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EMULGEL: A MODERN TOOL FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Topical drug delivery is most widely employed for the local dermatological action, but now a days new techniques are also utilized to enhancing its systemic effect. They are generally adopted for the purpose as antiseptics, antifungal agents, skin emollients, and protective. The activity of topical preparation reveal the various factors as drug solubility, contact time to skin, its lipophilicity, its permeability. Gels are a quite newer class of dosage form formulated by entrapment of large amounts of aqueous or hydro-alcoholic liquid with in the network of colloidal solid particles. Gel formulations generally provide faster drug release as compared to conventional topical drug delivery formulations. In spite of many advantages of gels, a major limitation is in the difficulty in delivery of hydrophobic drugs. So to overcome these limitations, emulgels are prepared. When gels and emulsions are used in combined form, the dosage forms are known as Emulgels. Emulsions have a certain degree of elegance and they are easily washed off whenever desired. Emulgels have numerous advantages in the area of dermatology such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent and pleasing appearance. Emulgel are being used for the delivery of analgesics, anti-inflammatory, anti-fungal, anti-acne drugs and various cosmetic formulations with still wide range to explore.

KEYWORDS: Topical Drug Delivery, Emulgel, Gel, Emulsion.

INTRODUCTION

Topically drug administration is a confined drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. The main advantage of topical delivery system is to evade first pass metabolism.[1,2] Avoidance of the risks and

inconveniences of parenteral therapy as well as varied conditions of absorption like changes in pH, presence of enzymes, gastric emptying time are other advantages of topical preparations.[3,4] Dermatological products are divers in formulation and varied in consistency from liquid to powder but the most popular products are semisolid preparation. Within the major group of semisolid preparations, the use of clear, translucent gels has expanded both in cosmetics and in pharmaceutical preparations. Gels are a somewhat newer class of dosage form formed by entrapment of large amounts of aqueous or hydro alcoholic liquid in a complex of colloidal solid particles. Gel formulations usually provide faster drug release as compared with traditional ointments and creams. Rather than the many advantages of gels a major limitation is the difficulty in delivery of hydrophobic drugs. To minimize this limitation emulgels are prepared so that even a hydrophobic drug can enjoy the unique properties of gels. When gels and emulsions are used in combined form the dosage forms are known as Emulgels. In fact, the presence of a gelling agent in the water phase converts a traditional emulsion into an emulgel. Oil-in-water system is used to entrap lipophilic drugs while hydrophilic drugs are captured in the water-in-oil system.[5] Emulsions possess a definite degree of elegance and are easily washable whenever required. They also have a high ability to cross the skin. Dermatological emulgels have several favourable properties such as thixotropic, easily spreadable, greaseless, easily removable, emollient, non-staining, longer shelf life, bio-friendly, transparent & pleasing appearance.[6]

Topical Drug Delivery System

Topical drug delivery system there are two basic types of topical drug delivery products, externally used topicals and internally used topicals. The externally used topicals are spread, sprayed or otherwise dispersed on the tissue to shield diseased area, while the internally used topicals are applied to mucous membrane orally, vaginally or on the rectal tissues for local activity. Main benefit of topical drug delivery system are avoiding first pass metabolism, avoiding gastrointestinal incompatibilities, specific site selective, improving patients compliance, possible and easy self-medication, and drugs with short half-life and narrow therapeutic index are also subjected to be utilized, facility is used to easily terminate medicines whenever required.[7] Disadvantages of topical drug delivery system are skin irritation on contact dermatitis, allergic reactions, poor drug permeability through skin, drugs of large particle size are not absorbed easily through skin. Skin is thick, complex in structure. Molecules moving from the external environs must penetrate the stratum corneum as well as any material of endogenous or exogenous origin on its surface. They must then penetrate the

viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph compartment, where upon they are removed from the skin by flow of blood or lymph. To move across the skin membrane is obviously a complex process and challenge in analysis. Factors affecting the topical drug delivery system can be physiological factors e.g. thickness, hydration, inflammation and pH of skin, lipid content, densities of hair follicles and sweat glands, blood flow etc., and physico-chemical factors like partition coefficient, molecular weight, degree of ionization, effect of vehicle etc.[8] When moiety touches intact skin, it contacts cellular debris, microorganisms, sebum and the other materials. The diffusion of drug will be done by various routes via hair follicles, sebaceous gland and sweat ducts across the continuous stratum corneum.

