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Review Article

EMULGEL EMERGENT SYSTEMS: AT A GLANCE FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Emulgels have been emerged both in cosmetics and pharmaceutical preparations. When gel and emulsion are used in the combined form, they are referred to as Emulgel. Emulgel is a promising drug delivery system for the delivery of hydrophobic drugs. Emulgel is an emulsion that is gelled by mixing it with gelling agents. Many advantages of gels have the major limitation of delivery of hydrophobic drugs. Hence, the emulsion-based approach is being used to overcome this limitation. Emulgel is an interesting topical drug delivery system as it has a dual release control system, i.e., gel and emulsion. The use of gels and emulsions as combined dosage form results in the formation of emulgel showing dual release. With this approach, polymers with enhanced effect in release patterns have emerged, providing sustained and controlled release. They are generally applied for antiseptics, antifungal agents, skin emollients, and protectants. The activity of topical preparation confides in various factors such as drug solubility, lipophilicity, contact time to the skin, and permeability. Emulgels have numerous advantages in dermatology, such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent and pleasing appearance. Emulgel is being used to deliver analgesics, anti-inflammatory, antifungal, anti-acne drugs, and various cosmetic formulations with a wide range to explore.

Keywords: Emulgels, Topical drug delivery.

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INTRODUCTION

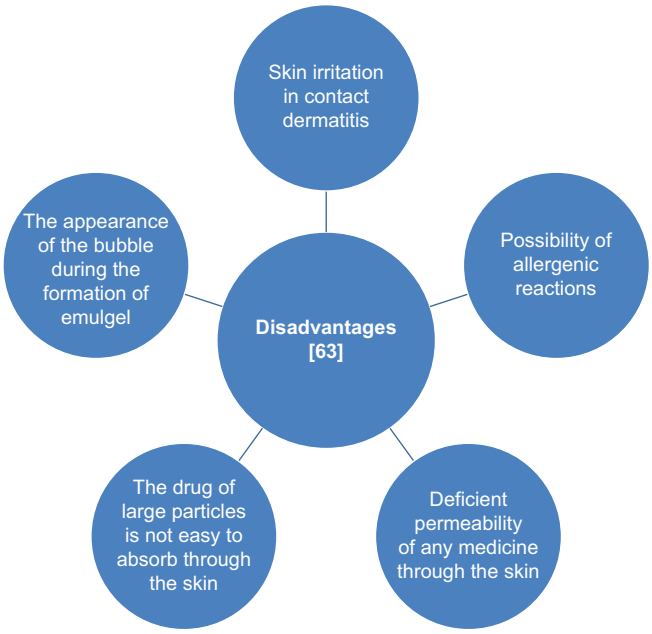
Topical drug delivery systems skin serves as one of the most easily easy to get to routes for drug administration. The topical drug delivery system has been used for centuries to manage local skin disorders and is a generalized drug delivery system wherever in the body through ophthalmic, rectal, vaginal, and skin as a topical route. Topical drug delivery can be distinct from the purpose of a drug-containing formulation to the skin to treat cutaneous disorder directly. The topical drug delivery system is generally used where the other routes (like oral, sublingual, rectal, parenteral) of drug administration fail or in local skin infection like a fungal infection. The topical drug delivery provides direct access to the skin as a target organ for diagnosis and treatment without fear of first-pass metabolism [1].

Drugs are administered to the human body through different routes such as oral, parenteral, rectal, sublingual, etc. [2]. Oral routes are considered versatile routes; however, they still have disadvantages such as poor solubility and bioavailability. In such a scenario, a topical drug delivery system can be considered an option. The topical system bypasses the first-pass metabolism, problems related to intravenous therapy, avoidance of the risks related to absorption, such as gastric emptying time, various enzymes, pH changes. However, the main disadvantage of a topical drug delivery system as a gel is that hydrophobic moiety cannot quickly be delivered through the skin easily [3].

The formulation in which emulsion containing oil and Aqueousphase is entrapped in gel phase called emulgel. Emulgels are emulsions, any oil-in-water or water-in-oil type, gelled by intercourse with a gelling agent. The emulsified gel is a stable and ideal vehicle for hydrophobic or poorly water-soluble drugs. In short, emulgels are a combination of emulsion and gel. Many advantages of gels the main limitation is in the delivery of hydrophobic drugs [4-6]. So to overcome this limitation, an emulsion-based method is used so that even a hydrophobic therapeutic moiety can appreciate the unique properties of gels. In current years, there has been great importance in the usage of novel polymers which can function as emulsifiers and thickeners because the gelling capability of these compounds consents to 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 (Fig. 1).

