INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

EMULGEL: A NOVEL APPROACH FOR TOPICAL DRUG DELIVERY SYSTEM

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Accepted Date: 09/08/2015; Published Date: 27/08/2015

Abstract: Emulgels having advantage of both gels & emulsion act as a controlled drug delivery system for topically applied drugs. They are emulsion of either water in oil type or oil in water type which are gelled by mixing with a gelling agent. Gels have extends the contact period of medication over the skin due to mucoadhessive property. Both water-in-oil & oil-in-water type of emulsion are used in topical preparation as water washable preparation & emollients for dry skin respectively. The process of penetration becomes easy if the emulsion becomes less thixotropic in nature i.e. less viscous on shearing. In order to increase emulsion stability & ability to penetrate stratum corneum it is jellified in a gel base & the resulting preparation is called Emulgels.

Keywords: Emulgels, Gelling agent

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PAPER-QR CODE

Access Online On:

www.ijprbs.com

How to Cite This Article:

Shailendra Panwar, IJPRBS, 2015; Volume 4(4): 209-223

INTRODUCTION

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[1]. These formulations range in physicochemical nature from solid through semisolid to liquid. In semisolid preparations, the use of transparent gels has been increased in cosmetics as well as in pharmaceutical preparations[2]. Drugs are delivered topically for their action at the site of application or for systemic effects[3]. The absorption of drug through the skin is improved if the drug substance is in solution, if it has a favorable lipid/water partition coefficient & if it is a nonelectrolyte. For their local action, drug applied to the skin comprise antiseptics, antifungal agent, skin emollients & protectant. The main advantages of topical delivery system are to bypass first pass metabolism. Other advantages of topical preparations are avoidance of the risks & inconveniences of intravenous therapy & of the varied conditions of absorption like pH alterations, presence of enzymes, gastric emptying time[4].[5]. The topical drug delivery system is usually used where the others system of drug administration fails or it is mainly used in fungal infection. Use of topical agents needs an appreciation of the factors that influence percutaneous absorption[6]. Molecules can enter the skin by three routes: through intact stratum corneum, through sweat ducts, or through sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption[7]. Rate limiting step for percutaneous absorption is the passage through this outer most layer. The main steps involved in percutaneous absorption comprise the establishment of a concentration gradient, which offers the driving force for drug movement across the skin, release of drug from the vehicle (partition coefficient), & drug diffusion across the layers of the skin (diffusion coefficient). Preferable characteristics of topical drugs include low molecular mass (600 Da), adequate solubility in oil and water, & a high partition coefficient. Except for very small particles, water soluble ions & polar molecules do not penetrate intact stratum corneum. To manipulate the barrier function of the skin topical formulation can be used, for example, topical antibiotics & antibacterials help a damaged barrier toward off infection, sun screening agents & the horny layer protect the viable tissues from Ultraviolet radiation & emollient preparations restore pliability to a desiccated horny layer[8].

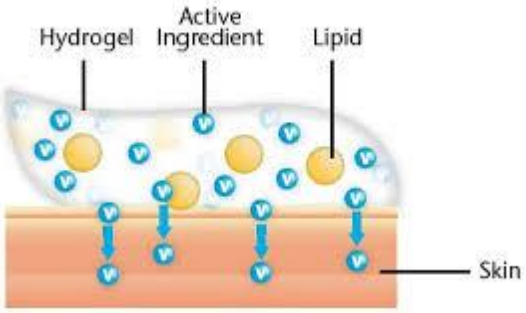
RATIONALE

Various widely used topical agents like ointment, cream, lotion have many disadvantages. They causing uneasiness to the patient due to sticky nature. They also have lesser spreading coefficient & need to apply with rubbing. And they also exhibit the stability problem. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics & in pharmaceutical preparations. A gel is colloid that is typically

99% wt. liquid, which is immobilized by surface tension between it & a macromolecular network of fibers built from a small amount of a gelating substance present. The major drawback of gel is in the delivery of hydrophobic drugs. So to overcome this an emulsion based method is being used so that even a hydrophobic drug can be efficaciously incorporated & delivered through gels[9].

