

Recent Advancement in Emulgel: An Updated Review

Riya Netam^{1*} Mrs. Anju Mishra²

Department of pharmaceuticals, School of Pharmacy, Chouksey Engineering College, Lalkhadan, Masturi Road, Bilaspur (C.G.)¹

Department of pharmaceuticals, School of Pharmacy, Chouksey Engineering College, Lalkhadan, Masturi Road, Bilaspur (C.G.)²

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ABSTRACT

This study to aim the increasing the drug permeation rate used the permeation enhancers, emulgel have been reported as a possible approach to improve low skin permeation method. Emulgel is prepared by continental method. Formulated gel was evaluated in terms of various physiochemical parameters, pH, viscosity and spreadibility. The obtained findings state that formulated emulgel is the suitable choice for the treatment of inflammation and such other indications.

Keyword: Emulgel, Gelling agents, Topical drug delivery, skin diseases.

I. INTRODUCTION

To drug delivery system can be defined as a direct effect of drug containing medication to the skin to get the effect of drug or to cure disorders. Major disadvantage of gel is the delivery of hydrophobic drug. This can be overcome by emulgels. Topical therapy has been used for centuries for the treatment of dermatological disorder. The spectrum of drug/agent applied directly to the skin ranges from antiinflammation, antiseptic, antibacterial, antifungal, antiviral, anti-acne, antipigmentary, anesthetic component to the skin emollient and protectants. Topical route has the main advantages of direct delivery of drug to the target tissues i.e skin and mucous membrane, bypassing the first-pass effect. However, skin permeation of a drug moiety from, diffusion through adhesive layer if it is present between the skin and drug loaded matrix, sorption or adhesion through stratum corneum, entry into the layer of the dermis stratum corneum is barrier which prevents drug penetration Topical formulation can vary in consistency from solid, semisolid to liquid depending on their physiochemical properties. Besides the active substance(drug), each formulation has many nonmedicinal ingredients (excipients) with diverse pharmacological functions

can be combined to enhance the drug delivery. When a classical gel formulation is combined with an emulsion it is called Emulgel.

EMULGEL

Emulgel is emerging field for the topical drug delivery and till date it has less marketed product, so it is interesting and challenging to focus on emulgel. Before going to emulgel we need to know the advantages of emulsion and get that is being used for the topical drug delivery. Emulsions are controlled release systems containing two immiscible phase in which one is dispersed (internal or discontinuous phase) into other (external or discontinuous phase), with the use of emulsifying agent to stabilize the system. Emulsion are of oil-in-water or water-in-oil type, where the drug particle entrapped in internal phase passes through the external phase and then slowly gets absorbed into the skin to provide controlled effect. USP defines gel as a semisolid system consisting of dispersions made up of either small inorganic particles or large organic molecules enclosing and interpenetrated by liquid. The gel contains the large amount of aqueous or hydro alcoholic liquid in a cross linked network of colloidal solid particles where it captures small drug particles and maintain the controlled release of drug. The liquid phase builds a three-dimensional polymeric matrix which results a physical or chemical cross linking. The continuous structure results solid like behavior that are homogenous structure results solid like behavior that are homogenous and clear. The emulsion and gel both are responsible for the controlled drug release from the systems[12-14]. The gels are of two types first the organic solvent based, hydrophobic or hydrogels. First one consist base liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, aluminium or zinc soaps and the second one with the base of water, glycerol, or propylene glycol[15,16]. Gels having various advantages has still limitation in the delivery of

hydrophobic drugs so to overcome this limitation and enjoy the delivery in the form of gel for the hydrophobic drug, the concept for emulgel was introduced where the hydrophobic drugs are incorporated in emulsion and then to gel. Emulgel is the approach using the benefits of both emulsion and gels, gaining the dual controlled release effect where the emulsion either oil in water or water in oil is gelled by incorporation in the gel base[18], simply the Emulgels are emulsion in gel. In emulsion the drug particles are incorporated in the internal phases through the external phase and to the skin and get adsorbed. Emulgel are seen better choice for the class 2 of drug as per the BCS classification systems that show poor solubility as thixotropic, grease less, easily spreadable, easily removable, emollient, nonstaining, water soluble, long shelf, bio friendly and pleasing appearance that improves the patients acceptability [4]. Emulgel are being used for treatment of various anti-inflammatory activity and other skin related viral, bacterial and fungal infection

