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TECHNIQUES FOR FORMULATION OF EMULGEL DRUG DELIVERY SYSTEM: A REVIEW

Guru Prasad Maurya*, Mahzbee Bano and Pradeep Kumar Srivastva

Institute of Pharmacy Harish Chandra P.G. College Bawan Beegha, Azamgarh Road Varanasi.

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***Corresponding Author**
Guru Prasad Maurya
Institute of Pharmacy Harish Chandra P.G. College Bawan Beegha, Azamgarh Road Varanasi.

ABSTRACT

Background: Emulgels are a types of drug delivery system that is becoming popular for delivering drugs that don't dissolve well in water. It's a mixture of two types of substances called emulsion and gel. **Objective:** The purpose of this review article is to discuss how emulgels are made and tested, and why they are important. In the future, they will likely to be used a widely because they are easy to use and help patients to follow their treatment. **Conclusion:** Emulgels are easy to apply and remove, they are not greasy, they look nice, they keep for a long time, and they are clear. Nowadays, emulgels are used to deliver many different types of drugs like painkillers, anti-inflammatory drugs, acne treatments, and antifungal medications. They are very important in pharmacology and usually don't cause many side effects.

KEYWORDS: Emulgel, emulsion, evaluation, gels, patient compliance, topical drug delivery.

INTRODUCTION

Emulgel is a combination of emulsion and gel, used as a versatile drug delivery system. It combines the benefits of both emulsion and gel formulations. Emulgel offers a dual release mechanism, with controlled release from the emulsion phase and the stability and ease of application of gels. It finds applications in pharmaceutical, cosmetic, and dermatological fields. Gels have advantages but struggle with delivering hydrophobic drugs. To overcome this limitation, an emulsion-based approach is used, allowing even hydrophobic drugs to benefit from the properties of gels. When gels and emulsions are combined, they form emulgel. Novel polymers have gained interest in recent years for emulgel formulations. The

skin serves as a target organ for diagnosis and treatment in dermatological pharmacology. The combination of hydrophilic cells and hydrophobic material in the skin creates a barrier for both types of substances. Transparent gels have gained popularity in cosmetics and pharmaceutical preparations. Polymers can act as emulsifiers and thickeners, creating stable emulsions and creams while increasing viscosity. The presence of a gelling agent in the water phase converts a regular emulsion into an emulgel. Emulgels have advantages over vesicular and conventional systems in various aspects. Permeation enhancers can be used to improve their effectiveness, making them better topical drug delivery systems compared to current methods. Emulgels can be extended for use with analgesics and antifungal drugs. This note provides an overview of the techniques used in formulating emulgel drug delivery systems.

Emulgels are often an emulsion and gel mix. Emulsions, whether they be of the water-in-oil or oil-in-water variety, are gelled by combining them with a gelling agent, and this emulsified gel serves as the best carrier for medications that aren't very water soluble or hydrophobic [Kute et al., 2013].

Despite its many benefits, this gel's main flaw is its inability to administer hydrophobic medications. Therefore, an emulsion-based strategy is being employed to get around this problem so that even a hydrophobic medicinal moiety can be benefited from gels' special qualities. Recently, there has been a lot of interest in the usage of novel polymers that can be utilised as emulsifiers and thickeners. Because these compounds have a higher gelling ability, they can be used to create stable emulsions and creams. It works by lowering surface and interfacial tension while also making the aqueous phase more viscous. The transformation of a traditional emulsion into an emulgel is caused by the presence of a gelling agent in the water phase. These topical emulgels are thixotropic, biocompatible, water-soluble, greaseless, readily spreadable, emollient, easily removable, non-staining, have a longer shelf life, and have a clear and appealing look [Yadav et al., 2017, Ashara et al., 2016].

