CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2586072

Available online at: http://www.iajps.com *Review Article*

MICROEMULGEL AS A NOVEL APPROACH FOR ENHANCING TOPICAL DRUG DELIVERY: A REVIEW

Akashdeep R. Udmale*, Pranav N. Jain, Mukeshkumar V. Choudhary
St. John institute of Pharmacy and Research, Palghar. 401404, Tal- Palghar, Dist- Palghar, Diploma in Pharmacy

Abstract:
Topical drug delivery is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal & skin as topical routes. These are apply a wide range of preparations for both cosmetic and dermatological to their healthy or diseased skin Microemulgel have emerged as one of the most intresting topical delivery system as it is a dual control release system i.e gel & emulsion. Both hydrophilic & hydrophobic types of drugs are incorporated into dosage forms. The major objective behind this formulation is delivery of hydrophobic drugs to systemic circulation via skin. Topical drug delivery has the main advantage of direct delivery of the drug to the target tissue i.e. skin & mucous membranes, by passing the first pass effect. Microemulgel with its micron sized globule has better penetration & with gelling property exhibit control drug release. The Microemulgel for dermatological & Cosmetic use have different favorable properties such as being thixotropic, easily spreadable, Non staining, emollient, bio-friendly, clear, transparent & elegant appearance, & these Microemulgel based formulations enhances the skin deposition of API , thereby ultimately enhancing its therapeutic activity.

Keywords: *Microemulgel, Topical drug delivery, hydrophobic drugs.*

Corresponding author:
Akashdeep R. Udmale
St. John College of Pharmacy & Research, Palghar, 401404
Maharashtra, India.
Department of Pharmaceutics (P.G)
Email: akashdeepudmale@gmail.com

QR code

Please cite this article in press Akashdeep R. Udmale et al., ***Microemulgel As A Novel Approach For Enhancing Topical Drug Delivery: A Review.,*** *Indo Am. J. P. Sci, 2019; 06(02).*

INTRODUCTION:

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. The main advantage of topical delivery system is that it has ability to deliver drugs more selectively to a specific site (local action). It provides utilization of drugs with short biological half life, narrow therapeutic window to increase the duration of action. [1] Micro emulsion based Gel formulation provides better application property and stability & makes it dual control release system in comparison to cream and ointment. Topical Microemulsion based gel drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation, Microemulsion based approach is being used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. Whenever, it is used for fungal disease for topical delivery system so it is good for compare to oral delivery. When gels and Micro emulsions are used in combined form the dosage form are referred as Microemulsion based gel. Skin is one of the most extensive and readily accessible organs on human body for topical administration and is main route of topical drug delivery system [2]

Introduction to Topical Drug Delivery System

Topical delivery administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal, and skin as topical routes. Efforts to cure diseases have been leading in the discovery of various drugs; Topical delivery administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal, and skin as topical routes. Efforts to cure diseases have been leading in the discovery of various drugs, medicine and delivery systems. Route of administration depends on type and severity of disease. For skin disorders topical route is most preferred. Topical drug delivery system can be defined as direct application of formulation containing medication to the skin to get localized effect of drug. Topical drug delivery system has several advantageous such as ability to deliver drug more selectivity to specific site. Most and favorable reason for using topical delivery is avoidance of gastro-intestinal incompatibility and metabolic degradation associate with oral administration. Moreover, topical delivery provides an increased bio-availability by avoiding first pass metabolism by liver and a consistent delivery for extended period release rates of drugs from topical preparation depend directly on the physiochemical properties of the carrier and the drug employed. [3] For topical delivery semisolid preparation are widely accepted over solid and liquid dosage forms. Microemulsions, which are optically isotropic and thermodynamically stable systems of water, oil, surfactant, and co-surfactant, can be used as drug delivery system because of their capacity to solubilise poorly water-soluble drugs as well as their enhancement of topical. For topical delivery micro emulsion is incorporated in to gel base to prolong the local contact to the skin. [4]

Anatomy and Physiology of Skin

The skin of average adult body covers surface area approximately 2 m2 and receive about one third of blood circulating through body. An average human skin surface is mainly contains forty to seventy hair follicles and two to three hundreds of sweat ducts per square meter of skin. The pH of skin varies from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of skin. The skin consists of four distinct layers of tissues, namely, nonviable epidermis, viable epidermis, viable dermis and subcutaneous connective tissues shows in figure 1. [5-7]

