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A REVIEW ON NEW APPROACH FOR ENHANCED TOPICAL DRUG DELIVERYOF HYDROPHOBIC DRUGS: EMULGEL

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ABSTRACT

In comparison with the other semisolid preparations, the use of gels has been emerged both in cosmetics and pharmaceutical preparations. When gel and emulsion used in the combined form, they are referred as Emulgel. Emulgel is the promising drug delivery system for the delivery of hydrophobic drugs. Emulgel is an emulsion which is gelled by mixing it with gelling agents. Emulgel is used to treat aches and pains caused by colds, headaches, muscle aches, backaches, arthritis and other conditions and injuries. Many advantages of gels have the major limitation of delivery of hydrophobic drugs. Hence, to overcome this limitation, the emulsion based approach is being used. Emulgel is an interesting topical drug delivery system as it has dual release control system, i.e., gel and emulsion. Emulgels have several favorable properties for dermatological use such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, transparent, and pleasing appearance. Hence, emulgels can be used as better topical drug delivery system over present systems. This review gives knowledge about emulgel including its properties, advantages, and formulation considerations and its recent advances in the research field.

KEYWORDS: Emulgel, Topical drug delivery, Skin diseases, emulsifiers, emulsion-based gel, hydrophobic drugs.

INTRODUCTION

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat the cutaneous disorder. The topical drug delivery system is generally used where other routes (such as oral, sublingual, rectal, and parental) of drug administration

fails or in local skin infection like fungal infection.[1] Topical drug delivery is an attractive route for local and systemic treatment. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment.[2] The main advantage of the topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and the varied conditions of absorption, such as pH changes, the presence of enzymes, and gastric emptying time are another advantage of the topical drug delivery system.[3] Topical drug administration is simplest and easiest route of localised drug delivery anywhere in the body by routes as ophthalmic, rectal, vaginal and skin. These are applied as a wide spectrum of preparations in case of both cosmetic and dermatological, to the healthy or diseased skin.[4] The formulations are available in different forms like from solid through semisolid to liquid. Drugs are administered topically for their action at the site of application or for systemic effects. Drug absorption is enhanced through the skin if the drug substance is in solution, if it has a favorable lipid/water partition coefficient and if it is a non-electrolyte.

Skin is one of the most readily accessible parts of human body for topical administration and molecules penetrate in the skin mainly by three routes: through intact stratum corneum, through sweat ducts, and through the sebaceous follicle. The topical drug delivery system such as emulgel (gellified emulsion) generally used where the other systems of drug administration fail to directly treat cutaneous disorders such as fungal infections, acne, psoriasis etc.[5] Since the mid-1980's, emulsion gels have been of growing importance in the field of pharmaceutical semisolid dosage forms. In spite, so advantageous gels show a major limitation in the delivery of hydrophobic drugs. Hence, to cover up this lacking, emulgel is prepared and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel.[6] As the name suggest, they are the combination of gel and emulsion. Both oil-in-water and water-in-oil type of emulsion are used as a vehicle to deliver various drugs to the skin. They also have a high ability to penetrate the skin. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption. Passage through this outer most 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).[7]

Advantages[8,9]

1. Avoidance of first pass metabolism.
2. Avoidance of gastrointestinal incompatibility.
3. More selective to a specific site.
4. Improve patient compliance.
5. Suitability 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 loading capacity
11. Better stability
12. Production feasibility and low preparation cost
13. Controlled release
14. No intensive sonication.

Disadvantages

1. Skin irritation on contact dermatitis.
2. The possibility 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 formation 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 has expanded both in cosmetics and in a pharmaceutical preparation. A gel is a 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 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 deliver through gels.[10]

Numbers of medicated products are applied to the skin or mucous membrane that either enhances or restores a fundamental function of skin or pharmacologically alters an action in the underlined tissues. Such products are referred as topical or dermatological products. Many widely used topical agents like ointments, creams lotions have many disadvantages. They are sticky in nature causing uneasiness to the patient when applied, have lesser spreading coefficient so applied by rubbing and they also exhibit the problem of stability. 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. In spite of many advantages of gels, a major limitation is in the delivery of hydrophobic drugs.