Classification of topical drug delivery system

Classification of topical drug delivery systems[9]

1. Solid: Powders, Plasters Ointments,

2. Semi solid: Creams, Poultices, Gels, Pastes

3. Liquid: Liniment, Lotions, solution, tinctures, Emulsions, Suspensions, Paints

4. Miscellaneous: Transdermal drug delivery systems, Tapes and Gauzes, Rubbing alcohols, Liquid cleanser, and Topical aerosol.

Rational

Topical dosage forms like cream, lotion, ointment have many disadvantages. Some of which are greasiness and stickiness, causing problems to patients in application and having low spreading coefficient and requirement of rubbing are also considered as disadvantages. Also may causes stability problem of hydrophilic drug formulation. Due to these shortcomings with the semisolid group of preparations, the use of gellified formulation has been expanded both in pharmaceutical preparations and in cosmetics. Gel is colloidal preparation containing 99 % part of liquid where macromolecular network of fibres built from a gelling agent and liquids are immobilized by surface tension between them. In spite of advantages a major problem is to delivery of hydrophobic natured drugs. Emulsion based strategies can be used to incorporate lipophilic therapeutic moiety in gel built system to overcome this problem.[10]

Emulgel

Emulgel is evolving field for the topical drug delivery, and up to the date it has less marketed product, so it is thought-provoking and challenging to focus on emulgel formulation. Before starting the concept of emulgel we need to know the concept of emulsion and gel that is being

used for the topical drug delivery. Emulsions are well-ordered drug release system containing two immiscible phase in which one is dispersed (internal phase) into other (external phase), with the use of emulsifying agent to make system stable. Emulsions are of oil-in-water or water-in-oil type, in which the drug particle entrapped in internal phase passes through the external phase and then slowly gets absorbed into the skin to deliver controlled effect. USP defines gel is a semisolid system comprises dispersions of either small inorganic particles or large organic molecules enfolding and interpenetrated by liquid. The gel contains the larger amount of aqueous or hydro alcoholic liquid entrapped in a network of colloidal solid particles where it entangled small drug particles and maintain the controlled release of drug. The liquid phase form a three-dimensional polymeric matrix like structure which results a physical or chemical cross-linking network. The continuous structure which behaves like solid that are homogenous and clear. The emulsion and gel both are liable for the controlled drug release from the systems.[11-13] There are two types of gels first the organic solvent based also known as hydrophobic or organogels and second the water based also known as hydrophilic or hydrogels. First one consist of liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, aluminium or zinc soaps along with base and the second one consist of base of water, glycerol, or propylene glycol.[14,15] Gels having many advantages has still restrictions in the delivery of hydrophobic drugs so to overcome this and enjoy the delivery in the form of gel for the hydrophobic drug, the theory for emulgel was introduced where the hydrophobic drugs are merged in emulsion and then to gel.[16] Emulgel is the approach using the aids of both emulsion and gels, gaining the twofold controlled release effect where the emulsion either oil in water or water in oil is gelled by incorporation in the gel base[17], Emulgel are seen better choice for the class II of drug as per the BCS classification systems that show poor solubility and high permeability.[18] Emulgel possess the properties as thixotropic, greaseless, water soluble, easily spreadable, nonstaining, easily removable, emollient, long shelf life, bio- friendly and attractive appearance that increases the patient acceptability.[19]

Factors Affecting Topical Absorption Of Drugs[20,21]

Physiochemical factors Drug substances	1.Molecular weight (<400 dalton) 2. Diffusion coefficient 3. Water/lipid partition coefficient 4. Permeability coefficient 5. Ionization- unionized drug are well absorbed 6. Protein binding capacity.	Physiological Factors	14. Skin thickness 15. Lipid content 16. Density of hair follicles 17. Density of sweat glands 18. Skin pH 19. Blood flow 20. Hydration of skin 21. Inflammation of skin
Vehicle	7.Solubility/polarity 8. Volatility 9. Concentration 10. Distribution in a stratum corneum 11. Excipients 12.Penetration enhancer 13. PH	Site of application	22. Skin area dose (film thickness, concentration) 23. Total skin area in contact with vehicle 24. Duration of exposure

Advantages of emulgel[22, 24]

1. Improved patient acceptability.
2. Offer targeted drug delivery.
3. Termination of the therapy at any time.
4. Enhance bioavailability as well as the low doses can be effective in comparison with other conventional semi solid preparation.
5. Became a stable formulation by decreasing surface interfacial tension which leads to increase the viscosity of aqueous phase, more stable as compare to transdermal preparations which are comparatively less stable.
6. Hydrophobic drug can be easily incorporated in emulgel form by using emulsion as the drug barrier which is finally dispersed in to gel.
7. Provide the controlled effect of that helps to prolong the effect of drug with short half-life.
8. Easy to formulate and cost effective preparation.
9. Drug loading capacity is better than other novel dosage forms like niosomes and liposomes
10. Skin penetration is enhanced due to both hydrophilic and hydrophobic nature.

