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Review Article

EMULGELS: A NOVEL FORMULATION APPROACH FOR TOPICAL DELIVERY OF HYDROPHOBIC DRUGS

Bhatt Preeti*, Gnanaranjan.G

Division of pharmaceutical sciences, S.G.R.R.I.T.S, Patel Nagar, Dehradun-248001, Uttarakhand, India

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*E-mail: preetibhatt03@gmail.com

ABSTRACT

A unique feature of topical drug delivery is the direct accessibility of the skin as a target organ for diagnosis and treatment. Among the various groups of semisolid preparations, the use of gels has expanded both in cosmetics and in pharmaceutical preparations. Despite of several advantages of gels there is a limitation in delivery of hydrophobic drug moiety. This limitation can be overcome by the use of novel topical drug delivery i.e, emulgel. When gel and emulsion are used in combined form the dosage form are referred as emulgel. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. The major objective behind this formulation is delivery of hydrophobic drugs to systemic circulation via skin. Emulgels show dual release control system i.e. gel and emulsion. These emulgel are having major advantages on novel vesicular systems as well as on conventional systems in various aspects. Emulgels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. Various permeation enhancers can potentiate the effect, So emulgels can be used as better topical drug delivery systems over present systems. The use of emulgels can be extended in analgesics, antifungal drugs and various cosmetic formulations.

Keyword: Emulgels, Hydrophobic drugs, Topical drug delivery.

INTRODUCTION

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorder[1,2]. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. These apply a wide spectrum of preparations for both cosmetic and dermatological, to their healthy or diseased skin[3]. Topical drug delivery is an attractive route for local and systemic treatment[4]. Topical preparations pertain to medicaments applied to the surface of a part of the body and is a term used to describe formulations that have effects only in a specific area of the body and are formulated in such a manner that the systemic absorption of the medicament is minimal[5]. Topical drug delivery offers several advantages over conventional routes[6,7]. It avoids the first-pass metabolism and the gastrointestinal tract. Topical delivery has the potential for sustained and controlled drug release. Moreover, it is a non-invasive mode of drug delivery with no trauma or risk of infection[8]. The most common examples of Topical dosage forms include solutions, suspensions, emulsions (e.g., lotions), semisolids (e.g., foams, ointments, pastes, creams, and gels), solids (e.g., powders and aerosols), and sprays[9].

Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles. In spite of many advantages offered by gels a major limitation is in the delivery of hydrophobic drugs. So this drawback can be overcome by using an emulsion based approach where gels & emulsions are combined to form EMULGEL[10]. Both oil-in water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin**.** In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows 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. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel[11]. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent & pleasing appearance[3].

FORMULATION CONSIDERATIONS[12]

The challenges in formulating topical emulgels are:

1. Determining systems that are non-toxic, non-irritating, non-comedogenic and non-sensitizing.
2. Formulating cosmetically elegant emulgel.
3.The emulgel formulation must have low allergic potential, good physiological compatibility and high biocompatibility.

ADVANTAGES OF EMULGELS AS A TOPICAL DRUG DELIVERY[13,14,11]

1. In comparison to the other topical preparations emulgels are more stable.
2. Hydrophobic drugs can be easily incorporated into gels using the o/w emulsions.
3. Emulgels exibit Production feasibility and low preparation cost.
4.Emulgels exibit Better loading capacity in comparison to other novel approaches like niosomes and liposomes which are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.

RATIONALE

Various types of topical formulations are available or used to apply on to the skin or mucous membrane restores a fundamental function of skin or pharmacologically alters an action in the underlined tissues. On the same time the topical agents such as ointment, cream, lotion have many disadvantages also. They are sticky causing uneasiness to the patient & also have lesser spreading coefficient and need to apply with rubbing. They exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Despite of offering several benefits Gels a

colloid system shows a major limitation 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 delivered through gels.