Factors affecting topical absorption of drug[11,12]

Physiological factors

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

Physicochemical factors

1. Partition coefficient.
2. The molecular weight (<400 Dalton).
3. The degree of ionisation (only unionised drugs gets absorbed well).
4. Effect of vehicles.

Physiology of Skin[13,14]: Most of the topical preparations are meant to be applied to the skin. Hence, 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 $2m^2$ 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 centimeter of the skin. The pH of the skin varies from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of the skin surface. The skin can be considered to have four distinct layers of tissue [Figure 1].

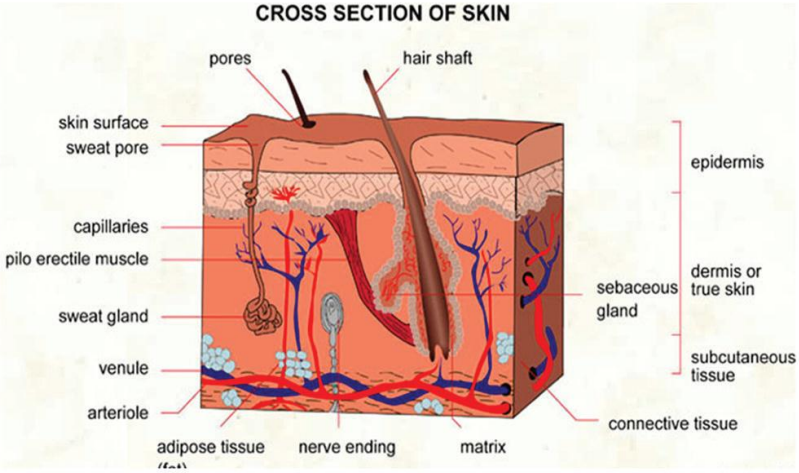

Fig. 1: Physiology of skin.

Non-viable epidermis: Stratum corneum is the outermost layer of skin, which is the actual physical barrier to the most substance that comes in contact with the skin. The stratum corneum is 10–20 cell layers thick over most of the body. Each cell is a flat, plate-like structure - 34–44 µm long, 25–36 µm wide, and 0.5–0.20 µm thick with a surface area of 750–1200 µm stocked up to each other in brick-like fashion. Stratum corneum consists of lipid (5–15%) including phospholipids, glycosphingolipid, cholesterol sulfate, and a neutral lipid, protein (75–85%) which is mainly keratin.

Viable epidermis

This layer of the skin resides between the stratum corneum and dermis and has a thickness ranging from 50 to 100 µm. The structures of the cells in the viable epidermis are physicochemically 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: Just beneath the viable epidermis is the dermis. It is structural fibrin, and very few cells are like it can be found histological in normal tissue. Dermis thickness ranges from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance.

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.

Drug Delivery Across the Skin[15, 16]

The epidermis is the most superficial layer of the skin and is composed of stratified keratinized squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibers. 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 are 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 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 through 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.

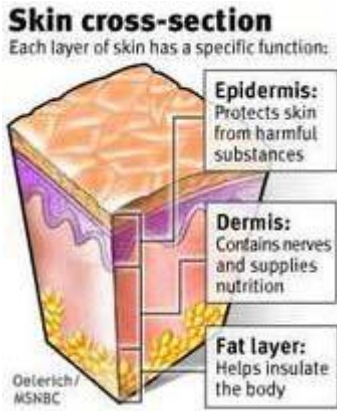

Fig. 2: Drug delivery cross of section.

Factors to Consider When Choosing A Topical Preparation[17,18]

1. Irritation or sensitization potential. In general, 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.

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. Effect of the vehicle, for example, an occlusive vehicle enhanced penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient, or protective action.