TYPES OF EMULGELS

- Macro-emulsion gel: The particle size of the globules in these emulgels is more than 400 nm. They are obscure. They can be offset using surface element agents [7,8]
- Nano-emulgel: These are confined by the joining of nanoemulsion into a gel. Nanoemulsions are thermodynamically enduring clear scatterings of oil and water offset by the proximity of surfactants and co-surfactants. These emulgels have a globule size of <100 nm [9-11]



- Micro-emulsion-based emulgel: These emulgels include joined properties of microemulsion and gel [12].

CONSTITUENTS REQUIRED FOR EMULGEL FORMULATION

Fabrication of emulgel for drug delivery through topical route requires a variety of materials suitable and compatible with the skin and consideration of some essential factors such as the amount of drug to be loaded, amount of water to be used, and route of permeation of the drug through the skin. A gel-based nanoemulsion formulation for topical use consists of unique materials other than lipids and surfactants such as gelling agents, penetration enhancers, preservatives, and antioxidants. These penetration enhancers compromise the skin barriers and help the drug enter systemic routes, finally achieving the desired therapeutic concentration.

AQUEOUS PHASE

For the formulation of emulgel, most commonly distilled water or ultra-purified water is used as the aqueous phase, and this phase is responsible for the conversion of emulsion form into the Emulgel in the presence of a gelling agent [14].

OILS AND LIPIDS

In nanoemulsion formulation, the selection of oils and lipids is the most crucial parameter and is responsible for selecting the other components such as surfactants and co-surfactants. Pharmaceutically approved long-chain triglycerides, medium-chain triglycerides, and short-chain triglycerides are mainly used for nanoemulsion formulation [15,16]. As most of the recently approved active pharmaceutical ingredients have solubility and permeability limitations, medium-chain triglycerides are more attractive than long-chain triglycerides for emulsification because of their more solubilizing capacity than long-chain triglycerides [17,18]. Usually, short-chain triglycerides like triacetin, tributyrin, tricaprin, etc., are preferred over long-chain triglycerides considering their better solubility for many drugs such as Paclitaxel [19,20]. When selecting oil and other lipid components, it must ensure that the oil phase is pure and free of objectionable components such as peroxides, free radicals, and various unsaponifiable matters like sterols and polymers [21].

VEGETABLE OILS

Plants are the source of these oils found in fatty acid glycerides. Many plant derivative oils are approved for the topical delivery of drugs such as soybean oil, olive oil, peanut oil, coconut oil, almond oil, and castor oil through various drug delivery systems [22,23]. Like sesame oil and soybean oil, many of these oils are also used to prepare Emulgel [24,25]. These oils are fixed in nature and comparatively less preferred in many nanolipoidal formulations due to the low solubility of drugs. In topical nanoemulsion formulation, in which these vegetable oils are used, it has been observed that these oils enhance the penetration of drug to the skin by lowering the resistance to permeation [26,27]. Among all the above-discussed vegetable oils, soybean oil is preferred either alone or combined with MCTs and short-chain triglycerides to prepare topical nanoemulsion [22]. In many topical nanoemulsion formulation approaches, it has been observed that soybean oil possesses better permeability than other oils such as Tributyrin and Myglyol [22]. Soybean oil contains some unique phospholipids known as lecithin, which function as a surface-active agent and show a higher affinity towards epidermal tissues [26-30]. Recently developed a gel-based nanolipoidal delivery system of Phenytoin, including nano and microemulsion with the help of soybean oil and coconut kernel oil in this work, they successfully demonstrated the fact that emulgel shows much better release as compared to cream-gel and macroemulgel [24]. In a similar work developed a topical nanoemulsion for a hydrophilic drug Insulin by using olive oil leading to a significant enhancement of about 5-15 fold [31, 32].