EMULGEL

Emulgels having advantage of both gels & emulsion act as a controlled drug delivery system for topically applied drugs. They are emulsion of either water in oil type or oil in water type which are gelled by mixing with a gelling agent. Gels have extends the contact period of medication over the skin due to mucoadhessive property. Both water-in-oil & oil-in-water type of emulsion are used in topical preparation as water washable preparation & emollients for dry skin respectively. The process of penetration becomes easy if the emulsion becomes less thixotropic in nature i.e. less viscous on shearing. In order to increase emulsion stability & ability to penetrate stratum corneum it is jellified in a gel base & the resulting preparation is called Emulgels. Gels in dermatological preparation have advantage of ease of application & offer better stability as compare to cream & ointements[10].



Emulgel structure

From the four classes of BCS classification of drugs class II drugs show poor solubility & high permeability. It is clear that for class II drugs having low ability to dissolve is a more significant drawback to their whole rate & amount of absorption then their ability to permeate through the membrane. Hence, when one is concerned with topical delivery of poorly water-soluble drug Emulgels may serve as better choice. Emulsified gel has proven a stable one and better vehicle for hydrophobic or poorly water-soluble drugs.

ADVANTAGES[11,12,13]

1. As topical agent: Most of the topical dermatological preparation like creams & ointments have disadvantage of less spreading coefficient, sticky nature & needs rubbing during

application. These drawbacks are overcome in gel preparation but despite of various advantage gels have major drawback in delivery of hydrophobic drugs. So to overcome this limitation emulgels are prepared and with their use even a hydrophobic drug can enjoy the unique properties of gels. Thus, emulgels have proved a boon in delivery of hydrophobic drugs topically & providing them advantages of gel formulation.

2. Stability: Several other topical preparation show less stability than emulgels. As creams show phase inversion, ointments show rancidity due to oily base & powders are hygroscopic in nature.

3. Better than other vesicular approaches: Niosomes & liposomes due to vesicular structures result in leakage and due to small size in lesser entrapment efficiency, thus have poor loading capacity. Whereas gels due to their vast polymeric three dimensional structure show better loading capacity.

4. Easy production: Production of emulgels is easy & done in short steps & no specific instruments are required thus low cost is needed for its formulation.

5. Controlled release: Emulgels act as a twin control preparation & thus is good for release of drugs with short half-life.

6 .No intensive sonication: While production of vesicular molecules likes liposomes, niosomes required sonication that may result in drug degradation and leakage. This is not needed in emulgels formulation.

7. Patient compliance: Emulgels improve patient compliance as they can be self applied & medication can be terminated whenever required.

DISADVANTAGES

1. Drugs having large particle size (>400 daltons) are not easily absorb or cross through the skin barrier.

2. Some drugs have poor permeability through skin.

3. On contact, skin irritation or allergic reaction may arise.

4. During formation of emulgel bubbles may occur.

DRUG DELIVERY ACROSS THE SKIN

The epidermis is the most superficial layer of the skin & is made up of stratified keratinized 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 defends the deeper & more delicate structures. Under the skin blood vessels are distributed profusely. Particularly important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries. In the most exposed parts 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 & treatment. The skin acts as a two-way barrier to avoid absorption or loss of water & electrolytes. The three basic mechanisms of topical drug absorption are: transcellular, intercellular, & follicular. Most drugs pass through the torturous path around corneocytes & through the lipid bilayer to viable layers of the skin. The next most common (& 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 & gels have been used for years to deliver pain medication and infection fighting drugs to an affected area of the body. These include, among others, gels & 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 but the whole body.

Factors Affecting Topical Absorption of Drug[8]

Physiological Factors

1. Skin thickness – It varies from epidermis to subcutaneous layer. Epidermis has high thickness about 100-150µm. Skin on the sole & palm has a high rate of diffusion.

2. Lipid content - It is an effective water barrier, when lipid weight in stratum corneum is low percutaneous penetration increases.

3. Density of hair follicles – hair follicle infundibulum has a large storage capacity approximately 10 times more than the stratum corneum.