Classification of Topical Drug Delivery: The delivery of drugs into and through the skin has been an important area of research for many years. Historically, topical pharmaceuticals were developed by incorporating new drug compound into the vehicles such as hydrophilic petrolatum. In last two decades there is radical change in the manner in which dermatological are formulated, developed and tested. Topical drug delivery means drug administration via the skin for local therapeutic effect on diseased skin. Topical preparations are applied to skin for surface, local, or systemic effects. They may be used for prophylaxis (e.g. sunscreens, astringents, etc.) or for treatment (e.g. inflammation, bacterial infection, viral infection, etc.). The primary goal of topical products is to increase the retention of drugs in the skin rather than penetration through the skin. It differs from the transdermal drug delivery as transdermal products are designed to deliver the drugs through the skin to achieve systemic effects; hence here skin is not the target site. The topical drug products are designed to deliver the drugs into the skin for treating various dermal disorders, and here skin is the target organ. It differs from the transdermal drug delivery as transdermal products are designed to deliver the drugs through the skin to achieve systemic effects; hence here skin is not the target site. The topical drug products are designed to deliver the drugs into the skin for treating various dermal disorders, and here skin is the target organ. But penetration of drugs through the stratum corneum is essential for both types of deliveries, and hence the rate limiting step in percutaneous absorption i.e. permeation through stratum corneum is common for both topical as well as transdermal drug products. Although some medication from topical products may unintentionally reach the systemic circulation, it is usually in sub-therapeutic concentrations, and hence does not produce side effects of any major concern.[19]

Formulation of Emulgel

Vehicle[20]

The vehicle has following properties:

• Efficiently deposit the drug on the skin with even distribution.

• Release the drug so it can migrate freely to the site of action.

• Deliver the drug to the target site.

• Sustain a therapeutic drug level in the target tissue for a sufficient duration to provide a pharmacologic effect.

• Appropriately formulated for the anatomic site to be treated.

• Cosmetically acceptable to the patient.

• Due to the efficiency of the epidermal barrier, the amount of topical drug that gets through the stratum corneum is generally low. Rate and extent of absorption vary depending on characteristics of the vehicle but is also influenced by the active agent itself.

Aqueous material[21]

This forms the aqueous phase of the emulsion. The commonly used agents are water and alcohols.

Oils[22]

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 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.

Emulsifiers[23]**:** 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, for example, polyethylene glycol 40 stearate, Sorbitan mono-oleate (Span 80), polyoxyethylene sorbitan monooleate (Tween 80), stearic acid, and sodium stearate.

Gelling agents[24,25]**:** These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.

Penetration enhancers[26]**:** To promote absorption of drugs, vehicles often include penetration enhancing ingredients that temporarily disrupt the skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into the skin.

Properties of penetration enhancers

• They should be non-toxic, non-irritating, and non- allergenic.

• They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.

• They should have no pharmacological activity within the body, i.e., should not bind to receptor sites.

• The penetration enhancers should work unidirectional, i.e., should allow therapeutic agents into the body while preventing the loss of endogenous material from the body.

• The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.

• They should be cosmetically acceptable with an appropriate skin "feel."

Mechanism of penetration enhancers[3,27]

Penetration enhancers may act by one or more of three main mechanisms:

1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, co enhancer, or solvent into the stratum corneum.

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.

Emulgel Preparation[28]

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 minor modification method. The gel in formulations was 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 is adjusted to 6 to 6.5 using triethanolamine. The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by

dissolving Tween 20 in purified water. Methyl and propylparaben were dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70°–80°C; then the oily phase was 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 [Figure 3].