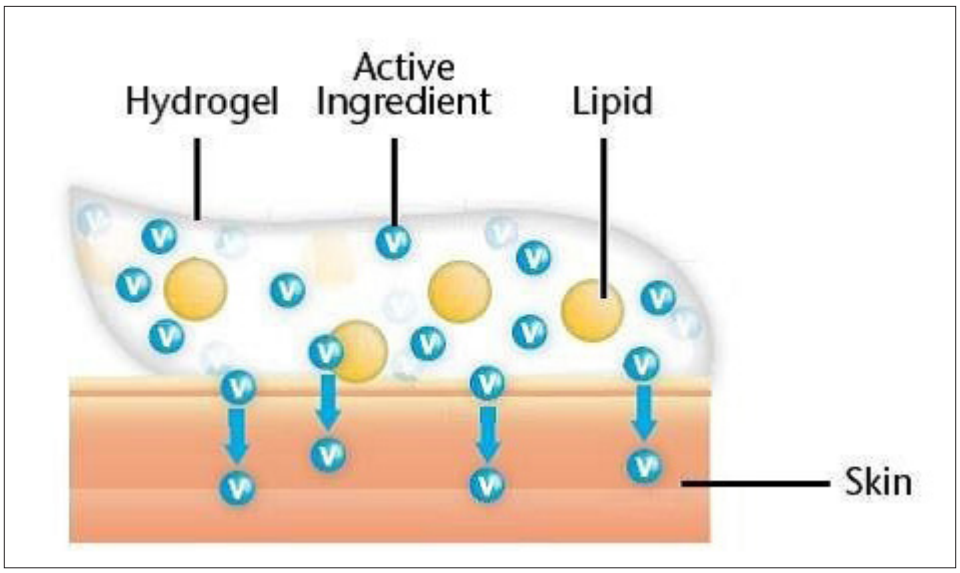


Fig. 1: Structure of Emulgel

Table 1 : List of oils [40]

Serial number	Chemical	Quantity (%)	Dosage form
1	Light liquid paraffin	7–7.5	Emulsion and Emulgel
2	Isopropyl stearate	7–7.5	Emulsion
3	Isopropyl myristate	7–7.5	Emulsion
4	Isopropyl palmitate	7–7.5	Emulsion
5	Propylene glycol	3–5	Gel

Table 2: List of various penetration enhancers used in Emulgel [40]

Serial number	Penetration enhancer	Quantity (%)	Dosage form
1	Clove oil	8	Emulgel
2	Menthol	8	Emulgel
3	Cinnamon	8	Emulgel
4	Oleic acid	1	Gel
5	Lecithin	5	Gel

Table 3: List of gelling agents [40]

Serial number	Chemical	Quantity (%)	Dosage form
1	Carbopol 934	0.5–2	Emulgel
2	Carbopol 940	0.5–2	Emulgel
3	HPMC 2910	2.5	Emulgel
4	HPMC	3.5	Gel
5	Sodium CMC	1	Gel

CMC: Carboxymethyl cellulose, HPMC: Hydroxypropylmethylcellulose

FATTY ACIDS AND ALCOHOLS

Many fatty acids are widely distributed in plant oils. Fatty acids are mainly carboxylic acids and a long aliphatic chain that are either saturated or unsaturated. Fatty alcohols (or long-chain alcohols) are usually of high molecular-weight, straight-chain primary alcohols, ranging from as few as 4-6 carbons to as many as [22-26] carbons from natural fats and oils. For topical drug delivery, US FDA has approved many oils belonging to the category of fatty acids and alcohols such as Oleic acid, Undecylenic acid, Cetyl alcohol, Stearyl alcohol, and Oleyl alcohol, etc. [22]. The fabricated emulgel shows enhanced permeation without using any chemical permeation enhancer [25].

SURFACTANTS AND CO-SURFACTANTS

In the fabrication of emulgel, the role of surfactants is to stabilize the final formulation and help in the solubility of the drug used. The surfactants can be of different chemical nature for the said purpose, such as cationic, anionic, and nonionic. Because of their role in emulsification, these surfactants are known as emulsifiers. Sorbitan fatty acid esters and polyoxyethylene sorbitan fatty acid esters are nonionic surfactants and are preferably used to prepare emulgel. In this category Tween 20, Tween 80, and span 80 are commonly used for the formulation. The selection of emulsifiers in nanoemulsion preparation is a serious issue associated with some toxicity factors. The increased amount of surfactants can lead to irritation of the skin and hence causing uneasiness. Nonionic surfactants are mostly preferred because of their comparatively lower toxicity than ionic surfactants [35]. Co-surfactants are mainly used to decrease the concentration of surfactants and for better thermodynamic stability of the final formulation.

PERMEATION ENHANCERS

The use of permeation or penetration enhancer is better to improve the transport rate through the skin and related layers [38]. Permeation enhancers are one of the main components of the topical drug delivery system and are preferably used in topical nanoemulsion or emulgel [33, 36]. These permeation enhancers mainly function by interacting with skin constituents and induce a temporary and reversible increase in skin permeability. It also provides an added driving force for drug transport into the skin [37].

GELLING AGENTS

The gelling agent is one of the significant components of emulgel, and it gives texture to the formulation. These are cross-linking agents. Carbopole, Poloxamer, Tragacanth, hydroxypropylmethylcellulose, etc. are some of the gelling agents used in emulgel preparation.