Emulsion

Emulsions are typically two-phase thermodynamically unstable systems containing two or more immiscible liquids, one of which is distributed in the other liquid as tiny droplets due to dispersion, making the system unstable. The biphasic system is stabilised or an emulsifying agent is utilised. There are o/w and w/o type emulsions that can be employed as medication delivery systems. Emulsifying agents are used to stabilise emulsions. They can simply be

removed from skin and have strong penetrating power [single et al., 2012]. Emulsions are classified into many categories according on the distribution or size of the droplets:

Macroemulsion

The most prevalent sort of emulsions are these macroemulsions. These macro emulsions may be seen under a microscope and have a particle size of roughly 400 nm. We can create a macro emulsion that is thermodynamically stable by utilising surface active agents. The macro emulsion may be O/W or W/O depending on the emulsifier used and the type of emulsification.

Microemulsion

Fundamentally, microemulsions are optically transparent and thermodynamically stable. The diameter of the spherical droplets in this microemulsion ranges from 20 nm to 200 nm.

Gel

The characteristics of the gel fall in between those of liquids and those of solids. These gels have the appearance of a solid, wet material. However, it is frequently misused to refer to any fluid system that demonstrates some stiffness. A gel is made of a polymer that expands when fluid is present and may even do so internally. The volume of fluid that the gel can hold determines how rigid it is. They have the ability to go through significant physical state changes, such as turning from solid to liquid [Sreevidya et al., 2019].

Emulgel

Emulgel is a combination of emulsion and gel, as indicated by its name. Different medications are delivered to the skin via emulsions, including oil-in-water and water-in-oil types. An emulgel is created when a traditional emulsion is present in the water phase. Additionally, they have a strong capacity for skin penetration. Emulgel for dermatological application offers a number of advantageous qualities, including being thixotropic, greaseless, readily spreadable, easily removable, emollient, non-staining, water-soluble, prolonged shelf life, bio-friendly, clear, and appealing look.

In general, molecules enter the skin through the intact stratum corneum, sweat ducts, or sebaceous follicle. More than 99% of the total skin area that is open to percutaneous medication absorption is found on the stratum corneum surface. The rate-limiting stage for percutaneous absorption is passage through this outermost layer. The main processes in

percutaneous absorption involve creating a concentration gradient, which acts as a propellant for drug release from the vehicle (partition coefficient), drug release from the skin (diffusion coefficient), and drug diffusion across the skin's layers [Kute et al., 2013].

Types of emulgels

1. Based on the Type of API
2. Based on the type of emulsion

Based on the Type of API

1. Natural/poly-herbal combination:

Example: i. Cosmetic Emulgel for skin care from field pumpkin.

2. Anti-psoriatic Emulgel from babchi oil and Gum Guggle.

Allopathic:

Example: Diclofenac diethyl Ammonium Emulgel (VOLTAREN) by Novartis pharma.

Based on the type of emulsion

1. Macroemulgel: Size of dispersed phase droplets more than 400 nm and prepared by High Energy and Low Energy Method.

Microemulgel: Droplet Size between 1 nm to 100 nm. Prepared by Phase Inversion And Phase

2. Titration Method.

Nanoemulgel: Droplet size is less than 1 nm.

Advantages

1. It prevents the first pass metabolism, for one.
2. It is possible to prevent gastrointestinal compatibility.
3. The more site specificity.

It is possible to increase patient compliance.

5. Self-treatment.
6. Making use of drugs with a limited therapeutic window and short biological half-life.
7. The capability to quickly stop taking medication when necessary.
8. It is practical and easily applied.
9. Drugs that are hydrophobic can be included.
10. Greater loading capacity

11. More stability compared to other T.D.D.S.
12. Low cost of preparation
13. It's possible to produce controlled release
14. There is no extensive sonication

Disadvantages

1. Dermatitis produces skin inflammation upon contact allergenic responses.
3. Some medications have limited skin absorption.
4. Large-particle drugs are difficult to absorb via the skin.
5. Sometimes emulgel creation will bubble.

