International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 6(3): May-June 2016

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 05-05-2016; Revised: 10-05-2016; Accepted: 11-05-2016

EMULGELS: EXPANDING HORIZONS FOR TOPICAL DRUG DELIVERY

Ankush Matlonia*, Neha Shama, Nimrata seth

Department of Pharmaceutics, Rayat Institute of Pharmacy, Railmajra, Ropar, Punjab, India.

Keywords:

Emulgels, Topical drugs delivery, Gelling agent, Anti fungal

For Correspondence:

Ankush Matlonia

Department of Pharmaceutics, Rayat Institute of Pharmacy, Railmajra, Ropar, Punjab, India

E-mail:

matloniaankush@gmail.com

ABSTRACT

Dermatological products are diverse in formulation and range in consistency from liquid to powder but the most popular products are semisolid preparation. Among the various semi-solid dosage forms, gel formulations generally provide faster drug release compared with conventional ointments and creams. 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. Emulgel is the one of the recent technologies in NDDS used for topical use. Emulgel is emulsions, either of the oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent. The emulgel for dermatological posses properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non- staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. These emulgel have major advantages on novel vesicular systems as well as on conventional systems in various aspects. This review article discusses various aspects of emulgel as drug delivery system viz., formulation techniques, merits, demerits and evaluation.

INTRODUCTION

Over last decades, the treatment of illness has been accomplished by conventional routes namely oral, topical, parental etc. Topical drug administration is a localized drug delivery system through ophthalmic, rectal, vaginal and skin as topical routes. The main advantage of topical delivery system is to bypass first pass metabolism[1, 2.] Avoidance of the risks and inconveniences of intravenous therapy and overcoming the varied conditions of absorption like pH changes, presence of enzymes, gastric emptying time are other advantages of topical preparations[3, 4]. Dermatological products are diverse in formulation and range in consistency from liquid to powder but the most popular products are semisolid preparation. Among the various semi-solid dosage forms, Emulgels have emerged as novel drug delivery systems thereby expanding horizons for topical drug delivery of hydrophobic drugs. When gels and emulsions are used in combined form the dosage forms are referred as Emulgels. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Direct (oil-in-water) system is used to entrap lipophilic drugs whereas hydrophilic drugs are encapsulated in the reverse (water-in-oil) system[5]. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skinner shelf life, bio-friendly, transparent & pleasing appearance[6.] . Emulgels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble and pleasing appearance.

1.1 Advantages of Emulgels

- Hydrophobic drugs can be easily incorporated into gels using w/o/w emulsion.
- Better stability.[7]
- Better loading capacity.[8]
- Production feasibility and low preparation cost.
- No intensive sonication is required.
- Avoidance of first pass metabolism.
- Avoidance of gastrointestinal incompatibility.[9]
- More selective to a specific site.
- Improve patient compliance and suitability for self medication.

1.2 Disadvantages of Emulgels

- Drug of larger molecular weight are not easy to absorb through the skin.
- Poor permeability of some drugs through skin.
- Skin irritation or contact dermatitis may occur due to the drug and/or excipients.[10]
- Occurrence of bubble during formulation of emulgel.

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 lipid bilayer 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).