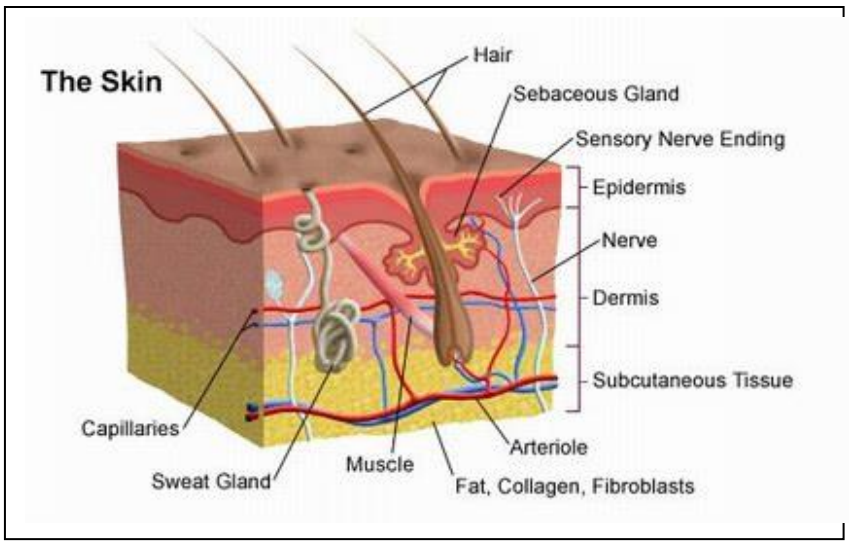

Fig No 01: Anatomy and Physiology of skin

Drug Delivery across the Skin

There are two important layers in the skin: the epidermis and dermis. Blood vessels are distributed profusely beneath the skin in the subcutaneous layer. There are three primary mechanisms for drug absorption through the skin: intercellular, Trans cellular and follicular. The next most common route of delivery is through the pilosebaceous route permeation tends to occur through the intercellular matrix, but through the transcellular pathway, it has been shown to provide a faster alternative route of highly polar molecules. In normal intact skin, it has been established that the keratinized corneocytes and the largely non-polar lipid intercellular cement of the horny layer are the major factors involved in the maintenance of efficient barrier for drugs [8]. The drug penetration for skin can be enhanced by using organic solvents such as propylene glycol, surfactants and DMSO. The permeation enhancers are altered the barrier properties of the stratum corneum by types of a mechanism including enhancing solubility, partitioning the stratum corneum, fluidising the crystalline structure of the stratum corneum [9]. Creams and gels that are rubbed onto the skin have been used for years for effective treatment against infections and pain by medication. New technologies now allow other drugs to be absorbed through the skin. These can be used to treat not just the affected areas of the skin but the whole body by systemic route [10].

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG [11, 12]:

There are different factor that affect absorption of drug

A. Physiological Factors

1. Thickness of skin
2. Skin pH
3. Blood flow
4. Inflammation of Skin
5. Hydration of Skin
6. Density of Hair follicle
7. Density of Sweat gland
8. Lipid Content.

B. Physiochemical Factors

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

Introduction to Microemulgel

Microemulsion was first introduced by hoar and schulman in 1943. Microemulsion based gel has been increased interest during recent years in the use of topical vehicle systems that could modify drug permeation through the skin. One of the most promising techniques for enhancement of transdermal permeation of drugs is microemulsion. Microemulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and co-surfactant molecules having a droplet size of less than 100nm. Microemulsions have improved transdermal permeation of many drugs over the conventional topical formulations such as emulsions and gels. Delivery of drugs using these microemulsions through skin increases the

local/systemic delivery of the drug by different mechanisms that make them suitable vehicles for the delivery of antifungal. [13]

Rationale of Microemulgel 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 immobilised by surface tension between it and a macromolecular network of fibres 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.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. [14]

FORMULATION OF MICROEMULGEL:

1. Vehicles: The vehicle is a basic association between medicine power and accommodating suitability. Two components are of essential importance in selecting the dermatological vehicle. They are: Solubilizing the medicine in the vehicle and boosting advancement of pharmaceutical from vehicle to stratum Corneum. [15]

Vehicles are of two types [16]

a. Aqueous solvents: These structure watery periods of the emulsion. Water and alcohols are generally utilized.

b. Oils: These structure slick period of the emulsion. Comprehensively used oils are non - biodegradable mineral and castor oils, fish liver oils, changed oils of vegetable starting, for instance, arachis, cotton seed and maize oils.

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, Sorbitan mono-oleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80),Stearic acid, Sodium stearate.

d. Gelling Agents: These are the agents used to increase the consistency of any dosage form can also be used as thickening agent given in table 2.