Factors affecting topical absorption of drug

Physiological factors

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

Physicochemical factors

1. Partition coefficient.
2. The molecular weight (<400 Daltons)
3. The degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles.

Selection of Emulsifying Agents

The stability and effectiveness of emulgel formulations depend on the use of the right emulsifying agents. Non-ionic surfactants like Tweens and Spans, anionic surfactants like sodium lauryl sulphate, and cationic surfactants like cetyltrimethylammonium bromide are examples of common emulsifiers. The type of emulsifier chosen will depend on a number of variables, including the drug's composition, pH, compatibility, and intended release profile.

Materials used in emul gel preparation

Aqueous material: The emulsion's aqueous phase is formed by this. Alcohols and water are frequently used substances [Ashara et al., 2016].

Oils: These substances create the oily phase. Mineral oils are frequently mixed or used alone with hard or soft paraffins in emulsions intended for external application. Castor oils, non-biodegradable minerals that have a local laxative action, and different fixed vegetable oils (such as arachis, cottonseed, and maize oils) or fish liver oils as dietary supplements are used in oral formulations [Yadav et al., 2017].

Emulsifier: Emulsifying chemicals are used to manage stability during shelf life as well as to encourage emulsification during production. For instance, Sodium stearate, Polyoxyethylene sorbitan monooleate (Tween 80), Sorbitan mono-oleate (Span 80), Polyethylene glycol 40 stearate, Stearic Acid [Kute et al., 2013].

Preservatives: Benzalkonium chloride, Benzyl alcohol, Propyl paraben, Benzalkonium chloride, Methyl paraben, etc.

Antioxidants: Ascorbyl palmitate, Butylated hydroxyanisole (BHA), Butylated Hydroxytoluene (BHT), etc.

Humectant: E.g. Glycerin, Propylene gylcol, etc.

Gelling agents: These are employed as consistency enhancers and thickening agents in all dosage forms. For instance, sodium CMC, carbapol 934, carbapol 940, HPMC, HPMC-2910.

Permeation enhancers: These are substances that enter the skin and interact with its components to cause a brief and reversible increase in skin permeability. Permeation enhancers ought to be non-toxic, non-irritating, and non-allergenic. These Permeation enhancers should not interact pharmacologically with the body's tissues or bind to receptor sites. They ought to have proper skin "feel" and be aesthetically pleasing. All medications and excipients should be compatible with permeation enhancers [Vasiljevic et al., 2006, Zainab et al., 2018, Sajid et al., 2012, Bhatt et al., 2013, Joshi et al., 2011, Rachit et al., 2011, Jain et al., 2010, Khullar et al., 2012].

Mechanism of penetration enhancer

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.

Emulsion Preparation

There are several ways to make emulsions, including the phase inversion temperature method, the hot homogenization method, and the cold homogenization approach. The oil and aqueous phases are heated separately and then blended using high shear homogenizers in the hot homogenization process. High-speed homogenizers operated at room temperature are used in the cold homogenization process. The phase inversion temperature approach depends on variations in the hydrophilic-lipophilic balance of the emulsifying ingredient brought on by temperature [Mohamed et al., 2004].

Gel Preparation

Gel formation is accomplished by introducing gelling chemicals into the emulsion, such as carbopol, hydroxyethyl cellulose, or methylcellulose. The production of a stable gel network is made possible by these gelling chemicals, which also contribute viscosity. When preparing a gel, the gelling agent is dissolved in the emulsion while being continuously stirred, and then, if necessary, the pH is neutralised to obtain the ideal gel formation. [Mohamed et al., 2004].

Optimization of Formulation

To obtain the desired qualities, such as rheology, stability, drug release kinetics, and skin compatibility, emulgel formulation must be optimised. The concentration of gelling agents, emulsifying agents, and medication loading are factors to take into account during optimisation. To evaluate the consistency and spreadability of the emulgel, rheological investigations, such as viscosity measurements, are used. Long-term stability is assessed using stability experiments comprising temperature cycling, centrifugation, and freeze-thaw cycles [Single et al., 2012].

