

AN OVERVIEW ON DEVELOPMENT AND EVALUATION OF NOVEL TOPICAL EMULGEL FORMULATION

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ABSTRACT

Over the last decade the treatment of illness has been accomplished by administering drug to human body via various routes namely oral, sublingual, rectal, parental etc. Many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. The topical drug delivery system is generally used where these systems of drug administration fails or in local skin infection like fungal infection. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorder. The combination of hydrophilic cornified cells in hydrophobic intercellular material provides a barrier to both hydrophilic and hydrophobic substances. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Polymer can function as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. These Emulgel are having major advantages on novel vesicular systems as well as on conventional systems in various aspects. Various permeation enhancers can potentiate the effect, So Emulgel can be used as better topical drug delivery systems over present systems.

Keywords: Emulgel, Topical drug delivery, Hydrophobic drugs, Polymer, Hydrated, Emulsifier, Novel, Thixotropic.

INTRODUCTION

The skin is a key site for systemic and local drug administration. Though the skin is an easily accessible route of drug administration, some drugs do not penetrate the skin. A variety of topical medicinal products are available from simple solutions and ointments to multiphase nanotechnology-based products.¹ In the forthcoming years, topical drug delivery systems will be used considerably to improve patient compliance. Gel is a convenient and preferred dosage form for delivering active ingredients to their site of action. Due to its cross-linked and three-dimensional nature, gel captures small drug particles and promotes their controlled release. The three-dimensional network is composed of macromolecules and is capable of entrapping a large amount of solvent molecules. Gels lengthen the contact time of drug over the skin due to its muco-adhesive property.^{2,3} Most common pharmaceutical gels are formulated by dispersing hydrophilic polymers within a sufficient aqueous phase. After dissolving within an aqueous phase, hydrophilic polymers become lyophilic colloids. Due to their unique physical properties, they are transformed into a self-association type of colloids. Gels have many favorable properties like spreadability, non-staining, greaseless, and thixotropic but a major drawback in delivering hydrophobic drugs to the skin. Active ingredients with a hydrophobic nature exhibit improper drug release in gels due to lack of solubility in the aqueous phase, hence they are not suitable to be added into the gel base. Therefore, to reduce these drawbacks, emulsion-gel based drug delivery systems are being used.

Emulsions are thermodynamically unstable biphasic dosage forms consisting of two immiscible liquids, one of which is uniformly dispersed as globules (internal phase) throughout the second phase (external phase).⁴ Emulsions allow the incorporation of hydrophobic medicinal agents into the oil phase which facilitates the dispersion of oil globules in the aqueous phase and produces an oil-in-water (O/W) emulsion.⁵ Furthermore, emulsions are capable of acting as controlled drug delivery systems where the medicinal agent to be delivered is stored inside the oil phase. This internal oil phase of an emulsion will function as a drug reservoir and the drug will be released to the skin in a controlled manner. Emulsions have many satisfactory properties; a major disadvantage is their reduced contact time on the skin surface. Both gel and emulsion individually possess many advantages but due to inherent drawbacks, another dosage form superior to each preparation was identified and thus the discovery of Emulgel was made.⁶ Hence, Emulgel possesses the characteristics of both gel and emulsion; thereby, it operates as a dual-control drug release system. Due to these benefits many pharmaceutical manufacturers have stepped into commercial production of emulgels. Such products are Voltaren Emulgel (Diclofenac sodium), Miconaz-H (Miconazole nitrate), Pernox® (Benzoyl peroxide) and CLINAGEL® (Clindamycin phosphate).⁷

Advantages of Emulgel

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.
8. Convenient and easy to apply.
9. Incorporation of hydrophobic drugs
10. Better loading capacity
11. Better stability
12. Production feasibility and low preparation cost
13. Controlled release
14. No intensive Sonication

Disadvantages of Emulgel

1. Skin irritation on contact dermatitis.
2. The possibility of allergenic reactions.
3. The poor permeability of some drug through the skin.
4. Drug of large particle size not easy to absorb through the skin.^{8,9}

RATIONALE OF EMULGEL FORMULATION

Many widely used topical agents like ointment, cream, lotion have many disadvantages. They have very sticky causing uneasiness to the patient when applied. Moreover, they also have lesser spreading coefficient and need to apply with rubbing. And they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparation, the use of transparent gels has expanded both in cosmetics and in a pharmaceutical preparation. A gel is a colloid that is typically 99% wt. liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelatin substance present.¹⁰

In spite of many advantages of gels, a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and deliver through gels. Numbers of medicated products are applied to the skin or mucous membrane that either enhances or restores a fundamental function of skin or pharmacologically alters an action in the underlined tissues. Such products are referred as topical or dermatological products. 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.^{11,12}

Skin

Most of the topical preparations are meant to be applied to the skin. So the basic knowledge of the skin and its physiology function are very important for designing topical formulation.

