

EMULGEL: AN ADVANCE APPROACH FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

OBJECTIVE: Currently Emulgels are very widely used technology for topical drug delivery system, and they could be oil in water type or water in oil type emulsion which has been made into emulgel by various gelling agents. This Procedure of mixing of emulsion and gel gives it a binary control release and provides better stability. **CONCLUSION:** Emulgels provides better drug delivery for hydrophobic drugs as well. The patient compliance for topical formulations is quite good for ailments like chronic skin diseases, fungal infections, psoriasis. Emulgels deliver both high compliance and better treatment possibilities. Following review will offer you a better understanding of Emulgel ideal properties, development, and characterization of emulgel.

KEYWORDS: Emulgel, Gelling agent, hydrophobic drugs, binary control release.

INTRODUCTION

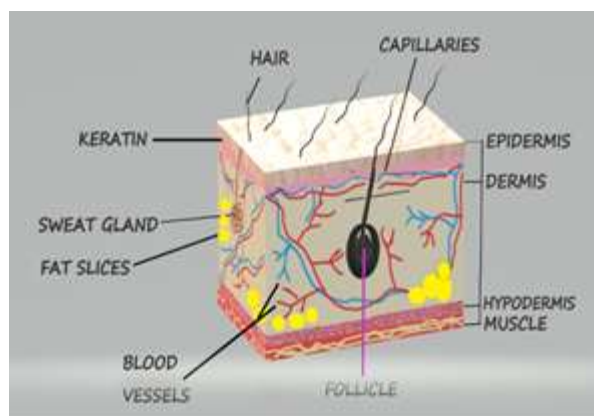
Drug delivery through topical route is used to cure cutaneous disorders. It is used when the oral drug delivery fails, or there may be more adverse effects of an oral system like in some fungal infection [1]. The merit of topical delivery is that it surpasses first pass metabolism and direct application of the drug onto the affected area [2, 3]. After topical drug delivery, the drug diffuses and reaches the site of action [4]. Molecules can penetrate the skin via three routes: through stratum corneum, sweat ducts, or sebaceous follicle [5]. Topical drug administration is very easiest and simplest of localised drug delivery and can be applied as ophthalmic, rectal, vaginal and on the skin. Various preparations either cosmetic and dermatological are used for healthy or diseased skin. These are available from solid to semisolid to liquid [6].

PHYSIOLOGY OF THE SKIN [2, 3, 7]

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

including protection against outer physical, chemical, and biologic attacker, it also prevents loss of excess water from the body and plays a role in thermoregulation. The skin is continuous, having mucous membranes lining the body's surface. The skin has three layers: the epidermis, the dermis, and subcutaneous tissue as seen in figure 1. The outermost is epidermis, consists of a specific groups of cells known as keratinocytes, which synthesize keratin, a long, threadlike protein with a protective role. The middle layer is dermis, which is made up of the fibrillar structural protein known as collagen. The dermis lies on the subcutaneous tissue, which consist small lobes of fat cells known as lipocytes. The thickness of these layers varies which considerably highly depending on the geographic location on the anatomy of the body. The eyelid, for example, has the thinnest layer of the epidermis, measuring >0.1 mm, whereas the palms and soles of the feet have the thickest epidermal layer, measuring approximately 1.5 mm. The dermis is thickest on the back, where it is 35–40 times as thick as the overlying epidermis.

Fig. 1: Physiology of Skin



DRUG ABSORPTION ON TOPICAL ADMINISTRATION [8, 9-11]

There are three pathways has been postulated for the diffusion of the solutes through the skin.

- Transcellular/Intracellular (Passive) Diffusion
- Intercellular (Paracellular) Diffusion

- Transappendageal- drug diffusion through: Hair follicles, sweat glands and sebaceous glands.

The next most common route of delivery is through the pilosebaceous route permeation tends to occur through the intercellular matrix which is for lipophilic drugs, but through the

transcellular diffusion, it has been shown faster alternative for hydrophilic drugs. [2, 3]

COMMONLY KNOWN TOPICAL PREPARATIONS [12]

- Ointments
- Cream
- Paste
- Lotion
- Gel

When emulsion and gel are combined form the resultant is *Emulgel*. Both O/W and W/O type of Emulsions are used as a vehicle for delivering various drugs to the skin. They have high penetrability than normal gels. Hydrophilic gelling agents are used for converting an emulsion into emulgel.