SITE OF DRUG DELIVERY

Skin

The skin is one of the most important parts of the body because it interfaces with the environment and is the first line of defence from external factors. For example, the skin plays a key role in protecting the body against pathogens[15] and excessive water loss[16]. Its other functions are insulation, temperature regulation, sensation, and the production of vitamin D folates.

Skin performs the following functions[15-18]:

Protection: an anatomical barrier from pathogens and damage between the internal and external environment in bodily defence; Langerhans cells in the skin are part of the adaptive immune system[15,16].

Sensation: contains a variety of nerve endings that jump to heat and cold, touch, pressure, vibration, and tissue injury (see somato-sensory system and haptic perception).

Thermoregulation: eccrine (sweat) glands and dilated blood vessels (increased superficial perfusion) aid heat loss, while constricted vessels greatly reduce cutaneous blood flow and conserve heat.

Control of evaporation: the skin provides a relatively dry and semi-impermeable barrier to fluid loss[16].

Storage and synthesis: acts as a storage centre for lipids and water.

Absorption: oxygen, nitrogen and carbon dioxide can diffuse into the epidermis in small amounts; some animals use their skin as their sole respiration organ (in humans, the cells comprising the outermost 0.25–0.40 mm of the skin are "almost exclusively supplied by external oxygen", although the "contribution to total respiration is negligible")[17].

Water resistance: The skin acts as a water resistant barrier so essential nutrients aren't washed out of the body. The nutrients and oils that help hydrate our skin are covered by our most outer skin layer, the epidermis. This is helped in part by the sebaceous glands that release sebum, an oily liquid. Water itself will not cause the elimination of oils on the skin, because the oils residing in our dermis flow and would be affected by water without the epidermis[18].

SKIN ANATOMY

Epidermis

The epidermis is composed of the outermost layers of the skin. It forms a protective barrier over the body's surface, responsible for keeping water in the body and preventing pathogens from entering, and is a stratified squamous epithelium[19], composed of proliferating basal and differentiated suprabasal keratinocytes.

Keratinocytes are the major cells, constituting 95% of the epidermis[19], while Merkel cells, melanocytes and Langerhans cells are also present. The epidermis can be further subdivided into the following strata or layers (beginning with the outermost layer)20.

- Stratum corneum
- Stratum lucidum (only in palms and soles)
- Stratum granulosum
- Stratum spinosum
- Stratum germinativum (also called the stratum basale)

The epidermis contains no blood vessels, and cells in the deepest layers are nourished by diffusion from blood capillaries extending to the upper layers of the dermis.

Dermoepidermal junction/basement membrane

This is a complex structure composed of two layers. The structure is highly irregular, with dermal papillae from the papillary dermis projecting perpendicular to the skin surface. It is via diffusion at this junction that the epidermis obtains nutrients and disposes of waste. The dermoepidermal junction flattens during ageing which accounts in part for some of the visual signs of ageing[21].

Dermis

The dermis is the layer of skin beneath the epidermis that consists of connective tissue and cushions the body from stress and strain. The dermis provides tensile strength and elasticity to the skin through an extracellular matrix composed of collagen fibrils, microfibrils, and elastic fibers, embedded in proteoglycans[22]. The dermis is tightly connected to the epidermis through a basement membrane and is structurally divided into two areas: a superficial area adjacent to the epidermis, called the papillary region, and a deep thicker area known as the reticular region.

Hypodermis

The hypodermis is not part of the skin, and lies below the dermis. Its purpose is to attach the skin to underlying bone and muscle as well as supplying it with blood vessels and nerves. It consists of loose connective tissue and elastin.

The main cell types are fibroblasts, macrophages and adipocytes (the hypodermis contains 50% of body fat). Fat serves as padding and insulation for the body. Another name for the hypodermis is the subcutaneous tissue.

FACTORS TO BE CONSIDERED WHEN CHOOSING A TOPICAL PREPARATION[23-24]

1. Effect of the vehicle e.g. an occlusive vehicle enhances penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient or protective action.
2. Match the type of preparation with the type of lesions. For example, avoid greasy ointments for acute weepy dermatitis.
3. Match the type of preparation with the site. (e.g., gel or lotion for hairy areas)
4. Irritation or sensitization potential. Generally, ointments and w/o creams are less irritating, while gels are irritating. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.