4. Density of sweat glands

5. Skin pH –The pH of the skin surface is influence by sweat and fatty acid secreted from sebum.

6. Hydration of skin –It can improve permeation of drug.

7. Inflammation of skin – that disrupts the continuity of stratum corneum increases permeability.

8. Skin temperature – When temperature is increase the rate of skin permeation is also increase.

9. Blood flow

Physiochemical Factors

1. Partition coefficient – more the value of log p more effortlessly will be the percutaneous absorption of the drug.

2. Molecular weight (< 400 dalton)

3. Degree of ionization – only unionized drug molecules get absorbed well.

4. Effect of vehicles – hydroalcoholic gel offer the most efficient absorption through skin.

Factors to be Considered When choosing a Topical Preparation[14,15]

1. Effect of the vehicle e.g. Penetration of the active ingredient & efficacy is improve by occlusive vehicle. The vehicle itself may have a cooling, drying, emollient or protective action.

2. Match the type of preparation with the type of lesions. For example, for acute weepy dermatitis avoid greasy ointments.

3. Match the type of preparation with the site. (e.g., gel or lotion for hairy parts)

4. Irritation or sensitization potential. Generally, gels are more irritating than ointments and water-in-oil creams. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.

Method to Enhance Drug Penetration & **Absorption**[16]

1. Chemical enhancement.

2. Physical enhancement.

3. Biochemical enhancement.

4. Super saturation enhancement.

FORMULATION OF EMULGEL

1. Vehicle:

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.

• To provide a pharmacologic effect it sustains therapeutic drug level in the target tissue for adequate period.

• Appropriately formulated for the anatomic site to be treated.

• Cosmetically acceptable to the patent. The amount of topical drug that gets through the stratum corneum is usually low due to the efficiency of the epidermal barrier. Depending on characteristics of the vehicle rate & amount of absorption vary but is also influenced by the active agent itself [17].

(A) Aqueous Material:

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

(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 commonly used both as the vehicle for the drug and for their occlusive & sensory characteristics. Widely used oils in oral preparations are non-biodegradable mineral & castor oils that provide a local laxative effect & fish liver oils or several fixed oils of vegetable origin (e.g., arachis, cottonseed & maize oils) as nutritional supplements[18].

2. Emulsifiers:

Emulsifying agents are used both to promote emulsification at the time of manufacture & 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 and Sodium stearate[19]**.**

3. Gelling Agents:

These agents are used to increase the consistency of any dosage form & can also be used as thickening agent[20].

4. Penetration Enhancers:

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

Properties of penetration enhancers[21]:

1. They should be non-toxic, non-irritating & non- allergenic.

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

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

4. They should work unidirectional i.e. avoiding the loss of endogenous material from the body whereas should allow therapeutic agents into the body.

5. They should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.

6. They should be cosmetically acceptable with an appropriate skin 'feel'.

Mechanism of penetration enhancers:

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

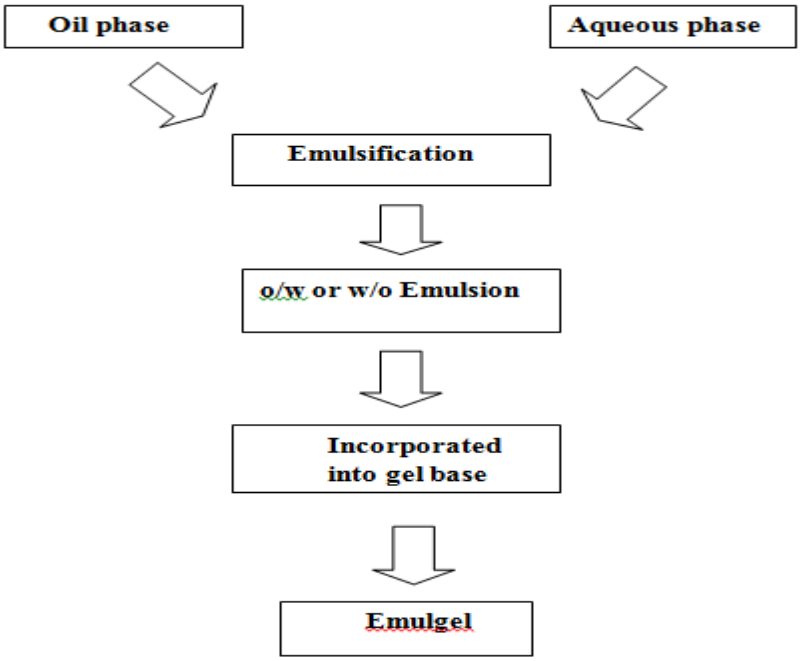
1. Disruption of the highly ordered structure of stratum corneum lipid.