Advantages of Emulgel [3, 6, 7, 13, 14]

1. Avoid first pass metabolism.
2. Gastrointestinal incompatibility avoided.
3. More sites specific
4. Good patient compliance.
5. Suitable for self-medication.
6. Easy to remove if needed
8. Easy to use and apply.
9. Hydrophobic drugs can be incorporated.
10. Good loading capacity superior than other novel approaches like liposomes and niosomes.
11. Improved Stability than Gels.
12. Preparation cost is quite low.
13. Controlled release

Disadvantages [3, 15]

1. Skin irritation or Allergic reaction can occur.
2. Some drugs had poor penetrability.
3. The large particle size of the drug may not cross through the skin.
4. Formation of the bubble during the preparation of emulgel.
5. Lesser spreading coefficient

Ideal properties of Emulgel [16, 17]



Figure 3: Ideal properties of Emulgel

FORMULATION OF EMULGEL

MATERIALS USED

Vehicle: Preferred properties [2]

- Even distribution of the drug
- Easy release of drug to site of action
- Delivering the drug to the target site
- Provide sustained pharmacological outcome
- Acceptable to the patient site

For crossing stratum corneum the rate and extent of absorption depends mainly on the vehicle but also the active ingredient too.

Aqueous material [18]

Used for the aqueous phase of the emulsion. Commonly used are alcohol and water.

Oils [1]

Used for making an oily phase of the emulsion. Depending upon the application, various oils used. Like mineral oils with or without soft or hard paraffin for externally applied emulsions. Mostly used oil preparations are castor oils and non-biodegradable mineral oils.

USES OF OIL

Table 1:Uses of Oil.

CHEMICAL	QUANTITY	DOSAGE FORM
Isopropylmyristate	7-7.5%	Emulsion
Isopropylstearate	7-7.5%	Emulsion
Isopropylpalmitate	7-7.5%	Emulsion
Light paraffin	liquid 7.5%	Emulsion and Emulgel
Propylene glycol	3-5%	Gel

Emulsifiers [15]

For promoting the emulsification and to control stability, emulsifying agents are used. For example, Sorbitan mono-oleate (Span 80), polyoxyethylene sorbitan monooleate (Tween 80), polyethylene glycol.

Gelling agents [19, 20]

It increased the consistency of formulation and used as a thickening agent. Example Carbopol, HPMC.

USES OF GELLING AGENTS

Table 2: Uses of Gelling Agents

GELLING AGENT	QUANTITY	DOSAGE FORM
Carbopol 940	1%	Emulgel
Carbopol 934	1%	Emulgel
HPMC 2910	2.5%	Emulgel
Sodium CMC	1%	Gel

Penetration enhancers [1]

For improving drug absorption, various penetration enhancers used, which temporarily disrupt the skin barriers, lipid channels will be fluidized and alter the partitioning of the drug and increases the delivery into the skin. They should be non-irritating, non-toxic, and non-allergenic with no pharmacological activity and should be compatible with excipients and active ingredients. Example Oleic acid

USES OF PENETRATION ENHANCERS

Table 3: Uses of Penetration Enhancers

PENETRATION ENHANCERS	QUANTITY	DOSAGE FORM
Clove oil	8%	Emulgel
Menthol	5%	Emulgel
Oleic acid	1%	Gel
Lecithin	5%	Gel
Linoleic acid	5%	Gel
Cinnamon	8%	Emulgel
Isopropyl Myristate	8%	Gel

STEPS IN FORMULATION [6, 15, 21]

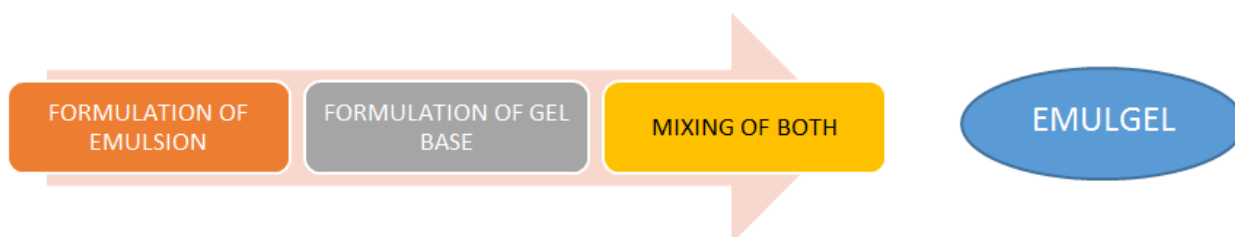


Figure 4:

Step 1: Formulation of emulsion either O/W or W/O.