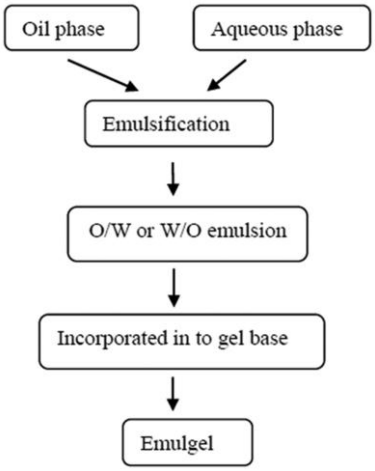

Figure. 3: Flowchart of emulgel formulation.

Evaluation of emulgel[29-31]

Fourier transforms infrared spectroscopy (FTIR)

The primary objective of this investigation was to identify a stable storage condition for the drug in solid state and identification of compatible excipients for formulation.

Physical examination

The Prepared emulgel formulations were inspected visually for their colour, homogeneity, consistency and phase separation.

Determination of pH

pH of the formulation was determined by using digital pH meter. pH meter electrode was washed by distilled water and then dipped into the formulation to measure pH and this process was repeated 3 times.

Measurement of viscosity

The viscosity of the formulated batches was determined using a Brookfield Viscometer with spindle 63. The formulation whose viscosity was to be determined was added to the beaker

and was allowed to settle down for 30 min at the assay temperature (25±1 °C) before the measurement was taken. Spindle was lowered perpendicularly into the centre of emulgel taking care that spindle does not touch the bottom of the jar and rotated at a speed of 50 rpm for 10 min. The viscosity reading was noted.

Spreadability

To determine spreadability of the gel formulations, two glass slides of standard dimensions were selected. Formulation whose spreadability was to be determined was placed over one slide and the other slide was placed over its top such that the gel is sandwiched between the two slides. The slides were pressed upon each other so as to displace any air present and the adhering gel was wiped off. The two slides were placed onto a stand such that only the lower slide is held firm by the opposite fangs of the clamp allowing the upper slide to slip off freely by the force of weight tied to it. 20 g weight was tied to the upper slide carefully. The time taken by the upper slide to completely detach from the lower slide was noted.

Globule size and its distribution in emulgel

Globule size and distribution is determined by Malvern zeta sizer. A 1.0 g sample is dissolved in purified water and agitated to get homogeneous dispersion. The sample was injected to photocell of zeta sizer. Mean globule diameter and distribution is obtained.

Swelling index

To determine the swelling index of prepared topical emulgel, 1 g 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 were removed from beakers at different time intervals and put it on a dry place for some time after it reweighed.

***In vitro* drug release study**

The *in vitro* drug release studies of the Emulgel were carried out on Diffusion cell using egg membrane. This was clamped carefully to one end of the hollow glass tube of dial y sis cell. Emulgel (1g) was applied onto the surface of egg membrane dialysis membrane. The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution to solubilize the drug. The receptor chamber was stirred by a magnetic stirrer. The samples (1 ml aliquots) were collected at suitable time interval sample were analyzed for drug content by UV-visible spectrophotometer after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug released at each time interval. The cumulative amount of drug

release across the egg membrane was determined as a function of time. The cumulative % drug release was calculated using standard calibration curve.

Microbiological assay

Ditch plate technique was used. It is a technique used for evaluation of bacteriostatic or fungi static activity of a compound. It is mainly applied for semisolid formulations. Previously prepared Sabouraud's agar dried plates were used. Three grammes of the Gellified emulsion are placed in a ditch cut in the plate. Freshly prepared culture loops are streaked across the agar at a right angle from the ditch to the edge of the plate.

Skin irritation test

A 0.5 g sample of the test article was then 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 was applied on the skin of a rabbit. Animals were returned to their cages. After a 24 h exposure, the Gellified emulsion is removed. The test sites were wiped with tap water to remove any remaining test article residue.[32]

Syneresis measurement test[33]

On rest gel shrinks and little liquid are pressed out called syneresis. This could be measured by means of centrifuge tubes in specific apparatus.