PRESERVATIVES

These are the chemical agents used to protect the formulation by the microbial attack and increase shelf life. Phenoxyethanol, Benzalkonium chloride, Benzoic acid, Methylparaben, and Propylparaben are generally used preservatives in the formulation of nanoemulsion [38].

ANTIOXIDANTS

These are the chemical agents used to protect the various components from oxidation. Butylated hydroxyl toluene, Ascorbyl palmitate, and Butylated hydroxyl anisole are the most preferred antioxidants in topical nanolipoidal preparation [39].

EVALUATION OF EMULGEL

Physical examination

The color, homogeneity, consistency, and phase separation are checked here [57].

Spreadability

Spreadability is checked by the "slip" and "drug" character of emulgel. To determine spreadability, the apparatus consisting of a wooden block is provided by a pulley at one end. Ground glass is fixed in the block. 2 g of emulgel is placed on it and covered with another glass slid as a sandwich. One kg of weight is placed on it, and the spreadability is checked [57].

Determination of pH

It is determined by using a digital pH meter. The pH meter is dipped into the emulgel, and the pH is checked; it is repeated 3 times [57].

Rheological study

In a Rheological study, the viscosity is determined at 25°C. The apparatus used is cone and plate viscometer [58].

In vitro drug release study

It is carried out by using the Franz diffusion cell. It helps to determine the drug release [59].

Microbiological assay

For this method, the Ditch plate technique is used. Through this method, the bacteriostatic or fungistatic activity is evaluated.

Accelerated stability studies

ICH guidelines perform it. The stability test is done in a hot air oven at 37±2°C, 45±2°C and 60±2°C for 3 months [60].

Drug content

The drug content is determined by ultraviolet spectroscopic analysis. The equation used is,

$$Drug\,content = (Concentration \times Dilution\ factor \times Volume\,taken) \times Conversion\ factor$$

Globule size and distribution in emulgel

Malvern Zetasizer determines it. The emulgel is dissolved in water, agitated, and inserted into the apparatus to determine the value.

Table 4: Current drug in development of emulgel for various drugs [41-56,64-70]

Drug used	Purpose	Indication
Amphotericin B	Evaluation of the *in vivo* leishmanicidal activity of amphotericin B emulgel: An alternative for the treatment of skin leishmaniasis	Leishmaniasis therapy
Metronidazole and ciprofloxacin	Groundnut oil-based emulsion gels for passive and iontophoretic delivery of therapeutics	Passive and iontophoretic delivery of therapeutics
Amlodipine besylate	Preparation of amlodipine besylate emulgels for transdermal administration and its percutaneous permeability *in vitro*	Transdermal delivery
Acyclovir and ketoconazole	Topical delivery of acyclovir and ketoconazole	Viral and fungal cutaneous manifestations
Lacidipine	Novel non-ionic surfactant proniosomes for transdermal delivery of lacidipine: Optimization using 23 factorial design and *in vivo* evaluation in rabbits	Antihypertensive
Diclofenac sodium	Evaluation of skin penetration of diclofenac from a novel topical nonaqueous solution: A comparative bioavailability study	Pain relief
Diclofenac sodium	Nanoemulsion-based gel formulation of diclofenac diethylamine: design, optimization, rheological behavior and *in vitro* diffusion studies	Management of pain
Pinhao starch	Pinhao starch and coat extract as new natural cosmetic ingredients: Topical formulation stability and sensory analysis	Antioxidant activity
Terpinen-4-ol	The effect of rheological behavior and microstructure of the emulgels on the release and permeation profiles of Terpinen-4-ol	Antimicrobial properties
Betamethasone dipropionate	Development of a topical ointment of betamethasone dipropionate loaded nanostructured lipid carrier	For the treatment of atopic dermatitis
Cyclosporin A	Formulation and evaluation of cyclosporin A emulgel for ocular delivery	Topical ocular delivery
Meloxicam	Formulation and characterisation of meloxicam loaded emulgel for topical application	Anti-inflammatory
Nimorazole	Preparation and evaluation of radiosensitizing agent nimorazole in topical emulgel	Hypoxic cell radiosensitizing agent
Ketoprofen	Formulation development, *in vitro* and *in vivo* evaluation of microemulsion-based gel loaded with ketoprofen	Anti-inflammatory
Calcipotriol	Calcipotriol delivery into the skin as emulgel for effective permeation	In treatment of psoriasis
Terbinafine hydrochloride	Formulation, development and in-vitro evaluation of Terbinafine hydrochloride emulgel for topical	In treatment of fungal infection
Capsicum frutescens L	Formulation, evaluation	Analgesic
Guggulsterone	Formulation, evaluation	Anti-arthritic
Lantana camara	Formulation, evaluation	Wound healing activity
Adapalene	Formulation, evaluation of nanoemulgel	Decrease systemic side effect and make more selective effect of adapalene
Loratadine	Formulation, evaluation	Treatment of localized skin allergy
Itraconazole	Formulation, evaluation	Antifungal
Indomethacin	Formulation, evaluation	Using two types of polymers