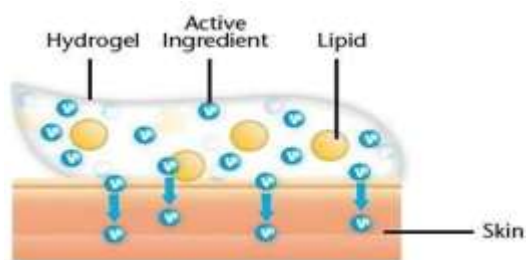


Fig.01: Emulgel

Advantages

1. Avoidance of first pass metabolism.
2. Avoidance of gastrointestinal incompatibility.
3. More selective to a specific site.
4. Improve patient compliance.
5. Suitable 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 Stability.
11. Production feasibility and low preparation cost.
12. Controlled release.

Disadvantages

1. Skin irritation on contact dermatitis.
2. The possibilities 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
5. The occurrence of the bubble during formulation of emulgel.

Rationale of emulgel as a topical drug delivery system

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 of semisolid preparation, the use of transparent gels has expanded both in cosmetics and in a pharmaceutical preparation.

A gel is a colloidal that is typically 99% wt. liquid, which is immobilization by surface tension between it and a macromolecular network of fibres built from a small amount of a gelatin substance present. 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 delivery through gel.

Numbers of medicated products are applied to the skin or mucous membrane that either enhance or restores a fundamental function of skin or pharmacologically alters an action in the underlined tissues. Such products are referred as topical or dermatologically products. Many widely used topical agents like ointments, cream lotions have many disadvantages. They are sticky in nature causing uneasiness to the patient when applied, have lesser spreading coefficients so applied by rubbing and they also exhibit the problem of stability. Due to all these factors within the major group of semisolid preparations, that use of transparent gels has expended both in cosmetics and in pharmaceutical preparation. In spite of many advantages of gel, a major limitation is in the delivery of hydrophobic drugs.

Factors affecting topical absorption of drugs

Physiological factors

1. Skin thickness.
2. Liquid content.
3. The density of hair follicles.
4. The density of sweat glands.
5. Blood flow.

6. Hydration of skin
7. Inflammation of skin

Physiochemical factors

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

Physiology of skin

Most of the topical preparations are meant to be applied to the skin. So a basic knowledge of the skin and its physiology function are very important for designing topical dosage form. The skin of an average adult body covers a surface area approximately 2m² and receives about one- third of the blood circulating through the body. An average human skin surface is known to contain, on the average 40-70 hair follicles and 200-300 sweat ducts on every square centimetre of the skin. The pH of the skin surface. The skin can be considered to have four distinct layers of tissue.

Viable epidermis

This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranges from 50-100 um. The structures of the cells in the viable epidermis are physiochemical similar to other living tissues. Cells are held together by tonofibrils. The density of this region is not much different than water. The water content is about 90%

Dermis

very few cells are like it can be found histological in normal tissue. Dermis thickness ranges from 2000 to 3000 um and consists of a matrix of loose connective tissue composed Just beneath the viable epidermis is the dermis. It is a structural fibrin and of fibrous protein embedded in an amorphouse ground

Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue which is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretary pores of the sweat gland and cutaneous nerves. Most investigators consider drug is permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

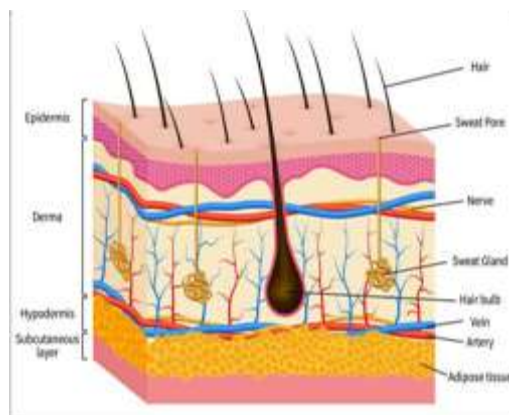


Fig.02: Image of skin

Emulgel preparation

Aqueous material

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols.