Constructions of Pseudo Ternary Phase Diagram Pseudoternary phase diagrams are constructed to obtain the concentration range of oil, surfactant, co surfactant, and water for microemulsion to enhance its permeability through the skin. Phase behaviour studies are essential for the study of surfactant systems and are performed by constructing phase diagrams that provide information on the boundaries of the different phases as a function of composition variables and temperatures, and, more important structural organization can also be inferred. One approach to characterize these multicomponent systems is by means of pseudo ternary diagrams that combine more than one component in the vertices of the ternary diagram. Surfactant and co surfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in free energy required for the micro emulsion formation consequently improves the thermodynamic stability of the micro emulsion formulation. Therefore, the selection of oil and surfactant, and the mixing ratio of oil to surfactant/ co surfactant play an important role in the formation of microemulsions.33 Pseudo-ternary phase diagrams were constructed by employing aqueous titration method in order to get concentration range of components of microemulsion. The ratio of surfactant to co surfactant (Smix) is altered at 3:1, 2:1, 1:1, 1:2, 1:3, 3:2. For the construction of pseudo-ternary phase diagram at each Smix ratio, the oily mixtures containing oil, surfactant and co surfactant are prepared with volume ratio of oil to Smix at 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 respectively. Double distilled water is added drop by drop to the oil and Smix mixture under magnetic stirring at ambient temperature. Transparent and clear micro emulsion is taken as the end point of aqueous titration method. The concentrations of components are then calculated in order to plot the pseudo-ternary phase diagram. [17, 18, 19]

METHOD OF PREPARATION:

There are various methods of formulation of Emulgel, employing different kinds of ingredient.

- Chemical enhancement
- Physical enhancement.
- Biochemical enhancement
- Super saturation enhancement

Research work (optimization of chlorphenesin in Emulgel) includes formation of emulsion (o/w or w/o), followed by addition of gelling agent to form Emulgel. Here first step involves formation of aqueous phase of emulsion. Aqueous phase of emulsion is prepared by first dissolving tween 20 in purified water, then solution of propylene glycol is prepared by dissolving methyl paraben and propyl paraben in propylene glycol and then both the solutions are mixed and set aside. Oily phase of emulsion is prepared by dissolving span 20 in light liquid paraffin. Formation of emulsion involves separate heating of oily and aqueous phase to 70–80 °C then both the phases are mixed with constant stirring until cooled to room temperature. Gel phase of Emulgel is prepared by dispersing HPMC or Carbopol in water. HPMC is required to soak overnight in water, while Carbopol gel is prepared by simply dispersing it in purified water. When both the components both emulsions & gel get ready then the Emulgel is prepared by mixing emulsion with gel in 1:1 ratio with gentle stirring. [20]

Research work based on design & characterization of Emulgel for buccal administration. Here formulation of Emulgel involves three steps

STEP1: Polymer dispersion in water

STEP 2: Neutralization of the polymeric aqueous dispersion and,

STEP 3 : Emulsification of the oil phase.

With respect to the first step, three different TR-1 percentages, namely 0.3, 0.4 and 0.5%, w/v, are required. First step involves suspension of polymer in deionized water with continuous stirring at 900 rpm for 20 min at room temperature using a mechanical stirrer equipped with a three blade helical impellers & then slurry is neutralized with NaOH solution (18%w/v) to final pH value of 5.5, 6.0 and 6.5. The neutralization process causes the distension of polymer chains resulting in clear stable gels. Now for the complete hydration of polymer gels are required to be stored at 4 0C for 24 h before the addition of oil phase. After completing the hydration of gel different quantities of oil phase at three o/w ratio (w/w) 0.5, 1.0 and 1.5 respectively are added with stirring at 800 rpm (80 °C) there after it is left for cooling and its pH is measured [21].

Research work based on different methods to develop Emulgel for clotrimazole delivery. This method involves the preparation of oily phase of emulsion by dissolving drug and span 60 in oily phase (jojoba oil) with the aid of magnetic stirrer at 75 0C with subsequent cooling followed by addition of carbopol to the oily phase. Secondly aqueous phase is prepared by dissolving Brij-35 in propylene glycol. Third step involves addition of oily phase to the aqueous phase following their emulsification using the over head mixer for 10 min at 1400 rpm, and then introducing emulsion into the homogenizer for 5 min at 10,000 rpm. Gellification of emulsion involves addition of gelling agent triethanolamine (formulae containing Carbopol either alone or in combination) and/or HPMC to the emulsion using over head mixer at 200 rpm for 45 min thereby adjusting the pH of formulation containing Carbopol to 5.5–6.5 using TEA [22] .The flow chart of emulgel preparation is as follows.

Steps Involved In Preparation of the Emulgel

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.