Table 5: Marketed products of emulgels [61]

Serial number	Brandname	Active ingredient	Manufacturer	Uses
1	Voltarol 1.16% emulgel	Diclofenac diethylammonium salt	Novartis	Anti-inflammatory
2	Miconaz-H-emulgel	Miconazole nitrate, hydrocortisone	Medical union pharma ceuticals	Topical corticosteroid and antifungal
3	Denacine emulgel	Clindamycin phosphate	Beit jala pharmaceutical company	Anti-acne
4	Diclon emulgel	Diclofenac diethylamine	Medpharma	Anti-inflammatory
5	Cataflam emulgel	Diclofenac potassium	Novartis	Anti-inflammatory

Centrifugation study

This method is used to determine the stability of emulgel. It is done only after one week of preparation. This study was done by using minicentrifuge at 3000 rpm for 30 min.

Swelling index

One gram of emulgel is taken in a porous aluminum foil and placed separately in a 50 ml beaker containing 10 ml of 0.1 N NaOH. Then, the samples are removed at different time intervals and reweighed. The equation determines the swelling index;

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

Where Wt=weight of swollen emulgel after time t, Wo=Original weight of emulgel at zero time.

Skin irritation test

This test is significant because the preparation is a topical formulation. The test is carried out on the animal skin. The emulgel is applied to the animal's skin, and then the animals are returned to their cages. After 24 h the animals are tested. Then the emulgel is removed from the site and wiped with tap water.

Stability studies

The emulgel was packed in collapsible aluminum tubes, stored in extreme conditions, and checked the stability.

APPLICATIONS OF EMULGEL [62]

Treatment of microbial and viral skin infections

Emulgel systems containing antibiotic drugs have been investigated to treat skin infections.

Table 6: Recent advances in formulation of plant based emulgel [71-83]

Serial number	Constituents	Dosage form	Purpose
1	Ethanolic extract of avena sativa	Emulgel	Antipigmentation effect
2	Leaf extract from the plant coccinia grandis	Emulgel	Anti-bacterial activity
3	Seed oil of the plant coriandrum sativum	Emulgel	Anti-inflammatory activity
4	Methanolic extract of the rhizomes of the medicinal plant zingiber officinalis	Emulgel	Antimicrobial activity
5	Methanolic extract of hibiscus rosa-sinensis	Emulgel	Antiinflammatory activity
6	Methanolic extract of the medicinal plant saussaria lappa	Emulgel	Better stability
7	Extracts of selected afghani medicinal plants	Emulgel	Sun protection
8	Oils from thyme, cinnamon and clove	Emulgel	Antioxidant activity
9	Extract from the bark of the medicinal plant terminalia arjuna	Emulgel	Hypertention
10	Medicinal plant solanum lycoperscicum	Emulgel	Enhance stability
11	Extract of the leaves of the medicinal plant cardiospermum helicacabum	Emulgel	Arthritic activity
12	Oils containing gingerol and piperine	Emulgel	Improve the topical drug delivery
13	Leaves of the medicinal plant lantana camera	Emulgel	Pharmacological potential
14	Guggulosterones, liquorice extract and serratiopeptidase	Emulgel	Arthritis

Anti-inflammatory emulgel systems

Emulgel systems have been investigated transdermal delivery of anti-inflammatory drugs.

Emulgel systems of menopausal syndromes

Emulgelcompositions have been tested for their efficiency in treating androgen deficiency associated with menopause in men and menopausal syndromes in women. A testosterone emulgel patch system, Testosome, was designed to treat androgen deficiency in men.

Analgesic and antipyretic emulgel systems

Emulgel systems have been investigated transdermal delivery of analgesic and antipyretic drugs.

CONCLUSION

Emulgel is an alternative approach of hydrophobic drugs to delivery topically with advantages of emulsion and gel to improve patient acceptability. Emulgel helps in enhancing spreadability, adhesion, viscosity, and extrusion. It is used in pharmaceutical and cosmetical applications and allows incorporating herbal formulations.

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AUTHORS CONTRIBUTION

Not applicable.

CONFLICTS OF INTERESTS

Authors have no conflicts of interest.

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