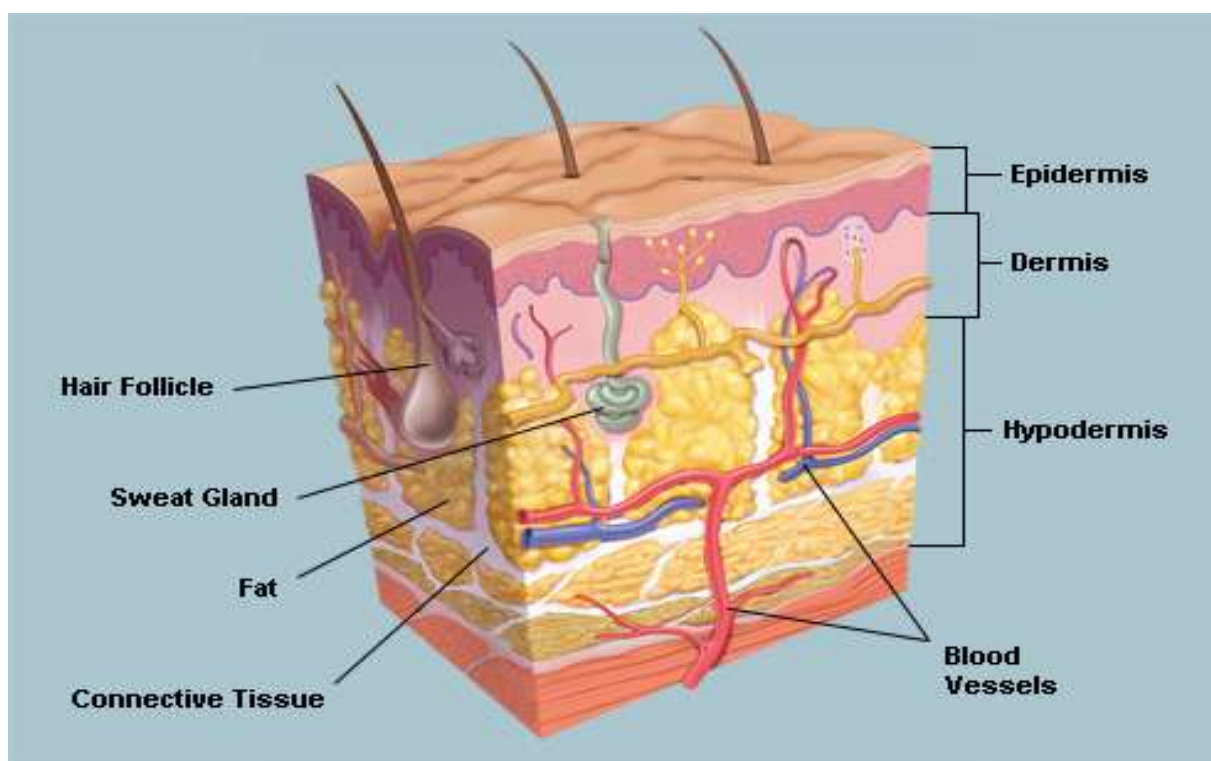


Fig.1. Diagram of Skin

The skin can be considered to have four distinct layers of tissue.

1. Non-viable epidermis
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue.

The Skin is structurally complex and thick membrane. The epidermis is the most superficial layer of the skin and is composed of stratified keratinized squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibers. The skin forms a relatively waterproof layer that protects the deeper and more delicate structures. Blood vessels are distributed profusely beneath the skin. Especially important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries. In the most exposed areas of the body-the hands, feet, and ears blood is also supplied to the plexus directly from the small arteries through highly muscular arteriovenous anastomoses.^{13,14}

There are three primary mechanisms of topical drug absorption: transcellular, intercellular, and follicular. Most drugs pass through the torturous path around corneocytes and through the lipid bilayer to viable layers of the skin. The next most common (and potentially under recognized in the clinical setting) route of delivery is via the pilosebaceous route. The barrier resides in the outermost layer of the epidermis, the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Creams and gels that are rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body.¹⁵

FACTOR EFFECTING DRUG ABSORPTION

(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.^{15,16,17}

METHOD TO ENHANCEMENT DRUG ABSORPTION

1. Chemical enhancement
2. Biochemical enhancement
3. Physical enhancement
4. Super saturation enhancement.¹⁸

Factors to be considered when choosing Emulgel Formulation

1. Effect of the vehicle e.g. An occlusive vehicle enhances penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient or protective action.
2. Match the type of preparation with the type of agent. 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.
5. Generally, ointments and w/o creams are less irritating, while gels are irritating.
6. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.¹⁹

Important Component of Emulgel Formulation

1. Aqueous Material:

This forms the aqueous phase of the emulsion and commonly used agents are Polar and Non-Polar solvent.

