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REVIEW ON EMULGEL A NOVEL APPROACH FOR TOPICAL DRUG DELIVERY SYSTEM

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Abstract:
Emulgel is currently attracting researchers for its potential as a drug delivery system by loading a broad range of drug molecules. Emulgel is formed by incorporating either o/w or w/o emulsion in a gel base formed by a gelling agent. By incorporating emulsion into a gel enhances the stability and makes it a dual control release system. When compared with other topical drug delivery systems emulgel shows better drug release and enhanced patient compliance due to the presence of soluble excipients. The current review gives an overview of ideal properties with special emphasis on the formulation and evaluation of emulgel.

Keywords: *Emulgel; Emulsion; Gelling agent; Dual controlled release; Topical agents*

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INTRODUCTION:

Topical drug delivery is defined as the application of drug-loaded formulations to the skin to treat various skin disorders and to obtain a localized effect of the drug. Further, these topical drug delivery systems are mainly used to treat various skin infections (bacterial or fungal) by bypassing the first-pass metabolism effectively [1]. In a topical drug delivery system, the desired drug reaches the site of action by diffusing out from the carrier and gets absorbed through the skin [2]. Absorption through the skin (percutaneous) can be enhanced by increasing the rate of drug release from the carrier [3]. The release rate enhancement of the desired drug from the topical formulations is entirely dependent on the physicochemical properties of both the drug and the carrier system [4].

In the last two decades emulsion in the form of gels is rapidly picking up significance in pharmaceutical research. Their usage as a carrier system originates from the wide use of emulsions for dermatological purposes. Emulgel is defined as emulsions either of water in oil or oil in water type which are converted to a gel by using a gelling agent [5]. Further, the emulsion can be used as a delivery system to deliver the desired drug in a controlled manner where the drug is entrapped in the internal phase which acts as a drug reservoir and reaches the skin through the external phase and gets absorbed slowly. Gel captures the drug particles and releases them in a controlled manner and the contact period can be prolonged by enhancing the mucoadhesive property of the carrier system [6]. Since Emulgel has the characteristics of both emulsion and a gel this carrier system can be used as a dual control release system where, w/o emulsions are widely used for moisturizing dry skin, and o/w emulsions are used as general cosmetics [7, 8]. Further, Emulgel when used as a topical drug delivery system possesses some advantages like emollient, greaseless, thixotropic, easily removable, non-staining, and compatible with the excipients used in the formulation [9]. Furthermore, the rate of drug release and stability of the loaded drug is entirely dependent on the type and concentration of polymer used in the formulation of gel. Emulgel also has improved patient compliance due to its non-greasy nature when compared with other topical drug delivery systems like ointments and creams [10, 11]. Emulgel may serve as an alternative approach for delivering hydrophobic drugs via skin [12].

Advantages [13]

1. Bypassing the first-pass metabolism
2. Delivery to a specific site.
3. Improves patient compliance
4. Self-medication is possible
5. Drugs with a narrow therapeutic window can be delivered.
6. Termination of medication is possible whenever desired.
7. Easy to apply
8. Drugs with poor aqueous solubility can be delivered
9. Drug loading capacity can be enhanced.
10. Drug stability can be improved.
11. Feasible for production with low preparation cost.
12. The desired drugs can be released in a controlled manner.

Disadvantages [14]

1. Skin irritation and a chance of contact dermatitis.
2. Allergic reactions are possible.
3. Poor permeability for some of the drugs through the skin.
4. Drugs with large particle sizes cannot be delivered.

Ideal properties of the drug candidate to formulate as Emulgel [15]

1. The dose of the desired drug should be less than 10 mg.
2. The molecular weight of the desired drug should be less than 400 Daltons
3. The half-life of the drug should be less than 10 hr.
4. The partition coefficient value should be between 0.4-0.8.
5. Oral bioavailability and therapeutic index should below.
6. Drugs should be non-irritating and they should have less polarity.

The rationale of choosing Emulgel as an alternative approach for delivering the desired drugs

Conventional topical drug delivery system possesses various disadvantages like their sticky nature which causes discomfort to the patient while applying the formulation on skin. Additionally, they also have a lower spreading coefficient and rubbing of the formulation is needed to apply the formulation and they also have drug stability issues. To overcome the above-mentioned limitations of conventional topical drug delivery systems usage of transparent gels came into existence for both cosmetic and pharmaceutical applications.