Step 2: Formulation of a gel base.

Step 3: Mixing of an emulsion into gel base with continuous stirring.

Emulgel was prepared by the method reported by Mohammad et al. (2004) with minor modification. The formulation of the gel was made by dispersing Carbopol 940 in distilled water separately with the constant stirring at moderate speed, and the pH is adjusted to 6-6.5 using triethanolamine. The oil phase was prepared by using span 20 in liquid paraffin while aqueous phase made by using Tween 20 in distilled water. Methyl paraben and propyl paraben dissolved in PEG while drug dissolved in ethanol. Both the oil and aqueous phase separately heated to 70-80° C after that oily phase added to the aqueous phase with continuous stirring. The obtained emulsion was mixed with the gel in the proportion 1:1 ratio for obtaining emulgel.

Evaluation of emulgel

Physical examination [3, 22] The Prepared emulgel is inspected visually for its color, consistency, homogeneity, and phase separation.

pH Determination

 [3, 22]

Formulation pH was determined by using a digital pH meter. Electrodes of pH meter were washed prior to using and then dipped in formulation, and pH was noted.

Spreadability

 [1, 23, 24]

Spreadability of the formulation is determined by a special apparatus suggested by Mutimer et al. (1956), which is modified in the laboratory and used for study purposes. It consists of a wooden block with one pulley at one end. By this method, spreadability is measured by characteristics of emulgel which is "slip and drag". A ground glass is fitted on the block. An excess of Emulgel (approx. 2g) is placed on the ground slide. Then Emulgel is sandwiched between this slide and another glass slide having dimensions of the fixed ground slide and provided with a hook. A 1Kg weight is applied on the top of two slides for 5 minutes to expel air and to provide a uniform film of emulgel between the slides. Excess of emulgel is scrapped off. The top plate is subjected to pull off 75gms. 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 is calculated by using the formula:

$$S = M \cdot L / T$$

Where M= weight tied to the upper slide

L= length of glass slides

T= time taken to separate the slides

Extrudability Test (Tube Test)

 [2]

This test based upon a determination of the force required to extrude 0.5cm ribbon of Emulgel in 10 sec from a lacquered

collapsible aluminum tube. The extrude ability is calculated by following formula.

EXTRUDABILITY = Applied weight to extrude Emulgel from the tube (in g) / Area (in cm²)

Globule size and its distribution in Emulgel

 [3, 23]

Globule size and distribution were determined by using Malvern Zeta sizer. 1.0 g of the sample is dissolved in distilled water and sonicated to get homogeneous dispersion. The sample was injected to photocell. Distribution and Mean globule diameter in formulation are obtained.

Measurement of viscosity

 [25]

The viscosity of the formulations was determined using a Brookfield Viscometer (Brookfield DV-2 + pro) with spindle S61. The formulation was added in the beaker and allowed to settle for 30 min. at a temp. around 25°C. Spindle was lowered perpendicular into the centre of the Emulgel without touching bottom of Jar. Rotation speed was around 12 rpm for 10 minutes. Viscosity reading obtained.

Swelling index

 [2, 24]

To determine the swelling index of prepared topical emulgel formulation, 1 g of gel is taken on porous aluminium foil and then separately placed 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 a dry place for some time after it reweighed. Swelling index can be calculated as follows:

$$\text{SWELLING INDEX (SW)\%} = [(W_t - W_0) / W_0] \times 100$$

Where, SWELLING INDEX (SW)% = Equilibrium percent swelling

W₀ = Original weight of emulgel at zero time after time t

W_t = Weight of swollen emulgel

In vitro drug release study

 [6, 24]

The in-vitro study was carried out in modified diffusion cell by using dialysis membrane which was soaked in Phosphate buffer solution (PBS) pH 7.4 for 10-12 hours was clamped to the one end of hollow glass tube of dialysis cell. Emulgel was spread evenly on dialysis membrane. 100ml of PBS pH 7.4 added in receptor compartment. This whole assembly kept on magnetic stirrer and solution on receptor side stirred continuously using a magnetic bead with temperature maintained at 37±0.5°C. At suitable time interval 10 ml sample is withdrawn and replaced with equal amount of fresh media. The sample was analysed spectrometrically at 273nm and cumulative percentage drug release calculated by using standard calibration curve.