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. By protein conformational change or solvent swelling the polar pathway is altered. The fluidity of the lipid protein portion of the stratum corneum is increased by fatty acid enhancers. By altering the multi laminate pathway for penetration some enhancers act on both polar and non-polar pathway. Drug diffusivity through skin proteins is increase by enhancer. On the design and development of the product significant effect is employed by type of enhancer[22].

EMULGEL PREPARATION



Flow chart for preparation of emulgel

Emulgel was prepared by the method reported by Mohammad et al (2004) with slight modification. The Gel in formulations were 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 are adjusted to 6 to 6.5 using Tri ethanol amine (TEA). The oil phase of the emulsion were prepared by dissolving Span 80 in light liquid paraffin having drug in ethanol solution while by dissolving Tween 80 in purified water the aqueous phase was prepared. Methyl & Propyl paraben was dissolved in propylene glycol & was mixed with the aqueous phase. Both the oily & aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. Then add glutaraldehyde in during of mixing of gel & emulsion in ratio 1:1 to obtain the emulgel.

EVALUATION PARAMETERS FOR THE FORMULATION

1. **Physical appearance[13]:**

The prepared emulsion preparations were examined visually for their color, homogeneity, consistency & pH.

2. **Spreadability:**

Spreadability is determined by apparatus recommended by Mutimer et al (1956) which is appropriately modified in the laboratory & 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' & 'Drag' characteristics of emulgels. A ground glass slide is fixed on this block. On this ground slide an excess of emulgel (about 2gm) under study is placed. The emulgel is then sandwiched between this slide & another glass slide having the dimension of fixed ground slide & provided with the hook. A 1 kg weight is placed On the top of the two slides for 5 minutes to expel air & 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 80gm. With the help of string attached to the hook & the time (in seconds) necessary for the top slide to cover a distance of 7.5cm be noted. Better spreadability is indicate by lesser time[23]. Spreadability was calculated by using the formula,

S= ML/T

Where, S = Spreadability,

M = Weight tied to upper slide,

L = Length of glass slide;

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

3. Rheological Studies:

The viscosity of the different emulgel formulations is determined at 25°C using a cone & plate viscometer with spindle 52 (Brookfield Engineering Laboratories,) & attached to a thermostatically controlled circulating water bath[24].

4. Swelling Index:

To determine the swelling index of prepared topical emulgel, 1 gm of gel is taken on porous aluminum foil & then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaoH. Then at different time intervals samples were removed from beakers and put it on dry place for some time after it reweighed. Swelling index is calculated as follows:

Swelling Index (SW) % = $[(W_t - W_o) / W_o] \times 100$.

Where (SW) % = Equilibrium percent swelling

W_t = Weight of swollen emulgel after time t[25].

5. Drug Content Determination[26]:

1gm of emulgel is mixed with appropriate solvent. Then filter it to get clear solution. Using UV spectrophotometer determine its absorbance. Standard plot of drug is prepared in the same solvent. Concentration & drug content can be determined by using the same standard plot by putting the value of absorbance in the standard plot equation:

Drug Content = (Concentration × Dilution Factor× Volume taken) × Conversion Factor.

6. Skin Irritation Test (Patch Test):

The preparation is applied on the properly shaven skin of rat & its adverse effect like change in color, change in skin morphology should be checked up to 24 hours. The total set of 8 rats can be used for the study. Test is passed if no irritation occurs. If the skin irritation symptom arises in more than 2 rats the study should be repeated[27].

7. *In-Vitro* Release/Permeation Studies:

Using Franz diffusion cell *In-vitro* release studies were carried out.

Drug release kinetic study[28]

The mechanism of drug release from the topical gel is analyzed by fitting the release data to following equations

Zero – order equation:

$Q = k_0 t$

Where, Q is the amount of drug released at time t

k_0 is the zero – order release rate.

First – order equation:

$\ln (100 - Q) = \ln 100 - k_1 t$

Where, Q is the percent of drug release at time t

k_1 is the first – order release rate constant.

Higuchi's equation:

$Q = k_2 \sqrt{t}$

Where, Q is the percent of drug release at time t

k_2 is the diffusion rate constant.