A gel is typically a colloid (99% of the weight is liquid) i.e. is immobilized by the surface tension between the liquid and macromolecular network of fibres built from a gelatin substance. Even though

this drug delivery system has various advantages the major limitation is the delivery of poorly water-soluble drugs. To overcome this drawback emulsion-based gel is being used to deliver even hydrophobic drugs [16].

Delivery of the loaded drugs through the skin

As depicted in Figure 1 there are two important layers so f skin (epidermis and dermis). Beneath the skin, in the subcutaneous layers, blood vessels are abundantly distributed. Further, drug absorption through the skin mainly occurs by three different mechanisms (intercellular, transcellular and follicular). Additionally, there is an alternative route to deliver the drugs i.e. pilosebaceous route where penetration happens through the intercellular matrix, but by the Transcellular pathway, polar drug molecules can be rapidly absorbed. In healthy skin, cell-like keratinized corneocytes and large non-polar lipid intercellular matrix serve as barriers for drugs [17]. Drug penetration through the skin can be enhanced by using permeation enhancers like propylene glycol, surfactants and DMSO. These permeation enhancers enhance the permeation of the drug by altering the barrier properties of the stratum corneum (enhancing solubility, partitioning the stratum corneum and fluidising the crystalline structure of the stratum corneum) [18].

Different excipients used in the formulation of Emulgel

Aqueous Materials

These materials in general form the aqueous phase of the emulsion. Commonly used agents are water and alcohols [19].

Oils

They are responsible for the oil phase of the emulsion. This oil phase plays a vital role in different formulations (emulsion, microemulsion and nanoemulsion) as the physicochemical properties of these oil phases govern the spontaneity in the formation of an emulsion. Further, oil with maximum ability to solubilize the drug is considered as oil phase for the preparation of emulsion which helps in attaining maximum drug loading. Therefore, the choice of oil is often a compromise between solubilizing the drug and the ability to facilitate the formation of respective emulsion with desired characteristics [20]. Various oils used in the preparation of emulsions are listed in Table 1.

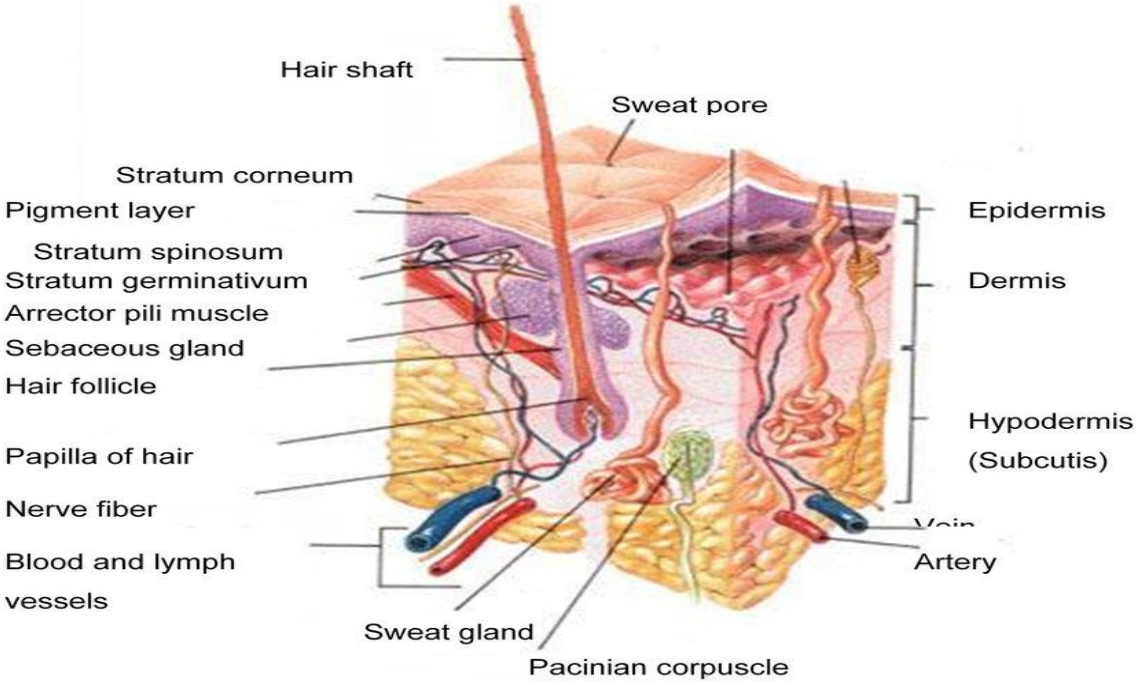

Figure 1: Cross-section of skin

Table 1: Oils used in the formulation of emulsion and their uses [14]