Oils

These agents form the oily phase if the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffin, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. Widely used oil in oral preparations are non biodegradable are non-biodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils or various fixed oils of vegetable origin (e.g, Arachis, cottonseed, and maize oils) as nutritional supplements

Use of oils

Chemical	Quantity	Dosage form
Light liquid paraffin	7.5%	Emulsion and Emulgel
Isopropylmyristate	7-7.5%	Emulsion
Isopropyl palmitate	7-7.5%	Emulsion
Isopropyl stearate	7-7.5%	Emulsion
Propylene glycol	3-5%	Gel

Emulsifiers

Emulsifying agents are use both to promote emulsification at the time of manufacturing and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsion to month or year for commercial preparations. E.g. polyethylene glycol 40 stearate [20], sorbitan monooleate (tween 80) [21], polyoxyethylene

sorbitan monooleate (tween 80) [22], Stearic acid [23], Sodium stearate[24].

Gelling agent

These are the agents used to increase the consistency of any dosage form can also use as thickening agent [25, 26]

Permeation enhancers

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

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

Use of penetration enhancers

Penetration 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

Formulation of emulgel

For the preparation of emulgel some constituents are used including drug, which are:

Vehicle

Vehicle should follow the idea characters given in the pharmacopeias

Aqueous material

The aqueous phase used water, alcohol, etc

Oil

Oils are used for preparation of emulsion. Mineral oils and paraffin are used either alone or in combination [16]

Emulsifiers

Emulsifiers used for preparation of emulsion. Some example is span 80, tween80, Stearic Acid, sodium stearate.

Gelling agents

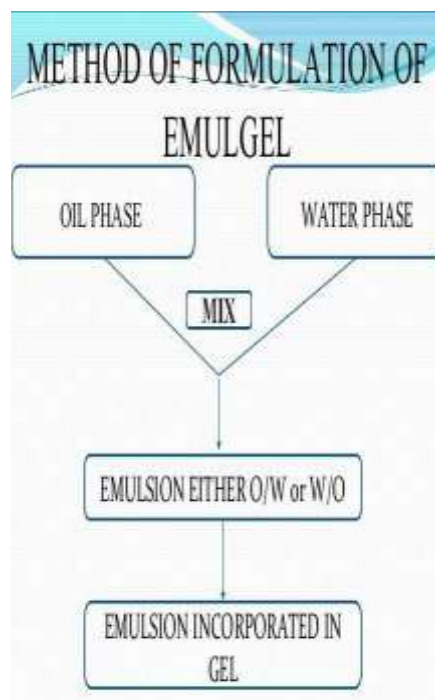
Gelling agents are used for prepare gels, which enhance consistency of preparation.

Penetration enhancers

Penetration enhancers help to absorb drug to the skin [17]

Preparation of emulgel

Emulgel are prepared by incorporating gel and emulsion the emulsion and gel are prepared separately and mixing together. For prepare emulsion, aqueous phase and oil phase are taken separately and mixed together. Then the gel is prepare by using gelling agent. After preparing gel and emulsion, they are mixed with gents stirring. The chemical are used as oil phase are castor oil, clove oil ,liquid paraffin, etc. water and alcohol are used as aqueous phase. The aqueous phase is prepared by mixing tween 80 and water and also the oil phase prepare by mixing tween 80 and water and also the oil phase prepared by mixing paraben and propylene glycol. The drug is dissolved in ethanol and the two phase are mixing with continuous stirring. Then the polymers are dissolved and gel separately, they are mixed together to get emulgel.