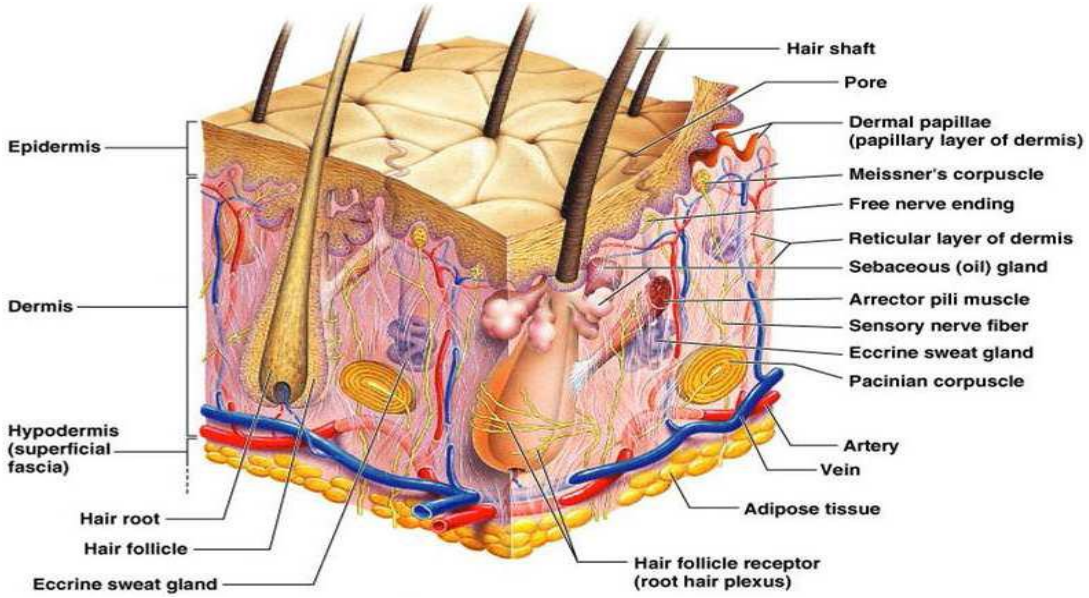

Figure 1: Structure of Skin

2. FACTOR AFFECTING DRUG ABSORPTION THROUGH SKIN

(A) **Physiological Factors**

- Skin thickness.
- Lipid content.
- Density of hair follicles.
- Density of sweat glands.
- Skin pH.
- Blood flow.
- Hydration of skin.
- Inflammation of skin

(B) **Physiochemical Factors**

- Partition coefficient.
- Molecular weight (<400 Dalton).
- Degree of ionization (only unionized drugs gets absorbed well).

3. SALIENT FEATURES OF EXCIPIENTS TO BE USED IN EMULGEL FORMULATION PROPERTIES

- They must be non-toxic.
- They must be commercially available in acceptable grade.

- Their cost must be acceptably cheap.
- They must be physically and chemically stable by themselves and in combination with drugs and other components.
- They must be colour compatible.

4. IMPORTANT CONSTITUENTS OF EMULGEL PREPARATIONS

A. **Aqueous Material:**

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols[11].

B. Oils:

These agents form the oily phase of 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 sensor characteristics[12,13].

Table1: Various Types of Oil Used in Emulgel

Chemical	Dosage Form
Light Liquid Paraffin	Emulsion & Emulgel
Isopropylmyristate	Emulsion
Isopropyl stearate	Emusion
Isopropyl palmitate	Emulsion
Propylene glycol	Gel

C. 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[14], Sorbitan monooleate (Span 80)[15], Polyoxyethylene sorbitan monooleate (Tween80)[16], Stearic acid[17], Sodium stearate[18].

D. Gelling Agent:

These are the agents used to increase the consistency of any dosage form, thus also referred to as thickening agent[19,20]. The various gelling agents along with their recommended quantity used in the various dosage forms has been shown in table 2.

Table 2: Various Types of Gelling Agents Used in Emulgel

Gelling agent	Dosage form
Carbopol-934	Emulgel
Carbopol-940	Emulgel
HPMC-2910	Emugel
HPMC	Gel
Sodium carboxymethylcellulose	Gel

E. Permeation Enhancers:

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.[21]

Table 3: Commonly used penetration enhancer for formulation of Emulgel

Penetration Enhancer	Dosage form
Oleic acid	Gel
Lecithin	Gel
Urea	Gel
Isopropyl myristate	Gel
Linoleic acid	Gel
Clove oil	Emulgel
Menthol	Emulgel
Cinnamon	Emulgel

5. METHOD OF PREPARATION OF EMULGEL[22,23]

- **Formulation of emulsion either o/w or w/o:** The emulsion is prepared by slowly mixing oil phase and aqueous phase of the emulsion containing an emulsifying agent like spans and tweens. Before mixing the two phases, both the oily and aqueous phase are separately heated to 70-80^{0}C; then the oily phase can be added to the aqueous phase with continuous stirring for 15 to 20 minutes and cooled to room temperature. Preservative may also be added to the emulsion in any phase depending on its solubility.

- **Formulation of gel base:** The gel in formulation are prepared by dispersing a suitable polymer in purified water with constant stirring at a moderate speed to allow complete hydration, swelling of polymer. pH is adjusted to 6 to 6.5 using Triethanolamine (TEA).
- **Incorporation of emulsion into gel base**: The obtained emulsion is mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel.

