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International Journal of Pharmacy and Biological Sciences (eISSN: 2230-7605)
IJPBS |Volume 1| Issue 3 |JULY- SEPT |2011|117-128

EMULGELS: A SURROGATE APPROACH FOR TOPICALLY USED HYDROPHOBIC DRUGS

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Review Article

RECEIVED ON 06-07-2011 **ACCEPTED ON 22-07-2011**

ABSTRACT

A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The combination of hydrophilic cornified cells in hydrophobic intercellular material provides a barrier to both hydrophilic and hydrophobic substances. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. 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 enjoy the unique properties of gels. When gels and emulsions are used in combined form the dosage forms are referred as emulgels. In recent years, there has been great interest in the use of novel polymers which can function 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. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. These emulgel are having major advantages on novel vesicular systems as well as on conventional systems in various aspects. 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 and antifungal drugs.

KEYWORDS: Emulgels, Hydrophobic Drugs, Topical drug delivery

Introduction

When gels and emulsions are used in combined form the dosage forms are referred as **emulgels**[1]. As the name suggest they are the combination of emulsion and gel. 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. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel[2]. Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance..Use of topical agents requires an appreciation of the

factors that influence percutaneous absorption[3]. Molecules can penetrate the skin by three routes: through intact stratum corneum, through sweat ducts, or through the sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption[4]. Passage through this outermost layer is the rate-limiting step for percutaneous absorption. The major steps involved in percutaneous absorption include the establishment of a concentration gradient, which provides the driving force for drug movement across the skin; release of drug from the vehicle (partition coefficient); and drug diffusion across the layers of the skin (diffusion coefficient). Preferable characteristics of topical drugs include low molecular mass (600 Da), adequate solubility in oil and water, and a high partition coefficient. Except for very small particles, watersoluble ions and polar molecules do not penetrate intact stratum corneum. Topical formulation can be used to manipulate the barrier function of the skin, for example, topical antibiotics and antibacterials help a damaged barrier to ward off infection, sun screening agents and the horny layer protect the viable tissues from Ultraviolet radiation and emollient preparations restore pliability to a desiccated horny layer [5].

Rationale of Emulgel as a Topical Drug Delivery System

Number of medicated products are applied to the skin or mucous membrane that either enhance or restore a fundamental function of skin or pharmacologically alter an action in the underlined tissues. Such products are referred as topical or dermatological products[6].Many widely used topical agents like ointments, creams lotions 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[7]. And 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. A gel is colloid that is typically 99% wt liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelating 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 delivered through gels.

Drug Delivery across the Skin

The epidermis is the most superficial layer of the skin and is composed of stratified keratinised squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibres. The skin forms a relatively waterproof layer that protects the deeper and more delicate structures. Blood vessels are distributed profusely beneath the skin. Especially important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries. In the most exposed areas of the body—the hands, feet, and ears blood is also supplied to the plexus directly from the small arteries through highly muscular arteriovenous anastomoses. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The skin acts as a two-way barrier to prevent absorption or loss of water and electrolytes. There are three primary mechanisms of topical drug absorption: transcellular,intercellular, and follicular.Most drugs pass through the torturous path around corneocytes and through the lipidbilayer to viable layers of the

skin. The next most common (and potentially under-recognized in the clinical setting) route of delivery is via the pilosebaceous route. The barrier resides in the outermost layer of the epidermis,the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Creams and gels that are rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body. These include, among others, gels and creams for vaginal yeast infections, topical creams for skin infections and creams to soothe arthritis pain. New technologies now allow other drugs to be absorbed through the skin (transdermal). These can be used to treat not just the affected areas (for example, the skin) but the whole body (systemic) [2,8].

Factors Affecting Topical Absorption of Drug [9,10]

Physiological Factors

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

Physiochemical Factors

1. Partition coefficient.
2. Molecular weight (<400 dalton).
3. Degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles

Factors to be Considered When choosing a Topical Preparation [11,12]

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.

