Hydroxy,Ascorbyl palmitate, BHA etc.

Humectant:

e.g. Glycerin, Propylene gylcol, etc

Gelling agents:

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent. e.g. Carbapol 934 carbapol 940 ,HPMC ,HPMC-2910, sodium CMC .

Table 3: various gelling agents used in pharmaceutical dosage forms

Sr.no	Gelling agents	Concentration used (%w/w)	Active pharmaceutical ingredient
1	Sodium CMC	3-4%	Benzydamine
2	Carbopol-934	1%	Chlorphenesin
3	Carbopol-940	1%	Mefenamic acid
4	HPMC	2.5%	Clorphenesin
5	Combination of HPMC & Carbopol	1.2%	Ketorolac, clotrimazole
6	Pluronic® F127	1-3%	Piroxicam
7	Pemulen	0.1-0.4%	Flurbiprofen

FORMULATION OF EMULGEL[23]

STEP 1: Formulation of Emulsion either O/W or W/O

STEP 2: Formulation of gel base

STEP 3: Incorporation of emulsion into gel base with continuous stirring

The flow chart of emulgel preparation is shown in figure 4.

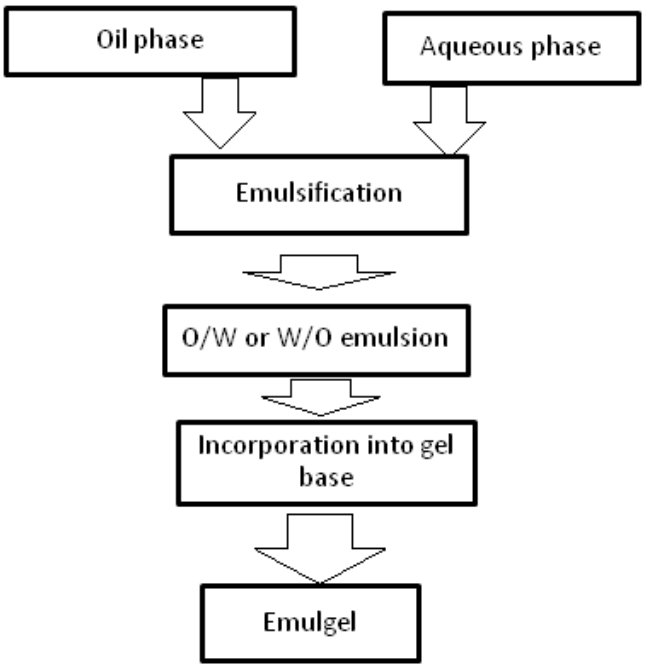

Figure 4: Method of emulgel preparation

CHARACTERIZATION OF EMULGEL

Physical Appearance[26]

The prepared emulgel formulation are inspected visually for there colour, homogeneity, consistency, and phase separation.

Spreading Cofficent[27]

Spreadability is determined by apparatus 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 emulgel. A ground glass slide is fixed on this block. An excess of emulgel (about 2 gm) 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 1 Kg 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 80 gms. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability .

pH:

The pH values of 1% aqueous solutions of the prepared gels were measured by a digital pH meter. Electrodes were completely dipped into these semisolid formulations and pH was noted.

Swelling Index[28]

For determination of swelling index of formulated emulgel following procedure adopted, 1 gm of the gel is taken on porous aluminum foil and then placed separately in a beaker of 50 ml containing 10 ml 0.1 N NaOH. Then samples were taken from beakers at different time points and put it on a dry place for some time after it reweighed. Swelling index is calculated as follows:

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

Where,

Wo = Initial weight of emulgel at zero time, Wt = Weight of swollen emulgel after time t, (SW) % = Percent swelling Index

Drug content Determination[29]

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.

Drug Content = (Concentration × Dilution Factor × Volume taken) ×(Conversion factor)

Skin Irritation Test (Patch Test):

The preparation is applied on the properly shaven skin of rat and its adverse like change in colour, change in skin morphology should be checked up to 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 repeated.