2. Oils:

These agents from the oily phase if the emulsion is for external application such as mineral oils, either alone or combined with soft or hard paraffin's, 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 or various fixed oils of vegetable origin.^{20,21}

3. 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 acid³⁴, Sodium stearate.

4. Permeation Enhancers:

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

5. Gelling Agent:

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.²²

Table 1: Use of Gelling Agents

Gelling agent	Quantity	Dosage form
Carbopol-934	1.0%-2.0%	Emulgel
Carbopol-940	0.5%-2.0%	Emulgel
HPMC-2910	2.0%	Emulgel
HPMC	3.0%	Gel
Sodium CMC	1.5%	Gel

Table 2: Use of Oils

Gelling agent	Quantity	Dosage form
Light Liquid Paraffin	7.0%	Emulsion and Emulgel
Isopropyl myristate	7.0-8.0%	Emulsion
Isopropyl stearate	3.5-7.5%	Emulsion
Isopropyl palmitate	6.0-7.0%	Emulsion
Propylene glycol	3.0-5.0%	Gel

Table 3: Use of Penetration Enhancers

Gelling agent	Quantity	Dosage form
Oleic acid	1.5%	Gel
Lecithin	4.5%	Gel
Urea	8.0%	Gel
Isopropyl myristate	5.0%	Gel
Linoleic acid	4.5%	Gel
Clove oil	7.0%	Emulgel
Menthol	4.5%	Emulgel

Properties of penetration enhancers

1. They should be non-toxic, non-irritating and non-allergenic.
2. They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.
3. They should have no pharmacological activity within the body i.e. should not bind to receptor sites.
4. 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.
5. The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both Excipient and drugs.
6. They should be cosmetically acceptable with an appropriate skin 'feel'.^{23,24}

Mechanism of penetration enhancers

Penetration enhancers may act by one or more of three main mechanisms:

1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, co-enhancer or solvent into the stratum corneum.^{25,26}

The enhancers act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. 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.²⁷

Preparation of Emulgel Formulation

Emulgel was prepared by the above reported method 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 and the pH are adjusted to 6 to 6.5 using triethanolamine (TEA).²⁸ The oil phase of the Emulsion was prepared by dissolving Span 80 in light Liquid Paraffin having the

drug in ethanol solution while the aqueous phase was prepared by dissolving Tween 80 in purified water.²⁹

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 was added to the aqueous phase with continuous stirring until cooled to room temperature and add Glutaraldehyde during the mixing of gel and emulsion in ratio of 1:1 to prepare the Emulgel.³⁰