Method to Enhance Drug Penetration and Absorption[13]

1. Chemical enhancement
2. Physical enhancement.
3. Biochemical enhancement
4. Supersaturation enhancement

Classification of Topical Drug Delivery System [14, 15]

Liquid preparations	*Semi-solid preparations*	*Solid preparations*	*Miscellaneous preparations*
• Liniment • Lotions • Paints • Topical solution • Topical tinctures • Collodions	• Ointments • Creams • Pastes • Gels • Poultices	• Topical powders • Poultices	• Transdermal drug delivery systems • Tapes and Gauzes • Rubbing alcohols • Liquid cleanser • Topical aerosol

Advantages of Using Emulgels as a Drug Delivery System[16, 17, 2]

1. **Hydrophobic drugs can be easily incorporated into gels using d/o/w emulsions:** Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.

2. **Better stability:** Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointkment shows rancidity due to oily base.

3. **Better loading capacity:** Other novel approaches like niosomes and liposomes 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.

4. **Production feasibility and low preparation cost:** Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.

5. **No intensive sonication**: Production of vesicular molecules need intensive sonication which may result in drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed.

6. **Controlled release:** Emulgels can be used to prolong the effect of drugs having shorter $T_{1/2}$.

Important Constituents of Emulgel Preparation [18, 19, 20, 21, 22]

1. Aqueous Material:

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

2. Oils:

These agents form the oily phase if the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. Widely used oils in oral preparations 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[23]. Some are discussed in ***table 1***.

Table 1: USE OF OILS

CHEMICAL	QUANTITY	DOSAGE FORM	REFERENCE
Isopropyl myristate	According to phase diagrams	Emulsion	Subramanian, N. Drug Dev. Ind. Pharm.
CAPMUL	According to phase diagr5ams	Emulsion	Subramanian, N. Drug Dev. Ind. Pharm.
Isopropyl Myristate	7-7.5%	Emulsion	Montenegro, L., Drug Dev. Ind. Pharm
Isopropyl palmitate	7-7.5%	Emulsion	Montenegro, L., Drug Dev. Ind. Pharm
Isopropyl stearate	7-7.5%	Emulsion	Montenegro, L., Drug Dev. Ind. Pharm
Light Liquid Paraffin	7.5%	Emulgel	Mohamed, M.I.,AAPS
Light Liquid Paraffin	7.5%	Emulgel	Jain, Ankur. IJPRD
Propylene glycol	3-5%	Gel	Arellano, A., European J. Pharm. Sci.

3. 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.eg Polyethylene glycol 40 stearate,Sorbitan mono-oleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate[23].

4. Gelling Agent:

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent [24]. The examples are given in ***table 2***.

Table 2:Use of Different Gelling Agents

GELLING AGENT	QUANTITY	DOSAGE FORM	REFERENCES
Carbapol-934	1%	Emulgel	Mohamed, M.I.,AAPS
HMPC 2910	2.5%	Emulgel	Mohamed, M.I. AAPS
Carbapol-940	1%	Emulgel	Jain, Ankur. IJPRD
HPMC	3.5%	Gel	Gupta, A., Drug Invention Today
Aegelmarmelos Polymer(natural)	1%	Gel	Kumar, L., Int. J. Drug Del.
Sodium CMC	1%	Gel	Singh, S., Pak J. Pharm. Sci.
Xanthan Gum	1%	Gel	Singh, S., Pak J. Pharm. Sci.
Poloxamer 407	1%	Gel	Singh, S., Pak J. Pharm. Sci.

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 included in **Table 3** [25].

Table 3: USE OF PENETRATION ENHANCERS

PERMEATION ENHANCER	QUANTITY	DOSAGE FORM	REFERENCE
Oleic Acid	1%	Gel	Mortazavi, S.A., Iranian Journal of Pharmaceutical Science
Lecithine	5%	Gel	Mortazavi, S.A., Iranian Journal of Pharmaceutical

			Science
Isopropyl myristate	5%	Gel	Mortazavi, S.A., Iranian Journal of Pharmaceutical Science
Urea	10%	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
Pyrrolidones	NA	None	Pathan, I.B. , Trop J Pharm Res
Laurocapran	NA	None	Pathan, I.B. , Trop J Pharm Res
Dimethyl sulphoxides	NA	None	Pathan, I.B. , Trop J Pharm Res
Linoelic Acid	5%	Gel	Kasliwal, N., AJPS
Menthol	4-6%	NA	Shojaei, A.H., European Jounal of Pharmaceutics