Syneresis (%) = Liquid separated from Emulgel/Total weight of Emulgel before centrifugation × 100

Stability studies

The prepared emulgels were packed in aluminium 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 mo. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles.[34]

Future Prospective

Hydrophobic behavior of drugs is one of the most common problems faced during formulation, as given in Table 8 and development of any new formulation. This behavior is responsible for poor water solubility and bioavailability of drugs. Many numbers of drugs are hydrophobic in nature. Their delivery to the biological system has been challenging. For topical delivery of drugs different delivery systems such as ointments, lotion, creams, and

pastes are applied. These topical formulations generally include large number of oleaginous bases such as petrolatum, beeswax, or vegetable oils those themselves are hydrophobic in nature that does not allow the inclusion of water or aqueous phase. It makes them an excellent emollient but retards the release of drugs and makes the product thick and greasy.

Whereas gel provides an aqueous environment to the drug, favors its dissolution and provides quicker release of drug as compared to other topical delivery systems. Emulsion-based gel provides a suitable medium for delivery of such hydrophobic drugs where such drugs can be incorporated into its oily phase and delivered to the skin. All such advantages of emulgel over other topical delivery systems make them more efficient and productive. In future, these properties will be used to deliver more number of topical drugs in the form of emulgel.

CONCLUSION

The topical drug delivery system will be used extensively due to 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. To concluded that emulgels have proven as most convenient, better, and effective delivery system. Due to its non-greasy, gel-like property, it provides and lacks of oily bases, and it provides better release of drugs as compared to other topical drug delivery system. Incorporation of emulsion into gel makes it a dual control release system further problem such as phase separation, creaming associated with emulsion gets resolved, and its stability improves. Emulgel loaded with specific drugs has been found effective in some topical disorders, and it is emerging as potential drug delivery system in the area of dermatology. In future, emulgel will provide a solution for topical delivery of hydrophobic drugs.

REFERENCES

1. Kullar R, Saini S, Steth N, Rana AC. Emulgel a surrogate approach for topical used hydrophobic drugs. Int J Pharm Biol Sci., 2011; 1: 117-28.
2. Single V, Saini S, Joshi B, Rana AC. Emulgel: a new platform for topical drug delivery. Int J Pharm Biol Sci., 2012; 3: 485-98.
3. Stan-Posthuma JJ, Vink J, Le Cessie S, Bruijn JA, Bergman W, Pavel S. Topical tretinoin under occlusion on a typical navei. Asian J Pharm Clin Res., 1998; 8: 539-48.
4. Mohamed MI. Optimization of chlorphenesin emugel formulation. AAPS J., 2004; 6: 81-7.