Enhancement of Drug Penetration

Techniques including the use of penetration enhancers and cutting-edge drug delivery technologies like liposomes, nanoparticles, and microemulsions can be added into emulgel

formulations to improve drug penetration into the skin. These methods can increase the drug's ability to penetrate deeper layers of skin, increasing its therapeutic effectiveness [Ahmad et al., 2016].

Method of preparation of emulgel [Ahmad et al., 2016]

Step-1: Oil/water or water/oil emulsion.

Step 2: Formation of gel base.

Step 3: Incorporation of emulsion in gel base.

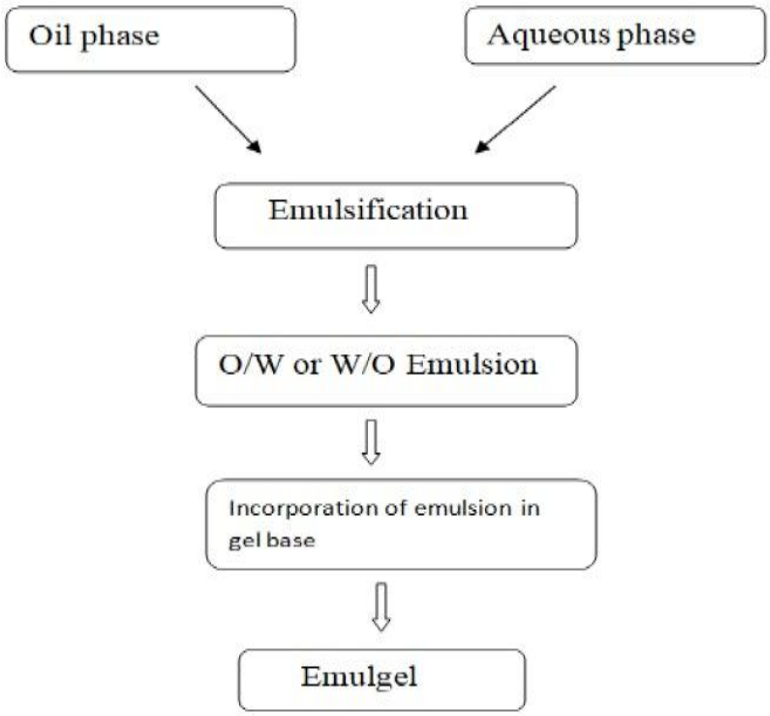
Preparation of gel phase: The gel phase is created by dispersing the polymer in purified water while stirring continuously at a moderate speed using a mechanical shaker. The pH was then adjusted to 6-6.5 using triethanolamine (TEA).

Preparation of oil phase of emulsion

Emulsifiers, such as span 20, are dissolved in the oil phase of the emulsion, which is made of light liquid paraffin.

Preparation of aqueous phase

When making the aqueous phase, emulsifiers like tween 20 are dissolved in clean water. Making a medication solution In ethanol, the medication is dissolved.



Evaluation of Emulgel Formulations [Chavda et al., 2013]**:**

Emulgel compositions are put through a number of evaluation processes to guarantee their effectiveness and quality. These include measures of viscosity, pH analyses, in vitro drug release investigations, and tests for skin irritancy. To avoid any interactions between the formulation and the components of the packaging, the emulgel's compatibility with the packaging materials should also be assessed.