Method of preparation

STEP 1: OIL/WATER EMULSION

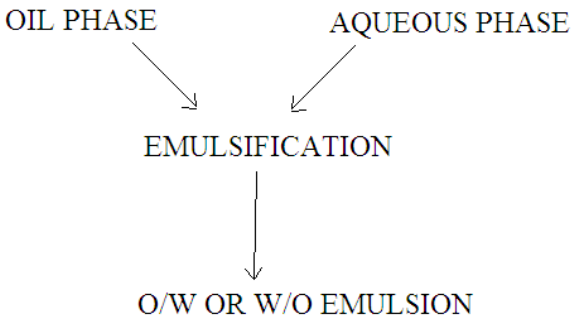

FIG. 1: Emulsification Process

Drug can be incorporated either in oil or aqueous phase depending upon its solubility

STEP 2: FORMATION OF GEL BASE

STEP 3: INCORPORATION OF EMULSION IN GEL BASE

Characterization [7, 26, 27, 28, 29, 30]

1. **Physical Examination:** The prepared emulgel formulations are inspected visually for their color, homogeneity, consistency and phase separation.

2. **Rhelogical 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 Cofficent:** Spreadability 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, spreadability 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 gms. 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 spreadability [31].

4. **Extrudability Study of Topical Emulgel (Tube Test):** It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow. In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in percentage of emulgel and emulgel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability. The measurement of extrudability of each formulation is in triplicate and the average values are presented. The extrudability is than calculated by using the following formula:

   Extrudability = Applied weight to extrude emulgel from tube (in gm) / Area (in cm^2)

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:

   Swelling Index (SW) % = [(Wt – Wo) / Wo] × 100.

   Where, (SW) % = Equilibrium percent swelling, Wt = Weight of swollen emulgel after time t, Wo = Original weight of emulgel at zero time [32].

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 same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance. [33].

   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 like change in color, change in skin morphology should be checked upto 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.

8. ***Ex–Vivo* Bioadhesive Strength Measurement of Topical Emulgel:**

   (MICE SHAVEN SKIN): The modified method is used for the measurement of bioadhesive strength. The fresh skin is cut into pieces and washed with 0.1 N NaoH. Two pieces of skin were tied to the two glass slide separately from that one glass slide is fixed on the wooden piece and other piece is tied with the balance on right hand side. The right and left pans were balanced by adding extra weight on the left – hand pan. 1 gm of topical emulgel is placed between these two slides containing hairless skin pieces, and extra weight from the left pan is removed to sandwich the two pieces of skin and some pressure is applied to remove the presence of air. The balance is kept in this position for 5 minutes. Weight is added slowly at 200 mg/ min to the left – hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the emulgel from the skin surface gave the measure of bioadhesive strength. The bioadhesive strength is calculated by using following: Bioadhesive Strength = Weight required (in gms) / Area (cm^2) [34]

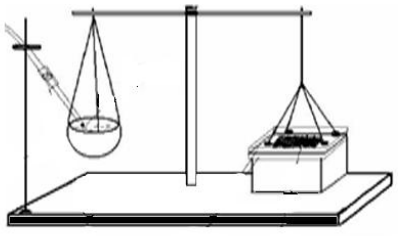

Fig2: Setup for bioadhesive test

9. ***In Vitro* Release/Permeation Studies**: In vitro release studies were carried out using Franz diffusion cell.[35]

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.[36]

Conclusion

In the coming years, topical drug delivery will be used extensively to impart better patient compliance. Since emulgel possesses an edge in terms of spreadibilty, adhesion, viscosity and extrusion, they will become a popular drug delivery system. Moreover, they will become a solution for loading hydrophobic drugs in an water soluble gel bases.

Acknowledgement

I am very thankful to Rayat Educational and Research Trust for supporting me at each and every step of my work.

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