Name of the oil	Quantity	Dosage form
Light liquid Paraffin	7.5%	Emulsion and Emulgel
Isopropylmyristate	7-7.5%	Emulsion
Isopropyl stereate	7-7.5%	Emulsion
Isopropyl palmitate	7-7.5%	Emulsion
Propylene glycol	3-5%	Gel

Emulsifiers

Emulsifiers are used as agents to control the process of emulsification and maintain the stability of the emulsion. Further, the stability of the emulsion can be enhanced because in general emulsions are thermodynamically unstable. To formulate o/w emulsions surfactants with HLB values greater than 8 like spans and tweens can be used. Similarly, to formulate w/o emulsions mineral oils like liquid paraffin having an HLB value less than 8 can be used. Furthermore, a mixture of tween and span results in the formation of more stable emulsion when compared to their individual use [21].

Permeation enhancers

Permeation enhancers are the agent that enhances the absorption of drugs through the skin by temporarily thinning the permeability of the skin. These agents should be inert, non-toxic, non-allergic, colourless, odourless, tasteless and should be compatible with the drugs and excipients. The permeation enhancers incorporated in the formulation should not cause and fluid loss from the body and other endogenous materials and on its removal skin should regain its barrier properties [22]. Various permeation enhancers used in the formulation of Emulgel are depicted in Table 2.

Table 2: Permeation enhancers used in the formulation of emulsion and their uses [14]

Permeation enhancer	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
Cinnamon	8%	Emulgel

Gelling agents

Gelling agents are used to forming the base for a gel which will be incorporated in the emulsion to form Emulgel. They are also termed thickening agents which enhances the viscosity of the dosage form by swelling the aqueous phase. Incorporating a gelling agent into the system makes it thixotropic [23, 24]. Various gelling agents used in the formulation of Emulgel are depicted n Table 3.

Table 3: Gelling agents used in the formulation of emulsion and their uses [14]

Gelling agent	Quantity	Dosage form
Carbopol-934	0.5-2%	Emulgel
Carbopol-940	0.5-2%	Emulgel
HPMC-2910	2.5%	Emulgel
HPMC	3.5%	Gel
Sodium CMC	1%	Gel

Formulation of Emulgel

A typical procedure for formulating an Emulgel primarily involves the preparation of the gel base by using a gelling agent. Where the required quantity of carbopol 940 (gelling agent) was weighed and dispersed onto warm distilled water with vigorous stirring and the solution is allowed to hydrate for 2 hr. To the above solution, other excipients like propylene glycol and glycerol were added with constant stirring. Further, the required quantity of the drug was weighed and dispersed and the solution is neutralized to pH 6 by using triethanolamine and the final volume was adjusted by using distilled water and kept aside overnight to remove the air bubbles. Post formulating the gel base the chosen emulsion (o/w or w/o) was formulated and finally, the emulsion will be fused into a gel base to form the desired drug-loaded emulgel [25]

Evaluation of the drug-loaded Emulgel

Fourier transform infrared spectroscopy (FTIR)

FTIR study was performed majorly to identify a stable storage condition for the drug in solid-state and to identify the compatibility between the drug and various excipients used in the formulation of the desired emulgel [26].

Physical appearance

The formulated drug-loaded emulgel is evaluated for its physical properties like color, consistency, and homogeneity [27].

pH

The pH of the formulated drug-loaded emulgel is analyzed by using a digital pH meter. Where electrodes are dipped into 1% of the aqueous solution of the prepared gel and pH is noted down [9].

Swelling index

The swelling index of the formulated emulgel is calculated by placing 1g of the formulated gel on an aluminum foil and placed in a beaker containing 10ml of 0.1N NaOH. Further, at predetermined time intervals samples were collected and allowed o to dry and the weight of the sample is noted. The swelling index is calculated by using the following formula.

$$Swelling\ index = \frac{Wt - Wo}{Wo} * 100$$

Where,

Wo = Initial weight of the emulgel

Wt = Weight of swollen emulgel at time t

SW (%) = Percent Swelling index [28]