Evaluation of emulgel

- **Physical examination:** The formulated emulgel's homogeneity, colour, consistency, and phase separation were all visually assessed (**Figure 1**).
- **Determination of pH:** The pH of the formulation is determined using a digital pH metre. After being cleaned with distilled water, the pH metre electrode was dipped into the formulation to measure pH. This procedure was repeated three times, and the results were recorded.
- **Rheological studies:** The viscosity of the formulation is determined using cone and plate viscometers. At 25°C, the viscosity of the various emulgel formulations is measured using spindle 52 attached to a thermostatically controlled water bath.
- **Stability studies:** The emulgels are made, packed in aluminium collapsible tubes (5 g), and then submitted to stability investigations over a three-month period at 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH. At intervals of 15 days, samples were taken out and examined for their physical characteristics, pH, rheological characteristics, drug content, and drug release profiles.
- **Fourier transforms infrared spectroscopy (FTIR):** Finding stable storage conditions for the medication in its solid state and appropriate excipients for formulation were the main goals of this work.

The produced Emulgel in vitro drug release tests were conducted using diffusion cells with egg membrane.

• **Swelling index:** A 50 ml beaker containing 10 ml of 0.1 N NaoH and 1 g of produced topical emulgel are used separately to calculate the swelling index of the gel. After then, samples were taken out of the beakers at various intervals and placed on a dry surface for a while before being weighed again.

This is how the swelling index is determined:

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

Where,

(SW) %=Equilibrium percent swelling.

Wt=Weight of swollen emulgel after time t.

Wo=Original weight of emulgel at zero time.

Spread ability: The apparatus suggested by Mutimer et al. (1956) that is adapted appropriately in the lab and used for the study is used to measure spread ability. It is made up of a wooden block that has a pulley at one end. The 'Slip' and 'Drag' properties of emulgels are used in this method to gauge spreadability. On this block is fastened a ground glass slide. On this ground slide, extra emulgel (approximately 2 gm) is being studied. The emulgel is then placed in a sandwich between this glass slide and another glass slide with a hook and a fixed ground slide dimension. To remove air from the slides and create a consistent coating of emulgel, a 1 kg weight is placed on top of the two slides for five minutes. The edges are scraped clean of excess emulgel.

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

Where, S = Spread ability. M=Weight tied to upper slide. L=Length of glass slides. T=Time taken to separate the slides completely from each other.

• **Skin irritation test:** The test article was then introduced into each site (two sites per rabbit) under a double layer of gauze to a skin region that was approximately 1" 1" (2.54 2.54 cm2 for stability studies). A rabbit's skin was treated with the Gellified Emulsion. The creatures were put back in their cages. The Gellified emulsion is removed after a 24-hour exposure. To eliminate any leftover test item residue, tap water was used to clean the test sites.

• **Drug content determination:** Consume 1 g of emulgel. Add a suitable solvent and combine. To get a clear solution, filter it. Utilise a UV spectrophotometer to ascertain its absorbance. The same solvent is used to prepare the standard drug plot. By including the value of absorbance in the standard plot, concentration and drug content may be calculated (**Table 1**).

Table 1: Examples of Marketed Preparations.

RODUCT NAME	DRUG	MANUFACTURER
Voltaren Emulgel	Diclofinac diethyl ammonium	Novartis Pharma
Dosanac Emulsion gel	Diclofenac	Siam Pharmaceuticls
Miconaz-H Emulgel	Micronazole nitrate, Hydrocortisone	Medical-Union Pharmaceutical

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

CONCLUSION

Emulgel formulations present a promising strategy for the targeted and controlled distribution of medication. The aforementioned formulation methods serve as a foundation for creating stable and efficient emulgel drug delivery systems. The use of emulgels in the pharmaceutical, cosmetic, and dermatological industries will be advanced by more study, formulation optimisation, and the incorporation of cutting-edge technology. Better patient compliance is a benefit of topical medication delivery systems. And emulgels are thought to be one of the greatest methods for topical administration, and many hydrophobic medications are made into emulgels for better outcomes. The impact is potentiated with a variety of penetration enhancers. Emulgels will be a well-liked drug delivery method because they have an advantage in terms of spreadability, adhesion, viscosity, and extrusion. Emulgels are thought to be the best traditional systems now on the market.

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