Disadvantages[25-27]

1. Create problem in absorption of macromolecules.
2. Entrapment of air bubble during formulation.

3. Only hydrophobic drugs are the best choice for such delivery systems.

Marketed Emulgels[28]

The preparations of emulgel that are market commercially are listed below in table 1.

Sr. No.	Brand Name	Active Ingredient	Manufacturer	Use
1.	Voltarol 1.16% emulgel	Diclofenac Diethylammonium salt	Novartis	Anti-inflammatory
2.	Diclon emulgel	Diclofenac diethylamine	medpharma	Anti-inflammatory
3.	Diclomax Emulgel	Diclofenac sodium	Torrent pharma	Anti-inflammatory
4.	Miconaz-H-emulgel	Miconazole nitrate, Hydrocortisone	Medical union Pharmaceuticals	Topical corticosteroid and antifungal
5.	Dermafeet Emulgel	Urea 40%	Herbitas Intense	moisturizing and exfoliation activity
6.	Denacine emulgel	Clindamycin phosphate	Beit jala pharmaceutical company	Antiacne
7.	Isofen emulgel	Ibuprofen	Beit jala pharmaceutical company	Anti-inflammatory
8.	Diclona emulgel	Diclofenac diethylamine	Kuwait Saudi pharmaceutical industries co.	Anti-inflammatory
9.	Dosanac emulsion gel	Diclofenac diethylammonium	Siam bheasach	Anti-inflammatory
10.	Cataflam emulgel	Diclofenac potassium	Novartis	Anti-inflammatory

Methods of Formulation

Emulgel is formulated by following steps,

a. Selection of components

b. Preparation of emulsion

c. Preparation of emulgel.

a. Screening of components

Drug Solubility was checked in various oils by excess addition of drug followed by continuously stirred for 72 hours to achieve equilibrium. After that samples centrifuged and supernatant was taken and solubility was determined by suitable analytical methods. Then, excipients in each category with the highest solubility of drug are selected for further studies.[29]

a. Psedoternary phase diagram: Surfactant and co-surfactant were mixed in different ratios (2:1, 3:1 and 5:1). Every ratio preferred in increasing amount of surfactant with respect to co surfactant while studying on the phase diagrams. In most of the cases aqueous phase

(Distilled water) used as dilution media. Oil along with Surfactant and co-surfactant was mixed at different ratios from 9:1 to 1:9 in different vials for its each mixture. Main importance of this is to cover the study which decide boundaries of phases formed in the diagrams. Slow titration of oil and surfactant and co-surfactant is performed and visually observed for transparency of emulsion.[30]

b. Preparation of emulsion: The drug is then solubilized in oil and oil is mixed into mixture of surfactant and co-surfactant, this mixture is then diluted with water to form emulsion of known drug.

c. Preparation of emulgel: Gel base is formulate using 1g of the Carbopol with a required quantity of water and kept for overnight soaking, then prepared emulsion is slowly added with continues stirring. Triethanolamine is added to maintain the pH of formulation. Finally required remaining volume is adjusted by distilled water.

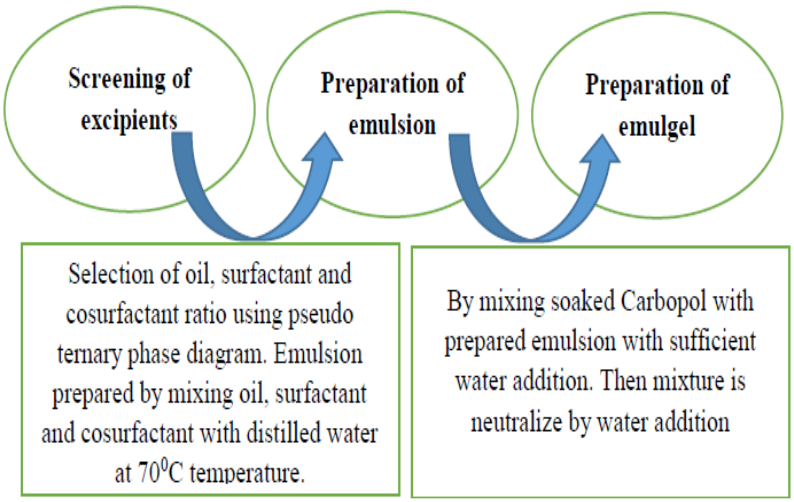

Fig. 1: Method of preparation for emulgel.