EVALUATION OF MICROEMULSION [22, 23]:

1. Droplet Size Measurements

Size analysis of microemulsion is carried out by dynamic light scattering with zetasizer (Malvern instruments ltd., Malvern, U.K). Polydispersity index of the formulation was determined by the same instrument.

2. Zeta potential measurements

This is used to identify the change of the droplets. In conventional emulsions, the charge on an oil droplet is negative due to presence of free fatty acids. Zeta potential for microemulsion is determined using zetasizer (Malvern instrument ltd. UK).

3. Conductivity measurement

The measurement of electrical conductivity gives the quantitative idea of the solubilization of water phase in the selected mature containing oil phase, surfactant and co-surfactant. It also gives the idea about the types of microemulsion. The oil, surfactant, and co-surfactant concentration is selected as per optimized formulation. Then the water phase is added drop wise to the mixture of the oil and amphiphiles and electrical conductivity of formulated is measured using a conductometer at ambient temperature

4. Transmission Electron Microscopy (TEM)

Oil globules of microemulsion were visualized using TEM, Philips Technai-20 electron microscope (Philips, Holland) with an accelerated voltage of 20-200 kv. The samples were negatively stained with a 1% aqueous solution of phosphotungestic acid (PTA). Microemulsion was dried on a carbon coated

copper grid. After drying, the samples were viewed under microscope 80 kv.

EVALUATION OF MICROEMULSION BASED GEL. [24-25]:

1. Physical appearance

The prepared gellified microemulsion formulations were inspected for their color, homogeneity, consistency and pH. The pH value of 1% aqueous solutions of the prepared Gellified microemulsion is measured by a pH meter.

2. Spreadability measurement

To determine the spreadability of microemulsion based gel, 0.5 g of gel was placed within a circle of 1 cm diameter pre-marked on a glass plate, over which a second glass plate was placed. A weight of 500g was allowed to rest on the upper glass plate for 5min. The increase in the diameter due to gel spreading was noted.

3. Rheological study

The viscosity of microemulsion based gel formulation was determined at 370C using a brook field viscometer (Brookfield DV-E viscometer). 62 number spindles were set at 12 rpm.

4. Drug content determination

Take 1gm microemulsion based gel. 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.

5. Extrudability (Tube test)

It is usual empirical test to measure the force required to extrude the material from tube. The method adopted for evaluating microemulsion based gel formulation for extrudability. And it is based upon the quantity in percentage of gel and gel extruded from aluminium collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of microemulsion based gel in 10 seconds. More quantity extruded better is extrudability. The extrudability is than calculated by using the following formula.

$$\textbf{Extrudability} = \frac{(\textit{Applied Weight to Extrude Microemulsion Gel From in Tube (Gm)})}{(\textit{Area (cm2)})}$$

6. In vitro release study/ permeation studies

Franz diffusion cell (with effective diffusion area 3.14 cm2 and 15.5 ml cell volume) was used for the drug release studies. Microemulsion based gel (1g) was applied onto the surface of cellophane membrane evenly. The cellophane membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution. The samples collected at suitable time interval. Samples were analyzed for drug content by UV spectrophotometer at suitable wavelength after appropriate dilutions. The cumulative amount of drug released across the mice shaven skin was determined as a function of time.

7. Antifungal activity

Antifungal activity of formulation is checked by cup-plate method. A definite volume of the Candidia Albicans suspension (inoculum) was poured into the sterilized sabouraud dextrose agar media (cooled at 400C) and mixed thoroughly. About 20 ml of this suspension was poured aseptically in the Petri plates and kept till the solidification. The surface of agar plates was pierced using a sterile cork borer. The prepared wells were filled with equal volume of drug containing microemulsion based gel, microemulsion based gel without drug. After incubation for 18 to 24 hours at 250C, the fungal growth was observed and the zone of inhibition was measured using antifungal zone reader.

8. Ex-vivo Bioadhesive strength measurement

The modified method used for the measurement of bioadhesive strength. The fresh skin is cut into pieces and washed with 0.1N 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. 1gm of topical microemulsion gel 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 pressure of air. The balance is kept in this position for 5 minutes. Weight is added slowly at 200mg/min to the left-hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the microemulsion gel from the skin surface gave the measure of bioadhesive strength. The bioadhesive strength is calculated by using following formula.

$$\textbf{Bioadhesive strength} = \frac{(\textbf{Weight required (gm)})}{\textbf{Area (cm2)}}$$

9. Stability studies

The prepared microemulsion based gel were packed in aluminium collapsible tubes (5gm) and subjected to stability studies at 50C, 250C/60% RH, 300C/65% RH, and 400C/75% RH for a period of 3months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles.