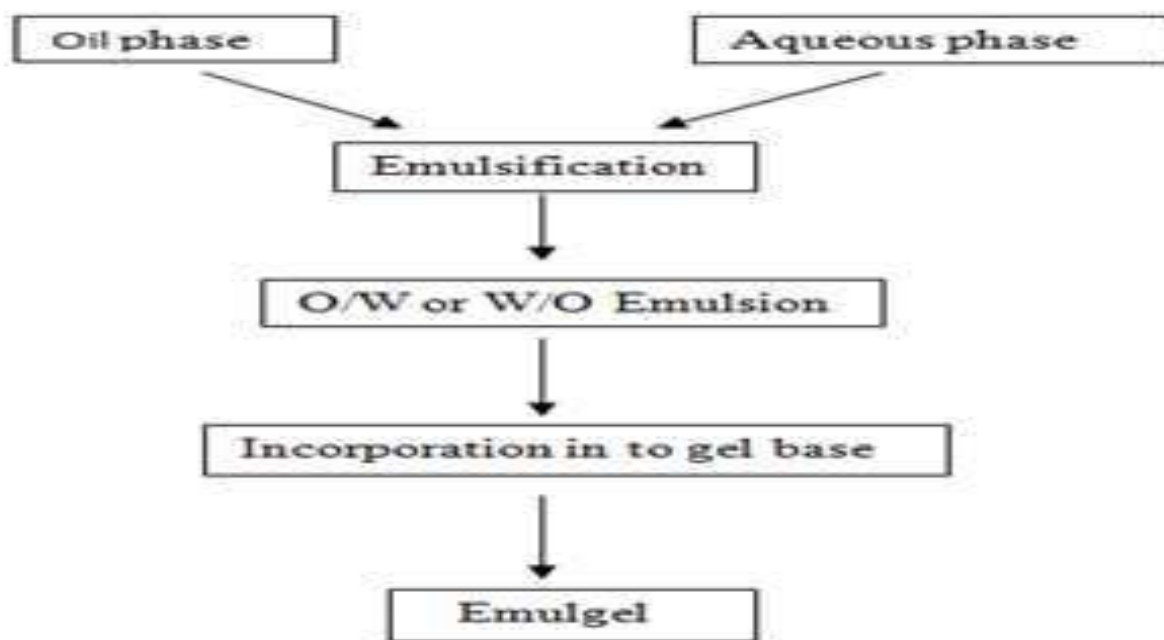


Fig.2. Flow chart of Emulgel Formulation

Characterization of Emulgel

(a) Physical appearance:

The Emulsion formulations were inspected visually for their Color, Homogeneity, Consistency and pH. The pH values of 1.5% aqueous solutions of the prepared Gellified Emulsion were measured by a pH meter (Digital pH meter DPH 115 pm).³¹

(b) Rheological Study:

The Viscosity of the different Emulgel formulation is determined at 27°C using a cone and plate viscometer with spindle 55 (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath.^{31,32}

(c) Swelling Index:

Determination of the swelling index of prepared topical Emulgel by using, 2 gm of gel is taken on aluminum foil and then placed separately in a 100 ml beaker containing 20 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 reweighed. Swelling index is calculated as follows:^{33,34}

$$\text{Swelling Index (SW) \%} = [(W_t - W_o) / W_o] \times 100.$$

Where, (SW) % = Equilibrium percent swelling,

W_o = Original weight of Emulgel at zero time after time t ,

W_t = Weight of swollen Emulgel

(d) In-vivo Bioadhesive Strength test of Topical Emulgel:

(MICE SKIN): The modified Bioadhesive strength method is used for the measurement of bioadhesive strength.

The fresh skin of mice was cut into pieces and washed with 0.1 N NaOH. Two pieces of mice 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.³⁵ The right and left pans were balanced by adding extra weight on the left-hand side of the pan.³⁶

2 gm of topical Emulgel formulation 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 the same position for 5 minutes.³⁷

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 showed the measurement of bioadhesive strength. The bioadhesive strength is calculated by using the following formula:

$$\text{Bioadhesive Strength} = \text{Weight required (in gms)} / \text{Area (cm}^2\text{)}^{38}$$

(e) Drug Content Estimation:

The concentration of drug in Emulgel was measured by Spectrophotometer. Drug content in Gellified Emulsion was measured by dissolving 2gm of Emulgel in solvent (methanol) by Sonication. Absorbance was measured after suitable dilution in UV visible spectroscopy (UV-1700 CE, Shimadzu Corporation, Japan).³⁹

(f) Determination of pH

pH of the formulation was determined by using Electronic digital pH meter. The Electrodes of pH meter was washed by distilled water and Calibrated by two different standard pH (pH 4 & 9) and then dipped into the formulation to measure the pH of Emulgel formulation and repeat the same procedure 3 times.^{40,41}

(g) Stability studies

The prepared Emulgel was packed in collapsible aluminum tubes (10 g) and subjected to stability studies at 10 °C/45% RH, 27 °C/55% RH, 30 °C/65% RH, and 40 °C/75% RH for a period of 3 Month. Samples were withdrawn at 15-days time interval and evaluated for Physical appearance, pH, Rheological properties, Drug Uniformity, and Drug release rate.^{42,43}

(h) Skin irritation test:

The Emulgel formulation is applied on the properly shaven skin of mice and its adverse effect like change in colour, change in skin morphology was checked up to 24 hrs.^{44,45} The total 10

set of mice was 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.⁴⁶

CONCLUSION

After the deep study we have reached into a conclusion that Emulgel have proven as most convenient, better and effective delivery system than other topical formulation due to its non-greasy gel like property and it provides better release of drugs as compare to other topical drug delivery system. Incorporation of emulsion into gel makes it a dual control release system. The topical drug delivery system will be used extensively due to better patient compliance. Since Emulgel possesses an advantage in terms of Spreadibility, Adhesion, Viscosity and Extrusion, it would become a popular drug delivery system.

Moreover, it would become a solution for loading hydrophobic drugs in a water soluble gel bases. A Stable Emulgel represents an effective approach for the resolution of problem in drug and cosmetic agent delivery.

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