8. Microbiological assay:

Ditch plate technique was used for microbiological assay. It is a technique used for evaluation of bacteriostatic or fungistatic activity of a compound. It is mainly applied for semisolid formulations. Previously prepared Sabouraud's agar dried plates were used. 3 grams 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. The fungal growth was observed after incubation for 18 to 24 hours at 25°C, & the percentage inhibition was measured as follows.

% inhibition = $L_2 / L_1 \times 100$

Where, L_1 = total length of the streaked culture,

L_2 =length of inhibition[29].

9. Stability Studies:

The prepared emulgels were packed in aluminum collapsible tubes (5 g) & subjected to stability studies at 5°C, 25°C/ 60% RH,30°C/65% RH, and 40°C/75% RH for a period of 3 months. Samples were withdrawn at 15-day time intervals & evaluated for physical appearance, pH, rheological properties, drug content, & drug release profiles[28].

FUTURE PROSPECTIVE OF EMULGEL AS TOPICAL DRUG DELIVERY

Emulgels are the present trend in delivery of hydrophobic drugs topically. Most of the drugs available today are hydrophobic in nature & difficulty arises due to their solubility & thus poor bioavailability during topical administration. Despite of several advantages emulgels face problem of bubble formation during its formulation & stratum corneum is permeable to small molecules so concerning these facts we can incorporate micro sponge that are highly porous micronized particles with unique ability to entrap pharmaceutical ingredient[30] into an emulgel base. They are better available choice for dermatological use due to characteristics such as better loading capacity than other vesicular system, less sticky nature & better spreading of emulgel formulation. Many herbal oils with medicinal properties can also be incorporated into the emulgel formulation that may act as synergistic approach for treating a disease. Emulgels can be a better substitute for delivery of sun shielding agents by formulating sunscreen in emulgel base. One such research was carried by M. Vettor et al who studied the ultra violet filter distribution & release in skin layer of octyl-methoxycinnamate loaded poly (D, L-lactide)

nanoparticles in emulsion gel base[31] but till date no such sunscreen based on emulsion gel base is prepared or studied. So this can offer a great field for study in emulgel evolution field. Microsizing & Nanosizing the particles of emulsion and then dispersing them into gel base can further be studied and these may cause enhancement of topical release of drugs with poor penetration ability. Addition of different penetration enhancers of natural as well as synthetic origin can be further explored for increasing topical penetrability of drugs through emulgel base. Buccal emulgels can also be prepared by incorporating mucoadhessive polymers and can provide relief in oral infections.

CONCLUSION

In the recent years, topical drug delivery system will be used widely due to better patient compliance. Emulgel is the recent technique for the topical drug delivery it is better suitable for hydrophobic drugs & clearly it is a very good technique for drug delivery of combination of both hydrophilic & hydrophobic drugs. Generally the hydrophobic drug formulation can be developed with emulgel technique because it contain both oil & aqueous (i.e. gel base) on the other hand hydrogel are not suitable for hydrophobic drugs. Since emulgel is enhancing spreadibility, adhesion, viscosity and extrusion this novel drug delivery becomes a popular formulation in future.

ACKNOWLEDGEMENT

I am very thankful to Mr. Sayantan Mukhopadhyay, SGRRITS, Dehradun, India, for providing me their guidance & support at each & every step.

REFERENCES

1. Kshirsagar N A. Drug Delivery Systems. Ind. J. Pharmacol. 2000; 32:S54- S61.

2. Dadwal Meenakshi, emulgel: a novel approach to topical drug delivery International journal of pharma and bio sciences, 4 (2013), 847-856.

3. Rashmi M. Topical gel: A review august vol. 2008; available from http:// www.pharmainfo.com

4. 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 2008; 6:1.

5. Laithy HM. and El shaboury KMF. The development of Cutina Lipogels and gel microemulsion for topical administration of fluconazole. Ame Pharm Sci. PharmSciTech. 2003; 3:10 25.

6. Stanos SP. Topical Agents for the Management of Musculoskeletal Pain .J Pain Symptom Manage March 2007; 33.

7. Jain A, Deveda P, Vyas N, Chauhan J et al. Development Of Antifungal Emulsion Based Gel For Topical Fungal Infection(S). IJPRD 2011; 2(12).