6. EVALUATION PARAMETERS OF EMULGEL

A. Physical appearance: Emulgels are generally inspected visually for their color, homogeneity, consistency etc.

B. Globule size and size distribution in emulgel:

Globule size and distribution are determined by Malvern zetasizer. Accurately weighed 1.0 gm sample is dissolved in purified water and agitated to get homogeneous dispersion. Sample is then injected to photocell of zetasizer. Mean globule diameter and distribution are obtained.[24]

C. Measurement of pH: The pH of emulgel formulation are determined by using digital pH meter. 1gm of gel is dissolved in 100 ml of distilled water and it is placed for 2 hours. The measurement of pH of each formulation are done in triplicate and average values are calculated.[25]

D. Spreadability: 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. About 1 g 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. Spreadability are calculated by using the formula, S = M.L/T

Where, S = spreadability,

M = Weight tied to upper slide,

L = Length of glass slides

T = Time taken to separate the slides completely from each other

E. Extrudability study:

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. The method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in extruded from lacquered aluminium collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. More the quantity of emulgel extruded, better is the extrudability. The extrudability is than calculated by using the following formula:

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

F. Rheological Study:

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.

G. Swelling Index:

To determine the swelling index of prepared topical emulgel, 1 gm of gel is taken on porous aluminium foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaOH. Then samples are 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,

Wo = Original weight of emulgel at zero time

after time t, Wt = Weight of swollen emulgel

H. Drug Content Determination:

Drug concentration in Gellified Emulsion is measured by spectrophotometer by dissolving known quantity of Gellified Emulsion in suitable solvent. Absorbance are measured after suitable dilution in UV/VIS spectrophotometer.[26]

I .*In Vitro* Release Study:

Franz diffusion cell (with effective diffusion area 3.14 cm^2 and 15.5 ml cell volume) are used for the drug release studies. Gellified Emulsion (200 mg) are applied onto the surface of cellophane membrane evenly. The cellophane membrane is clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber is filled with freshly prepared PBS (pH 5.5) solution to solubilize the drug. The receptor chamber is stirred by magnetic stirrer. The samples (1.0 ml aliquots) are collected at suitable time interval. Samples are analyzed for drug content by UV visible spectrophotometer after appropriate dilutions. Cumulative corrections are made to obtain the total amount of drug release at each time interval .The cumulative amount of drug released across the cellophane membrane are determined as a function of time.[27]

J. Skin irritation test:

A 0.5 gm sample of the test article could be applied to each site (two sites per rabbit) by introduction under a double gauze layer to an area of skin approximately 1" x 1" (2.54 x 2.54 cm^2). The Gellified Emulsion is applied on the skin of rabbit. Animals are returned to their cages. After a 24 hour exposure, the emulgel formulation is removed. The test sites are wiped with tap water to remove any remaining test article residue. Skin is then examined or any kind of redness or rash.

K. Accelerated stability studies of emulgels:

Stability study is performed according to ICH guidelines. The formulations are stored in hot air oven at 37 ± 2°, 45 ± 2° and 60 ± 2° for a period of 3 months. The samples are analyzed for physical appearance visually and for drug content every two weeks by UV-Visible spectrophotometer.[28]

Marketed preparation Available In emulgel Form

Marketed Products which are commercially available in emulgel type of dosage form are listed in table no. 4**.**

Table 4: Marketed preparation of emulgel

Product name	**Drug**	**Manufacturer**
Voltaren emulgel	Diclofenac diethyl ammonium	Novartis Pharma
Miconaz-H-emulgel	Miconazole nitrate,Hydrocortisone	Medical union pharmaceuticals

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 a water soluble gel bases.