ADDITIVES / EXEPIENTS USED IN EMULGEL FORMULATION

Ideal Properties of Additives

1. They must be non toxic.
2. They must be commercially available in acceptable grade.
3. Their cost must be acceptably cheap.
4. They must not be contraindicated.
5. They must be physically and chemically stable by themselves and in combination with drugs and other components.
6. They must be colour compatible.

1. Aqueous Material & oils

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols. Oils form the oily phase if the emulsion. Widely used oils in oral preparations are non-biodegradable mineral and castor oils which provides 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[25].

2. Emulsifiers:

Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations e.g. Polyethylene glycol 40 stearate, Sorbitan mono-oleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid and Sodium stearate[26].

4. Gelling Agent:

These are used to increase the consistency of any dosage form. they can also be used as thickening agent[27]. The examples are given in table 2 & 3.

5. Permeation Enhancers:

These are agents that partition into, and interact with skin constituents to induce a temporary and reversible increase in skin permeability. Some of these materials are given in Table 4[28].

MECHANISM OF PENETRATION ENHANCERS:

The enhancers act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increased the fluidity of the lipid protein portion of the stratum corneum. Some enhancers act on both polar and non-polar pathway by altering the multi laminate pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development of the product[29].

METHOD OF PREPARATION[30-32]

Step 1: Formulation of Emulsion either O/W or W/O

Step 2: Formulation of gel base

Step 3: Incorporation of emulsion into gel base with continuous stirring

Emulgel was prepared by the method reported by Mohammad et al (2004) with minor modification. The Gel in formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed and Carbopol 940 in purified water with constant stirring at a moderate speed then the pH are adjusted to 6 to 6.5 using Tri ethanol amine (TEA). The oil phase of the emulsion were prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and Propyl paraben was dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions was mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. And add Glutaraldehyde in during of mixing of gel and emulsion in ratio 1:1 to obtain the emulgel[32].

EVALUATION PARAMETERS FOR THE FORMULATION [30,33-37]

1. Organoleptic properties

The prepared emulgel formulations are inspected visually for their color, homogeneity, consistency and phase separation.

2. Rheological Studies

The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath.

3. Spreading Coefficient:

Spreadibility is determined by apparatus suggested by Mutimer *et al* (1956) which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spreadibility is measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide is fixed on this block. An excess of emulgel (about 2 gm) under study is placed on this ground slide. The emulgel is then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges. The top plate is then subjected to pull of 80 gm. 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 spreadibility[37].

5. Swelling Index:

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

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

Where (SW) % = Equilibrium percent swelling,

Wt = Weight of swollen emulgel after time t,

Wo = Original weight of emulgel at zero time[38].

6. Drug Content Determination:

Take 1gm of emulgel. Mix it in suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. Standard plot of drug is prepared in the same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance in the standard plot equation:

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

7. Skin Irritation Test (Patch Test):

The preparation is applied on the properly shaven skin of rat and its adverse effect like change in color, change in skin morphology should be checked up to 24 hours. The total set of 8 rats can be used of the study. If no irritation occurs the test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated.

9. In Vitro Release/Permeation Studies:

In vitro release studies were carried out using Franz diffusion cell.

DRUG RELEASE KINETIC STUDY[39]

To analyze the mechanism of drug release from the topical gel, the release data were fitted to following equations

Zero – order equation:

$$Q = k\,0t$$

Where Q is the amount of drug released at time t, and k0 is the zero – order release rate.

First – order equation:

$$\text{In}\,(100 - Q) = \text{In}\,100 - k1t$$

Where Q is the percent of drug release at time t, and k1 is the first – order release rate constant.