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.

Globule size and its distribution in emulgel

Globule size and distribution is determined by Malvern zeta sizer. A 1.0 gm sample is dissolved in purified water and agitated to get homogeneous dispersion. Sample was injected to photocell of zeta sizer. Mean globule diameter and distribution is obtained.

Extrudability

The prepared emulgel formulations were filled in clean, lacquered aluminium collapsible tubes with a 5 mm opening nasal tip. Extrudability was then determined by measuring the amount of gel extruded through the tip when a constant load of 1 kg. Was placed over the pan. The Extrudability of prepared Emulgel formulations was calculated by using following

Extrudability =Amount of gel extruaded from the tube x 100 /Total amount of gel filled in the tube

Microbiological Assay:

A ditch plate technique is used in this method. This technique is used for the bacteriostatic and fungistatic activity of a compound. It is mainly applied for semisolid formulations. Previously prepared Sabouraud's agar dried plates were used. Three grams of the Gellified Emulsion are placed in a ditch cut in the plate. Freshly prepared culture loops are streaked across the agar at a right angle from the ditch to the edge of the plate. After incubation for 18 to 24 hours at 25°C, the fungal growth was observed and the percentage inhibition was measured as follows

% imbibitions = L2/L1 × 100

Where, L1= Total length of the streaked culture, L2= Length of inhibition

In Vitro Release/Permeation Studies:

In vitro release studies were carried out using Franz diffusion cell.

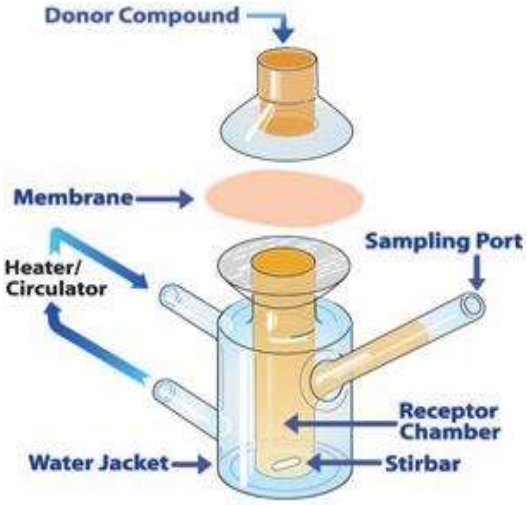

Figure 5: Franz diffusion cell

Kinetics Modeling[30]

Data obtained from ex- vivo permeation studies were fitted into zero order, first order, Higuchi, and mathematical models for evaluation of drug release kinetics. The model for best fit was predicted from the value of R2. For an ideal fit, value of R2 i.e. higher, the value of R2 best was the model fitted. Hence, the model which gives the R2 value nearest to 1 describes the best order of drug release.

Zero – order equation: Q = k0 t

Where, Q is the amount of drug released at time

t, and k0 is zero – order release rate.

First – order equation: In (100 – Q) = In 100 –k1 t

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

Higuchi's equation: $Q = k2\sqrt{t}$

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

Stability Studies:

The prepared emulgels were packed in aluminum collapsible tubes (5 g) and subjected to stability studies at 5°C, 25°C/ 60% RH, 30°C/65% RH, and 40°C/75% RH for a period of 3 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles.

Marketed Formulations

Table 4: 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	Pernox gel	Benzoyl peroxide	Cosme Remedies Ltd.
4	Zorotene gel	Tezarotene	Elder Pharmaceuticals
5	Cloben gel	Clotrimazole, Beclomethasone	Indoco Remedies
6	Acent gel	Aceclofenac	Intra Labs India Pvt. Ltd.
7	Clinagel	Clindamycin phosphate, Allantion	Stiefel Pharma
8	Avindo gel	Azithromycin	Cosme Pharma Lab
9	Lupigyl gel	Metronidazole, Clindamycin	Lupin Pharma
10	Kojivit gel	Kojic acid, Dipalmitate Arbuti	Micro Gratia Pharma

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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