REFERENCES

1. Surver C, "Bioavailability and Bioequivalence In: K.A Walter (eds.), Dermatological and Transdermal Formulation, Marcal Dekker", New York, 2002; 323- 327, 403.
2. Sharma S., "Topical drug delivery system". Available from: http://www.pharmainfo.net/ Section/science-news/. [Cited in 2011 Aug 9].
3. Sharma S., "Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes", Pharmaceutical reviews, 2008Vol .6:(1).
4. Laithy H.M., "Shaboury El K.M.F", The development of Cutina Lipogels and gel microemulsion for topical administration of fluconazole. Ame Pharm Sci. PharmSciTech 2003; Vol. 3(1): 10-25.
5. Kuller R, Saini S, Seth N, Rana A.C., "Emulgel: A surrogate approach for topical used hydrophobic drug", *Int J Pharm Bio Sci*, 2011;Vol. 1(3): 117-128.
6. Jain A, Gautam S.P, Gupta, Jain S., and "characterization of Ketoconazole emulgel for topical drug delivery", Der Pharmacia Sinica, 2010; Vol. 1(3): 221 -223.
7. Bhowmik D, Gopinath H, Kumar B.P, Duraivel S, Kumar K.P, "Recent Advances in Novel Topical Drug Delivery System", The Pharma. Innovation, 2012 Vol.1(9): 12-31.
8. Nayank S.H, Nkhat P.D, Yeole P.G., The Indian Pharmacist,2002, Vol. 3(27): 7-14.
9. Kumar L., Verma R., "In vitro evaluation of topical gel prepared using natural polymer", Int J drug Deli, 2010;Vol. 2: 58- 63.
10. Rushmer R.F, Buettner K.J.K., Short JM . Odland, Science,1966; Vol. 3 (4). 154, 343.
11. Curr A.E.B.,"Transdermal Drug Delivery: Penetration Enhancement Techniques Heather. Drug Deliver" , 2005; Vol. 2: 22-23.
12. Rutrer N., "Drug absorption through the skin: a mixed blessing" .Arch Dis Child 1987; Vol. 62: 220-221.

13. Zhang X.L.,Zhao R, Qian W. "Preparation of an emulgel for treatment of aphthous ulcer on the basis of carbomers", Chin Pharm. J. 1995; Vol. 30: 417-418.
14. Swarbrick J., "Encyclopedia of pharmaceutical technology", 3rd ed.,1551 .
15. Gibson., "M. Pharmaceutical formulation and preformulation" , Interpharm, 2004.
16. Zhang X.L, Zhao R, Qian W., "Preparation of an emulgel for treatment of aphthous ulcer on the basis of carbomers", Chin. Pharm. J, 1995;Vol. 30: 417-41.
17. Swarbrick, J., "Encyclopedia of pharmaceutical technology", 3rd ed, 1551 .
18. Gibson., "M. Pharmaceutical formulation and preformulation" , Interpharm ,2004.
19. Mortazavi S.A, Aboofazeli R., "An Investigation into the Effect of Various Penetration Enhancers on Percutaneous Absorption of Piroxicam", Iranian Journal of Pharmaceutical Research, 2003; 135-140.
20. Kumar. L, Verma. R., "Int. J Drug Delivery", 2010, 58-63.
21. Jacob S.W, Francone C.A., "Structure and Function of Man", (2).WB Saunders Co. Philadelphia, 1970; 55-60.
22. Laithy H.M, Shaboury El K.M.F., "The development of Cutina Lipogels and gel microemulsion for topical administration of fluconazole", Ame Pharm Sci, PharmSciTech 2003; vol. 3(1): 10-25.
23. Jain A, Gautam S.P, Gupta, Jain S., and "characterization of Ketoconazole emulgel for topical drug delivery", Der Pharmacia Sinica,2010; vol.1(3): 221 – 231.
24. Gondaliya D.P., and Pundarikakshudu K., "*Indian drugs"*, 2002; Vol. 39: 465-473.
25. Kaur L.P, Garg R, Gupta G.D. Development and evaluation of topical gel of minoxidil from different polymer bases in application of alopecia. Asian J Pharma 2010;Vol. 2(3): 43-47.
26. Chaudhari P, Ajab A, Malpure P, Kolsure P, Sanap D, "Development and in-vitro evaluation of thermo reversible nasal gel formulations of Rizatriptan benzoate", Indian J. Pharm, Edu. Res., 2009;Vol. 43: 55-62.
27. Masmoudi H, Piccerelle P, Le Dréau Y, Kister J., "A rheological method to evaluate the physical stability of highly viscous pharmaceutical oil-in-water emulsions" Pharm Res, 2006; Vol. 23 8:1937–47
28. Tadros T.F., "Future developments in cosmetic formulations", Int J Cos Sci, 1992; Vol. 14 (3): 93- 111.