Higuchi's equation:

$$Q = k2\sqrt{t}$$

Where Q is the percent of drug release at time t, and K2 is the diffusion rate constant.

10. Stability Studies:

The prepared emulgels were packed in aluminum collapsible 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 were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles.

TABLE 1 FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG[40, 41]

Physiological factors	Physiochemical factors
Skin thickness	Partition coefficient
Lipid content	Molecular weight (<400 dalton)
Skin ph	Degree of ionization (unionized drug get adsorbed well)
Density of hair follicles & sweat glands	Effect of vehicles
Blood flow	
Hydration & inflammation of skin	

TABLE 2. USE OF DIFFERENT GELLING AGENTS

Gelling agents	Quantity	Dosage form	References
Carbopol 934	1%	Emulgel	Mohamed, M.I.,AAPS
Carbopol 940	1%	Emulgel	Jain, Ankur. IJPRD
HPMC 2910	2.5%	Emulgel	Mohamed, M.I.,AAPS
HPMC	3.5%	Gel	Gupta,A.,Drug Invention Today
Poloxamer 407	1%	Gel	Singh,S.,Pak J. Pharm. Sci.

TABLE 3. DIFFERENT GRADES OF CARBOPOL

Polymer	Viscosity	Properties
Carbopol 910	3000-7000	Effective in low concentrations and will provide a low viscosity formulation
Carbopol 934	30,500-39,400	Effective in thick formulations such as emulsions, suspensions, sustain release formulations, transdermals, and topicals forms clear gels with water.
Carbopol 934 P	29,400-39,400	Same properties as 934, but intended for pharmaceutical formulation purified product.
Carbopol 940	40,000-60,000	Effective in thick formulations, very good clarity in water or hydro alcoholic topical gels. Form clear gels with hydro alcoholic systems.
Carbopol 940	4,000-11,000	Produces low viscosity gels, very good clarity.

TABLE 4. USE OF PENETRATION ENHANCERS

Permeation enhancers	Quantity	Dosage form	References
Oleic acid	1%	Gel	Mortazavi, S.A., Iranian Journal, of Pharmaceutical Science
Lecithin	5%	Gel	Mortazavi, S.A., Iranian Journal, of Pharmaceutical Science
Eucalyptus oil	NA	None	Pathan, I.B.,Trop J Pharm Res.
Chenopodium oil	NA	None	Pathan, I.B.,Trop J Pharm Res.
Isopropyl myristate	5%	Gel	Mortazavi, S.A., Iranian Journal, of Pharmaceutical Science
Urea	10%	Gel	Mortazavi, S.A., Iranian Journal, of Pharmaceutical Science
Linoleic acid	5%	Gel	Kasliwal, N., AJPS

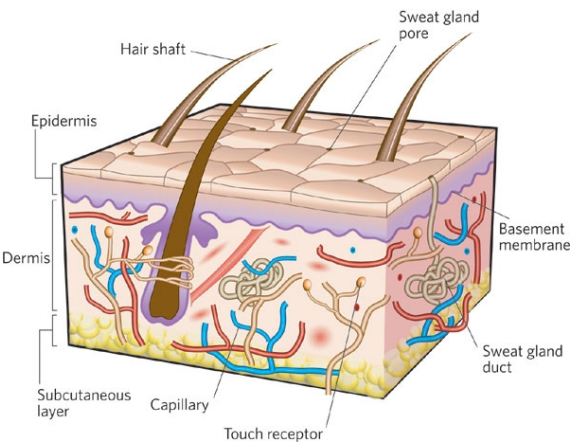

Figure 1 The layers of skin

CONCLUSION

In the recent years, topical drug delivery will be used extensively due to better patient compliance. Since emulgel had appeared as a new & novel technique for topical drug delivery so it can be a very effective technique for hydrophobic drugs. Since It is also capable in enhancing spreadibility, adhesion, viscosity and extrusion, they will become a popular drug delivery system. Moreover, they will become a solution for loading hydrophobic drugs in a water soluble gel bases.

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