Optimization and Evaluation

1. Determination of pH: Numerous Topical formulations have pH range in between of 5-6 measured by using pH meter. For pH determination, take 1g of product and dissolve in 10ml water. PH of each formulation is done on triplicate to minimize error.[31]

2. Globules size measurement: To measure this parameter 1.0 gm of product was dissolved in water and stirred to become dispersion and then sample was inserted into the photocell of Malvern zetasizer.

3. Swelling Index: 1 gm of prepared emulgel is taken on porous aluminum foil which is then dispered in 10 ml of 0.1 N NaOH solutions. Sample removed on various time interval and weight is noted till no further change in weight:

Swelling Index (SW) % = [[Wt-Wo]/Wo]*100

Where, (SW) % = Percentage swelling,

Wo = Original weight of emulgel

Wt = Weight of swollen emulgel at time t

4. Measurement of Bio adhesive strength: Accurately 1 gm of emulgel is applied between slides containing rat's hairless skin pieces. Putting weight on single glass slide create some pressure to removed sandwich of two slides. Adding extra weight is concidered as 200 mg/min to until the detachment of the skin surface. Required weight to detach the emulgel from skin will give bio adhesive strength. It is calculated by using following formula:

Bio adhesive Strength = W / A

Where, W= Weight required (in gms) and A=Area (cm2)

5. Determination of Rheological properties: 20gm of prepared emulgel filled in 25ml beaker was used to measure viscosity by using Spindle number S64 by Brookfield viscometer.[32]

6. Accelerated stability studies: As given in ICH guidelines, the formulations are kept in oven at 37±2°C, 45±2°C and 60±2°C differently for 3 months. Drug content is examined every two week by appropriate analytical method. Stability measurement is based on change in pH of gel or degradation of drug.[33]

7. Determination of % drug content: 1 g of prepared emulgel is mixed with 25 ml of methanol. This resultant solution is sonicated for 30 min. Drug content was analyzed using the suitable analytical method from this solution.

8. Determination of emulgel spreadability: It can be determined by using Slip and Drag method, as suggested by Mutimer, For this take 2gm of emulgel and applied on lower side slide which is mounted with wooden block and sandwiched is prepared by using other glass slide having same size which is bind with hook having 500mg weight placed. After 5 min additional weight was placed on pan which connected with second slide. Time to cover 5cm

distance for upper slide was recorded and used to calculate spreadability by using following formula:

$$\text{Spreadability (S)} = M*L / T$$

Where, M = Weight tied to upper slide,

L = Length of glass slides

T = Time taken to cover distance by upper slide

9. Skin irritation test: 0.25 gm of prepared emulgel is applied to each different site (two to three sites/rabbit). When 24 Hrs of application rabbit skin site are wiped and cleaned, Colour change of skin or undesirable change in morphology is recorded.

10. *In-vitro* Diffusion studies: Franz diffusion cell is used to demonstrate diffusion study of prepared emulgel. A cellophane membrane is used during the study and 0.5g of sample spread on membrane and diffusion is conducted for 8 Hrs at 37±1°C using phosphate buffer (pH 7.4). At the time interval of 1 Hr. 1 ml sample is collected and replaced with fresh buffer solution. Collected samples are analyzed by using suitable analytical method.[34]

11. Determination of Skin Permeation: The chemical and structural changes in epidermal layer are studied by using differential scanning calorimetry (DSC). To assess the mechanism of permeation, thermal transitions in desiccated SC membranes of rats is investigated by using of DSC technique. Both treated and untreated skin samples were previously hydrated on 27% Sodium-Br solution for at least 48 Hrs. to ensure lowering hydration to 20%. The skin samples are stored at silica gel, for 3 days in desiccators prior to analysis. The skin layer is cut into pieces and 4 mg weighted pieces is sealed in 10µL aluminium pans and placed in the differential scanning calorimetry unit along with empty pan as a reference. Flow of Nitrogen is adjusted to 20ml/ min which is served as purge gas. Samples are heated continuously at 10°C/min rate for the range of 30-400°C and fluctuation in DSC Graph is noted and studied.[35]

CONCLUSION

Emulgel is a modern tool for topical delivery of hydrophobic drugs with advantages of emulsion and gel to improve patient acceptability. Emulgel helps in enhancing spread ability, adhesion, viscosity, and extrusion. It is used both pharmaceutical and cosmetical applications as well as it allow to incorporate herbal formulations.

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