Ex-vivo drug release study

 [26]

This study is carried out in modified Franz diffusion (FD) cell, using a wistar male rat skin. A section of skin was placed between the donor and receptor compartment of FD cell, keeping dorsal side upward. Phosphate buffer pH 7.4 was used as dissolution media. The temperature of the cell was maintained at 32°C by circulating water jacket. The whole assembly was kept on a magnetic stirrer

and stirred continuously with the help of the magnetic bead. A similar blank run was set simultaneously. The samples are withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. The samples are analysed spectrometrically.

Microbiological Studies [5, 27]

It is done by Ditch plate technique. This is used for the evaluation of bacteriostatic or fungistatic activity of a formulation. Sabouraud's agar dried plates are used in which three grammes of emulgel are placed. Freshly prepared culture loops are streaked on agar at right angle from the ditch to the edge of the plate.

Drug content determination [15, 28]

Weigh accurately 1 g of emulgel. And dissolved in 100 ml of 0.1 N NaOH. The volumetric flask is kept for 2 hours and shaken well. The solution was passed through filter paper and filtered. The absorbance measured approximately at 375nm.

DRUG CONTENT = (concentration x dilution factor x volume taken) x conversion factor

Skin irritation test [6, 29]

A 1 g of formulation is applied to each site (two sites per guinea pig) by introduction double gauze layer to an area of skin approximately 1" x 1" (2.54 x 2.54 cm²) The sample reapplied on the skin of the guinea pig. After 24 hours of exposure sample is removed. The test sites are wiped out by tap water and made clean without any test residue left.

Stability Studies [30, 6]

The prepared formulation was packed in collapsible aluminium 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 are drawn at 15 days intervals and evaluated for their physical appearance, pH, rheological properties and drug content.

MARKETED FORMULATIONS [6]

The various preparations of Emulgels available in market are shown in this Table

Table 4: Various preparations of Emulgels available in market

PRODUCT NAME	DRUG	MANUFACTURER
Micono-H-Emulgel	Miconazole nitrate,	Medical union
Voltaren Emulgel	Hydrocortisone	Pharmaceuticals
Zorotene gel	Diclofenac-diethyl-ammonium	gsk Pharma
Nadicin cream	Tazarotene	Elder Pharmaceuticals
Avindo gel	Nadifloxacin	Psycho remedies
Accent gel	Azithromycin	Cosme Pharma Lab
Topinate gel	Aceclofenac	Intra Lab India Pvt. Ltd.
Clinagel	Clobetasol propionate	Systopic pharma
Pernox gel	Clindamycin phosphate, allantoin	Stiefel Pharma
Exces gel	Benzoyl Peroxide	Cosme remedies Ltd.
Lupigyl gel	Clindamycin, Adapalene	Zee laboratories
	Metronidazole, Clindamycin	Lupin Pharma

FUTURE OUTCOMES

The future trends of drug delivery systems will bring new innovations and possibilities. For emulgel use of various other gelling agents may be used, which can be the natural polymer with proper stability. The use of microemulsion, nanosponges and nanoemulsion in emulgel for increasing performance may be used which is still under process. In future, emulgels will be able to deliver more number of topical drugs.

CONCLUSION

After thorough literature survey, we reached into a conclusion that emulgels have proven as most convenient, better and effective delivery system. They have many advantages like non-greasy, gel-like property, lacks of oily bases, and better release of drugs as compared to other topical drug delivery system. Incorporation of Emulsion into gel makes it a binary control release system further problems such as phase separation, creaming associated with emulsion gets resolved, and its stability improves. Many specific drugs loaded in emulgel showed very effective and very potential results in topical disorder, most of these potential drugs used in skin disorders are hydrophobic in nature and emulgel is now a solution for these kinds of drugs. Many drugs like Adapalene, Retinoic acid, Betamethasone, Dexamethasone etc. are still under process.

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