Flow chart of Emulgel formation

Challenges in formulated Emulgel

Temperature:

Processing at the right temperature is crucial for successful manufacturing. Too much heating during processing can result in chemical degradation. Insufficient heat can lead to batch failures and excess cooling can result in the precipitation of solubilised ingredients. An example of the need for good temperature control is the emulsification step of a traditional oil-in-water emulsion. If the temperature of the oil phase, the melted constituents of the oil phase and never properly from the emulsion, possibly even result in solid matter in the batch.

Rates of heating and cooling:

Heating too slowly can result in poor yield from evaporative loss. Heating too rapidly may burn areas of the batch in contact with the heating surface, which raises the potential for burnt material in the batch. Rapid cooling can result in potential for burnt material in the batch. Rapid cooling can result in precipitation/ crystallization of ointment, for example, depends on proper Rates of heating and cooling.

Mixing method and speeds:

It is essential to determine the required amount of shear and the optimal mixing method and speeds. Emulsification typically requires high shear or homogenization to obtain the optimal droplet size and dispersion, while the mixing of a gel may require low shear to polymer into the medium. If the process involves only very low shear mixing, a polymer may never be completely dispersed and hydrated, which may result in an out-of-specification viscosity.

Mixing times:

Optimizing flow rate involved determining the amount of shear or throughput needed. For example, a water-in-oil emulsion may required a slower addition speed than a traditional, oil-in water emulsion, and the flow rate must be modified appropriately. Care must be taken for any product using a pump. Over shearing can occur if the formulation will experience extra time in an in-line homogenizer, thus also exposing the formulation to additional shear.

Two processes that required experimentation to optimize flow rates are the use of a power education system and an in-line homogenizer. Theoretical calculation can determine the number of times a sample will pass through either, but actually performing the experiments is necessary to achieve optimal results.

Evaluation Techniques

Physical examination:

The colour, homogeneity, Consistency and phase separation are checked

Spread ability:

Spread ability is checked by “Slip” and “drug” character of emulgel. To determine spread ability, the apparatus consisting a wooden block is provided by a pulley at one end. In the block a ground glass is fixed. 2 g of emulgel is placed on it, and is covered with another glass slid as a sandwich. One kg of weight is placed on it and the spread ability is checked.

Determination of pH:

It is determined by using digital pH meter. The pH meter is dipped into the emulgel and the pH is checked; it is repeated for 3 times.

Rheological study:

In Rheological study the viscosity is determined at 25 .C the apparatus used is cone is cone and plate viscometer (22).

In vitro drug release study:

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

Microbiological assay:

For this method ditch plate technique is used. Through this method the bacteriostatic or fungistsic activity is evaluate.

Accelerated stability studies:

It is performed by ICH guideline. The stability test is done in hot air over at 37±2 °C, 45± 2°C and 60± 2°C for 3 month.

Drug content:

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

$$\text{Drug content} = (\text{concentration} \times \text{Dilution factor} \times \text{Volume taken}) \times \text{Conversion factor}$$

Globule size and distribution in Emulgel:

It is determined by Malvern Zetasizer. The Emulgel. It is done only after one week of preparation. This study was done by using minicentrifuge at 300 rpm for 30 minutes.

Swelling index:

One gram of Emulgel is taken in a porous aluminium foil and place separately in a 50 ml beaker containing 10 ml of 0.1 N NaoH. Then, the sample are removed at different time intervals, and reweighed. Swelling index is determined by the equation.

Stability studies:

The Emulgel were packed in aluminium collapsible tubes, stored in extreme conditions, and the Stability is checked.

II. CONCLUSION

The topical drug delivery system will be used extensively due to better patient's compliance. Since Emulgel possesses an edge in terms of spreadibility, adhesion, viscosity and extrusion, they will become a solution for loading hydrophobic drugs in a water solution gel bases.

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