5. Mishra AN. Controlled and novel drug delivery. 4th ed. CS Publisher and Distributers, Delhi, 1997; 107-9.
6. Swarbrick J. Encyclopedia of pharmaceutical technology. 3rd ed. Vol. 1. Informa Healthcare, 2007; 1311-23.
7. Cecv G, Mazgareanu S, Rother M. Preclinical characterisation of NSAIDs in ultra deformable carriers or conventional topical gels. Int J Pharm, 2008; 360: 29-39.
8. Kalia YN, Guy RH. Modeling transdermal drug release. Adv Drug Delivery Rev., 2001; 48: 159-72.
9. Ayub AC, Gomes AD, Lima MV, Vianna-Soares CD, Ferreira LA. Topical delivery of fluconazole: in vitro skin penetration and permeation using emulsions as dosage forms. Drug Dev Ind Pharm, 2007; 33: 273-80.
10. Tortora GJ, Derrickson B. Principles of anatomy and physiology. 11th ed. John Wiley and Sons, 2007; 144-70.
11. Ranade VV, Hollinger MA. Drug delivery system. 2nd ed. CRC Press; 2010. p. 207-27.
12. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal drug delivery system: a review. Asian J Pharm Clin Res., 2009; 2: 14-20.
13. Subramanian N, Ghosal SK, Moulik SP. Enhanced in in vitro percutaneous absorption and in vivo anti-inflammatory effect of a selective cyclooxygenase inhibitor using microemulsion. Drug Dev Ind Pharm, 2005; 31: 405-16.
14. Elias PM, Menon GK. Structural and lipid biochemical correlates of the epidermal permeability barrier. Adv Lipid Res., 1991; 24: 1-26.
15. Butler H. Poucher's perfumes cosmetics and soaps. 10th ed. Springer, India; 2010. p. 402.
16. Bruton L, Keith P, Blumenthal D, Buxton L. Goodman and Gillman's manual of pharmacology and therapeutics. 2nd ed. Mc Graw's Hill, 2008; 1086-94.
17. Lachman L, Lieberman HA. The Theory and Practice of Industrial Pharmacy. 3rd ed. Varghese Publishing house, 1990; 534.
18. Vyas SP, Khar RK. Controlled drug delivery. 1st ed. Vallabh Prakashan, 2002; 416-7.
19. Bonacucina G, Cespi M, Palmieri GF. Characterization and stability of emulsion gels based on acrylamide/sodium acryloyldimethyltaurate copolymer. AAPS Pharm Sci Tech, 2009; 10: 368-75.
20. Benson HA. Transdermal drug delivery: penetration enhancement techniques. Curr Drug Delivery, 2005; 2: 23-33.
21. Rutter N. Drug absorption through the skin: a mixed blessing. Arch Dis Child, 1987; 62: 220-1.

22. Zhang X, Zhao R, Qian W. Preparation of an emulgel for the treatment of aphthous ulcer on the basis of carbomers. Chin Pharm J., 1995; 30: 417-8.
23. Swarbrick J. Encyclopedia of Pharmaceutical Technology. 3rd ed., 2006; 1551.
24. Gibson M. Pharmaceutical Preformulation and Formulation, Interpharm; 2004.
25. Mortazavi SA, Aboofazeli R. An investigation into the effect of various penetration enhancers on percutaneous absorption of piroxicam. Iranian J Pharm Res., 2003; 2: 135-40.
26. Kumar L, Verma R. In vitro evaluation of topical gel prepared using natural polymer. Int J Drug Delivery, 2010; 2: 58-63.
27. Jacob SW, Francone CA. Structure and function of man. WB Saunders Co. Philadelphia, 1970; 55-60.
28. Williams AC, Barry BW. Terpenes and the lipid-protein partitioning theory of skin penetration enhancement. Pharm Res., 1997; 8: 17-24.
29. Sundari P, Mullapudi D, Srinivas P. Formulation and Evaluation of Anti-Arthritic Poly Herbal Emulgel. International Journal of Pharmaceutical Technology, 2014; 6(2): 6608-6621.
30. Shaheda S, Devi S, Nirmala J. Formulation and evaluation of herbal emulgel of Lantana camara leaves extract for wound healing activity in diabetic rats. Indo Am J Pharm Res., 2016; 6: 6404-17.
31. Kusuma R, Rao S. Formulation, development and evaluation of indomethacin emulgel using pregelatinized starch from Ipomoea batata Tubers. Asian J Pharm, 2015; 9: 43-50.
32. Bhura R, Bhagat K. Formulation and evaluation of topical nano emulgel of adapalene. World J Pharm Pharm Sci., 2015; 3: 1013-24.
33. Sawant A, Mohite S. Formulation and evaluation of itraconazole emulgel for topical drug delivery. Asian J Pharmacol Toxicol, 2015; 5: 91-6.
34. Ambala R, Vemula S. Formulation and characterization of ketoprofen emulgels. J Appl Pharm Sci., 2015; 5: 112-7.
35. Mulye S, Wadkar K, Kondawar M. Formulation development and evaluation of indomethacin emulgel. Pelagia Res Der Pharm Sin, 2013; 4: 31-45.