8. Bruton L, Keith P, Blumenthal D, Buxton Z. Goodman & Gillman's Manual of Pharmacology & Therapeutics. Mc Graw's Hill. 2008. pp.1086-1094.

9. Cecv G. Preclinical characterisation of NSAIDs in ultradeformable carriers or conventional topical gels. International journal of pharmaceutics; 2008.

10. Bhoyar N, Giri T.K, Tripathi D.K, Alexender .A and Ajazuddin: Recent advances in novel drug delivery system through gels: review, J. Pharm. allied health sci, 2012, 2(2), 21-39.

11. Khullar Rachit,Saini S, Seth N and Rana A C:Emulgels: A surrogate approach for topically used hydrophobic drugs,IJPBS, 2011, 1 (3), 117-128.

12. Prajapati Mehulkumar N, Patel M R, Patel K R & Patel N M:Emulgels: a novel approach to topical drug delivery, IJUPBS, 2013, 2(1), 134- 148

13. Joshi baibhav, Singh Gurpreet, Rana A C, Saini Seema & Singla Vikas: Emulgel: A comprehensive review on recent advancement on topical drug delivery, IRJP, 2011, 2(11), 66-70.

14. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal Drug Delivery System: A Review. AJPCR 2009; 2: 14-20.

15. Subranayam N, Ghosal SK, Moulik SP. Enhanced *In-Vitro* Percutaneous Absorption & *In-Vivo* Anti-Inflammatory Effect of a Selective Cyclooxygenase Inhibitor Using Microemulsion. Drug Dev. & IndustrialPharm., 2005.

16. Pathan, I.B.; Setty, C.M. Chemical penetration enhancers for transdermal drug delivery systems. Trop J Pharm Res. April 2009; 8:173-179.

17. Bonacucina G, Cespi M, Palmieri GF, Characterization & Stability of Emulsion Gels Based on Acrylamide/Sodium Acryloyldimethyl Taurate Copolymer. AAPS PharmSciTech, 10 (2): 34-45, (2009).

18. Curr AEB. Transdermal Drug Delivery: Penetration Enhancement Techniques Heather. Drug Deliv, 5(2):23-33, (2005).

19. Rutrer N, Drug absorption through the skin: a mixed blessing. Arch Dis Child, 62:220- 221, (1987).

20. Zhang XL, Zhao R, Qian W. Preparation of an emulgel for treatment of aphthous ulcer on the basis of carbomers. Chin Pharm J, 30:417-418, (1995).

21. Swarbrick, J. Encyclopedia of pharmaceutical technology, 3rd ed., 1551.

22. WB Saunders Co. Philadelphia, 1970, 55-60.

23. Gupta GD, Gound RS. Release rate of nimesulide from different gellants. Indian J Pharm Sci, 61(1): 229-23, (1999).

24. 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; 43: 55-62.

25. Patel RP, Patel G, Baria A. Formulation and evaluation of transdermal patch of aceclofenac, Int J Drug Del, 1(3): 41 – 51, (2009).

26. Sanjay Jain, B. D., Padsalg, A., Patel, K., & Mokale, V. (2007). Formulation, development and evaluation of Fluconazole gel in various polymer bases, *Asi. J. Pharm., 1*, 63-68.

27. Masmoudi, H., Piccerelle, P., Le Dreau, Y., & Kister, J. (2006). A rheological method to evaluate the physical stability of highly viscous pharmaceutical oil-in-water emulsions, Pharm. Res., 23 (8), 1937–1947.

28. Jones DB, Woolfson AD, Brown AF. Textural, viscoelastic and mucoadhesive properties of pharmaceutical gels composed of cellulose polymers. Int J Pharm, 151:223–33, (1997).

29. Tadros TF, Future developments in cosmetic formulations. Int J Cos Sci 1992; 14 (3): 93-111.

30. Alookar N.H, Kulkarni A.S, Ingale D.J and Patil R.A:Microsponge as innovative drug delivery system, IJPSN, 2012, 5(1), 1597-1606.

31. M. Vettor, S. Bourgeois, H. Fessi, J. Pelletier, P. Perugini, F. Pavanetto and M. A. Bolzinger: Skin absorption studies of octylmethoxycinnamateloaded poly (D, L-lactide).