Spreadability

To understand the ability of the formulated emulgel to spread a special apparatus was designed. Spreadability is expressed in the terms of time (seconds) taken by the slides to slip off from the gel under the application of a certain amount of load, the lesser the time is taken to separate better is the spreadability. A typical setup involves selecting two glass slides of 6*2 cm each and placing the selected quantity of the formulation (500 mg) over one of the slides. The selected slides were placed in such a manner that the gel will be sandwiched between two slides. The formulation was squeezed continuously to form a thin layer by applying a weight of 100g on the upper slide and the excess formulation on the sides of the slides is scrapped off. Further, the lower slide is fixed on the apparatus and the upper slide is tied to a string, and to the sting, a load of 20g is applied with the help of the pulley. Post application of weight time taken for the upper slide to move to a distance of 6m and separate from the lower slide is noted and spreadability was evaluated.

$$\text{Spreadability} = \frac{\text{M}}{\text{T}} * \text{L}$$

Where,

M = Weight tied to upper slide (20 g)

L = Length of glass slide (6 cm)

T= Time taken [28]

Extrudability study (tube test)

An extrudability study is performed to measure the force required to expel the gel from the tube. The formulated emulgel is checked and filled in clean aluminum collapsible tubes. Further, the tubes are pressed with a certain amount of force with the help of a finger to extrude the gel. Extrudability is analyzed by calculating the force required to extrude 0.5 cm of ribbon in 10 seconds [24].

Bio-adhesive strength measurement

To measure the bio-adhesive strength a modified balance method is used. A typical procedure involves removing both the pans from the balance. Post removing on the left side a glass slide was hanged and on the right side, a 100 ml beaker was placed, and to balance the assembly a 20g weight is placed on the left side. Another glass slide is placed below the hanged slide. On both sides, a small portion of rat skin was attached and one gram of gel is applied to the skin. A little pressure was applied to form the bio adhesion bond and slowly water is added to the beaker till the applied gel is separated from the skin surfaces. The volume of water added is converted into mass and bio-adhesive strength was calculated [29].

Determination of drug content

To measure the gel content required quantity of formulated gel (1 g) was dissolved in a suitable solvent and filtered to obtain a clear solution. The obtained solution absorbance was measured by using UV Visible Spectrophotometer and drug content was determined by using a calibration curve of the loaded drug [30].

***In-vitro* drug release studies**

In-vitro drug release studies of the loaded drugs in the emulgel by using an egg shell membrane. An eggshell membrane will have keratin-like human skin. To obtain the eggshell a whole egg is dissolved in 0.5 M HCl where the outer shell of a whole egg is dissolved resulting in a membrane. Post dissolution other contents of the egg are removed and the membrane is collected, washed, and stored in a refrigerator. Franz diffusion cell is used to perform the study where one gram of gel was applied on 9.8 cm^2 area of egg membrane and tied to the donor compartment and the volume of the receptor fluid is reserved to 37.5 ml, the temperature is maintained at 37 °C and stirred at 100 rpm using a magnetic stirrer. At predetermined time intervals, a sample of 3 ml was analyzed by using the UV spectrophotometric method [31].

***Ex-vivo* skin permeation studies**

Ex-vivo skin permeation studies were performed on Albino rats weighing 200-250 g was used. The skin was excided from the selected animals and placed on aluminum foil and the dermal side of the skin was scraped off for fat or subcutaneous tissue. Further, the skin was washed with physiological buffer and freshly obtained skin should be used in all experiments.

The *ex-vivo* skin permeation studies from different formulations were studied using Franz diffusion cell where the receptor compartment is loaded with 37.5 ml of buffer. Skin loaded with gel sandwiched between donor and receptor compartment with donor compartment having epidermis site. The donor compartment is maintained at 37 ± 1°C with constant stirring. At predetermined time intervals, 3 ml of samples were collected and replaced with an equal volume of buffer, and the cumulative percentage of drug diffused across the membrane was calculated at each time point [31].

Stability studies

The optimized emulgel formulation is subjected to stability studies. Where a sufficient quantity of emulgel was sealed in 10g of collapsible tubes in triplicate and subjected to stability studies at 5 °C, 25 °C / 60% RH, 30°C/ 65% RH, and 40°C/ 75%RH for 3 months and the samples were analyzed at predetermined time intervals for pH, Physical appearance and drug content [32].

CONCLUSION:

Emulgel is widely used as an alternative option for topical drug delivery systems due to its improved patient compliance. Further, emulgel possess various advantages like better spreadability, adhesion, viscosity, and extrusion. Moreover, this emulgel can be used as an alternative approach for loading hydrophobic drugs in water-soluble gels. From the above findings, it can be concluded that emulgel can be a potential approach to deliver the drugs effectively through the skin.

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Conflict of Interest

The authors confirm that this article's content has no conflict of interest.

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