REFERENCES:

1. Mitchel J. Transdermal drug delivery. Americal academy of dermatology- 58 th Annual Meeting, San Francisco, CA, 2000.
2. RR Patel, KR Patel, MR Patel, Formulation and Characterization of Microemulsion based Gel of Antifungal Drug, PharmaTutor, 2014, 2(2), 79-89.
3. Joshi B et al; "Emulgel: A Comprehensive Review on the Recent Advances in Topical Drug Delivery." International Research Journal of Pharmacy. 2011, 2(11), 66-70.
4. Sevgi G, Sedef Erdal M, Buket A; "New Formulation Stratagies in Topical Antifungal Therapy." Journal of Cosmetics, Dermatological Sciences and Application. 2013, 3, 56-65.
5. Kanikkannan N, Kandimalla K, Lamba SS, Singh M. Structure activity relationship of chemical penetration enhancers in transdermal drug delivery. Curr Med Chem 1999; 7: 593-608.
6. Singh PB, Choudhury PK. Penetration enhancers for transfer drug delivery of systemic agents. J Pharm Res 2007; 6: 44-50.
7. US National Institute of Health. Anatomy of the skin. Bethesda: US National Institute of Health. [Online] Available from: http:// training.seer.cancer.gov /images/melanoma/skin.jpg.
8. Elias PM, Menon GK. Structural and lipid biochemical correlates of the epidermal permeability barrier. Adv Lipid Res 1991; 24:1-26.
9. Butler H. Poucher's perfumes cosmetics and soaps. 10th ed. Springer, India; 2010. p. 402.
10. Bruton L, Keith P, Blumenthal D, Buxton L. Goodman and Gillman's manual of pharmacology and therapeutics. 2nd ed. Mc Graw's Hill; 2008. p. 1086-94.
11. Kalia YN, Guy RH. Modeling transdermal drug release. Adv Drug Deliv Rev, 48:159172, (2001).
12. Ayub, CA, Gomes ADM, Lima MVC, Vianna-Soares CD, FerreiraLMA. Topical Delivery of Fluconazole: In Vitro Skin Penetration and Permeation Using Emulsions as Dosage Forms Drug. Dev. Ind. Pharm, 33:273-280, (2007).
13. Drehar F, Walde P, Walthar P, Wehrli E; "Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport." Journal of Controlled Release. 1997, 45, 131140.
14. 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.
15. Hyma P, Noorjahan, Raheemunnisa, Sreelekha G, Babu K (2014) Emulgel: a review. International journal of pharmaceutical3:1-11.
16. Singla V, Saini S, Joshi B, Rana AC (2012) Emulgel: A New Platform for Topical DrugDelivery. International Journal of Pharma and Bio Sciences3: 485-498.
17. Patel, H. K., Barot, B. S., Parejiya, P. B., Shelat, P. K., & Shukla, A. (2013). Topical delivery of clobetasol propionate loaded microemulsion based gel for effective treatment of vitiligo: ex vivo permeation and skin irritation studies. Colloids and Surfaces B: Biointerfaces, 102, 86-94.
18. Bachhav, Y. G., & Patravale, V. B. (2009). Microemulsion based vaginal gel of fluconazole: Formulation, in vitro and in vivo evaluation. International Journal of Pharmaceutics, 365(1), 175-179.
19. Doh, H. J., Jung, Y., Balakrishnan, P., Cho, H. J., & Kim, D. D. (2013). A novel lipid nanoemulsion system for improved permeation of granisetron. Colloids and Surfaces B: Biointerfaces, 101, 475-480.
20. Mohamed MI, Optimization of chlorphenesin emulgel formulation. AAPS J 2004; 6: 26.
21. Perioli L, Panago C, Mazzitelli S., Rheological and functional characterization of new anti-inflammatory delivery system designed for buccal administration, Int. J. Pharm 2008; 356:19–28
22. Waghmare N, Waghmare P, Wani S, Yerawar A; "Development of isotretinoin gel for the treatment of acne vulgaris." Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2011, 2(1), 220 -230.
23. Bhowmik D, Gopinath H, Pragati B, Duraivel S; "Recent advances in topical drug delivery system." The Pharma Innovation. 2012, 1(9), 12-31.
24. Shah R, Magdum C, Wadkar K, Naikwade N; "Fluconazole Topical Microemulsion: Preparation and Evaluation." Research Journal of Pharmacy and Technology. 2009, 2(2), 353-357.
25. Moghimipour E, Salimi A, Leis F; "Preparation and Evaluation of Tretinoin Microemulsion based on Pseudo-Ternary phase Diagram." Advanced Pharmaceutical Bulletin. 2012, 2(2), 141-147.